National Institute for Health and Care Excellence

Guideline version (for example, Draft, Consultation, Final)

Joint replacement (primary): hip, knee and shoulder

[G] Evidence review on tranexamic acid to minimise blood loss

NICE guideline

Intervention evidence review

October 2019

Draft for Consultation

This evidence review was developed by the National Guideline Centre, hosted by the Royal College of Physicians

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ISBN

Contents

1 Tranexamic acid

1.1 Review question: In adults having primary elective joint replacement, what is the clinical and cost effectiveness of tranexamic acid (TXA) for minimising blood loss from surgery?

1.2 Introduction

Significant blood loss may occur during joint replacement surgery. Treatments to reduce the blood loss offer advantages to patients, reducing the need for blood products, which are expensive, and reducing recovery time and improving the recovery experience. Tranexamic acid has been utilised both systemically and topically to reduce blood loss in joint replacement surgery. There is currently no agreed national standard on which method of delivery is the best. This review seeks to assess whether tranexamic acid is effective and what the most effective method of delivery is.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	Adults having primary elective joint replacement
Interventions	• Perioperative use of topical/intra-articular tranexamic acid • Perioperative use of intravenous tranexamic acid • Perioperative use of oral tranexamic acid • Perioperative use of topical/intra-articular and intravenous tranexamic acid • Perioperative use of topical/intra-articular and oral tranexamic acid • Perioperative use of intravenous and oral tranexamic acid • Perioperative use of topical/intra-articular, intravenous and oral tranexamic acid
Comparison	• Comparison versus interventions or versus placebo or no treatment.

Outcomes	**Critical**
	• Mortality: 30 day (dichotomous)
	• Blood (allogeneic or autologous) transfusion (dichotomous)
	• Adverse events
	  ○ Acute myocardial infarction (dichotomous)
	  ○ Postoperative thrombosis (dichotomous)
	• Quality of life within 6 weeks (continuous)
	• Surgical bleeding (continuous)
	Important
	• Postoperative anaemia (dichotomous)
	• Postoperative bleeding (continuous)
	• Length of stay (continuous)

Study design	Randomised controlled trials If no well-conducted RCTs are available, then observational studies with multivariate analysis will be investigated.

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1.4 Clinical evidence

1.4.1 Included studies

A search was conducted for randomised trials investigating the effectiveness of tranexamic acid for reducing blood loss during primary elective joint replacement surgery.

108 randomised controlled trials were included in the review; [1, 5-7, 12, 13, 18, 22-25, 27-30, 38, 42, 44, 45, 48, 56, 60, 64, 74-78, 84, 85, 87, 90-92, 104, 107, 109, 111, 114, 116, 118, 122, 126, 127, 129, 131, 135, 138, 140, 142-145, 147, 154, 155, 161, 162, 166, 167, 170-172, 175, 176, 180, 183, 191, 193, 195-197, 200, 201, 203, 206, 210, 214, 215, 225, 227, 233, 241, 246-248, 251, 253-256, 259, 263, 264, 270, 276, 280, 282, 285, 287, 289, 291, 302, 303, 305, 307] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

1.4.2 Excluded studies

See the excluded studies list in appendix I.

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1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies under each comparison in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
IA/topical versus no treatment				
Aguilera 2015[7]	After prosthesis inserted and cemented, operative field was rinsed and dried. 1g in 10mL solution topically applied by syringe spray to the posterior capsule, surrounding soft tissue, fatty and subcutaneous tissue, exposed surfaces of femur and tibia. versus No treatment	Adults having elective total knee replacement due to OA or RA or other degenerative knee disorders	• Transfusion • Blood loss via haemoglobin level after surgery • Total blood loss • Surgical bleeding • Postoperative bleeding • Length of stay	
Antinolfi 2014[18]	500mg injected inside the joint, while no knee flexion or compression was applied versus No treatment	People with primary knee osteoarthritis and scheduled to undergo unilateral primary TKA	• Blood loss via haemoglobin level after surgery • Total blood loss • Adverse events: DVT	
Digas 2015[56]	2g after skin closure versus No treatment	People under 85 years old with primary osteoarthritis who we scheduled for total knee arthroplasty.	• Transfusion • Blood loss via haemoglobin level after surgery • Total blood loss • Surgical bleeding • Adverse events: DVT	
Guerreiro 2017[91]	1g in 50ml versus No treatment	People undergoing total knee arthroplasty	• Transfusion • Blood loss via haemoglobin level after surgery	

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Study	Intervention and comparison	Population	Outcomes	Comments
			• Adverse events: DVT	
Keyhani 2016[129]	3g in 100ml normal saline. Half of the solution was used to irrigate the joint before joint closure. The remaining half of the volume was administered in the joint after wound closure by a portovac drain versus No treatment	People with osteoarthritis of the knee scheduled to undergo primary unilateral TKA	• Transfusion • Blood loss via haemoglobin level after surgery	
Lacko 2017[138]	3g in 50 mL of saline, applied directly into surgical wound following the cementing of the implant. versus No treatment	People with primary or secondary osteoarthritis and having unilateral cemented primary total knee replacement	• Adverse events: DVT	
Laoruengthana 2019[140]	15mg/kg poured into knee joint before closure of the arthrotomy. versus No treatment	People with primary osteoarthritis who are scheduled for primary unilateral total knee arthroplasty	• Transfusion • Length of stay	
Mehta 2019[175]	2.5g (25ml) in 25ml saline. Equally given to each knee joint after wound closure. versus No treatment	People having primary bilateral total knee arthroplasty due to advanced osteoarthritis of the knee.	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Surgical bleeding • Length of stay	
Oztas 2015[196]	2g was applied locally on the proximal-medial surface of the patella with intra-articular injection after the joint capsule	People with inflammatory arthritis, history of thromboembolism, myocardial infarction and	• Transfusion • Adverse events: DVT • Total blood loss	

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Study	Intervention and comparison	Population	Outcomes	Comments
	closure in the final stage of the operation before the tourniquet deflation versus No treatment	stroke and allergy to tranexamic acid.	• Length of stay	
Perez-Jimeno, 2018[203]	2g administered following skin closure through the deeper drainage tube. versus No treatment	People scheduled for cemented or non-cemented primary elective total hip arthroplasty	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss	
Ugurlu 2017[246]	3g in 100ml saline. 50ml administered with infiltration to wound lips following suturing of the capsular incision. 50ml administered into the joint. versus No treatment	People undergoing primary total knee arthroplasty for degenerative osteoarthritis.	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery	
Zhang 2016[302]	1g in 100ml saline via the drainage tubes. versus No treatment	Diabetes, bleeding disorders, preoperative anaemia, malignancies, history of thrombosis disease, arteriosclerosis, varicose veins and other cardiovascular diseases, allergy to tranexamic acid, kidney dysfunction.	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery	
Oral versus no treatment				
Lee 2017a[142]	1g 2 hours before induction of anaesthesia and then two more doses 6 hours and 12 hours postoperatively versus	People undergoing primary total knee arthroplasty	• Mortality • Adverse events: DVT • Blood loss via haemoglobin level after	

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Study	Intervention and comparison	Population	Outcomes	Comments
	No treatment		surgery • Total blood loss • Length of stay	
IV versus no treatment				
Aguilera 2015[7]	2 doses of 1g. 15-30 minutes before tourniquet inflated and again when tourniquet is removed versus No treatment	Adults having elective total knee replacement due to OA or RA or other degenerative knee disorders	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Surgical bleeding • Postoperative bleeding • Length of stay	
Digas 2015[56]	15mg/kg before deflation of the tourniquet.	People under 85 years old with primary osteoarthritis who we scheduled for total knee arthroplasty.	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Surgical bleeding	
Gautam 2013[76]	10 mg/kg slow injection 10 minutes before deflation of tourniquet. versus No treatment	People having total knee arthroplasty	• Total blood loss • Adverse events: DVT	
Imai 2012[111]	1g administered 10 minutes before surgery and again 6 hours later versus No treatment	People undergoing primary total hip replacement for osteoarthritis of the hip.	• Transfusion • Adverse events: DVT	
Keyhani 2016[129]	500mg in 100cc saline	People with osteoarthritis of	• Transfusion	

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Study	Intervention and comparison	Population	Outcomes	Comments
	administered at the end of surgery versus No treatment	the knee scheduled to undergo primary unilateral TKA	• Blood loss via haemoglobin level after surgery	
Kim 2014[131]	10mg/kg 30 min before tourniquet deflation, and the same amount was repeated 3 hours later. versus No treatment	People undergoing total knee arthroplasty	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss	
Lacko 2017[138]	2 doses of 10mg/kg. The first dose was administered 20 minutes prior to incision and the second dose was administered three hours after the first dose versus No treatment	People with primary or secondary osteoarthritis and having unilateral cemented primary total knee replacement	• Adverse events: DVT	
Laoruengthana 2019[140]	10mg/kg administered before closure of the arthrotomy. versus No treatment	People with primary osteoarthritis who are scheduled for primary unilateral total knee arthroplasty	• Transfusion • Length of stay	
Mehta 2019[175]	1g administered after regional anaesthesia but before tourniquet inflation. versus No treatment	People having primary bilateral total knee arthroplasty due to advanced osteoarthritis of the knee.	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Surgical bleeding • Length of stay	
Mcconnell 2011[172]	10 mg/kg at the start of surgery	People who were scheduled to undergo elective primary	• Adverse events: DVT	

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Study	Intervention and comparison	Population	Outcomes	Comments
	versus No treatment	unilateral cemented hip arthroplasty.		
Melo 2017[176]	15mg/kg IV 20 minutes before incision (maximum dose 2g). Half of the people received an extra dose of 10mg/kg using an infusion pump throughout the surgical procedure. versus No treatment	People undergoing primary THA	• Blood loss via haemoglobin level after surgery	
Molloy 2007[180]	500mg five minutes before deflation of the tourniquet and a repeat dose three hours later versus No treatment	People with a pre-operative haemoglobin (Hb) level of 13.0 g/dl or less who were scheduled to undergo a primary TKR	• Mortality • Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss	
Oztas 2015[196]	20mg/kg dose administered 15 minutes before tourniquet inflated. versus No treatment	People with degenerative knee osteoarthritis who did not respond to conservative treatment and underwent unilateral primary TKR	• Transfusion • Adverse events: DVT • Total blood loss • Length of stay	
Pachauri 2014[197]	1g given 1 hour before surgery and a second dose 6 hours later. versus No treatment	People with osteoarthritis scheduled for total knee replacement	No outcomes of interest identified	
Ugurlu 2017[246]	3g in 100ml saline. 50ml administered with infiltration to wound lips following suturing of the capsular incision. 50ml administered into the joint. versus	People undergoing primary total knee arthroplasty for degenerative osteoarthritis.	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery	

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Study	Intervention and comparison	Population	Outcomes	Comments
	No treatment			
Zhang 2016[302]	1g diluted in 250ml saline and administered via IV infusion 10 minutes before the surgery. versus No treatment	People scheduled for unilateral primary total hip replacement for osteonecrosis of the femoral head and a BMI between 18.5 and 30.	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery	
IA/topical versus placebo				
Alshryda 2013a[12]	1g in 50ml saline sprayed into the wound end of the total hip replacement immediately before the wound is dressed. versus Saline placebo	People undergoing primary unilateral total hip replacement.	• Quality of life • Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Length of stay	
Alshryda 2013b[13]	1g in 50ml saline sprayed into the wound end of the total knee replacement immediately before the wound is dressed. versus Saline placebo	People undergoing primary unilateral total knee replacement.	• Quality of life • Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Length of stay	
Georgiadis 2013[78]	2g in 75mLsaline versus Saline placebo	Patients undergoing unilateral primary total knee arthroplasty (TKA)	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Length of stay	

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Study	Intervention and comparison	Population	Outcomes	Comments
Gillespie 2015[84]	2g in 100ml saline poured into surgical wound before closure and left in place for 5 minutes. versus Saline placebo	People undergoing conventional total shoulder arthroplasty or reverse total shoulder arthroplasty.	• Transfusion • Adverse events: DVT	
Ishida 2011[114]	2g in 20ml into the knee joint versus Saline placebo	People with osteoarthritis scheduled for primary TKA	• Transfusion	
Lin 2015[155]	1g in 20mL normal saline using IA application intraoperatively after joint capsule closure versus Saline placebo	People scheduled for unilateral TKA	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss	
Martin 2014[170]	2g in 100 ml of normal saline into the joint space prior to surgical closure. versus Saline placebo	Aged 18 years and older, who were scheduled for a primary TKA or primary THA with or without cement	• Transfusion • Adverse events: DVT	
Onodera 2012[193]	1g in 50ml saline with 50g carbazochrome sodium sulfonate injected through the drain immediately after wound closure. versus Saline placebo	People having primary total knee replacement	• Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Length of stay	
Prakash 2017[210]	3g in 50ml saline applied to joint cavity 5 minutes before closure. OR 3g in saline retrograde through the drain after closure. versus Saline placebo	People with primary osteoarthritis who were scheduled for primary unilateral total knee arthroplasty.	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss	

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Study	Intervention and comparison	Population	Outcomes	Comments
Roy 2012[214]	Two drain tubes were placed inside the joint through which 500mg in 5ml was administered versus Saline placebo	People under 80 years of age with osteoarthritis scheduled for elective primary unilateral cemented-TKA	• Transfusion • Blood loss via haemoglobin level after surgery • Surgical bleeding • Postoperative bleeding	
Sa-Ngasoongsong 2011[215]	250mg in 25mL of physiologic saline injected into knee joint after completion of fascial closure. versus Saline placebo	People with primary knee osteoarthritis and undergoing unilateral primary cemented computer-assisted TKR	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Postoperative bleeding	
Song 2017[227]	1.5g in 50 mL of saline retrograde through the drain after wound closure versus Saline placebo	People with primary osteoarthritis of knee awaiting navigation assisted TKA	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss	
Stowers 2017[233]	1.5g in 20mL of saline after implantation of prosthesis and closure of arthrotomy followed by standard closure. versus Saline placebo	Adults undergoing primary unilateral TKA	• Transfusion • Adverse events: DVT • Total blood loss	
Wang 2015a[256]	1g in 50 ml saline and injected after prosthesis implantation and before cavity closed. versus Saline placebo	People undergoing primary unilateral TKA. All patients were treated with patellar medial approach, and the implants were CR knee bone cement prosthesis Gemini MKII	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss	
Wang 2015b[253]	Immediately after skin closure, 10mL saline with 0.5g TXA was	Primary varus knee osteoarthritis and scheduled	• Transfusion	

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Study	Intervention and comparison	Population	Outcomes	Comments
	7injected into the joint. versus Saline placebo	for unilateral primary TKA.	• Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Length of stay	
Wang 2017[259]	1g in 50 mL saline was administered right before skin closure. versus Saline placebo	People aged 30 years and older, who were scheduled for primary unilateral TKA for end-stage osteoarthritis	• Transfusion • Adverse events: DVT • Total blood loss • Length of stay	
Wei 2014[264]	3g mixed with 100ml saline. During surgery, the acetabulum was bathed in 20ml. Following femoral canal broach preparation, the femoral canal was filled with 20ml.The remaining 60ml was injected into the hip joint following fascia closure. versus Saline placebo	People aged 45–80 years who were scheduled for unilateral cementless primary total hip replacement.	• Transfusion • Adverse events: DVT • Total blood loss • Length of stay	
Wong 2010[270]	1.5g OR 3g in saline solution. After all components were cemented in place, the joint was thoroughly irrigated and the solution was applied to the joint surfaces using a bulb syringe and left in contact for 5 minutes. versus Saline placebo	People undergoing total knee arthroplasty.	• Transfusion • Blood loss via haemoglobin level after surgery • Total blood loss • Length of stay	
Yang 2015[280]	500mg in 20ml into knee joint cavity after completion of the	People >60 years old with OA, traumatic arthritis or RA	• Transfusion	

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Study	Intervention and comparison	Population	Outcomes	Comments
	facial closure. versus Saline placebo	and a BMI <40kg/m².	• Adverse events: DV • Blood loss via haemoglobin level after surgeryT • Surgical bleeding • Postoperative bleeding	
Yuan 2017[285]	3g total 60mL solution administered after the subcutaneous tissue was sutured. Oral and IV placebo used. versus Saline placebo	People with osteoarthritis or rheumatoid arthritis who were scheduled for primary unilateral TKA at were enrolled.	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery	
Yue 2014[287]	3g TXA in 150 mL saline was used at three time points. First, after the acetabular preparation then, after femoral canal broach preparation. The remaining 50 mL TXA fluid was injected to the hip joint after fascia closure. versus Saline placebo	People undergoing primary unilateral total hip arthroplasty for OA or ONFH	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Postoperative bleeding • Length of stay	
Zekcer 2016[289]	1.5g in 50 ml of saline which was sprayed over the operated area for 5 minutes, before the tourniquet was released. versus Saline placebo	People scheduled for unilateral TKA due to arthrosis (Albach grades III and IV)	• Mortality • Transfusion • Adverse events: DVT	
Zhou 2018[307]	3g in 60ml saline soaking the hip cavity before the end of surgery. versus	Adults scheduled to undergo primary unilateral THA	• Transfusion • Adverse events: DVT • Total blood loss • Surgical bleeding	

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Study	Intervention and comparison	Population	Outcomes	Comments
	Placebo		• Postoperative bleeding	
IV versus placebo				
Almeida 2018[11]	1g injected before the pneumatic cuff was inflated. versus Placebo	People with primary knee osteoarthrosis who were scheduled for TKA	• Transfusion • Blood loss via haemoglobin level after surgery • Total blood loss	
Barrachina 2016[22]	IV infusion of 15 mg/kg in 100 mL saline over a 10-minute period after the institution of regional anaesthesia and before the start of surgery. Three hours later they received a second infusion over 10 minutes. In this case half of the people received only saline and half tranexamic acid infusion. versus Saline infusions.	Hip replacement surgery (unilateral, bicompartmental, primary, uncemented, posterolateral, or anterolateral) for arthrosis in adults with ASA physical status I to III and no known allergy to tranexamic acid.	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Surgical bleeding	
Benoni 1996[23]	10 mg/kg (maximum 1g) a slow injection towards the end of the operation at a median time of 12 minutes (1 to 40) before deflation of the tourniquet. This dose was repeated after three hours. versus Two placebo infusions	A diagnosis of osteoarthritis or aseptic bone necrosis, but not of rheumatoid arthritis; primary, unilateral, bicompartmental knee arthroplasty	• Transfusion • Adverse events: DVT • Total blood loss	
Benoni 2001[24]	10 mg/kg (maximum 1g) in a slow injection immediately before the operation started versus Saline infusion	People scheduled for a unilateral, primary total hip replacement for osteoarthrosis or osteonecrosis.	• Transfusion • Adverse events: DVT	

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Study	Intervention and comparison	Population	Outcomes	Comments
Bidolegui 2014[25]	Two 10-minute infusions of 15mg/kg (diluted in 100 cc of normal saline) versus Placebo	People with osteoarthritis who are scheduled to have primary, unilateral total knee arthroplasty. All people had normal preoperative platelet count, normal prothrombin time, normal partial thromboplastin time, normal international normalized ratio	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Length of stay	
Camarasa 2006[28]	2 doses of 10mg/kg. First during 30 minutes before tourniquet release, second 3 hours after first dose. versus 2 saline doses	People who needed unilateral, bicompartmental, primary, cemented TKR because of osteoarthritis or rheumatoid arthritis and were in the anaesthetic risk groups ASA I–III were invited to participate in the study.	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss	
Chen 2016a[42]	1g in 100 mL 10 minutes before the tourniquet was inflated versus Saline placebo	Patients eligible for simultaneous bilateral cemented total knee arthroplasty (TKAs) with a diagnosis of primary osteoarthritis	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss	
Claeys 2007[44]	15mg/kg single slow injection 15 minutes before first incision. versus Saline slow IV injection	People ASA I-II undergoing unilateral elective primary total hip replacement.	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Surgical bleeding	
Clave 2019[45]	2 IV groups. 1 group received 1g at 0 (incision) and then 3, 7 and 11 hours after surgery. The	Adults awaiting primary elective THA	• Mortality • Transfusion	

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Study	Intervention and comparison	Population	Outcomes	Comments
	other group had placebo for the later 2 time points. versus Placebo		• Adverse events: DVT • Acute coronary syndrome • Total blood loss • Length of stay	
Cvetanovich 2018[48]	1g diluted in 10mL normal saline 10 minutes before incision versus 10mL of normal saline	Patients undergoing a unilateral primary anatomic or reverse primary total shoulder arthroplasty TSA at a single institution.	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Length of stay	
Ekback 2000[60]	10 mg/kg before surgical incision. A continuous infusion of 1.0 mg/ kg/h for 10 h was then started immediately after the first dose. A second dose of 10mg/kg body weight was given 3 h later. versus Saline as placebo	Patients undergoing total hip replacement (THR)	• Transfusion • Adverse events: DVT	
Garneti 2004[74]	10mg/kg dose versus Saline placebo	Patients with a diagnosis of primary osteoarthritis of the hip necessitating total hip arthroplasty (THA)	• Transfusion • Total blood loss • Postoperative bleeding	
Gautam 2011[75]	10mg/kg approximately half an hour before deflation of tourniquet versus Saline placebo	People scheduled for elective primary unilateral TKR for osteoarthritis	• Transfusion • Blood loss via haemoglobin level after surgery • Total blood loss • Postoperative bleeding	
Good 2003[87]	10mg/ kg infusion and dose	Patients who had elective	• Transfusion	

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Study	Intervention and comparison	Population	Outcomes	Comments
	was repeated after 3 hours. versus placebo	total primary unilateral tricompartmental knee arthroplasty because of osteoarthrosis, and were all classified as ASA I or II.	• Adverse events: DVT	
Hsu 2015[104]	2 doses of 1g in 20ml. The first 10 minutes before incision and the second 3 hours later. versus Saline placebo	People undergoing hip arthroplasty	• Adverse events: DVT • Surgical bleeding • Blood loss via haemoglobin level after surgery • Total blood loss • Postoperative bleeding • Length of stay	
Husted 2003[109]	10 mg/kg (maximum 1g) sloq infusion before the incision, followed by a continuous infusion of 1 mg/kg/hour dissolved in 1L of saline for 10 hours (maximum 1 g/10 hours). versus Saline placebo	Patients scheduled for primary total hip arthroplasty due to arthrosis or osteonecrosis of the femoral head.	• Transfusion • Adverse events: DVT • Total blood loss • Postoperative bleeding	
Kakar 2009[122]	10mg/kg followed by an infusion of 1mg/kg/hr until skin closure. versus Saline placebo	People undergoing primary cemented unilateral(U/L) or bilateral(B/L) total knee arthroplasties.	• Adverse events: DVT	
Kazemi 2010[127]	15mg/kg was given slowly for 5 minutes preoperatively versus Saline placebo	People having cementless hip replacement	• Adverse events: DVT • Blood loss via haemoglobin level after surgery • Length of stay	
Kundu 2015[135]	20mg/kg diluted to 25cc with normal saline administered	American Society of Anesthesiologists I-II	• Transfusion • Adverse events: DVT	

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Study	Intervention and comparison	Population	Outcomes	Comments
	before surgery versus Saline placebo	patients scheduled for unilateral total knee replacement (TKR)	• Blood loss via haemoglobin level after surgery • Surgical bleeding • Postoperative bleeding	
Lee 2013a[145]	15 mg/kg administered slowly over 10 minutes before the surgical incision was made then a continuous infusion of 15 mg/kg in saline until skin closure. versus Saline placebo	ASA physical status 1 and 2 patients scheduled to undergo primary unilateral cementless total hip replacement	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Surgical bleeding • Postoperative bleeding • Length of stay	
Lee 2013b[143]	2 doses of 10 mg/kg. The first infusion after implantation before tourniquet release and the second infusion 6 hours after the first. versus Placebo	People undergoing elective primary TKA	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss	
Lemay 2004[147]	10mg/kg followed by an infusion of 1 mg/kg/hr until skin closure. versus Saline placebo	Patients were eligible for this study if they were ASA classI to III and were undergoing primary total hip replacement (THR)	• Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss	
Lin 2012[154]	Half the people received 10 mg/kg five minutes before the incision. All people received 10 mg/kg by slow intravenous infusion five minutes before deflation of the tourniquet.	People having unilateral minimally invasive primary TKR	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss	

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Study	Intervention and comparison	Population	Outcomes	Comments
	versus Saline placebo		• Length of stay	
Malhotra 2011[166]	15kg/mg 15 minutes before incision. versus Saline placebo	People undergoing unilateral cementless total hip arthroplasty.	• Transfusion • Adverse events: DVT	
Motififard 2015[183]	2 doses of 500mg diluted in saline. First dose was infused in over 10 minutes about 30 minutes before inflation of tourniquet and the second dose after staying in the recovery room for three hours. versus Saline placebo	People with osteoarthritis who were indicated for primary TKA.	• Adverse events: DVT • Blood loss via haemoglobin level after surgery • Surgical bleeding • Length of stay	
Niskanen 2005[191]	3 dosesof 10 mg/kg mixed in 100 mL saline. The first injection was given intravenously over 5–10 min, immediately before the operation. The next two doses were given 8 hours and 16 hours after the first injection. versus Saline placebo	Consecutive people who were scheduled for a cemented hip arthroplasty for osteoarthritis.	• Transfusion • Total blood loss • Surgical bleeding	
Orpen 2006[195]	15mg/kg at the time that cement mixing commenced. versus Saline placebo	People scheduled for total knee arthroplasty	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Surgical bleeding • Postoperative bleeding	

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Study	Intervention and comparison	Population	Outcomes	Comments
Pauzenberger 2017[201]	1g in 100ml saline 30 minutes prior to incision. 1g in 100ml saline during wound closure. versus Saline placebo	People over 40 years old undergoing primary TSA or RTSA	• Transfusion • Total blood loss	
Prakash 2017[210]	10mg/kg administered 3 times. 20 minutes before tourniquet application, 15 minutes before deflation of the tourniquet, 3 hours after the previous dose in the postoperative period. versus Saline placebo	People with primary osteoarthritis who were scheduled for primary unilateral total knee arthroplasty.	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss	
Shinde 2015[225]	3 doses of 10 mg/kg. The first dose was prior to inflation of the tourniquet after induction, the second dose was 4 hours after the first dose either in the recovery room or in the ward and the third dose was after 12 hours of the first dose. versus Saline placebo	People with tricompartmental osteoarthritis of the knee and scheduled for unilateral total knee replacement were included in the study	• Transfusion • Adverse events: DVT • Surgical bleeding • Postoperative bleeding	
Song 2017[227]	10mg/kg 20 minutes before tourniquet application as a preoperative dose, 10 mg/kg 15 minutes before deflation of the tourniquet as an intraoperative dose, and 10 mg/kg 3 hours after the second dose as a postoperative dose. As placebo, the group received 50 mL of saline retrograde through	People with primary osteoarthritis of knee awaiting navigation assisted TKA	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss	

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Study	Intervention and comparison	Population	Outcomes	Comments
	drain after surgery. versus Saline placebo			
Stowers 2017[233]	1.5g at the before release of tourniquet versus Saline placebo	Adults undergoing primary unilateral TKA	• Transfusion • Adverse events: DVT • Total blood loss	
Tanaka 2001[241]	One or two doses: 20mg/kg minutes before surgery and/or 20mg/kg ten minutes before deflation of the tourniquet versus Saline placebo	People with rheumatoid arthritis or osteoarthritis who were scheduled to have a unilateral bicondylar cemented TKA	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery	
Vara 2017[247]	2 doses of 10mg/kg. Firstly within 60 minutes of surgery. Secondly at wound closure. versus Saline placebo	Adults undergoing primary RTSA for massive cuff deficiency with or without glenohumeral arthrosis.	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Postoperative bleeding	
Veien 2002[248]	10mg/kg given just before release of tourniquet and again 3 hours later. versus Saline placebo	Adults undergoing primary cemented TKR.	• Transfusion • Adverse events: DVT	
Wang 2016[251]	10mg/kg or 15mg/kg before surgery begins. versus Saline placebo	People with OA scheduled to have primary unilateral total hip replacement.	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Postoperative bleeding	

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Study	Intervention and comparison	Population	Outcomes	Comments
Wang 2017[259]	1g in 50 mL saline was administered right before skin closure. versus Saline placebo	People aged 30 years and older, who were scheduled for primary unilateral TKA for end-stage osteoarthritis	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Length of stay	
Wei 2014[264]	3g infusion 10 minutes prior to incision. Physiological saline solution (0.85%) was used as placebo. versus Saline placebo	People aged 45–80 years, without low preoperative hemoglobin, normal international normalized ratio (INR), prothrombin time, partial thromboplastin time (PTT) values, no history of previous hip surgery who were scheduled for unilateral cementless primary total hip replacement.	• Transfusion • Adverse events: DVT • Total blood loss • Length of stay	
Yi 2016[282]	15mg/kg 5 minutes before incision. 20ml normal saline solution used to topically on acetabulum and placed within femoral canal. 60ml normal saline solution injected into hip joint. versus Saline placebo	People undergoing hip replacement	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Postoperative bleeding • Length of stay	
Yuan 2017[285]	20 mg/kg intravenously 30 minutes before incising the skin, and the same dose 12 hours after TKA. Oral and IA placebo used. versus Saline placebo	People with osteoarthritis or rheumatoid arthritis who were scheduled for primary unilateral TKA at were enrolled.	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery	

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Study	Intervention and comparison	Population	Outcomes	Comments
Zekcer 2016[289]	20mg/kg, diluted in 100 ml of saline, infused over a 10-minute period at the same time as anaesthesia was administered. versus Saline placebo	People scheduled for unilateral TKA due to arthrosis (Albach grades III and IV)	• Mortality • Transfusion • Adverse events: DVT	
Zhao 2018[305]	15mg/kg 10 minutes before incision. 4 ascorbic acid tablets used for oral placebo. versus Saline placebo and 4 ascorbic acid tablets used for oral placebo.	People having elective primary unilateral total hip arthroplasty for osteoarthritis of femoral head necrosis	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Surgical bleeding • Length of stay	
Zhou 2018[307]	10mg/kg in 100 ml saline by intravenous infusion approximately 15 min before skin incision, and a second identical dose administered 3 hours later. versus Placebo	Adults scheduled to undergo primary unilateral THA	• Transfusion • Adverse events: DVT • Total blood loss • Surgical bleeding • Postoperative bleeding	
Oral versus placebo				
Bradshaw 2012[27]	4 doses of 1500mg encapsulated tranexamic acid. First dose 8 hours before admission, unclear when second dose was given, third dose within 2 hours of surgery, fourth dose 6-8 hours after surgery. versus	People with osteoarthritis undergoing primary total knee replacement.	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery	

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Study	Intervention and comparison	Population	Outcomes	Comments
	4 doses of encapsulated inactive comparator.			
Yuan 2017[285]	20mg/kg orally 2 hours before the operation and the same dose 12 hours after TKA. IV and IA placebo used. versus Saline placebo	People with osteoarthritis or rheumatoid arthritis who were scheduled for primary unilateral TKA at were enrolled.	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery	
Zhao 2018[305]	20mg/kg 2 hours before surgery and 3 hours after surgery. IV saline given to enable blinding with IV group. versus Saline placebo	People having elective primary unilateral total hip arthroplasty for osteoarthritis of femoral head necrosis	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Surgical bleeding • Length of stay	
IV plus IA/topical versus placebo				
Lin 2015[155]	1g IV injection 15 minutes before skin incision and 1g IA application intraoperatively after joint capsule closure. versus Saline placebo	People scheduled for unilateral TKA	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery	
Song 2017[227]	10mg/kg 20 minutes before tourniquet application as a preoperative dose and 10 mg/kg as a postoperative dose. 1.5g in 50mL of saline retrograde through the drain after wound closure. As placebo, these patients received 5mL of normal saline at the time of intraoperative	People with primary osteoarthritis of knee awaiting navigation assisted TKA	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery	

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Study	Intervention and comparison	Population	Outcomes	Comments
	dose. versus Saline placebo			
Yi 2016[282]	15mg/kg IV 5 minutes before incision. 200mg in 20ml solution used to topically on acetabulum and placed within femoral canal. 600mg in 60ml injected into hip joint. versus Saline placebo	People undergoing hip replacement	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Postoperative bleeding • Length of stay	
Zeng 2017[291]	15mg/kg IV in saline. Topical administration 1g in 100ml saline administered during surgery. versus Saline placebo	Adults (18-90 years old) undergoing primary unilateral total hip replacement	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Surgical bleeding • Postoperative bleeding • Length of stay	
IA/topical versus IV				
Abdel 2018[1]	3g diluted in 45mL of saline applied to open joint surfaces after cementation of the implant and prior to tourniquet release versus 1g administered prior to tourniquet inflation.	People with osteoarthritis having primary elective unilateral total knee arthroplasty.	• Transfusion • Adverse events: DVT • Total blood loss • Surgical bleeding	
Aggarwal 2016[6]	15 mg/kg in 100 mL of normal saline solution which was applied to the joint surface and left in contact for 10 minutes. versus 15 mg/kg 30 minutes before	People undergoing bilateral primary TKA for severe arthritis of the knee with tricompartmental involvement.	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery	

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Study	Intervention and comparison	Population	Outcomes	Comments
	tourniquet deflation.		• Total blood loss	
Aguilera 2015[7]	After prosthesis inserted and cemented, operative field was rinsed and dried. 1g in 10mL solution topically applied by syringe spray to the posterior capsule, surrounding soft tissue, fatty and subcutaneous tissue, exposed surfaces of femur and tibia. versus 2 doses of 1g. 15-30 minutes before tourniquet inflated and again when tourniquet is removed	Adults having elective total knee replacement due to OA or RA or other degenerative knee disorders	• Transfusion • Blood loss via haemoglobin level after surgery • Total blood loss • Surgical bleeding • Postoperative bleeding • Length of stay	
Chen 2016b[38]	1500mg diluted in 100ml saline was given as an IA wash after cementing the prostheses. versus 1500mg diluted in 100ml saline given as an infusion over 20 minutes after cementing the prostheses.	People aged from 50 to 85 with osteoarthritis of the knee and scheduled for an elective primary TKA	• Transfusion • Adverse events: DVT • Total blood loss	
Digas 2015[56]	2g after skin closure versus 15mg/kg before deflation of the tourniquet.	People under 85 years old with primary osteoarthritis who we scheduled for total knee arthroplasty.	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Surgical bleeding	
George 2018[77]	1.5g in 100 mL of saline poured into the joint before wound	People with osteoarthritis who are scheduled for a	• Transfusion	

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Study	Intervention and comparison	Population	Outcomes	Comments
	closure. versus 10mg/kg before tourniquet inflation and again at tourniquet release.	primary unilateral cemented TKA	• Adverse events: DVT • Total blood loss	
Gomez-Barrena 2014[85]	3g in 100ml of saline. Half administered by irrigation before joint closure. Half administered after joint closure. IV placebo with saline. versus 15mg/kg in 100ml saline slowly infused before tourniquet release. A second identical dose given 3 hours after surgery. IA placebo with saline.	Adults scheduled for primary unilateral total knee replacement with cemented implants.	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Length of stay	
Goyal 2017[90]	3,000mg (30mL) IA in the knee joint after wound closure. IV saline placebo. versus 1,000mg (10 mL) IV 10 minutes before deflation of the tourniquet (if a tourniquet was used) or 10 minutes before incision (if a tourniquet was not used). IA saline placebo. 2 more 1,000mg (10mL) doses of IV were given at 8 hourly intervals postoperatively.	People having primary total knee arthroplasty	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Length of stay	
Laoruengthana 2019[140]	15mg/kg poured into knee joint before closure of the arthrotomy. versus 10mg/kg administered before closure of the arthrotomy.	People with primary osteoarthritis who are scheduled for primary unilateral total knee arthroplasty	• Transfusion • Length of stay	

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Study	Intervention and comparison	Population	Outcomes	Comments
Lee 2017b[144]	10 mg/kg 30 minutes before tourniquet deflation; the same dose was repeated 3 hours after surgery. Both doses by slow infusion. versus 2g of in 30mL of normal saline was injected in the joint after closure of the retinaculum and quadriceps tendon but before subcutaneous closure.	"People with osteoarthritis having elective unilateral primary TKA "	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss	
Luo 2018[162]	2g diluted in 150mL of normal saline. Following the acetabular preparation, the acetabulum was soaked with 50mL of solution for 3 minutes. After the femoral canal broach preparation, 50mL solution was injected into the femoral canal and removed by suction 3 minutes later. After reduction of the final hip components, 50mL solution was applied to the wound and allowed to remain undisturbed for 3 minutes, after which it was removed by suction. 100mL saline IV placebo used. versus 20 mg/kg diluted in 100ml normal saline given as an IV bolus 5 minutes before the skin incision	People with osteoarthritis or osteonecrosis of the femoral head and scheduled to undergo cementless primary unilateral THA	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Length of stay	
Maniar 2012[167]	3g diluted in 100 mL normal	People with osteoarthritis	• Transfusion	

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Study	Intervention and comparison	Population	Outcomes	Comments
	saline applied locally after cementing the implant and before tourniquet release. versus 10 mg/kg 15 minutes before deflation of the tourniquet as an intraoperative dose. Half of the people received a postoperative dose. Half of the people received a preoperative dose.	scheduled to have primary, unilateral TKA.	• Adverse events: DVT • Total blood loss	
May 2016[171]	2g in 50ml saline. Injected into capsular closure. 100ml saline used as IV placebo. versus 2 doses of 1g in 100ml normal saline. The first dose after anaesthetic induction, the second dose after capsular closure. Saline used for IA placebo.	Adults over 18 years old undergoing primary unilateral total knee arthroplasty	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Length of stay	
Mehta 2019[175]	2.5g (25ml) in 25ml saline. Equally given to each knee joint after wound closure. versus 1g administered after regional anaesthesia but before tourniquet inflation.	People having primary bilateral total knee arthroplasty due to advanced osteoarthritis of the knee.	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Surgical bleeding • Length of stay	
Oztas 2015[196]	2g was applied locally on the proximal-medial surface of the patella with intra-articular injection after the joint capsule closure in the final stage of the	People with degenerative knee osteoarthritis who did not respond to conservative treatment and underwent unilateral primary TKR	• Transfusion • Adverse events: DVT • Total blood loss • Length of stay	

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Study	Intervention and comparison	Population	Outcomes	Comments
	operation before the tourniquet deflation versus 15mg/kg given 1 hour before the inflation of the tourniquet and 1 hour after the deflation of the tourniquet, and 10 mg/kg in saline given through one-hour infusion.			
Patel 2014[200]	2g in 100 ml of normal saline put directly into the surgical site and bathed in the solution, undisturbed for 2 minutes prior to tourniquet release versus 10mg/kg 10 minutes prior to tourniquet deflation.	Adults with osteoarthritis undergoing elective unilateral primary TKA	• Mortality • Transfusion • Adverse events: acute myocardial infarction • Blood loss via haemoglobin level after surgery	
Pinsornsak 2016[206]	750mg in 15 mL saline injected into the soft tissue around medial capsule (5 ml), lateral capsule (5 ml) and around the quadriceps muscle (5 ml). versus 750mg in 15ml saline.	Adults with osteoarthritis scheduled for TKA.	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Length of stay	
Prakash 2017[210]	10mg/kg administered 3 times. 20 minutes before tourniquet application, 15 minutes before deflation of the tourniquet, 3 hours after the previous dose in the postoperative period. Topical saline as placebo. versus 3g in 50ml saline applied to joint cavity 5 minutes before closure OR 3g in saline	People with primary osteoarthritis who were scheduled for primary unilateral total knee arthroplasty.	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss	

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Study	Intervention and comparison	Population	Outcomes	Comments
	retrograde through the drain after closure. IV saline as placebo.			
Song 2017[227]	1.5g in 50 mL of saline retrograde through the drain after wound closure, and as placebo, saline utilised at the same points as the IV treatment. versus 10mg/kg 20 minutes before tourniquet application as a preoperative dose, 10 mg/kg 15 minutes before deflation of the tourniquet as an intraoperative dose, and 10 mg/kg 3 hours after the second dose as a postoperative dose. As placebo, the group received 50 mL of saline retrograde through drain after surgery.	People with primary osteoarthritis of knee awaiting navigation assisted TKA	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss	
Stowers 2017[233]	1.5g in 20mL of saline after implantation of prosthesis and closure of arthrotomy followed by standard closure. Saline IV placebo used. versus 1.5g intravenously at the same time before release of tourniquet. IA saline used as placebo.	Adults undergoing primary unilateral TKA	• Transfusion • Adverse events: DVT • Total blood loss	
Ugurlu 2017[246]	3g in 100ml saline. 50ml administered with infiltration to wound lips following suturing of the capsular incision. 50ml	People undergoing primary total knee arthroplasty for degenerative osteoarthritis.	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after	

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Study	Intervention and comparison	Population	Outcomes	Comments
	administered into the joint. versus 20mg/kg dose administered 15 minutes before tourniquet inflated.		surgery	
Wang 2017[259]	1g in 50 mL saline was administered right before skin closure. versus 1g IV in 50 mL saline was administered right before skin closure.	People aged 30 years and older, who were scheduled for primary unilateral TKA for end-stage osteoarthritis	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Length of stay	
Wang 2018b[254]	2g in 100 mL of saline solution, administered intra-articularly at two time points. Oral and IV placebos used. versus 20mg/kg dose in 100 mL of normal saline solution administered 5 minutes prior to incision. Oral and IA placebos used.	Adults with primary knee osteoarthritis who were scheduled for elective primary unilateral total knee replacement	• Mortality • Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss	
Wei 2014[264]	3g mixed with 100ml saline. During surgery, the acetabulum was bathed in 20ml. Following femoral canal broach preparation, the femoral canal was filled with 20ml.The remaining 60ml was injected into the hip joint following fascia closure. versus 3g infusion 10 minutes prior to incision. Saline placebo used.	People aged 45–80 years, without low preoperative haemoglobin, normal international normalized ratio (INR), prothrombin time, partial thromboplastin time (PTT) values, no history of previous hip surgery who were scheduled for unilateral cementless primary total hip replacement.	• Transfusion • Adverse events: DVT • Total blood loss • Length of stay	

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Study	Intervention and comparison	Population	Outcomes	Comments
Wei 2018[263]	1g diluted in 50ml of normal saline, injected into the surgical site (posterior and anterior capsule, medial and lateral retinaculum), and the surgical site was soaked in the solution for 5 min before deflation of the tourniquet. versus 10mg/kg 10 min after placement of a loose tourniquet.	Adults with knee osteoarthritis and an American Society of Anesthesiologists (ASA) score 3 or under who are scheduled for unilateral primary TKA	• Adverse events: DVT • Blood loss via haemoglobin level after surgery • Postoperative bleeding • Surgical bleeding	
Xie 2016[276]	3g in 150ml saline was utilised. Gauze with 50ml used to soak the acetabulum for 3 minutes and gauze with 50ml used to soak the femoral canal for 3 minutes. Remaining 50ml injected into joint space through the drainage tube after fascia closure. versus 1.5g 15 minutes before skin incision.	People undergoing hip replacement surgery	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Length of stay	
Yuan 2017[285]	3g total 60 mL solution administered after the subcutaneous tissue was sutured. Oral and IV placebo used. 20 mg/kg 30 minutes before incising the skin, and the same dose 12 hours after surgery. IA and oral placebo used.	People with osteoarthritis or rheumatoid arthritis who were scheduled for primary unilateral TKA at were enrolled.	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery	
Zekcer 2016[289]	1.5g in 50 ml of saline which was sprayed over the operated	People scheduled for unilateral TKA due to	• Mortality • Transfusion	

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Study	Intervention and comparison	Population	Outcomes	Comments
	area for 5 minutes, before the tourniquet was released. versus 20mg/kg, diluted in 100 ml of saline, infused over a 10-minute period at the same time as anaesthesia was administered.	arthrosis (Albach grades III and IV)	• Adverse events: DVT	
Zhang 2016[302]	After skin sutures closed, the IA group were injected with 1g in 100ml saline via the drainage tubes. versus 1g diluted in 250ml saline and administered via IV infusion 10 minutes before the surgery.	People scheduled for unilateral primary total hip replacement for osteonecrosis of the femoral head and a BMI between 18.5 and 30.	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery	
Zhang 2019[303]	Articular injection of 3.0g after it was sutured versus IV injection of 20mg/kg TXA before the incision	People 40 to 80 years old scheduled for TKA	• Quality of life • Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss	
Zhou 2018[307]	3g in 60ml saline soaking the hip cavity before the end of surgery. versus 10mg/kg in 100 ml saline by intravenous infusion approximately 15 min before skin incision, and a second identical dose administered 3 hours later.	Adults scheduled to undergo primary unilateral THA	• Transfusion • Adverse events: DVT • Total blood loss • Surgical bleeding • Postoperative bleeding	
Oral versus IV				

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Study	Intervention and comparison	Population	Outcomes	Comments
Cao 2018[30]	20mg/kg IV administered 5-10 minutes before first incision. 2g given orally in 4 tablets at 4 hours, 10 hours and 16 hours after surgery. IV saline given at the same time points as the higher IV dose group. versus 20mg/kg IV administered 5-10 minutes before fist incision. 1g given IV in saline 6 hours, 12 hours and 18 hours after surgery. Oral placebo taken at the corresponding time points.	People undergoing primary unilateral total hip arthroplasty for osteoarthritis, osteonecrosis of the femoral head and developmental dysplasia of the hip.	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss	Oral group received small IV dose and the study was considered indirect evidence.
Fillingham 2016[64]	1950 mg (3 tablets of 650 mg) approximately 2 hours before incision and given an IV placebo of 10-mL normal saline immediately before wound closure. versus 1g in 10 mL saline immediately before wound closure and received 750 mg of placebo (ascorbic acid in 3 tablets of 250 mg) approximately 2 hours before incision	People scheduled to undergo unilateral primary TKA	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Length of stay	
Jaszczyk 2015[118]	1950mg in 3 tablets 2 hours before incision and an IV placebo dose of saline immediately before incision. versus 1g in 10mL saline as bolus immediately before incision. Placebo tablets 2 hours before	People undergoing primary total hip arthroplasty.	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Length of stay	

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Study	Intervention and comparison	Population	Outcomes	Comments
	incision.			
Kayupov 2017[126]	1960mg given in 3 tablets 2 hours before incision. IV saline given immediately prior to incision versus 1g in saline given immediately prior to incision, placebo for oral group in ascorbic acid given 2 hours before incision.	People having cementless primary hip arthroplasty	• Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Length of stay	
Luo 2018[162]	2g approximately 2 hours before the incision. 100mL saline IV placebo infusion administered 5 minutes before the skin incision. versus 20 mg/kg diluted in 100ml normal saline given as an IV bolus 5 minutes before the skin incision.4 placebo tablets, identical in appearance with no active ingredient, were administered	People with osteoarthritis or osteonecrosis of the femoral head and scheduled to undergo cementless primary unilateral THA	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Length of stay	
Wang 2018b[254]	2g in 500mg tablets taken approximately 2 hours before incision. IA and IV placebos used. versus 20mg/kg dose in 100 mL of normal saline solution administered 5 minutes prior to incision. Oral and IA placebos used.	Adults with primary knee osteoarthritis who were scheduled for elective primary unilateral total knee replacement	• Mortality • Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss	
Yuan 2017[285]	20mg/kg orally 2 hours before the operation and the same	People with osteoarthritis or rheumatoid arthritis who	• Transfusion	

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Study	Intervention and comparison	Population	Outcomes	Comments
	dose 12 hours after surgery. IV and IA placebo used. versus 20 mg/kg intravenously 30 minutes before incising the skin, and the same dose 12 hours after surgery. Oral and IA placebo used.	were scheduled for primary unilateral TKA were enrolled.	• Adverse events: DVT • Blood loss via haemoglobin level after surgery	
Zhao 2018[305]	20mg/kg 2 hours before surgery and 3 hours after surgery. IV saline placebo used. versus 15mg/kg 10 minutes before incision. 4 ascorbic acid tablets used for placebo.	People having elective primary unilateral total hip arthroplasty for osteoarthritis of femoral head necrosis	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Surgical bleeding • Length of stay	
IA/topical versus oral				
Luo 2018a[161]	3g diluted in 150ml saline utilised. 50ml to soak the acetabulum for 3 minutes. After the femoral canal broach preparation, 50ml injected into the femoral canal and removed 3 minutes later. After reduction of femoral components, 50ml was soaked and removed 3 minutes later. Placebo tablets used to keep blinding. versus 2g administered 2 hours before surgery. 2 1g doses were administered postoperatively with a 6 hour interval. Saline IA wash was used to keep	People undergoing hip replacement surgery	• Mortality • Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Surgical bleeding • Length of stay	

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Study	Intervention and comparison	Population	Outcomes	Comments
	blinding.			
Luo 2018b[162]	2g diluted in 150mL of normal saline. Following the acetabular preparation, the acetabulum was soaked with 50mL of solution for 3 minutes. After the femoral canal broach preparation, 50mL solution was injected into the femoral canal and removed by suction 3 minutes later. After reduction of the final hip components, 50mL solution was applied to the wound and allowed to remain undisturbed for 3 minutes, after which it was removed by suction. 100mL saline IV placebo used. 4 placebo tablets, identical in appearance with no active ingredient, were administered versus 2g approximately 2 hours before the incision.. IA saline placebo used.	People with osteoarthritis or osteonecrosis of the femoral head and scheduled to undergo cementless primary unilateral THA	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Length of stay	
Wang 2018a[255]	2g 2 hours before incision. A postoperative dose of 1g was repeated 6 and 12 hours after surgery. Saline IA placebo. versus 3g in 100 mL of saline solution administered is 2 doses. After all components have been cemented and the joint was thoroughly irrigated, the first half is applied to soak the open	People scheduled for primary unilateral total knee arthroplasty	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Surgical bleeding • Mortality	

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Study	Intervention and comparison	Population	Outcomes	Comments
	joint surface and tissue for 5 min and the second half administered using a needle to achieve tissue impregnation. Placebo pills identical to oral TXA in appearance were given 2 hours before incision.			
Yuan 2017[285]	3g total 60mL solution administered after the subcutaneous tissue was sutured. Oral and IV placebo utilised. versus 20mg/kg orally 2 hours before the operation and the same dose 12 hours after surgery. IV placebo joint injection of saline. IA placebo of saline	People with osteoarthritis or rheumatoid arthritis who were scheduled for primary unilateral TKA were enrolled.	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery	
Wang 2018b[254]	2g in 500mg tablets taken approximately 2 hours before incision. IA and IV placebos used. versus 2g in 100 mL of saline solution, administered intra-articularly at two time points. Oral and IV placebos used.	Adults with primary knee osteoarthritis who were scheduled for elective primary unilateral total knee replacement	• Mortality • Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss	
IV plus IA/topical versus IV				
Adravanti 2018[5]	1g IV 30 minutes before induction of anaesthesia, then at 3 and 9 hours after surgery. 3g topical injected into the joint after closure of the capsule. versus 1g IV 30 minutes before	Adults 18 to 95 years old undergoing primary TKA.	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Postoperative bleeding	

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Study	Intervention and comparison	Population	Outcomes	Comments
	induction of anaesthesia and then at 3 and 9 hours after surgery			
Gulabi 2019[92]	1g in saline given as a slow IV injection 30 minutes before incision. Dose repeated 3 hours later. 3g diluted in isotonic saline and applied intra-articularly. versus 1g in saline given as a slow IV injection 30 minutes before incision. Dose repeated 3 hours later.	Adults scheduled for elective primary unilateral THA.	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Length of stay	
Huang 2014[107]	1.5g dissolved in 50 mL saline was irrigated in the wound after implantation of the components and 1.5g IV was administered before inflation of the tourniquet versus 3g administered before inflation of the tourniquet.	Adults scheduled for a primary TKA for end-stage osteoarthritis	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Length of stay	
Jain 2016[116]	3 IV doses: 15 mg/kg 30 minutes before skin incision. 10mg/kg repeated 3 and 6 hours after surgery. 2g diluted in 30 mL saline applied IA for about 5minutes before closure of arthrotomy. versus 3 doses: 15 mg/kg 30 minutes before skin incision. 10mg/kg repeated 3 and 6 hours after surgery. Saline IA placebo.	People with primary osteoarthritis undergoing elective unilateral primary TKAs	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss	
Song 2017[227]	10mg/kg 20 minutes before	People with primary	• Transfusion	

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Study	Intervention and comparison	Population	Outcomes	Comments
	tourniquet application as a preoperative dose and 10 mg/kg as a postoperative dose. 1.5g in 50mL of saline retrograde through the drain after wound closure. As placebo, these patients received 5mL of normal saline at the time of intraoperative dose. versus 10mg/kg 20 minutes before tourniquet application as a preoperative dose, 10 mg/kg 15 minutes before deflation of the tourniquet as an intraoperative dose, and 10 mg/kg 3 hours after the second dose as a postoperative dose. As placebo, the group received 50 mL of saline retrograde through drain after surgery.	osteoarthritis of knee awaiting navigation assisted TKA	• Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss	
Xie 2016[276]	1g IV dose 15 minutes before skin incision. 2g in 150ml physiological saline was utilised. Gauze with 50ml used to soak the acetabulum for 3 minutes and gauze with 50ml used to soak the femoral canal for 3 minutes. Remaining 50ml injected into joint space through the drainage tube after fascia closure. versus 1.5g IV dose 15 minutes before skin incision.	People undergoing hip replacement	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Length of stay	

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Study	Intervention and comparison	Population	Outcomes	Comments
Yi 2016[282]	15mg/kg IV 5 minutes before incision. 200mg in 20ml solution used to topically on acetabulum and placed within femoral canal. 600mg in 60ml injected into hip joint. versus 15mg/kg IV 5 minutes before incision. Saline IA placebo used.	People undergoing hip replacement	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Postoperative bleeding • Length of stay	
Zhang 2019[303]	IV injection of 20mg/kg before the incision and articular injection of 3g TXA after it was sutured. versus IV injection of 20mg/kg TXA before the incision	People 40 to 80 years old scheduled for TKA	• Quality of life • Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss	
IA/topical plus oral versus IA/topical				
Cankaya 2017[29]	Oral 25mg/kg (maximum 2g) given 2 hours before surgery. 1.5g in saline administered to the joint cavity during surgery. versus 1.5g in saline administered to the joint cavity during surgery.	People 55 to 85 years old with knee osteoarthrosis, undergoing primary total knee arthroplasty	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Postoperative bleeding	
IV plus IA/topical versus IA/topical				
Lin 2015[155]	1g IV injection 15 minutes before skin incision and 1g IA application intraoperatively after joint capsule closure. versus 1g in 20 mL normal saline using IA application	People scheduled for unilateral TKA	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss	

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Study	Intervention and comparison	Population	Outcomes	Comments
	intraoperatively after joint capsule closure			
Song 2017[227]	10mg/kg 20 minutes before tourniquet application as a preoperative dose and 10 mg/kg as a postoperative dose. 1.5g in 50mL of saline retrograde through the drain after wound closure. versus 1.5g in 50 mL of saline retrograde through the drain after wound closure, and as placebo, saline utilised at the same points as the IV treatment.	People with primary osteoarthritis of knee awaiting navigation assisted TKA	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss	
Xie 2016[276]	1g IV dose 15 minutes before skin incision. 2g in 150ml physiological saline was utilised. Gauze with 50ml used to soak the acetabulum for 3 minutes and gauze with 50ml used to soak the femoral canal for 3 minutes. Remaining 50ml injected into joint space through the drainage tube after fascia closure. versus 3g in 150ml physiological saline was utilised. Gauze with 50ml used to soak the acetabulum for 3 minutes and gauze with 50ml used to soak the femoral canal for 3 minutes. Remaining 50ml injected into joint space through the drainage tube after	People undergoing hip replacement surgery	• Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss • Length of stay	

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Study	Intervention and comparison	Population	Outcomes	Comments
	fascia closure.			
Zhang 2019[303]	IV injection of 20mg/kg before the incision and articular injection of 3g TXA after it was sutured. versus Articular injection of 3.0g after it was sutured	People 40 to 80 years old scheduled for TKA	• Quality of life • Transfusion • Adverse events: DVT • Blood loss via haemoglobin level after surgery • Total blood loss	

1 See appendix D for full evidence tables.

1.4.4 2 Quality assessment of clinical studies included in the evidence review

3 **Table 3: Clinical evidence summary: IA/topical versus no treatment**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No treatment	Risk difference with IA/topical tranexamic acid (95% CI)
Mortality	Not reported				
Transfusion	1078 (10 studies) ranged from while admitted in hospital to 2 months after surgery	MODERATE[1] due to risk of bias	RR 0.46 (0.37 to 0.56)	362 per 1000	195 fewer per 1000 (from 159 fewer to 228 fewer)
Acute myocardial infarction	Not reported				
DVT	850 (9 studies) ranged from in hospital period to 1 year after surgery	MODERATE[1] due to risk of bias	RD -0.00 (-0.02 to 0.01)[3]	7 per 1000	0 fewer per 1000 (from 20 fewer to 10 more)[2]
Quality of life	Not reported				

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No treatment	Risk difference with IA/topical tranexamic acid (95% CI)
Blood loss via haemoglobin level after surgery	906 (9 studies) ranges from 12 hours to 5 days after surgery	VERY LOW[1,4,5] due to risk of bias, inconsistency, imprecision		The mean blood loss via haemoglobin level after surgery in the control groups was 9	The mean blood loss via haemoglobin level after surgery in the intervention groups was 0.43 higher (0.11 lower to 0.97 higher)
Total blood loss	709 (6 studies) ranges from 1 to 5 days after surgery	VERY LOW[1,4,5] due to risk of bias, inconsistency, imprecision		The mean total blood loss in the control groups was 1200 mL	The mean total blood loss in the intervention groups was 1.5 standard deviations lower (2.3 to 0.71 lower)
Surgical bleeding	355 (3 studies)	VERY LOW[1,4,5] due to risk of bias, inconsistency, imprecision		The mean surgical bleeding in the control groups was 500 mL	The mean surgical bleeding in the intervention groups was 0.65 standard deviations lower (1.51 lower to 0.2 higher)
Postoperative bleeding	95 (1 study) 24 hours after surgery	HIGH		The mean postoperative bleeding in the control groups was 538.06 mL	The mean postoperative bleeding in the intervention groups was 337.96 lower (435.16 to 240.76 lower)
Length of stay	312 (3 studies)	LOW[1] due to risk of bias		The mean length of stay in the control groups was 5 days	The mean length of stay in the intervention groups was 0.06 lower (0.28 lower to 0.17 higher)

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Risk difference utilised to calculate absolute effect
[3] Risk difference used to analyse data due to very low event rates
[4] Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects (DerSimonian and Laird) model was employed.
[5] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

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1 **Table 4: Clinical evidence summary: Oral versus no treatment**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No treatment	Risk difference with Oral tranexamic acid (95% CI)
Mortality at 30 days	189 (1 study) 30 days after surgery	LOW[3,4] due to risk of bias, imprecision	RD 0 (-0.02 to 0.02)[2]	0 per 1000	0 fewer per 1000 (from 20 fewer to 20 more)[1]
Transfusion	189 (1 study) unclear	VERY LOW[3,4] due to risk of bias, imprecision	RR 0.34 (0.04 to 3.18)	32 per 1000	21 fewer per 1000 (from 30 fewer to 69 more)
Acute myocardial infarction	Not reported				
DVT	189 (1 study) within 7 days of surgery	VERY LOW[3,4] due to risk of bias, imprecision	Peto OR 7.47 (0.15 to 376.39)	0 per 1000	10 more per 1000 (from 20 fewer to 40 more)[1]
Quality of life	Not reported				
Blood loss via haemoglobin level after surgery	189 (1 study) unclear	MODERATE[3] due to risk of bias		The mean blood loss via haemoglobin level after surgery in the control groups was -2.5 g/dL	The mean blood loss via haemoglobin level after surgery in the intervention groups was 0.8 higher (0.56 to 1.04 higher)
Total blood loss	189 (1 study) unclear	MODERATE[3] due to risk of bias		The mean total blood loss in the control groups was 626 mL	The mean total blood loss in the intervention groups was 228 lower (293.22 to 162.78 lower)
Length of stay	189 (1 study)	MODERATE[3] due to risk of bias		The mean length of stay in the control groups was 5.8 days	The mean length of stay in the intervention groups was 0.1 higher (0.46 lower to 0.66 higher)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No treatment	Risk difference with Oral tranexamic acid (95% CI)

[1] Absolute effect calculated using risk difference
[2] Analysis via risk difference due to low event rate
[3] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[4] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 5: Clinical evidence summary: IV versus no treatment

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No treatment	Risk difference with IV tranexamic acid (95% CI)
Mortality at 30 days	100 (1 study) within 90 days of surgery	VERY LOW[3,5,6] due to risk of bias, indirectness, imprecision	RD 0 (-0.04 to 0.04)[2]	0 per 1000	0 fewer per 1000 (from 40 fewer to 40 more)[1]
Transfusion	1324 (15 studies) ranged from in-hospital period to 90 days after surgery	VERY LOW[3,4] due to risk of bias, inconsistency	RD -0.14 (-0.21 to -0.08)[2]	307 per 1000	140 fewer per 1000 (from 210 fewer to 80 fewer)[1]
Acute myocardial infarction	Not reported				
DVT	1135 (15 studies) ranged from 2 days to 1 year after surgery	MODERATE[3] due to risk of bias	RD 0 (-0.02 to 0.01)[2]	13 per 1000	0 fewer per 1000 (from 20 fewer to 10 more)[1]
Quality of life	Not reported				
Blood loss via haemoglobin level after	1038 (11 studies)[7]	LOW[3,5] due to risk of bias,		The mean blood loss via haemoglobin level after surgery	The mean blood loss via haemoglobin level after surgery

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No treatment	Risk difference with IV tranexamic acid (95% CI)
surgery	ranges from 1 to 5 days after surgery	imprecision		in the control groups was 9.5	in the intervention groups was 0.53 higher (0.38 to 0.67 higher)
Total blood loss	873 (8 studies) either unclear or 3 days after surgery	VERY LOW[3,4] due to risk of bias, inconsistency		The mean total blood loss in the control groups was 1250 mL	The mean total blood loss in the intervention groups was 1.33 standard deviations lower (2.1 to 0.56 lower)
Surgical bleeding	356 (3 studies)	VERY LOW[3,4,5] due to risk of bias, inconsistency, imprecision		The mean surgical bleeding in the control groups was 500 mL	The mean surgical bleeding in the intervention groups was 0.88 standard deviations lower (2.62 lower to 0.86 higher)
Postoperative bleeding	96 (1 study) 24 hours after surgery	HIGH		The mean postoperative bleeding in the control groups was 538.06	The mean postoperative bleeding in the intervention groups was 393.16 lower (483.74 to 302.58 lower)
Length of stay	312 (3 studies)	LOW[3] due to risk of bias		The mean length of stay in the control groups was 5 days	The mean length of stay in the intervention groups was 0.03 lower (0.24 lower to 0.19 higher)

1 Risk difference utilised to calculate absolute effect
2 Results analysed using risk difference due to low event rates
3 Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
4 Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects (DerSimonian and Laird) model was employed.
5 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
6 Considered indirect due to the study follow-up period extending beyond 30 days
7 Two intervention groups reported in Melo 2017. The numbers of people in the control groups have been halved to prevent double counting.

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1 **Table 6: Clinical evidence summary: IA/topical versus placebo**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with IA/topical tranexamic acid (95% CI)
Mortality at 30 days	60 (1 study) 15 days after surgery	VERY LOW[3,4] due to risk of bias, imprecision	RD 0 (-0.06 to 0.06)[2]	0 per 1000	0 fewer per 1000 (from 60 fewer to 60 more)[1]
Transfusion	2589 (24 studies) ranged from 3 days to 3 months of surgery	HIGH	RR 0.36 (0.29 to 0.45)	197 per 1000	126 fewer per 1000 (from 108 fewer to 140 fewer)
Acute myocardial infarction	Not reported				
DVT	2428 (23 studies) ranged from 5 days to 3 months after surgery	VERY LOW[3,6] due to risk of bias, imprecision	RD 0 (-0.01 to 0.01)[2]	19 per 1000	0 fewer per 1000 (from 10 fewer to 10 more)[1]
Quality of life within 6 weeks EuroQol Index (EQ-5D)	190 (2 studies) 3 months after surgery	VERY LOW[3,5] due to risk of bias, indirectness		The mean quality of life within 6 weeks in the control groups was 0.75	The mean quality of life within 6 weeks in the intervention groups was 0.06 lower (0.14 lower to 0.03 higher)
Blood loss via haemoglobin level after surgery	1853 (18 studies) ranges from 24 hours to 5 days after surgery	VERY LOW[3,7] due to risk of bias, inconsistency		The mean blood loss via haemoglobin level after surgery in the control groups was 9 g/dL	The mean blood loss via haemoglobin level after surgery in the intervention groups was 1.04 higher (0.8 to 1.29 higher)
Total blood loss	1617 (17 studies) ranges from 1 to 5 days after surgery or until hospital discharge	LOW[3,7] due to risk of bias, inconsistency		The mean total blood loss in the control groups was 1100 mL	The mean total blood loss in the intervention groups was 0.94 standard deviations lower (1.16 to 0.72 lower)
Surgical bleeding	243	VERY LOW[6,7]		The mean surgical bleeding in	The mean surgical bleeding in

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with IA/topical tranexamic acid (95% CI)
	(3 studies)	due to inconsistency, imprecision		the control groups was 200 mL	the intervention groups was 0.25 standard deviations lower (0.93 lower to 0.44 higher)
Postoperative bleeding	394 (5 studies) ranges from 36 hours to 4 days after surgery	MODERATE[7] due to inconsistency		The mean postoperative bleeding ranged across control groups from 55 to 400	The mean postoperative bleeding in the intervention groups was 0.94 standard deviations lower (1.35 to 0.53 lower)
Length of stay	1108 (10 studies)	LOW[3,7] due to risk of bias, inconsistency		The mean length of stay in the control groups was 5 days	The mean length of stay in the intervention groups was 0.01 lower (0.2 lower to 0.18 higher)

[1] Risk difference used to calculate absolute effect
[2] Results analysed using risk difference due to low event rates
[3] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[4] Study considered imprecise because it is small and there were no events in either treatment group
[5] Considered indirect evidence as the outcome was outside of the specified time point
[6] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[7] Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects (DerSimonian and Laird) model was employed.

Table 7: Clinical evidence summary: IV versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with IV tranexamic acid (95% CI)
Mortality at 30 days	290 (3 studies) either during hospital stay or within 15 days of	MODERATE[5] due to imprecision	RD 0 (-0.03 to 0.03)[2]	See comment	0 fewer per 1000 (from 30 fewer to 30 more)[1]

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with IV tranexamic acid (95% CI)
	surgery				
Transfusion	3383 (44 studies) ranged from 24 hours to 6 months after surgery	LOW[3,4] due to risk of bias, inconsistency	RR 0.39 (0.32 to 0.49)	343 per 1000	209 fewer per 1000 (from 175 fewer to 233 fewer)
Acute coronary syndrome	230 (2 studies) during hospital stay	MODERATE[5] due to imprecision	RD 0 (-0.02 to 0.04)[2]		10 more per 1000 (from 20 fewer to 40 more)[1]
DVT	3356 (45 studies) ranged from in hospital period to 6 months after surgery	MODERATE[3] due to risk of bias	RD 0 (-0.01 to 0.01)[2]	16 per 1000	0 fewer per 1000 (from 10 fewer to 10 more)[1]
Quality of life	Not reported				
Blood loss via haemoglobin level after surgery	2489 (32 studies) ranges from 1 day after surgery to discharge from hospital	VERY LOW[3,4,6] due to risk of bias, inconsistency, imprecision		The mean blood loss via haemoglobin level after surgery in the control groups was 9.5 g/dL	The mean blood loss via haemoglobin level after surgery in the intervention groups was 0.64 higher (0.49 to 0.78 higher)
Total blood loss	2624 (33 studies) ranges from 1 to 6 days after surgery or until hospital discharge	LOW[3,4] due to risk of bias, inconsistency		The mean total blood loss ranged across control groups from 590 to 2393 mL	The mean total blood loss in the intervention groups was 0.84 standard deviations lower (1 to 0.68 lower)
Surgical bleeding	744 (13 studies)	VERY LOW[3,4,6] due to risk of bias, inconsistency, imprecision		The mean surgical bleeding ranged across control groups from 140 to 790	The mean surgical bleeding in the intervention groups was 0.61 standard deviations lower (0.97 to 0.25 lower)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with IV tranexamic acid (95% CI)
Postoperative bleeding	762 (13 studies) ranges from 48 hours of surgery to in-hospital period	VERY LOW[3,4] due to risk of bias, inconsistency		The mean postoperative bleeding ranged across control groups from 244 to 1074 mL	The mean postoperative bleeding in the intervention groups was 1.38 standard deviations lower (1.87 to 0.89 lower)
Length of stay	1272 (14 studies)	HIGH		The mean length of stay in the control groups was 7 days	The mean length of stay in the intervention groups was 0.09 lower (0.18 to 0.01 lower)

[1] Absolute effect calculated using risk difference
[2] Analysis by risk difference due to low events rate
[3] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[4] Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects (DerSimonian and Laird) model was employed.
[5] No explanation was provided
[6] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 8: Clinical evidence summary: Oral versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Oral tranexamic acid (95% CI)
Mortality	Not reported				
Transfusion	406 (3 studies)	MODERATE[1] due to risk of	RR 0.38	225 per 1000	139 fewer per 1000 (from 81 fewer to 173 fewer)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Oral tranexamic acid (95% CI)
	ranged from in hospital period to 3 months after surgery	bias	(0.23 to 0.64)		
Acute myocardial infarction	Not reported				
DVT	406 (3 studies) ranged from 2 weeks to 3 months after surgery	MODERATE[1] due to risk of bias	RD 0 (-0.03 to 0.02)[3]	10 per 1000	10 fewer per 1000 (from 30 fewer to 20 more)[2]
Quality of life	Not reported				
Blood loss via haemoglobin level after surgery	406 (3 studies) ranges from 1 to 3 days after surgery	LOW[1,4] due to risk of bias, imprecision		The mean blood loss via haemoglobin level after surgery in the control groups was -3	The mean blood loss via haemoglobin level after surgery in the intervention groups was 0.47 higher (0.37 to 0.57 higher)
Total blood loss	126 (2 studies) 3 days after surgery	MODERATE[1] due to risk of bias		The mean total blood loss in the control groups was 948.5 mL	The mean total blood loss in the intervention groups was 1.13 standard deviations lower (1.51 to 0.75 lower)
Surgical bleeding	80 (1 study)	LOW[1,4] due to risk of bias, imprecision		The mean surgical bleeding in the control groups was 156.3 mL	The mean surgical bleeding in the intervention groups was 21.5 lower (34.91 to 8.09 lower)
Length of stay	80 (1 study)	MODERATE[1] due to risk of bias		The mean length of stay in the control groups was 1.9 days	The mean length of stay in the intervention groups was 0.1 lower (0.69 to 0.49 lower)

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Absolute effect calculated using risk difference

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Oral tranexamic acid (95% CI)

[3] Analysed using risk difference due to low events rates
[4] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

1

2 **Table 9: Clinical evidence summary: IV plus IA/topical versus placebo**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with IV+IA/topical tranexamic acid (95% CI)
Mortality	Not reported				
Transfusion	380 (4 studies) while admitted in hospital	MODERATE[1] due to risk of bias	RR 0.08 (0.03 to 0.22)	258 per 1000	237 fewer per 1000 (from 201 fewer to 250 fewer)
Acute myocardial infarction	Not reported				
DVT	380 (4 studies) ranged from 2 weeks to 6 months after surgery	MODERATE[1] due to risk of bias	RD 0.01 (-0.02 to 0.04)[3]	5 per 1000	10 more per 1000 (from 20 fewer to 40 more)[2]
Quality of life	Not reported				
Blood loss via haemoglobin level after surgery	380 (4 studies) 3 days after surgery	MODERATE[1] due to risk of bias		The mean blood loss via haemoglobin level after surgery in the control groups was -4 g/dL	The mean blood loss via haemoglobin level after surgery in the intervention groups was 1.45 higher (1.19 to 1.7 higher)
Total blood loss	380 (4 studies) 3 days after surgery	LOW[1,4] due to risk of bias,		The mean total blood loss in the control groups was 1100 ml	The mean total blood loss in the intervention groups was 294.44 lower

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with IV+IA/topical tranexamic acid (95% CI)
	or in-hospital period	inconsistency			(405.92 to 182.97 lower)
Surgical bleeding	100 (1 study)	MODERATE[1] due to risk of bias		The mean surgical bleeding in the control groups was 288.2 mL	The mean surgical bleeding in the intervention groups was 94.4 lower (132.77 to 56.03 lower)
Postoperative bleeding	200 (2 studies) 3 days after surgery	MODERATE[1] due to risk of bias		The mean postoperative bleeding in the control groups was 243 mL	The mean postoperative bleeding in the intervention groups was 0.92 standard deviations lower (1.21 to 0.63 lower)
Length of stay	200 (2 studies)	MODERATE[1] due to risk of bias		The mean length of stay in the control groups was 6.6 days	The mean length of stay in the intervention groups was 0.33 lower (0.76 lower to 0.1 higher)

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Absolute effect calculated using risk difference
[3] Analysed via risk difference due to low event rates
[4] Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects (DerSimonian and Laird) model was employed.

Table 10: Clinical evidence summary: IA/topical versus IV

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with IV tranexamic acid	Risk difference with IA/topical tranexamic acid (95% CI)
Mortality at 30 days	269 (3 studies) ranged from 15 to 30 days after surgery	VERY LOW[3,4] due to risk of bias, imprecision	RD 0.01 (-0.02 to	0 per 1000	10 more per 1000 (from 20 fewer to 40 more)[1]

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with IV tranexamic acid	Risk difference with IA/topical tranexamic acid (95% CI)
			0.04)[2]		
Transfusion	3978 (32 studies) ranged from in hospital period to 3 months after surgery	HIGH	RD 0.01 (-0.01 to 0.02)[2]	64 per 1000	10 more per 1000 (from 10 fewer to 20 more)[1]
Acute myocardial infarction	89 (1 study) unclear	VERY LOW[3,5] due to risk of bias, imprecision	Peto OR 6.64 (0.13 to 336.89)	0 per 1000	20 more per 1000 (from 40 fewer to 80 more)[1]
DVT	3833 (30 studies) ranged from within 96 hours of surgery to 1 year after surgery	HIGH	RD 0 (-0.01 to 0)[2]	14 per 1000	0 fewer per 1000 (from 10 fewer to 0 more)[1]
Quality of life (mental component score) within 6 weeks SF-36 . Scale from: 0 to 100.	100 (1 study) unclear	LOW[3,5] due to risk of bias, imprecision		The mean quality of life (mental component score) within 6 weeks in the control groups was 63	The mean quality of life (mental component score) within 6 weeks in the intervention groups was 2.5 lower (6.87 lower to 1.87 higher)
Quality of life (physical component score) within 6 weeks SF-36 . Scale from: 0 to 100.	100 (1 study) unclear	LOW[3,5] due to risk of bias, imprecision		The mean quality of life (physical component score) within 6 weeks in the control groups was 57	The mean quality of life (physical component score) within 6 weeks in the intervention groups was 2.26 lower (6.18 lower to 1.66 higher)
Blood loss via haemoglobin	2558	LOW[3,6]		The mean blood loss via	The mean blood loss via

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with IV tranexamic acid	Risk difference with IA/topical tranexamic acid (95% CI)
level after surgery	(19 studies) ranges from 12 hours to 5 days after surgery	due to risk of bias, inconsistency		haemoglobin level after surgery in the control groups was 10 g/dL	haemoglobin level after surgery in the intervention groups was 0.03 higher (0.09 lower to 0.14 higher)
Total blood loss	2806 (26 studies) ranges from 1 to 5 days after surgery	LOW[3,6] due to risk of bias, inconsistency		The mean total blood loss ranged across control groups from 456 to 1626	The mean total blood loss in the intervention groups was 0.12 standard deviations lower (0.27 lower to 0.04 higher)
Surgical bleeding	1172 (6 studies)	VERY LOW[3,5,6] due to risk of bias, inconsistency, imprecision		The mean surgical bleeding ranged across control groups from 123 to 685 mL	The mean surgical bleeding in the intervention groups was 0.1 standard deviations higher (0.73 lower to 0.92 higher)
Postoperative bleeding	272 (3 studies) ranges from 24 to 96 hours after surgery	LOW[5,6] due to inconsistency, imprecision		The mean postoperative bleeding in the control groups was 135 mL	The mean postoperative bleeding in the intervention groups was 0.09 standard deviations higher (0.33 lower to 0.5 higher)
Length of stay	1312 (11 studies)	HIGH		The mean length of stay in the control groups was 4.5 days	The mean length of stay in the intervention groups was 0.04 higher (0.05 lower to 0.12 higher)

[1] Absolute effect calculated using risk difference
[2] Results analysed using risk difference due to low event rates
[3] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[4] Outcome considered imprecise because of the small number of participants and a single event
[5] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[6] Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects (DerSimonian and Laird) model was employed.

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1 **Table 11: Clinical evidence summary: Oral versus IV**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with IV tranexamic acid	Risk difference with Oral tranexamic acid (95% CI)
Mortality at 30 days	120 (1 study) 30 days after surgery	MODERATE[3] due to imprecision	RD 0 (-0.03 to 0.03)[2]	0 per 1000	0 fewer per 1000 (from 30 fewer to 30 more)[1]
Transfusion	862 (7 studies) ranged from in hospital period to 1 month after surgery	VERY LOW[4,5] due to risk of bias, imprecision	RR 0.94 (0.56 to 1.56)	65 per 1000	4 fewer per 1000 (from 28 fewer to 36 more)
Acute myocardial infarction	Not reported				
DVT	945 (7 studies) ranged from 30 days to 3 months after surgery	MODERATE[4] due to risk of bias	RD -0.01 (-0.02 to 0.01)[2]	10 per 1000	10 fewer per 1000 (from 20 fewer to 10 more)[1]
Quality of life	Not reported				
Blood loss via haemoglobin level after surgery	945 (8 studies) ranges from 1 day after surgery to hospital discharge	MODERATE[4] due to risk of bias		The mean blood loss via haemoglobin level after surgery in the control groups was -3.2 g/dL	The mean blood loss via haemoglobin level after surgery in the intervention groups was 0.01 higher (0.07 lower to 0.09 higher)
Total blood loss	665 (7 studies) ranges from 1 to 3 days after surgery or until hospital discharge	MODERATE[4] due to risk of bias		The mean total blood loss ranged across control groups from 692 to 1301 mL	The mean total blood loss in the intervention groups was 0.0 standard deviations higher (0.16 lower to 0.15 higher)
Surgical bleeding	200 (2 studies)	MODERATE[4] due to risk of bias		The mean surgical bleeding in the control groups was 140 mL	The mean surgical bleeding in the intervention groups was 0.46 higher (6.43 lower to 7.34 higher)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with IV tranexamic acid	Risk difference with Oral tranexamic acid (95% CI)
Length of stay	437 (5 studies)	MODERATE[4] due to risk of bias		The mean length of stay in the control groups was 3 days	The mean length of stay in the intervention groups was 0.02 lower (0.17 lower to 0.12 higher)

[1] Absolute effect calculate through risk difference
[2] Analysis using risk difference due to low event rates
[3] Results considered imprecise due to zero events in both intervention groups
[4] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
5 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 12: Clinical evidence summary: IA/topical versus oral

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Oral tranexamic acid	Risk difference with IA/topical tranexamic acid (95% CI)
Mortality at 30 days	384 (3 studies) 30 days after surgery	MODERATE[4] due to imprecision	RD 0 (-0.02 to 0.02)[2]	0 per 1000	0 fewer per 1000 (from 20 fewer to 20 more)[1]
Transfusion	787 (5 studies) ranged from in hospital period to 2 weeks after surgery	VERY LOW[3,4] due to risk of bias, imprecision	RR 1.28 (0.78 to 2.11)	63 per 1000	18 more per 1000 (from 14 fewer to 70 more)
Acute myocardial infarction	Not reported				
DVT	784 (5 studies) ranged from 2 weeks to 3 months after surgery	LOW[3,5] due to risk of bias, imprecision	RD -0.01 (-0.02 to	5 per 1000	10 fewer per 1000 (from 20 fewer to 10 more)[1]

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Oral tranexamic acid	Risk difference with IA/topical tranexamic acid (95% CI)
			0.01)[2]		
Quality of life	Not reported				
Blood loss via haemoglobin level after surgery	784 (5 studies) ranges from 2 days after surgery until hospital discharge	MODERATE[3] due to risk of bias		The mean blood loss via haemoglobin level after surgery in the control groups was -3 g/dL	The mean blood loss via haemoglobin level after surgery in the intervention groups was 0.04 lower (0.13 lower to 0.05 higher)
Total blood loss	504 (4 studies) ranges from 3 days after surgery or until hospital discharge	MODERATE[3] due to risk of bias		The mean total blood loss in the control groups was 900 mL	The mean total blood loss in the intervention groups was 0.15 standard deviations higher (0.02 lower to 0.33 higher)
Surgical bleeding	384 (3 studies)	HIGH		The mean surgical bleeding in the control groups was 175 mL	The mean surgical bleeding in the intervention groups was 0.06 standard deviations higher (0.15 lower to 0.26 higher)
Length of stay	237 (2 studies)	MODERATE[3] due to risk of bias		The mean length of stay in the control groups was 3.5 days	The mean length of stay in the intervention groups was 0.07 higher (0.16 lower to 0.29 higher)

[1] Absolute effect calculated using risk difference
[2] Analysis via risk difference due to low event rates
[3] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[4] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[5] Outcome considered imprecise because of the small number of participants and two events

1 **Table 13: Clinical evidence summary: IV plus IA/topical versus IV**

Outcomes	No of Participants	Quality of the	Relativ	Anticipated absolute effects

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	(studies) Follow up	evidence (GRADE)	e effect (95% CI)	Risk with IV tranexamic acid	Risk difference with IV+IA/topical tranexamic acid (95% CI)
Mortality	Not reported				
Transfusion	791 (7 studies) ranged from while admitted in hospital to 6 weeks after surgery	MODERATE[1] due to risk of bias	Peto OR 0.32 (0.16 to 0.67)	60 per 1000	41 fewer per 1000 (from 20 fewer to 51 fewer)
Acute myocardial infarction	Not reported				
DVT	891 (8 studies) ranged from in hospital period to 6 months after surgery	MODERATE[1] due to risk of bias	RD 0 (-0.02 to 0.03)[4]	36 per 1000	0 fewer per 1000 (from 20 fewer to 30 more)[3]
Quality of life (mental component score) within 6 weeks SF-36. Scale from: 0 to 100.	100 (1 study) unclear	LOW[1,2] due to risk of bias, imprecision		The mean quality of life (mental component score) within 6 weeks in the control groups was 63.3	The mean quality of life (mental component score) within 6 weeks in the intervention groups was 1.32 lower (5.86 lower to 3.22 higher)
Quality of life (physical component score) within 6 weeks SF-36. Scale from: 0 to 100.	100 (1 study) unclear	LOW[1,2] due to risk of bias, imprecision		The mean quality of life (physical component score) within 6 weeks in the control groups was 57	The mean quality of life (physical component score) within 6 weeks in the intervention groups was 1.22 lower (5.27 lower to 2.83 higher)
Blood loss via haemoglobin level after surgery	891 (8 studies) ranges from 3 to 5 days after surgery	VERY LOW[1,2,5] due to risk of bias, inconsistency, imprecision		The mean blood loss via haemoglobin level after surgery in the control groups was 10	The mean blood loss via haemoglobin level after surgery in the intervention groups was 0.39 lower (0.69 to 0.09 lower)
Total blood loss	691 (6 studies)	VERY LOW[1,2,5] due to risk of		The mean total blood loss in the control groups was	The mean total blood loss in the intervention groups was

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with IV tranexamic acid	Risk difference with IV+IA/topical tranexamic acid (95% CI)
	ranges from 3 to 5 days after surgery	bias, inconsistency, imprecision		850 mL	0.76 standard deviations lower (1.33 to 0.19 lower)
Postoperative bleeding	200 (2 studies) ranges from within 3 days of surgery to during in hospital period	LOW[1,2] due to risk of bias, imprecision		The mean postoperative bleeding in the control groups was 500 mL	The mean postoperative bleeding in the intervention groups was 0.18 standard deviations lower (0.46 lower to 0.1 higher)
Length of stay	472 (4 studies)	MODERATE[1] due to risk of bias		The mean length of stay in the control groups was 6 days	The mean length of stay in the intervention groups was 0.19 lower (0.38 to 0.01 lower)

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[3] Absolute effect calculated using risk difference
[4] Data analysed using risk difference due to low event rates
[5] Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects (DerSimonian and Laird) model was employed.

1 **Table 14: Clinical evidence summary: IA/topical plus oral versus IA/topical**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with IA/topical tranexamic acid	Risk difference with IA/topical+oral tranexamic acid (95% CI)
Mortality	Not reported				
Transfusion	100 (1 study) within 3	VERY LOW[1,2] due to risk of bias,	OR 0.13 (0.01 to	60 per 1000	52 fewer per 1000 (from 59 fewer to 16 more)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with IA/topical tranexamic acid	Risk difference with IA/topical+oral tranexamic acid (95% CI)
	days of surgery	imprecision	1.28)		
Acute myocardial infarction	Not reported				
DVT	100 (1 study) 1 year after surgery	LOW[1,5] due to risk of bias, imprecision	RD 0 (-0.04 to 0.04)[4]	0 per 1000	0 fewer per 1000 (from 40 fewer to 40 more)[3]
Quality of life	Not reported				
Blood loss via haemoglobin level after surgery	100 (1 study) 3 days after surgery	LOW[1,2] due to risk of bias, imprecision		The mean blood loss via haemoglobin level after surgery in the control groups was 9.9 g/dL	The mean blood loss via haemoglobin level after surgery in the intervention groups was 0.9 higher (0.37 to 1.43 higher)
Total blood loss	100 (1 study) 3 days after surgery	LOW[1,2] due to risk of bias, imprecision		The mean total blood loss in the control groups was 731 mL	The mean total blood loss in the intervention groups was 103 lower (169.02 to 36.98 lower)
Postoperative bleeding	100 (1 study) 3 days after surgery	LOW[1,2] due to risk of bias, imprecision		The mean postoperative bleeding in the control groups was 128 mL	The mean postoperative bleeding in the intervention groups was 47 lower (67.16 to 26.84 lower)

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[3] Absolute effect calculated using risk difference
[4] Analysed via risk difference due to low event rate
[5] Outcome considered imprecise because of the small number of participants and zero events

1 **Table 15: Clinical evidence summary: IV plus IA/topical versus IA/topical**

Outcomes	No of Participants	Quality of the	Relativ	Anticipated absolute effects

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	(studies) Follow up	evidence (GRADE)	e effect (95% CI)	Risk with IA/topical tranexamic acid	Risk difference with IV+IA/topical tranexamic acid (95% CI)
Mortality	Not reported				
Transfusion	320 (3 studies) while admitted in hospital or within 5 days of surgery	⊕⊕⊕⊖ MODERATE[1] due to risk of bias	OR 0.13 (0.03 to 0.66)	38 per 1000	32 fewer per 1000 (from 12 fewer to 36 fewer)
Acute myocardial infarction	Not reported				
DVT	420 (4 studies) 3 or 6 months after surgery	⊕⊕⊖⊖ LOW[1,5] due to risk of bias, imprecision	RD 0.02 (-0.02 to 0.06)[4]	38 per 1000	20 more per 1000 (from 20 fewer to 60 more)[3]
Quality of life (mental component score) within 6 weeks SF-36. Scale from: 0 to 100.	100 (1 study) unclear	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision		The mean quality of life (mental component score) within 6 weeks in the control groups was 61	The mean quality of life (mental component score) within 6 weeks in the intervention groups was 1.18 higher (2.84 lower to 5.2 higher)
Quality of life (physical component score) within 6 weeks SF-36. Scale from: 0 to 100.	100 (1 study) unclear	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision		The mean quality of life (physical component score) within 6 weeks in the control groups was 55	The mean quality of life (physical component score) within 6 weeks in the intervention groups was 1.04 higher (2.57 lower to 4.65 higher)
Blood loss via haemoglobin level after surgery	420 (3 studies) ranges from 3 to 5 days after surgery	⊕⊖⊖⊖ VERY LOW[1,2,6] due to risk of bias, inconsistency, imprecision		The mean blood loss via haemoglobin level after surgery in the control groups was -3 g/dL	The mean blood loss via haemoglobin level after surgery in the intervention groups was 0.54 higher (0.21 to 0.87 higher)
Total blood loss	420 (3 studies)	⊕⊖⊖⊖ VERY LOW[1,2,6]		The mean total blood loss in the control groups was	The mean total blood loss in the intervention groups was

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with IA/topical tranexamic acid	Risk difference with IV+IA/topical tranexamic acid (95% CI)
	ranges from 3 to 5 days after surgery or until hospital discharge	due to risk of bias, inconsistency, imprecision		900 mL	0.60 standard deviations lower (0.8 to 0.41 lower)
Length of stay	140 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean length of stay in the control groups was 4 days	The mean length of stay in the intervention groups was 0.15 higher (0.24 lower to 0.54 higher)

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[3] Absolute effect calculated using risk difference
[4] Analysis using risk difference due to low event rate
[5] Outcome considered imprecise due to small number of participants and low event rate
[6] Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects (DerSimonian and Laird) model was employed.

1 See appendix F for full GRADE tables.

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1.5 Economic evidence

1.5.1 Included studies

Three health economic studies were identified with the relevant comparison and have been included in this review. [12,13,50] These are summarised in the health economic evidence profile below (see Table 16,Table 17 and Table 18) and the health economic evidence tables in appendix H.

An original network meta-analysis and cost comparison was conducted for this review and can be found in the TXA Network meta-analysis and cost comparison appendix.

1.5.2 Excluded studies

Two economic studies relating to this review question were identified but were selectively excluded due to the availability of more applicable evidence. [249, 112.] Four economic studies were found but excluded due to very serious limitations.[39,89,173,198]

These are listed in appendix I with reasons for exclusion given.

See also the health economic study selection flow chart in appendix G.

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1.5.3 Summary of studies included in the economic evidence review

Table 16: Health economic evidence profile: Topical (intra-articular) tranexamic acid versus Placebo (knee replacements)

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Alshryda 2013[13] [UK]	Partially applicable[(a)]	Potentially serious limitations[(b)]	A cost utility within-trial analysis (TRANX-K RCT) of tranexamic acid in knee replacements. Analysed patient level outcomes (transfusion, OKS and EQ-5D) and resource use over 3 months. Unit costs applied.	Tranexamic acid saves £333 per person	Tranexamic acid gave 0.0053 less QALYs per person [(c)]	Placebo costs £63,429 per QALY gained compared to tranexamic acid[(d)]	Costs were bootstrapped due to skewness of the cost data. The results showed a similar cost saving of £333 for the use of tranexamic acid.

Abbreviations: OKS: Oxford Knee Score; QALY: quality-adjusted life years; RCT: randomised controlled trial; TRANX-K: Topical (intra-articular) tranexamic acid reduces blood loss and transfusion rates following total knee replacement: a randomized controlled trial
(a) A within trial analysis with cost consequence which included relevant costs and outcomes. EQ-5D recorded but not used as part of the cost effectiveness calculations.
(b) Costs of complications during the trial were not accounted for. Unit costs are not referenced. Outcomes are from a single RCT rather than a systematic review.
(c) Quality of life is reported amongst other outcomes but the difference in baseline values mean inference should be treated with caution
(d) ICER was not reported in the study

Table 17: Health economic evidence profile: Topical (intra-articular) tranexamic acid versus Placebo (hip replacements)

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Alshryda 2013[12] [UK]	Partially applicable[(a)]	Potentially serious limitations[(b)]	A cost utility within-trial analysis (TRANX-H RCT) of tranexamic acid in hip replacements. Analysed patient level outcomes (transfusion, OHS and EQ-5D) and resource use over 3 months. Unit costs applied.	Tranexamic acid saves £305 per person	Tranexamic acid gave 0.027 less QALYs per person [(c)]	Placebo costs £11,509 per QALY gained compared to tranexamic acid[(d)]	Costs were bootstrapped due to skewness of the cost data. The results showed a similar cost saving of £305 for the use of tranexamic acid.

Abbreviations: OHS: Oxford Hip Score; QALY: quality-adjusted life years; RCT: randomised controlled trial; TRANX-H: Topical (intra-articular) tranexamic acid reduces blood loss and transfusion rates following total hip replacement: a randomized controlled trial

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(a) A within trial analysis with cost consequence which included relevant costs and outcomes. EQ-5D recorded but not used as part of the cost effectiveness calculations.
(b) Costs of complications during the trial were not accounted for. Unit costs are not referenced. Outcomes are from a single RCT rather than a systematic review.
(c) Quality of life is reported amongst other outcomes but the difference in baseline values mean inference should be treated with caution.
(d) ICER was not reported in the study

Table 18: Health economic evidence profile: Intravenous tranexamic acid versus No tranexamic acid

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Davies 2018[50] [UK]	Partially applicable [(a)]	Potentially serious limitations[(b)]	Cost comparison of intravenous tranexamic acid versus no tranexamic acid in lower limb joint replacement. The study is a retrospective cohort analysis with multivariate regression.	Tranexamic acid saves £67.89 (min) and £155.90 (max)	N/A	Tranexamic acid is cost saving	Two estimates of cost difference are given to account for the minimum and maximum cost of a bed day. Tranexamic acid was cost saving in both analyses.

Abbreviations: N/A; not applicable
(a) Cost comparison from a UK perspective with a relevant intervention and comparator. No QALYs or health outcomes
(b) Observational data from a single study used, although data is adjusted; no health outcomes or adverse events are factored into cost calculations.

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1.5.3.1 Health economic modelling

The committee agreed that new economic analysis of the different ways to administer TXA was the highest priority for the guideline due to other high economic priorities being downgraded or an inability to model. The cost differences between the methods was not considered to be large, however the clinical review showed a difference in transfusion rates, which can have large cost implications. It was felt that a new cost analysis could reduce the uncertainty around the cost of transfusions and different methods of administration.

1.5.3.1.1 Method

A technical report for this analysis including full details of all methods is available in the TXA Network meta-analysis and cost comparison appendix.

A network meta-analysis (NMA) with cost comparison was undertaken in WinBUGs software to compare the costs of different methods of administering TXA when considering the cost of a transfusion. The population was people indicated for primary elective joint replacement, it was assumed that all of these surgeries have a moderate risk of blood loss (500ml-1000ml), as agreed by the committee. The time horizon was initial inpatient stay.

The comparators selected for the model were:

- Topical (Intra-articular) (IA) TXA, (monotherapy)
- Intra-venous (IV) TXA, (monotherapy)
- Oral TXA, (monotherapy)
- IA and IV TXA, (combination therapy)
- IA and oral TXA, (combination therapy

The outcome selected for the model was:

- Transfusion events

As agreed with the committee, placebo and no treatment were not included as comparators as it is established practice that administration of some form of TXA is clinically and cost-effective in comparison. Following a review of all of the studies included in the clinical review, 36 reported transfusion as an outcome with 2 or more relevant comparators. Four of these studies were 3- arm trials such that there were 44 pairwise comparisons in total. All of the included studies were for a hip or knee replacement population, No relevant studies were found for a shoulder replacement population.

Baseline model

One study was chosen to inform the baseline model[7]. The study was chosen as it was the only European study that was graded as having a low risk of bias. Therefore it was considered best to represent a UK population. As only one study was included in the baseline model there was no need to account for between study heterogeneity and therefore, the fixed effects baseline model was chosen.

Main model

For the main model both a random and fixed effects model was run. No meaningful difference was found in the sum of residual deviances or DIC between the two models. Therefore fixed effect model results were used as this is the simplest model available.

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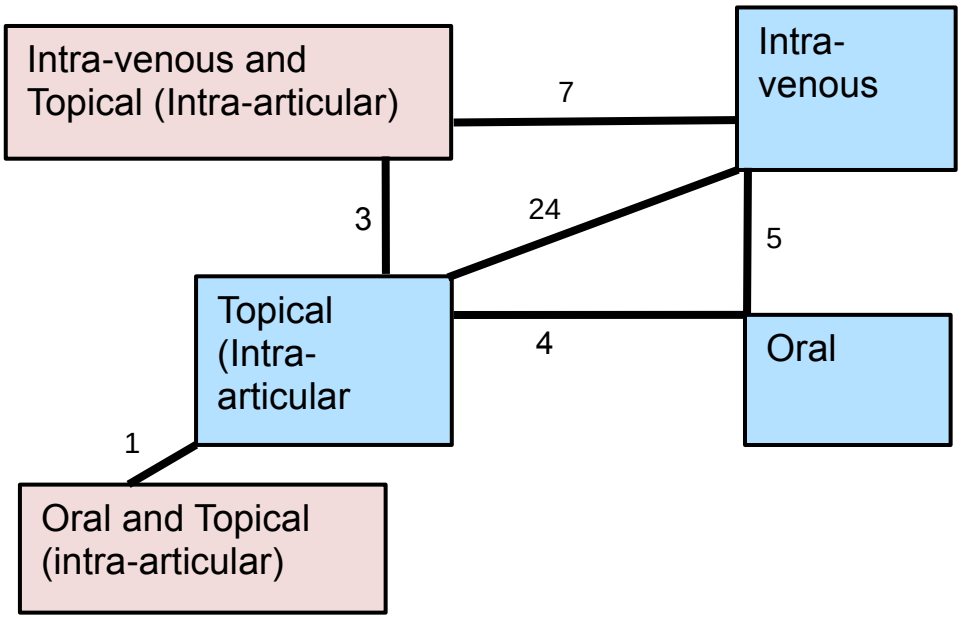
Figure 1. TXA transfusion event NMA structure. Blue shapes indicate a monotherapy and red shapes indicate a combination therapy. Numbers show the amount of studies comparing the relevant interventions



Inconsistency

To determine if there is evidence of inconsistency, the selected consistency model (fixed or random effects) was compared to an "inconsistency", or unrelated mean effects, model.[53, 55] The posterior mean of the residual deviance, which measures the magnitude of the differences between the observed data and the model predictions of the data, was used to assess and compare the goodness of fit of each model.[54] In addition to assessing how well the models fit the data using the posterior mean of the residual deviance, models were compared using the DIC.

Further checks for evidence of inconsistency were run through node-splitting. This method permits the direct and indirect evidence contributing to an estimate of a relative effect to be split and compared.

Costs

For the cost comparison costs were divided into the intervention costs and the cost of a transfusion. Intervention costs were calculated through an unweighted average intervention cost of each arm in the included studies. The cost for each arm of the included studies was calculated by extracting the dosage of TXA used, the saline volume used (if applicable) and disposables used (if applicable). Unit costs for TXA solution, TXA tablets, saline and syringes were then obtained from eMIT[46] or NHS Supply Chain Catalogue 2018[188] and multiplied by the relevant resource use for each treatment in each included study.

The cost of a transfusion was calculated from Stokes 2018[232] and the NICE Blood Transfusion guideline.[185] The standard volume of a unit of red blood cells (RBCs) was assumed as 280ml with a range of 220-340ml.

The total NHS cost for each administration method was given by the formula:

$$P(\text{transfusion.event}) \times (C(\text{first.unit}) + C(\text{subs.unit})) + C(\text{intervention})$$

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Where the probability of a transfusion event occurring [P(transfusion.event)] is the output of the NMA. The cost of a transfusion event [C(first.unit) + C(subs.unit)] is the cost of transfusing an initial unit and 1 subsequent unit, and C(intervention) is the intervention cost. Results Table 8 shows the base case results, including the probability of a transfusion event occurring for the different administration methods and the NHS cost of each administration method when factoring in the probability of a transfusion occurring.

1.5.3.1.27 Results

Table 19 summarises the fixed effects results of the conventional meta-analyses in terms of risk ratios generated from studies directly comparing different interventions, together with the results of the NMA in terms of risk ratios for every possible treatment comparison. Table 20 shows the base case absolute results, including the probability of a transfusion event occurring for the different administration methods and the NHS cost of each administration method when factoring in the probability of a transfusion occurring.

Table 19: Risk ratios for transfusion events; direct pairwise meta-analysis results and NMA results

Comparator	Intervention	Direct (95% confidence interval)	Fixed effects NMA - median (95% credible interval)
IA	IV	Presented as risk difference in clinical review	0.925 (0.732, 1.161)
	Oral	0.781 (0.474, 1.282)[(a)]	0.840 (0.518, 1.319)
	IA + IV	Presented as Peto odds ratio in clinical review	0.294 (0.126, 0.611)
	IA + Oral	Presented as Peto odds ratio in clinical review	0.070 (0.000, 1.102)
IV	Oral	1.01 (0.59, 1.73)	0.909 (0.561, 1.432)
	IA + IV	0.27 (0.11, 0.67)	0.318 (0.140, 0.642)
	IA + Oral	n/a	0.076 (0.000, 1.208)
Oral	IA + IV	n/a	0.350 (0.137, 0.816)
	IA + Oral	n/a	0.083 (0.000, 1.377)
IA + IV	IA + Oral	n/a	0.239 (0.000, 4.311)

(a)The inverse risk ratio to the one presented in the evidence review is presented here for comparison

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Table 20. Absolute outcomes and ranking of interventions

Transfusions			
	Probability of a transfusion event - median (95% CrIs)	**Intervention rank - median (95% CrIs)** 1=least transfusions, 5=most	**Probability that intervention is best (least transfusions)**
IA	0.072 (0.025, 0.187)	5 (3, 5)	0.00%
IV	0.066 (0.023, 0.178)	4 (3, 5)	0.00%
Oral	0.060 (0.019, 0.175)	3 (2, 5)	0.06%
IA + IV	0.021 (0.005, 0.74)	2 (1, 2)	20.14%
IA + Oral	0.005 (0.000, 0.098)	1 (1, 5)	79.80%
NHS cost			
	Cost of each intervention including transfusion costs – mean (95% CrIs)	**Intervention rank - median (95% CrIs)** 1=least cost, 5=most cost	**Probability that intervention is best (least cost)**
IA	£31.13 (11.76, 68.36)	5 (3, 5)	0.00%
IV	£28.63 (10.22, 64.65)	4 (3, 5)	0.00%
Oral	£24.70 (6.92, 61.65)	3 (2, 5)	1.15%
IA + IV	£14.34 (7.23, 31.42)	2 (1, 3)	12.23%
IA + Oral	£7.76 (2.31, 36.82)	1 (1, 5)	86.62%

The inconsistency (FE) model showed no meaningful difference to the consistency model suggesting the consistency (FE) model fits the data well. The fixed effect node split models also found no evidence of inconsistency.

The results indicated that topical (intra-articular) in combination with oral had the lowest probability of a transfusion event and was also the cheapest. However, the committee were keen to note that the intervention was linked to the network by a single study that had a high risk of bias in the clinical review. Furthermore, use of oral tranexamic acid is off label and generally not part of current practice, use of topical (intra-articular) tranexamic acid is also off label but is part of current practice. As both methods of administration are off label, the committee agreed they did not want to make a recommendation for topical (intra-articular) in combination with oral. Although as previously noted, topical (intra-articular) tranexamic acid is off license; its use in combination with IV tranexamic acid is not uncommon in current practice. Given the clinical and economic evidence in favour of this combination, the committee decided to make an offer this combination.

1.5.4 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 21: UK unit costs of tranexamic acid

Resource	**Dose**	**Unit cost**

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Resource	Dose	Unit cost
Oral tranexamic acid (tablet)	500 mg	£0.05
Intravenous/Intra-articular tranexamic acid solution	500 mg/5ml	£0.55
Syringe[(a)]	-	£0.35
Saline ampoule (20ml of 0.9%)[(a)]	-	£0.11

Source: eMIT [88] and NHS Supply chain Catalogue [188]
(a) Required for administration of intravenous/intraarticular tranexamic acid

Table 22: UK costs of blood transfusion

Resource	Unit cost
Administration of first unit of RBCs	£57.19
Administration of subsequent unit of RBCs	£36.13
Unit of RBCs (first and subsequent)	£128.99
Total cost of first RBC unit	**£186.18**
Total cost of a subsequent RBC unit	**£165.12**

Source: Stokes2018[232], NHSBT 2017/18[187]

1.6 Evidence statements

1.6.1 Clinical evidence statements

One hundred and eight RCTs covering 13 comparisons were included in the evidence review.

Topical (intra-articular) versus no treatment (12 RCTs)

A benefit was found for topical (intra-articular) tranexamic acid in transfusion (n=1078, low quality), total blood loss (n=709, very low quality), surgical bleeding (n=355, very low quality) and postoperative bleeding (n=95, high quality). No difference was seen in terms of DVT (n=850, moderate quality), blood loss via haemoglobin level after surgery (n=906, very low quality), and length of stay (n=312, low quality). No outcomes favoured no treatment.

Oral versus no treatment (1 RCT)

A benefit was found for oral tranexamic acid in transfusion (189, very low quality), blood loss via haemoglobin level after surgery (n=189, moderate quality), and total blood loss (n=189, moderate quality). No difference was found in mortality (n=189, low quality), DVT (n=189, very low quality), or length of stay (n=189, moderate quality). No outcomes favoured no treatment.

IV versus no treatment (16 RCTs)

A benefit was found for IV tranexamic acid in transfusion (n=1324, very low quality), total blood loss (n=873, very low quality), and postoperative bleeding (n=96, high quality). No difference was found for mortality (n=100, very low quality), DVT (n=1135, moderate quality), blood loss through haemoglobin level (n=1038, low quality), surgical bleeding (n=356, very low quality), and length of stay (n=213, low quality). No outcomes favoured no treatment.

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Topical (intra-articular) versus placebo (23 RCTs)

A benefit was found for topical (intra-articular) tranexamic acid in transfusion (n=2589, high quality), transfusion (n=2589, high quality), blood loss via haemoglobin level after surgery (n=1853, very low quality),total blood loss (n=1617, low quality), and postoperative bleeding (n=394, moderate quality). No difference was seen in terms of mortality (n=60, very low quality), quality of life (n=190, very low quality), DVT (n=2428, very low quality), surgical bleeding (n=243, very low quality), or length of stay (n=1108, low quality). No outcomes favoured placebo.

Oral versus placebo (3 RCTs)

A benefit was found for oral tranexamic acid in transfusion (n=406, moderate quality), blood loss via haemoglobin level after surgery (n=406, low quality), total blood loss (n=126, moderate quality), and surgical bleeding (n=80, low quality). No difference was seen in terms of DVT (n=406, moderate quality) or length of stay (n=80, moderate quality). No outcomes favoured placebo.

IV versus placebo (43 RCTs)

A benefit was found for IV tranexamic acid in transfusion (n=3383, low quality) blood loss via haemoglobin level after surgery (n=2489, very low quality), total blood loss (n=2624, low quality), surgical bleeding (n=744, very low quality), and postoperative bleeding (n=762, very low quality). No difference was seen in terms of mortality (n=290, moderate quality), DVT (n=3356, moderate quality), acute coronary syndrome (n=230, moderate quality), or length of stay (n=1272, high quality). No outcomes favoured placebo.

IV plus topical (intra-articular) versus placebo (4 RCTs)

A benefit was found for IV tranexamic acid plus IA/topical tranexamic acid in transfusion (n=380, moderate quality) blood loss via haemoglobin level after surgery (n=380, moderate quality), total blood loss (n=380, low quality), surgical bleeding (n=100, moderate quality), and postoperative bleeding (n=200, moderate quality). No difference was seen in terms of DVT (n=380, moderate quality) or length of stay (n=200, moderate quality). No outcomes favoured placebo.

Topical (intra-articular) versus IV (31 RCTs)

None of the 11 outcomes indicated difference between treatment groups: mortality at 30 days (n=269, very low quality), quality of life (mental component score) (n=100, low quality), quality of life (physical component score) (n=100, low quality), transfusion (n=3978, high quality), DVT (n=3833, high quality), acute myocardial infarction (n=89, very low quality), blood loss via haemoglobin level after surgery (n=2558, low quality), total blood loss (n=2806, low quality), surgical bleeding (n=1172, very low quality), postoperative bleeding (n=272, low quality), and length of stay (n=1312, high quality).

Oral versus IV (8 RCTs)

None of the 7 outcomes indicated difference between treatment groups: mortality (n=120, moderate quality), transfusion (n-862, very low quality), DVT (n=945, moderate quality), blood loss via haemoglobin level after surgery (n=945, moderate quality), total blood loss (n=665, moderate quality), surgical bleeding (n=200, moderate quality), and length of stay (n=437, moderate quality).

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Topical (intra-articular) versus oral (5 RCTs)

A benefit was found for oral tranexamic in the transfusion (n=787, very low quality) and no outcomes indicated a comparative benefit for topical (intra-articular) tranexamic acid. The other 6 outcomes indicated no difference between treatment groups: mortality (n=384, moderate quality), DVT (n=784, moderate quality), blood loss via haemoglobin level after surgery (n=784, moderate quality), total blood loss (n=504, moderate quality), surgical bleeding (n=384, high quality), and length of stay (n=237, moderate quality).

IV plus topical (intra-articular) versus IV (8 RCTs)

A benefit was found for IV tranexamic acid plus Topical (intra-articular) tranexamic acid in transfusion (n=791, moderate quality), blood loss via haemoglobin level after surgery (n=891, very low quality), total blood loss (n=691, very low quality), and postoperative bleeding (n=200, low quality). No difference was seen in terms of DVT (n=891, moderate quality) or length of stay (n=472, moderate quality). No outcomes favoured IV tranexamic acid alone.

Topical (intra-articular) plus oral versus topical (intra-articular) (1 RCT)

A benefit of topical (intra-articular) tranexamic acid plus oral tranexamic acid was found in transfusion (n=100, very low quality), blood loss via haemoglobin level after surgery (n=100, low quality), total blood loss (n=100, low quality), and postoperative bleeding (n=100, low quality). No difference was found for DVT (n=100, very low quality). No outcomes favoured IV tranexamic acid alone.

IV plus topical (intra-articular) versus topical (intra-articular) (4 RCTs)

A benefit for IV tranexamic acid plus topical (intra-articular) tranexamic acid was found in transfusion (n=320, moderate quality), blood loss via haemoglobin level after surgery (n=420, very low quality), and total blood loss (n=420, very low quality). No clinical difference was seen for quality of life (mental component score) (n=100, low quality), quality of life (physical component score) (n=100, low quality), DVT (n=420, low quality), or length of stay (n=140, very low quality). No outcomes favoured topical (intra-articular) tranexamic acid alone.

1.6.2 Health economic evidence statements

One cost utility analysis found that placebo was not cost effective (£63,429 per QALY gained) compared to topical (intra-articular) tranexamic acid for people undergoing total knee replacement. Topical (intra-articular) tranexamic acid was cost saving but was also less effective than placebo. This study was assessed as partially applicable with potentially serious limitations.

One cost utility analysis found that placebo was cost effective (£11,509 per QALY gained) compared to topical (intra-articular) tranexamic acid. Topical (intra-articular) tranexamic acid was cost saving but was also less effective than placebo. The result should be treated with caution due to a much higher baseline quality of life reported for the intervention arm. This study was assessed as partially applicable with potentially serious limitations.

One comparative cost study found that intravenous tranexamic acid was cost saving (saves a minimum of £68 per person for hip and knee replacements) compared to no tranexamic acid. This study was assessed as partially applicable with potentially serious limitations.

An original network meta-analysis with cost comparison found that when factoring in the cost of a transfusion, using topical (intra-articular) tranexamic acid with oral tranexamic acid was the most cost saving method of administration compared to using either: topical (intra-articular) tranexamic acid with intravenous tranexamic acid; oral, intravenous, or topical (intra-articular) alone. Topical (intra-articular) tranexamic acid with intravenous tranexamic

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acid was found to be more cost saving than using oral, intravenous or topical (intra-articular) alone. The most cost saving method, topical (intra-articular) tranexamic acid with oral tranexamic acid, was linked to the network by a single study that was graded as having a high risk of bias. This analysis was assessed as partially applicable with minor limitations.

1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

The critical outcomes chosen by the committee were mortality, adverse events, transfusion, quality of life and surgical bleeding. The important outcomes were postoperative anaemia, postoperative bleeding, and length of stay. The outcomes that represent blood loss are transfusion, surgical bleeding, postoperative anaemia, and postoperative bleeding. Surgical bleeding and postoperative bleeding were often reported within the same outcome, blood loss measured via change in haemoglobin and total blood loss. The adverse events associated with tranexamic acid use are postoperative thrombosis such as deep vein thrombosis (DVT), and acute myocardial infarction. Therefore the evidence review sought to assess the possible positives of tranexamic acid treatment in joint replacement surgery around reduction in blood loss and consequently reduction in transfusions, with the possible negative postoperative thrombosis outcomes.

1.7.1.2 The quality of the evidence

The overall outcome quality ranged from high to very low. More outcomes were assessed as low or very low quality than moderate or high quality.

The outcome quality was often downgraded due to risk of bias because studies that did not state an adequate method of randomisation or gave an adequate description of allocation concealment. This could have led to results that favoured tranexamic acid treatment. There were many studies where participants and surgeons were not blinded to the treatment. This was often not considered a risk of bias where outcomes were assessed objectively.

Many outcomes were found to be inconsistent and also a smaller number showed imprecision in the meta-analysis results. This could be explained by the tranexamic acid treatments in the RCTs which were allocated to intervention groups based on route of administration rather than the specific joint being replaced, timing of administration, and dose. These aspects were investigated singly in subgroup analysis where heterogeneity was found. None were found alone to explain the heterogeneity but there could well have been more complex interactions between these factors that led to not only inconsistency but also imprecision.

1.7.1.3 Benefits and harms

107 studies covering 13 comparisons were found.

All 3 routes of tranexamic acid administration were compared alone or in one case, in combination, to no treatment or placebo. These results consistently found a clinically important benefit of tranexamic acid in the blood loss and also in terms of the number of people requiring transfusions. In all cases there was no clinically important difference in DVT between the treatment groups.

The 3 routes of tranexamic acid administration were compared against each other singly. When topical (intra-articular) and oral were each compared to IV administration, all outcomes indicated no clinically important difference. Topical (intra-articular) versus oral administration

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found no clinically important difference for all outcomes except for transfusion which indicated 18 fewer people per thousand requiring a transfusion.

The last group of analyses compared multiple routes of administration of tranexamic acid to a single route of administration. IV combined with topical (intra-articular) versus IV alone found no clinical difference for 5 outcomes though the transfusion outcome indicated a benefit for combination treatment. IA/topical combined with oral versus IA/topical alone was reported by 1 RCT and this indicated a clinically important benefit of the combination treatment in terms of 4 blood loss outcomes and no difference in DVT. IV combined with IA/topical versus IA/topical alone found a benefit for combination treatment in blood loss via change in haemoglobin and in number of people transfused but no difference in total blood loss.

103 of the RCTs investigated knee or hip joint replacement and 4 RCTs investigated shoulder joint replacement. These 4 studies covered the IA/topical versus placebo and IV versus placebo comparisons. Thus the 11 other comparisons presented in the evidence review did not have include data from people having shoulder joint replacement surgery. The 4 studies that included people having shoulder joint replacement surgery indicated tranexamic acid was effective versus placebo but did not give an indication of its effectiveness when utilised across multiple routes.

Some benefits and no harms were found when multiple treatment routes were utilised versus single routes. The committee spoke about a reduction in transfusions found in all 3 comparisons to support combination treatment and thought this to be a compelling factor. In terms of the comparisons, all of the combination routes included IA/topical and the committee were mindful of this. The committee made a recommendation to offer IV in combination with IA/topical tranexamic acid in people having primary elective hip, knee or shoulder joint replacement surgery. While there is evidence showing a benefit of tranexamic acid in people having primary elective shoulder replacement there was no evidence for combination treatment. However the committee agreed to extrapolate the advantages of combination therapy found in the hip and knee replacement population to the shoulder replacement population. This decision was based on the basic similarities of each form of joint replacement surgery and despite shoulder replacement not yielding as high blood loss as hip or knee replacement surgery it is important to reduce blood loss where possible. There are many fewer transfusions in shoulder replacement surgery but reducing bleeding reduces bruising and reduces postoperative haematoma. There were no adverse events associated with this treatment in any of the evidence and no overt economic pressures given the use of tranexamic acid via a single route is standard care and so the committee agreed to include shoulder replacement surgery in the recommendation.

The BNF states tranexamic acid is indicated for local fibrinolysis via oral or slow intravenous injection with dosage stated. It does not mention usage topically or give a dosage for this. The committee are satisfied it is a safe and effective treatment topically and in combination through the large evidence base and their own experience.

The committee thought that topical (intra-articular) should be given after the final washout of the wound and before wound closure.

The committee noted the BNF indicates people with renal impairment require a reduced dose of tranexamic acid. The IV dose is indicated in the product literature but the absorption is uncertain via topical (intra-articular) usage. Consequently, only IV is recommended for this sub-group. Instead the committee agreed that IV alone should be offered to those with renal impairment. The rationale for this was that it is easier to control dosage and absorption through this method of administration.

1.7.2 Cost effectiveness and resource use

The studies in the economic review included 2 cost utility analyses and 1 cost comparison. The cost utility analyses only differed by site of joint replacement, otherwise they were from the same author and used the same methodology. Neither of these studies presented

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ICERs, these were calculated from the incremental costs and health related quality of life values presented in the papers. The results from the first cost utility analysis suggested that for people with total knee replacements (TKR) placebo was not cost effective (£63,428 per QALY gained) compared to topical (intra-articular) tranexamic acid. The results from the second cost utility analysis suggested that for people with total hip replacements (THR) placebo was cost effective (£11,509 per QALY gained) compared to topical (intra-articular) tranexamic acid. The interpretation of the ICER for these studies was the cost per QALY of the placebo (as opposed to the intervention) because tranexamic acid was cost saving but also gave less improved outcomes compared to placebo. Therefore the incremental values fall into the south-west quadrant on the cost effectiveness plane, which alters interpretation to the cost per QALY of the comparator compared to the intervention.

The results of the cost utility analyses should be treated with caution due to large differences in baseline quality of life (EQ-5D) between the study arms, despite being within-trial RCTs. For the study that concerned the THR population, the baseline EQ-5D for the placebo group was 0.205 whereas the value was 0.34 (a difference of 0.135) for the tranexamic acid group. The higher baseline value in the tranexamic acid group may have left less room for improvement in health related quality of life compared to the placebo group. Although it was not stated in the paper, it may be for this reason that the ICER was not presented in either paper.

The cost comparison study showed similar results to the 2 cost utility analyses, suggesting that using tranexamic acid over placebo or no tranexamic acid was cost saving. However, there were no studies that compared the cost of administering tranexamic acid by different methods. Additionally, all included studies only covered hip and knee replacements, there were no studies included which looked at the cost of tranexamic acid during shoulder surgery.

Current practice with tranexamic acid is varied, although for hip and knee replacements IV is often used in combination with topical (intra-articular). There was notion that oral is less favoured on the NHS. For shoulder replacements, use of topical (intra-articular) may be less common than for hip and knee replacements. Dosage use, and therefore costs are variable.

Given there was evidence presented for the clinical benefit of combination therapies and there was a lack of economic evidence for them, an original network meta-analysis with cost comparison was conducted. No studies with a primary elective shoulder replacement population were includable. In agreement with the committee, placebo and no treatment were excluded from the analysis given that using any form of tranexamic acid is established as current practice.

The results showed that average intervention costs were cheapest for oral and most expensive for IA and IV (oral, £0.27; IV, £2.25; IA and oral, £2.31; IA, £2.82; IA and IV, £5.34). The committee noted that the median dose used for combination therapy arms was generally greater than the dosage used for single therapies.

The results of the network meta-analysis for blood transfusions confirmed the committee's thoughts that the combination therapies were associated with a lower probability of a transfusion event occurring. Allogeneic blood transfusions carry a significant cost; transfusing 2 units of blood has an overall cost of £351.30. Once the cost and probability of a transfusion was added onto the cost of each intervention, the combination therapies were the least costly interventions (IA, £31.13; IV, £28.63; oral, £24.70; IA and IV, £14.34; IA and oral, £7.76). A sensitivity analysis showed that the overall costs were most sensitive to the cost of a blood transfusion. However, running the cost comparison with 1 unit transfused per transfusion

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event (instead of 2 units in the base case analysis), still did not change the order of cost. The results were less sensitive to the mean intervention costs.

The results indicated that topical (intra-articular) in combination with oral had the lowest probability of a transfusion event and was also the cheapest. However, the committee were keen to note that the intervention was linked to the network by a single study that had a high risk of bias in the clinical review. Furthermore, use of oral tranexamic acid is off label and generally not part of current practice, use of topical (intra-articular) tranexamic acid is also off label but it is part of current practice. As both methods of administration are off licence, the committee agreed they did not want to make a recommendation for topical (intra-articular) in combination with oral. Although as previously noted, topical (intra-articular) tranexamic acid is off license; its use in combination with IV tranexamic acid is not uncommon in current practice. Given the clinical and economic evidence in favour of this combination, the committee decided to make an offer for IV in combination with topical (intra-articular). There was discussion about the higher median dosage used in the topical (intra-articular) with intravenous method that was recommended. The median dosage for each tranexamic acid administration method in the network was:

- 2.00 grams for topical (intra-articular)
- 1.54 grams for intravenous
- 3.07 grams for oral
- 3.02 grams for topical (intra-articular) and intravenous
- 3.50 grams for topical (intra-articular) and oral

Although there was suggestion that this could have been a contributing factor to the results, the committee still felt the evidence was strong enough to offer topical (intra-articular) in combination with IV. The median dosage was considered over the mean as the mean was skewed towards higher values. The committee discussed the total dosage they use in current practice, which varied between 2-3g when combining IV and topical (intra-articular). The median dosage of topical (intra-articular) in combination with IV study arms included in the network roughly equated to the upper end of dosage discussed by the committee. Therefore the committee agreed that dosage should not exceed 3g in total. It was noted that the dosage of topical (intra-articular) used in the combination arms was generally between 1-2g.

The NMA and cost comparison analysis is directly applicable to hip and knee replacements as the clinical data concerned only these populations. Although no evidence was available for tranexamic acid use for shoulder replacements, the committee agreed that the analysis could support a recommendation for the shoulder population. This was done on the basis that although blood loss may be slightly less for shoulder replacements, there is still benefit in reducing bleeding. The recommendation is likely to lead to an increase in topical (intra-articular) tranexamic acid use in shoulder replacements. Overall, it is expected that the recommendation will be cost saving for shoulder replacements (although the savings will be relatively less than for hip and knee replacements). This is because avoided transfusions drive cost savings and shoulder replacements generally require less transfusions than knee/hip replacements.

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Appendices

Appendix A: Review protocols

Table 23: Review protocol: tranexamic acid

ID	Field	Content
0.	PROSPERO registration number	Not registered
1.	Review title	Tranexamic acid in joint replacement surgery.
2.	Review question	In adults having primary elective joint replacement, what is the clinical and cost effectiveness of tranexamic acid (TXA) for minimising blood loss from surgery?
3.	Objective	Major bleeding is associated with joint replacement surgery. One way to reduce bleeding is the perioperative use of tranexamic acid. The objective of this review is to investigate whether it is effective for prevention of bleeding and this reduction in bleeding is not outweighed by possible adverse events.
4.	Searches	The following databases will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Embase MEDLINE Searches will be restricted by: English language Human studies Letters and comments are excluded. Other searches: Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain	Primary elective joint replacement surgery

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ID	Field	Content
	being studied	
6.	Population	Inclusion: Adults having primary elective joint replacement Exclude studies including people meeting any of the following criteria: Adults having joint replacement as immediate treatment following fracture. Adults having revision joint replacement. Adults having joint replacement as treatment for primary or secondary cancer affecting the bones. Studies comparing doses within the same route of administration will not be included
7.	Intervention/Exposure/Test	Perioperative use of topical/intra-articular tranexamic acid Perioperative use of intravenous tranexamic acid Perioperative use of oral tranexamic acid Perioperative use of topical/intra-articular and intravenous tranexamic acid Perioperative use of topical/intra-articular and oral tranexamic acid Perioperative use of intravenous and oral tranexamic acid Perioperative use of topical/intra-articular, intravenous and oral tranexamic acid
8.	Comparator/Reference standard/Confounding factors	Comparison of interventions. Placebo. No treatment.
9.	Types of study to be included	Systematic reviews RCTs If no well-conducted RCTs are available, then observational studies with multivariate analysis will be investigated.
10.	Other exclusion criteria	Non-English language studies. Abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	N/A
12.	Primary outcomes (critical outcomes)	Mortality: 30 day (dichotomous) Adverse events: acute myocardial infarction(dichotomous)

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ID	Field	Content
		postoperative thrombosis (dichotomous) Blood (allogeneic or autologous) transfusion (dichotomous) Quality of life within 6 weeks (continuous) Surgical bleeding (continuous)
13.	Secondary outcomes (important outcomes)	Postoperative anaemia (dichotomous) Postoperative bleeding (continuous) Length of stay (continuous)
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed for eligibility in line with the criteria outlined above. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. An in-house developed database; EviBase, will be used for data extraction. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings. A second reviewer will quality assure the extracted data. Discrepancies will be identified and resolved through discussion (with a third reviewer where necessary).
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed: Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) Randomised Controlled Trial: Cochrane RoB (2.0) Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and

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ID	Field	Content	
		95% confidence intervals will be calculated for each outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects. GRADE pro will be used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. If the population included in an individual study includes children aged under 12, it will be included if the majority of the population is aged over 12, and downgraded for indirectness if the overlap into those aged less than 12 is greater than 20%. Publication bias is tested for when there are more than 5 studies for an outcome. Other bias will only be taken into consideration in the quality assessment if it is apparent. Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis.	
17.	Analysis of sub-groups	Tranexamic acid dose Intravenous: ≤1,000mg, >1,000 mg to <3,000 mg, ≥3,000 mg Topical: ≤1,000mg, >1,000 mg to <3,000 mg, ≥3,000 mg Oral: ≤1,000mg, >1,000 mg to <3,000 mg, ≥3,000 mg Co-morbidities: via ASA grade Joint replaced: hip, shoulder, knee	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic

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ID	Field	Content		
		☐	Service Delivery	
		☐	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	20/01/18		
22.	Anticipated completion date	20/03/19		
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☐	☑
		Piloting of the study selection process	☐	☑
		Formal screening of search results against eligibility criteria	☐	☑
		Data extraction	☐	☑
		Risk of bias (quality) assessment	☐	☑
		Data analysis	☐	☑
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail Headches@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Carlos Sharpin [Guideline lead] Alex Allen [Senior Systematic Reviewer]		

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ID	Field	Content	
		Rafina Yarde [Systematic reviewer] Robert King [Health economist] Agnès Cuyàs [Information specialist] Eleanor Priestnall [Project Manager]	
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.	
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].	
29.	Other registration details		
30.	Reference/URL for published protocol		
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Joint replacement surgery, arthroplasty, tranexamic acid	
33.	Details of existing review of same topic by same authors	N/A	
34.	Current review status	☒	Ongoing
		☐	Completed but not published

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ID	Field	Content	
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	N/A	
36.	Details of final publication	www.nice.org.uk	

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1

2 **Table 24: Health economic review protocol**

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from low or middle-income countries (e.g. most non-OECD countries) or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[186] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example,

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	France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2003 or later but that depend on unit costs and resource data entirely or predominantly from before 2003 will be rated as 'Not applicable'. • Studies published before 2003 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

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Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[186]

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the searches where appropriate.

Table 25: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 01 May 2019	Exclusions Randomised controlled trials Systematic review studies Observational studies
Embase (OVID)	1974 – 01 May 2019	Exclusions Randomised controlled trials Systematic review studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2019 Issue 5 of 12 CENTRAL to 2019 Issue 5 of 12	None

Medline (Ovid) search terms

1.	arthroplasty/ or arthroplasty, replacement/ or arthroplasty, replacement, hip/ or arthroplasty, replacement, knee/ or arthroplasty, replacement, shoulder/ or hemiarthroplasty/
2.	joint prosthesis/ or hip prosthesis/ or knee prosthesis/ or shoulder prosthesis/
3.	((joint* or knee* or shoulder* or hip*) adj5 (surger* or replace* or prosthe* or endoprosthe* or implant* or artificial or arthroplast* or hemiarthroplast*)).ti,ab.
4.	or/1-3
5.	letter/
6.	editorial/
7.	news/
8.	exp historical article/
9.	Anecdotes as Topic/
10.	comment/
11.	case report/
12.	(letter or comment*).ti.
13.	or/5-12
14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animals/ not humans/
17.	exp Animals, Laboratory/

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18.	exp Animal Experimentation/
19.	exp Models, Animal/
20.	exp Rodentia/
21.	(rat or rats or mouse or mice).ti.
22.	or/15-21
23.	4 not 22
24.	limit 23 to English language
25.	Tranexamic Acid/
26.	(tranexamic or txa or cyklokapron).ti,ab.
27.	or/25-26
28.	24 and 27
29.	randomized controlled trial.pt.
30.	controlled clinical trial.pt.
31.	randomi#ed.ti,ab.
32.	placebo.ab.
33.	randomly.ti,ab.
34.	Clinical Trials as topic.sh.
35.	trial.ti.
36.	or/29-35
37.	Meta-Analysis/
38.	exp Meta-Analysis as Topic/
39.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
40.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
41.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
42.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
43.	(search* adj4 literature).ab.
44.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
45.	cochrane.jw.
46.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
47.	or/37-46
48.	Epidemiologic studies/
49.	Observational study/
50.	exp Cohort studies/
51.	(cohort adj (study or studies or analys* or data)).ti,ab.
52.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
53.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
54.	Controlled Before-After Studies/
55.	Historically Controlled Study/
56.	Interrupted Time Series Analysis/
57.	(before adj2 after adj2 (study or studies or data)).ti,ab.
58.	or/48-57
59.	exp case control study/

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60.	case control*.ti,ab.
61.	or/59-60
62.	58 or 61
63.	Cross-sectional studies/
64.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
65.	or/63-64
66.	58 or 65
67.	58 or 61 or 65
68.	28 and (36 or 47 or 67)

1 **Embase (Ovid) search terms**

1.	*arthroplasty/ or *replacement arthroplasty/ or *hip replacement/ or *knee replacement/ or *shoulder replacement/ or *hemiarthroplasty/
2.	*joint prosthesis/ or *hip prosthesis/ or *knee prosthesis/ or *shoulder prosthesis/
3.	((joint* or knee* or shoulder* or hip*) adj5 (surger* or replace* or prosthe* or endoprosthe* or implant* or artificial or arthroplast* or hemiarthroplast*)).ti,ab.
4.	or/1-3
5.	letter.pt. or letter/
6.	note.pt.
7.	editorial.pt.
8.	case report/ or case study/
9.	(letter or comment*).ti.
10.	or/5-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice).ti.
20.	or/12-19
21.	4 not 20
22.	limit 21 to English language
23.	tranexamic acid/
24.	(tranexamic or txa or cyklokapron).ti,ab.
25.	1197-18-8.rn.
26.	or/23-25
27.	22 and 26
28.	random*.ti,ab.
29.	factorial*.ti,ab.
30.	(crossover* or cross over*).ti,ab.
31.	((doubl* or singl*) adj blind*).ti,ab.
32.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
33.	crossover procedure/

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34.	single blind procedure/
35.	randomized controlled trial/
36.	double blind procedure/
37.	or/28-36
38.	systematic review/
39.	meta-analysis/
40.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
41.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
42.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
43.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
44.	(search* adj4 literature).ab.
45.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
46.	cochrane.jw.
47.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
48.	or/38-47
49.	Clinical study/
50.	Observational study/
51.	family study/
52.	longitudinal study/
53.	retrospective study/
54.	prospective study/
55.	cohort analysis/
56.	follow-up/
57.	cohort*.ti,ab.
58.	56 and 57
59.	(cohort adj (study or studies or analys* or data)).ti,ab.
60.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
61.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
62.	(before adj2 after adj2 (study or studies or data)).ti,ab.
63.	or/49-55,58-62
64.	exp case control study/
65.	case control*.ti,ab.
66.	or/64-65
67.	63 or 66
68.	cross-sectional study/
69.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
70.	or/68-69
71.	63 or 70
72.	63 or 66 or 70
73.	27 and (37 or 48 or 72)

1

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Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Arthroplasty] this term only
#2.	MeSH descriptor: [Arthroplasty, Replacement] this term only
#3.	MeSH descriptor: [Arthroplasty, Replacement, Hip] this term only
#4.	MeSH descriptor: [Arthroplasty, Replacement, Knee] this term only
#5.	MeSH descriptor: [Arthroplasty, Replacement, Shoulder] this term only
#6.	MeSH descriptor: [Hemiarthroplasty] this term only
#7.	(or #1-#6)
#8.	MeSH descriptor: [Joint Prosthesis] this term only
#9.	MeSH descriptor: [Hip Prosthesis] this term only
#10.	MeSH descriptor: [Knee Prosthesis] this term only
#11.	MeSH descriptor: [Shoulder Prosthesis] this term only
#12.	(or #8-#11)
#13.	((joint* or knee* or shoulder* or hip*) near/5 (surger* or replace* or prosthe* or endoprosthe* or implant* or artificial or arthroplast* or hemiarthroplast*)):ti,ab
#14.	(or #7, #12-#13)
#15.	MeSH descriptor: [Tranexamic Acid] this term only
#16.	(tranexamic or txa or cyklokapron):ti,ab
#17.	#15 OR #16
#18.	#14 AND #17

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to the joint replacement population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional health economics searches were run in Medline and Embase.

Table 26: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 01 May 2019	Exclusions Health economics studies
Embase	2014 – 01 May 2019	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 01 May 2019 NHSEED - Inception to March 2015	None

Medline (Ovid) search terms

1.	arthroplasty/ or arthroplasty, replacement/ or arthroplasty, replacement, hip/ or arthroplasty, replacement, knee/ or arthroplasty, replacement, shoulder/ or hemiarthroplasty/
2.	joint prosthesis/ or hip prosthesis/ or knee prosthesis/ or shoulder prosthesis/
3.	((joint* or knee* or shoulder* or hip*) adj5 (surger* or replace* or prosthe* or endoprosthe* or implant* or artificial or arthroplast* or hemiarthroplast*)).ti,ab.
4.	or/1-3
5.	letter/

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6.	editorial/
7.	news/
8.	exp historical article/
9.	Anecdotes as Topic/
10.	comment/
11.	case report/
12.	(letter or comment*).ti.
13.	or/5-12
14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animals/ not humans/
17.	exp Animals, Laboratory/
18.	exp Animal Experimentation/
19.	exp Models, Animal/
20.	exp Rodentia/
21.	(rat or rats or mouse or mice).ti.
22.	or/15-21
23.	4 not 22
24.	limit 23 to English language
25.	Economics/
26.	Value of life/
27.	exp "Costs and Cost Analysis"/
28.	exp Economics, Hospital/
29.	exp Economics, Medical/
30.	Economics, Nursing/
31.	Economics, Pharmaceutical/
32.	exp "Fees and Charges"/
33.	exp Budgets/
34.	budget*.ti,ab.
35.	cost*.ti.
36.	(economic* or pharmaco?economic*).ti.
37.	(price* or pricing*).ti,ab.
38.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
39.	(financ* or fee or fees).ti,ab.
40.	(value adj2 (money or monetary)).ti,ab.
41.	or/25-40
42.	24 and 41

1 **Embase (Ovid) search terms**

1.	*arthroplasty/ or *replacement arthroplasty/ or *hip replacement/ or *knee replacement/ or *shoulder replacement/ or *hemiarthroplasty/
2.	*joint prosthesis/ or *hip prosthesis/ or *knee prosthesis/ or *shoulder prosthesis/
3.	((joint* or knee* or shoulder* or hip*) adj5 (surger* or replace* or prosthe* or endoprosthe* or implant* or artificial or arthroplast* or hemiarthroplast*)).ti,ab.
4.	or/1-3

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5.	letter.pt. or letter/
6.	note.pt.
7.	editorial.pt.
8.	case report/ or case study/
9.	(letter or comment*).ti.
10.	or/5-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice).ti.
20.	or/12-19
21.	4 not 20
22.	limit 21 to English language
23.	health economics/
24.	exp economic evaluation/
25.	exp health care cost/
26.	exp fee/
27.	budget/
28.	funding/
29.	budget*.ti,ab.
30.	cost*.ti.
31.	(economic* or pharmaco?economic*).ti.
32.	(price* or pricing*).ti,ab.
33.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
34.	(financ* or fee or fees).ti,ab.
35.	(value adj2 (money or monetary)).ti,ab.
36.	or/23-35
37.	22 and 36

1 NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR arthroplasty
#2.	MeSH DESCRIPTOR arthroplasty, replacement
#3.	MeSH DESCRIPTOR arthroplasty, replacement, hip
#4.	MeSH DESCRIPTOR arthroplasty, replacement, knee
#5.	MeSH DESCRIPTOR arthroplasty, replacement, shoulder
#6.	MeSH DESCRIPTOR hemiarthroplasty
#7.	MeSH DESCRIPTOR joint prosthesis

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#8.	MeSH DESCRIPTOR hip prosthesis
#9.	MeSH DESCRIPTOR knee prosthesis
#10.	MeSH DESCRIPTOR shoulder prosthesis
#11.	(((joint* or knee* or shoulder* or hip*) adj5 (surger* or replace* or prosthe* or endoprosthe* or implant* or artificial or arthroplast* or hemiarthroplast*)))
#12.	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11) IN NHSEED
#13.	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11) IN HTA

1

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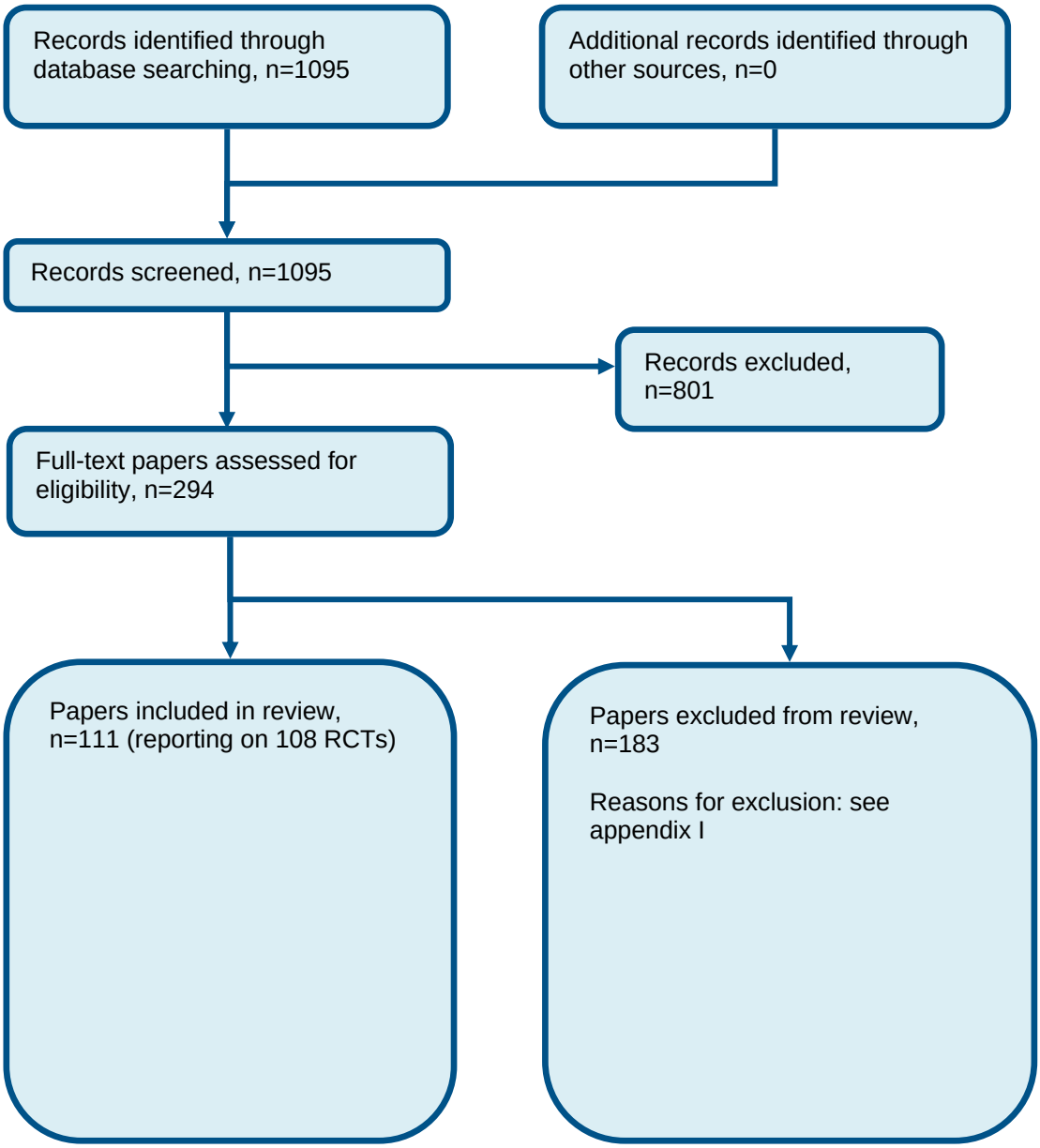
Appendix C: Clinical evidence selection

Figure 2: Flow chart of clinical study selection for the review of tranexamic acid



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Appendix D: Clinical evidence tables

Study	Abdel 2018[1]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=664)
Countries and setting	Conducted in USA; Setting: 2 high volume academic tertiary care referral centres.
Line of therapy	Not applicable
Duration of study	Intervention time: Surgery and in hospital period
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with osteoarthritis having primary elective unilateral total knee arthroplasty.
Exclusion criteria	Allergy to tranexamic acid, preoperative hepatic or renal dysfunction, serious cardiac or renal disease, congenital or acquired coagulopathy, thrombocytopenia, history of prothrombotic condition, pregnancy, breastfeeding, donated preoperative autologous blood, inflammatory arthritis, under 18 years old, low preoperative Hb level.
Age, gender and ethnicity	Age - Mean (SD): 66. Gender (M:F): 260/380. Ethnicity: Not detailed

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Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness
Interventions	(n=320) Intervention 1: Perioperative use of tranexamic acid - IV. 1g IV administered prior to tourniquet inflation. . Duration During surgery. Concurrent medication/care: VTE prophylaxis: aspirin twice daily for 6 weeks prior to surgery. Warfarin used to hit a target INR. Mechanical prophylaxis prior to hospital discharge. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≤1000 mg (n=320) Intervention 2: Perioperative use of tranexamic acid - IA/topical. 3g diluted in 45mL of saline applied to open joint surfaces after cementation of the implant and prior to tourniquet release. . Duration During surgery. Concurrent medication/care: VTE prophylaxis: aspirin twice daily for 6 weeks prior to surgery. Warfarin used to hit a target INR. Mechanical prophylaxis prior to hospital discharge. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≥3000 mg
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus IA/TOPICAL

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: VTE at In-hospital or post discharge; Group 1: 4/320, Group 2: 2/320
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: Serious indirectness, Comments: VTE rather than only DVT; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion rate at Unclear; Group 1: 2/320, Group 2: 5/320
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover -

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Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Surgical bleeding at - - Actual outcome: Calculated blood loss at During surgery; Group 1: mean 271 mL (SD 238); n=320, Group 2: mean 324 mL (SD 238); n=320 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Total blood loss at - - Actual outcome: Total drain output at 24 hours after surgery; Group 1: mean 456 mL (SD 336); n=320, Group 2: mean 560 mL (SD 336); n=320 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -; Blood loss: Haemoglobin level at 3 days after surgery

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Study	Adravanti 2018[5]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in Italy
Line of therapy	Not applicable
Duration of study	Intervention time: During surgery. Unclear follow-up.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults 18 to 95 years old undergoing primary TKA.
Exclusion criteria	Knee flexion deformity >20 ; varus and valgus deformity >20 ; revision unicompartmental or total knee replacement; pregnancy; known allergy to TXA, low-molecularweight heparin, and local anesthetics; congenital or acquired coagulopathy; history of thromboembolism; use of anticoagulants or contraceptive pills 5 days before surgery; anemia; severe cardiovascular and respiratory disorders; ischemic heart disease; renal and/hepatic insufficiency; and refusal of blood transfusion for religious reasons.
Recruitment/selection of patients	September 2015 to February 2016,
Age, gender and ethnicity	Age - Mean (SD): 70. Gender (M:F): 25/75. Ethnicity: Not detailed

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Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Perioperative use of tranexamic acid - IV. 1g IV 30 minutes before induction of anaesthesia and then at 3 and 9 hours after surgery. Duration During and immediately after surgery. Concurrent medication/care: Low-molecular-weight heparin was administered according to weight the day before surgery and then repeated every 24 hours.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≥3000 mg (n=50) Intervention 2: Perioperative use of tranexamic acid - IV+IA/topical. 1g IV 30 minutes before induction of anaesthesia, then at 3 and 9 hours after surgery plus 3 g topical tranexamic acid, which was injected into the joint after closure of the capsule.. Duration During and immediately after surgery. Concurrent medication/care: Low-molecular-weight heparin was administered according to weight the day before surgery and then repeated every 24 hours.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≥3000 mg
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus IV+IA/TOPICAL

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at During hospital stay and follow up; Group 1: 0/50, Group 2: 0/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at During hospital stay; Group 1: 2/50, Group 2: 0/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 3: Postoperative bleeding at - - Actual outcome: Postoperative blood loss at During hospital stay; Group 1: mean 853.9 mL (SD 294.2); n=50, Group 2: mean 746.2 mL (SD 291.5); n=50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Haemoglobin level at 4 days after surgery; Group 1: mean 10.4 g/dL (SD 1.3); n=50, Group 2: mean 11.1 g/dL (SD 1.2); n=50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Length of stay at -; Total blood loss at -

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Study	Aggarwal 2016[6]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=70)
Countries and setting	Conducted in India; Setting: Single tertiary centre
Line of therapy	Not applicable
Duration of study	Intervention + follow up: During surgery and at least 6 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People undergoing bilateral primary TKA for severe arthritis of the knee with tricompartmental involvement.
Exclusion criteria	Allergy to tranexamic acid, acquired disturbances of color vision, preoperative use of anticoagulants within 5 days of surgery, fibrinolytic disorders requiring intraoperative antifibrinolytics, coagulopathy, history of arteriolar or venous thromboembolic disease, pregnancy, breastfeeding, plasma creatinine of >115 mmol/L in males and >100 mmol/L in females or hepatic failure, and hemoglobin (Hb) <8 g/dL.
Recruitment/selection of patients	From January 2012 to June 2014.
Age, gender and ethnicity	Age - Mean (SD): 57. Gender (M:F): 45/25. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty

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Indirectness of population	No indirectness
Interventions	(n=35) Intervention 1: Perioperative use of tranexamic acid - IV. IV injection of 15 mg/kg 30 minutes before tourniquet deflation.. Duration During surgery. Concurrent medication/care: Antithrombolytic prophylaxis with oral aspirin (150 mg 1 day before surgery and 150mg daily continued through the 10th postoperative day) was used. Ankle pumps, use of DVT stockings, and early mobilization were administered postoperatively. Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=35) Intervention 2: Perioperative use of tranexamic acid - IA/topical. 15 mg/kg in 100 mL of normal saline solution which was applied topically on to the joint surface and left in contact for 10 minutes followed by meticulous suturing.. Duration During surgery. Concurrent medication/care: Antithrombolytic prophylaxis with oral aspirin (150 mg 1 day before surgery and 150mg daily continued through the 10th postoperative day) was used. Ankle pumps, use of DVT stockings, and early mobilization were administered postoperatively. Further details: 1. Tranexamic acid dose: Not stated / Unclear
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus IA/TOPICAL

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at In hospital and during follow-up; Group 1: 0/35, Group 2: 0/35
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at In hospital period; Group 1: 7/35, Group 2: 0/35
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Postoperative haemoglobin at 3 days after surgery; Group 1: mean 9.66 g/dL (SD 1.47); n=35, Group 2: mean 10.3 g/dL (SD 1.11); n=35 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Total blood loss at - - Actual outcome: Total blood loss at 3 days after surgery; Group 1: mean 1039 mL (SD 483); n=35, Group 2: mean 543 mL (SD 264); n=35 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -

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Study	Aguilera 2015[7]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=150)
Countries and setting	Conducted in Spain; Setting: Multicentre.
Line of therapy	Not applicable
Duration of study	Intervention time: During joint replacement surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults having elective total knee replacement due to OA or RA or other degenerative knee disorders
Exclusion criteria	Allergy to tranexamic acid, history of coagulopathy or thromboembolic event, previous bypass surgery, use of anticoagulant or contraceptive treatment, cardiovascular prosthesis, refusal to participate.
Recruitment/selection of patients	February 2012 to October 2012.
Age, gender and ethnicity	Age - Mean (SD): 73 (7). Gender (M:F): 48/102. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness

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Interventions	(n=50) Intervention 1: Perioperative use of tranexamic acid - IA/topical. 1g in 10mL solution. After prosthesis inserted and cemented, operative field was rinsed and dried. Topical tranexamic acid applied by syringe spray to the posterior capsule, surrounding soft tissue, fatty and subcutaneous tissue, exposed surfaces of femur and tibia. . Duration During surgery. Concurrent medication/care: Routine hemostasis performed. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≤1000 mg (n=50) Intervention 2: Perioperative use of tranexamic acid - IV. 2 doses of 1g. 15-30 minutes before tourniquet inflated and then once tourniquet is removed (60-90 minutes after the first). . Duration During surgery. Concurrent medication/care: Routine hemostasis performed.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg (n=50) Intervention 3: No treatment. No treatment. Duration during surgery. Concurrent medication/care: Routine hemostasis performed: consisting of electro-coagulation of all possible bleeding points and vessels. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Equipment / drugs provided by industry

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus IV

Protocol outcome 1: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at within 2 months of surgery; Group 1: 4/50, Group 2: 0/50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Surgical bleeding at -
- Actual outcome: Hidden blood loss at During surgery; Group 1: mean 851.64 mL (SD 464.71); n=47, Group 2: mean 685.02 mL (SD 314.08); n=48
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 2

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Protocol outcome 3: Postoperative bleeding at -
- Actual outcome: Blood loss from drains at 24 hours after surgery; Group 1: mean 200.1 mL (SD 163.5); n=47, Group 2: mean 144.9 mL (SD 108.49); n=48
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 2

Protocol outcome 4: Length of stay at -
- Actual outcome: Length of stay in hospital at .; Group 1: mean 5.71 days (SD 1.85); n=50, Group 2: mean 5.95 days (SD 2.61); n=50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Haemoglobin level at 12-24 hours after surgery; Group 1: mean 9 g/dL (SD 2.39); n=50, Group 2: mean 9.2 g/dL (SD 2.74); n=50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 6: Total blood loss at -
- Actual outcome: Total blood loss at 24 hours after surgery; Group 1: mean 1021.57 mL (SD 481.09); n=47, Group 2: mean 817.54 mL (SD 324.82); n=48
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 2

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus NO TREATMENT

Protocol outcome 1: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at within 2 months of surgery; Group 1: 4/50, Group 2: 13/50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Surgical bleeding at -
- Actual outcome: Hidden blood loss at During surgery; Group 1: mean 851.64 mL (SD 464.71); n=47, Group 2: mean 884.49 mL (SD 665.58); n=48
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 2

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Protocol outcome 3: Postoperative bleeding at -
- Actual outcome: Blood loss from drains at 24 hours after surgery; Group 1: mean 200.1 mL (SD 163.5); n=47, Group 2: mean 538.06 mL (SD 301.26); n=48
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 2

Protocol outcome 4: Length of stay at -
- Actual outcome: Length of stay in hospital at .; Group 1: mean 5.71 days (SD 1.85); n=50, Group 2: mean 5.63 days (SD 1.51); n=50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Haemoglobin level at 12-24 hours after surgery; Group 1: mean 9 g/dL (SD 2.39); n=50, Group 2: mean 9.6 g/dL (SD 1.97); n=50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 6: Total blood loss at -
- Actual outcome: Total blood loss at 24 hours after surgery; Group 1: mean 1021.57 mL (SD 481.09); n=47, Group 2: mean 1415.72 mL (SD 595.11); n=48
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 2

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus NO TREATMENT

Protocol outcome 1: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at within 2 months of surgery; Group 1: 0/50, Group 2: 13/50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Surgical bleeding at -
- Actual outcome: Hidden blood loss at During surgery; Group 1: mean 685.02 mL (SD 314.08); n=48, Group 2: mean 884.49 mL (SD 665.58); n=48
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover -

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Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 2 Protocol outcome 3: Postoperative bleeding at - - Actual outcome: Blood loss from drains at 24 hours after surgery; Group 1: mean 144.9 mL (SD 108.49); n=48, Group 2: mean 538.06 mL (SD 301.26); n=48 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 2 Protocol outcome 4: Length of stay at - - Actual outcome: Length of stay in hospital at .; Group 1: mean 5.95 days (SD 2.61); n=50, Group 2: mean 5.63 days (SD 1.51); n=50 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Haemoglobin level at 12-24 hours after surgery; Group 1: mean 9.2 g/dL (SD 2.74); n=50, Group 2: mean 9.6 g/dL (SD 1.97); n=50 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: Total blood loss at - - Actual outcome: Total blood loss at 24 hours after surgery; Group 1: mean 817.54 mL (SD 324.82); n=48, Group 2: mean 1415.72 mL (SD 595.11); n=48 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 2	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Adverse events: DVT at -; Quality of life at within 6 weeks; Postoperative anaemia at -

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Study	Almeida 2018[11]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=101)
Countries and setting	Conducted in Brazil; Setting: Conducted at Centro de Cirurgia do Joelho, Instituto Nacional de Traumatologia e Ortopedia (INTO), Rio de Janeiro, RJ, Brazil from September 2014 to January 2015.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 24 hours follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with primary knee osteoarthrosis who were scheduled for TKA
Exclusion criteria	Previous surgery in the same joint, evidence of joint infection, people with congenitalor acquired coagulopathies, active intravascular coagulation,acute occlusive vasculopathy, hypersensitivity to components of the Transamin formula, chronic use of oral anticoagulants and corticosteroids, history of severe or moderate allergy to plasma transfusion, people with chronic heart disease, people with malignant neoplasms and autoimmune dis-eases, major bone defects requiring bone grafting, and kneearthroplasty revision surgeries, not consenting.
Age, gender and ethnicity	Age - Mean (SD): 69 and 67. Gender (M:F): 31/70. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty

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Indirectness of population	No indirectness
Interventions	(n=51) Intervention 1: Perioperative use of tranexamic acid - IV. 1g, divided into four 5 ml ampoules of 250 mg each before the pneumatic cuff was inflated.. Duration Surgery. Concurrent medication/care: All patients underwent spinal anesthe-sia associated with femoral and sciatic nerves peripheral block. The surgeries were performed under ischemia witha pneumatic cuff inflated to a pressure 125 mmHg higher than the person's systolic blood pressure after limb exsanguination. All surgeries were performed with the patientin the supine position through the classical medial para-patellar approach; in all cases, the Hemovac drain wasremoved 24 hours after the procedure, and its output was recorded. In all people, post-stabilized Press Fit Condylar Sigma implants with patellar replace-ment were used.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≤1000 mg (1g). (n=50) Intervention 2: Placebo. Unclear what was injected. Duration Surgery. Concurrent medication/care: All patients underwent spinal anesthe-sia associated with femoral and sciatic nerves peripheral block. The surgeries were performed under ischemia witha pneumatic cuff inflated to a pressure 125 mmHg higher than the person's systolic blood pressure after limb exsanguination. All surgeries were performed with the patientin the supine position through the classical medial para-patellar approach; in all cases, the Hemovac drain wasremoved 24 hours after the procedure, and its output was recorded. In all people, post-stabilized Press Fit Condylar Sigma implants with patellar replace-ment were used.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Funding not stated (It was stated that the authors have no conflicts of interest)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion required at 1st postoperative day; Group 1: 0/51, Group 2: 6/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Some difference in haematocrit and haemoglobin; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 2: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Haemoglobin reduction at 1st postoperative day; Group 1: mean -2.2 g/dl (SD 1.43); n=51, Group 2: mean -3.2 g/dl (SD 1.43); n=50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Some difference in haematocrit and haemoglobin; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Total blood loss at - - Actual outcome: Blood loss volume at 1st postoperative day; Group 1: mean 800 ml (SD 678); n=51, Group 2: mean 1200 ml (SD 678); n=50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Some difference in haematocrit and haemoglobin; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Adverse events: DVT at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -

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Study	Antinolfi 2014[18]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Belgium, Italy
Line of therapy	Not applicable
Duration of study	--: Surgery with 90 days follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with primary knee osteoarthritis and scheduled to undergo unilateral primary TKA
Exclusion criteria	Allergy to tranexamic acid, history of thromboembolism, previous surgery to the knee (with the exception of an eventual meniscectomy), bleeding disorders, platelet or bone marrow disorders, and a high level of creatinine.
Age, gender and ethnicity	Age - Mean (SD): 72 (6). Gender (M:F): 28/32. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Perioperative use of tranexamic acid - IA/topical. 500mg injected inside the joint.

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	while no knee flexion or compression was applied. Duration Surgery and 6 weeks follow-up. Concurrent medication/care: Thromboprophylaxis: low molecular weight heparin (LMWH) as a single dose the evening before surgery and daily for six weeks postoperatively.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=20) Intervention 2: No treatment. No use of tranexamic acid. Duration Surgery and 6 weeks follow-up. Concurrent medication/care: Thromboprophylaxis: low molecular weight heparin (LMWH) as a single dose the evening before surgery and daily for six weeks postoperatively.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus NO TREATMENT Protocol outcome 1: Adverse events: DVT at - - Actual outcome: DVT at Within 90 days of surgery; Group 1: 0/20, Group 2: 0/20 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Haemoglobin at 3 days after surgery; Group 1: mean 10.1 g/dL (SD 1.2); n=20, Group 2: mean 9.7 g/dL (SD 0.9); n=20 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Total blood loss at - - Actual outcome: Blood loss at 2 days after surgery; Group 1: mean 658.5 mL (SD 211.4); n=20, Group 2: mean 1093 mL (SD 189.9); n=20 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the	Mortality at 30 day: Adverse events: acute myocardial infarction at -: Blood (allogeneic or autologous)

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study	transfusion at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -

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Study	Barrachina 2016[22]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=113)
Countries and setting	Conducted in Spain; Setting: 2 hospitals
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 3 months post hospital discharge follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Hip replacement surgery (unilateral, bicompartmental, primary, uncemented, posterolateral, or anterolateral) for arthrosis in adults with ASA physical status I to III and no known allergy to tranexamic acid.
Exclusion criteria	Pregnant or breastfeeding, severe vascular ischemia, history of venous thrombosis, pulmonary embolism or diseases causing embolism, known coagulopathies, longterm treatment with acetylsalicylic acid or nonsteroidal anti-inflammatory drugs not discontinued before surgery, a hemoglobin (Hb) concentration <10 mg/dL, moderate renal impairment, liver cirrhosis, or any contraindications to prophylaxis with enoxaparin
Recruitment/selection of patients	March 2011 to December 2012
Age, gender and ethnicity	Age - Mean (SD): 66 (12). Gender (M:F): 57/51. Ethnicity: Not detailed

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Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Hip replacement
Indirectness of population	No indirectness
Interventions	(n=38) Intervention 1: Perioperative use of tranexamic acid - IV. IV infusion of 15 mg/kg in 100 mL saline over a 10-minute period after the institution of regional anaesthesia and before the start of surgery. Three hours after the first infusion, they received a second infusion over 10 minutes but this time with 100 mL of saline alone.. Duration Surgery with follow-up of 40 days after surgery. Concurrent medication/care: All patients were treated with enoxaparin (40 mg/24 h if they had a body weight <80 kg or 60 mg/24 h if they had a body weight >80 kg) from the day before surgery and until day 40 after surgery.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=38) Intervention 2: Perioperative use of tranexamic acid - IV. IV infusion of 10 mg/kg diluted in 100 mL saline over 10 minutes, after instituting regional anaesthesia and before starting surgery. 3 hours later after the start of surgery, they received a second infusion at the same dose and rate as the first.. Duration Surgery with follow-up of 40 days after surgery. Concurrent medication/care: All patients were treated with enoxaparin (40 mg/24 h if they had a body weight <80 kg or 60 mg/24 h if they had a body weight >80 kg) from the day before surgery and until day 40 after surgery.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=40) Intervention 3: Placebo. IV infusion of 100 mL saline over a 10-minute period after instituting regional anaesthesia and before starting surgery. Three hours later, they received a further of 100 mL of saline over 10 minutes.. Duration Surgery with 40 days follow-up treatment after surgery. Concurrent medication/care: All patients were treated with enoxaparin (40 mg/24 h if they had a body weight <80 kg or 60 mg/24 h if they had a body weight >80 kg) from the day before surgery and until day 40 after surgery.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	No funding

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RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: Thrombosis
at 3 days after surgery; Group 1: 1/35, Group 2: 2/34
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Unclear; Group 2 Number missing: 3, Reason: 2 discontinued and 1 didn't receive intervention

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at During hospital admission; Group 1: 8/35, Group 2: 14/37
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Unclear; Group 2 Number missing: 3, Reason: 2 discontinued and 1 didn't receive intervention

Protocol outcome 3: Surgical bleeding at -
- Actual outcome: Intraoperative blood loss at .; Group 1: mean 470 mL (SD 283); n=35, Group 2: mean 435 mL (SD 217); n=37
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Unclear; Group 2 Number missing: 3, Reason: 2 discontinued and 1 didn't receive intervention

Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Haemoglobin level at 2 days after surgery; Group 1: mean 11.3 g/dL (SD 1.5); n=35, Group 2: mean 10.2 g/dL (SD 1.3); n=37
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Unclear; Group 2 Number missing: 3, Reason: 2 discontinued and 1 didn't receive intervention

Protocol outcome 5: Total blood loss at -
- Actual outcome: Total blood loss at 6 days after surgery; Group 1: mean 1377 mL (SD 689); n=35, Group 2: mean 2215 mL (SD 1136); n=37
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Unclear; Group 2 Number missing: 3, Reason: 2

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discontinued and 1 didn't receive intervention

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: Thrombosis
at 3 days after surgery; Group 1: 1/35, Group 2: 2/34
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 1 did not receive, `1 discontinued. ; Group 2 Number missing: 3, Reason: 2 discontinued and 1 didn't receive intervention

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at During hospital admission; Group 1: 4/36, Group 2: 14/37
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 1 did not receive, `1 discontinued. ; Group 2 Number missing: 3, Reason: 2 discontinued and 1 didn't receive intervention

Protocol outcome 3: Surgical bleeding at -
- Actual outcome: Intraoperative blood loss at .; Group 1: mean 421 mL (SD 199); n=36, Group 2: mean 435 mL (SD 217); n=37
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 1 did not receive, `1 discontinued. ; Group 2 Number missing: 3, Reason: 2 discontinued and 1 didn't receive intervention

Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Haemoglobin level at 2 days after surgery; Group 1: mean 11.6 g/dL (SD 1.4); n=36, Group 2: mean 10.2 g/dL (SD 1.3); n=37
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 1 did not receive, `1 discontinued. ; Group 2 Number missing: 3, Reason: 2 discontinued and 1 didn't receive intervention

Protocol outcome 5: Total blood loss at -
- Actual outcome: Total blood loss at 6 days after surgery; Group 1: mean 1308 mL (SD 641); n=36, Group 2: mean 2215 mL (SD 1136); n=37
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

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- Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 1 did not receive, `1 discontinued. ; Group 2 Number missing: 3, Reason: 2 discontinued and 1 didn't receive intervention	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -

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Study	Benoni 1996[23]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=86)
Countries and setting	Conducted in Denmark; Setting: Medical Faculty at Lund University
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	No history of bleeding disorders or warfarin medication; a diagnosis of osteoarthritis or aseptic bone necrosis, but not of rheumatoid arthritis; primary, unilateral, bicompartmental knee arthroplasty; either both or no components cemented; continuous epidural anaesthesia; and the use of only balanced electrolyte solutions and/or albumin for plasma volume restitution.
Exclusion criteria	NR
Recruitment/selection of patients	NR
Age, gender and ethnicity	Age - Mean (SD): TXA: 76 (7); placebo: 74 (7). Gender (M:F): TXA: 13/30; placebo: 10/33. Ethnicity: not stated

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Further population details	1. Co-morbidities: 2. Site/type of joint replacement:
Indirectness of population	No indirectness
Interventions	(n=43) Intervention 1: Perioperative use of tranexamic acid - IV. The dose of tranexamic acid of 10 mg/kg body-weight, maximum 1 g = 10 ml, or an equivalent volume of placebo, was given as a slow intravenous injection towards the end of the operation at a median time of 12 minutes (1 to 40) before deflation of the tourniquet. This dose was repeated after three hours from the other ampoule of the pair provided in an envelope. For patients with severe postoperative bleeding, an extra dose of tranexamic acid was given, without breaking the randomisation code. The cut-off values for this level of blood loss were set at >500 ml of blood lost via the drains within one hour or >1000 ml within four hours after the end of the operation. The decision to administer this dose of tranexamic acid was made by the anaesthetist in charge. Fifteen patients were given this extra dose at 1 to 5.7 hours (median 2.8) after the operation entirely because of heavy blood loss. All these patients were in the original placebo group and were referred to as the ‘placebo + extra’ group . Duration end of the operation at a median time of 12 minutes (1 to 40) before deflation of the tourniquet. Concurrent medication/care: All patients received low-molecular-weight heparin, as thromboprophylaxis, either dalteparin sodium (Fragmin, Pharmacia, Stockholm, Sweden), 5000 units (n = 49) or enoxaparin (Klexane; Rhone-Poulenc Rorer, Paris, France), 40 mg (n = 37), as a daily subcutaneous injection for seven to ten days, starting the evening before surgery. A dose of cloxacillin (Ekvacillin; Astra, Södertälje, Sweden) 2 g was given intravenously shortly before operation and two more doses of 1 g were given at six and 12 hours after the first dose. For patients with an allergy to penicillin, clindamycin was used. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Comments: After premedication, analgesia was achieved in all patients by continuous epidural anaesthesia through an indwelling catheter, which was removed in the early morning of the first postoperative day. No patient received NSAIDs during the first two postoperative days. All the operations were performed in a

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	bloodless field. After elevation of the limb and exsanguination with an Esmarch bandage, a tourniquet was inflated to 350 to 400 mmHg. At the end of the operation, the tourniquet was deflated and major bleeding was controlled. (n=43) Intervention 2: Placebo. A dose of 10 mg/kg body-weight of placebo was given intravenously shortly before the release of the tourniquet, and repeated three hours later. . Duration end of the operation at a median time of 12 minutes (1 to 40) before deflation of the tourniquet. Concurrent medication/care: All patients received low-molecular-weight heparin, as thromboprophylaxis, either dalteparin sodium (Fragmin, Pharmacia, Stockholm, Sweden), 5000 units (n = 49) or enoxaparin (Klexane; Rhone-Poulenc Rorer, Paris, France), 40 mg (n = 37), as a daily subcutaneous injection for seven to ten days, starting the evening before surgery. A dose of cloxacillin (Ekvacillin; Astra, Södertälje, Sweden) 2 g was given intravenously shortly before operation and two more doses of 1 g were given at six and 12 hours after the first dose. For patients with an allergy to penicillin, clindamycin was used. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose:
Funding	Equipment / drugs provided by industry
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO Protocol outcome 1: Adverse events: DVT at - - Actual outcome: DVT at postoperative; Group 1: 4/43, Group 2: 3/43	

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Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Blood (allogeneic or autologous) transfusion at - - Actual outcome: Number of patients receiving transfusions at perioperative; Group 1: 8/43, Group 2: 24/43 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Total blood loss at - - Actual outcome: Total blood loss (ml) at perioperative; Group 1: mean 730 (SD 280); n=43, Group 2: mean 1410 (SD 480); n=43 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -; Blood loss: Haemoglobin level at 3 days after surgery

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Study	Benoni 2001[24]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=40)
Countries and setting	Conducted in Sweden
Line of therapy	1st line
Duration of study	Intervention + follow up: 1 week FUs
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients scheduled for a unilateral, primary total hip replacement for osteoarthrosis or osteonecrosis. The study protocol stated that the indication for surgery was osteoarthrosis or osteonecrosis but not rheumatoid arthritis.
Exclusion criteria	Patients who were to undergo bone grafting or had bleeding disorders or signs of renal insufficiency were excluded, since tranexamic acid is eliminated through the kidneys.
Age, gender and ethnicity	Age - Mean (SD): 67 (9.45). Gender (M:F): 19 male, 19 female. Ethnicity: N/A
Further population details	1. Co-morbidities: Not applicable 2. Site/type of joint replacement: Hip replacement
Indirectness of population	No indirectness

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Interventions	(n=18) Intervention 1: Perioperative use of tranexamic acid - IV. The patients received tranexamic acid 100 mg/mL (Cyklokapron, Pharmacia & Upjohn, Sweden), 10 mg/kg body weight (maximum 1 g), in a slow (5–10 minutes) intravenous injection or a similar volume of placebo (saline) immediately before the operation started, contained in specially-prepared ampoules with 10 mL of the substance, identified by their numbers only.. Duration 5-10 mins. Concurrent medication/care: The operations were performed with the patients in a supine position, using a lateral approach without trochanteric osteotomy. All patients were operated on using the Charnley Elite total hip prosthesis (DePuy) with both components cemented. As thromboprophylaxis, all patients received low molecular weight heparin (Klexane, Rhone-Poulenc Rorer), 40 mg subcutaneously, starting the day before surgery and continuing for 7–10 days. Cloxacillin or clindamycin was routinely given as antibiotic prophylaxis before surgery and on two more occasions on the day of surgery.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: (n=20) Intervention 2: Placebo. The patients received placebo (saline) 100 mg/mL, 10 mg/kg body weight (maximum 1 g), in a slow (5–10 minutes) intravenous injection immediately before the operation started, contained in specially-prepared ampoules with 10 mL of the substance, identified by their numbers only. . Duration 5-10 mins. Concurrent medication/care: The operations were performed with the patients in a supine position, using a lateral approach without trochanteric osteotomy. All patients were operated on using the Charnley Elite total hip prosthesis (DePuy) with both components cemented. As thromboprophylaxis, all patients received low molecular weight heparin (Klexane, Rhone-Poulenc Rorer), 40 mg subcutaneously, starting the day before surgery and continuing for 7–10 days. Cloxacillin or clindamycin was routinely given as antibiotic prophylaxis before surgery and on two more occasions on the day of surgery.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose:
Funding	Academic or government funding (Financial support was obtained from Malmö University Hospital funds.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -

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- Actual outcome: DVT at 43 days post-op; Group 1: 0/18, Group 2: 0/20 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 1 patient in the tranexamic acid group was operated on in a lateral recumbent position, using a posterior incision. Another patient in this group received 500 mL of dextran 70 as colloid substitution instead of Haes-steril.; Group 2 Number missing: 0 Protocol outcome 2: Blood (allogeneic or autologous) transfusion at - - Actual outcome: Number of people who had blood transfusions at During intervention; Group 1: 4/18, Group 2: 8/20 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 1 patient in the tranexamic acid group was operated on in a lateral recumbent position, using a posterior incision. Another patient in this group received 500 mL of dextran 70 as colloid substitution instead of Haes-steril.; Group 2 Number missing: 0 Protocol outcome 3: Total blood loss at - - Actual outcome: Total blood loss (perioperative and drains) at After intervention; Mean; , Comments: Mean (CI interval) TA group - 759 (630 - 889) Placebo - 996 (818 - 1174) ; Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 1 patient in the tranexamic acid group was operated on in a lateral recumbent position, using a posterior incision. Another patient in this group received 500 mL of dextran 70 as colloid substitution instead of Haes-steril.; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -; Blood loss: Haemoglobin level at 3 days after surgery

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Study	Bidolegui 2014[25]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in Argentina
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 6 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with osteoarthritis who are scheduled to have primary, unilateral total knee arthroplasty. All people had normal preoperative platelet count, normal prothrombin time, normal partial thromboplastin time, normal international normalized ratio
Exclusion criteria	Allergy to tranexamic acid, a prior history of thromboembolic disease, congenital or acquired coagulopathy, renal or liver dysfunction, myocardial infarction within the last 6 months or retinopathy.
Age, gender and ethnicity	Age - Mean (SD): Unclear. Gender (M:F): Unclear. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not applicable 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness

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Interventions	(n=25) Intervention 1: Perioperative use of tranexamic acid - IV. Two 15mg/kg (diluted in 100 cc of normal saline) 10-minute intravenous infusions.. Duration Surgery and 6 months follow-up. Concurrent medication/care: People were asked to perform a mechanical ankle pumping exercise regimen for deep vein thrombosis prophylaxis as soon as possible. All patients received subcutaneous enoxaparin 40 mg for 30 days starting 12 hours after surgery.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=25) Intervention 2: Placebo. Not detailed. Duration Surgery and 6 months follow-up. Concurrent medication/care: People were asked to perform a mechanical ankle pumping exercise regimen for deep vein thrombosis prophylaxis as soon as possible. All patients received subcutaneous enoxaparin 40 mg for 30 days starting 12 hours after surgery.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear
Funding	Other (Authors indicate no conflicts of interest)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 6 months of surgery; Group 1: 0/25, Group 2: 0/25
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Tranfsusion at Within 6 months of surgery;
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Length of stay at -
- Actual outcome: Length of stay at .; Group 1: mean 4.1 Days (SD 8.3); n=25, Group 2: mean 3.8 Days (SD 9.4); n=25
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low,

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Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Haemoglobin at 48 hours after surgery; Group 1: mean 10.3 g/dL (SD 1.2); n=25, Group 2: mean 9.3 g/dL (SD 0.9); n=25 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Total blood loss at -

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Study	Bradshaw 2012[27]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=46)
Countries and setting	Conducted in Australia
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Joint replacement surgery and 3 months follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with osteoarthritis undergoing primary total knee replacement.
Exclusion criteria	History of thromboembolic events, anticoagulation that could not be ceased within recommended timeframe, peripheral vascular disease, oral contraception, pregnancy, current bleeding at any site, immunocompromise from any condition, hypersensitivity to study medication, low creatinine clearance, significant hepatic disease.
Recruitment/selection of patients	People recruited from waiting list for surgery
Age, gender and ethnicity	Age - Mean (SD): 68. Gender (M:F): 27/19. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty

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Indirectness of population	No indirectness
Interventions	(n=26) Intervention 1: Perioperative use of tranexamic acid - Oral. 4 doses of 1500mg encapsulated tranexamic acid. First dose 8 hours before admission, unclear when second dose was given, third dose within 2 hours of surgery, fourth dose 6-8 hours after surgery. . Duration Surgical and post surgical period. Concurrent medication/care: 40mg enoxaparin administered daily beginning 12 hours after surgery and continuing for 14 days. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≥3000 mg (n=20) Intervention 2: Placebo. 4 doses of encapsulated inactive comparator. First dose 8 hours before admission, unclear when second dose was given, third dose within 2 hours of surgery, fourth dose 6-8 hours after surgery.. Duration During surgery and postoperative period. Concurrent medication/care: 40mg enoxaparin administered daily beginning 12 hours after surgery and continuing for 14 days.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Equipment / drugs provided by industry (Pfizer Australia provided active medication)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Surgery and 3 months follow-up; Group 1: 0/26, Group 2: 1/20
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at Surgery and 3 months follow-up; Group 1: 0/26, Group 2: 1/20
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Decrease in Hb at 24 hours after surgery; Group 1: mean -1.75 g/dL (SD 1.02); n=26, Group 2: mean -2.47 g/dL (SD 1.02); n=20 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -; Total blood loss at -

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Study	Camarasa 2006[28]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=95)
Countries and setting	Conducted in Spain
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 6 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People who needed unilateral, bicompartmental, primary, cemented TKR because of osteoarthritis or rheumatoid arthritis and were in the anaesthetic risk groups ASA I–III were invited to participate in the study.
Exclusion criteria	History of coagulopathy or thrombosis, embolism, or both or had received acenocoumarol,aspirin or platelet antiaggregant treatment in the week before surgery, or nonsteroidal antiinflammatory agents in the 2 days before surgery, preoperative plasma creatinine were greater than 130 mmol litre, they had a history of myocardial infarction or chronic arteriopathy, had unstable angina in the previous 12 months, or their mental states prevented them from understanding the study proposal.
Recruitment/selection of patients	March 2004 to March 2005.
Age, gender and ethnicity	Age - Mean (range): 72 (52-85), 73 (61-84). Gender (M:F): 21/74. Ethnicity: Not detailed

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of

Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness
Interventions	(n=35) Intervention 1: Perioperative use of tranexamic acid - IV. 2 doses of 10mg/kg. First during 30 minutes before tourniquet release, second 3 hours after first dose. All mixed with saline. . Duration During surgery and 40 days follow-up. Concurrent medication/care: Antithrombotic prophylaxis was started the night before surgery with dalteparin sodium 5000 iu and was continued daily for 40 days.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=60) Intervention 2: Placebo. 2 doses of saline. First during 30 minutes before tourniquet release, second 3 hours after first dose. All mixed with saline. . Duration During surgery and 40 days follow-up. Concurrent medication/care: Antithrombotic prophylaxis was started the night before surgery with dalteparin sodium 5000 iu and was continued daily for 40 days.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Academic or government funding (The trial was financed by a grant from the 'Acade`mia de Cie`ncies Me`diques de Catalunya i Balears'.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT
at 3 months after surgery; Group 1: 0/35, Group 2: 0/60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at In hospital period; Group 1: 1/35, Group 2: 23/60

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Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Reduction in haemoglobin at 5 days after surgery; Group 1: mean -2.6 g/dL (SD 1); n=35, Group 2: mean -3.4 g/dL (SD 1.2); n=60 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Total blood loss at - - Actual outcome: Total blood loss at 5 days after surgery; Group 1: mean 1095 mL (SD 473); n=35, Group 2: mean 1784 mL (SD 660); n=60 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -

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Study	Cankaya 2017[29]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in Turkey
Line of therapy	Not applicable
Duration of study	Intervention + follow up: During surgery and in-hospital period with 12 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People 55 to 85 years old with knee osteoarthrosis, undergoing primary total knee arthroplasty
Exclusion criteria	Rheumatological joint disease, allergic to tranexamic acid, previous knee surgery, anticoagulant therapy, preoperative anaemia, metabolic bone disease.
Age, gender and ethnicity	Age - Mean (SD): 66. Gender (M:F): 16/84. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Perioperative use of tranexamic acid - IA/topical+oral. Oral 25mg/kg (max 2g) given 2 hours before surgery. 1.5g in saline administered to the joint cavity during surgery. . Duration Perioperative

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	period. . Concurrent medication/care: Low dose LMWH administered to all people 12 hours before surgery. LMWH was also administered for 4 weeks after the surgery. A daily dose of enoxaparin sodium was administered subcutaneously. Compression socks used on postoperative day 2. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=50) Intervention 2: Perioperative use of tranexamic acid - IA/topical. 1.5g in saline administered to the joint cavity during surgery. . Duration Perioperative period. Concurrent medication/care: Low dose LMWH administered to all people 12 hours before surgery. LMWH was also administered for 4 weeks after the surgery. A daily dose of enoxaparin sodium was administered subcutaneously. Compression socks used on postoperative day 2. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL+ORAL versus IA/TOPICAL

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at 12 months after surgery; Group 1: 0/50, Group 2: 0/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at 3 days after surgery; Group 1: 0/50, Group 2: 3/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Postoperative bleeding at -
- Actual outcome: Post-operative drainage at 3 days after surgery; Group 1: mean 81 mL (SD 38); n=50, Group 2: mean 128 mL (SD 62); n=50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Hb level at 3 days after surgery; Group 1: mean 10.8 g/dL (SD 1.4); n=50, Group 2: mean 9.9 g/dL (SD 1.3); n=50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Total blood loss at - - Actual outcome: Calculated blood loss at 3 days after surgery; Group 1: mean 628 mL (SD 156); n=50, Group 2: mean 731 mL (SD 180); n=50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Length of stay at -

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Study	Cao 2018[30]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=108)
Countries and setting	Conducted in China; Setting: Single centre.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 3 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People undergoing primary unilateral total hip arthroplasty for osteoarthritis, osteonecrosis of the femoral head and developmental dysplasia of the hip.
Exclusion criteria	People with cardiovascular problems, history of DVT or PE, history of arterial thromboembolic event, known allergy to interventions of interest, renal insufficiency.
Age, gender and ethnicity	Age - Mean (SD): 56. Gender (M:F): 43/65. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Hip replacement
Indirectness of population	No indirectness
Interventions	(n=54) Intervention 1: Perioperative use of tranexamic acid - Oral. 20mg/kg IV administered 5-10 minutes

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	before fist incision. 2g given orally in 4 tablets at 4 hours, 10 hours and 16 hours after surgery. IV saline given at the same timepoints as the higher IV dose group. . Duration Before surgery and immediate postoperative period. Concurrent medication/care: Thromboprophylaxis: LMWH injected 6 hours after surgery and repeated every 24 hours until discharge. Then 10mg rivaroxaban taken once a day for 10 days.. Indirectness: Serious indirectness; Indirectness comment: Oral group given IV injection of tranexamic acid at an early stage. Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=54) Intervention 2: Perioperative use of tranexamic acid - IV. 20mg/kg IV administered 5-10 minutes before fist incision. 1g given IV in saline 6 hours, 12 hours and 18 hours after surgery. Oral placebo taken at the corresponding timepoint.. Duration During surgery and postoperative period. Concurrent medication/care: LMWH injected 6 hours after surgery and repeated every 24 hours until discharge. Then 10mg rivaroxaban taken once a day for 10 days.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL versus IV

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at within 3 months of surgery; Group 1: 0/54, Group 2: 2/54
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at During surgery or postoperative period; Group 1: 0/54, Group 2: 0/54
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Hb drop at 2 days after surgery; Group 1: mean -2.48 g/dL (SD 0.88); n=54, Group 2: mean -2.56 g/dL (SD 1.2); n=54

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Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Total blood loss at - - Actual outcome: Total blood loss at 24 hours after surgery; Group 1: mean 728.4 mL (SD 302); n=54, Group 2: mean 703.6 mL (SD 480); n=54 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -

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Study	Chen 2016[42]
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in China; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients eligible for simultaneous bilateral cemented total knee arthroplasty (TKAs) with a diagnosis of primary osteoarthritis
Exclusion criteria	Age less than 18, age greater than 80, bleeding or clotting disorders, preoperative anticoagulation therapy, renal disorders or insufficiency,cardiovascular problems, cerebrovascular conditions, thromboembolic disorders, preoperative anaemia, and allergy to TXA.
Recruitment/selection of patients	Between January 2013 and June 2015, all consecutive patients that were candidates for simultaneous bilateral cemented TKAs with a diagnosis of primary osteoarthritis at our institution were offered enrollment in the study.
Age, gender and ethnicity	Age - Mean (SD): TXA -66.5 (7.1) ; control- 64.2 (6.2). Gender (M:F): (%) females: TXA- 73.3; control- 76.7. Ethnicity: not stated

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Further population details	1. Co-morbidities: 2. Site/type of joint replacement:
Extra comments	.
Indirectness of population	--
Interventions	(n=60) Intervention 1: Perioperative use of tranexamic acid - IV. TXA group received one dose of TXA (10 mg/mL, total 1 g/100 mL) IV only 10 minutes before the tourniquet was inflated on the first knee for operation.. Duration 10 mins. Concurrent medication/care: Preventive oral anticoagulant therapy using rivaroxaban 10 mg per day was initiated 8 hours postoperatively for 14 days.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Comments: During the operation, all the drugs were handled by the circuit nurse, who was not involved in the study. The surgical procedures were performed by the same surgical team and conducted under general anaesthesia. After elevation of the lower extremity, a pneumatic tourniquet around the upper part of the thigh was inflated to a pressure of 300mmHg. A midline skin and medial parapatellar capsular incision was made to expose the knee joint.Appropriate type and size of knee prosthesis (NexGen [Zimmer, Warsaw, IN] orGenesis II [Smith & Nephew, Memphis TN]) was used. Closure was performed after haemostasis was achieved with electrocautery. A drain was placed in either knee and clamped for 120 minutes. The drainage volumes of bilateral knees were recorded until removal of the drains on the first postoperative day. The same protocol for postoperative management was used in both groups, which included bedside continuous passive motion machine therapy, physical therapy with partial weightbearing, and quadriceps and hamstring strengthening exercises starting on the second postoperative day. (n=60) Intervention 2: Placebo. Those in the control group received the equivalent volume of normal saline, with the same timing as the TXA group.. Duration 10 mins. Concurrent medication/care: Preventive oral anticoagulant therapy using rivaroxaban 10 mg per day was initiated 8 hours postoperatively for 14 days.. Indirectness: No indirectness; Indirectness comment: Transfusion indication protocols during the study period included a trigger threshold of haemoglobin (Hb) less than 80 g/L and anaemic or hypovolemic signs and symptoms unresponsive to fluid resuscitation. Further details: 1. Tranexamic acid dose:

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Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO Protocol outcome 1: Adverse events: DVT at - - Actual outcome: Adverse events (DVT, PE and transfusion related complications) at end of follow-up; Group 1: 0/60, Group 2: 0/60 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Blood (allogeneic or autologous) transfusion at - - Actual outcome: Patients transfused with allogenic blood at end of follow-up; Group 1: 36/60, Group 2: 58/60 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Maximum decline of Hb at end of follow-up; Group 1: mean -4.24 g/dL (SD 1.47); n=60, Group 2: mean -4.84 g/dL (SD 1.43); n=60 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Total blood loss at - - Actual outcome: Total blood loss (ml) at peri operative; Group 1: mean 1739.5 (SD 609.1); n=60, Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -

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Study	Chen 2016[38]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in Singapore; Setting: One hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery with 30 days follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People aged from 50 to 85 with osteoarthritis of the knee and scheduled for an elective primary TKA
Exclusion criteria	People with a history of renal impairment, cardiovascular diseases, cerebrovascular conditions, history of thromboembolic disease, bleeding disorder or receiving anticoagulant drug treatment.
Recruitment/selection of patients	October 2013 to March 2014
Age, gender and ethnicity	Age - Mean (SD): 65 (8). Gender (M:F): 25/75. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness

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Interventions	(n=50) Intervention 1: Perioperative use of tranexamic acid - IV. 1500mg diluted in 100ml saline given as an infusion over 20 minutes after cementing the prostheses.. Duration Surgery and followed for 30 days after hospital discharge. Concurrent medication/care: Pneumatic calf pumps were given immediately postoperative until the person begins to ambulate. LMWH given from first postoperative day until hospital discharge. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg (n=50) Intervention 2: Perioperative use of tranexamic acid - IA/topical. 1500mg diluted in 100ml saline was given as an IA wash after cementing the prostheses.. Duration Surgery and followed for 30 days after hospital discharge. Concurrent medication/care: Pneumatic calf pumps were given immediately postoperative until the person begins to ambulate. LMWH given from first postoperative day until hospital discharge. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg
Funding	No funding (Authors not funded)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus IA/TOPICAL

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at within 30 days of surgery; Group 1: 0/50, Group 2: 0/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at In hospital period; Group 1: 2/50, Group 2: 1/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Hb level at 4 days after surgery; Group 1: mean 10.9 g/dL (SD 2.7); n=50, Group 2: mean 10.3 g/dL (SD 3.4); n=50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Total blood loss at - - Actual outcome: Total blood loss at 4 days after surgery; Group 1: mean 730 mL (SD 725); n=50, Group 2: mean 799 mL (SD 909); n=50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -

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Study	Claeys 2007[44]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Belgium
Line of therapy	Not applicable
Duration of study	Intervention time: During surgery with follow-up until at least 10 days after surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People ASA I-II undergoing unilateral elective primary total hip replacement.
Exclusion criteria	Allergy to tranexamic acid, preoperative renal or hepatic dysfunction, known bleeding disorder, preoperative coagulation anomalies, anticoagulant or aspirine-like medication, long acting NSAID medication.
Age, gender and ethnicity	Age - Mean (SD): 70. Gender (M:F): 12/28. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Hip replacement
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Perioperative use of tranexamic acid - IV. 15mg/kg single slow IV injection 15 minutes before first incision. . Duration Surgical period. Concurrent medication/care: LMWH on evening before

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	surgery and continued postoperatively for 10 days. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=20) Intervention 2: Placebo. Saline slow IV injection 15 minutes before first incision. . Duration Surgical period. Concurrent medication/care: LMWH on evening before surgery and continued postoperatively for 10 days.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at 10 days after surgery; Group 1: 3/17, Group 2: 0/18
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: TXA group older and heavier; Group 1 Number missing: 3, Reason: Refused assessment; Group 2 Number missing: 2, Reason: Refused assessment

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at After 24 hours; Group 1: 1/20, Group 2: 6/20
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: TXA group older and heavier; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Surgical bleeding at -
- Actual outcome: Peroperative blood loss at .; Group 1: mean 423 mL (SD 174); n=20, Group 2: mean 516 mL (SD 167); n=20
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: TXA group older and heavier; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery

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- Actual outcome: Hb level at After 24 hours; Group 1: mean 11.1 g/dL (SD 1.4); n=20, Group 2: mean 10.5 g/dL (SD 1); n=20 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: TXA group older and heavier; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Total blood loss at - - Actual outcome: Total blood loss at After 24 hours; Group 1: mean 801 mL (SD 244); n=20, Group 2: mean 1038 mL (SD 289); n=20 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: TXA group older and heavier; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -

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Study	Clave 2019[45]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=229)
Countries and setting	Conducted in France; Setting: 4 French medical centres,
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 3 months follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults awaiting primary elective THA
Exclusion criteria	Did not consent, rapidly destructive osteoarthritis of the hip, not registered with national social security system, major TXA contraindications such as epilepsy or renal failure, already receiving antiplatelet agents or anticoagulants, ischaemic arterial disease, previous VTE, contraindication to rivaroxaban, Child B-Stage cirrhosis with coagulopathy.
Recruitment/selection of patients	Enrolled October 2015 to May 2017.
Age, gender and ethnicity	Age - Mean (SD): 64 (12), 65 (12), 67 (11). Gender (M:F): 98/131. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Hip replacement

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Indirectness of population	No indirectness
Interventions	(n=75) Intervention 1: Placebo. Placebo IV at 0, 3, 7 and 11 hours after surgery. . Duration Surgery and 3 months follow-up. Concurrent medication/care: 10mg oral rivaroxaban beginning 6 to 10 hours after surgery and then daily for 35 days. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable (n=76) Intervention 2: Perioperative use of tranexamic acid - IV. Short acting tranexamic acid at 0 (incision) and then 3 hours postoperatively. Placebo at 7 and 11 hours after surgery. . Duration Surgery and 3 months follow-up. Concurrent medication/care: 10mg oral rivaroxaban beginning 6 to 10 hours after surgery and then daily for 35 days. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg (2g). (n=78) Intervention 3: Perioperative use of tranexamic acid - IV. Tranexamic acid at 0 (incision) and then 3, 7 and 11 hours after surgery. . Duration Surgery and 3 months follow-up. Concurrent medication/care: 10mg oral rivaroxaban beginning 6 to 10 hours after surgery and then daily for 35 days. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≥3000 mg (4g).
Funding	Study funded by industry (Bayer Pharmaceutical grant)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SHORT IV versus PLACEBO

Protocol outcome 1: Mortality at 30 day
- Actual outcome: Fatal bleeding at During hospital stay; Group 1: 0/76, Group 2: 0/75
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Adverse events: acute myocardial infarction at -
- Actual outcome: Acute coronary syndrome at During hospital stay; Group 1: 0/76, Group 2: 0/75

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Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Adverse events: DVT at -
- Actual outcome: VTE at During hospital stay; Group 1: 0/76, Group 2: 0/75
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Blood transfusion at During hospital stay; Group 1: 4/70, Group 2: 5/64
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: 1 withdrew consent, 1 missing data, 3 population, 1 unclear; Group 2 Number missing: 11, Reason: 2 withdrew consent, 3 missing data, 1 population, 5 unclear

Protocol outcome 5: Length of stay at -
- Actual outcome: Length of stay at .; Group 1: mean 4.7 days (SD 2.86); n=76, Group 2: mean 4.8 days (SD 1.7); n=75
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 6: Total blood loss at -
- Actual outcome: Real blood loss at 3 days after surgery; Group 1: mean 833.1 ml (SD 584.1); n=74, Group 2: mean 1361.6 ml (SD 861.5); n=70
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 1 withdrew consent, 1 missing data; Group 2 Number missing: 5, Reason: 2 withdrew consent, 3 missing data

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LONG IV versus PLACEBO

Protocol outcome 1: Mortality at 30 day
- Actual outcome: Fatal bleeding at During hospital stay; Group 1: 0/78, Group 2: 0/75
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 2: Adverse events: acute myocardial infarction at -
- Actual outcome: Acute coronary syndrome at During hospital stay; Group 1: 1/78, Group 2: 0/75
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Adverse events: DVT at -
- Actual outcome: VTE at During hospital stay; Group 1: 0/78, Group 2: 0/75
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Blood transfusion at During hospital stay; Group 1: 2/70, Group 2: 5/64
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8, Reason: 1 withdrew consent, 3 missing data, 3 population, 1 unclear; Group 2 Number missing: 11, Reason: 2 withdrew consent, 3 missing data, 1 population, 5 unclear

Protocol outcome 5: Length of stay at -
- Actual outcome: Length of stay at .; Group 1: mean 4.3 days (SD 2.06); n=78, Group 2: mean 4.8 days (SD 1.8); n=75
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 6: Total blood loss at -
- Actual outcome: Real blood loss at 3 days after surgery; Group 1: mean 807.8 ml (SD 506.7); n=74, Group 2: mean 1361.6 ml (SD 861.5); n=70
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: 1 withdrew consent, 3 missing data; Group 2 Number missing: 5, Reason: 2 withdrew consent, 3 missing data

Protocol outcomes not reported by the study	Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Blood loss: Haemoglobin level at 3 days after surgery

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Study	Cvetanovich 2018[48]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=110)
Countries and setting	Conducted in USA; Setting: Hospital
Line of therapy	1st line
Duration of study	Follow up (post intervention):
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing a unilateral primary anatomic or reverse primary total shoulder arthroplasty TSA at a single institution.
Exclusion criteria	Allergy to TXA, acquired disturbances of colour vision,preoperative use of anticoagulant therapy within 5 days of surgery, history of arterial or venous thromboembolic disease (including deep venous thrombosis,pulmonary embolism, stroke, transient ischemic attack), ongoing pregnancy or breast-feeding,recent myocardial infarction (within 6 months before surgery), cardiac stent placement, renal impairment, haemophilia, refusal of blood products, revisionTSA, TSA performed for the indications of acute proximal humeral fracture, or prior open shoulder surgery, including failed open reduction and internal fixation of proximal humeral fractures.
Recruitment/selection of patients	Enrollment period from September 2015 to November 2016. 376 patients underwent primary anatomic or

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	reverse TSA.
Age, gender and ethnicity	Age - Mean (SD): 66.4 ± 10.1. Gender (M:F): 47.2% were male (51 of 108). Ethnicity: not stated
Further population details	1. Co-morbidities: 2. Site/type of joint replacement: Shoulder arthroplasty
Extra comments	Patients who underwent prior arthroscopic shoulder procedures were eligible to participate.
Indirectness of population	No indirectness
Interventions	(n=52) Intervention 1: Perioperative use of tranexamic acid - IV. 1g of IV TXA diluted in 10 mL normal saline (X-GenPharmaceuticals, Inc., Horseheads, NY, USA). This dose of TXA was chosen because it was a standard practice at the institution to administer 1 g IV TXA 10 minutes before the incision for total hip and knee arthroplasty.. Duration 10 mins before incision. Concurrent medication/care: NR. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Comments: Patients underwent standard postoperative care, including admission to the hospital for at least 1 night. Patients were monitored by a hospitalist while in the hospital and received occupational therapy. Patients had sequential compression devices for deep venous thrombosis prophylaxis during their hospital stay. The patients underwent daily complete blood count,including measurement of haemoglobin, for as long as they remained in the hospital. (n=56) Intervention 2: Placebo. 10 mL of IV normal saline placebo. Duration 10 min before incision. Concurrent medication/care: NR. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Comments: Patients underwent transfusion if their postoperative haemoglobin dropped below 7.0 g/dL or for higher haemoglobin values only for specific medical indications specified by the consulting hospitalist attending.
Funding	Funding not stated

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RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at end of follow-up; Group 1: 0/52, Group 2: 1/56
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Patients needing transfusion at end of follow-up; Group 1: 0/52, Group 2: 0/56
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Length of stay at -
- Actual outcome: Length of stay at end of follow-up; Group 1: mean 1.8 (SD 1); n=52, Group 2: mean 1.8 (SD 1.2); n=56
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Total haemoglobin loss at peri-operative; Group 1: mean -1.522 g/dL (SD 0.573); n=52, Group 2: mean -1.78 g/dL (SD 0.658); n=56
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Total blood loss at -
- Actual outcome: Post-operative blood loss at post-operative; Group 1: mean 1100.9 ml (SD 367.4); n=52, Group 2: mean 1274.5 ml (SD 460); n=56;
Comments: The outcome is based on a formula accounting for initial patient haemoglobin, the lowest post-operative haemoglobin and patient blood volume approximated based on patient sex, height and weight. This method of calculating blood loss intended to account for intraoperative and post-operative losses including bleeding in to soft tissues.
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover -

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Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -

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Study	Digas 2015[56]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in Greece
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery period and 12 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People under 85 years old with primary osteoarthritis who we scheduled for total knee arthroplasty.
Exclusion criteria	Secondary osteoarthritis, history of thromboembolic disease, bleeding disorders, history of hepatic or renal dysfunction, severe cardiac respiratory disease.
Recruitment/selection of patients	February 2012 to May 2013.
Age, gender and ethnicity	Age - Mean (SD): 70. Gender (M:F): 11/79. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness

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Interventions	(n=30) Intervention 1: No treatment. No details provided. Duration Surgical period. Concurrent medication/care: Thromboprophylaxis: 3,500 IU tinzaparin sodium for 30 days from first postoperative day. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable (n=30) Intervention 2: Perioperative use of tranexamic acid - IV. 15mg/kg IV before deflation of the tourniquet. . Duration Surgical period. . Concurrent medication/care: Thromboprophylaxis: 3,500 IU tinzaparin sodium for 30 days from first postoperative day.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=30) Intervention 3: Perioperative use of tranexamic acid - IA/topical. 2g IA after skin closure. Duration Surgical period. . Concurrent medication/care: Thromboprophylaxis: 3,500 IU tinzaparin sodium for 30 days from first postoperative day.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus NO TREATMENT

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at within 1 year of surgery; Group 1: 1/30, Group 2: 0/30
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at 5 days after surgery; Group 1: 7/30, Group 2: 13/30
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Surgical bleeding at -

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- Actual outcome: Intra-operative blood loss at .; Group 1: mean 285 mL (SD 26); n=30, Group 2: mean 277 mL (SD 22); n=30
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Change in Hb at 5 days after surgery; Group 1: mean -2.24 g/dL (SD 0.93); n=30, Group 2: mean -2.8 g/dL (SD 0.77); n=30
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Total blood loss at -
- Actual outcome: Total blood loss at 5 days after surgery; Group 1: mean 1086 mL (SD 559); n=30, Group 2: mean 1455 mL (SD 635); n=30
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus IA/TOPICAL

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at within 1 year of surgery; Group 1: 1/30, Group 2: 0/30
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at 5 days after surgery; Group 1: 7/30, Group 2: 5/30
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Surgical bleeding at -
- Actual outcome: Intra-operative blood loss at .; Group 1: mean 285 mL (SD 26); n=30, Group 2: mean 235 mL (SD 23); n=30
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery

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- Actual outcome: Change in Hb at 5 days after surgery; Group 1: mean -2.24 g/dL (SD 0.93); n=30, Group 2: mean -2.26 g/dL (SD 0.99); n=30
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Total blood loss at -
- Actual outcome: Total blood loss at 5 days after surgery; Group 1: mean 1086 mL (SD 559); n=30, Group 2: mean 943 mL (SD 477); n=30
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus NO TREATMENT

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at within 1 year of surgery; Group 1: 0/30, Group 2: 0/30
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at 5 days after surgery; Group 1: 5/30, Group 2: 13/30
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Surgical bleeding at -
- Actual outcome: Intra-operative blood loss at .; Group 1: mean 235 mL (SD 23); n=30, Group 2: mean 277 mL (SD 22); n=30
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Change in Hb at 5 days after surgery; Group 1: mean -2.26 g/dL (SD 0.99); n=30, Group 2: mean -2.8 g/dL (SD 0.77); n=30
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Total blood loss at -

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- Actual outcome: Total blood loss at 5 days after surgery; Group 1: mean 943 mL (SD 477); n=30, Group 2: mean 1455 mL (SD 635); n=30 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -

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Study	Ekback 2000[60]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Sweden; Setting: hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing total hip replacement (THR)
Exclusion criteria	NR
Recruitment/selection of patients	NR
Age, gender and ethnicity	Age - Mean (SD): TXA 66.4 (9.0); control: 65.6 (8.8) . Gender (M:F): TXA: 9/11; control: 11/9. Ethnicity: not stated
Further population details	1. Co-morbidities: 2. Site/type of joint replacement:
Indirectness of population	No indirectness

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Interventions	(n=20) Intervention 1: Perioperative use of tranexamic acid - IV. Patients received a first bolus dose of 10 mg/kg of TXA before surgical incision. A continuous infusion of 1.0 mg/ kg/h for 10 h was then started immediately after the first bolus dose. A second bolus dose of 10mg/kg body weight was given 3 h later to counteract potential dilutive effects of intraoperative auto transfusion on TXA concentrations in blood.. Duration Pre and post surgical period. Concurrent medication/care: Preoperative oral iron therapy (100– 200 mg) was given daily. Platelet-inhibiting drugs had been withdrawn 10 days preoperatively. Thromboprophylaxis with low molecular weight heparin (Dalteparin; Pharmacia-Upjohn, Stockholm, Sweden) was administered subcutaneously from the evening before surgery up to Day 10 postoperatively. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Comments: The patients were operated on in a horizontal lateral position. After lavage with saline, a polyethylene plug was inserted in the bottom of the drilled cavity. Vacuum-mixed cement was injected with a syringe in a retrograde direction. The proximal femur was sealed, and additional cement was injected under pressure. The femoral prosthesis was inserted during the viscous phase of the cement. (n=20) Intervention 2: Placebo. Control group and got the same treatment as TXA group but with a placebo drug (physiological saline).. Duration Pre and post operative period. Concurrent medication/care: Preoperative oral iron therapy (100– 200 mg) was given daily. Platelet-inhibiting drugs had been withdrawn 10 days preoperatively. Thromboprophylaxis with low molecular weight heparin (Dalteparin; Pharmacia-Upjohn, Stockholm, Sweden) was administered subcutaneously from the evening before surgery up to Day 10 postoperatively. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose:

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Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO Protocol outcome 1: Adverse events: DVT at - - Actual outcome: DVT at Post operative; Group 1: 1/20, Group 2: 1/20 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Blood (allogeneic or autologous) transfusion at - - Actual outcome: Allogenic transfused patients at Peri operative; Group 1: 1/20, Group 2: 1/20 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -; Blood loss: Haemoglobin level at 3 days after surgery; Total blood loss at -

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Study	Fillingham 2016[64]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=78)
Countries and setting	Conducted in USA; Setting: Single centre
Line of therapy	Not applicable
Duration of study	Intervention time: Surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People scheduled to undergo unilateral primary TKA
Exclusion criteria	Known allergy to TXA, history of renal failure or kidney transplant, a history of arterial thromboembolic event within the past year, placement of an arterial stent within the past year, a history of thromboembolic event, or refusal to receive blood products.
Age, gender and ethnicity	Age - Mean (SD): 62 (11), 63 (10). Gender (M:F): 24/47. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Perioperative use of tranexamic acid - Oral. 1950 mg (3 tablets of 650 mg)

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	approximately 2 hours before incision and given an IV placebo of 10-mL normal saline immediately before wound closure.. Duration Surgery with unclear follow-up. Concurrent medication/care: Thromboprophylaxis: warfarin with initiated a therapeutic INR goal of 1.8-2.2 on the international normalized ratio on postoperative day 0. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg (n=38) Intervention 2: Perioperative use of tranexamic acid - IV. 1 g TXA (diluted in 10-mL normal saline) given as an IV bolus immediately before wound closure and received 750 mg of placebo (ascorbic acid in 3 tablets of 250 mg) approximately 2 hours before incision. Duration Surgery with unclear follow-up. Concurrent medication/care: Thromboprophylaxis: warfarin with initiated a therapeutic INR goal of 1.8-2.2 on the international normalized ratio on postoperative day 0. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≤1000 mg
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL versus IV

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: Thromboembolic event at within 30 days of discharge; Group 1: 0/34, Group 2: 0/37
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: 6 did not receive intervention ; Group 2 Number missing: 1, Reason: 1 did not receive intervention

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at By discharge from hospital; Group 1: 1/34, Group 2: 1/37
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: 6 did not receive intervention ; Group 2 Number missing: 1, Reason: 1 did not receive intervention

Protocol outcome 3: Length of stay at -
- Actual outcome: Length of hospital stay at .; Group 1: mean 3 days (SD 1); n=34, Group 2: mean 3 days (SD 1); n=37

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Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: 6 did not receive intervention ; Group 2 Number missing: 1, Reason: 1 did not receive intervention Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Reduction in haemoglobin at Discharge from hospital; Group 1: mean -3.45 g/dL (SD 0.93); n=34, Group 2: mean -3.31 g/dL (SD 0.95); n=37 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: 6 did not receive intervention ; Group 2 Number missing: 1, Reason: 1 did not receive intervention Protocol outcome 5: Total blood loss at - - Actual outcome: Total blood loss at By discharge from hospital; Group 1: mean 1281 mL (SD 265); n=34, Group 2: mean 1231 mL (SD 253); n=37 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: 6 did not receive intervention ; Group 2 Number missing: 1, Reason: 1 did not receive intervention	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -

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Study	**Garneti 2004**[74]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in United Kingdom; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with a diagnosis of primary osteoarthritis of the hip necessitating total hip arthroplasty (THA)
Exclusion criteria	NR
Recruitment/selection of patients	Fifty patients with a diagnosis of primary osteoarthritis of the hip necessitating THA were recruited.
Age, gender and ethnicity	Age - Mean (SD): NR. Gender (M:F): NR. Ethnicity: not stated
Further population details	1. Co-morbidities: 2. Site/type of joint replacement:

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Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Perioperative use of tranexamic acid - IV. 10 mg/kg of intravenous tranexamic acid as a bolus at anaesthesia. A dose of 10 mg/kg was suggested by the Drug Information Department at Cheltenham General Hospital, after contacting Pharmacia . Duration Intra-operative. Concurrent medication/care: All patients were given regular medication peri-operatively. None of them received medication that will influence surgical blood loss. Thromboembolic deterrent stockings and foot pumps were used postoperatively, but no patient received pharmacologic thrombotic prophylaxis for 48 hours after surgery. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: (n=25) Intervention 2: Placebo. 10 mg/kg of intravenous normal saline (placebo) as a bolus at anaesthesia . Duration intra-operative. Concurrent medication/care: All patients were given regular medication peri-operatively. None of them received medication that will influence surgical blood loss. Thromboembolic deterrent stockings and foot pumps were used postoperatively, but no patient received pharmacologic thrombotic prophylaxis for 48 hours after surgery. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose:
Funding	Funding not stated

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RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO Protocol outcome 1: Blood (allogeneic or autologous) transfusion at - - Actual outcome: Transfusion at Peri operative; Group 1: 14/25, Group 2: 16/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Postoperative bleeding at - - Actual outcome: Post-operative blood loss (ml) at Post operative; Group 1: mean 411 (SD 220); n=25, Group 2: mean 353 (SD 311); n=25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Total blood loss at - - Actual outcome: External and internal blood loss (ml) at Post operative; Group 1: mean 1443 (SD 809); n=25, Group 2: mean 1340 (SD 665); n=25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Adverse events: DVT at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Length of stay at -; Blood loss: Haemoglobin level at 3 days after surgery

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Study	**Gautam 2011[75]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 study (n=40)
Countries and setting	Conducted in India; Setting: Tertiary care hospital,
Line of therapy	Not applicable
Duration of study	Intervention time: Surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People scheduled for elective primary unilateral TKR for osteoarthritis
Exclusion criteria	History or evidence of coagulopathy and bleeding disorders, renal dysfunction, current use of antiplatelet medication and anticoagulants, acute infection, history of malignancy or coronary artery disease and thromboembolic event, 1 year prior to surgery, haemoglobin less than 8 g/dl.
Age, gender and ethnicity	Age - Mean (SD): 66 (6), 65 (10). Gender (M:F): 16/24. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness

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Interventions	(n=20) Intervention 1: Perioperative use of tranexamic acid - IV. 10 mg/kg IV, approximately half an hour before deflation of tourniquet. Duration Surgical period. Concurrent medication/care: No thromboprophylaxis detailed. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=20) Intervention 2: Placebo. Normal saline (placebo) at the same time as the test group . Duration During surgery. Concurrent medication/care: No thromboprophylaxis detailed. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at During hospital period; Group 1: 7/20, Group 2: 15/20
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Postoperative bleeding at -
- Actual outcome: Postoperative blood loss at During hospital period; Group 1: mean 272.5 mL (SD 122.51); n=20, Group 2: mean 685 mL (SD 118.21); n=20
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Hb level at 5 days after surgery; Group 1: mean 11.11 g/dL (SD 1.56); n=20, Group 2: mean 10.42 g/dL (SD 1.44); n=20
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 4: Total blood loss at - - Actual outcome: Total blood loss (calculated) at During hospital period; Group 1: mean 427.6 mL (SD 129.56); n=20, Group 2: mean 911.5 mL (SD 261.08); n=20 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Adverse events: DVT at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Length of stay at -

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Study	Gautam 2013[76]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=27)
Countries and setting	Conducted in India; Setting: Department of orthopaedics, Maulana Azad Medical College and associated Lok Nayak Hospital
Line of therapy	Not applicable
Duration of study	Intervention time: Surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People having total knee arthroplasty
Exclusion criteria	Allergic to tranexamic acid or having inherited or acquired hypercoagulable state, abnormal coagulation profile (BT, CT, platelet count, prothrombin time, aPTT), patients who had taken aspirin or other NSAIDS 3 days prior to surgery, patients with renal insufficiency or history of deep vein thrombosis or pulmonary embolism and people who were at risk of these
Age, gender and ethnicity	Age - Mean (range): 61 (45-80), 56 (45-65). Gender (M:F): 10/17. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness

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Interventions	(n=14) Intervention 1: Perioperative use of tranexamic acid - IV. 10 mg/kg body weight given by slow intravenous injection ten minutes before deflation of tourniquet.. Duration Surgical period. Concurrent medication/care: Thromboprophylaxis: In the immediate postoperative period static quadriceps exercises and ankle range of motion exercises were started. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=13) Intervention 2: No treatment. Tranexamic acid not administered. Duration Surgical period. Concurrent medication/care: Thromboprophylaxis: In the immediate postoperative period static quadriceps . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus NO TREATMENT Protocol outcome 1: Adverse events: DVT at - - Actual outcome: DVT at 2nd postoperative day; Group 1: 0/14, Group 2: 0/13 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Total blood loss at - - Actual outcome: Blood loss at Unclear; Group 1: mean 266.2 mL (SD 83.87); n=14, Group 2: mean 667.5 mL (SD 111.48); n=13 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Blood (allogeneic or autologous)

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study	transfusion at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -; Blood loss: Haemoglobin level at 3 days after surgery

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Study	George 2018[77]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=113)
Countries and setting	Conducted in India
Line of therapy	Unclear
Duration of study	Intervention + follow up: Surgery and 6 weeks follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with osteoarthritis who are scheduled for a primary unilateral cemented TKA
Exclusion criteria	Allergy to tranexamic acid, elevated renal function tests, history of thromboembolic events, coronary artery heart disease, malignancies. Ssevere preoperative anaemia, thrombocytopenia, coagulation test abnormalities, treatment with Aspirin, NSAIDs or anticoagulants within one week of surgery
Recruitment/selection of patients	January 2017 and June 2017.
Age, gender and ethnicity	Age - Mean (SD): 64. Gender (M:F): 38/75. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty

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Indirectness of population	No indirectness
Interventions	(n=58) Intervention 1: Perioperative use of tranexamic acid - IA/topical. 1.5g in 100 mL of normal saline solution, which was poured into the joint before wound closure. . Duration Surgery and 6 weeks follow up. Concurrent medication/care: Prophylaxis protocol against venous thromboembolism included bilateral intermittent pneumatic calf pumps (mechanical) and Enoxaparin 40 mg subcutaneous daily for the first two postoperative days followed by oral Aspirin 300 mg daily for six weeks.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg (n=55) Intervention 2: Perioperative use of tranexamic acid - IV. 10 mg/kg body weight over 10 min before tourniquet inflation and again 10 mg/kg at tourniquet release. Maximum rate of administration did not exceed 100 mg/min.. Duration Surgery and 6 weeks follow up. Concurrent medication/care: Prophylaxis protocol against venous thromboembolism included bilateral intermittent pneumatic calf pumps (mechanical) and Enoxaparin 40 mg subcutaneous daily for the first two postoperative days followed by oral Aspirin 300 mg daily for six weeks.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	No funding (No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus IV

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at within 6 weeks of surgery; Group 1: 0/58, Group 2: 0/55
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at 3 days after surgery; Group 1: 3/58, Group 2: 0/55

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Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Total blood loss at - - Actual outcome: Total blood loss at 3 days after surgery; Group 1: mean 672.2 mL (SD 368); n=58, Group 2: mean 666.1 mL (SD 368); n=55 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -; Blood loss: Haemoglobin level at 3 days after surgery

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Study (subsidiary papers)	Georgiadis 2013[78] (Georgiadis 2013[79])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=101)
Countries and setting	Conducted in USA; Setting: Tertiary care Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing unilateral primary total knee arthroplasty (TKA)
Exclusion criteria	Religious objection to autologous blood transfusion,preoperative use of anticoagulant medication seven days prior to surgery,history of fibrinolytic disorder or blood dyscrasia, cerebrovascular accident(CVA), myocardial infarction (MI), New York Heart Association Class III or IVheart failure (NYHA III-IV), atrial fibrillation, history of deep vein thrombosis (DVT) or pulmonary embolus (PE), preoperative International Normalized Ratio (INR) N 1.4, activated partial thromboplastin time (aPTT) N 1.4× normal, platelets b 140,000/mm3, or renal failure defined as creatinine N 1.1mg/dL or glomerular filtration rate b 60 mL/min/1.73 m2
Recruitment/selection of patients	All patients undergoing unilateral primary TKA between June2011 and September 2012 were considered eligible for inclusion

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Age, gender and ethnicity	Age - Mean (SD): placebo: 64.5 (8.2); TXA: 67 (9). Gender (M:F): M/F: placebo- 12/39; TXA: 19/31. Ethnicity: not stated
Further population details	1. Co-morbidities: 2. Site/type of joint replacement:
Extra comments	All patients meeting inclusion criteria were identified prior to a scheduled outpatient visit 1–3 weeks antedating their arthroplasty.
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Perioperative use of tranexamic acid - IA/topical. Topical application of TXA. Tranexamic acid (2.0 g in 75 mLnormal saline) was sterilely prepared by a non-affiliated compounding pharmacy with no involvement in patient care and was delivered to the institution's research pharmacy. Pre-trial testing was performed on compounded TXA beyond the recommended refrigerated shelf life of two weeks. Greater than 97.6% potency was confirmed after four weeks at room temperature, and these storage conditions were used for the remainder of the trial. The treatment dose of TXA in this study was chosen by past studies suggesting that 10 to 20 mg/kg intravenously or 1.5–3.0 g topically had high efficacy in decreasing blood loss in TKA.. Duration Post-operative period. Concurrent medication/care: For DVT prophylaxis all patients were maintained on two weeks of a low-molecular-weight heparin, enoxaparin (Lovenox, Sanofi-Aventis, Bridgewater,NJ), administered subcutaneously twice daily. First administration of enoxaparin was performed on the evening of the operative day unless this fell less than 6 h from surgical end time, in which case it would be administered the morning of the first postoperative day.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: (n=51) Intervention 2: Placebo. Topical application. placebo solution (75 mL normal saline)was sterilely prepared by a non-affiliated compounding pharmacy with no involvement in patient care and was delivered to the institution's research pharmacy.. Duration post-operative period. Concurrent medication/care: For DVT prophylaxis all patients were maintained on two weeks of a low-molecular-weight heparin, enoxaparin (Lovenox, Sanofi-Aventis, Bridgewater,NJ), administered subcutaneously twice daily. First administration of enoxaparin was performed on the evening of the operative day unless this fell less than 6 h from surgical end time, in which case it would be administered the morning of the first postoperative day.. Indirectness:

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	No indirectness Further details: 1. Tranexamic acid dose: Comments: All participants underwent femoral nerve block preoperatively,and were administered spinal or general anaesthetic after patient discussion with the anaesthesia team.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at perioperative; Group 1: 4/50, Group 2: 9/51
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: transfusion at perioperative; Group 1: 0/50, Group 2: 4/51
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Length of stay at -
- Actual outcome: length of stay (days) at perioperative; Group 1: mean 2.7 (SD 1); n=50, Group 2: mean 2.8 (SD 0.8); n=51
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Hb loss (g/dl) at post-operative; Group 1: mean -2.5 g/dL (SD 0.8); n=50, Group 2: mean -3.3 g/dL (SD 1.2); n=51
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2

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Number missing: Protocol outcome 5: Total blood loss at - - Actual outcome: blood loss (ml) at perioperative; Group 1: mean 940.2 (SD 327.1); n=50, Group 2: mean 1293.1 (SD 532.7); n=51 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -

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Study	Gillespie 2015[84]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=118)
Countries and setting	Conducted in USA; Setting: 2 treatment centres with 2 surgeons undertaking the operations.
Line of therapy	Not applicable
Duration of study	Intervention time: During surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People undergoing conventional total shoulder arthroplasty or reverse total shoulder arthroplasty.
Exclusion criteria	Revision surgery, history of cardiac disease, liver disease, renal disease, low preoperative Hb level or hematocrit level, severe joint deformity, history of peripheral vascular disease, history of joint infection, history of bleeding, history of DVT or PE, person unwilling to accept blood transfusion, allergy to tranexamic acid.
Recruitment/selection of patients	Volunteers. October 2012 to June 2014.
Age, gender and ethnicity	Age - Mean (SD): 67. Gender (M:F): 52/66. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Shoulder arthroplasty

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Indirectness of population	No indirectness
Interventions	(n=61) Intervention 1: Perioperative use of tranexamic acid - IA/topical. 2g in 100ml saline poured into surgical wound before closure and left in place for 5 minutes. . Duration During surgery. Concurrent medication/care: No thromboembolic prophylaxis specified. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg (n=57) Intervention 2: Placebo. 100ml saline poured into surgical wound before closure and left in place for 5 minutes.. Duration During surgery. Concurrent medication/care: No thromboembolic prophylaxis specified. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: Postoperative complications at Unclear; Group 1: 0/56, Group 2: 0/55
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at Unclear; Group 1: 0/56, Group 2: 0/55
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -; Blood loss: Haemoglobin level at 3 days after surgery; Total blood loss at -

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Study	Gomez-Barrena 2014[85]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=78)
Countries and setting	Conducted in Spain; Setting: Single centre.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 30 days follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults scheduled for primary unilateral total knee replacement with cemented implants.
Exclusion criteria	Allergic to tranexamic acid, major comorbidities, coagulopathy, history of arterial or venous thromboembolic disease, hematologic disorder, retinopathy, refusal of blood products, pregnant or breastfeeding, participation in another trial in the previous year.
Age, gender and ethnicity	Age - Mean (SD): 70 (9), 72 (10). Gender (M:F): 27/51. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness
Interventions	(n=39) Intervention 1: Perioperative use of tranexamic acid - IA/topical. 3g in 100ml of saline. Half

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	administered by irrigation before joint closure. Half administered after joint closure. IV placebo with saline. . Duration Surgery and 2 weeks follow-up. Concurrent medication/care: Thromboprophylaxis: daily subcutaneous injection of 40mg enoxaparin for 2 weeks beginning 6 hours after surgery. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≥3000 mg (n=39) Intervention 2: Perioperative use of tranexamic acid - IV. 15mg/kg in 100ml saline slowly infused for fifteen to twenty minutes before tourniquet release. A second identical dose given 3 hours after surgery. IA placebo with saline. . Duration Surgery and 2 weeks follow-up. Concurrent medication/care: Thromboprophylaxis: daily subcutaneous injection of 40mg enoxaparin for 2 weeks beginning 6 hours after surgery. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear
Funding	Study funded by industry (Research grant from SERDOSA)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus IV

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 30 days of surgery; Group 1: 1/39, Group 2: 0/39
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: More people with ASA III in IV group. ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at During hospitalisation; Group 1: 0/39, Group 2: 0/39
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: More people with ASA III in IV group. ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Length of stay at -
- Actual outcome: Length of stay at .; Group 1: mean 3.5 days (SD 0.9); n=39, Group 2: mean 3.9 days (SD 1.6); n=39

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Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: More people with ASA III in IV group. ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Change in preop. Hb at 48 hours after surgery; Group 1: mean -3.4 g/dL (SD 0.9); n=39, Group 2: mean -3.1 g/dL (SD 1); n=39 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: More people with ASA III in IV group. ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Total blood loss at - - Actual outcome: Total blood loss at 48 hours after surgery; Group 1: mean 1574.5 mL (SD 542.9); n=39, Group 2: mean 1626 mL (SD 519.2); n=39 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: More people with ASA III in IV group. ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -

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Study	**Good 2003[87]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=51)
Countries and setting	Conducted in Sweden; Setting: Hospital
Line of therapy	1st line
Duration of study	--:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients who had elective total primary unilateral tricompartmental knee arthroplasty because of osteoarthrosis, and were all classified as ASA I or II.
Exclusion criteria	History of coagulopathy, an abnormally great prothrombin or activated partial thrombin time, previous history of a thromboembolic event,treatment with aspirin or non-steroidal anti-inflammatory agents (NSAID) in the previous week, plasma creatinine greater than 115 mmol per litre in men and 100 mmol/litre in women, acute infection (e.g. with leucocytosis or fever), and malignant disease. Patients with myocardial infarction in the preceding 12 months or those with unstable angina or coronary disease that would not allow haemdilution were also excluded, as were those who were given plasma or other treatment affecting coagulation during the perioperative period.
Recruitment/selection of patients	NR

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Age, gender and ethnicity	Age - Mean (range): TXA- 72 (46-83); placebo- 72 (50-84) . Gender (M:F): M/F: TXA: 9/18 ; placebo- 6/18. Ethnicity: not stated
Further population details	1. Co-morbidities: 2. Site/type of joint replacement:
Extra comments	Two randomized patients in the control group were found not to fulfil the criteria for inclusion: in one the serum creatinine was too great and the other had rheumathoid arthritis.
Indirectness of population	No indirectness
Interventions	(n=27) Intervention 1: Perioperative use of tranexamic acid - IV. Coded ampoules containing tranexamic acid 100 mg/ml (Cyklokapronâ, Pharmacia). At the end of the surgical procedure, just before release of the tourniquet, tranexamic acid 10 mg/ kg was infused i.v. (maximum dose 1000 mg). The dose was repeated after 3 h. . Duration End of the surgery just before release of the tourniquet. Concurrent medication/care: Treatment with aspirin or NSAIDs was stopped one week before the operation. For thrombosis prophylaxis, dalteparin sodium (Fragminâ, Rhone-Poulenc Rorer) 5000 IU was injected s.c. on the evening after surgery. Patients were then given 5000 IU daily for 10 days. Oral premedication was with different combinations of diazepam, acetaminophen and codeine. In addition, ibuprofen 600 mg was given to 20 patients. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Comments: Subarachnoid spinal anaesthesia was with isobaricbupivacaine (Marcain spinalâ, Astra) 17.5-20 mg. Midazolam or propofol were given i.v. for sedation if needed. Non-invasive arterial pressure and heart rate were noted every 5 min and patients were given cloxacillin i.v. (n=24) Intervention 2: Placebo. Coded ampoules containing saline were prepared by Apoteksbolaget.

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	UmeaÊ, Sweden. Just before release of the tourniquet placebo was infused i.v. (maximum dose 1000 mg). The dose was repeated after 3 h.. Duration At the end of the surgical procedure, just before release of the tourniquet. Concurrent medication/care: Treatment with aspirin or NSAIDs was stopped one week before the operation. For thrombosis prophylaxis, dalteparin sodium (Fragminâ, Rhone-Poulenc Rorer) 5000 IU was injected s.c. on the evening after surgery. Patients were then given 5000 IU daily for 10 days. Oral premedication was with different combinations of diazepam, acetaminophen and codeine. In addition, ibuprofen 600 mg was given to 20 patients. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose:
Funding	Academic or government funding (The study was supported by grants from the County Council of Ostergotland.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Post-operative ; Group 1: 2/27, Group 2: 2/24
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Number of patients transfused at Peri-operative ; Group 1: 3/27, Group 2: 14/24
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -; Blood loss: Haemoglobin level at 3 days after surgery; Total blood loss at -

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Study	Goyal 2017[90]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=168)
Countries and setting	Conducted in Australia
Line of therapy	Not applicable
Duration of study	Intervention time: Surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People having primary total knee arthroplasty
Exclusion criteria	Bilateral TKA, those with history of thromboembolic events (deep vein thrombosis (DVT), pulmonary embolism, or cerebrovascular accident), renal dysfunction (plasma creatinine level >130 mmol/L), or coagulopathy (international normalized ratio > 1.4), preoperative anaemia (men with Hb < 13 g/dL; women with Hb < 12 g/dL)
Age, gender and ethnicity	Age - Mean (SD): 67 (9), 69 (7). Gender (M:F): 78/90. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness

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Interventions	(n=83) Intervention 1: Perioperative use of tranexamic acid - IA/topical. 10 mL of saline IV 10 minutes before deflation of the tourniquet (if a tourniquet was used) or 10 minutes before incision (if a tourniquet was not used), 3000mg (30mL) of IA tranexamic acid to the knee joint after wound closure, and 2 more 10 mL doses of IV saline were given at 8 hourly intervals postoperatively. The syringes used to inject tranexamic acid into the knee joint after wound closure were covered with an opaque dressing to keep the operating team blinded.. Duration During surgery. Concurrent medication/care: All patients received bilateral intermittent pneumatic calf compressors and thromboembolic deterrent stockings. In addition, all patients received either aspirin 300 mg daily (3 surgeons) or enoxaparin 40 mg daily (1 surgeon) for chemotherapeutic prophylaxis and the choicewas based on the preference of the surgeon.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≥3000 mg (n=85) Intervention 2: Perioperative use of tranexamic acid - IV. 1000mg (10 mL) of IV tranexamic acid 10 minutes before deflation of the tourniquet (if a tourniquet was used) or 10 minutes before incision (if a tourniquet was not used), 30mL of IA saline to the knee joint after wound closure, and 2 more 1000mg (10mL) doses of IV tranexamic acid were given at 8 hourly intervals postoperatively.. Duration During surgery. Concurrent medication/care: All patients received bilateral intermittent pneumatic calf compressors and thromboembolic deterrent stockings. In addition, all patients received either aspirin 300 mg daily (3 surgeons) or enoxaparin 40 mg daily (1 surgeon) for chemotherapeutic prophylaxis and the choice was based on the preference of the surgeon.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≥3000 mg
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus IV

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Unclear; Group 1: 3/83, Group 2: 2/85
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 2: Blood (allogeneic or autologous) transfusion at - - Actual outcome: Transfusion at Unclear; Group 1: 0/83, Group 2: 0/85 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Length of stay at - - Actual outcome: Length of stay at .; Group 1: mean 4.3 days (SD 1.7); n=83, Group 2: mean 4.1 days (SD 1); n=85 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Hb difference at Preop to day 2 after surgery; Group 1: mean -2.5 g/dL (SD 0.8); n=83, Group 2: mean -2.4 g/dL (SD 0.9); n=85 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Total blood loss at -

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Study	Guerreiro 2017[91]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=43)
Countries and setting	Conducted in Brazil; Setting: Brotherhood of Santa Casa de Londrina, Philanthropic Hospital (Irmandade da Santa Casa de Londrina, Hospital Filantrópico)
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery with 2 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People undergoing total knee arthroplasty
Exclusion criteria	Major deformities that would lead to bone cuts or release of a more extensive area of soft tissue; presence of inflammatory diseases; patients who had undergone previous surgeries of the same knee; use of anticoagulation medication up to seven days before surgery; and patients with history of atrial fibrillation, deep vein thrombosis or prior pulmonary embolism
Recruitment/selection of patients	June 2014 to October 2015.
Age, gender and ethnicity	Age - Mean (range): 68 (55-81), 69 (55-86). Gender (M:F): 11/32. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty

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Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Perioperative use of tranexamic acid - IA/topical. Intra-articular application of 1g TXA in 50ml. Duration During surgery and follow-up treatment for 10 days after discharge. Concurrent medication/care: Prophylaxis for deep venous thrombosis: 40 mg of enoxaparin 12, 24 and 48 hours after surgery and were prescribed 10 mg Rivaroxaban daily for 10 days at home.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≤1000 mg (n=21) Intervention 2: No treatment. No application of tranexamic acid or any other intra-articular sealant substance. Duration During surgery with follow-up treatment for 10 days after hospital discharge. Concurrent medication/care: Prophylaxis for deep venous thrombosis: 40 mg of enoxaparin 12, 24 and 48 hours after surgery and were prescribed 10 mg Rivaroxaban daily for 10 days at home.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus NO TREATMENT

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: Thromboembolism at Within 2 months of surgery; Group 1: 0/22, Group 2: 0/21
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at In hospital period; Group 1: 0/22, Group 2: 0/21
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery

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- Actual outcome: Fall in Hb at 2 days after surgery; Group 1: mean -1.53 g/dL (SD 0.91); n=22, Group 2: mean -2.28 g/dL (SD 0.91); n=21 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -; Total blood loss at -

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Study	Gulabi 2019[92]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=57)
Countries and setting	Conducted in Turkey; Setting: All surgeries undertaken by the same surgeon.
Line of therapy	Not applicable
Duration of study	Intervention time: Surgery and in-hospital period
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults scheduled for elective primary unilateral THA.
Exclusion criteria	Not primary OA, prior history of DVT, blood clotting problem, cardiac stents, chronic renal or hepatic failure, bilateral joint arthroplasty, revision surgery, acute subarachnoid haemorhage, TXA allergy, cerebrovascular disease
Recruitment/selection of patients	September 2016 to September 2017.
Age, gender and ethnicity	Age - Mean (SD): 64 (10) and 63 (8). Gender (M:F): 20/28. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear (Mean ASA was 2.2.). 2. Site/type of joint replacement: Hip replacement

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Indirectness of population	No indirectness
Interventions	(n=26) Intervention 1: Perioperative use of tranexamic acid - IV. 1g given in isotonic saline solution given as a slow IV injection 30 minutes before incision. Dose repeated 3 hours later. . Duration Surgery until hospital discharge. Concurrent medication/care: Enoxaparin and LMWH 6 hours after surgery. This was repeated every 24 hours until discharge from hospital. Antiembolic socks used. Postoperative pain management ladder used. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg (2g). (n=22) Intervention 2: Perioperative use of tranexamic acid - IV+IA/topical. 1g given in isotonic saline solution given as a slow IV injection 30 minutes before incision. Dose repeated 3 hours later. 3g diluted in isotonic saline and applied intra-articularly. . Duration Surgery until hospital discharge. Concurrent medication/care: Enoxaparin and LMWH 6 hours after surgery. This was repeated every 24 hours until discharge from hospital. Antiembolic socks used. Postoperative pain management ladder used. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≥3000 mg (5g).
Funding	No funding (No funding stated)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV+IA/TOPICAL versus IV

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at In-hospital period; Group 1: 2/22, Group 2: 2/26
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at In-hospital period; Group 1: 2/22, Group 2: 3/26
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 3: Length of stay at - - Actual outcome: Hospital stay at .; Group 1: mean 4.46 days (SD 0.91); n=22, Group 2: mean 4.46 days (SD 1.21); n=26 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Haemoglobin level at Postoperative day 3; Group 1: mean 2.87 g/dl (SD 0.98); n=22, Group 2: mean 3.16 g/dl (SD 0.82); n=26 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Total blood loss at - - Actual outcome: Total blood loss at 3 days after surgery; Group 1: mean 772.22 ml (SD 322.07); n=22, Group 2: mean 848.871 ml (SD 224.1); n=26 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -

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Study	Hsu 2015[104]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=70)
Countries and setting	Conducted in Taiwan
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 3 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	June 2011 to June 2013.
Age, gender and ethnicity	Age - Mean (SD): 58. Gender (M:F): Define. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Hip replacement
Indirectness of population	No indirectness
Interventions	(n=34) Intervention 1: Perioperative use of tranexamic acid - IV. 2 doses of 1g in 20ml. The first 10 minutes

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	before incision and the second 3 hours later. . Duration During surgery. Concurrent medication/care: Thromboprophylaxis: 40mg enoxaparin subcutaneously administered. From first postoperative day until hospital discharge. Then Indomethacin 3 times a day for 4 weeks. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg (n=36) Intervention 2: Placebo. 20ml saline injected at the same time as the tranexamic acid in the intervention group. . Duration During surgery. Concurrent medication/care: Thromboprophylaxis: 40mg enoxaparin subcutaneously administered. From first postoperative day until hospital discharge. Then Indomethacin 3 times a day for 4 weeks. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at 6 month follow-up; Group 1: 0/30, Group 2: 0/30
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference in ASA grade and platelet count; Group 1 Number missing: 4, Reason: 2 refused study, 2 incomplete data; Group 2 Number missing: 6, Reason: 4 refused study, 2 incomplete data

Protocol outcome 2: Surgical bleeding at -
- Actual outcome: Intra-operative blood loss at During surgery; Group 1: mean 441 mL (SD 327); n=30, Group 2: mean 615 mL (SD 327); n=30
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference in ASA grade and platelet count; Group 1 Number missing: 4, Reason: 2 refused study, 2 incomplete data; Group 2 Number missing: 6, Reason: 4 refused study, 2 incomplete data

Protocol outcome 3: Postoperative bleeding at -
- Actual outcome: Total drainage at 4 days after surgery; Group 1: mean 285 mL (SD 128); n=30, Group 2: mean 392 mL (SD 128); n=30
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference in ASA grade and platelet count; Group 1 Number missing:

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4, Reason: 2 refused study, 2 incomplete data; Group 2 Number missing: 6, Reason: 4 refused study, 2 incomplete data Protocol outcome 4: Length of stay at - - Actual outcome: Hospital length of stay at .; Group 1: mean 5.66 days (SD 1.5); n=30, Group 2: mean 5.86 days (SD 1.5); n=30 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference in ASA grade and platelet count; Group 1 Number missing: 4, Reason: 2 refused study, 2 incomplete data; Group 2 Number missing: 6, Reason: 4 refused study, 2 incomplete data Protocol outcome 5: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Haemoglobin level at 4 days after surgery; Group 1: mean 9.8 g/dL (SD 1.8); n=30, Group 2: mean 9.3 g/dL (SD 1.8); n=30 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference in ASA grade and platelet count; Group 1 Number missing: 4, Reason: 2 refused study, 2 incomplete data; Group 2 Number missing: 6, Reason: 4 refused study, 2 incomplete data Protocol outcome 6: Total blood loss at - - Actual outcome: Actual blood loss at 4 days after surgery; Group 1: mean 1070 mL (SD 345); n=30, Group 2: mean 1337 mL (SD 345); n=30 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference in ASA grade and platelet count; Group 1 Number missing: 4, Reason: 2 refused study, 2 incomplete data; Group 2 Number missing: 6, Reason: 4 refused study, 2 incomplete data	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Blood (allogeneic or autologous) transfusion at -; Quality of life at within 6 weeks; Postoperative anaemia at -

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Study	Huang 2014[107]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=184)
Countries and setting	Conducted in China; Setting: West China Hospital.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 3 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults scheduled for a primary TKA for end-stage osteoarthritis
Exclusion criteria	Revisions, bilateral procedures, flexion deformity ≥30°, varus/valgus deformity ≥30°, contraindications for the use of TXAand coagulation disorders
Age, gender and ethnicity	Age - Mean (SD): 65 (10), 65 (9). Gender (M:F): 67/117. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Extra comments	

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Indirectness of population	No indirectness
Interventions	(n=92) Intervention 1: Perioperative use of tranexamic acid - IV. 3g administered before inflation of the tourniquet.. Duration Surgery with treatment continuing for 10 days after hospital discharge. Concurrent medication/care: Half dose of low-molecular weight heparin (LMWH) (0.2 mL 2000 IU) was started 6 h postoperatively and repeated at 24-h intervals with a full dose (0.4 mL 4000 IU) in the subsequent days. An intermittent foot slope pump system was used as a routine practice to prevent deep-vein thrombosis (DVT). After the discharge, 10 mg rivaroxaban was administered orally to the patients for 10 days.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≥3000 mg (n=92) Intervention 2: Perioperative use of tranexamic acid - IV+IA/topical. 1.5g dissolved in 50 mL normal saline was irrigated in the wound after implantation of the components and 1.5g IV was administered before inflation of the tourniquet. Duration Surgery with treatment continuing for 10 days after hospital discharge. Concurrent medication/care: Half dose of low-molecular weight heparin (LMWH) (0.2 mL 2000 IU) was started 6 h postoperatively and repeated at 24-h intervals with a full dose (0.4 mL 4000 IU) in the subsequent days. An intermittent foot slope pump system was used as a routine practice to prevent deep-vein thrombosis (DVT). After the discharge, 10 mg rivaroxaban was administered orally to the patients for 10 days.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≥3000 mg
Funding	Academic or government funding (Funded by the China Health Ministry Program)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus IV+IA/TOPICAL

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 3 months of surgery; Group 1: 1/92, Group 2: 0/92
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 2: Blood (allogeneic or autologous) transfusion at - - Actual outcome: Transfusion rate at Within 10 days of surgery; Group 1: 4/92, Group 2: 3/92 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Length of stay at - - Actual outcome: Length of hospital stay at .; Group 1: mean 7.2 days (SD 0.8); n=92, Group 2: mean 6.9 days (SD 0.9); n=92 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Hb decline at 3 days after surgery; Group 1: mean -2.73 g/dL (SD 0.55); n=92, Group 2: mean -2.56 g/dL (SD 0.53); n=92 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Total blood loss at - - Actual outcome: Total blood loss at 3 days after surgery; Group 1: mean 957 mL (SD 285); n=92, Group 2: mean 867 mL (SD 374); n=92 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -

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Study	Husted 2003[109]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Denmark; Setting: Department of Orthopedics in Hvidovre University Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients scheduled for primary total hip arthroplasty due to arthrosis or osteonecrosis of the femoral head.
Exclusion criteria	Rheumatoid arthritis, malignancy, previous thrombo-embolic episodes, ischemic heart disease, previous subarachnoidal bleeding, haematuria and body weight > 100 kg. All patients had discontinued using nonsteroidal anti-inflammatory drugs and ASA 14 days before surgery.

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Recruitment/selection of patients	NR
Age, gender and ethnicity	Age - Other: Age (mean): TXA: 65; placebo: 67. Gender (M:F): TXA: 13/7; placebo: 14/6. Ethnicity: not stated
Further population details	1. Co-morbidities: 2. Site/type of joint replacement:
Extra comments	-. -
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Perioperative use of tranexamic acid - IV. TXA- Patients in the Tranexamic acid group were given a bolus intravenous injection of 10 mg/kg (maximum 1 g) during 10 minutes about 15 minutes before the incision, followed by a continuous infusion of 1 mg/kg/hour dissolved in 1 L of saline for 10 hours (maximum 1 g/10 hours). . Duration 10 mins (15 mins before the incision). Concurrent medication/care: Thromboprophylaxis with low molecular weight heparin starting on the day before surgery and until discharge. . Indirectness: No indirectness; Indirectness comment: The operations were performed via the posterolateral approach, by 3 surgeons, all orthopaedic specialists with experience in total hip replacement. The prostheses used were an uncemented acetabular cup and a femoral stem, which was cemented or uncemented. All patients had spinal analgesia, using bupivacaine. Further details: 1. Tranexamic acid dose: (n=20) Intervention 2: Placebo. Patients randomised to receiving placebo (saline) were given a bolus

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	intravenous injection of 20 mL about 15 minutes before the operation followed by a continuous infusion of 1 L of saline during 10 hours. . Duration 10 mins (15 mins before the incision). Concurrent medication/care: Thromboprophylaxis with low molecular weight heparin starting on the day before surgery and until discharge. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose:
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at end of follow-up; Group 1: 0/20, Group 2: 0/20
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Number of patients receiving blood transfusions at end of follow-up; Group 1: 2/20, Group 2: 7/20
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Postoperative bleeding at -
- Actual outcome: Post-operative blood loss (ml) at post-operative ; Group 1: mean 334 ml (SD 703); n=20, Group 2: mean 609 ml (SD 1104); n=20
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2

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Number missing: Protocol outcome 4: Total blood loss at - - Actual outcome: Total blood loss (ml) at pre and post-operative ; Group 1: mean 814 (SD 1351); n=20, Group 2: mean 1231 (SD 1727); n=20 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Length of stay at -; Blood loss: Haemoglobin level at 3 days after surgery

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Study	Imai 2012[111]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=117)
Countries and setting	Conducted in Japan; Setting: Shibata Prefectural Hospital
Line of therapy	Not applicable
Duration of study	Intervention time: Surgery with 10 days continuing treatment after hospital discharge
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People undergoing primary total hip replacement for osteoarthritis of the hip.
Exclusion criteria	Previous hip operation, history of ischemic heart disease, severe chronic heart failure, hepatic dysfunction, chronic renal failure, hemodialysis, cerebral infarction, bleeding disorder, currently receiving anticoagulant treatment.
Recruitment/selection of patients	September 2009 to June 2011
Age, gender and ethnicity	Age - Mean (range): 62 (47-85). Gender (M:F): 21/96. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Hip replacement
Indirectness of population	No indirectness

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Interventions	(n=24) Intervention 1: Perioperative use of tranexamic acid - IV. 1g IV administered 10 minutes before skin closure . Duration Hospital period with 10 days thromboprophylaxis. . Concurrent medication/care: Compressive stockings for legs for 2 postoperative days. 20mg enoxaparin 24 hours after surgery and then twice daily for 10 days. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≤1000 mg (n=20) Intervention 2: Perioperative use of tranexamic acid - IV. 1g 10 minutes before skin closure and again 6 hours later. . Duration Hospital period with 10 days thromboprophylaxis. . Concurrent medication/care: Compressive stockings for legs for 2 postoperative days. 20mg enoxaparin 24 hours after surgery and then twice daily for 10 days.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg (n=25) Intervention 3: Perioperative use of tranexamic acid - IV. 1g IV administered 10 minutes before surgery. . Duration Hospital period with 10 days thromboprophylaxis.. Concurrent medication/care: Compressive stockings for legs for 2 postoperative days. 20mg enoxaparin 24 hours after surgery and then twice daily for 10 days.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≤1000 mg (n=26) Intervention 4: Perioperative use of tranexamic acid - IV. 1g administered 10 minutes before surgery and again 6 hours later. Duration Hospital period with 10 days thromboprophylaxis.. Concurrent medication/care: Compressive stockings for legs for 2 postoperative days. 20mg enoxaparin 24 hours after surgery and then twice daily for 10 days.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg (n=22) Intervention 5: No treatment. No tranexamic acid treatment. Duration Hospital period with 10 days thromboprophylaxis.. Concurrent medication/care: Compressive stockings for legs for 2 postoperative days. 20mg enoxaparin 24 hours after surgery and then twice daily for 10 days.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Funding not stated

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RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus NO TREATMENT

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within hospital and unclear follow-up; Group 1: 3/24, Group 2: 3/22
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Allogenic transfusion at Within hospital period; Group 1: 0/24, Group 2: 0/22
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus NO TREATMENT

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within hospital and unclear follow-up; Group 1: 2/20, Group 2: 3/22
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Allogenic transfusion at Within hospital period; Group 1: 0/20, Group 2: 0/22
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus NO TREATMENT

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within hospital and unclear follow-up; Group 1: 2/25, Group 2: 3/22
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 2: Blood (allogeneic or autologous) transfusion at - - Actual outcome: Allogenic transfusion at Within hospital period; Group 1: 0/25, Group 2: 0/22 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus NO TREATMENT Protocol outcome 1: Adverse events: DVT at - - Actual outcome: DVT at Within hospital and unclear follow-up; Group 1: 3/26, Group 2: 3/22 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Blood (allogeneic or autologous) transfusion at - - Actual outcome: Allogenic transfusion at Within hospital period; Group 1: 0/26, Group 2: 0/22 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -; Blood loss: Haemoglobin level at 3 days after surgery; Total blood loss at -

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Study	Ishida 2011[114]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in Japan
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery with 4 weeks follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with osteoarthritis scheduled for primary TKA
Exclusion criteria	Rheumatoid arthritis, revision TKA and simultaneous bilateral TKA
Recruitment/selection of patients	Consecutive people. January 2008 to May 2009.
Age, gender and ethnicity	Age - Mean (SD): 73 (5), 74 (6). Gender (M:F): 12/88. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Perioperative use of tranexamic acid - IA/topical. Drain clamping was performed after

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	2g in 20ml into the knee joint. Duration Surgery with 4 weeks follow-up. Concurrent medication/care: Arteriovenous impulse system for 24 hours after surgery. 10,000 IU heparin sodium was administered intravenously for 24 hours. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg (n=50) Intervention 2: Placebo. Drain clamping was performed after 20ml saline into the knee joint. Duration Surgery with 4 weeks follow-up. Concurrent medication/care: Arteriovenous impulse system for 24 hours after surgery. 10,000 IU heparin sodium was administered intravenously for 24 hours. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus PLACEBO Protocol outcome 1: Blood (allogeneic or autologous) transfusion at - - Actual outcome: Allogeneic blood transfusion at Within 4 weeks of surgery; Group 1: 0/50, Group 2: 1/50 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Adverse events: DVT at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -; Blood loss: Haemoglobin level at 3 days after surgery; Total blood loss at -

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Study	Jain 2016[116]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=119)
Countries and setting	Conducted in India
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 6 weeks follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 70 (7), 68 (9)
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with primary osteoarthritis undergoing elective unilateral primary TKAs
Exclusion criteria	People undergoing simultaneous bilateral TKA, patients diagnosed with coagulopathy (acquired or congenital), patients on current anticoagulation therapy, patients with history of thromboembolic disease, and those with hepatic or renal dysfunction or previous ischemic heart disease
Recruitment/selection of patients	September 2014 to December 2014
Age, gender and ethnicity	Age - Mean (SD): . Gender (M:F): 44/75. Ethnicity: All people were Asian
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness

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Interventions	(n=60) Intervention 1: Perioperative use of tranexamic acid - IV. 3 doses: 15 mg/kg 30 minutes before skin incision. 10mg/kg repeated 3 and 6 hours after surgery. Isotonic sodium chloride solution was applied intraarticularly for 5 minutes before closure of arthrotomy.. Duration Surgery and 6 weeks follow-up. Concurrent medication/care: Below-knee thromboembolic disease stockings for both lower limbs were used. Chemical prophylaxis 75mg tablet aspirin once a day for 6 weeks. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≥3000 mg (n=59) Intervention 2: Perioperative use of tranexamic acid - IV+IA/topical. 3 IV doses: 15 mg/kg 30 minutes before skin incision. 10mg/kg repeated 3 and 6 hours after surgery. 2g diluted in 30 mL of isotonic sodium chloride solution was used as mop soaked in TXA solution and applied intraarticularly for about 5minutes before closure of arthrotomy.. Duration Surgery and 6 weeks follow-up. Concurrent medication/care: Below-knee thromboembolic disease stockings for both lower limbs were used. Chemical prophylaxis 75mg tablet aspirin once a day for 6 weeks. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus IV+IA/TOPICAL

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: Symptomatic DVT at Within 6 weeks of surgery; Group 1: 1/60, Group 2: 0/59
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at Within 6 weeks of surgery; Group 1: 4/60, Group 2: 1/59
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery

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- Actual outcome: Hb drop at 3 days after surgery; Group 1: mean -1.82 g/dL (SD 0.6); n=60, Group 2: mean -1.14 g/dL (SD 0.5); n=59 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Total blood loss at - - Actual outcome: Calculated total blood loss at 3 days after surgery; Group 1: mean 590.69 mL (SD 191.1); n=60, Group 2: mean 385.68 mL (SD 182.5); n=59 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -

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Study	Jaszczyk 2015[118]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=89)
Countries and setting	Conducted in USA; Setting: Single centre.
Line of therapy	Not applicable
Duration of study	Intervention time: During JR surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People undergoing primary total hip arthroplasty.
Exclusion criteria	History of renal failure, kidney transplat, history of arterial thromboembolic event, stroke within a year, arterial stent within a year, previous DVT or PE.
Age, gender and ethnicity	Age - Mean (SD): 58. Gender (M:F): 42/41. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Hip replacement
Indirectness of population	No indirectness
Interventions	(n=43) Intervention 1: Perioperative use of tranexamic acid - IV. 1g in 10mL saline as bolus immediately before incision. Placebo tablets 2 hours before incision. . Duration During surgery. Concurrent

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	medication/care: Thromboembolic prophylaxis utilising warfarin to hit a INR goal of 2 from day 0. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≤1000 mg (n=46) Intervention 2: Perioperative use of tranexamic acid - Oral. 1950mg in 3 tablets 2 hours before incision and an IV placebo dose of saline immediately before incision. . Duration During surgery. Concurrent medication/care: Thromboembolic prophylaxis utilising warfarin to hit a INR goal of 2 from day 0. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL versus IV

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Unclear; Group 1: 0/40, Group 2: 0/43
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: 3 received wrong medication. 3 incomplete drug dose. ; Group 2 Number missing: 0

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at Unclear; Group 1: 3/40, Group 2: 1/43
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: 3 received wrong medication. 3 incomplete drug dose. ; Group 2 Number missing: 0

Protocol outcome 3: Length of stay at -
- Actual outcome: Length of hospital stay at .; Group 1: mean 2 days (SD 1); n=40, Group 2: mean 2 days (SD 1); n=43
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: 3 received wrong medication. 3 incomplete drug dose. ; Group 2 Number missing: 0

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Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Reduction of haemoglobin at Unclear; Group 1: mean -3.67 g/dL (SD 1.2); n=40, Group 2: mean -3.53 g/dL (SD 1.2); n=43 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: 3 received wrong medication. 3 incomplete drug dose. ; Group 2 Number missing: 0 Protocol outcome 5: Total blood loss at - - Actual outcome: Total blood loss at Unclear; Group 1: mean 1339 mL (SD 375); n=40, Group 2: mean 1301 mL (SD 424); n=43 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: 3 received wrong medication. 3 incomplete drug dose. ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -

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Study	Kakar 2009[122]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in India
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 7 days follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People undergoing primary cemented unilateral(U/L) or bilateral(B/L) total knee arthroplasties.
Exclusion criteria	Unclear if thromboembolic prophylaxis was used.
Age, gender and ethnicity	Age - Mean (SD): 67 (7), 63 (17), 66 (5), 62 (9). Gender (M:F): 14/36. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness
Interventions	(n=12) Intervention 1: Perioperative use of tranexamic acid - IV. People received a 10 mg/kg followed by an infusion of 1mg/kg/hr until skin closure.. Duration Surgery and in-hospital period. Concurrent medication/care: Unclear thromboprophylaxis . Indirectness: No indirectness

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	Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=13) Intervention 2: Perioperative use of tranexamic acid - IV. People received a 10 mg/kg followed by an infusion of 1mg/kg/hr until skin closure.. Duration Surgery and in-hospital period . Concurrent medication/care: Unclear thromboprophylaxis. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=12) Intervention 3: Placebo. People received a dose of saline followed by an infusion of saline until skin closure.. Duration Surgery and in-hospital period. Concurrent medication/care: Unclear thromboprophylaxis. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable (n=13) Intervention 4: Placebo. People received a dose of saline followed by an infusion of saline until skin closure.. Duration Surgery and in-hospital period . Concurrent medication/care: Unclear thromboprophylaxis . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV UNI versus PLACEBO UNI

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 7 days of surgery; Group 1: 0/12, Group 2: 0/12
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV BI versus PLACEBO BI

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 7 days of surgery; Group 1: 0/13, Group 2: 0/13

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Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Blood (allogeneic or autologous) transfusion at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -; Blood loss: Haemoglobin level at 3 days after surgery; Total blood loss at -

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Study	Kayupov 2017[126]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=89)
Countries and setting	Conducted in USA
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and unclear follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People having cementless primary hip arthroplasty
Exclusion criteria	History of renal failure, kidney transplant, history of arterial thromboembolic event, stroke within a year, history of DVT, placement of arterial stent within last year, history of DVT or PE, decline blood products
Age, gender and ethnicity	Age - Mean (SD): 6 (10), 55 (12). Gender (M:F): 42/41. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Hip replacement
Indirectness of population	No indirectness
Interventions	(n=43) Intervention 1: Perioperative use of tranexamic acid - IV. 1g in saline given immediately prior to incision, placebo for oral group in ascorbic acid given 2 hours before incision. . Duration Surgery. Concurrent

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	medication/care: Thromboprophylaxis: warfarin initiated the the same day as surgery with an INR goal of 2. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≤1000 mg (n=46) Intervention 2: Perioperative use of tranexamic acid - Oral. 1960mg given in 3 tablets 2 hours before incision. IV saline given immediately prior to incision. Duration Surgery. Concurrent medication/care: Thromboprophylaxis: warfarin initiated the the same day as surgery with an INR goal of 2.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≥3000 mg
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL versus IV

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: Thromboembolic event at Unclear; Group 1: 0/40, Group 2: 0/43
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: £ received wrong drug, 3 did not receive complete dose. ; Group 2 Number missing: 0

Protocol outcome 2: Length of stay at -
- Actual outcome: Length of hospital stay at .; Group 1: mean 2 days (SD 1); n=40, Group 2: mean 2 days (SD 1); n=43
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: £ received wrong drug, 3 did not receive complete dose. ; Group 2 Number missing: 0

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Reduction in haemoglobin at Unclear; Group 1: mean -3.67 g/dL (SD 1.2); n=40, Group 2: mean -3.53 g/dL (SD 1.2); n=43
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: £ received wrong drug, 3 did not receive complete dose. ; Group 2 Number missing: 0

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Protocol outcome 4: Total blood loss at - - Actual outcome: Total blood loss at Unclear; Group 1: mean 1339 mL (SD 375); n=40, Group 2: mean 1301 mL (SD 424); n=43 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: £ received wrong drug, 3 did not receive complete dose. ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Blood (allogeneic or autologous) transfusion at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -

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Study	Kazemi 2010[127]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=64)
Countries and setting	Conducted in Iran
Line of therapy	Not applicable
Duration of study	Intervention time: Surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People having cementless hip replacement
Exclusion criteria	People with previous hip surgery, drug sensitivity, anemia (hemoglobin 11.5 for females and 12.5 for males), congenital or acquired haemostatic disease, disturbed coagulation and platelet count, hepatic or renal failure, pregnancy, history of DVT (deep vein thrombosis) or embolism and atherosclerotic vascular disease
Recruitment/selection of patients	2006-2008
Age, gender and ethnicity	Age - Mean (SD): 45 (17), 47 (16). Gender (M:F): 43/21. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Hip replacement
Indirectness of population	No indirectness

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Interventions	(n=32) Intervention 1: Perioperative use of tranexamic acid - IV. 15mg/kg was given slowly for 5 minutes preoperatively. Duration Surgery and follow-up for 10 days. Concurrent medication/care: Thromboprophylaxis: 40mg enoxaparin subcutaneously once a day for 10 days. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=32) Intervention 2: Placebo. 15mg/kg saline given slowly for 5 minutes preoperatively. Duration Surgery and 10 days follow-up. Concurrent medication/care: Thromboprophylaxis: 40mg enoxaparin subcutaneously once a day for 10 days. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Other ("Drs Kazemi, Mosaffa, Eajazi, Kaffashi, Daftari Besheli, Bigdeli, and Zanganeh have no relevant financial relationships to disclose")

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at 3 days after hospial discharge; Group 1: 0/32, Group 2: 1/32
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Allogenic blood transfusion at Within 10 days of surgery; Group 1: 4/32, Group 2: 11/32
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Length of stay at -
- Actual outcome: Duration of hospital stay at .; Group 1: mean 13 days (SD 12.4); n=32, Group 2: mean 15.5 days (SD 7.44); n=32
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Haemoglobin level at 24 hours after surgery; Group 1: mean 10.5 g/dL (SD 1.28); n=32, Group 2: mean 9.84 g/dL (SD 1.24); n=32 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Total blood loss at -

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Study	Keyhani 2016[129]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in Iran
Line of therapy	Not applicable
Duration of study	Not clear: Surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with osteoarthritis of the knee scheduled to undergo primary unilateral TKA
Exclusion criteria	People with coagulation disorders, history of cardiovascular diseases, history of cerebrovascular disorders, history of thromboembolic problems, renal and hepatic diseases, pregnant women, anemia, abnormal thrombin and prothrombin time, and abnormal platelet counts were excluded.
Age, gender and ethnicity	Age - Mean (SD): 68 (10), 67 (12), 64 (9). Gender (M:F): 68/52. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Perioperative use of tranexamic acid - IV. 500mg in 100cc saline at the end of surgery.

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	Duration Surgery and 2 weeks follow-up. Concurrent medication/care: Thromboprophylaxis: low molecular-weight heparin (40mg daily) which was administered subcutaneously for 2 weeks.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≤1000 mg (n=40) Intervention 2: Perioperative use of tranexamic acid - IA/topical. 3g in 100ml normal saline. Half of the solution was used to irrigate the joint before joint closure. The remaining half of the volume was administered in the joint after wound closure by a portovac drain. Duration Surgery and 2 weeks follow-up. Concurrent medication/care: Thromboprophylaxis: low molecular-weight heparin (40mg daily) which was administered subcutaneously for 2 weeks.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≥3000 mg (n=40) Intervention 3: No treatment. No treatment. Duration Surgery and 2 weeks follow-up. Concurrent medication/care: Thromboprophylaxis: low molecular-weight heparin (40mg daily) which was administered subcutaneously for 2 weeks.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	No funding (No funding source played a role in the study.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus NO TREATMENT

Protocol outcome 1: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Blood transfusion at Within hospitalised period; Group 1: 2/40, Group 2: 10/40
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Hb level at 24 hours after surgery; Group 1: mean 11.3 g/dL (SD 0.8); n=40, Group 2: mean 10.1 g/dL (SD 1.5); n=40
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus NO TREATMENT Protocol outcome 1: Blood (allogeneic or autologous) transfusion at - - Actual outcome: Blood transfusion at Within hospitalised period; Group 1: 3/40, Group 2: 10/40 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Hb level at 24 hours after surgery; Group 1: mean 11.8 g/dL (SD 1.6); n=40, Group 2: mean 10.1 g/dL (SD 1.5); n=40 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Adverse events: DVT at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -; Total blood loss at -

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Study	Kim 2014[131]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=330)
Countries and setting	Conducted in South Korea
Line of therapy	Not applicable
Duration of study	Intervention time: Surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People undergoing total knee arthroplasty
Exclusion criteria	A diagnosis other than primary OA, those with an acquired or congenital coagulopathy, those on current anticoagulation therapy, those with preoperative hepatic or renal dysfunction or severe ischaemic heart disease, and those with a history of thromboembolic disease.
Recruitment/selection of patients	October 2009 to May 2011
Age, gender and ethnicity	Age - Mean (SD): . Gender (M:F): 23/157. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness

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Interventions	(n=90) Intervention 1: Perioperative use of tranexamic acid - IV. 10mg/kg 30 min before tourniquet deflation, and the same amount was repeated 3 hours after the commencement of the first injection.. Duration Surgery with 6 weeks follow-up. Concurrent medication/care: Low molecular heparin (40 mg once daily) was administered for 7–10 days after surgery, for a high risk of bleeding and a standard risk of PE—an intermittent pneumatic pump was used for7–10 days, and (3) for a high risk of both PE and bleeding—an intermittent pneumatic pump was used for 7–10 days followed by aspirin for 6 weeks.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable (n=90) Intervention 2: No treatment. No tranexamic acid treatment. Duration During surgery with 6 weeks follow-up. Concurrent medication/care: Low molecular heparin (40 mg once daily) was administered for 7–10 days after surgery, for a high risk of bleeding and a standard risk of PE—an intermittent pneumatic pump was used for7–10 days, and (3) for a high risk of both PE and bleeding—an intermittent pneumatic pump was used for 7–10 days followed by aspirin for 6 weeks.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable (n=75) Intervention 3: No treatment. No tranexamic acid treatment. Duration During surgery with 6 weeks follow-up. Concurrent medication/care: Low molecular heparin (40 mg once daily) was administered for 7–10 days after surgery, for a high risk of bleeding and a standard risk of PE—an intermittent pneumatic pump was used for7–10 days, and (3) for a high risk of both PE and bleeding—an intermittent pneumatic pump was used for 7–10 days followed by aspirin for 6 weeks.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable (n=75) Intervention 4: Perioperative use of tranexamic acid - IV. 10mg/kg 30 min before tourniquet deflation, and the same amount was repeated 3 hours after the commencement of the first injection.. Duration Surgery with 6 weeks follow-up. Concurrent medication/care: Low molecular heparin (40 mg once daily) was administered for 7–10 days after surgery, for a high risk of bleeding and a standard risk of PE—an intermittent pneumatic pump was used for7–10 days, and (3) for a high risk of both PE and bleeding—an intermittent pneumatic pump was used for 7–10 days followed by aspirin for 6 weeks.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear

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Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV UNI versus NO TREATMENT UNI

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: Symptomatic DVT

at Within 6 months of surgery; Group 1: 0/90, Group 2: 0/90
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Allogenic transfusion

at During hospitalisation; Group 1: 1/90, Group 2: 6/90
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Hb drop

at 5 days after surgery; Group 1: mean -3.4 g/dL (SD 1.2); n=90, Group 2: mean -3.8 g/dL (SD 1.2); n=90
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Total blood loss at -
- Actual outcome: Calculated total blood loss
at 5 days after surgery; Group 1: mean 905 mL (SD 299.2); n=90, Group 2: mean 1018 mL (SD 321.3); n=90
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

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- Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV BI versus NO TREATMENT BI

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: Symptomatic DVT

at Within 6 months of surgery; Group 1: 0/75, Group 2: 0/75
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Allogenic transfusion

at During hospitalisation; Group 1: 5/75, Group 2: 20/75
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Hb drop

at 5 days after surgery; Group 1: mean -4.7 g/dL (SD 1.2); n=75, Group 2: mean -5.1 g/dL (SD 1.3); n=75
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Total blood loss at -
- Actual outcome: Calculated total blood loss
at 5 days after surgery; Group 1: mean 1282.6 mL (SD 308.5); n=75, Group 2: mean 1379.6 mL (SD 353.4); n=75
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -

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Study	Kundu 2015[135]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in India; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	American Society of Anesthesiologists I-II patients scheduled for unilateral total knee replacement (TKR)
Exclusion criteria	Patients with history of previous ipsilateral knee surgery, suspected allergy to medication (TXA, local anaesthetics, low-molecular weight heparin), anaemia (haemoglobin [Hb] <10 mg/dl for women and Hb <12 mg/dl for men), abnormalities in coagulation screening tests, aspirin intake within 7 days of surgery, renal (serum creatinine >2 standard deviation [SD] for age) or hepatic insufficiency, pregnancy and history of deep vein thrombosis (DVT) or pulmonary embolism, transient ischemic attack and stroke were excluded. Pre-operative haemostatic assessment included platelet count, bleeding time, activated partial thromboplastin time and prothrombin time.

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Recruitment/selection of patients	Study conducted between July 2011 to January 2014
Age, gender and ethnicity	Age - Mean (SD): TXA: 60.3 (12.56); placebo: 59.6 (12.2). Gender (M:F): TXA: 8/22; placebo: 7/23. Ethnicity: not stated
Further population details	1. Co-morbidities: 2. Site/type of joint replacement:
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Perioperative use of tranexamic acid - IV. TXA- the prepared solution was administered before the surgery. After a test dose of 1 ml, patients received TXA in a dose of 20 mg/kg diluted to 25 cc with normal saline. . Duration Intra-operative : 5 min. Concurrent medication/care: For thromboprophylaxis, injection enoxaparin 40 U was given once daily subcutaneously. All patients were put on 40 mg of Enoxaparin subcutaneously once a day on the evening before surgery and continued until the patient was discharged or fully mobilised. The patients were prescribed 10 mg of diazepam at the night before surgery to reduce anxiety. Aspiration prophylaxis was maintained with metoclopramide. (tablet) and ranitidine (tablet). . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Comments: Combined spinal epidural anaesthesia was given to all patients. Under aseptic conditions, spinal anaesthesia was induced with isobaric 0.5% bupivacaine and a lumbar epidural catheter was inserted in L2-3/L3-4 space in sitting a position and an infusion of (0.1% bupivacaine and 5 mcg/ml of fentanyl at the rate of 4-6 ml/h) was continued for

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	postoperative pain analgesia. After institution of combined spinal epidural anaesthesia, the study agent was given to the patients over 5 min through intravenous route. Then pneumatic tourniquet around thigh was inflated to a pressure of 350-400 mm Hg after elevating and draining the extremity with a sterile rubber bandage and operation was started within 5 min. (n=30) Intervention 2: Placebo. After a test dose of 1 ml, patients received an equivalent volume of normal saline. . Duration Intra-operative: 5 mins. Concurrent medication/care: For thromboprophylaxis, injection enoxaparin 40 U was given once daily subcutaneously. All patients were put on 40 mg of Enoxaparin subcutaneously once a day on the evening before surgery and continued until the patient was discharged or fully mobilised. The patients were prescribed 10 mg of diazepam at the night before surgery to reduce anxiety. Aspiration prophylaxis was maintained with metoclopramide (tablet) and ranitidine (tablet). . Indirectness: No indirectness Further details: 1. Tranexamic acid dose:
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO	

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Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at post-operative; Group 1: 3/30, Group 2: 2/30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: , Reason: The post-operative epidural analgesia of one patient failed and had to be replaced with parenterally administrated opioids. He became disorientated and removed the wound drains before due time. ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Number of patients requiring transfusion at post-operative; Group 1: 3/30, Group 2: 24/30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: , Reason: The post-operative epidural analgesia of one patient failed and had to be replaced with parenterally administrated opioids. He became disorientated and removed the wound drains before due time. ; Group 2 Number missing:

Protocol outcome 3: Surgical bleeding at -
- Actual outcome: Intra-operative bleeding at Intra-operative ; Group 1: mean 40.83 (SD 25.87); n=30, Group 2: mean 139.67 (SD 57.28); n=30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: , Reason: The post-operative epidural analgesia of one patient failed and had to be replaced with parenterally administrated opioids. He became disorientated and removed the wound drains before due time. ; Group 2 Number missing:

Protocol outcome 4: Postoperative bleeding at -
- Actual outcome: Post-operative bleeding at post-operative; Group 1: mean 105.16 ml (SD 24.9); n=30, Group 2: mean 438 ml (SD 151.72); n=30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: , Reason: The post-operative epidural analgesia of one patient failed and had to be replaced with parenterally administrated opioids. He became disorientated and removed the wound drains before due time. ; Group 2 Number missing:

Protocol outcome 5: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Hb% at 24th hour post-operative; Group 1: mean 10.4 d/dL (SD 1.2); n=30, Group 2: mean 9.07 d/dL (SD 1.3); n=30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover -

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Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: , Reason: The post-operative epidural analgesia of one patient failed and had to be replaced with parenterally administrated opioids. He became disorientated and removed the wound drains before due time. ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Postoperative anaemia at -; Length of stay at -; Total blood loss at -

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Study	**Lacko 2017[138]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in Slovakia; Setting: University Hospital of L. Pasteur in Kosice
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 3 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with primary or secondary osteoarthritis and having unilateral cemented primary total knee replacement
Exclusion criteria	Allergy to tranexamic acid, history of thromboembolism, cerebrovascular accidents, severe liver and kidney disease or blood clotting disorders.
Recruitment/selection of patients	February 2014 to May 2015.
Age, gender and ethnicity	Age - Mean (range): 69 (47 to 82). Gender (M:F): 36/54. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty

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Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Perioperative use of tranexamic acid - IV. 2 doses of 10mg/kg. The first dose was administered 20 minutes prior to incision and the second dose was administered three hours after the first dose. Duration Surgery. Concurrent medication/care: Prevention of thromboembolism using left ventricular mass by height was the same in all people.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=30) Intervention 2: Perioperative use of tranexamic acid - IA/topical. Local (intra-articular) administration involved the application of 3g in 50 mL of saline, applied directly into surgical wound following the cementing of the implant. Subsequently, the wound was not flushed anymore and after five minutes of exposure, the wound was sutured.. Duration Surgery. Concurrent medication/care: Prevention of thromboembolism using left ventricular mass by height was the same in all people.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≥3000 mg (n=30) Intervention 3: No treatment. No tranexamic acid treatment. Duration Surgery. Concurrent medication/care: Prevention of thromboembolism using left ventricular mass by height was the same in all people.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Other (The authors received no financial support for the research)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus IA/TOPICAL

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: Postoperative complications at Within 3 months ; Group 1: 0/30, Group 2: 0/30
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus NO TREATMENT Protocol outcome 1: Adverse events: DVT at - - Actual outcome: Postoperative complications at Within 3 months ; Group 1: 0/30, Group 2: 0/30 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus NO TREATMENT Protocol outcome 1: Adverse events: DVT at - - Actual outcome: Postoperative complications at Within 3 months ; Group 1: 0/30, Group 2: 0/30 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Blood (allogeneic or autologous) transfusion at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -; Blood loss: Haemoglobin level at 3 days after surgery; Total blood loss at -

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Study	Laoruengthana 2019[140]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=228)
Countries and setting	Conducted in Thailand; Setting: All surgery performed by 1 of 2 surgeons.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and inpatient period
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with primary osteoarthritis who are scheduled for primary unilateral total knee arthroplasty
Exclusion criteria	History of thromboembolic events, cardiovascular disease, cerebrovascular accident, low haemoglobin level, bleeding disorder, requiring anticoagulant therapy.
Age, gender and ethnicity	Age - Mean (SD): 64 (7), 65 (8), 64 (8). Gender (M:F): 42/184. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness
Interventions	(n=76) Intervention 1: No treatment. No tranexamic acid treatment. Duration Surgery and in-hospital period. Concurrent medication/care: Subcutaneous LMWH administered 24 hours after surgery. Oral warfarin

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	continued for 10 days. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable (n=76) Intervention 2: Perioperative use of tranexamic acid - IV. 10mg/kg administered before closure of the arthrotomy. . Duration Surgery and in-patient period. Concurrent medication/care: Subcutaneous LMWH administered 24 hours after surgery. Oral warfarin continued for 10 days. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (10mg/kg). (n=76) Intervention 3: Perioperative use of tranexamic acid - IA/topical. 15mg/kg poured into knee joint before closure of the arthrotomy. . Duration Surgery and in-patient period. Concurrent medication/care: Subcutaneous LMWH administered 24 hours after surgery. Oral warfarin continued for 10 days. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (15mg/kg).
Funding	Funding not stated (It was stated that the authors had no conflicts of interest)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus NO TREATMENT

Protocol outcome 1: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at In-hospital period; Group 1: 14/76, Group 2: 25/76
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Length of stay at -
- Actual outcome: Length of stay at .; Group 1: mean 6.5 days (SD 1.13); n=76, Group 2: mean 6.49 days (SD 0.98); n=76
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus NO TREATMENT

Protocol outcome 1: Blood (allogeneic or autologous) transfusion at -

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- Actual outcome: Transfusion at In-hospital period; Group 1: 15/76, Group 2: 25/76 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Length of stay at - - Actual outcome: Length of stay at .; Group 1: mean 6.41 days (SD 0.85); n=76, Group 2: mean 6.49 days (SD 0.98); n=76 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus IV Protocol outcome 1: Blood (allogeneic or autologous) transfusion at - - Actual outcome: Transfusion at In-hospital period; Group 1: 15/76, Group 2: 14/76 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Length of stay at - - Actual outcome: Length of stay at .; Group 1: mean 6.41 days (SD 0.85); n=76, Group 2: mean 6.5 days (SD 1.13); n=76 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Adverse events: DVT at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Blood loss: Haemoglobin level at 3 days after surgery; Total blood loss at -

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Study	Lee 2013[145]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=68)
Countries and setting	Conducted in South Korea; Setting: University affiliated hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA physical status 1 and 2 patients scheduled to undergo primary unilateral cementless total hip replacement
Exclusion criteria	Patients older than 70 years, those with previous hip surgery, drug sensitivity, anaemia (haemoglobin [Hb] b 12 g/dL for men and b 11 g/dL for women), coagulopathy, thrombocytopenia, hepatic or renal failure, history of deep vein thrombosis (DVT) or embolism, severe aortic or mitral valve stenosis, or neurological or cerebrovascular disease.

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Recruitment/selection of patients	NR
Age, gender and ethnicity	Age - Mean (SD): HEATXA: 51.4 (11.2); HEA: 52.8 (10.7. Gender (M:F): HEATXA: 22/12; HEA: 20/14. Ethnicity: not stated
Further population details	1. Co-morbidities: 2. Site/type of joint replacement:
Extra comments	-. -
Indirectness of population	No indirectness
Interventions	(n=34) Intervention 1: Perioperative use of tranexamic acid - IV. For all patients, intraoperative Hypotensive epidural anaesthesia (HEA) was used after general anaesthesia was induced. Those patients assigned to the HEATXA (HEA and TXA) group (n = 34) first received a bolus dose of 15 mg/kg of TXA (mixed in normal saline [NS]; total volume = 50 mL), administered slowly 10 minutes before the surgical incision was made, then a continuous infusion of 15 mg/kg of TXA (mixed in NS; total volume = 50 mL) until skin closure. . Duration 10 minutes before the surgical incision was made, then a continuous infusion of until skin closure. Concurrent medication/care: NR. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Comments: To manage postoperative pain, patient-controlled epidural analgesia was administered with 0.25% bupivacaine for up to two days after surgery. (n=34) Intervention 2: Placebo. Patients in the HEA (HEA + NS) group (n = 34) received NS in place of TXA in the same manner and at the same volume as the HEATXA group.

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	. Duration 10 minutes before the surgical incision was made, then a continuous infusion of until skin closure . Concurrent medication/care: NR. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Comments: Patients were premedicated with 0.2 mg of glycopyrrolate and 0.05 mg/kg of midazolam 30 minutes before arrival at the operating room (OR). Hypotensive epidural anaesthesia was induced with 10 to 20 mL of 0.5% bupivacaine to reach a mean arterial pressure (MAP) of 50 to 60 mmHg. If mean arterial pressure decreased to 50 mmHg, then 4 to 8 mg of ephedrine was injected intravenously (IV).
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at end of follow-up; Group 1: 0/34, Group 2: 0/34
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion (incidence) at Intra-operative and post-operative; Group 1: 9/34, Group 2: 20/34
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 3: Surgical bleeding at - - Actual outcome: Intra-operative blood loss (ml) at Intra-operative; Group 1: mean 234.9 (SD 93.9); n=34, Group 2: mean 251.8 (SD 109.9); n=34 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Postoperative bleeding at - - Actual outcome: Post-operative blood loss (ml) at Post-operative; Group 1: mean 439.3 (SD 171.6); n=34, Group 2: mean 1074.4 (SD 287.1); n=34 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Length of stay at - - Actual outcome: Length of stay (days) at end of follow-up; Group 1: mean 15.4 (SD 3.3); n=4, Group 2: mean 15.2 (SD 3.1); n=34 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Hb 48 hours after surgery at post-operative; Group 1: mean 10.8 (SD 1.1); n=34, Group 2: mean 10.7 (SD 1); n=34 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 7: Total blood loss at - - Actual outcome: Total blood loss (ml) at Intra and post-operative; Group 1: mean 674.2 (SD 216.4); n=34, Group 2: mean 1362.2 (SD 347.8); n=34 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Postoperative anaemia at -

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Study	Lee 2013[143]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=72)
Countries and setting	Conducted in South Korea; Setting: Single centre
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 90 days follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People undergoing elective primary TKA
Exclusion criteria	Planned bilateral knee or multiple joint replacements, evidence of chronic or acute preoperative DVT on color Doppler ultrasonography, rheumatoid arthritis, haemophilia or post-traumatic osteoarthritis, history of thromboembolic disease, renal insufficiency (serum creatinine[1.5 mg/dL), severe cardiovascular or respiratory disease, severe ischaemic or heart disease, acquired disturbances of colour vision, preoperative anaemia (a haemoglobin value \11 g/dL in females and \12 g/dL in males), congenital or acquired coagulopathy, or preoperative use of anticoagulant therapy within 5 days before surgery.
Recruitment/selection of patients	2010 to 2011
Age, gender and ethnicity	Age - Mean (SD): 70 (8), 69 (8). Gender (M:F): 10/62. Ethnicity: Not detailed

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Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness
Interventions	(n=36) Intervention 1: Perioperative use of tranexamic acid - IV. 2 doses of 10 mg/kg. The first infusion after implantation before tourniquet release and the second infusion 6 hours after the first.. Duration Surgery and 5 days treatment. Concurrent medication/care: Prophylaxis against venous thromboembolism in all patients was administered with subcutaneous doses of 2.5mg of fondaparinux at 6 h after surgery and for 5 days after surgery.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=36) Intervention 2: Placebo. 2 doses of placebo. The first infusion after implantation before tourniquet release and the second infusion 6 hours after the first.. Duration Surgery and 5 days treatment. Concurrent medication/care: Prophylaxis against venous thromboembolism in all patients was administered with subcutaneous doses of 2.5mg of fondaparinux at 6 h after surgery and for 5 days after surgery.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	No funding (This study did not receive any external funding.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: Doppler ultrasonography diagnosed DVT at Within 90 days of surgery; Group 1: 3/36, Group 2: 4/36
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at Within hospital period; Group 1: 4/36, Group 2: 15/36

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Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Hb drop at 2 days after surgery; Group 1: mean -3.5 g/dL (SD 1); n=36, Group 2: mean -3.2 g/dL (SD 1); n=36 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Total blood loss at - - Actual outcome: Drained total at 5 days after surgery; Group 1: mean 306 mL (SD 214); n=36, Group 2: mean 590 mL (SD 287); n=36 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -

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Study	Lee 2017[142]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=189)
Countries and setting	Conducted in China; Setting: Single centre
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery with a mean follow-up 8.2 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People undergoing primary total knee arthroplasty
Exclusion criteria	Absence of written informed consent, bilateral arthroplasties, complicated primary total knee arthroplasty with previous osteotomy, simultaneous fracture fixation, implant removal or bone grafting, thromboembolic diseases, presence of clotting disorder or current treatment with an antiplatelet agent, anticoagulant or deep vein thrombosis (DVT) prophylaxis in the perioperative period, renal disease and history of allergy to tranexamic acid.
Recruitment/selection of patients	January 2015 to December 2015
Age, gender and ethnicity	Age - Mean (SD): 70 (8), 68 (8). Gender (M:F): 60/129. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty

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Indirectness of population	No indirectness
Interventions	(n=94) Intervention 1: Perioperative use of tranexamic acid - Oral. 1g 2 hours before induction of anaesthesia and then two more doses 6 hours and 12 hours postoperatively. Duration Surgery and postoperative care. Concurrent medication/care: Thromboprophylaxis unclear. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≥3000 mg (n=95) Intervention 2: No treatment. No tranexamic acid administered. Duration Surgery and postoperative care. Concurrent medication/care: Thromboprophylaxis unclear. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Other (No potential conflict of interest relevant to this article was reported.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL versus NO TREATMENT

Protocol outcome 1: Mortality at 30 day
- Actual outcome: Mortality at Within 30 days; Group 1: 0/94, Group 2: 0/95
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Adverse events: DVT at -
- Actual outcome: Proximal DVT at Within 7 days of surgery; Group 1: 1/94, Group 2: 0/95
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at Unclear; Group 1: 1/94, Group 2: 3/95
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 4: Length of stay at - - Actual outcome: Length of stay at .; Group 1: mean 5.9 days (SD 2.2); n=94, Group 2: mean 5.8 days (SD 1.7); n=95 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Hb drop at Unclear; Group 1: mean -1.7 g/dL (SD 0.8); n=94, Group 2: mean -2.5 g/dL (SD 0.9); n=95 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: Total blood loss at - - Actual outcome: Total blood loss at Unclear; Group 1: mean 398 mL (SD 186); n=94, Group 2: mean 626 mL (SD 265); n=95 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -

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Study	Lee 2017[144]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=396)
Countries and setting	Conducted in South Korea
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery with treatment continuing for 5 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with osteoarthritis having elective unilateral primary TKA
Exclusion criteria	An acquired or congenital coagulopathy, patients receiving current anticoagulation therapy, preoperative hepatic or renal dysfunction or severe ischemic heart disease, and a history of thromboembolic disease
Recruitment/selection of patients	March 2014 to March 2015.
Age, gender and ethnicity	Age - Mean (SD): 73 (6), 72 (7). Gender (M:F): 11/175. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty

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Indirectness of population	No indirectness
Interventions	(n=93) Intervention 1: Perioperative use of tranexamic acid - IV. Intraoperative dosage (10 mg/kg) 30 minutes before tourniquet deflation; the same dose was repeated 3 hours after surgery. The calculated dose of tranexamic acid was mixed in 100 mL of normal saline and given as a slow IV injection.. Duration Surgery and 5 weeks follow-up. Concurrent medication/care: Thromboprophylaxis according to clinical assessment.1: standard risk for pulmonary embolism and bleeding: intermittent pneumatic compression during admission and aspirin 100mg once a day for 5 weeks; 2: elevated risk for pulmonary embolism and standard risk for bleeding: intermittent pneumatic compression during admission and 10 mg rivaroxaban once a day for 10 days followed by 100mg aspirin once a day for 25 days; 3: standard risk for pulmonary embolism and elevated risk for bleeding: intermittent pneumatic compression only during admission; and 4: elevated risk for pulmonary embolism and bleeding: intermittent pneumatic compression during admission and 100 mg aspirin once a day for 5 weeks.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=93) Intervention 2: Perioperative use of tranexamic acid - IA/topical. 2g of in 30mL of normal saline was injected in the joint after closure of the retinaculum and quadriceps tendon but before subcutaneous closure.. Duration Surgery and 5 weeks follow-up. Concurrent medication/care: Thromboprophylaxis according to clinical assessment.1: standard risk for pulmonary embolism and bleeding: intermittent pneumatic compression during admission and aspirin 100mg once a day for 5 weeks; 2: elevated risk for pulmonary embolism and standard risk for bleeding: intermittent pneumatic compression during admission and 10 mg rivaroxaban once a day for 10 days followed by 100mg aspirin once a day for 25 days; 3: standard risk for pulmonary embolism and elevated risk for bleeding: intermittent pneumatic compression only during admission; and 4: elevated risk for pulmonary embolism and bleeding: intermittent pneumatic compression during admission and 100 mg aspirin once a day for 5 weeks.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg
Funding	Other ("Each author certifies that neither he or she, nor any member of his or her immediate family, have funding or commercial associations (consultancies, stock ownership, equity interest, patent/licensing arrangements, etc) that might pose a conflict of interest in connection with the submitted article.")

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RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus IA/TOPICAL

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: Symptomatic DVT

at Within 5 weeks of surgery; Group 1: 0/93, Group 2: 0/93
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: -- ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Allogeneic transfusion
at While in hospital; Group 1: 0/93, Group 2: 0/93
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: -- ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Hb drop at 5 days after surgery; Group 1: mean -2.9 g/dL (SD 0.9); n=93, Group 2: mean -2.4 g/dL (SD 0.8); n=93
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: -- ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Total blood loss at -
- Actual outcome: Total blood loss at 5 days after surgery; Group 1: mean 764 mL (SD 217); n=93, Group 2: mean 633 mL (SD 205); n=93
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: -- ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -

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Study	Lemay 2004[147]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=39)
Countries and setting	Conducted in Canada; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients were eligible for this study if they were ASA classI to III and were undergoing primary total hip replacement (THR)
Exclusion criteria	History of previous ipsilateral hip surgery, known or suspected allergy to medications used (TA, local anaesthetics, midazolam,fentanyl, propofol, or dalteparin), anaemia [hemoglobin (Hb) < 115 g·L–1 forwomen, Hb < 130 g·L–1 for men], inherited or acquired haemostatic diseases,abnormal coagulation screening tests (platelet count, prothrombin time,activated partial thromboplastin time), ingestion of aspirin or other nonsteroidal anti-inflammatory drugs within seven days of surgery, renal (serumcreatinine > two standard deviation for age) or hepatic insufficiency,pregnancy, history of deep venous thrombosis (DVT) or pulmonary embolism as well as a history of ocular pathology or ophthalmological procedure other than corrective lenses
Recruitment/selection of patients	NR

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Age, gender and ethnicity	Age - Mean (SD): TXA: 59.7 ± 10.3; control- 53.6 ± 12.8 . Gender (M:F): male/female - TXA: 12 / 8; control- 13 / 6 . Ethnicity: NR
Further population details	1. Co-morbidities: 2. Site/type of joint replacement:
Extra comments	A preoperative autologous donation of three units of blood was offered to all patients.
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Perioperative use of tranexamic acid - IV. TXA was given immediately before the surgery. After a test dose of 1 mL, patients received a dose of 10mg·kg–1 iv followed by an infusion of 1 mg·kg–1·hr–1until skin closure. Duration not stated. Concurrent medication/care: Thromboprophylaxis included twice daily sc dalteparin 5,000 U started on the day of surgery, anti-stasis stocking, and early postoperative mobilisation.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Comments: All patients had spinal anaesthesia with 12.5 to 15 mg of isobaric 0.5% bupivacaine for the surgery and intrathecal morphine 0.1 to 0.25mg for postoperative pain analgesia. Intraoperative sedation was tailored to individual needs using midazolam and fentanyl or propofol (maximum dose 50 µg·kg–1·min–1). Monitoring included five-lead electrocardiography (ECG),pulse oximetry, and blood pressure monitoring with a non-invasive cuff and radial artery cannula. (n=19) Intervention 2: Placebo. Patients in control group received an equivalent volume of physiologic saline.. Duration before surgery. Concurrent medication/care: Thromboprophylaxis included twice daily sc dalteparin 5,000 U started on the day of surgery, anti-stasis stocking, and early postoperative mobilisation.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Comments: Before the surgery, a Hb transfusion trigger point was determined for each patient according to the following criteria: for men over 60 yr, women over 65 yr, and patients with a history of atherosclerotic disease, left ventricular dysfunction (ejection fraction < 35%), severe pulmonary obstructive disease (forced expiratory volume in one second < 1.5 L·min–1),or ingestion of calcium channel blockers, the transfusion trigger was 90 g·L–1.For all other patients, the transfusion trigger was 70 g·L–1. but they could be reclassified

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	to the higher trigger by the attending physician (anaesthesiologistor physician in charge of the postoperative period) if they had signs of hemodynamic instability (heart rate > 120 beats·min–1 or asystolic blood pressure decrease by > 20% of preoperative value) despite adequate volume replacement.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: Thromboembolic complications
at end of follow-up; Group 1: 0/20, Group 2: 0/19
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: allogenic red blood Transfusion at end of follow-up; Group 1: 0/20, Group 2: 8/19
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Haemoglobin values at postoperative day 4 ; Group 1: mean 9.3 g/dl (SD 1.34); n=20, Group 2: mean 9.29 g/dl (SD 1.14); n=19
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Total blood loss at -
- Actual outcome: Total blood loss at peri-operative; Group 1: mean 1308 ml (SD 462); n=20, Group 2: mean 1469 ml (SD 405); n=19
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2

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Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -

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Study	Lin 2012[154]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=151)
Countries and setting	Conducted in Taiwan
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 3 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People having unilateral minimally invasive primary TKR
Exclusion criteria	People with a history of previous surgery on the same knee, thromboembolic disease, myocardial infarction, cerebrovascular disease or a pre-operative haemoglobin < 10 g/dl
Recruitment/selection of patients	Consecutive people,Between July 2009 and August 2010,
Age, gender and ethnicity	Age - Mean (SD): 70 (8), 71 (8), 70 (8). Gender (M:F): 24/127. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness

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Interventions	(n=52) Intervention 1: Perioperative use of tranexamic acid - IV. 10 mg/kg by slow intravenous infusion five minutes before deflation of the tourniquet, having initially received an equivalent volume of normal saline five minutes before the incision.. Duration Surgery and continued treatment for 4 weeks. . Concurrent medication/care: 20mg enoxaparin subcutaneously every 12 hours until discharge. After that,indomethacin orally or by suppository for at least four weeks . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=49) Intervention 2: Perioperative use of tranexamic acid - IV. 10 mg/kg five minutes before the incision and another five minutes before deflation of the tourniquet.. Duration Surgery and continued treatment for 4 weeks. Concurrent medication/care: 20mg enoxaparin subcutaneously every 12 hours until discharge. After that,indomethacin orally or by suppository for at least four weeks. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=50) Intervention 3: Placebo. IV saline twice, five minutes before the skin incision and before deflation of the tourniquet.. Duration Surgery and continued treatment for 4 weeks. Concurrent medication/care: 20mg enoxaparin subcutaneously every 12 hours until discharge. After that,indomethacin orally or by suppository for at least four weeks. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Academic or government funding (This study was supported by the Kaohsiung Chang Gung Memorial Hospital, research fund (CMRPG890431). No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV 1 versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: Confirmed DVT at Within 3 months of surgery; Group 1: 0/52, Group 2: 0/50
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Blood transfusion required at During time in hospital; Group 1: 2/52, Group 2: 11/50
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Length of stay at -
- Actual outcome: Mean hospital stay at .; Group 1: mean 5.3 days (SD 0.61); n=52, Group 2: mean 5.5 days (SD 0.95); n=50
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Haemoglobin at 4 days after surgery; Group 1: mean 9.78 g/dL (SD 1.08); n=52, Group 2: mean 9.31 g/dL (SD 1.03); n=50
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Total blood loss at -
- Actual outcome: Total blood loss at 4 days after surgery; Group 1: mean 1035 mL (SD 259); n=52, Group 2: mean 1222 mL (SD 261); n=50
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV 2 versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: Confirmed DVT at Within 3 months of surgery; Group 1: 1/49, Group 2: 0/50
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Blood transfusion required at During time in hospital; Group 1: 3/49, Group 2: 11/50
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 3: Length of stay at - - Actual outcome: Mean hospital stay at .; Group 1: mean 5.7 days (SD 1.11); n=49, Group 2: mean 5.5 days (SD 0.95); n=50 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Haemoglobin at 4 days after surgery; Group 1: mean 10 g/dL (SD 1.12); n=49, Group 2: mean 9.31 g/dL (SD 1.03); n=50 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Total blood loss at - - Actual outcome: Total blood loss at 4 days after surgery; Group 1: mean 986 mL (SD 297); n=49, Group 2: mean 1222 mL (SD 261); n=50 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -

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Study	**Lin 2015[155]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in Taiwan
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 3 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People scheduled for unilateral TKA
Exclusion criteria	Allergy to tranexamic acid, a known history of thromboembolic disease; preoperative renal or hepatic dysfunction; cardiovascular disease, a history of myocardial infarction or angina); cerebral vascular disease (a history of stroke); preoperative anemia (a hemoglobin (Hb) value less than 11 g/dL in female and less than 12 g/dL in male); and preoperative coagulopathy (a platelet count less than 150,000/mm3 or an international normalized ratio greater than 1.4).
Recruitment/selection of patients	March 2013 to October 2013
Age, gender and ethnicity	Age - Mean (SD): 71 (7), 71 (8), 70 (8). Gender (M:F): 22/98. Ethnicity: Not detailed

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Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Perioperative use of tranexamic acid - IA/topical. 1g in 20 mL normal saline using intraarticular application intraoperatively after joint capsule closure. Duration Surgery and 2 weeks follow-up treatment. Concurrent medication/care: Thromboprophylaxis: rivaroxaban (10 mg, administered orally) from the first postoperative day and continued for 14 days. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≤1000 mg (n=40) Intervention 2: Perioperative use of tranexamic acid - IV+IA/topical. 1g IV injection 15 minutes before skin incision and 1g intraarticular application intraoperatively after joint capsule closure.. Duration Surgery and 2 weeks treatment follow-up. Concurrent medication/care: Thromboprophylaxis: rivaroxaban (10 mg, administered orally) from the first postoperative day and continued for 14 days. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg (n=40) Intervention 3: Placebo. 20mL of normal saline using intraarticular application intraoperatively after joint capsule closure. Duration Surgery and 2 weeks treatment follow-up. Concurrent medication/care: Thromboprophylaxis: rivaroxaban (10 mg, administered orally) from the first postoperative day and continued for 14 days. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Other (One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus IV+IA/TOPICAL Protocol outcome 1: Adverse events: DVT at -	

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- Actual outcome: Symptomatic thromboembolic event at Surgery and 3 months follow-up; Group 1: 0/40, Group 2: 0/40
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at Surgery and hospital period; Group 1: 1/40, Group 2: 0/40
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Hb drop at 3 days after surgery; Group 1: mean -2.4 g/dL (SD 0.9); n=40, Group 2: mean -1.9 g/dL (SD 0.8); n=40
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Total blood loss at -
- Actual outcome: Total blood loss at 3 days after surgery; Group 1: mean 705.1 mL (SD 213.5); n=40, Group 2: mean 578.7 mL (SD 246.9); n=40
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: Symptomatic thromboembolic event at Surgery and 3 months follow-up; Group 1: 0/40, Group 2: 0/40
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at Surgery and hospital period; Group 1: 1/40, Group 2: 6/40
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery

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- Actual outcome: Hb drop at 3 days after surgery; Group 1: mean -2.4 g/dL (SD 0.9); n=40, Group 2: mean -3.4 g/dL (SD 1); n=40
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Total blood loss at -
- Actual outcome: Total blood loss at 3 days after surgery; Group 1: mean 705.1 mL (SD 213.9); n=40, Group 2: mean 948.8 mL (SD 278.5); n=40
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV+IA/TOPICAL versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: Symptomatic thromboembolic event at Surgery and 3 months follow-up; Group 1: 0/40, Group 2: 0/40
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at Surgery and hospital period; Group 1: 0/40, Group 2: 6/40
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Hb drop at 3 days after surgery; Group 1: mean -1.9 g/dL (SD 0.8); n=40, Group 2: mean -3.4 g/dL (SD 1); n=40
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Total blood loss at -
- Actual outcome: Total blood loss at 3 days after surgery; Group 1: mean 578.7 mL (SD 246.9); n=40, Group 2: mean 948.8 mL (SD 278.5); n=40
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks;

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study	Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -

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Study	Luo 2018[161]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=117)
Countries and setting	Conducted in China
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 3 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	All relevant adults were approached, February 2017 to June 2017.
Age, gender and ethnicity	Age - Mean (SD): 64. Gender (M:F): Define. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Hip replacement
Indirectness of population	No indirectness
Interventions	(n=59) Intervention 1: Perioperative use of tranexamic acid - Oral. 2g was administered 2 hours before

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	surgery. 2 1g doses were administered postoperatively with a 6 hour interval. Saline IA wash was used to keep blinding. . Duration Surgery and immediate postoperative period. Concurrent medication/care: Intermittent inflatable pump utilised on the ward. LMWH was stated 6 hours after surgery and continued on a daily basis for 3 days. Then 10mg Rivaroxaban administered to person for 10 days. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≥3000 mg (n=58) Intervention 2: Perioperative use of tranexamic acid - IA/topical. 3g diluted in 150ml saline utilised. 50ml to soak acetabulum for 3 minutes. After the femoral canal broach preparation, 50ml injected into the femoral canal and removed 3 minutes later. After reduction of femoral components, 50ml was soaked and removed 3 minutes later. Placebo tablets used to keep blinding. . Duration During surgery and immediately afterwards. Concurrent medication/care: Intermittent inflatable pump utilised on the ward. LMWH was stated 6 hours after surgery and continued on a daily basis for 3 days. Then 10mg Rivaroxaban administered to person for 10 days. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≥3000 mg
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL versus IA/TOPICAL

Protocol outcome 1: Mortality at 30 day
- Actual outcome: 30-day mortality at .; Group 1: 0/59, Group 2: 0/58
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Adverse events: DVT at -
- Actual outcome: DVT at Within 3 months of surgery; Group 1: 0/59, Group 2: 0/58
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood (allogeneic or autologous) transfusion at -

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- Actual outcome: Transfusion at Unclear; Group 1: 1/59, Group 2: 2/58 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Surgical bleeding at - - Actual outcome: Intraoperative blood loss at .; Group 1: mean 230.44 mL (SD 56.02); n=59, Group 2: mean 219.66 mL (SD 59.63); n=58 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Length of stay at - - Actual outcome: Length of stay at .; Group 1: mean 3.75 days (SD 0.86); n=59, Group 2: mean 3.93 days (SD 1.04); n=58 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Haemoglobin drop at Unclear; Group 1: mean -3.07 g/dL (SD 1.44); n=59, Group 2: mean -3.12 g/dL (SD 1.49); n=58 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 7: Total blood loss at - - Actual outcome: Total blood loss at Unclear; Group 1: mean 863 mL (SD 432); n=59, Group 2: mean 902 mL (SD 418); n=58 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Postoperative anaemia at -; Postoperative bleeding at -

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Study	Luo 2018[162]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=180)
Countries and setting	Conducted in China
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 3 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with osteoarthritis or osteonecrosis of the femoral head and scheduled to undergo cementless primary unilateral THA
Exclusion criteria	Planned revision surgery, bilateral arthroplasty, or complicated primary THA with osteotomy; a history of deep vein thrombosis (DVT), pulmonary embolism (PE), congenital or acquired clotting disorders, and/or ongoing anticoagulant treatment; preoperative hepatic or renal dysfunction and serious cardiac and/or cerebrovascular comorbidities; allergy to TXA; and refusal to participate
Recruitment/selection of patients	From March 2016 to April 2017,
Age, gender and ethnicity	Age - Mean (SD): 68 (10), 67 (9), 65 (8). Gender (M:F): 80/100. Ethnicity: Not detailed

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Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Hip replacement
Indirectness of population	No indirectness
Interventions	(n=60) Intervention 1: Perioperative use of tranexamic acid - Oral. 2g approximately 2 hours before the incision. 100mL normal saline IV infusion administered 5 minutes before the skin incision. 150mL of normal saline administered using the same method as in the topical group. Duration Surgery until 15 days after hospital discharge. Concurrent medication/care: After anesthesia recovery, an intermittent inflatable pump system was applied to all patients before ambulation. A halfdose of low-molecular-weight heparin was administered subcutaneously 6 hours postoperatively and a full dose was repeated at 24-hour intervals subsequently until hospital discharge. After discharge, all patients routinely received 10mg rivaroxaban for 15 days. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg (n=60) Intervention 2: Perioperative use of tranexamic acid - IV. 20 mg/kg diluted in 100ml normal saline given as an IV bolus 5 minutes before the skin incision. 4 placebo tablets, identical in appearance with no active ingredient, were administered. 100-mL normal saline IV infusion administered 5 minutes before the skin incision. . Duration Surgery until 15 days after hospital discharge. Concurrent medication/care: After anesthesia recovery, an intermittent inflatable pump system was applied to all patients before ambulation. A halfdose of low-molecular-weight heparin was administered subcutaneously 6 hours postoperatively and a full dose was repeated at 24-hour intervals subsequently until hospital discharge. After discharge, all patients routinely received 10mg rivaroxaban for 15 days. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=60) Intervention 3: Perioperative use of tranexamic acid - IA/topical. 2g diluted in 150mL of normal saline. Following the acetabular preparation, the acetabulumwas soaked with 50mL of solution for 3 minutes. After the femoral canal broach preparation, 50mL solution was injected into the femoral canal and removed by suction 3 minutes later. After reduction of the final hip components, 50mL solution was applied to the wound and allowed to remain undisturbed for 3 minutes, after which it was removed by suction. 4 placebo tablets, identical in appearance with no active ingredient, were administered. 100mL normal saline IV infusion administered 5 minutes before the skin incision. Duration Surgery until 15 days after hospital

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	discharge. Concurrent medication/care: After anesthesia recovery, an intermittent inflatable pump system was applied to all patients before ambulation. A halfdose of low-molecular-weight heparin was administered subcutaneously 6 hours postoperatively and a full dose was repeated at 24-hour intervals subsequently until hospital discharge. After discharge, all patients routinely received 10mg rivaroxaban for 15 days. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg
Funding	Academic or government funding (This research was funded by the National Health and Family Planning Commission of the People's Republic of China (program 201302007).)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL versus IV

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 3 months of surgery; Group 1: 0/60, Group 2: 0/60
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at During hsopitalised period; Group 1: 4/60, Group 2: 5/60
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Length of stay at -
- Actual outcome: Length of stay at .; Group 1: mean 3.43 days (SD 0.95); n=60, Group 2: mean 3.58 days (SD 1.17); n=60
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Reduction in heamoglobin at 3 days after surgery; Group 1: mean -3.48 g/dL (SD 1.32); n=60, Group 2: mean -3.58 g/dL (SD 1.07); n=60
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 5: Total blood loss at -
- Actual outcome: Total blood loss at 3 days after surgery; Group 1: mean 1004 mL (SD 415); n=60, Group 2: mean 1032 mL (SD 350); n=60
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL versus IA/TOPICAL

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 3 months of surgery; Group 1: 0/60, Group 2: 0/60
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at During hsopitalised period; Group 1: 4/60, Group 2: 7/60
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Length of stay at -
- Actual outcome: Length of stay at .; Group 1: mean 3.43 days (SD 0.95); n=60, Group 2: mean 3.41 days (SD 0.72); n=60
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Reduction in heamoglobin at 3 days after surgery; Group 1: mean -3.48 g/dL (SD 1.32); n=60, Group 2: mean -3.66 g/dL (SD 1.26); n=60
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Total blood loss at -
- Actual outcome: Total blood loss at 3 days after surgery; Group 1: mean 1004 mL (SD 415); n=60, Group 2: mean 1064 mL (SD 410); n=60
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus IA/TOPICAL

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 3 months of surgery; Group 1: 0/60, Group 2: 0/60
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at During hsopitalised period; Group 1: 5/60, Group 2: 7/60
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Length of stay at -
- Actual outcome: Length of stay at .; Group 1: mean 3.58 days (SD 1.17); n=60, Group 2: mean 3.41 days (SD 0.72); n=60
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Reduction in heamoglobin at 3 days after surgery; Group 1: mean -3.58 g/dL (SD 1.07); n=60, Group 2: mean -3.66 g/dL (SD 1.26); n=60
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Total blood loss at -
- Actual outcome: Total blood loss at 3 days after surgery; Group 1: mean 1032 mL (SD 350); n=60, Group 2: mean 1064 mL (SD 410); n=60
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -

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Study	Malhotra 2011[166]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in India
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery with at least 10 days follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People undergoing unilateral cementless total hip arthroplasty.
Exclusion criteria	History of severe ischemic heart disease, chronic renal failure, cirrhosis of the liver, bleeding disorders, currently receiving anticoagulant therapy.
Age, gender and ethnicity	Age - Mean (SD): 54. Gender (M:F): 22/28. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Hip replacement
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Perioperative use of tranexamic acid - IV. IV 15kg/mg 15 minutes before incision. . Duration During surgery. Concurrent medication/care: LMWH and elastic leg dressing used in all people.

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	Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=25) Intervention 2: Placebo. Normal saline injected as placebo. Duration During surgery. Concurrent medication/care: LMWH and elastic leg dressing used in all people. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO Protocol outcome 1: Adverse events: DVT at - - Actual outcome: DVT at During hospital period and follow-up; Group 1: 0/25, Group 2: 0/25 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Blood (allogeneic or autologous) transfusion at - - Actual outcome: Transfusion at During hospital period; Group 1: 6/25, Group 2: 18/25 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -; Blood loss: Haemoglobin level at 3 days after surgery; Total blood loss at -

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Study	Maniar 2012[167]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=206)
Countries and setting	Conducted in India; Setting: This work was conducted at Lilavati Hospital and Research Centre.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 3 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with osteoarthritis scheduled to have primary, unilateral TKA.
Exclusion criteria	Known allergy to tranexamic acid; preoperative hepatic or renal dysfunction; serious cardiac or respiratory disease; congenital or acquired coagulopathy; and a history of thromboembolic disease
Recruitment/selection of patients	August 2010 to April 2011.
Age, gender and ethnicity	Age - Mean (SD): 66 (7), 67 (9), 68 (8), 67 (8), 67 (7), 67 (8). Gender (M:F): 46/194. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness

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Interventions	(n=40) Intervention 1: Perioperative use of tranexamic acid - IV. 10 mg/kg 15 minutes before deflation of the tourniquet as an intraoperative dose. Duration Surgery until hospital discharge. Concurrent medication/care: Thromboprophylaxis: ankle and foot movement exercises were started as soon the anesthesia effect wore off; low molecular-weight heparin beginning on Day 1 and continued until the time of discharge; and below-knee stockings.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=40) Intervention 2: Perioperative use of tranexamic acid - IV. 10 mg/kg 15 minutes before deflation of the tourniquet and 10 mg/kg 3 hours after the first dose as a postoperative dose. Duration Surgery until hospital discharge. Concurrent medication/care: Thromboprophylaxis: ankle and foot movement exercises were started as soon the anesthesia effect wore off; low molecular-weight heparin beginning on Day 1 and continued until the time of discharge; and below-knee stockings.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=40) Intervention 3: Perioperative use of tranexamic acid - IV. 10mg/kg at least 20 minutes before tourniquet inflation as a preoperative dose and 10mg/kg 15 minutes before deflation of the tourniquet as an intraoperative dose. Duration Surgery until hospital discharge . Concurrent medication/care: Thromboprophylaxis: ankle and foot movement exercises were started as soon the anesthesia effect wore off; low molecular-weight heparin beginning on Day 1 and continued until the time of discharge; and below-knee stockings.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: (n=40) Intervention 4: Perioperative use of tranexamic acid - IV. 10mg/kg 20 minutes before tourniquet application as a preoperative dose, 10mg/kg 15 minutes before deflation of the tourniquet as an intraoperative dose, and 10mg/kg 3 hours after the second dose as a postoperative dose. Duration Surgery until hospital discharge. Concurrent medication/care: Thromboprophylaxis: ankle and foot movement exercises were started as soon the anesthesia effect wore off; low molecular-weight heparin beginning on Day 1 and continued until the time of discharge; and below-knee stockings.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=40) Intervention 5: Perioperative use of tranexamic acid - IA/topical. 3g diluted in 100 mL normal saline applied locally after cementing the implant and before tourniquet release. At least 5 minutes of contact time

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	was allowed before the tourniquet was deflated.. Duration Surgery until hospital discharge. Concurrent medication/care: Thromboprophylaxis: ankle and foot movement exercises were started as soon the anesthesia effect wore off; low molecular-weight heparin beginning on Day 1 and continued until the time of discharge; and below-knee stockings. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear
Funding	Other (Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV IO versus IA/TOPICAL LA

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 3 months of surgery; Group 1: 0/40, Group 2: 0/40
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: People receiving transfusions at During hospital period; Group 1: 5/40, Group 2: 3/40
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Total blood loss at -
- Actual outcome: Total blood loss at Within 5 days of surgery; Group 1: mean 824 mL (SD 226.8); n=40, Group 2: mean 809 mL (SD 341.1); n=40
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV IOPO versus IA/TOPICAL LA

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 3 months of surgery; Group 1: 0/40, Group 2: 0/40

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Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: People receiving transfusions at During hospital period; Group 1: 7/40, Group 2: 3/40
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Total blood loss at -
- Actual outcome: Total blood loss at Within 5 days of surgery; Group 1: mean 864 mL (SD 315); n=40, Group 2: mean 809 mL (SD 341.1); n=40
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV POIO versus IA/TOPICAL LA

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 3 months of surgery; Group 1: 0/40, Group 2: 0/40
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: People receiving transfusions at During hospital period; Group 1: 1/40, Group 2: 3/40
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Total blood loss at -
- Actual outcome: Total blood loss at Within 5 days of surgery; Group 1: mean 782 mL (SD 233.1); n=40, Group 2: mean 809 mL (SD 341.1); n=40
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV POIOPO versus IA/TOPICAL LA

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Protocol outcome 1: Adverse events: DVT at - - Actual outcome: DVT at Within 3 months of surgery; Group 1: 0/40, Group 2: 0/40 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Blood (allogeneic or autologous) transfusion at - - Actual outcome: People receiving transfusions at During hospital period; Group 1: 3/40, Group 2: 3/40 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Total blood loss at - - Actual outcome: Total blood loss at Within 5 days of surgery; Group 1: mean 688 mL (SD 308.2); n=40, Group 2: mean 809 mL (SD 341.1); n=40 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -; Blood loss: Haemoglobin level at 3 days after surgery

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Study	Martin 2014[170]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in USA; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 18 years and older, who were scheduled for a primary TKA or primary THA with or without cement
Exclusion criteria	Revisions, bilateral joint arthroplasty procedures, known hypersensitivity to TXA or its ingredients, active intravascular clotting disorders, and acute subarachnoid haemorrhage. Patients with a history of DVT or PE were not excluded as the current literature does not indicate TXA has an increased risk for thromboembolic events
Recruitment/selection of patients	From January 2012 through July 2012, 117 patients scheduled for a primary TKA or THA with a single surgeon were screened and assessed for eligibility.
Age, gender and ethnicity	Age - Mean (SD): TXA: 67.16 ± 10.55; control-64.28 ± 9.68. Gender (M:F): female (%): TXA: 44%; Control-56%. Ethnicity: not stated

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Further population details	1. Co-morbidities: 2. Site/type of joint replacement:
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Perioperative use of tranexamic acid - IA/topical. 2 g TXA in 100 ml of normal saline (NS) into the joint space prior to surgical closure. The treatment arm was prepared by removing 20 ml of NS from a 100 ml NS IV piggyback and adding 2 g/20 ml TXA to the NS piggyback to provide a total volume of 100 ml.. Duration not stated . Concurrent medication/care: For antibiotic prophylaxis, patients were given cefazolin IV unless a documented allergy was listed, in which case vancomycin IV was administered. For venous thromboembolism prophylaxis, mechanical foot compression was applied in the postoperative recovery room. Unless contraindicated, patients were placed on warfarin while in the hospital and then discharged on aspirin 325 mg orally twice daily for 30 days. Those patients that were on therapeutic anticoagulation therapy prior to surgery were discharged on their pre-surgical anticoagulant regimen.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Comments: All procedures were primary total knee and total hiparthroplasties performed by the same surgeon and conducted under general or spinal anaesthesia. (n=25) Intervention 2: Placebo. Placebo (NS) (equivalent volume of TXA) into the joint space prior to surgical closure. The placebo arm was prepared by removing 20 ml of NS from a 100 ml NS IV piggyback and adding 20 ml NS back into the NS piggyback to provide a total volume of 100 ml.. Duration not stated. Concurrent medication/care: For antibiotic prophylaxis, patients were given cefazolin IVunless a documented allergy was listed, in which case vancomycin IV was administered. For venous thromboembolism prophylaxis, mechanical foot compression was applied in the postoperative recovery room. Unless contraindicated, patients were placed on warfarin while in the hospital and then discharged on aspirin 325 mg orally twice daily for 30 days. Those patients that were on therapeutic anticoagulation therapy prior to surgery were discharged on their pre-surgical anticoagulant regimen.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Comments: Patients were considered for blood transfusion if they demonstrated symptomatic hypotension, or had a postoperative haemoglobin level less than 7g/dL. The decision to transfuse was made without knowledge of the treatment arm in which the patient was enrolled. Standards of practice for anaesthesia and postoperative monitoring and care were performed by the orthopaedics surgeon's routine practice.

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Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus PLACEBO Protocol outcome 1: Adverse events: DVT at - - Actual outcome: Venous thromboembolism events at end of follow-up; Group 1: 0/25, Group 2: 0/25 Risk of bias: All domain - ; Indirectness of outcome: No indirectness Protocol outcome 2: Blood (allogeneic or autologous) transfusion at - - Actual outcome: Transfusion at end of follow-up; Group 1: 4/25, Group 2: 5/25 Risk of bias: All domain - ; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -; Blood loss: Haemoglobin level at 3 days after surgery; Total blood loss at -

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Study	May 2016[171]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=131)
Countries and setting	Conducted in USA; Setting: Performed by 2 senior surgeons.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 30 days of follow-up after hospital discharge
Method of assessment of guideline condition	--
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults over 18 years old undergoing primary unilateral total knee arthroplasty
Exclusion criteria	Previous reconstructive procedures, renal impairment, bleeding or platelet disorders, history of thromboembolic event, history of vascular procedures, pregnant or breastfeeding, religious objection to receiving blood products, acquired colour blindness, hypersensitivity, inability to cease anticoagulant therapies except aspirin.
Age, gender and ethnicity	Age - --: . Gender (M:F): Define. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	--

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Interventions	(n=69) Intervention 1: Perioperative use of tranexamic acid - IV. 2 doses of 1g in 100ml normal saline. The first dose after anaesthetic induction, the second dose after capsular closure. Saline used for IA placebo. . Duration Surgery and hospital period. Concurrent medication/care: Thromboprophylaxis: based on surgeon preference, either LMWH or oral direct factor Xa inhibitor. Also bilateral short leg sequential compression device used postoperatively while in bed. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg (n=62) Intervention 2: Perioperative use of tranexamic acid - IA/topical. 2g in 50ml saline. Injected into capsular closure. 100ml saline used as IV placebo.. Duration Surgery and hospital period. Concurrent medication/care: Thromboprophylaxis: based on surgeon preference, either LMWH or oral direct factor Xa inhibitor. Also bilateral short leg sequential compression device used postoperatively while in bed.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg
Funding	Other (Funding not stated but authors have declared possible conflicts of interest)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus IA/TOPICAL

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at within 30 days of hospital discharge; Group 1: 2/69, Group 2: 1/62
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at within 30 days of hospital discharge; Group 1: 1/69, Group 2: 0/62
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Length of stay at -
- Actual outcome: Length of stay at .; Group 1: mean 2.4 days (SD 0.8); n=69, Group 2: mean 2.2 days (SD 0.6); n=62

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Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Haemoglobin at 3 days after surgery; Group 1: mean 10.2 g/dL (SD 1.4); n=69, Group 2: mean 10.7 g/dL (SD 1.5); n=62 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Total blood loss at - - Actual outcome: Cumulative blood loss at 3 days after surgery; Group 1: mean 1075.5 mL (SD 419); n=69, Group 2: mean 977.7 mL (SD 342.6); n=62 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -

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Study	Mcconnell 2011[172]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=66)
Countries and setting	Conducted in United Kingdom
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 35 days follow-up treatment
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People who were scheduled to undergo elective primary unilateral cemented hip arthroplasty.
Exclusion criteria	Taking anticoagulant medication or had a known coagulopathy, contraindications the medications in the study: known allergy to the medications used, including allergy to aspirin; previous reaction to blood products; ethical/religious objection to receiving blood products; or previous thromboembolism.
Recruitment/selection of patients	June 2006 through May 2008.
Age, gender and ethnicity	Age - Mean (SD): Not detailed. Gender (M:F): 16/28. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Hip replacement

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Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Perioperative use of tranexamic acid - IV. 10 mg/kg dose of tranexamic acid as an intravenous bolus at the start of surgery. Duration Surgery and 35 days postoperatively . Concurrent medication/care: Thromboprophylaxis: graduated compression stockings, early mobilization, and 150 mg of aspirin by mouth for 35 days postoperatively.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=22) Intervention 2: No treatment. No treatment with tranexamic acid. Duration Surgery and 35 days postoperatively. Concurrent medication/care: Thromboprophylaxis: graduated compression stockings, early mobilization, and 150 mg of aspirin by mouth for 35 days postoperatively.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Other (No competing interests declared.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus NO TREATMENT

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: Adverse outcomes at Unclear; Group 1: 0/22, Group 2: 0/22
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Blood (allogeneic or autologous) transfusion at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -; Blood loss: Haemoglobin level at 3 days after surgery; Total blood loss at -

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Study	Mehta 2019[175]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=300)
Countries and setting	Conducted in India
Line of therapy	Not applicable
Duration of study	Intervention time: Surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People having primary bilateral total knee arthroplasty due to advanced osteoarthritis of the knee.
Exclusion criteria	Previous ipsilateral knee surgery, allergy or hypersensitivity to tranexamic acid, history of thromboembolic disease, renal/hepatic insufficiency, preoperative coagulopathy.
Recruitment/selection of patients	April 2016 to October 2017.
Age, gender and ethnicity	Age - Mean (SD): 61 (7), 63 (6), 62 (5). Gender (M:F): 123/177. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness

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Interventions	(n=100) Intervention 1: Perioperative use of tranexamic acid - IV. 1g administered after regional anaesthesia but before tourniquet inflation. . Duration Surgery and 12 days follow-up. Concurrent medication/care: 2.5mg oral apixaban starting 24 hours after surgery given twice per day for 12 days. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≤1000 mg (1g). (n=100) Intervention 2: Perioperative use of tranexamic acid - IA/topical. 2.5g (25ml) in 25ml saline. Equally given to each knee joint after wound closure. . Duration Surgery and 12 days follow-up. Concurrent medication/care: 2.5mg oral apixaban starting 24 hours after surgery given twice per day for 12 days. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg (2.5g). (n=100) Intervention 3: No treatment. No tranexamic acid given. Duration Surgery and 12 days follow-up. Concurrent medication/care: 2.5mg oral apixaban starting 24 hours after surgery given twice per day for 12 days. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus NO TREATMENT

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT or PE at In hospital period; Group 1: 0/100, Group 2: 0/100
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: No ASA or equivalent; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion rate at While in hospital; Group 1: 37/100, Group 2: 76/100
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

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- Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: No ASA or equivalent; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Surgical bleeding at -
- Actual outcome: Intraoperative blood loss at Surgery; Group 1: mean 165.8 ml (SD 64.71); n=100, Group 2: mean 332.3 ml (SD 64.71); n=100
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: No ASA or equivalent; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Haemoglobin at 2 days after surgery; Group 1: mean 10.41 g/dl (SD 1); n=100, Group 2: mean 9.96 g/dl (SD 1.12); n=100
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: No ASA or equivalent; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Total blood loss at -
- Actual outcome: Total blood loss at Postoperative day 2; Group 1: mean 607.9 ml (SD 94.37); n=100, Group 2: mean 1061.3 ml (SD 170.06); n=100
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: No ASA or equivalent; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus IV

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT or PE at In hospital period; Group 1: 0/100, Group 2: 0/100
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: No ASA or equivalent; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion rate at While in hospital; Group 1: 44/100, Group 2: 37/100
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

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- Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: No ASA or equivalent; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Surgical bleeding at -
- Actual outcome: Intraoperative blood loss at Surgery; Group 1: mean 317.8 ml (SD 86.15); n=100, Group 2: mean 165.8 ml (SD 49.75); n=100
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: No ASA or equivalent; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Haemoglobin at 2 days after surgery; Group 1: mean 1.041 g/dl (SD 0.117); n=100, Group 2: mean 1.041 g/dl (SD 0.1); n=100
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: No ASA or equivalent; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Total blood loss at -
- Actual outcome: Total blood loss at Postoperative day 2; Group 1: mean 614.15 ml (SD 128.73); n=100, Group 2: mean 607.9 ml (SD 94.37); n=100
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: No ASA or equivalent; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus NO TREATMENT

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT or PE at In hospital period; Group 1: 0/100, Group 2: 0/100
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: No ASA or equivalent; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion rate at While in hospital; Group 1: 44/100, Group 2: 74/100
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

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- Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: No ASA or equivalent; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Surgical bleeding at - - Actual outcome: Intraoperative blood loss at Surgery; Group 1: mean 317.8 ml (SD 86.15); n=100, Group 2: mean 332.3 ml (SD 64.71); n=100 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: No ASA or equivalent; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Haemoglobin at 2 days after surgery; Group 1: mean 1.041 g/dl (SD 0.117); n=100, Group 2: mean 0.996 g/dl (SD 0.112); n=100 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: No ASA or equivalent; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Total blood loss at - - Actual outcome: Total blood loss at Postoperative day 2; Group 1: mean 614.15 ml (SD 128.73); n=100, Group 2: mean 1061.3 ml (SD 170.06); n=100 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: No ASA or equivalent; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -

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Study	Melo 2017[176]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=42)
Countries and setting	Conducted in Brazil
Line of therapy	Not applicable
Duration of study	Intervention time: Surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People undergoing primary THA
Exclusion criteria	Not detailed
Age, gender and ethnicity	Age - Mean (SD): Not detailed. Gender (M:F): Not detailed. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Hip replacement
Indirectness of population	No indirectness
Interventions	(n=14) Intervention 1: Perioperative use of tranexamic acid - IV. 15mg/kg IV bolus dose 20 min before incision (maximum dose 2g). Duration Surgery. Concurrent medication/care: Thromboprophylaxis unclear. Indirectness: No indirectness

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	Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=14) Intervention 2: Perioperative use of tranexamic acid - IV. 15mg/kg IV bolus dose 20 min before incision and an extra dose of 10mg/kg using an infusion pump throughout the surgical procedure.. Duration Surgery. Concurrent medication/care: Thromboprophylaxis unclear. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=14) Intervention 3: No treatment. Did not receive tranexamic acid. Duration Surgery. Concurrent medication/care: Thromboprophylaxis unclear. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Other (The authors declare no conflicts of interest.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV 1 versus NO TREATMENT

Protocol outcome 1: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Haemoglobin level at 48 hours after surgery; Group 1: mean 10.92 g/dL (SD 2.7); n=14, Group 2: mean 9.7 g/dL (SD 2.4); n=14
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV 2 versus NO TREATMENT

Protocol outcome 1: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Haemoglobin level at 48 hours after surgery; Group 1: mean 10.89 g/dL (SD 2.8); n=14, Group 2: mean 9.7 g/dL (SD 2.4); n=14
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Adverse events: DVT at -; Blood (allogeneic or autologous) transfusion at -; Quality of life at within 6 weeks: Surgical bleeding at -;

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Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -; Total blood loss at -

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Study	Molloy 2007[180]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in United Kingdom
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery with 90 days follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with a pre-operative haemoglobin (Hb) level of 13.0 g/dl or less who were scheduled to undergo a primary TKR
Exclusion criteria	Previous surgery to the knee, with the exception of meniscectomy, bleeding disorders, platelet or bone-marrow disorders, a level of creatinine > 250 µmol/l since this is a contraindication to the administration of tranexamic acid, or a history of thromboembolism
Recruitment/selection of patients	December 2004 to October 2005,
Age, gender and ethnicity	Age - Mean (SD): Not detailed. Gender (M:F): Not detailed. Ethnicity: Not detailed

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Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Perioperative use of tranexamic acid - IV. 500mg five minutes before deflation of the tourniquet and a repeat dose three hours later. Duration Surgery and 6 weeks follow-up treatment. Concurrent medication/care: Thromboprophylaxis: 150 mg of aspirin as a single dose the evening before surgery and daily for 6 weeks post-operatively. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≤1000 mg (n=50) Intervention 2: No treatment. No tranexamic acid treatment. Duration Surgery and 6 weeks follow-up treatment. Concurrent medication/care: Thromboprophylaxis: 150 mg of aspirin as a single dose the evening before surgery and daily for 6 weeks post-operatively. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Other (Although none of the authors has received or will receive benefits for personal or professional use from a commercial party related directly or indirectly to the subject of this article, benefits have been or will be received but will be directed solely to a research fund, foundation, educational institution, or other nonprofit organisation with which one or more of the authors are associated.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus NO TREATMENT

Protocol outcome 1: Mortality at 30 day
- Actual outcome: Mortality at Within 90 days of surgery; Group 1: 0/50, Group 2: 0/50
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Outcome reported at 90 days rather than 30 days as stated in the protocol; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Adverse events: DVT at -
- Actual outcome: DVT at Within 90 days of surgery; Group 1: 0/50, Group 2: 0/50

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Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Blood (allogeneic or autologous) transfusion at - - Actual outcome: Transfusion at Within 90 days of surgery; Group 1: 5/50, Group 2: 11/50 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Hb drop at Unclear: 1 2 or 3 days after surgery; Group 1: mean -2.75 g/dL (SD 1.03); n=50, Group 2: mean -3.2 g/dL (SD 1.12); n=50 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Total blood loss at - - Actual outcome: Total blood loss at unclear; Group 1: mean 1225 mL (SD 499); n=50, Group 2: mean 1415 mL (SD 416); n=50 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -

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Study	Motififard 2015[183]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=95)
Countries and setting	Conducted in Iran; Setting: Kashani teaching hospital, a tertiary referral center in Isfahan
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 48 hours follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with osteoarthritis who were indicated for primary TKA.
Exclusion criteria	People with previous history of cerebrovascular disease, thromboembolism, myocardial infarction, and those who were candidates for bilateral TKA were excluded.
Age, gender and ethnicity	Age - Mean (SD): 66. Gender (M:F): Unclear. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness
Interventions	(n=45) Intervention 1: Perioperative use of tranexamic acid - IV. IV Tranexamic acid (500mg) diluted in

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	100mL of 0.9% saline chloride twice; the first dose was infused in over 10 minutes about 30 minutes before inflation of tourniquet and the second dose after staying in the recovery room for three hours.. Duration During surgery and early recovery. Concurrent medication/care: No details of thromboprophylaxis. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≤1000 mg (n=45) Intervention 2: Placebo. IV slow infusion of 100mL of 0.9% sodium chloride twice.Timing same as intervention group.. Duration During surgery and early recovery. Concurrent medication/care: No details of thromboprophylaxis. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at During or after surgery; Group 1: 0/45, Group 2: 0/45
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Surgical bleeding at -
- Actual outcome: Drain output at during surgery; Group 1: mean 268.66 ml (SD 116.68); n=45, Group 2: mean 478.11 ml (SD 254.19); n=45
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Length of stay at -
- Actual outcome: Duration of hospitalisation at .; Group 1: mean 6.02 days (SD 2.97); n=45, Group 2: mean 6.93 days (SD 2.71); n=45
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery

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- Actual outcome: Hb level at 2 days after surgery; Group 1: mean 10.92 g/dL (SD 0.97); n=45, Group 2: mean 10.23 g/dL (SD 0.98); n=45 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Blood (allogeneic or autologous) transfusion at -; Quality of life at within 6 weeks; Postoperative anaemia at -; Postoperative bleeding at -; Total blood loss at -

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Study	Niskanen 2005[191]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Finland; Setting: Päijät-Häme hospital district
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery with final observations at 24 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Consecutive people who were scheduled for a cemented hip arthroplasty for osteoarthritis.
Exclusion criteria	People with rheumatoid arthritis and osteonecrosis, and with known coagulation disturbances including thromboembolic events, were not considered eligible for the study. Patients using warfarin related preparations, or with allergy to tranexamic acid, or with signs of renal insufficiency were also excluded.
Recruitment/selection of patients	Volunteers
Age, gender and ethnicity	Age - Mean (SD): 65. Gender (M:F): 13/26. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Hip replacement

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Extra comments	A cemented Elite Plus or C-Stem prosthesis (DePuy, Leeds, UK) was used in all patients. Spinal anesthesia followed by epidural analgesia until the next morning was used in 39 patients, and 1 patient had general anesthesia.
Indirectness of population	No indirectness
Interventions	(n=19) Intervention 1: Perioperative use of tranexamic acid - IV. 3 doses of tranexamic acid (10 mg/kg) mixed in 100 mL saline.The first injection was given intravenously over 5–10 min, immediately before the operation. The next two doses were given 8 hours and 16 hours after the first injection.. Duration During and immediate aftermath of surgery. Concurrent medication/care: The same antithrombotic prophylaxis during hospitalization, low-molecular-weight heparin (dalteparin) and elastic leg dressing were used for all patients.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (10mg/kg). (n=20) Intervention 2: Placebo. 3 doses of saline.The first injection was given intravenously over 5–10 min, immediately before the operation. The next two doses were given 8 hours and 16 hours after the first injection.. Duration During and immediate aftermath of surgery. Concurrent medication/care: The same antithrombotic prophylaxis during hospitalization, low-molecular-weight heparin (dalteparin) and elastic leg dressing were used for all patients.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Equipment / drugs provided by industry (Pharmacia (later Pfizer) implemented the study)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Allogenic blood transfusion at During or after surgery; Group 1: 5/19, Group 2: 8/20
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 2: Surgical bleeding at - - Actual outcome: Peroperative bleeding at During surgery; Group 1: mean 626 ml (SD 299); n=19, Group 2: mean 790 ml (SD 436); n=20 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Total blood loss at - - Actual outcome: Bleeding + drainage at 24 hours after surgery; Group 1: mean 792 ml (SD 386); n=19, Group 2: mean 1102 ml (SD 495); n=20 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Adverse events: DVT at -; Quality of life at within 6 weeks; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -; Blood loss: Haemoglobin level at 3 days after surgery

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Study	Onodera 2012[193]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in Japan
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 10 days follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People having primary total knee replacement
Exclusion criteria	Unclear
Recruitment/selection of patients	Consecutive people from 2006 to 2009
Age, gender and ethnicity	Age - Mean (SD): 70 (10), 71 (8). Gender (M:F): 17/83. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Perioperative use of tranexamic acid - IA/topical. 1g in 50ml saline with 50g

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	carbazochrome sodium sulfonate injected through the drain immediately after wound closure. . Duration Surgery. Concurrent medication/care: No thromboprophylaxis detailed. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≤1000 mg (n=50) Intervention 2: Placebo. 50ml of saline through the drain after closure. Duration Surgery. Concurrent medication/care: No thromprophylaxis detailed. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: Proximal DVT at Unclear; Group 1: 2/50, Group 2: 1/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Length of stay at -
- Actual outcome: Drainage period at .; Group 1: mean 3.36 days (SD 1.16); n=50, Group 2: mean 3.24 days (SD 0.82); n=50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Reduction in haemoglobin level at 24 hours after surgery; Group 1: mean -2.2 g/dL (SD 1.11); n=50, Group 2: mean -3.11 g/dL (SD 1.26); n=50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Total blood loss at -
- Actual outcome: Total blood loss at 24 hours after surgery; Group 1: mean 380.4 mL (SD 271.2); n=50, Group 2: mean 676.4 mL (SD 306.2); n=50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

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- Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Blood (allogeneic or autologous) transfusion at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -

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Study	Orpen 2006[195]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in United Kingdom
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Operative and post-operative period
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People scheduled for total knee arthroplasty
Exclusion criteria	People with a history of thromboembolic disease, cerebrovascular disease, recent myocardial infarction or unstable angina, a coagulation defect, those with an allergy to TA and those who, for whatever reason, are not fit to undergo surgery under general anaesthetic.
Recruitment/selection of patients	Consecutive patients on the waiting list were approached
Age, gender and ethnicity	Age - Mean (SD): 71. Gender (M:F): 10/19. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty

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Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Perioperative use of tranexamic acid - IV. 15 mg/kg IV at the time that cement mixing commenced. . Duration During surgery and postoperative period. Concurrent medication/care: All people received standard thrombo-prophylaxis in the form of post-operative low molecular weight heparin, subcutaneously, in accordance with existing practice.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (15mg/kg). (n=15) Intervention 2: Placebo. 15mg/kg IV saline at the time that cement mixing commenced. Duration During surgery and postoperative period. Concurrent medication/care: All people received standard thrombo-prophylaxis in the form of post-operative low molecular weight heparin, subcutaneously, in accordance with existing practice.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at During surgery and postoperative 5 days; Group 1: 0/15, Group 2: 0/14
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: drains had fallen out in the immediate postoperative period

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: People transfused at .; Group 1: 1/15, Group 2: 3/14
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: drains had fallen out

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in the immediate postoperative period Protocol outcome 3: Surgical bleeding at - - Actual outcome: Intraoperative blood loss at .; Group 1: mean 220 (SD 174); n=15, Group 2: mean 169 (SD 201); n=14 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: drains had fallen out in the immediate postoperative period Protocol outcome 4: Postoperative bleeding at - - Actual outcome: Recovery period blood loss at .; Group 1: mean 95 (SD 76); n=15, Group 2: mean 218 (SD 158); n=14 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: drains had fallen out in the immediate postoperative period Protocol outcome 5: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Drop in Hb at 3 days after surgery; Group 1: mean -2.49 g/dL (SD 3.9); n=15, Group 2: mean -3.27 g/dL (SD 4.2); n=14 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: drains had fallen out in the immediate postoperative period Protocol outcome 6: Total blood loss at - - Actual outcome: Total blood loss at 24 hours after surgery; Group 1: mean 660 ml (SD 324); n=15, Group 2: mean 726 ml (SD 340); n=14 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: drains had fallen out in the immediate postoperative period	
Protocol outcomes not reported by the	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks;

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Postoperative anaemia at -; Length of stay at -	
study	

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Study	Oztas 2015[196]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in Turkey
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 3 month follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with degenerative knee osteoarthritis who did not respond to conservative treatment and underwent unilateral primary TKR
Exclusion criteria	People with inflammatory arthritis, history of thromboembolism, myocardial infarction and stroke and allergy to tranexamic acid.
Recruitment/selection of patients	2012 to 2013
Age, gender and ethnicity	Age - Mean (SD): 69 (5), 67 (7), 67 (6). Gender (M:F): 14/76. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness

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Interventions	(n=30) Intervention 1: Perioperative use of tranexamic acid - IV. 15mg/kg given 1 hour before the inflation of the tourniquet and 1 hour after the deflation of the tourniquet, and 10 mg/kg was given (in 100 ml isotonic sodium chloride) through one-hour infusion.. Duration Surgery and 4 weeks follow-up treatment. Concurrent medication/care: Thromboprophylaxis: calf muscle pump exercises after surgery. Enoxaparin sodium 0.4 ml subcutaneous was started 8 hours after the operation and was continued once a day for 4 weeks.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=30) Intervention 2: Perioperative use of tranexamic acid - IA/topical. 2g was applied locally on the proximal-medial surface of the patella with intra-articular injection after the joint capsule closure in the final stage of the operation before the tourniquet deflation. Duration Surgery and 4 weeks follow-up treatment. Concurrent medication/care: Thromboprophylaxis: calf muscle pump exercises after surgery. Enoxaparin sodium 0.4 ml subcutaneous was started 8 hours after the operation and was continued once a day for 4 weeks.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg (n=30) Intervention 3: No treatment. No tranexamic acid used. . Duration Surgery and 4 weeks follow-up treatment. Concurrent medication/care: Thromboprophylaxis: calf muscle pump exercises after surgery. Enoxaparin sodium 0.4 ml subcutaneous was started 8 hours after the operation and was continued once a day for 4 weeks.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus IA/TOPICAL

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 30 days of surgery; Group 1: 0/30, Group 2: 0/30
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Blood transfusion at Within 30 days of surgery; Group 1: 0/30, Group 2: 0/30
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Length of stay at -
- Actual outcome: Hospitalisation at .; Group 1: mean 3.26 days (SD 0.58); n=30, Group 2: mean 3.3 days (SD 0.95); n=30
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Total blood loss at -
- Actual outcome: Total blood loss at 3 days after surgery; Group 1: mean 898.03 mL (SD 298.21); n=30, Group 2: mean 823.64 mL (SD 224.33); n=30
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus NO TREATMENT

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 30 days of surgery; Group 1: 0/30, Group 2: 0/30
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Blood transfusion at Within 30 days of surgery; Group 1: 0/30, Group 2: 8/30
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Length of stay at -
- Actual outcome: Hospitalisation at .; Group 1: mean 3.26 days (SD 0.58); n=30, Group 2: mean 3.36 days (SD 0.61); n=30
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 4: Total blood loss at -
- Actual outcome: Total blood loss at 3 days after surgery; Group 1: mean 898.03 mL (SD 298.21); n=30, Group 2: mean 1263.77 mL (SD 298.79); n=30
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus NO TREATMENT

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 30 days of surgery; Group 1: 0/30, Group 2: 0/30
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Blood transfusion at Within 30 days of surgery; Group 1: 0/30, Group 2: 8/30
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Length of stay at -
- Actual outcome: Hospitalisation at .; Group 1: mean 3.3 days (SD 0.95); n=30, Group 2: mean 3.36 days (SD 0.61); n=30
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Total blood loss at -
- Actual outcome: Total blood loss at 3 days after surgery; Group 1: mean 823.64 mL (SD 224.33); n=30, Group 2: mean 1263.77 mL (SD 298.79); n=30
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Blood loss: Haemoglobin level at 3 days after surgery

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Study	Pachauri 2014[197]
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	1 (n=99)
Countries and setting	Conducted in India; Setting: Single centre
Line of therapy	Not applicable
Duration of study	Intervention time: Surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with osteoarthritis scheduled for total knee replacement
Exclusion criteria	Coagulation abnormalities, recurrent gastrointestinal bleeding, iron deficiency altered renal perimeters, known allergy to tranexamic acid.
Age, gender and ethnicity	Age - Other: 33<56 years and under, 66>55 years. Gender (M:F): 18/81. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Perioperative use of tranexamic acid - IV. 1g given 1 hour before surgery and a second dose 6 hours later. . Duration Surgery. Concurrent medication/care: No details of thromboprophylaxis.

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	Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg (n=49) Intervention 2: No treatment. Not detailed. Duration Surgery. Concurrent medication/care: No thromboprophylaxis stated. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Funding not stated
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Adverse events: DVT at -; Blood (allogeneic or autologous) transfusion at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -; Blood loss: Haemoglobin level at 3 days after surgery; Total blood loss at -

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Study	Patel 2014[200]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=89)
Countries and setting	Conducted in USA
Line of therapy	Not applicable
Duration of study	Intervention time: Surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with osteoarthritis undergoing elective unilateral primary TKA
Exclusion criteria	Secondary osteoarthritis (rheumatoid arthritis, posttraumatic arthritis, gouty arthritis), simultaneous bilateral TKA, cardiovascular problems (history of myocardial infarction, atrial fibrillation, angina, heart failure — Class III or IV), cerebrovascular conditions (history of previous stroke or peripheral vascular surgery), clotting disorders or blood dyscrasia, thromboembolic disorders (history of Deep Venous Thrombosis (DVT) or Pulmonary Embolism (PE)), religious objection to autologous blood transfusion, preoperative hemoglobin N15.0 g/dl, known allergy to TXA, and pregnancy.
Recruitment/selection of patients	March 2013 to November 2013 by a single surgeon at a single institution
Age, gender and ethnicity	Age - Mean (SD): 65 (8), 65 (10). Gender (M:F): 23/66. Ethnicity: Not detailed

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Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness
Interventions	(n=42) Intervention 1: Perioperative use of tranexamic acid - IV. 10mg/kg 10 minutes prior to tourniquet deflation.. Duration Surgery and 2 weeks follow-up treatment. Concurrent medication/care: Thromboprophylaxis: Physical therapy and continuous passive motion machines were started on the day after surgery. Low molecular weight heparin also begun on the day after surgery and continued for 14 days.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=47) Intervention 2: Perioperative use of tranexamic acid - IA/topical. 2g in 100 ml of normal saline put directly into the surgical site and bathed in the solution, undisturbed for 2 minutes prior to tourniquet release. Duration Surgery and 2 weeks follow-up treatment. Concurrent medication/care: Thromboprophylaxis: Physical therapy and continuous passive motion machines were started on the day after surgery. Low molecular weight heparin also begun on the day after surgery and continued for 14 days.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus IA/TOPICAL

Protocol outcome 1: Mortality at 30 day
- Actual outcome: Mortality at Unclear; Group 1: 0/42, Group 2: 1/47
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Some difference in BMI and approach; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Adverse events: acute myocardial infarction at -

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- Actual outcome: Myocardial infraction at Unclear; Group 1: 0/42, Group 2: 1/47
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Some difference in BMI and approach; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at Unclear; Group 1: 0/42, Group 2: 1/47
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Some difference in BMI and approach; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Hb change at 3 days after surgery; Group 1: mean -3.06 g/dL (SD 1.02); n=42, Group 2: mean -3.42 g/dL (SD 1.07); n=47
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Some difference in BMI and approach; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Adverse events: DVT at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -; Total blood loss at -

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Study	Pauzenberger 2017[201]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=56)
Countries and setting	Conducted in Austria
Line of therapy	Not applicable
Duration of study	Intervention time: During surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People over 40 years old undergoing primary TSA or RTSA
Exclusion criteria	Refusal to participate, revision surgery, indication for hemiarthroplasty, known allergy to tranexamic acid, anticoagulative medication, sever comorbidities, history of arterial or venous thromboembolic events, coagulopathy, haematological disorders, retinopathy, refusal to receive blood transfusion, pregnancy, breast feeding,
Recruitment/selection of patients	July to December 2015.
Age, gender and ethnicity	Age - Mean (SD): 71. Gender (M:F): 38/16. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Shoulder arthroplasty

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Indirectness of population	No indirectness
Interventions	(n=28) Intervention 1: Perioperative use of tranexamic acid - IV. 1g IV in 100ml saline 30 minutes prior to incision. 1g in 100ml saline during wound closure. . Duration During surgery. Concurrent medication/care: 40mg enoxaparin administered subcutaneously for 5 days after surgery. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg (n=28) Intervention 2: Placebo. 100ml saline administered within 30 minutes of incision and also during wound closure. . Duration During surgery. Concurrent medication/care: 40mg enoxaparin administered subcutaneously for 5 days after surgery. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO Protocol outcome 1: Blood (allogeneic or autologous) transfusion at - - Actual outcome: Transfusion at Hospital admission period; Group 1: 0/27, Group 2: 0/27 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: No drain; Group 2 Number missing: 1, Reason: Arthroplasty system Protocol outcome 2: Total blood loss at - - Actual outcome: Total blood loss at 5 days after surgery; Group 1: mean 871 mL (SD 472.8); n=27, Group 2: mean 1248.2 mL (SD 550.2); n=27 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: No drain; Group 2 Number missing: 1, Reason: Arthroplasty system	
Protocol outcomes not reported by the	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Adverse events: DVT at -; Quality of life

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study	at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -; Blood loss: Haemoglobin level at 3 days after surgery

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Study	Perez-Jimeno 2018[203]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=254)
Countries and setting	Conducted in Spain; Setting: "Miguel Servet" University Hospital during a 2-year period
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 60 days follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People scheduled for cemented or non-cemented primary elective THA
Exclusion criteria	People presenting with hyper- or hypo-coagulability disorders, known allergy to TXA, intravenous iron, folic acid or recombinant human erythropoietin, epilepsy or hip fracture
Age, gender and ethnicity	Age - Mean (SD): 67 (12). Gender (M:F): 137/117. Ethnicity: Not detailed
Further population details	1. Co-morbidities: ASA grade (I-IV). 2. Site/type of joint replacement: Hip replacement (THA).
Indirectness of population	No indirectness
Interventions	(n=142) Intervention 1: Perioperative use of tranexamic acid - IA/topical. 2g administered following skin

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	closure through the deeper drainage tube, which was subsequently clamped during the first 30 minutes after dosing.. Duration Surgery. Concurrent medication/care: Thromboprophylaxis via once-daily, weight-adjusted dosing of low molecular weight heparin starting 12 hours after surgery and maintained for the first 30 post-operative days. Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg (2g). (n=151) Intervention 2: No treatment. No treatment. Duration Surgery. Concurrent medication/care: Thromboprophylaxis via once-daily, weight-adjusted dosing of low molecular weight heparin starting 12 hours after surgery and maintained for the first 30 post-operative days.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus NO TREATMENT

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: Thromboembolic complications at Within 60 dyas of surgery; Group 1: 0/125, Group 2: 0/129
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 17, Reason: 4 non compliance with protocol, 13 incomplete records; Group 2 Number missing: 22, Reason: 7 non compliance with protocol, 15 incomplete records

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at During hospital stay; Group 1: 15/125, Group 2: 42/129
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 17, Reason: 4 non compliance with protocol, 13 incomplete records; Group 2 Number missing: 22, Reason: 7 non compliance with protocol, 15 incomplete records

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Change in haemoglobin at Postoperative day 1; Group 1: mean 3.7 g/dl (SD 1.3); n=125, Group 2: mean 4.6 g/dl (SD 1.3); n=129
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 17, Reason: 4 non compliance with protocol, 13 incomplete

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records; Group 2 Number missing: 22, Reason: 7 non compliance with protocol, 15 incomplete records Protocol outcome 4: Total blood loss at - - Actual outcome: Lost RBC mass at 24 hours after surgery; Group 1: mean 539 ml (SD 243); n=125, Group 2: mean 728 ml (SD 252); n=129 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 17, Reason: 4 non compliance with protocol, 13 incomplete records; Group 2 Number missing: 22, Reason: 7 non compliance with protocol, 15 incomplete records	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -

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Study	Pinsornsak 2016[206]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Thailand; Setting: 1 surgeon using the same surgical technique throughout the study
Line of therapy	Not applicable
Duration of study	Intervention time: Surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with osteoarthritis scheduled for TKA.
Exclusion criteria	People with inflammatory arthritis, post-traumatic arthritis, a history of or current venous thromboembolic disease, any underlying disease of haemostasis, cirrhosis, chronic renal failure, patients on anticoagulants or strong antiplatelet drugs (e.g. warfarin, clopidogrel), know allergy to tranexamic acid, defective color vision, and a low preoperative hemoglobin or a low platelet count.
Recruitment/selection of patients	October 2012 to October 2013
Age, gender and ethnicity	Age - Mean (SD): 68 (8), 70 (8). Gender (M:F): 12/48. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty

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Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Perioperative use of tranexamic acid - IA/topical. 750mg in 15 mL saline injected into the soft tissue around medial capsule (5 ml), lateral capsule (5 ml) and around the quadriceps muscle (5 ml).. Duration Surgery. Concurrent medication/care: Thromboprophylaxis unclear. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≤1000 mg (n=30) Intervention 2: Perioperative use of tranexamic acid - IV. 750mg in 15ml saline.. Duration Surgery. Concurrent medication/care: Thromboprophylaxis unclear. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	No funding (No external funding)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus IV

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: Symptomatic VTE at Within 14 days of surgery; Group 1: 0/30, Group 2: 0/30
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at During hospitalisation; Group 1: 9/30, Group 2: 7/30
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Length of stay at -
- Actual outcome: Hospital stay at .; Group 1: mean 5.37 days (SD 1.46); n=30, Group 2: mean 5.3 days (SD 0.84); n=30
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Hb change at 2 days after surgery; Group 1: mean -1.85 g/dL (SD 0.95); n=30, Group 2: mean -1.87 g/dL (SD 1.37); n=30 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Total blood loss at -

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Study (subsidiary papers)	Prakash 2017[210] (North 2016[192])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=200)
Countries and setting	Conducted in India; Setting: 2 centres
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 3 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with primary osteoarthritis who were scheduled for primary unilateral total knee arthroplasty.
Exclusion criteria	Secondary arthritis, allergy to tranexamic acid, major comorbidities, coagulopathies, previous stroke or sever ischemic cardiopathy, bilateral arthroplasty.
Recruitment/selection of patients	September 2014 to February 2015
Age, gender and ethnicity	Age - Mean (SD): 69. Gender (M:F): Unclear though number of women was higher than men. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness

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Interventions	(n=50) Intervention 1: Perioperative use of tranexamic acid - IV. 10mg/kg administered 3 times. 20 minutes before tourniquet application, 15 minutes before deflation of the tourniquet, 3 hours after the previous dose in the postoperative period. Topical saline and saline through the drain administered as placebo. . Duration Surgical and immediate postoperative period. Concurrent medication/care: No thromboembolic prophylaxis. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=50) Intervention 2: Perioperative use of tranexamic acid - IA/topical. 3g in 50ml saline applied to joint cavity 5 minutes before closure. IV saline and saline through the drain administered as placebo.. Duration Surgical and immediate postoperative period. Concurrent medication/care: No thromboembolic prophylaxis.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≥3000 mg (n=50) Intervention 3: Perioperative use of tranexamic acid - IA/topical. 3g in saline retrograde through the drain after closure. IV saline and Topical saline as placebo.. Duration Surgical and immediate postoperative period. Concurrent medication/care: No thromboembolic prophylaxis.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≥3000 mg (n=50) Intervention 4: Placebo. IV, topical and IA saline administered as placebo. . Duration Surgical and immediate postoperative period. Concurrent medication/care: No thromboembolic prophylaxis.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus IA/TOPICAL

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at within 3 months of surgery; Group 1: 1/50, Group 2: 0/50
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low,

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Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at Within 5 days of surgery; Group 1: 3/50, Group 2: 5/50
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Total blood loss at -
- Actual outcome: Total blood loss at After day 1; Group 1: mean 580.6 mL (SD 996); n=50, Group 2: mean 557.6 mL (SD 996); n=50
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus IA/TOPICAL

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at within 3 months of surgery; Group 1: 0/50, Group 2: 0/50
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at Within 5 days of surgery; Group 1: 3/50, Group 2: 3/50
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Haemoglobin drop at from day 1; Group 1: mean -1.6 g/dL (SD 1); n=50, Group 2: mean -2.1 g/dL (SD 1); n=50
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: Haemoglobin drop at from day 1; Group 1: mean -1.6 g/dL (SD 1); n=50, Group 2: mean -1.6 g/dL (SD 1); n=50
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 4: Total blood loss at -
- Actual outcome: Total blood loss at After day 1; Group 1: mean 580.6 mL (SD 1000); n=50, Group 2: mean 514.5 mL (SD 1000); n=50
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at within 3 months of surgery; Group 1: 0/50, Group 2: 1/50
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at Within 5 days of surgery; Group 1: 3/50, Group 2: 12/50
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Haemoglobin drop at from day 1; Group 1: mean -1.6 g/dL (SD 1.38); n=50, Group 2: mean -2.3 g/dL (SD 1.38); n=50
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Total blood loss at -
- Actual outcome: Total blood loss at After day 1; Group 1: mean 580.6 mL (SD 370); n=50, Group 2: mean 886.5 mL (SD 370); n=50
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at within 3 months of surgery; Group 1: 1/50, Group 2: 1/50
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low,

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Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at Within 5 days of surgery; Group 1: 5/50, Group 2: 12/50
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Haemoglobin drop at from day 1; Group 1: mean -2.1 g/dL (SD 1.2); n=50, Group 2: mean -2.3 g/dL (SD 1.2); n=50
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Total blood loss at -
- Actual outcome: Total blood loss at After day 1; Group 1: mean 557.6 mL (SD 472); n=50, Group 2: mean 886.5 mL (SD 472); n=50
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at within 3 months of surgery; Group 1: 0/50, Group 2: 1/50
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at Within 5 days of surgery; Group 1: 3/50, Group 2: 12/50
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Haemoglobin drop at from day 1; Group 1: mean -1.6 g/dL (SD 1.48); n=50, Group 2: mean -2.3 g/dL (SD 1.48); n=50
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low,

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Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Total blood loss at - - Actual outcome: Total blood loss at After day 1; Group 1: mean 514.5 mL (SD 540); n=50, Group 2: mean 886.5 mL (SD 540); n=50 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -

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Study	Roy 2012[214]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in India
Line of therapy	Not applicable
Duration of study	Intervention time: Surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People under 80 years of age with osteoarthritis scheduled for elective primary unilateral cemented-TKA
Exclusion criteria	People with known allergy to tranexamic acid, severe anaemia, hepatic/cardio-respiratory/renal insufficiency, congenital or acquired coagulopathy and recent history of thromboembolic episode were excluded from the study. Patients with severe deformity and restricted range of motion.
Age, gender and ethnicity	Age - Mean (SD): 66 (7), 67 (8). Gender (M:F): 19/31. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Perioperative use of tranexamic acid - IA/topical. Two drain tubes were placed inside

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	the joint through which 500mg in 5ml was administered. Duration Surgery and hospitalised time. Concurrent medication/care: Thromboprophylaxis: mechanical measures (compression stockinet and early mobilization) and low molecular weight heparin (Dalteparin 5,000 IU subcutaneous once a day) initiated on first post-operative day.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≤1000 mg (n=25) Intervention 2: Placebo. Two drain tubes were placed inside the joint through which 5ml 0.9% saline was administered. Duration Surgery and hospitalised time. Concurrent medication/care: Post-operative DVT prophylaxis included both mechanical measures (compression stockinet and early mobilization) and low molecular weight heparin (Dalteparin 5,000 IU subcutaneous once a day) initiated on first post-operative day.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Other (No potential conflict of interest of any of the authors in relation to this manuscript)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus PLACEBO

Protocol outcome 1: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at During time in hospital; Group 1: 2/25, Group 2: 7/25
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Surgical bleeding at -
- Actual outcome: Per-operative blood loss at During surgery; Group 1: mean 109.6 mL (SD 71.54); n=25, Group 2: mean 194 mL (SD 79.66); n=25
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Postoperative bleeding at -
- Actual outcome: Drain collection at 6-48 hours after surgery; Group 1: mean 151.6 mL (SD 82.1); n=25, Group 2: mean 400 mL (SD 180.27); n=25
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Hb loss at 5 days after surgery; Group 1: mean -1.94 g/dL (SD 0.98); n=25, Group 2: mean -3.04 g/dL (SD 1.33); n=25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Adverse events: DVT at -; Quality of life at within 6 weeks; Postoperative anaemia at -; Length of stay at -; Total blood loss at -

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Study	Sa-ngasoongsong 2011[215]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=48)
Countries and setting	Conducted in Thailand; Setting: Single centre
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery with 6 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with primary knee osteoarthritis and undergoing unilateral primary cemented computer-assisted TKR
Exclusion criteria	Previous knee surgery; risk of abnormal bleeding tendency or bleeding disorder, contra-indication for tranexamic acid use, acquired defective colour vision, subarachnoid hemorrhage, hypersensitivity to tranexamic acid, history of serious adverse effects, thrombotic disorder and hematuria, incomplete data collection, for example, malfunctioned drain or accidental drain removal.
Age, gender and ethnicity	Age - Mean (SD): 69 (8). Gender (M:F): 8/40. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness

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Interventions	(n=24) Intervention 1: Perioperative use of tranexamic acid - IA/topical. 250mg in 25mL of physiologic saline injected into knee joint after completion of fascial closure in order to prevent leakage.. Duration Surgery. Concurrent medication/care: Thromboprophylaxis unclear. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≤1000 mg (n=24) Intervention 2: Placebo. 25mL physiologic saline injected into knee joint after completion of fascial closure in order to prevent leakage.. Duration Surgery. Concurrent medication/care: Thromboprophylaxis unclear. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Academic or government funding (Department of Orthopaedics, Faculty of Medicine, Ramathibodi hospital, Mahidol University provided help and permission to carry out this study.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 6 months of surgery; Group 1: 0/24, Group 2: 0/24
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at Hospital period after surgery; Group 1: 1/24, Group 2: 8/24
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Postoperative bleeding at -
- Actual outcome: Calculated blood loss (postoperative) at 4 days after surgery; Group 1: mean 206.3 mL (SD 115.4); n=24, Group 2: mean 385.1 mL (SD 145.2); n=24
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Total Hb loss at 4 days after surgery; Group 1: mean -2.1 g/dL (SD 0.9); n=24, Group 2: mean -3 g/dL (SD 0.7); n=24 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Length of stay at -; Total blood loss at -

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Study	Shinde 2015-1[225]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=56)
Countries and setting	Conducted in India
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and postsurgical hospital period
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with tricompartmental osteoarthritis of the knee and scheduled for unilateral total knee replacement were included in the study
Exclusion criteria	Allergy to tranexamic acid, rheumatoid arthritis, revision total knee arthroplasty, coagulopathy (preoperative platelet count ≤1,50,000/mm 3, BT, PT, CT abnormality), previous history of thromboembolic disease (cerebrovascular accident, deep vein thrombosis, myocardial infarction), severe ischemic heart disease, NYHA class 3 and 4, serum creatinine >1.5 mg/dL, severe pulmonary disease, e.g. FEV1 ≤50% normal, hepatic failure and preoperative anemia (Hb <10 g/dL).
Recruitment/selection of patients	2011 and 2012.
Age, gender and ethnicity	Age - Mean (SD): 65. Gender (M:F): Not detailed. Ethnicity: People of Indian origin

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Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness
Interventions	(n=14) Intervention 1: Perioperative use of tranexamic acid - IV. 3 intravenous administrations of tranexamic acid at a dose of 10 mg/kg of body weight. The first dose was prior to inflation of the tourniquet after induction, the second dose was 4 h after the first dose either in the recovery room or in the ward and the third dose was after 12 h of the first dose.. Duration Surgery and postsurgical period. Concurrent medication/care: All people received DVT prophylaxis in the form of dalteparin sodium 5000 IU SC for 5 days or tablet rivaroxaban 10 mg for 10 days. Along with this, a mechanical DVT prophylaxis in the form of pump or DVT stockings was given.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (10mg/kg). (n=14) Intervention 2: Placebo. IV saline (NS) at 0, 4 and 12 hours.. Duration Surgery and postsurgical period. Concurrent medication/care: All people received DVT prophylaxis in the form of dalteparin sodium 5000 IU SC for 5 days or tablet rivaroxaban 10 mg for 10 days. Along with this, a mechanical DVT prophylaxis in the form of pump or DVT stockings was given.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: Evidence of DVT at During or after surgery; Group 1: 2/14, Group 2: 0/14
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at During or after surgery; Group 1: 1/14, Group 2: 9/14

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Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Surgical bleeding at - - Actual outcome: Intraoperative blood loss at During surgery; Group 1: mean 142 ml (SD 80); n=14, Group 2: mean 310 ml (SD 149); n=14 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Postoperative bleeding at - - Actual outcome: Postoperative blood loss at 48 hours after surgery; Group 1: mean 295 ml (SD 218); n=14, Group 2: mean 482 ml (SD 186); n=14 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Postoperative anaemia at -; Length of stay at -; Blood loss: Haemoglobin level at 3 days after surgery; Total blood loss at -

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Study	Shinde 2015-2[225]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=28)
Countries and setting	Conducted in India
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and postsurgical hospital period
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with tricompartmental osteoarthritis of the knee and scheduled for bilateral total knee replacement were included in the study
Exclusion criteria	Allergy to tranexamic acid, rheumatoid arthritis, revision total knee arthroplasty, coagulopathy (preoperative platelet count ≤1,50,000/mm 3, BT, PT, CT abnormality), previous history of thromboembolic disease (cerebrovascular accident, deep vein thrombosis, myocardial infarction), severe ischemic heart disease, NYHA class 3 and 4, serum creatinine >1.5 mg/dL, severe pulmonary disease, e.g. FEV1 ≤50% normal, hepatic failure and preoperative anemia (Hb <10 g/dL).
Recruitment/selection of patients	2011 and 2012.
Age, gender and ethnicity	Age - Mean (SD): 65. Gender (M:F): Not detailed. Ethnicity: People of Indian origin

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Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness
Interventions	(n=14) Intervention 1: Perioperative use of tranexamic acid - IV. 3 intravenous administrations of tranexamic acid at a dose of 10 mg/kg of body weight. The first dose was prior to inflation of the tourniquet after induction, the second dose was 4 h after the first dose either in the recovery room or in the ward and the third dose was after 12 h of the first dose.. Duration Surgery and postsurgical period. Concurrent medication/care: All people received DVT prophylaxis in the form of dalteparin sodium 5000 IU SC for 5 days or tablet rivaroxaban 10 mg for 10 days. Along with this, a mechanical DVT prophylaxis in the form of pump or DVT stockings was given.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (10mg/kg). (n=14) Intervention 2: Placebo. IV saline (NS) at 0, 4 and 12 hours.. Duration Surgery and postsurgical period. Concurrent medication/care: All people received DVT prophylaxis in the form of dalteparin sodium 5000 IU SC for 5 days or tablet rivaroxaban 10 mg for 10 days. Along with this, a mechanical DVT prophylaxis in the form of pump or DVT stockings was given.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: Evidence of DVT at During or after surgery; Group 1: 1/14, Group 2: 2/14
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at During or after surgery; Group 1: 2/14, Group 2: 14/14

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Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Surgical bleeding at - - Actual outcome: Intraoperative blood loss at During surgery; Group 1: mean 282 ml (SD 64); n=14, Group 2: mean 425 ml (SD 108); n=14 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Postoperative bleeding at - - Actual outcome: Postoperative blood loss at 48 hours after surgery; Group 1: mean 596 ml (SD 235); n=14, Group 2: mean 1349 ml (SD 412); n=14 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Postoperative anaemia at -; Length of stay at -; Blood loss: Haemoglobin level at 3 days after surgery; Total blood loss at -

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Study	Song 2017[227]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=200)
Countries and setting	Conducted in South Korea; Setting: Single-institution 2 hospital based study.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 3 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with primary osteoarthritis of knee awaiting navigation assisted TKA
Exclusion criteria	Secondary osteoarthritis (rheumatoid and other inflammatory arthritis, posttraumatic arthritis), known allergies to tranexamic acid, major comorbidities (American Society of Anesthesiology (ASA) grade 4 and above), coagulopathies (INR >1.4), history of previous deep vein thrombosis (DVT) or people on antithrombotic treatment, previous history of stroke or severe ischemic cardiopathy, and people undergoing bilateral total knee arthroplasty, people with low hemoglobin levels.
Recruitment/selection of patients	From January 2015 to December 2015
Age, gender and ethnicity	Age - Mean (SD): 69 (6), 70 (7), 71 (7), 7 (7). Gender (M:F): 27/173. Ethnicity: Not detailed

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Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Perioperative use of tranexamic acid - IV. 10mg/kg 20 minutes before tourniquet application as a preoperative dose, 10 mg/kg 15 minutes before deflation of the tourniquet as an intraoperative dose, and 10 mg/kg 3 hours after the second dose as a postoperative dose. As placebo, the group received 50 mL of saline retrograde through drain after surgery.. Duration Surgery. Concurrent medication/care: Thromboprophylaxis: Pneumatic calf pumps were used in all patients until they started ambulation. Chemical prophylaxis using low molecular weight heparin was given only in high-risk patients screened preoperatively.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=50) Intervention 2: Perioperative use of tranexamic acid - IA/topical. 1.5g in 50 mL of saline retrograde through the drain after wound closure, and as placebo, saline utilised at the same points as the IV treatment.. Duration Surgery. Concurrent medication/care: Thromboprophylaxis: Pneumatic calf pumps were used in all patients until they started ambulation. Chemical prophylaxis using low molecular weight heparin was given only in high-risk patients screened preoperatively.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg (n=50) Intervention 3: Perioperative use of tranexamic acid - IV+IA/topical. 10mg/kg 20 minutes before tourniquet application as a preoperative dose and 10 mg/kg as a postoperative dose. 1.5g in 50mL of saline retrograde through the drain after wound closure. As placebo, these patients received 5mL of normal saline at the time of intraoperative dose.. Duration Surgery. Concurrent medication/care: Thromboprophylaxis: Pneumatic calf pumps were used in all patients until they started ambulation. Chemical prophylaxis using low molecular weight heparin was given only in high-risk patients screened preoperatively.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=50) Intervention 4: Placebo. No tranexmic acid. PLacebo gicen to match IV and IA treatments. . Duration Surgery. Concurrent medication/care: Thromboprophylaxis: Pneumatic calf pumps were used in all patients until they started ambulation. Chemical prophylaxis using low molecular weight heparin was given only in

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	high-risk patients screened preoperatively. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Other (No author associated with this paper disclosed any potential or pertinent conflicts which may be perceived to have impending conflict with this work.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus IA/TOPICAL

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 3 months of surgery; Group 1: 0/50, Group 2: 0/50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at During hospital period; Group 1: 0/50, Group 2: 1/50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Haemoglobin drop at Unclear; Group 1: mean -2.9 g/dL (SD 1.2); n=50, Group 2: mean -2.5 g/dL (SD 1.2); n=50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Total blood loss at -
- Actual outcome: Total loss (Gross formula) at In hospital period; Group 1: mean 972.29 mL (SD 268.8); n=50, Group 2: mean 998.12 mL (SD 256.78); n=50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus IV+IA/TOPICAL

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Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 3 months of surgery; Group 1: 0/50, Group 2: 0/50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at During hospital period; Group 1: 0/50, Group 2: 0/50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Haemoglobin drop at Unclear; Group 1: mean -2.9 g/dL (SD 1.2); n=50, Group 2: mean -2.4 g/dL (SD 1.05); n=50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Total blood loss at -
- Actual outcome: Total loss (Gross formula) at In hospital period; Group 1: mean 972.29 mL (SD 268.8); n=50, Group 2: mean 946.13 mL (SD 162.21); n=50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 3 months of surgery; Group 1: 0/50, Group 2: 0/50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at During hospital period; Group 1: 0/50, Group 2: 7/50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Haemoglobin drop at Unclear; Group 1: mean -2.9 g/dL (SD 1.2); n=50, Group 2: mean -3.98 g/dL (SD 2.1); n=50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Total blood loss at -
- Actual outcome: Total loss (Gross formula) at In hospital period; Group 1: mean 972.29 mL (SD 268.8); n=50, Group 2: mean 1121.12 mL (SD 226.65); n=50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus IV+IA/TOPICAL

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 3 months of surgery; Group 1: 0/50, Group 2: 0/50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at During hospital period; Group 1: 1/50, Group 2: 0/50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Haemoglobin drop at Unclear; Group 1: mean -2.5 g/dL (SD 1.2); n=50, Group 2: mean -2.4 g/dL (SD 1.05); n=50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Total blood loss at -
- Actual outcome: Total loss (Gross formula) at In hospital period; Group 1: mean 998.12 mL (SD 256.78); n=50, Group 2: mean 946.13 mL (SD 162.21); n=50

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Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 3 months of surgery; Group 1: 0/50, Group 2: 0/50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at During hospital period; Group 1: 1/50, Group 2: 7/50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Haemoglobin drop at Unclear; Group 1: mean -2.5 g/dL (SD 1.2); n=50, Group 2: mean -3.98 g/dL (SD 2.1); n=50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Total blood loss at -
- Actual outcome: Total loss (Gross formula) at In hospital period; Group 1: mean 998.12 mL (SD 256.78); n=50, Group 2: mean 1121.12 mL (SD 226.65); n=50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV+IA/TOPICAL versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 3 months of surgery; Group 1: 0/50, Group 2: 0/50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 2: Blood (allogeneic or autologous) transfusion at - - Actual outcome: Transfusion at During hospital period; Group 1: 0/50, Group 2: 7/50 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Haemoglobin drop at Unclear; Group 1: mean -2.4 g/dL (SD 1.05); n=50, Group 2: mean -3.98 g/dL (SD 2.1); n=50 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Total blood loss at - - Actual outcome: Total loss (Gross formula) at In hospital period; Group 1: mean 946.13 mL (SD 162.21); n=50, Group 2: mean 1121.12 mL (SD 226.65); n=50 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -

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Study	Stowers 2017[233]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=150)
Countries and setting	Conducted in New Zealand
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery with 6 weeks follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults undergoing primary unilateral TKA
Exclusion criteria	History or risk of thrombosis, active thromboembolic disease, refused blood products, known hypersensitivity to tranexamic acid or any of its ingredients, complex hematologic disorders requiring manipulation, pregnant and lactating women, taking anticoagulant therapy within 5 days of surgery (warfarin, dabigatran, heparin, rivaroxaban), or had severe renal failure (estimated glomerular filtration rate <29).
Recruitment/selection of patients	5 New Zealand centres between July 2014 and November 2015.
Age, gender and ethnicity	Age - Mean (SD): 70 (8), 70 (9), 71 (9). Gender (M:F): 59/75. Ethnicity: Not detailed

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Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Placebo. 20mL of normal saline intra-articularly after implantation of prosthesis and closure of arthrotomy followed by standard closure. Administration of 20mL of normal saline intravenously at the same time before release of tourniquet B. Duration Surgery with 6 weeks follow-up. Concurrent medication/care: Unclear thromboprophylaxis. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable (n=60) Intervention 2: Perioperative use of tranexamic acid - IA/topical. 1.5g in 20mL of saline intra-articularly after implantation of prosthesis and closure of arthrotomy followed by standard closure. Administration of 20 mL of normal saline (in a 20-mL syringe) intravenously at the same time before release of tourniquet C. Duration Surgery with 6 weeks follow-up. Concurrent medication/care: Unclear thromboprophylaxis. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg (n=60) Intervention 3: Perioperative use of tranexamic acid - IV. 20mL of normal saline intra-articularly after implantation of prosthesis and closure of arthrotomy followed by standard closure. 1.5g intravenously at the same time before release of tourniquet . Duration Surgery with 6 weeks follow-up. Concurrent medication/care: Unclear thromboprophylaxis. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg
Funding	No funding (This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus PLACEBO Protocol outcome 1: Adverse events: DVT at -	

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- Actual outcome: DVT at Within 30 days of surgery; Group 1: 0/60, Group 2: 0/30
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfused at While hospitalised; Group 1: 1/60, Group 2: 2/30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Total blood loss at -
- Actual outcome: Perioperative fluids at By day 3 after surgery; Group 1: mean 1613 mL (SD 622); n=60, Group 2: mean 1765 mL (SD 1088); n=30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 30 days of surgery; Group 1: 0/60, Group 2: 0/60
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfused at While hospitalised; Group 1: 0/60, Group 2: 2/30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Total blood loss at -
- Actual outcome: Perioperative fluids at By day 3 after surgery; Group 1: mean 1807 mL (SD 893); n=60, Group 2: mean 1765 mL (SD 1088); n=30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus IA/TOPICAL

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Protocol outcome 1: Adverse events: DVT at - - Actual outcome: DVT at Within 30 days of surgery; Group 1: 0/60, Group 2: 0/60 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Blood (allogeneic or autologous) transfusion at - - Actual outcome: Transfused at While hospitalised; Group 1: 0/60, Group 2: 1/60 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Total blood loss at - - Actual outcome: Perioperative fluids at By day 3 after surgery; Group 1: mean 1807 mL (SD 893); n=60, Group 2: mean 1613 mL (SD 622); n=30 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -; Blood loss: Haemoglobin level at 3 days after surgery

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Study	Tanaka 2001[241]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=99)
Countries and setting	Conducted in Japan
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 2 weeks follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with rheumatoid arthritis or osteoarthritis who were scheduled to have a unilateral bicondylar cemented TKA
Exclusion criteria	Allergy to tranexamic acid, preoperative hepatic or renal dysfunction, serious cardiac or respiratory disease, congenital or acquired coagulopathy, and a history of thromboembolic disease.
Age, gender and ethnicity	Age - Mean (range): 65 (58-70), 65 (59-70), 65 (60-71), 65 (59-69). Gender (M:F): 31/68. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness

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Interventions	(n=26) Intervention 1: Placebo. 2 doses of saline. First ten minutes before surgery and second on deflation of the tourniquet. Duration Surgery and hospitalisation. Concurrent medication/care: Unclear thromboprophylaxis. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable (n=24) Intervention 2: Perioperative use of tranexamic acid - IV. 20mg/kg minutes before surgery and saline ten minutes before deflation of the tourniquet. Duration Surgery and hospitalisation. Concurrent medication/care: Unclear thromboprophylaxis . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=22) Intervention 3: Perioperative use of tranexamic acid - IV. Saline ten minutes before surgery and 20mg/kg ten minutes before deflation of the tourniquet. Duration Surgery and hospitalisation. Concurrent medication/care: Unclear thromboprophylaxis. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=27) Intervention 4: Perioperative use of tranexamic acid - IV. 10mg/kg of TNA ten minutes before surgery and again ten minutes before deflation of the tourniquet. Duration Surgery and hospitalisation. Concurrent medication/care: Unclear thromboprophylaxis. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear
Funding	Other (No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV 1 versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 14 days of surgery; Group 1: 0/24, Group 2: 0/24
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at Surgery and hospitalisation; Group 1: 16/24, Group 2: 26/26
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Haemoglobin at 4 days after surgery; Group 1: mean 10.2 g/dL (SD 1); n=24, Group 2: mean 10.3 g/dL (SD 1.17); n=26
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV 2 versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 14 days of surgery; Group 1: 0/22, Group 2: 0/26
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at Surgery and hospitalisation; Group 1: 17/22, Group 2: 26/26
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Haemoglobin at 4 days after surgery; Group 1: mean 9.9 g/dL (SD 1.2); n=22, Group 2: mean 10.3 g/dL (SD 1.17); n=26
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV 3 versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 14 days of surgery; Group 1: 0/27, Group 2: 0/26

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Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Blood (allogeneic or autologous) transfusion at - - Actual outcome: Transfusion at Surgery and hospitalisation; Group 1: 14/27, Group 2: 26/26 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Haemoglobin at 4 days after surgery; Group 1: mean 10.3 g/dL (SD 1.3); n=27, Group 2: mean 10.3 g/dL (SD 1.17); n=26 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -; Total blood loss at -

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Study	TRANX-H trial: Alshryda 2013[12]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=161)
Countries and setting	Conducted in United Kingdom; Setting: 2 hospitals
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 3 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Age, gender and ethnicity	Age - Mean (SD): 63 (11), 66 (9). Gender (M:F): Define. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Hip replacement
Indirectness of population	No indirectness
Interventions	(n=80) Intervention 1: Perioperative use of tranexamic acid - IA/topical. 1g in 50ml saline sprayed into the wound end of the total hip replacement immediately before the wound is dressed. . Duration Surgery and hospital period. Concurrent medication/care: Calf pump and people with BMI >30 received dose of LMWH. A

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	weight based dose of tinzaparin sodium was sued on the first postoperative day until discharge. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≤1000 mg (n=81) Intervention 2: Placebo. 50ml saline sprayed into the wound end of the total hip replacement immediately before the wound is dressed.. Duration Surgery and hospital period. Concurrent medication/care: Calf pump and people with BMI >30 received dose of LMWH. A weight based dose of tinzaparin sodium was sued on the first postoperative day until discharge.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Academic or government funding (University hospitals of North Tees and Hartlepool)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 2 months of surgery; Group 1: 2/80, Group 2: 2/81
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Blood transfusion at During hospital period; Group 1: 10/80, Group 2: 26/81
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Quality of life at within 6 weeks
- Actual outcome: EuroQol Index (EQ-5D) at 3 months after surgery; Group 1: mean 0.686 (SD 0.33); n=47, Group 2: mean 0.715 (SD 0.3); n=45; EQ-5D 0-1 Top=High is good outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: Serious indirectness, Comments: Time point of outcome is outside that specified in the protocol; Baseline details: Baseline QOL in control group is much lower than intervention group; Group 1 Number missing: 33, Reason: Unclear; Group 2 Number missing: 36, Reason: Unclear

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Protocol outcome 4: Length of stay at - - Actual outcome: Length of stay at .; Group 1: mean 5.2 days (SD 3.6); n=79, Group 2: mean 6.2 days (SD 4.4); n=80 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Unclear ; Group 2 Number missing: 1, Reason: Unclear Protocol outcome 5: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Postoperative haemoglobin at 48 hours after surgery; Group 1: mean 10.62 g/dL (SD 1.34); n=80, Group 2: mean 9.78 g/dL (SD 1.45); n=81 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: Total blood loss at - - Actual outcome: Total blood loss at During hospital period; Group 1: mean 1617 mL (SD 188); n=56, Group 2: mean 1981 mL (SD 1007); n=38 Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 24, Reason: Unclear; Group 2 Number missing: 43, Reason: Unclear	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -

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Study	TRANX-K trial: Alshryda 2013[13]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=157)
Countries and setting	Conducted in United Kingdom; Setting: 2 university hospitals
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 3 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 67 (10), 66 (10)
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People undergoing primary unilateral total knee replacement.
Exclusion criteria	Allergy to tranexamic acid, receiving warfarin or heparin, history of hemophilia, DVT, PE, renal impairment or pregnant.
Age, gender and ethnicity	Age - Mean (SD): . Gender (M:F): 74/83. Ethnicity: Not detailed
Further population details	1. Co-morbidities: 2. Site/type of joint replacement:
Indirectness of population	No indirectness
Interventions	(n=79) Intervention 1: Perioperative use of tranexamic acid - IA/topical. 1g in 50ml saline sprayed into the wound end of the total knee replacement immediately before the wound is dressed. . Duration Surgery and

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	hospital period. Concurrent medication/care: Calf pump and people with BMI >30 received dose of LMWH. A weight based dose of tinzaparin sodium was sued on the first postoperative day until discharge. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≤1000 mg (n=78) Intervention 2: Placebo. 50ml saline sprayed into the wound end of the total knee replacement immediately before the wound is dressed.. Duration Surgery and hospital period. Concurrent medication/care: Calf pump and people with BMI >30 received dose of LMWH. A weight based dose of tinzaparin sodium was sued on the first postoperative day until discharge. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Academic or government funding (University hospitals of North Tees and Hartlepool)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 2 months of surgery; Group 1: 2/79, Group 2: 0/78
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Blood transfusion at During hospital period; Group 1: 1/79, Group 2: 13/78
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Quality of life at within 6 weeks
- Actual outcome: EuroQol Index (EQ-5D) at 3 months after surgery; Group 1: mean 0.705 (SD 0.31); n=52, Group 2: mean 0.78 (SD 0.24); n=46; EQ-5D 0-1 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: Serious indirectness, Comments: Timepoint of outcome is outside that specified in the protocol; Group 1 Number missing: 27, Reason: Unclear; Group 2 Number missing: 32, Reason: Unclear

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Protocol outcome 4: Length of stay at - - Actual outcome: Length of stay at .; Group 1: mean 4.8 days (SD 2.3); n=77, Group 2: mean 6.1 days (SD 4.6); n=72 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Unclear; Group 2 Number missing: 6, Reason: Unclear Protocol outcome 5: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Postoperative haemoglobin at 48 hours after surgery; Group 1: mean 11.52 g/dL (SD 1.33); n=79, Group 2: mean 10.69 g/dL (SD 1.35); n=78 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: Total blood loss at - - Actual outcome: Total blood loss at During hospital period; Group 1: mean 919 mL (SD 487); n=64, Group 2: mean 1725 mL (SD 823); n=61 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: Unclear; Group 2 Number missing: 7, Reason: Unclear	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -

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Study	Ugurlu 2017[246]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=123)
Countries and setting	Conducted in Turkey
Line of therapy	Not applicable
Duration of study	Intervention time: Surgery with unclear length of follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People undergoing primary total knee arthroplasty for degenerative osteoarthritis.
Exclusion criteria	Flexion deformity over 30 degrees, varus/valgu over 30 degrees, preoperative anticoagulants, abnormalities in coagulation screening tests, history of DVT or PE, transient ischaemic attack, stroke, renal or hepatic insufficiency, pregnancy.
Recruitment/selection of patients	2013 to 2015.
Age, gender and ethnicity	Age - Mean (SD): 54. Gender (M:F): 26/97. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness

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Interventions	(n=40) Intervention 1: Perioperative use of tranexamic acid - IV. 20mg/kg dose administered 15 minutes before tourniquet inflated.. Duration During surgery. Concurrent medication/care: Thromboembolic prophylaxis: subcutaneous enoxaparin administered 6 hours after the operation and repeated every 24 hours for 10 days. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=42) Intervention 2: Perioperative use of tranexamic acid - IA/topical. 3g in 100ml saline. 50ml administered with infiltration to wound lips following suturing of the capsular incision. 50ml administered into the joint. . Duration During surgery. Concurrent medication/care: Thromboembolic prophylaxis: subcutaneous enoxaparin administered 6 hours after the operation and repeated every 24 hours for 10 days.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≥3000 mg (n=41) Intervention 3: No treatment. No use of tranexamic acid. Duration During surgery. Concurrent medication/care: Thromboembolic prophylaxis: subcutaneous enoxaparin administered 6 hours after the operation and repeated every 24 hours for 10 days.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus IA/TOPICAL

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at In hospital period; Group 1: 1/40, Group 2: 1/42
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at In hospital period; Group 1: 2/40, Group 2: 2/42
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

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- Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Haemoglobin value at 2 days after surgery; Group 1: mean 10.96 g/dL (SD 1.65); n=40, Group 2: mean 10.52 g/dL (SD 1.24); n=42
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus NO TREATMENT

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at In hospital period; Group 1: 1/40, Group 2: 1/41
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at In hospital period; Group 1: 2/40, Group 2: 8/40
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Haemoglobin value at 2 days after surgery; Group 1: mean 10.96 g/dL (SD 1.65); n=40, Group 2: mean 9.65 g/dL (SD 1.33); n=41
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus NO TREATMENT

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at In hospital period; Group 1: 1/42, Group 2: 1/41
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -

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- Actual outcome: Transfusion at In hospital period; Group 1: 2/42, Group 2: 8/41 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Haemoglobin value at 2 days after surgery; Group 1: mean 10.52 g/dL (SD 1.24); n=42, Group 2: mean 9.65 g/dL (SD 1.33); n=41 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -; Total blood loss at -

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Study	Vara 2017[247]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=102)
Countries and setting	Conducted in USA; Setting:
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery with 6 weeks follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults undergoing primary RTSA for massive cuff deficiency with or without glenohumeral arthrosis.
Exclusion criteria	Acute proximal humeral fracture, concomitant procedures, known allergy to tranexamic acid, preoperative anaemia, low Hb level, refusal of blood products, coagulopathy, history of thromboembolic event, major comorbidities.
Age, gender and ethnicity	Age - Mean (SD): 67. Gender (M:F): 42/60. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Shoulder arthroplasty
Indirectness of population	No indirectness
Interventions	(n=53) Intervention 1: Perioperative use of tranexamic acid - IV. 2 doses of 10mg/kg. Firstly within 60

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	minutes of surgery. Secondly at wound closure. . Duration During surgery. Concurrent medication/care: DVT prophylaxis: subcutaneous unfractionated heparin every 8 hours after surgery until discharge. Aspiring twice daily after discharge. Compression stockings on both legs until discharge from hospital. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=49) Intervention 2: Placebo. Normal saline given IV at the same times as the intervention.. Duration During surgery. Concurrent medication/care: DVT prophylaxis: subcutaneous unfractionated heparin every 8 hours after surgery until discharge. Aspiring twice daily after discharge. Compression stockings on both legs until discharge from hospital. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Other (Senior author reported conflicts of interest.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: Thromboembolic events at Within 6 weeks for surgery; Group 1: 0/53, Group 2: 0/49
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at In hospital period; Group 1: 3/53, Group 2: 7/49
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Postoperative bleeding at -
- Actual outcome: Drain output at 0-48 hours after surgery; Group 1: mean 221 mL (SD 126); n=53, Group 2: mean 372 mL (SD 166); n=49
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Haemoglobin at 2 days after surgery; Group 1: mean 10.4 g/dL (SD 1.5); n=53, Group 2: mean 9.8 g/dL (SD 1.4); n=49 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Total blood loss at - - Actual outcome: Total blood loss at 2 days after surgery; Group 1: mean 1122.4 mL (SD 411.6); n=53, Group 2: mean 1472.6 mL (SD 475.4); n=49 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Length of stay at -

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Study	Veien 2002[248]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in Denmark; Setting:
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 5 days follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults undergoing primary cemented TKR.
Exclusion criteria	Myocardial infarction within 6 months, unstable angina, severe aortic or mitral valve stenosis, previous stroke, unmedicated hypertension, history of thromboembolic episodes, warfarin medication.
Age, gender and ethnicity	Age - Mean (SD): 70. Gender (M:F): 5/25. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Perioperative use of tranexamic acid - IV. 10mg/kg given just before release of tourniquet and again 3 hours later. . Duration During surgery. Concurrent medication/care: 500 IE LMWH

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	given daily for thromboprophylaxis. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=15) Intervention 2: Placebo. Unclear how placebo was administered. Duration During surgery. Concurrent medication/care: 500 IE LMWH given daily for thromboprophylaxis.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO Protocol outcome 1: Adverse events: DVT at - - Actual outcome: Thromboembolic episodes at Within 5 days of surgery; Group 1: 0/15, Group 2: 0/15 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference in gender and weight; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Blood (allogeneic or autologous) transfusion at - - Actual outcome: Transfusion at Within 5 days of surgery; Group 1: 0/15, Group 2: 2/15 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference in gender and weight; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -; Blood loss: Haemoglobin level at 3 days after surgery; Total blood loss at -

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Study	Wang 2015[256]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in China
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and postoperative hospital period
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People undergoing primary unilateral TKA. All patients were treated with patellar medial approach, and the implants were CR knee bone cement prosthesis Gemini MKII
Exclusion criteria	People with preoperative anemia or coagulopathy, infectious active diseases like lower limb infection or systemic infection disease, TXA contraindications, history of venous thromboembolic disease or thromboembolic disorders, clotting problem like liver tumor or cirrhosis, people who intended to participate in autologous blood transfusion
Recruitment/selection of patients	January 2012 to December 2014
Age, gender and ethnicity	Age - Mean (SD): 53. Gender (M:F): 47/53. Ethnicity: Not detailed

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Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Perioperative use of tranexamic acid - IA/topical. 1g tranexamic acid dissolved in 50 ml 0.9% sodium chloride solution and injected after prosthesis implantation and before cavity closed. Conventional pipe clamping was carried for 4 hours and the drainage tube was removed 48 hours after surgery.. Duration Surgical and post surgery hospital period. Concurrent medication/care: Anticoagulant therapy of 5000 iu low molecular weight heparin was applied to both groups 8 hours after operation.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≤1000 mg (n=50) Intervention 2: Placebo. 50 ml 0.9% sodium chloride solution and injected after prosthesis implantation and before cavity closed. Conventional pipe clamping was carried for 4 hours and the drainage tube was removed 48 hours after surgery.. Duration Surgery and post surgery hospital period. Concurrent medication/care: Anticoagulant therapy of 5000 iu low molecular weight heparin was applied to both groups 8 hours after operation.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Academic or government funding (This work was supported by a grant from the National Natural Science Foundation of China)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at 5 days after surgery; Group 1: 3/50, Group 2: 2/50
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -

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- Actual outcome: Transfusion at 5 days after surgery; Group 1: 2/50, Group 2: 9/50 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Hb D-value at 5 days after surgery; Group 1: mean -2.29 g/dL (SD 0.827); n=50, Group 2: mean -3.973 g/dL (SD 1.001); n=50 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Total blood loss at - - Actual outcome: Total blood loss at 5 days after surgery; Group 1: mean 678.45 ml (SD 112.77); n=50, Group 2: mean 1136.3 ml (SD 224.52); n=50 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -

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Study	Wang 2015[253]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in China; Setting: August 1st 2013 and September 30th 2013 in one medical centre
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and postoperative period in hospital
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Primary varus knee osteoarthritis, no previous knee open surgery, a tibiofemoral angle between 0 and 15 degrees varus, and scheduled for unilateral primary TKA. Surgery for all patients was performed by one surgical team and all knees were operated under spinal anesthesia.
Exclusion criteria	People with a body mass index (BMI) < 35 kg/m2, rheumatoid arthritis, simultaneous bilateral TKA, allergy to TXA, preoperative anemia (a hemoglobin [Hb] value of <11 g/dL in females and <12 g/dL in males), refusal of allogeneic blood products, or a history of coagulopathy or a thromboembolic event
Age, gender and ethnicity	Age - Mean (SD): 65 (7). Gender (M:F): 15/45. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty

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Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Perioperative use of tranexamic acid - IA/topical. Immediately after skin closure, 10 mL saline with 0.5g TXA was injected into the joint.. Duration Surgery and postsurgery hospital period. Concurrent medication/care: For the prevention of DVT, rivaroxaban (10 mg administered orally) was started on the day after surgery and continued for 17 days.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≤1000 mg (n=30) Intervention 2: Placebo. Immediately after skin closure, 10 mL saline was injected into the joint.. Duration Surgery and postsurgery hospital period. Concurrent medication/care: For the prevention of DVT, rivaroxaban (10 mg administered orally) was started on the day after surgery and continued for 17 days. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Academic or government funding (Natural Science Foundation of Tianjin (14JCQNJC11700) and the Tianjin Health Bureau Science and Technology Foundation (No. 2011kz117).)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: Thromboembolic events at During surgery and postsurgery; Group 1: 0/30, Group 2: 0/30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at Postoperative period; Group 1: 0/30, Group 2: 7/30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Length of stay at -

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- Actual outcome: Hospital stay at .; Group 1: mean 6.43 days (SD 0.68); n=30, Group 2: mean 8.17 days (SD 2.7); n=30 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Hb level at 3 days after surgery; Group 1: mean 10.51 g/dL (SD 1.06); n=30, Group 2: mean 9.1 g/dL (SD 0.99); n=30 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Total blood loss at - - Actual outcome: Total blood loss at 3 days after surgery; Group 1: mean 974.6 ml (SD 283.65); n=30, Group 2: mean 1393.2 ml (SD 353.48); n=30 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -

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Study	Wang 2016[251]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=124)
Countries and setting	Conducted in China
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 3 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with OA scheduled to have primary unilateral total hip replacement.
Exclusion criteria	Hemophilia, DVT, PE, shunts, ischemic heart disease, anticoagulant medication, serious liver or renal dysfunction, allergy to tranexamic acid.
Recruitment/selection of patients	September 2014 to November 2014.
Age, gender and ethnicity	Age - Mean (SD): 60. Gender (M:F): 47/72. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Hip replacement
Indirectness of population	No indirectness

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Interventions	(n=39) Intervention 1: Perioperative use of tranexamic acid - IV. 10mg/kg before surgery begins.. Duration During surgery. Concurrent medication/care: Thromboprophylaxis: half dose of LMWH starting 6 hours after surgery. Then a full dose very 24 hour hours. People hooked up to an intermittent slope pump system. Rivaroxaban taken orally for 14 days after discharge. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=42) Intervention 2: Perioperative use of tranexamic acid - IV. 15mg/kg before surgery begins.. Duration During surgery. Concurrent medication/care: Thromboprophylaxis: half dose of LMWH starting 6 hours after surgery. Then a full dose very 24 hour hours. People hooked up to an intermittent slope pump system. Rivaroxaban taken orally for 14 days after discharge. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=38) Intervention 3: Placebo. 10 or 15ml saline given as placebo . Duration During surgery. Concurrent medication/care: Thromboprophylaxis: half dose of LMWH starting 6 hours after surgery. Then a full dose very 24 hour hours. People hooked up to an intermittent slope pump system. Rivaroxaban taken orally for 14 days after discharge. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Academic or government funding (China Health Ministry Program)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 6 weeks of surgery; Group 1: 1/39, Group 2: 0/38
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at In hospital period; Group 1: 8/39, Group 2: 10/38
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

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- Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Postoperative bleeding at -
- Actual outcome: Drainage at In hospital period; Group 1: mean 271.5 mL (SD 111.7); n=39, Group 2: mean 399.5 mL (SD 147.7); n=38
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Decrease in haemoglobin at In hospital period; Group 1: mean -3.828 g/dL (SD 1); n=39, Group 2: mean -4.758 g/dL (SD 1.04); n=38
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Total blood loss at -
- Actual outcome: Total blood loss at In hospital period; Group 1: mean 1000.1 mL (SD 252.9); n=39, Group 2: mean 1228.9 mL (SD 296.3); n=38
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 6 weeks of surgery; Group 1: 0/42, Group 2: 0/38
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at In hospital period; Group 1: 1/42, Group 2: 10/38
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Postoperative bleeding at -
- Actual outcome: Drainage at In hospital period; Group 1: mean 213.57 mL (SD 65.32); n=42, Group 2: mean 399.5 mL (SD 147.7); n=38
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

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- Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Decrease in haemoglobin at In hospital period; Group 1: mean -3.212 g/dL (SD 0.885); n=42, Group 2: mean -4.758 g/dL (SD 1.04); n=38 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Total blood loss at - - Actual outcome: Total blood loss at In hospital period; Group 1: mean 871.1 mL (SD 244.9); n=42, Group 2: mean 1228.9 mL (SD 296.3); n=38 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Length of stay at -

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Study	Wang 2017[259]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=150)
Countries and setting	Conducted in China
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and postsurgery hospital period
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People aged 30 years and older, who were scheduled for primary unilateral TKA for end-stage osteoarthritis
Exclusion criteria	People with preoperative Hb <110 g/L, thromboembolic history or preoperative situation such as DVT or PE, or arterial stenosis with or without concomitant coronary artery bypass grafting, preoperative D-dimer >3 times normal level, cardiovascular history, such as myocardial infraction, angina, or atrial fibrillation, cerebrovascular history of previous stroke, clotting disorders including prolonged prothrombin, time or activated partial thromboplastin time, or abnormal international normalized ratio, allergic history of TXA, Pregnant or lactating women, drug abusers or alcoholics, severe complications, such as severe liver and kidney diseases, New York Heart Association class III or above, heart failure, or patients with severe infection, combined the use of other medicine that may have an impact on the outcome of the study, diagnosed as inflammatory arthritis including rheumatoid arthritis, pigmented villonodular synovitis.
Age, gender and ethnicity	Age - Mean (SD): 68. Gender (M:F): 44/106. Ethnicity: Not detailed

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Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Perioperative use of tranexamic acid - IA/topical. 1g intra-articular tranexamic acid dissolved in 50 mL intra-articular saline was administered right before skin closure.. Duration Surgery and unclear number of years afterwards. Concurrent medication/care: People received subcutaneous enoxaparin 40 mg once daily, starting the evening of surgery, for hospitalization; and oral rivaroxaban, 10 mg once daily, for 10 days after discharge. Patients were dressed elastic bandage right after surgery and were encouraged to follow standard rehabilitation protocol including lower extremity muscle strength training and walk exercises.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≤1000 mg (n=50) Intervention 2: Perioperative use of tranexamic acid - IV. 1g IV tranexamic acid and 50 mL intra-articular saline was administered right before skin closure.. Duration Surgery and unclear number of years afterwards. Concurrent medication/care: People received subcutaneous enoxaparin 40 mg once daily, starting the evening of surgery, for hospitalization; and oral rivaroxaban, 10 mg once daily, for 10 days after discharge. Patients were dressed elastic bandage right after surgery and were encouraged to follow standard rehabilitation protocol including lower extremity muscle strength training and walk exercises.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≤1000 mg (n=50) Intervention 3: Placebo. 50 mL intra-articular saline right before skin closure.. Duration Surgery and unclear number of years afterwards. Concurrent medication/care: People received subcutaneous enoxaparin 40 mg once daily, starting the evening of surgery, for hospitalization; and oral rivaroxaban, 10 mg once daily, for 10 days after discharge. Patients were dressed elastic bandage right after surgery and were encouraged to follow standard rehabilitation protocol including lower extremity muscle strength training and walk exercises.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Academic or government funding (Financial support from the research program of Shanghai Municipal

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	Health and Family Planning Commission (201440421).)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus IV

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 5 weeks of surgery; Group 1: 0/50, Group 2: 0/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at Within 5 weeks of surgery; Group 1: 0/50, Group 2: 1/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Length of stay at -
- Actual outcome: Length of stay at .; Group 1: mean 7 days (SD 0.3); n=50, Group 2: mean 6.9 days (SD 0.4); n=50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Hb drift at 2 days after surgery; Group 1: mean -2.74 g/dL (SD 0.85); n=50, Group 2: mean -3.37 g/dL (SD 1.18); n=50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Total blood loss at -
- Actual outcome: Total blood loss at 3 days after surgery; Group 1: mean 770.3 mL (SD 237.3); n=50, Group 2: mean 919.7 mL (SD 327.7); n=50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus PLACEBO

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Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 5 weeks of surgery; Group 1: 0/50, Group 2: 0/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at Within 5 weeks of surgery; Group 1: 0/50, Group 2: 1/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Length of stay at -
- Actual outcome: Length of stay at .; Group 1: mean 7 (SD 0.3); n=50, Group 2: mean 7 (SD 0.4); n=50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Hb drift at 2 days after surgery; Group 1: mean -2.74 g/dL (SD 0.85); n=50, Group 2: mean -4.06 g/dL (SD 0.94); n=50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Total blood loss at -
- Actual outcome: Total blood loss at 3 days after surgery; Group 1: mean 770.3 mL (SD 237.3); n=50, Group 2: mean 1079.9 mL (SD 297.4); n=50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 5 weeks of surgery; Group 1: 0/50, Group 2: 0/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 2: Blood (allogeneic or autologous) transfusion at - - Actual outcome: Transfusion at Within 5 weeks of surgery; Group 1: 1/50, Group 2: 1/50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Length of stay at - - Actual outcome: Length of stay at .; Group 1: mean 6.9 days (SD 0.4); n=50, Group 2: mean 7 days (SD 0.4); n=50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Hb drift at 2 days after surgery; Group 1: mean -3.37 g/dL (SD 1.18); n=50, Group 2: mean -4.06 g/dL (SD 0.94); n=50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Total blood loss at - - Actual outcome: Total blood loss at 3 days after surgery; Group 1: mean 919.7 mL (SD 327.7); n=50, Group 2: mean 1079.9 mL (SD 297.4); n=50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -

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Study	Wang 2018[254]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=189)
Countries and setting	Conducted in China; Setting: Department of Orthopaedic Surgery at West China Hospital from March 2016 to January 2017
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery with 90 days follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with primary knee osteoarthritis who were scheduled for elective primary unilateral total knee replacement
Exclusion criteria	Secondary osteoarthritis (e.g., post-septic arthritis and post-traumatic arthritis), simultaneous bilateral or revision TKA, allergic reaction to TXA, history of major comorbidities (severe arterial thromboembolic event, severe renal failure, or severe pulmonary disease), history of hematopoietic disease, history of pulmonary embolism (PE) or deep venous thrombosis (DVT), alcohol or drug abuse, and current anticoagulant therapy (warfarin or heparin) within one week.
Age, gender and ethnicity	Age - Mean (SD): 64 (13), 67 (9), 63 (12). Gender (M:F): 49/131. Ethnicity: Not detailed
Further population details	1. Co-morbidities: ASA grade (I-III). 2. Site/type of joint replacement: Total knee arthroplasty (TKA).

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Indirectness of population	No indirectness
Interventions	(n=63) Intervention 1: Perioperative use of tranexamic acid - Oral. 2g of through four 500mg tablets taken approximately 2 hours before incision. 100mL of an IV and IA placebo solution (normal saline) in a manner identical to administration in the other treatment IV and IA groups.. Duration Surgery. Concurrent medication/care: While hospitalized, chemical prophylaxis consisted of subcutaneous administration of low-molecular-weight heparin (2000 IU) beginning 8 hours postoperatively, which was then administered once daily (4000 IU). Rivaroxaban (10 mg orally), was administered daily, which continued for 10 days after discharge.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg (n=63) Intervention 2: Perioperative use of tranexamic acid - IV. The IV group received a 20mg/kg dose of TXA in 100 mL of normal saline solution administered 5 minutes prior to incision. 100mL of a placebo solution administered intra-articularly. Oral and IA placebos used.. Duration Surgery. Concurrent medication/care: While hospitalized, chemical prophylaxis consisted of subcutaneous administration of low-molecular-weight heparin (2000 IU) beginning 8 hours postoperatively, which was then administered once daily (4000 IU). Rivaroxaban (10 mg orally), was administered daily, which continued for 10 days after discharge.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg (2g). (n=63) Intervention 3: Perioperative use of tranexamic acid - IA/topical. 2g dose of TXA, diluted in 100 mL of saline solution, administered intra-articularly at two time points: (1) the open joint surface was soaked with 50 mL of a 1g TXA solution following component implantation and was left in contact with the tissue for five minutes; (2) the remaining 50 mL of a 1g TXA solution was given using a needle to penetrate the tissue of knee capsule before capsule closure. Oral and IV placebos used.. Duration Surgery. Concurrent medication/care: While hospitalized, chemical prophylaxis consisted of subcutaneous administration of low-molecular-weight heparin (2000 IU) beginning 8 hours postoperatively, which was then administered once daily (4000 IU). Rivaroxaban (10 mg orally), was administered daily, which continued for 10 days after discharge.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg (2g).

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Funding	Funding not stated (Authors declared no competing interests)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL versus IV

Protocol outcome 1: Mortality at 30 day
- Actual outcome: All cause mortality at Within 30 days of surgery; Group 1: 0/60, Group 2: 0/60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Some difference in age. Higher age in IV group. ; Group 1 Number missing: 3; Group 2 Number missing: 3

Protocol outcome 2: Adverse events: DVT at -
- Actual outcome: DVT or PE at Within 90 days of surgery; Group 1: 0/60, Group 2: 1/60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Some difference in age. Higher age in IV group. ; Group 1 Number missing: 3; Group 2 Number missing: 3

Protocol outcome 3: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Allogeneic blood transfusion at While still admitted in hospital; Group 1: 2/60, Group 2: 4/60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Some difference in age. Higher age in IV group. ; Group 1 Number missing: 3; Group 2 Number missing: 3

Protocol outcome 4: Surgical bleeding at -
- Actual outcome: Intraoperative blood loss at .; Group 1: mean 147.12 ml (SD 25.64); n=60, Group 2: mean 148.92 ml (SD 31.43); n=60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Some difference in age. Higher age in IV group. ; Group 1 Number missing: 3; Group 2 Number missing: 3

Protocol outcome 5: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Change in haemoglobin level at 72 hours after surgery; Group 1: mean -2.91 g/dl (SD 1.13); n=60, Group 2: mean -3.13 g/dl (SD 0.89); n=60

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Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Some difference in age. Higher age in IV group. ; Group 1 Number missing: 3; Group 2 Number missing: 3

Protocol outcome 6: Total blood loss at -
- Actual outcome: Calculated blood loss at 72 hours after surgery; Group 1: mean 1003.99 ml (SD 414.44); n=60, Group 2: mean 1108.31 ml (SD 392.11); n=60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Some difference in age. Higher age in IV group. ; Group 1 Number missing: 3; Group 2 Number missing: 3

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL versus IA/TOPICAL

Protocol outcome 1: Mortality at 30 day
- Actual outcome: All cause mortality at Within 30 days of surgery; Group 1: 0/60, Group 2: 0/60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 3

Protocol outcome 2: Adverse events: DVT at -
- Actual outcome: DVT or PE at Within 90 days of surgery; Group 1: 0/60, Group 2: 0/60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 3

Protocol outcome 3: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Allogeneic blood transfusion at While still admitted in hospital; Group 1: 2/60, Group 2: 2/60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 3

Protocol outcome 4: Surgical bleeding at -
- Actual outcome: Intraoperative blood loss at .; Group 1: mean 147.12 ml (SD 25.64); n=60, Group 2: mean 150.16 ml (SD 28.22); n=60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 3

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Protocol outcome 5: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Change in haemoglobin level at 72 hours after surgery; Group 1: mean -2.91 g/dl (SD 1.13); n=60, Group 2: mean -2.99 g/dl (SD 1.03); n=60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 3

Protocol outcome 6: Total blood loss at -
- Actual outcome: Calculated blood loss at 72 hours after surgery; Group 1: mean 1003.99 ml (SD 414.44); n=60, Group 2: mean 1059.37 ml (SD 422.99); n=60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 3

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus IV

Protocol outcome 1: Mortality at 30 day
- Actual outcome: All cause mortality at Within 30 days of surgery; Group 1: 0/60, Group 2: 0/60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Some difference in age. Higher age in IV group. ; Group 1 Number missing: 3; Group 2 Number missing: 3

Protocol outcome 2: Adverse events: DVT at -
- Actual outcome: DVT or PE at Within 90 days of surgery; Group 1: 0/60, Group 2: 1/60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Some difference in age. Higher age in IV group. ; Group 1 Number missing: 3; Group 2 Number missing: 3

Protocol outcome 3: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Allogeneic blood transfusion at While still admitted in hospital; Group 1: 2/60, Group 2: 4/60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Some difference in age. Higher age in IV group. ; Group 1 Number missing: 3; Group 2 Number missing: 3

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Protocol outcome 4: Surgical bleeding at - - Actual outcome: Intraoperative blood loss at .; Group 1: mean 150.16 ml (SD 28.22); n=60, Group 2: mean 148.92 ml (SD 31.43); n=60 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Some difference in age. Higher age in IV group. ; Group 1 Number missing: 3; Group 2 Number missing: 3 Protocol outcome 5: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Change in haemoglobin level at 72 hours after surgery; Group 1: mean -2.99 g/dl (SD 1.03); n=60, Group 2: mean -3.13 g/dl (SD 0.89); n=60 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Some difference in age. Higher age in IV group. ; Group 1 Number missing: 3; Group 2 Number missing: 3 Protocol outcome 6: Total blood loss at - - Actual outcome: Calculated blood loss at 72 hours after surgery; Group 1: mean 1059.37 ml (SD 422.99); n=60, Group 2: mean 1108.31 ml (SD 392.11); n=60 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Some difference in age. Higher age in IV group. ; Group 1 Number missing: 3; Group 2 Number missing: 3	
Protocol outcomes not reported by the study	Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -

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Study	Wang 2018[255]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=)
Countries and setting	Conducted in China
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 3 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People scheduled for primary unilateral total knee arthroplasty
Exclusion criteria	Tourniquet application, medication not prepared in time, and withdrawn consent
Age, gender and ethnicity	Age - Mean (SD): 65 (13), 64 (12). Gender (M:F): 33/114. Ethnicity:
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness
Interventions	(n=75) Intervention 1: Perioperative use of tranexamic acid - Oral. 2g by oral bolus appropriately 2 hours before incision. A postoperative dose of 1g was repeated 6 and 12 hours after surgery. 100mL of an intra-articular place of solution (0.9% physiological saline solution) in a manner identical to the application of the

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	solution in the IA group.. Duration Surgery and treatment until 10 days after hospital discharge. Concurrent medication/care: Thromboprophylaxis: mechanical prophylaxis by means of an intermittent inflatable lower-extremity pump on the first day after surgery, and lower-extremity strength training and passive and active physiotherapy were performed under the supervision of a professional physiotherapist. People were administered LMWH subcutaneously appropriately 8 hours after surgery and followed by 4000 IU once a day during hospitalization. 10mg Rivaroxaban was administered orally once a day for 10 days after discharge. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg (n=75) Intervention 2: Perioperative use of tranexamic acid - IA/topical. Intraarticular administration of 3g in 100 mL of saline solution administered is 2 doses. After all components have been cemented and the joint was thoroughly irrigated, the first half is applied to soak the open joint surface and tissue for 5 min and the second half administered using a needle to achieve tissue impregnation. Placebo pills identical to oral TXA in appearance were given 2 hours before incision.. Duration Surgery and treatment until 10 days after hospital discharge . Concurrent medication/care: Thromboprophylaxis: mechanical prophylaxis by means of an intermittent inflatable lower-extremity pump on the first day after surgery, and lower-extremity strength training and passive and active physiotherapy were performed under the supervision of a professional physiotherapist. People were administered LMWH subcutaneously appropriately 8 hours after surgery and followed by 4000 IU once a day during hospitalization. 10mg Rivaroxaban was administered orally once a day for 10 days after discharge.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≥3000 mg
Funding	No funding (No funding was obtained for this study.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL versus IA/TOPICAL Protocol outcome 1: Mortality at 30 day - Actual outcome: All cause mortality at Within 30 days of surgery; Group 1: 0/73, Group 2: 0/74	

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Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: 1 did not receive trial medication; Group 2 Number missing: 2, Reason: 1 tourniquet application and 1 withdrew from study.

Protocol outcome 2: Adverse events: DVT at -
- Actual outcome: DVT
at Within 3 months of surgery; Group 1: 1/74, Group 2: 0/73
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: 1 did not receive trial medication; Group 2 Number missing: 2, Reason: 1 tourniquet application and 1 withdrew from study.

Protocol outcome 3: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at Before discharged from hospital; Group 1: 3/75, Group 2: 4/75
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: 1 did not receive trial medication; Group 2 Number missing: 2, Reason: 1 tourniquet application and 1 withdrew from study.

Protocol outcome 4: Surgical bleeding at -
- Actual outcome: Intro-operative blood loss at .; Group 1: mean 143.1 mL (SD 25.4); n=74, Group 2: mean 145.6 mL (SD 27.1); n=73
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: 1 did not receive trial medication; Group 2 Number missing: 2, Reason: 1 tourniquet application and 1 withdrew from study.

Protocol outcome 5: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Reduction of hemoglobin
at Before discharged from hospital; Group 1: mean -2.2 g/dL (SD 0.9); n=74, Group 2: mean -2.4 g/dL (SD 1.1); n=73
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: 1 did not receive trial medication; Group 2 Number missing: 2, Reason: 1 tourniquet application and 1 withdrew from study.

Protocol outcome 6: Total blood loss at -
- Actual outcome: Total blood loss at In hospital after surgery; Group 1: mean 788.8 mL (SD 349.1); n=74, Group 2: mean 872.4 mL (SD 393.1); n=73

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Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: 1 did not receive trial medication; Group 2 Number missing: 2, Reason: 1 tourniquet application and 1 withdrew from study.	
Protocol outcomes not reported by the study	Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -

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Study	Wei 2014[264]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=303)
Countries and setting	Conducted in China; Setting: 1 surgeon performed all surgeries.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 3 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People aged 45–80 years, without low preoperative hemoglobin, normal international normalized ratio (INR), prothrombin time, partial thromboplastin time (PTT) values, no history of previous hip surgery who were scheduled for unilateral cementless primary total hip replacement.
Exclusion criteria	Documented history of thrombo-embolism, allergy to tranexamic acid, high risk of venous thrombosis for intravenous use of tranexamic acid
Age, gender and ethnicity	Age - Mean (SD): 64 (7), 60 (7), 64 (7). Gender (M:F): 113/190. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Hip replacement

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Indirectness of population	No indirectness
Interventions	(n=102) Intervention 1: Perioperative use of tranexamic acid - IA/topical. 3g mixed with 100ml saline. During surgery, the acetabulum was bathed in 20ml. Following femoral canal broach preparation, the femoral canal was filled with 20ml.The remaining 60ml was injected into the hip joint following fascia closure.. Duration Surgery until hospital discharge. Concurrent medication/care: LMWH (low molecular weight heparin) was used for prophylaxis against deep vein thrombosis (DVT).. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≥3000 mg (n=101) Intervention 2: Perioperative use of tranexamic acid - IV. 3g intravenous infusion 10 minutes prior to incision. Physiological saline solution (0.85%) was used as placebo. . Duration Surgery until hospital discharge. Concurrent medication/care: LMWH (low molecular weight heparin) was used for prophylaxis against deep vein thrombosis (DVT). Physiological saline solution (0.85%) was used as placebo. no TXA group. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≥3000 mg (n=100) Intervention 3: Placebo. Physiological saline solution (0.85%) was used as placebo. Duration Surgery until hospital discharge. Concurrent medication/care: LMWH (low molecular weight heparin) was used for prophylaxis against deep vein thrombosis (DVT).. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Academic or government funding (Linyi People's Hospital and the First Affiliated Hospital of Guangzhou University of Chinese Medicine aided in carrying out the study.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus IV

Protocol outcome 1: Adverse events: DVT at -

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- Actual outcome: DVT at within 3 months of surgery; Group 1: 1/102, Group 2: 1/101
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Blood transfusion at Surgery and before discharge; Group 1: 6/102, Group 2: 6/101
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Length of stay at -
- Actual outcome: Length of stay at .; Group 1: mean 5 days (SD 0.7); n=102, Group 2: mean 4.8 days (SD 0.5); n=101
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Total blood loss at -
- Actual outcome: Total blood loss at After surgery and before discharge; Group 1: mean 963.4 mL (SD 421.3); n=102, Group 2: mean 958.5 mL (SD 422.1); n=101
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at within 3 months of surgery; Group 1: 1/102, Group 2: 0/100
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Blood transfusion at Surgery and before discharge; Group 1: 6/102, Group 2: 26/100
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 3: Length of stay at -
- Actual outcome: Length of stay at .; Group 1: mean 5 days (SD 0.7); n=102, Group 2: mean 4.9 days (SD 0.6); n=100
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Total blood loss at -
- Actual outcome: Total blood loss at After surgery and before discharge; Group 1: mean 963.4 mL (SD 421.3); n=102, Group 2: mean 1364.2 mL (SD 278.6); n=100
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at within 3 months of surgery; Group 1: 1/101, Group 2: 0/100
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Blood transfusion at Surgery and before discharge; Group 1: 6/101, Group 2: 26/100
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Length of stay at -
- Actual outcome: Length of stay at .; Group 1: mean 4.8 days (SD 0.5); n=101, Group 2: mean 4.9 days (SD 0.6); n=100
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Total blood loss at -
- Actual outcome: Total blood loss at After surgery and before discharge; Group 1: mean 958.5 mL (SD 422.1); n=101, Group 2: mean 1364.2 mL (SD 278.6); n=100
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover -

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Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Blood loss: Haemoglobin level at 3 days after surgery

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Study	Wei 2018[263]
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	1 (n=64)
Countries and setting	Conducted in China; Setting: All operations were carried out by the same surgeon
Line of therapy	Not applicable
Duration of study	--: Surgery and 96 hours follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with knee osteoarthritis and an American Society of Anesthesiologists (ASA) score 3 or under who are scheduled for unilateral primary TKA
Exclusion criteria	Cardiovascular problems, cerebrovascular conditions, thromboembolic disorders, renal insufficiency
Age, gender and ethnicity	Age - Mean (SD): 66 (8). Gender (M:F): 30/34. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness
Interventions	(n=32) Intervention 1: Perioperative use of tranexamic acid - IV. 10mg/kg 10 min after placement of a loose

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	tourniquet.. Duration Surgery and 96 hours follow-up. Concurrent medication/care: Thromboprophylaxis: people given low-molecular-weight heparin unless they took another cardiovascular medication before surgery.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=32) Intervention 2: Perioperative use of tranexamic acid - IA/topical. 1g diluted in 50ml of normal saline, injected into the surgical site (posterior and anterior capsule, medial and lateral retinaculum), and the surgical site was soaked in the solution for 5 min before deflation of the tourniquet.. Duration Surgery and 96 hours follow-up. Concurrent medication/care: Thromboprophylaxis: people given low-molecular-weight heparin unless they took another cardiovascular medication before surgery.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≤1000 mg
Funding	Other (The authors declare that they have no competing interests.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus IA/TOPICAL

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: Post-operative thromboembolic complications at Within 96 hours of surgery; Group 1: 0/32, Group 2: 0/32
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Surgical bleeding at -
- Actual outcome: Intra-operative blood loss at .; Group 1: mean 122.81 mL (SD 41.6); n=32, Group 2: mean 109.06 mL (SD 33.38); n=32
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Postoperative bleeding at -
- Actual outcome: Post-operative blood loss at 96 hours after surgery; Group 1: mean 125.31 mL (SD 41.6); n=32, Group 2: mean 111 mL (SD 30.9); n=32
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Hb at 96 hours after surgery; Group 1: mean -2.84 g/dL (SD 0.68); n=32, Group 2: mean -2.66 g/dL (SD 0.6); n=32 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Blood (allogeneic or autologous) transfusion at -; Quality of life at within 6 weeks; Postoperative anaemia at -; Length of stay at -; Total blood loss at -

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Study	Wong 2010[270]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=124)
Countries and setting	Conducted in Canada; Setting: Toronto Western Hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 6 weeks follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Age, gender and ethnicity	Age - Mean (SD): 68 (10), 67 (12), 64 (11). Gender (M:F): Define. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness
Interventions	(n=44) Intervention 1: Perioperative use of tranexamic acid - IA/topical. 1.5g in saline solution. After all components were cemented in place, the joint was thoroughly irrigated and the solution was applied to the joint surfaces using a bulb syringe and left in contact for 5 minutes. Excess then suctioned away and wound

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	closed. . Duration Surgical period. Concurrent medication/care: Thromboprophylaxis: LMWH used for 10 days after surgery. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg (n=40) Intervention 2: Perioperative use of tranexamic acid - IA/topical. 3g in saline solution. After all components were cemented in place, the joint was thoroughly irrigated and the solution was applied to the joint surfaces using a bulb syringe and left in contact for 5 minutes. Excess then suctioned away and wound closed.. Duration Surgical period. Concurrent medication/care: Thromboprophylaxis: LMWH used for 10 days after surgery. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≥3000 mg (n=40) Intervention 3: Placebo. Normal saline solution. After all components were cemented in place, the joint was thoroughly irrigated and the saline solution was applied to the joint surfaces using a bulb syringe and left in contact for 5 minutes. Excess then suctioned away and wound closed.. Duration Surgical period. Concurrent medication/care: Thromboprophylaxis: LMWH used for 10 days after surgery.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Academic or government funding (PSI Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 6 weeks of surgery; Group 1: 2/31, Group 2: 1/35
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 13, Reason: 13 did not receive medication; Group 2 Number missing: 5, Reason: 5 did not receive medication

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at Within 3 days of surgery; Group 1: 4/31, Group 2: 5/35

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Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 13, Reason: 13 did not receive medication; Group 2 Number missing: 5, Reason: 5 did not receive medication

Protocol outcome 3: Length of stay at -
- Actual outcome: Length of hospital stay at .; Group 1: mean 4.7 days (SD 1.85); n=31, Group 2: mean 4.3 days (SD 1.06); n=35
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 13, Reason: 13 did not receive medication; Group 2 Number missing: 5, Reason: 5 did not receive medication

Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Lowest postoperative haemoglobin at Within 3 days of surgery; Group 1: mean 10 g/dL (SD 1.28); n=31, Group 2: mean 8.6 g/dL (SD 1.21); n=35
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 13, Reason: 13 did not receive medication; Group 2 Number missing: 5, Reason: 5 did not receive medication

Protocol outcome 5: Total blood loss at -
- Actual outcome: Total blood loss at 3 days after surgery; Group 1: mean 1295 mL (SD 362.2); n=31, Group 2: mean 1610 mL (SD 389.4); n=35
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 13, Reason: 13 did not receive medication; Group 2 Number missing: 5, Reason: 5 did not receive medication

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 6 weeks of surgery; Group 1: 1/33, Group 2: 1/35
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences in age, weight and platelet count; Group 1 Number missing: 6, Reason: 6 did not receive medication; Group 2 Number missing: 5, Reason: 5 did not receive medication

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -

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- Actual outcome: Transfusion at Within 3 days of surgery; Group 1: 0/33, Group 2: 5/35 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences in age, weight and platelet count; Group 1 Number missing: 6, Reason: 6 did not receive medication; Group 2 Number missing: 5, Reason: 5 did not receive medication Protocol outcome 3: Length of stay at - - Actual outcome: Length of hospital stay at .; Group 1: mean 4.5 days (SD 0.73); n=33, Group 2: mean 4.3 days (SD 1.06); n=35 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences in age, weight and platelet count; Group 1 Number missing: 6, Reason: 6 did not receive medication; Group 2 Number missing: 5, Reason: 5 did not receive medication Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Lowest postoperative haemoglobin at Within 3 days of surgery; Group 1: mean 10.1 g/dL (SD 1.03); n=33, Group 2: mean 8.6 g/dL (SD 1.21); n=35 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences in age, weight and platelet count; Group 1 Number missing: 6, Reason: 6 did not receive medication; Group 2 Number missing: 5, Reason: 5 did not receive medication Protocol outcome 5: Total blood loss at - - Actual outcome: Total blood loss at 3 days after surgery; Group 1: mean 1208 mL (SD 382.5); n=33, Group 2: mean 1610 mL (SD 389.4); n=35 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences in age, weight and platelet count; Group 1 Number missing: 6, Reason: 6 did not receive medication; Group 2 Number missing: 5, Reason: 5 did not receive medication	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -

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Study	Xie 2016[276]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=210)
Countries and setting	Conducted in China
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 30 days follow-up after hospital discharge
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	May 2014 to February 2015.
Age, gender and ethnicity	Age - Mean (SD): 60 (12), 62 (11), 61 (11). Gender (M:F): Define. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Hip replacement
Indirectness of population	No indirectness
Interventions	(n=70) Intervention 1: Perioperative use of tranexamic acid - IV. 1.5g IV dose 15 minutes before skin incision.

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	. Duration Hospital period and 30 days after discharge. Concurrent medication/care: Half dose of enoxaparin given 6 hours after the operation and repeated every 24 hours with full dose until discharge from hospital. Intermittent pneumatic compression device used. After discharge 10mg rivaroxaban administered orally for 30 days. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg (n=70) Intervention 2: Perioperative use of tranexamic acid - IA/topical. 3g in 150ml physiological saline was utilised. Gauze with 50ml used to soak the acetabulum for 3 minutes and gauze with 50ml used to soak the femoral canal for 3 minutes. Remaining 50ml injected into joint space through the drainage tube after fascia closure. . Duration Surgery and 30 days follow-up after hospital discharge. Concurrent medication/care: Half dose of enoxaparin given 6 hours after the operation and repeated every 24 hours with full dose until discharge from hospital. Intermittent pneumatic compression device used. After discharge 10mg rivaroxaban administered orally for 30 days.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≥3000 mg (n=70) Intervention 3: Perioperative use of tranexamic acid - IV+IA/topical. 1g IV dose 15 minutes before skin incision. 2g in 150ml physiological saline was utilised. Gauze with 50ml used to soak the acetabulum for 3 minutes and gauze with 50ml used to soak the femoral canal for 3 minutes. Remaining 50ml injected into joint space through the drainage tube after fascia closure.. Duration Surgery and 30 days after hospital discharge. Concurrent medication/care: Half dose of enoxaparin given 6 hours after the operation and repeated every 24 hours with full dose until discharge from hospital. Intermittent pneumatic compression device used. After discharge 10mg rivaroxaban administered orally for 30 days.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≥3000 mg
Funding	Academic or government funding (China Health Ministry)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus IA/TOPICAL Protocol outcome 1: Adverse events: DVT at - - Actual outcome: DVT at within 3 months of surgery; Group 1: 1/70, Group 2: 0/70	

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Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at within 5 days of surgery; Group 1: 3/70, Group 2: 4/70
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Length of stay at -
- Actual outcome: Length of hospital stay at .; Group 1: mean 4.43 days (SD 1.33); n=70, Group 2: mean 4.24 days (SD 1.07); n=70
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Maximum haemoglobin drop at within 5 days of surgery; Group 1: mean -3.36 g/dL (SD 0.78); n=70, Group 2: mean -3.89 g/dL (SD 0.72); n=70
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Total blood loss at -
- Actual outcome: Total blood loss at 5 days after surgery; Group 1: mean 878.03 mL (SD 210); n=70, Group 2: mean 905.07 mL (SD 237.7); n=70
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus IV+IA/TOPICAL

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at within 3 months of surgery; Group 1: 1/70, Group 2: 2/70
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -

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- Actual outcome: Transfusion at within 5 days of surgery; Group 1: 3/70, Group 2: 0/70
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Length of stay at -
- Actual outcome: Length of hospital stay at .; Group 1: mean 4.43 days (SD 1.33); n=70, Group 2: mean 4.39 days (SD 1.28); n=70
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Maximum haemoglobin drop at within 5 days of surgery; Group 1: mean -3.36 g/dL (SD 0.78); n=70, Group 2: mean -2.98 g/dL (SD 0.78); n=70
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Total blood loss at -
- Actual outcome: Total blood loss at 5 days after surgery; Group 1: mean 878.03 mL (SD 210); n=70, Group 2: mean 776.75 mL (SD 188.95); n=70
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus IV+IA/TOPICAL

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at within 3 months of surgery; Group 1: 0/70, Group 2: 2/70
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at within 5 days of surgery; Group 1: 4/70, Group 2: 0/70
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 3: Length of stay at - - Actual outcome: Length of hospital stay at .; Group 1: mean 4.24 days (SD 1.07); n=70, Group 2: mean 4.39 days (SD 1.28); n=70 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Maximum haemoglobin drop at within 5 days of surgery; Group 1: mean -3.89 g/dL (SD 0.72); n=70, Group 2: mean -2.98 g/dL (SD 0.78); n=70 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Total blood loss at - - Actual outcome: Total blood loss at 5 days after surgery; Group 1: mean 905.07 mL (SD 237.7); n=70, Group 2: mean 776.75 mL (SD 188.95); n=70 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -

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Study	Yang 2015[280]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=80)
Countries and setting	Conducted in China; Setting: One hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery with 2 weeks follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People >60 years old with OA, traumatic arthritis or RA and a BMI <40kg/m².
Exclusion criteria	Haemorrhagic blood disease, low preoperative haemoglobin level, peripheral nerve vascular disease, history of thromboembolic disease, affected lower limb with history of infection, ASA rating >3.
Recruitment/selection of patients	January 2011 to October 2103.
Age, gender and ethnicity	Age - Mean (SD): 68. Gender (M:F): 22/58. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness

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Interventions	(n=40) Intervention 1: Perioperative use of tranexamic acid - IA/topical. IA injection (500mg) in 20ml into knee joint cavity after completion of the facial closure. . Duration During surgery. Concurrent medication/care: 0.6ml LMWH administered subcutaneously 12 hours after surgery and repeated daily until discharge. People were encouraged to perform ankle pumping exercises. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≤1000 mg (n=40) Intervention 2: Placebo. IA injection of 20ml saline into knee joint cavity after completion of the facial closure. . Duration During surgery. Concurrent medication/care: 0.6ml LMWH administered subcutaneously 12 hours after surgery and repeated daily until discharge. People were encouraged to perform ankle pumping exercises. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at within 2 weeks of surgery; Group 1: 0/40, Group 2: 0/40
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at within 1 week of surgery; Group 1: 10/40, Group 2: 19/40
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Surgical bleeding at -
- Actual outcome: Intra-operative blood loss at During surgery; Group 1: mean 124 mL (SD 40); n=40, Group 2: mean 114 mL (SD 47); n=40

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Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Postoperative bleeding at - - Actual outcome: Postoperative blood loss at 4 days after surgery; Group 1: mean 45 mL (SD 13); n=40, Group 2: mean 55 mL (SD 15); n=40 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Haemoglobin level at 4 days after surgery; Group 1: mean 9.4 g/dL (SD 1.3); n=40, Group 2: mean 8.2 g/dL (SD 1.5); n=40 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Postoperative anaemia at -; Length of stay at -; Total blood loss at -

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Study	Yi 2016[282]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=150)
Countries and setting	Conducted in China; Setting: West China Hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 6 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	December 2013 to May 2014.
Age, gender and ethnicity	Age - Mean (SD): 54 (15), 54 (13), 57 (12). Gender (M:F): Define. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Hip replacement
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Perioperative use of tranexamic acid - IV+IA/topical. 15mg/kg IV 5 minutes before

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	incision. 20ml (200mg TXA) solution used to topically on acetabulum and placed within femoral canal. 60ml (600mg TXA) injected into hip joint. . Duration Surgery and for 14 days after hospital discharge. Concurrent medication/care: Thrombprophylaxis: low extremity strength training preoperatively and started active and passive physiotherapy after anaesthesia resolution. Inflatable lower-extremity venous pump applied on the first day after surgery. All people required to walk with full weight bearing twice before discharge. LMWH administered 8 hours after surgery and then every 24 hours until hospital discharge. 10mg rivaroxaban given for 14 days after hospital discharge.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=50) Intervention 2: Perioperative use of tranexamic acid - IV. 15mg/kg IV 5 minutes before incision. 20ml normal saline solution used to topically on acetabulum and placed within femoral canal. 60ml normal saline solution injected into hip joint.. Duration Surgery and for 14 days after hospital discharge. Concurrent medication/care: Thrombprophylaxis: low extremity strength training preoperatively and started active and passive physiotherapy after anaesthesia resolution. Inflatable lower-extremity venous pump applied on the first day after surgery. All people required to walk with full weight bearing twice before discharge. LMWH administered 8 hours after surgery and then every 24 hours until hospital discharge. 10mg rivaroxaban given for 14 days after hospital discharge.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=50) Intervention 3: Placebo. IV saline 5 minutes before incision. 20ml saline solution used to topically on acetabulum and placed within femoral canal. 60ml saline injected into hip joint.. Duration Surgery and for 14 days after hospital discharge. Concurrent medication/care: Thrombprophylaxis: low extremity strength training preoperatively and started active and passive physiotherapy after anaesthesia resolution. Inflatable lower-extremity venous pump applied on the first day after surgery. All people required to walk with full weight bearing twice before discharge. LMWH administered 8 hours after surgery and then every 24 hours until hospital discharge. 10mg rivaroxaban given for 14 days after hospital discharge.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Academic or government funding (China Health Ministry Program)

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RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV+IA/TOPICAL versus IV

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 6 months of surgery; Group 1: 2/50, Group 2: 2/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at Within hospital stay; Group 1: 1/50, Group 2: 8/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Postoperative bleeding at -
- Actual outcome: Drainage at 3 days after surgery; Group 1: mean 127.2 mL (SD 113.52); n=50, Group 2: mean 126.8 mL (SD 91.91); n=50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Length of stay at -
- Actual outcome: Length of hospital stay at .; Group 1: mean 6.4 days (SD 0.97); n=50, Group 2: mean 6.52 days (SD 1.2); n=50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Haemoglobin at 3 days after surgery; Group 1: mean 10.238 g/dL (SD 1.68); n=50, Group 2: mean 9.28 g/dL (SD 1.228); n=50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 6: Total blood loss at -
- Actual outcome: Total blood loss at 3 days after surgery; Group 1: mean 835.49 mL (SD 343.5); n=50, Group 2: mean 1002.62 mL (SD 366.85); n=50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV+IA/TOPICAL versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 6 months of surgery; Group 1: 2/50, Group 2: 1/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at Within hospital stay; Group 1: 1/50, Group 2: 19/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Postoperative bleeding at -
- Actual outcome: Drainage at 3 days after surgery; Group 1: mean 127.2 mL (SD 113.52); n=50, Group 2: mean 244.4 mL (SD 146.14); n=50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Length of stay at -
- Actual outcome: Length of hospital stay at .; Group 1: mean 6.4 days (SD 0.97); n=50, Group 2: mean 6.58 days (SD 1.67); n=50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Haemoglobin at 3 days after surgery; Group 1: mean 10.238 g/dL (SD 1.68); n=50, Group 2: mean 8.74 g/dL (SD 1.495); n=50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 6: Total blood loss at -
- Actual outcome: Total blood loss at 3 days after surgery; Group 1: mean 835.49 mL (SD 343.5); n=50, Group 2: mean 1221.11 mL (SD 386.25); n=50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 6 months of surgery; Group 1: 2/50, Group 2: 1/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at Within hospital stay; Group 1: 8/50, Group 2: 19/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Postoperative bleeding at -
- Actual outcome: Drainage at 3 days after surgery; Group 1: mean 126.8 mL (SD 91.91); n=50, Group 2: mean 244.4 mL (SD 146.14); n=50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Length of stay at -
- Actual outcome: Length of hospital stay at .; Group 1: mean 6.52 days (SD 1.2); n=50, Group 2: mean 6.58 days (SD 1.67); n=50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Haemoglobin at 3 days after surgery; Group 1: mean 9.28 g/dL (SD 1.228); n=50, Group 2: mean 8.74 g/dL (SD 1.495); n=50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 6: Total blood loss at -
- Actual outcome: Total blood loss at 3 days after surgery; Group 1: mean 1002.62 mL (SD 366.85); n=50, Group 2: mean 1221.11 mL (SD 386.25); n=50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -

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Study	Yuan 2017[285]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=560)
Countries and setting	Conducted in China; Setting: One hospital from September 2013 to June 2016
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery with at least 3 weeks follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with osteoarthritis or rheumatoid arthritis who were scheduled for primary unilateral TKA at were enrolled.
Exclusion criteria	Previous bilateral TKA, revision TKA, severe hepatic and/or renal diseases, coagulopathy, or a bleeding disorder.
Age, gender and ethnicity	Age - Mean (SD): 64 (8), 63 (7), 63 (7), 65 (8). Gender (M:F): 198/302. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness
Interventions	(n=140) Intervention 1: Perioperative use of tranexamic acid - IV. 20 mg/kg intravenously 30 minutes before

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	incising the skin, and the same dose 12 hours after TKA. Administered an oral placebo pill [calcium tablet].IA placebo of saline. Duration Surgery and 3 weeks follow-up. Concurrent medication/care: Thrmoboprophylaxis: physiotherapy and medication. An inflatable lower extremity venous pump was applied the first day after TKA. Rivaroxaban was taken orally at 10mg/d until day 15 after TKA. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=140) Intervention 2: Perioperative use of tranexamic acid - IA/topical. 3g total 60 mL solution administered after the subcutaneous tissue was sutured. Administered an oral placebo pill [calcium tablet].IV placebo joint injection of saline. Duration Surgery and 3 weeks follow-up. Concurrent medication/care: Thrmoboprophylaxis: physiotherapy and medication. An inflatable lower extremity venous pump was applied the first day after TKA. Rivaroxaban was taken orally at 10mg/d until day 15 after TKA. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≥3000 mg (n=140) Intervention 3: Perioperative use of tranexamic acid - Oral. 20mg/kg orally 2 hours before the operation and the same dose 12 hours after TKA. IV placebo joint injection of saline. IA placebo of saline. Duration Surgery and 3 weeks follow-up. Concurrent medication/care: Thrmoboprophylaxis: physiotherapy and medication. An inflatable lower extremity venous pump was applied the first day after TKA. Rivaroxaban was taken orally at 10mg/d until day 15 after TKA . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=140) Intervention 4: Placebo. No TXA was used in the control group. Administered an oral placebo pill [calcium tablet].IA placebo of saline.IV placebo joint injection of saline . Duration Surgery and 3 weeks follow-up. Concurrent medication/care: Thrmoboprophylaxis: physiotherapy and medication. An inflatable lower extremity venous pump was applied the first day after TKA. Rivaroxaban was taken orally at 10mg/d until day 15 after TKA. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Other (No author associated with this paper has disclosed any potential or pertinent conflicts which may be perceived to have impending conflict with this work.)

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RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus IA/TOPICAL

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 2 weeks of surgery; Group 1: 2/140, Group 2: 0/140
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Number of people transfused at Within 2 weeks of surgery; Group 1: 15/140, Group 2: 17/140
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Hb loss at 48 hours after surgery; Group 1: mean -2.92 g/dL (SD 0.41); n=140, Group 2: mean -2.92 g/dL (SD 0.42); n=140
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus ORAL

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 2 weeks of surgery; Group 1: 2/140, Group 2: 1/140
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Number of people transfused at Within 2 weeks of surgery; Group 1: 15/140, Group 2: 15/140
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Hb loss at 48 hours after surgery; Group 1: mean -2.92 g/dL (SD 0.42); n=140, Group 2: mean -2.9 g/dL (SD 0.4); n=140

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Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 2 weeks of surgery; Group 1: 2/140, Group 2: 1/140
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Number of people transfused at Within 2 weeks of surgery; Group 1: 15/140, Group 2: 36/140
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Hb loss at 48 hours after surgery; Group 1: mean -2.92 g/dL (SD 0.41); n=140, Group 2: mean -3.34 g/dL (SD 0.48); n=140
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus ORAL

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 2 weeks of surgery; Group 1: 0/140, Group 2: 1/140
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Number of people transfused at Within 2 weeks of surgery; Group 1: 17/140, Group 2: 15/140
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Hb loss at 48 hours after surgery; Group 1: mean -2.92 g/dL (SD 0.42); n=140, Group 2: mean -2.9 g/dL (SD 0.43); n=140
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 2 weeks of surgery; Group 1: 0/140, Group 2: 1/140
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Number of people transfused at Within 2 weeks of surgery; Group 1: 17/140, Group 2: 36/140
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Hb loss at 48 hours after surgery; Group 1: mean -2.92 g/dL (SD 0.42); n=140, Group 2: mean -3.34 g/dL (SD 0.48); n=140
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 2 weeks of surgery; Group 1: 1/140, Group 2: 1/140
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Number of people transfused at Within 2 weeks of surgery; Group 1: 15/140, Group 2: 36/140
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

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- Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Hb loss at 48 hours after surgery; Group 1: mean -2.9 g/dL (SD 0.43); n=140, Group 2: mean -3.34 g/dL (SD 0.48); n=140 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -; Total blood loss at -

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Study	Yue 2014[287]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=101)
Countries and setting	Conducted in China; Setting: West China hospital, Sichuan University.
Line of therapy	Not applicable
Duration of study	Intervention time: Surgery and post-surgical period in hospital
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People undergoing primary unilateral total hip arthroplasty for OA or ONFH
Exclusion criteria	People who were receiving anticoagulant therapy, history of haemophilia, deep venous thrombosis, pulmonary embolism or ischemic heart disease or allergic to tranexamic acid.
Recruitment/selection of patients	September 2013 to October 2013
Age, gender and ethnicity	Age - Mean (SD): 62. Gender (M:F): 39/62. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Hip replacement
Indirectness of population	No indirectness

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Interventions	(n=52) Intervention 1: Perioperative use of tranexamic acid - IA/topical. 3g TXA in 150 mL saline was used at three time points. First, after the acetabular preparation, gauze (25 cm × 25 cm, monolayer) which was full of 50 mL of the TXA solution to soak the acetabulum for three minutes, an cementless acetabular component was then impacted. Then, after femoral canal broach preparation, another gauze (25 cm × 25 cm, monolayer) with 50 mL of the same concentration TXA was inserted in the femoral canal for three minutes, and then the cementless femoral stem was impacted. The remaining 50 mL TXA fluid was injected to the hip joint after fascia closure. A drain was used and clamped for 30 minutes. Duration During surgery. Concurrent medication/care: Chemical thromboprophylaxis by low-molecular-weight heparin (LMWH) combined with mechanical thromboprophylaxis by a leg pump.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≥3000 mg (n=51) Intervention 2: Placebo. 150 mL saline was used at three time points. First, after the acetabular preparation, gauze (25 cm × 25 cm, monolayer) which was full of 50 mL of the saline solution to soak the acetabulum for three minutes, an cementless acetabular component was then impacted. Then, after femoral canal broach preparation, another gauze (25 cm × 25 cm, monolayer) with 50 mL of the saline was inserted in the femoral canal for three minutes, and then the cementless femoral stem was impacted. The remaining 50 mL saline was injected to the hip joint after fascia closure. A drain was used and clamped for 30 minutes. Duration During surgery. Concurrent medication/care: Chemical thromboprophylaxis by low-molecular-weight heparin (LMWH) combined with mechanical thromboprophylaxis by a leg pump.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Academic or government funding (Registered and approved by the Institutional Review Board of Sichuan University, West China Medical Center (No. 201302007).)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at 3 months after surgery; Group 1: 1/52, Group 2: 0/49
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

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- Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 2 Protocol outcome 2: Blood (allogeneic or autologous) transfusion at - - Actual outcome: Transfusion at 3 months after surgery; Group 1: 3/52, Group 2: 11/49 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 2 Protocol outcome 3: Postoperative bleeding at - - Actual outcome: Postoperative blood loss at In hospital period; Group 1: mean 217.5 mL (SD 89.9); n=52, Group 2: mean 296.9 mL (SD 109); n=51 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Length of stay at - - Actual outcome: Postoperative hospitalisation days at .; Group 1: mean 5.1 days (SD 0.5); n=52, Group 2: mean 4.9 days (SD 0.7); n=51 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Hb drop at 3 days after surgery; Group 1: mean -4.002 g/dL (SD 0.974); n=51, Group 2: mean -5.327 g/dL (SD 0.479); n=51 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 6: Total blood loss at - - Actual outcome: Total blood loss at In hospital period; Group 1: mean 945.5 mL (SD 331.7); n=52, Group 2: mean 1255.5 mL (SD 193.5); n=51 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -

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Study (subsidiary papers)	Zekcer 2016[289] (Zekcer 2017[290])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in Brazil
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 15 days follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People scheduled for unilateral TKA due to arthrosis (Albach grades III and IV)
Exclusion criteria	Previously undergone any orthopaedic surgery to the legs or if they had secondary arthrosis, history of DVT or PE or identified risks for DVT or PE, coagulation or cardiovascular disorders, or vascular diseases, currently using anticoagulation drugs.
Age, gender and ethnicity	Age - Mean (range): 66 (48-88). Gender (M:F): 20/70. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Perioperative use of tranexamic acid - IA/topical. 1.5g in 50 ml of saline which was

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	sprayed over the operated area for 5 minutes, before the tourniquet was released.. Duration Surgery and 15 days follow-up. Concurrent medication/care: Thromboprophylaxis: with elastic stockings, and 40mg sodium enoxapar administered subcutaneously once a day for 10 days.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg (n=30) Intervention 2: Perioperative use of tranexamic acid - IV. 20mg/kg, diluted in 100 ml of saline, infused over a 10-minute period at the same time as anaesthesia was administered.. Duration Surgery and 15 days follow-up. Concurrent medication/care: Thromboprophylaxis: with elastic stockings, and 40mg sodium enoxapar administered subcutaneously once a day for 10 days.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=30) Intervention 3: Placebo. 100 ml of saline solution, also at the same time as anaesthesia, over a period of 10 minutes.. Duration Surgery and 15 days follow-up. Concurrent medication/care: Thromboprophylaxis: with elastic stockings, and 40mg sodium enoxapar administered subcutaneously once a day for 10 days.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	No funding (Financial support: None.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus IV

Protocol outcome 1: Mortality at 30 day
- Actual outcome: Death at Within 15 days of surgery; Group 1: 0/30, Group 2: 0/30
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Adverse events: DVT at -
- Actual outcome: DVT at Within 15 days of surgery; Group 1: 1/30, Group 2: 0/30
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 3: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at Within 15 days of surgery; Group 1: 0/30, Group 2: 0/30
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus PLACEBO

Protocol outcome 1: Mortality at 30 day
- Actual outcome: Death at Within 15 days of surgery; Group 1: 0/30, Group 2: 0/30
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Adverse events: DVT at -
- Actual outcome: DVT at Within 15 days of surgery; Group 1: 1/30, Group 2: 4/30
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at Within 15 days of surgery; Group 1: 0/30, Group 2: 6/30
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Mortality at 30 day
- Actual outcome: Death at Within 15 days of surgery; Group 1: 0/30, Group 2: 0/30
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Adverse events: DVT at -
- Actual outcome: DVT at Within 15 days of surgery; Group 1: 0/30, Group 2: 4/30

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Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Blood (allogeneic or autologous) transfusion at - - Actual outcome: Transfusion at Within 15 days of surgery; Group 1: 0/30, Group 2: 6/30 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -; Blood loss: Haemoglobin level at 3 days after surgery; Total blood loss at -

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Study	Zeng 2017[291]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in China; Setting: West China Hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and follow-up for 3 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults (18-90 years old) undergoing primary unilateral total hip replacement
Exclusion criteria	Allergy to tranexamic acid, preoperative hepatic or renal dysfunction, preoperative (within 7 days) use of anticoagulant medication, history of fibrinolytic disorder, blood dyscrasia, cerebrovascular accident, myocardial infarction, heart failure, AF, history of DVT or PE, High preoperative INR, failure to give consent.
Age, gender and ethnicity	Age - Mean (SD): 51 (15), 56 (11). Gender (M:F): 60/40. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Hip replacement
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Perioperative use of tranexamic acid - IV+IA/topical. 15mg/kg IV in 1.5ml saline.

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	Topical administration 1g in 100ml saline administered during surgery. . Duration Surgery and 3 weeks follow-up. Concurrent medication/care: Thromboprophylaxis: active and passive physiotherapy after anaesthesia awareness, lower extremity venous pump first day after surgery. LMWH given 8 hours after surgery and every day until discharge. After discharge rivaroxaban given daily for 15 days. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: >1000 mg to <3000 mg (n=50) Intervention 2: Placebo. 1.5ml IV saline. Topical administration of 100ml saline administered during surgery.. Duration Surgery and 3 weeks follow-up. Concurrent medication/care: Thromboprophylaxis: active and passive physiotherapy after anaesthesia awareness, lower extremity venous pump first day after surgery. LMWH given 8 hours after surgery and every day until discharge. After discharge rivaroxaban given daily for 15 days. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	Other (No conflicts of interest)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV+IA/TOPICAL versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: Venous thrombosis at Within 2 weeks of surgery; Group 1: 1/50, Group 2: 0/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Slightly higher age in placebo group; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at During hospital period; Group 1: 2/50, Group 2: 17/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Slightly higher age in placebo group; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Surgical bleeding at -

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- Actual outcome: Intraoperative Blood Loss at During surgery; Group 1: mean 193.8 mL (SD 90); n=50, Group 2: mean 288.2 mL (SD 105.2); n=50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Slightly higher age in placebo group; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Postoperative bleeding at - - Actual outcome: Drain blood loss at 3 days after surgery; Group 1: mean 118.8 mL (SD 94.9); n=50, Group 2: mean 242.4 mL (SD 155.4); n=50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Slightly higher age in placebo group; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Length of stay at - - Actual outcome: Length of stay after surgery at .; Group 1: mean 6.2 days (SD 1.7); n=50, Group 2: mean 6.8 days (SD 2); n=50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Slightly higher age in placebo group; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Haemoglobin change at 3 days after surgery; Group 1: mean -3.22 g/dL (SD 1.21); n=50, Group 2: mean -4.49 g/dL (SD 1.22); n=50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Slightly higher age in placebo group; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 7: Total blood loss at - - Actual outcome: Total blood loss at 3 days after surgery; Group 1: mean 822 mL (SD 335); n=50, Group 2: mean 1100 mL (SD 379); n=50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Slightly higher age in placebo group; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Postoperative anaemia at -

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Study	Zhang 2016[302]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=75)
Countries and setting	Conducted in China; Setting: Luoyang Orthopedic Traumatology Hospital.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and at least 1 year follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People scheduled for unilateral primary total hip replacement for osteonecrosis of the femoral head and a BMI between 18.5 and 30.
Exclusion criteria	Diabetes, bleeding disorders, preoperative anaemia, malignancies, history of thrombosis disease, arteriosclerosis, varicose veins and other cardiovascular diseases, allergy to tranexamic acid, kidney dysfunction.
Age, gender and ethnicity	Age - Mean (SD): 45 (2), 44 (4), 43 (4). Gender (M:F): 39/36. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Hip replacement
Indirectness of population	No indirectness

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Interventions	(n=25) Intervention 1: Perioperative use of tranexamic acid - IV. 1g diluted in 250ml saline and administered via IV infusion 10 minutes before the surgery. . Duration Surgery and followed every 3 months for a year. Concurrent medication/care: Thromboprophylaxis: LMWH given 12 hours after surgery and then daily for 2 weeks. Functional exercises in bed after recovering from anaesthesia and approved for ambulation with crutches 3 or 5 days after surgery. Further details: 1. Tranexamic acid dose: ≤1000 mg (n=25) Intervention 2: Perioperative use of tranexamic acid - IA/topical. After skin sutures closed, the IA group were injected with 1g in 100ml saline via the drainage tubes. . Duration Surgery and followed every 3 months for a year. Concurrent medication/care: Thromboprophylaxis: LMWH given 12 hours after surgery and then daily for 2 weeks. Functional exercises in bed after recovering from anaesthesia and approved for ambulation with crutches 3 or 5 days after surgery. Further details: 1. Tranexamic acid dose: ≤1000 mg (n=25) Intervention 3: No treatment. No tranexamic acid treatment. Duration Surgery and followed every 3 months for a year. Concurrent medication/care: Thromboprophylaxis: LMWH given 12 hours after surgery and then daily for 2 weeks. Functional exercises in bed after recovering from anaesthesia and approved for ambulation with crutches 3 or 5 days after surgery.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus IA/TOPICAL

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: Venous thrombosis at Within 1 year of surgery; Group 1: 1/25, Group 2: 0/25
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Unclear; Group 2 Number missing: 1, Reason: Unclear

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Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at During hospital stay; Group 1: 1/23, Group 2: 0/24
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Unclear; Group 2 Number missing: 1, Reason: Unclear

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Haemoglobin at 3 days after surgery; Group 1: mean 8.5 g/dL (SD 0.9); n=23, Group 2: mean 8.9 g/dL (SD 1.1); n=24
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Unclear; Group 2 Number missing: 1, Reason: Unclear

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus NO TREATMENT

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: Venous thrombosis at Within 1 year of surgery; Group 1: 1/25, Group 2: 2/25
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Unclear; Group 2 Number missing: 3, Reason: Unclear

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at During hospital stay; Group 1: 1/23, Group 2: 2/22
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Unclear; Group 2 Number missing: 3, Reason: Unclear

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Haemoglobin at 3 days after surgery; Group 1: mean 8.5 g/dL (SD 0.9); n=23, Group 2: mean 8.2 g/dL (SD 1.3); n=22
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Unclear; Group 2 Number missing: 3, Reason: Unclear

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RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus NO TREATMENT

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: Venous thrombosis at Within 1 year of surgery; Group 1: 0/25, Group 2: 2/25
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Unclear; Group 2 Number missing: 3, Reason: Unclear

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at During hospital stay; Group 1: 0/24, Group 2: 2/22
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Unclear; Group 2 Number missing: 3, Reason: Unclear

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Haemoglobin at 3 days after surgery; Group 1: mean 8.9 g/dL (SD 1.1); n=24, Group 2: mean 8.2 g/dL (SD 1.3); n=22
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Unclear; Group 2 Number missing: 3, Reason: Unclear

Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -; Total blood loss at -

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Study	Zhang 2019[303]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=150)
Countries and setting	Conducted in China; Setting: Weifang People's Hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 6 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People 40 to 80 years old scheduled for TKA. They were included in the study if they were treated with supplemental blood volume 2000mL within 20 hours following surgery, had a normal platelet amount and coagulation function before TKA operation, the surgery was performed by the same group of doctors and nurses, the people had no abnormality in the venous system of the lower limbs with Colour Doppler ultrasonography before TKA operation.
Exclusion criteria	Previous TKA surgery, people in need of antibiotic treatment for their pulmonary infection or urinary tract infection; contraindication to TKA; at a high risk of developing thrombosis, suffered from malignant tumors.
Recruitment/selection of patients	From January 2015 to December 2016

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Age, gender and ethnicity	Age - Mean (SD): 63 (9), 60 (12), 63 (13). Gender (M:F): 38/112. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Total knee arthroplasty
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Perioperative use of tranexamic acid - IV+IA/topical. IV plus IA group underwent intravenous injection of 20mg/kg before the incision, who also received articular injection of 3g TXA after it was sutured.. Duration Surgery. Concurrent medication/care: Twelve hours after the operation, patients were continuously given 10mg rivaroxaban (1 time/d) for 2 weeks.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≥3000 mg (n=50) Intervention 2: Perioperative use of tranexamic acid - IV. IV alone group had intravenous injection of 20mg/kg TXA before the incision. Duration Surgery. Concurrent medication/care: Twelve hours after the operation, patients were continuously given 10mg rivaroxaban (1 time/d) for 2 weeks.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=50) Intervention 3: Perioperative use of tranexamic acid - IA/topical. IA alone group received articular injection of 3.0g TXA after it was sutured. Duration Surgery. Concurrent medication/care: Twelve hours after the operation, patients were continuously given 10mg rivaroxaban (1 time/d) for 2 weeks.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≥3000 mg (3g).
Funding	No funding ("Funding: not applicable")

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus IV+IA/TOPICAL

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: Thromboembolism: IVT, DVT, PE at Within 6 months of surgery; Group 1: 9/50, Group 2: 10/50

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Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Quality of life at within 6 weeks
- Actual outcome: Quality of life (SF-36: PCS) at Unclear; Group 1: mean 57.28 (SD 11.05); n=50, Group 2: mean 56.06 (SD 9.56); n=50; SF-36: physical component score 0-100 Top=High is good outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: Quality of life (SF-36: MCS) at Unclear; Group 1: mean 63.3 (SD 12.37); n=50, Group 2: mean 61.98 (SD 10.74); n=50; SF-36: mental component score 0-100 Top=High is good outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Maximum haemoglobin drop at Within 3 days of surgery; Group 1: mean -2.734 g/dl (SD 0.941); n=50, Group 2: mean -1.682 g/dl (SD 0.65); n=50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Total blood loss at -
- Actual outcome: Total blood loss at 3 days after surgery; Group 1: mean 621.44 ml (SD 102.4); n=50, Group 2: mean 394.44 ml (SD 86.94); n=50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus IV+IA/TOPICAL

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: Thromboembolism: IVT, DVT, PE at Within 6 months of surgery; Group 1: 8/50, Group 2: 10/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Quality of life at within 6 weeks

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- Actual outcome: Quality of life (SF-36: PCS) at Unclear; Group 1: mean 55.02 (SD 8.85); n=50, Group 2: mean 56.06 (SD 9.56); n=50; SF-36: physical component score 0-100 Top=High is good outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: Quality of life (SF-36: MCS) at Unclear; Group 1: mean 60.8 (SD 9.76); n=50, Group 2: mean 61.98 (SD 10.74); n=50; SF36: mental component score 0-100 Top=High is good outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Maximum haemoglobin drop at Within 3 days of surgery; Group 1: mean -2.214 g/dl (SD 1.09); n=50, Group 2: mean -1.682 g/dl (SD 0.65); n=50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Total blood loss at -
- Actual outcome: Total blood loss at 3 days after surgery; Group 1: mean 501.34 ml (SD 106.79); n=50, Group 2: mean 394.44 ml (SD 86.94); n=50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus IV

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: Thromboembolism: IVT, DVT, PE at Within 6 months of surgery; Group 1: 8/50, Group 2: 9/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Quality of life at within 6 weeks
- Actual outcome: Quality of life (SF-36: PCS) at Unclear; Group 1: mean 55.02 (SD 8.85); n=50, Group 2: mean 57.28 (SD 11.05); n=50; SF-36 physical component score 0-100 Top=High is good outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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- Actual outcome: Quality of life (SF-36: MCS) at Unclear; Group 1: mean 60.8 (SD 9.76); n=50, Group 2: mean 63.3 (SD 12.37); n=50; SF-36: mental component score 0-100 Top=High is good outcome Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Maximum haemoglobin drop at Within 3 days of surgery; Group 1: mean -2.214 g/dl (SD 1.09); n=50, Group 2: mean -2.734 g/dl (SD 0.941); n=50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Total blood loss at - - Actual outcome: Total blood loss at 3 days after surgery; Group 1: mean 501.34 ml (SD 106.79); n=50, Group 2: mean 621.44 ml (SD 102.4); n=50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Blood (allogeneic or autologous) transfusion at -; Surgical bleeding at -; Postoperative anaemia at -; Postoperative bleeding at -; Length of stay at -

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Study	Zhao 2018[305]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in China; Setting: West China Hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery with follow-up 2 weeks after hospital discharge
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People having elective primary unilateral total hip arthroplasty for osteoarthritis of femoral head necrosis
Exclusion criteria	BMI over 30, Crowe type 3 or 4 dysplasia, prior hip surgery, inability to tolerate general aneathesia, allergy to tranexamic acid, bilateral arthroplasty, history of renal failure, kidney transplant, recent arterial thromboembolic event, hypercoagulation, haemophilia, DVT, PE.
Recruitment/selection of patients	September 2016 to June 2017
Age, gender and ethnicity	Age - Mean (SD): 60 (10), 60 (11), 60 (11). Gender (M:F): 70/50. Ethnicity: Not detailed
Further population details	1. Co-morbidities: Not stated / Unclear 2. Site/type of joint replacement: Hip replacement
Indirectness of population	No indirectness

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Interventions	(n=40) Intervention 1: Perioperative use of tranexamic acid - IV. 15mg/kg 10 minutes before incision. 4 ascorbic acid tablets given to enable blinding with oral group. . Duration Surgery and 10 days after hospital discharge. Concurrent medication/care: Thromboembolic prophylaxis: LMWH after the operation and daily until postoperative day 3. After hospital discharge people were given 10mg oral rivaroxaban daily for 10 days. . Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=40) Intervention 2: Perioperative use of tranexamic acid - Oral. 20mg/kg 2 hours before surgery and 3 hours after surgery. IV saline given to enable blinding with IV group. . Duration Surgery and 10 days after hospital discharge. Concurrent medication/care: Thromboembolic prophylaxis: LMWH after the operation and daily until postoperative day 3. After hospital discharge people were given 10mg oral rivaroxaban daily for 10 days.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=40) Intervention 3: Placebo. IV saline given to enable blinding with IV group. 4 ascorbic acid tablets given to enable blinding with oral group. Duration Surgery and 10 days after hospital discharge. Concurrent medication/care: Thromboembolic prophylaxis: LMWH after the operation and daily until postoperative day 3. After hospital discharge people were given 10mg oral rivaroxaban daily for 10 days.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus ORAL

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 30 days of surgery; Group 1: 0/40, Group 2: 0/40
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at During in hospital period; Group 1: 2/40, Group 2: 1/40
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Surgical bleeding at -
- Actual outcome: Intraoperative blood loss at During surgery; Group 1: mean 132.5 mL (SD 17.7); n=40, Group 2: mean 134.8 mL (SD 24.15); n=40
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Length of stay at -
- Actual outcome: Postoperative hospital stay at .; Group 1: mean 2.8 days (SD 0.63); n=40, Group 2: mean 2.8 days (SD 0.2); n=40
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Largest drop in haemoglobin level at At 1, 2 or 3 days after surgery; Group 1: mean -2.69 g/dL (SD 0.6); n=40, Group 2: mean -2.75 g/dL (SD 0.6); n=40
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 6: Total blood loss at -
- Actual outcome: Total blood loss at 3 days after surgery; Group 1: mean 692.7 mL (SD 172.2); n=40, Group 2: mean 694.1 mL (SD 142.3); n=40
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 30 days of surgery; Group 1: 0/40, Group 2: 0/40
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

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Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at During in hospital period; Group 1: 2/40, Group 2: 8/40
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Surgical bleeding at -
- Actual outcome: Intraoperative blood loss at During surgery; Group 1: mean 132.5 mL (SD 17.7); n=40, Group 2: mean 156.3 mL (SD 35.9); n=40
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Length of stay at -
- Actual outcome: Postoperative hospital stay at .; Group 1: mean 2.8 days (SD 0.63); n=40, Group 2: mean 2.9 days (SD 1.9); n=40
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Largest drop in haemoglobin level at At 1, 2 or 3 days after surgery; Group 1: mean -2.69 g/dL (SD 0.6); n=40, Group 2: mean -3.52 g/dL (SD 1.2); n=40
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 6: Total blood loss at -
- Actual outcome: Total blood loss at 3 days after surgery; Group 1: mean 692.7 mL (SD 172.7); n=40, Group 2: mean 948.5 mL (SD 193.4); n=40
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at Within 30 days of surgery; Group 1: 0/40, Group 2: 0/40
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

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- Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion at During in hospital period; Group 1: 1/40, Group 2: 8/40
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Surgical bleeding at -
- Actual outcome: Intraoperative blood loss at During surgery; Group 1: mean 134.8 mL (SD 24.15); n=40, Group 2: mean 156.3 mL (SD 35.9); n=40
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Length of stay at -
- Actual outcome: Postoperative hospital stay at .; Group 1: mean 2.8 days (SD 0.2); n=40, Group 2: mean 2.9 days (SD 1.9); n=40
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Largest drop in haemoglobin level at At 1, 2 or 3 days after surgery; Group 1: mean -2.75 g/dL (SD 0.6); n=40, Group 2: mean -3.52 g/dL (SD 1.2); n=40
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 6: Total blood loss at -
- Actual outcome: Total blood loss at 3 days after surgery; Group 1: mean 694.1 mL (SD 142.3); n=40, Group 2: mean 948.5 mL (SD 193.4); n=40
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Postoperative anaemia at -; Postoperative bleeding at -

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Study	Zhou 2018[307]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=174)
Countries and setting	Conducted in China; Setting: Single centre study
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Surgery and 6 weeks follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults scheduled to undergo primary unilateral THA
Exclusion criteria	Allergy to tranexamic acid, coagulopathy, any indicator of prolonged partial thromboplastin, history of thromboembolic disease, myocardial infarction (MI), and cerebral infarction (CI); taking anticoagulant drugs within a week before surgery; major comorbidities, including severe ischemic heart disease, renal dysfunction, or hepatic dysfunction retinopathy; pregnancy; participated in another clinical trial within a year; and those who completely stay in bed for more than 3 weeks.
Age, gender and ethnicity	Age - Mean (SD): 65 (11), 63 (10), 66 (9). Gender (M:F): 43/127. Ethnicity: Not detailed
Further population details	1. Co-morbidities: ASA grade (I-III). 2. Site/type of joint replacement: Hip replacement

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Indirectness of population	No indirectness
Interventions	(n=58) Intervention 1: Placebo. 60ml 0.9% sodium chloride solution by soaking the hip cavity at least 3 min before being suctioned at the end of surgery.. Duration Surgery. Concurrent medication/care: 10mg oral rivaroxaban tablets for anticoagulation for 15 days from postoperative day 1. Cephalosporin was used to prevent infection, and clindamycin was used when patients were allergic to cephalosporin.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not applicable (n=58) Intervention 2: Perioperative use of tranexamic acid - IV. 10mg/kg TXA in 100 ml 0.9% sodium chloride by intravenous infusion approximately 15 min before skin incision, and a second identical dose administered 3 hours later.. Duration Surgery. Concurrent medication/care: 10mg oral rivaroxaban tablets for anticoagulation for 15 days from postoperative day 1. Cephalosporin was used to prevent infection, and clindamycin was used when patients were allergic to cephalosporin.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: Not stated / Unclear (n=58) Intervention 3: Perioperative use of tranexamic acid - IA/topical. 3g in 60ml 0.9% sodium chloride solution by soaking the hip cavity for at least 3 min before being suctioned at the end of surgery.. Duration Surgery. Concurrent medication/care: 10mg oral rivaroxaban tablets for anticoagulation for 15 days from postoperative day 1. Cephalosporin was used to prevent infection, and clindamycin was used when patients were allergic to cephalosporin.. Indirectness: No indirectness Further details: 1. Tranexamic acid dose: ≥3000 mg (3g).
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at In-hospital period; Group 1: 0/57, Group 2: 0/57
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

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- Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: 1 did not receive intervention; Group 2 Number missing: 1, Reason: 1 protocol broken

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion requirement at In-hospital period; Group 1: 24/57, Group 2: 30/57
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: 1 did not receive intervention; Group 2 Number missing: 1, Reason: 1 protocol broken

Protocol outcome 3: Surgical bleeding at -
- Actual outcome: Intraoperative blood loss at During surgery; Group 1: mean 402 ml (SD 229); n=57, Group 2: mean 397 ml (SD 239); n=57
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: 1 did not receive intervention; Group 2 Number missing: 1, Reason: 1 protocol broken

Protocol outcome 4: Postoperative bleeding at -
- Actual outcome: Drainage output at 36 hours after surgery; Group 1: mean 204 ml (SD 169); n=57, Group 2: mean 301 ml (SD 181); n=57
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: 1 did not receive intervention; Group 2 Number missing: 1, Reason: 1 protocol broken

Protocol outcome 5: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Haemoglobin loss at Postoperative day 3; Group 1: mean -3.7 g/dl (SD 1.54); n=57, Group 2: mean -4.83 g/dl (SD 1.48); n=57
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: 1 did not receive intervention; Group 2 Number missing: 1, Reason: 1 protocol broken

Protocol outcome 6: Total blood loss at -
- Actual outcome: Total blood loss at 36 hours after surgery; Group 1: mean 1125 ml (SD 514); n=57, Group 2: mean 1464 ml (SD 556); n=57
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: 1 did not receive intervention; Group 2 Number missing: 1, Reason: 1 protocol broken

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RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus PLACEBO

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at In-hospital period; Group 1: 0/56, Group 2: 0/57
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 2 did not receive intervention; Group 2 Number missing: 1, Reason: 1 did not receive intervention

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion requirement at In-hospital period; Group 1: 20/56, Group 2: 30/57
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 2 did not receive intervention; Group 2 Number missing: 1, Reason: 1 did not receive intervention

Protocol outcome 3: Surgical bleeding at -
- Actual outcome: Intraoperative blood loss at During surgery; Group 1: mean 404 ml (SD 213); n=56, Group 2: mean 397 ml (SD 239); n=57
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 2 did not receive intervention; Group 2 Number missing: 1, Reason: 1 protocol broken

Protocol outcome 4: Postoperative bleeding at -
- Actual outcome: Drainage output at 36 hours after surgery; Group 1: mean 232 ml (SD 132); n=56, Group 2: mean 301 ml (SD 181); n=57
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 2 did not receive intervention; Group 2 Number missing: 1, Reason: 1 did not receive intervention

Protocol outcome 5: Blood loss: Haemoglobin level at 3 days after surgery
- Actual outcome: Haemoglobin loss at Postoperative day 3; Group 1: mean -4.02 g/dl (SD 1.33); n=56, Group 2: mean -4.83 g/dl (SD 1.48); n=57
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 2 did not receive intervention; Group 2 Number missing: 1, Reason: 1 did not receive intervention

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Protocol outcome 6: Total blood loss at -
- Actual outcome: Total blood loss at 36 hours after surgery; Group 1: mean 1211 ml (SD 425); n=56, Group 2: mean 1464 ml (SD 556); n=57
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 2 did not receive intervention; Group 2 Number missing: 1, Reason: 1 did not receive intervention

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IA/TOPICAL versus IV

Protocol outcome 1: Adverse events: DVT at -
- Actual outcome: DVT at In-hospital period; Group 1: 0/56, Group 2: 0/57
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 2 did not receive intervention; Group 2 Number missing: 1, Reason: 1 protocol broken

Protocol outcome 2: Blood (allogeneic or autologous) transfusion at -
- Actual outcome: Transfusion requirement at In-hospital period; Group 1: 20/56, Group 2: 24/57
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 2 did not receive intervention; Group 2 Number missing: 1, Reason: 1 protocol broken

Protocol outcome 3: Surgical bleeding at -
- Actual outcome: Intraoperative blood loss at During surgery; Group 1: mean 404 ml (SD 213); n=56, Group 2: mean 402 ml (SD 229); n=57
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 2 did not receive intervention; Group 2 Number missing: 1, Reason: 1 protocol broken

Protocol outcome 4: Postoperative bleeding at -
- Actual outcome: Drainage output at 36 hours after surgery; Group 1: mean 232 ml (SD 132); n=56, Group 2: mean 204 ml (SD 169); n=57
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 2 did not receive intervention; Group 2 Number missing: 1, Reason: 1 protocol broken

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Protocol outcome 5: Blood loss: Haemoglobin level at 3 days after surgery - Actual outcome: Haemoglobin loss at Postoperative day 3; Group 1: mean -4.02 g/dl (SD 1.33); n=56, Group 2: mean -3.7 g/dl (SD 1.54); n=57 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 2 did not receive intervention; Group 2 Number missing: 1, Reason: 1 protocol broken Protocol outcome 6: Total blood loss at - - Actual outcome: Total blood loss at 36 hours after surgery; Group 1: mean 1211 ml (SD 425); n=56, Group 2: mean 1125 ml (SD 514); n=57 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 2 did not receive intervention; Group 2 Number missing: 1, Reason: 1 protocol broken	
Protocol outcomes not reported by the study	Mortality at 30 day; Adverse events: acute myocardial infarction at -; Quality of life at within 6 weeks; Postoperative anaemia at -; Length of stay at -

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1 Appendix E: Forest plots

E.1 2 IA/topical versus no treatment

Figure 3: Transfusion

Study or Subgroup	IA/topical Events	IA/topical Total	no treatment Events	no treatment Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Aguilera 2015	0	24	2	22	1.3%	0.18 [0.01, 3.63]
Digas 2015	2	42	8	41	4.1%	0.24 [0.06, 1.08]
Guerreiro 2017	0	22	0	21		Not estimable
Keyhani 2016	3	40	10	40	5.1%	0.30 [0.09, 1.01]
Laoruengthana 2019	15	76	25	76	12.8%	0.60 [0.34, 1.05]
Mehta 2019	44	100	74	100	37.8%	0.59 [0.46, 0.76]
Oztas 2015	0	30	8	30	4.3%	0.06 [0.00, 0.98]
Perez-Jimeno 2018	15	125	42	129	21.1%	0.37 [0.22, 0.63]
Ugurlu 2017	5	30	13	30	6.6%	0.38 [0.16, 0.94]
Zhang 2016	4	50	13	50	6.6%	0.31 [0.11, 0.88]
Total (95% CI)		**539**		**539**	**100.0%**	**0.46 [0.37, 0.56]**
Total events	88		195			

Heterogeneity: Chi² = 10.08, df = 8 (P = 0.26); I² = 21%
Test for overall effect: Z = 7.50 (P < 0.00001)

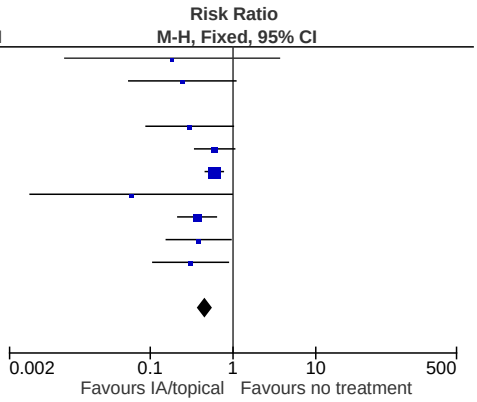

Figure 4: Adverse events: DVT

Study or Subgroup	IA/topical Events	IA/topical Total	no treatment Events	no treatment Total	Weight	Risk Difference M-H, Fixed, 95% CI
Antinolfi 2014	0	20	0	20	4.7%	0.00 [-0.09, 0.09]
Digas 2015	0	30	0	30	7.1%	0.00 [-0.06, 0.06]
Guerreiro 2017	0	22	0	21	5.1%	0.00 [-0.09, 0.09]
Lacko 2017	0	30	0	30	7.1%	0.00 [-0.06, 0.06]
Mehta 2019	0	100	0	100	23.5%	0.00 [-0.02, 0.02]
Oztas 2015	0	30	0	30	7.1%	0.00 [-0.06, 0.06]
Perez-Jimeno 2018	0	125	0	129	29.9%	0.00 [-0.02, 0.02]
Ugurlu 2017	1	42	1	41	9.8%	-0.00 [-0.07, 0.07]
Zhang 2016	0	25	2	25	5.9%	-0.08 [-0.21, 0.05]
Total (95% CI)		**424**		**426**	**100.0%**	**-0.00 [-0.02, 0.01]**
Total events	1		3			

Heterogeneity: Chi² = 2.10, df = 8 (P = 0.98); I² = 0%
Test for overall effect: Z = 0.59 (P = 0.55)

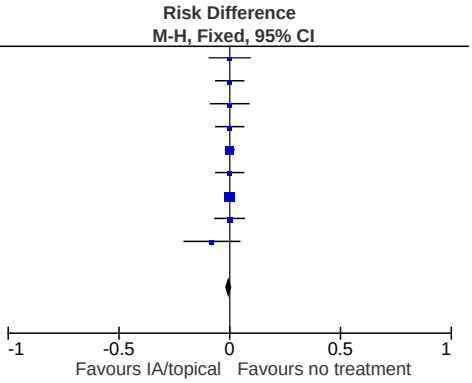

Figure 5: Blood loss via haemoglobin level after surgery

Study or Subgroup	IA/topical Mean	IA/topical SD	IA/topical Total	no treatment Mean	no treatment SD	no treatment Total	Weight	Mean Difference IV, Random, 95% CI
Aguilera 2015	9	2.39	50	9.6	1.97	50	9.6%	-0.60 [-1.46, 0.26]
Antinolfi 2014	10.1	1.2	20	9.7	0.9	20	10.7%	0.40 [-0.26, 1.06]
Digas 2015	-2.26	0.99	30	-2.8	0.77	30	11.7%	0.54 [0.09, 0.99]
Guerreiro 2017	-1.53	0.91	22	-2.28	0.91	21	11.3%	0.75 [0.21, 1.29]
Keyhani 2016	11.8	1.6	40	10.1	1.5	40	10.6%	1.70 [1.02, 2.38]
Mehta 2019	10.41	1.17	100	9.96	1.12	100	12.2%	0.45 [0.13, 0.77]
Perez-Jimeno 2018	3.7	1.3	125	4.6	1.3	129	12.2%	-0.90 [-1.22, -0.58]
Ugurlu 2017	10.52	1.24	42	9.65	1.33	41	11.2%	0.87 [0.32, 1.42]
Zhang 2016	8.9	1.1	24	8.2	1.3	22	10.5%	0.70 [0.00, 1.40]
Total (95% CI)			**453**			**453**	**100.0%**	**0.43 [-0.11, 0.97]**

Heterogeneity: Tau² = 0.60; Chi² = 83.84, df = 8 (P < 0.00001); I² = 90%
Test for overall effect: Z = 1.55 (P = 0.12)

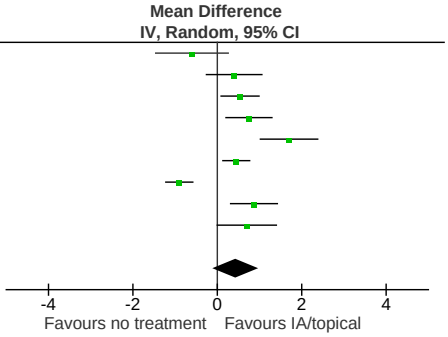

Figure 6: Total blood loss

Study or Subgroup	IA/topical Mean	IA/topical SD	IA/topical Total	no treatment Mean	no treatment SD	no treatment Total	Weight	Std. Mean Difference IV, Random, 95% CI
Aguilera 2015	1,021.57	481.09	47	1,415.72	595.11	48	17.1%	-0.72 [-1.14, -0.31]
Antinolfi 2014	658.5	211.4	20	1,093	189.9	20	15.2%	-2.12 [-2.91, -1.33]
Digas 2015	943	477	30	1,455	635	30	16.6%	-0.90 [-1.43, -0.37]
Mehta 2019	614.15	128.73	100	1,061.3	170.06	100	17.1%	-2.95 [-3.36, -2.55]
Oztas 2015	823.64	224.33	30	1,263.77	298.79	30	16.3%	-1.64 [-2.23, -1.05]
Perez-Jimeno 2018	539	243	125	728	252	129	17.6%	-0.76 [-1.02, -0.51]
Total (95% CI)			**352**			**357**	**100.0%**	**-1.50 [-2.30, -0.71]**

Heterogeneity: Tau² = 0.92; Chi² = 96.91, df = 5 (P < 0.00001); I² = 95%
Test for overall effect: Z = 3.70 (P = 0.0002)

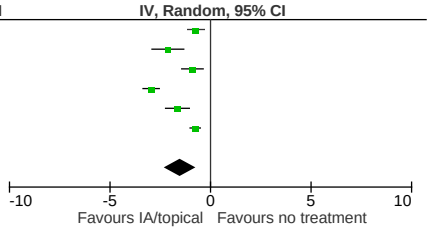

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Figure 7: Surgical bleeding

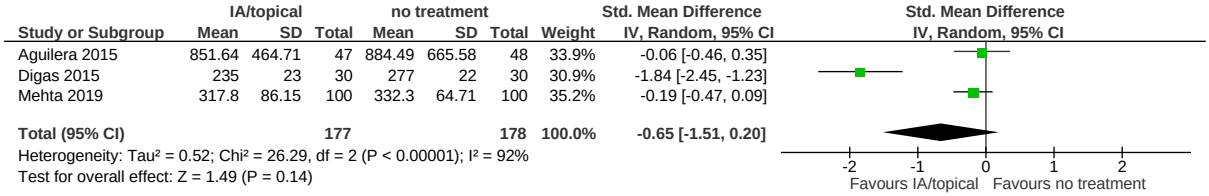


Figure 8: Length of stay

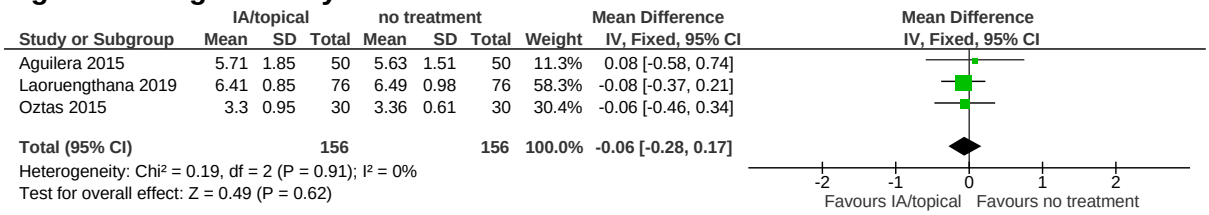
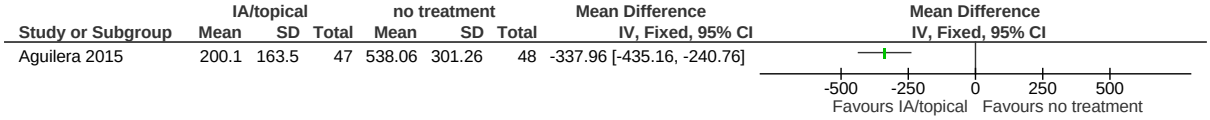


Figure 9: Postoperative bleeding



E.2 1 Oral versus no treatment

Figure 10: Mortality

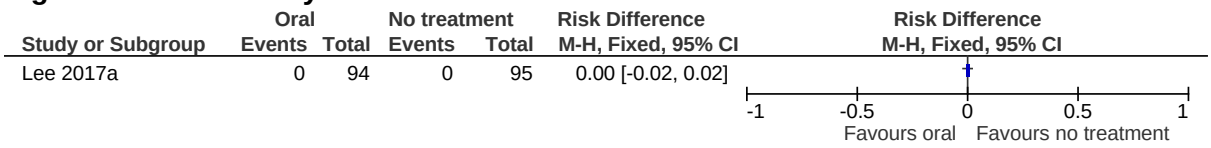


Figure 11: Transfusion

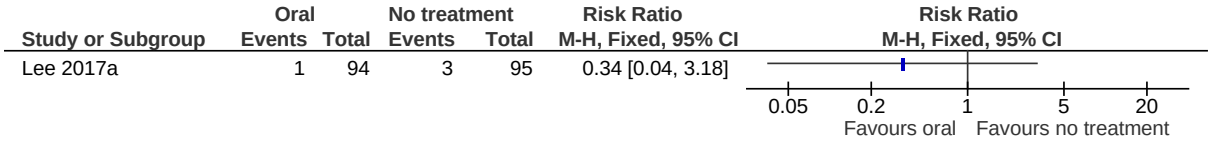


Figure 12: Adverse events: DVT

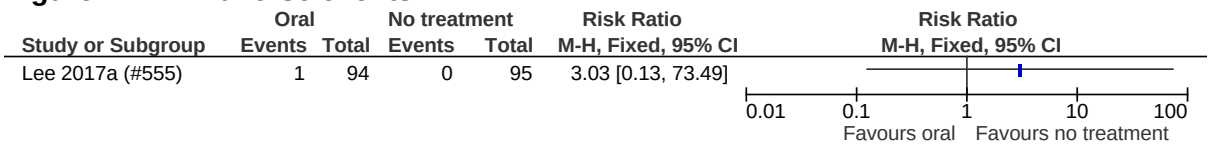
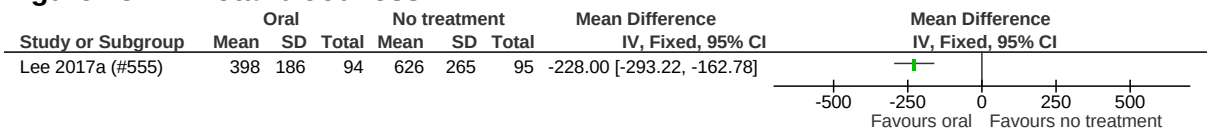


Figure 13: Total blood loss



2 **Figure 14: Blood loss via haemoglobin level after surgery**

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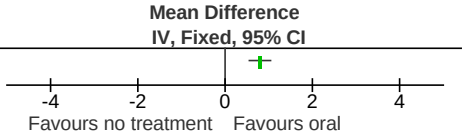
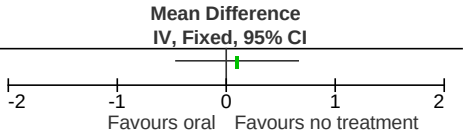
Study or Subgroup	Oral Mean	SD	Total	No treatment Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Lee 2017a (#555)	-1.7	0.8	94	-2.5	0.9	95	0.80 [0.56, 1.04]



1

Figure 15: Length of stay

Study or Subgroup	Oral Mean	SD	Total	No treatment Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Lee 2017a	5.9	2.2	94	5.8	1.7	95	0.10 [-0.46, 0.66]



E.32 IV versus no treatment

Figure 16: Mortality

Study or Subgroup	IV Events	Total	No treatment Events	Total	Risk Difference M-H, Fixed, 95% CI
Molloy 2007	0	50	0	50	0.00 [-0.04, 0.04]

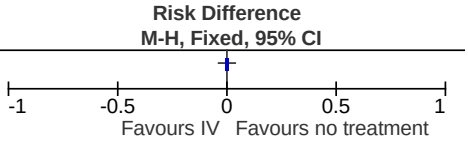


Figure 17: Transfusion

Study or Subgroup	IV Events	Total	No treatment Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Aguilera 2015	0	50	13	50	7.7%	-0.26 [-0.38, -0.14]
Digas 2015	7	30	13	30	4.7%	-0.20 [-0.43, 0.03]
Imai 2012-1	0	20	0	6	5.4%	0.00 [-0.20, 0.20]
Imai 2012-2	0	24	0	6	5.5%	0.00 [-0.20, 0.20]
Imai 2012-3	0	25	0	5	4.8%	0.00 [-0.23, 0.23]
Imai 2012-4	0	26	0	5	4.8%	0.00 [-0.23, 0.23]
Keyhani 2016	2	40	10	40	6.9%	-0.20 [-0.35, -0.05]
Kim 2014-1	5	75	20	75	8.0%	-0.20 [-0.31, -0.09]
Kim 2014-2	1	90	6	90	9.6%	-0.06 [-0.11, 0.00]
Laoruengthana 2019	14	76	25	76	7.3%	-0.14 [-0.28, -0.01]
Mehta 2019	37	100	76	100	7.6%	-0.39 [-0.52, -0.26]
Molloy 2007	5	50	11	50	7.1%	-0.12 [-0.26, 0.02]
Oztas 2015	0	30	8	30	6.5%	-0.27 [-0.43, -0.10]
Ugurlu 2017	2	40	8	40	7.1%	-0.15 [-0.29, -0.01]
Zhang 2016	1	23	2	22	7.0%	-0.05 [-0.19, 0.10]
Total (95% CI)		**699**		**625**	**100.0%**	**-0.14 [-0.21, -0.08]**
Total events	74		192			

Heterogeneity: Tau² = 0.01; Chi² = 49.55, df = 14 (P < 0.00001); I² = 72%
Test for overall effect: Z = 4.11 (P < 0.0001)

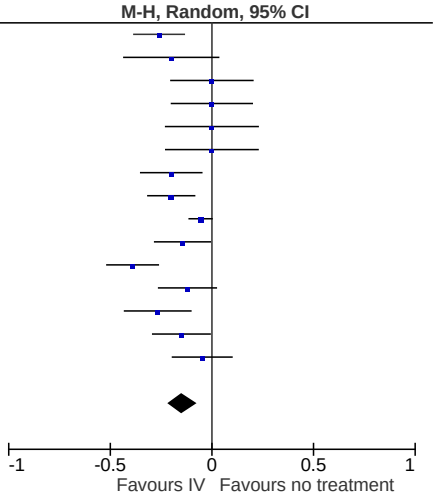


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Figure 18: Adverse events: DVT

Study or Subgroup	IV Events	IV Total	No treatment Events	No treatment Total	Weight	Risk Difference M-H, Fixed, 95% CI
Digas 2015	1	30	0	30	5.5%	0.03 [-0.05, 0.12]
Gautam 2011	0	14	0	13	2.5%	0.00 [-0.13, 0.13]
Imai 2012-1	2	20	1	7	1.9%	-0.04 [-0.33, 0.25]
Imai 2012-2	3	24	1	7	2.0%	-0.02 [-0.31, 0.27]
Imai 2012-3	2	25	1	7	2.0%	-0.06 [-0.34, 0.22]
Imai 2012-4	3	26	1	7	2.0%	-0.03 [-0.31, 0.26]
Kim 2014-1	0	75	0	75	13.7%	0.00 [-0.03, 0.03]
Kim 2014-2	0	90	0	90	16.4%	0.00 [-0.02, 0.02]
Lacko 2017	0	30	0	30	5.5%	0.00 [-0.06, 0.06]
Mcconnell 2011	0	22	0	22	4.0%	0.00 [-0.08, 0.08]
Mehta 2019	0	100	0	100	18.2%	0.00 [-0.02, 0.02]
Molloy 2007	0	50	0	50	9.1%	0.00 [-0.04, 0.04]
Oztas 2015	0	30	0	30	5.5%	0.00 [-0.06, 0.06]
Ugurlu 2017	1	40	1	41	7.4%	0.00 [-0.07, 0.07]
Zhang 2016	1	25	2	25	4.6%	-0.04 [-0.17, 0.09]
Total (95% CI)		**601**		**534**	**100.0%**	**-0.00 [-0.02, 0.01]**
Total events	13		7			

Heterogeneity: Chi² = 1.52, df = 14 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.32 (P = 0.75)

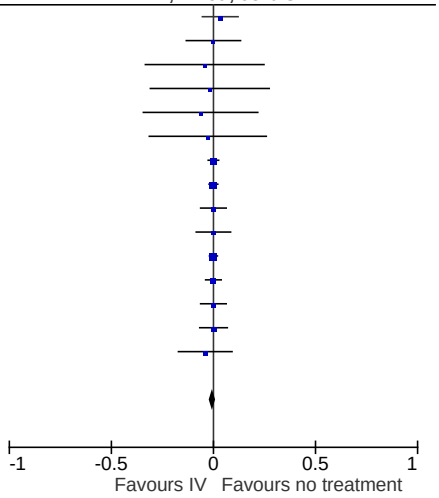

Figure 19: Blood loss via haemoglobin level after surgery

Study or Subgroup	IV Mean	IV SD	IV Total	No treatment Mean	No treatment SD	No treatment Total	Weight	Mean Difference IV, Fixed, 95% CI
Aguilera 2015	9.2	2.74	50	9.6	1.97	50	2.4%	-0.40 [-1.34, 0.54]
Digas 2015	-2.24	0.93	30	-2.8	0.77	30	11.5%	0.56 [0.13, 0.99]
Keyhani 2016	11.3	0.8	40	10.1	1.5	40	7.7%	1.20 [0.67, 1.73]
Kim 2014-1	-4.7	1.2	75	-5.1	1.3	75	13.4%	0.40 [-0.00, 0.80]
Kim 2014-2	-3.4	1.2	90	-3.8	1.2	90	17.4%	0.40 [0.05, 0.75]
Mehta 2019	10.41	1	100	9.96	1.12	100	24.7%	0.45 [0.16, 0.74]
Melo 2017-1	10.89	2.8	14	9.7	2.4	7	0.4%	1.19 [-1.11, 3.49]
Melo 2017-2	10.92	2.7	14	9.7	2.4	7	0.4%	1.22 [-1.05, 3.49]
Molloy 2007	-2.75	1.03	50	-3.2	1.12	50	12.0%	0.45 [0.03, 0.87]
Ugurlu 2017	10.96	1.65	40	9.65	1.33	41	5.0%	1.31 [0.66, 1.96]
Zhang 2016	8.5	0.9	23	8.2	1.3	22	5.0%	0.30 [-0.36, 0.96]
Total (95% CI)			**526**			**512**	**100.0%**	**0.53 [0.38, 0.67]**

Heterogeneity: Chi² = 17.99, df = 10 (P = 0.06); I² = 44%
Test for overall effect: Z = 7.05 (P < 0.00001)

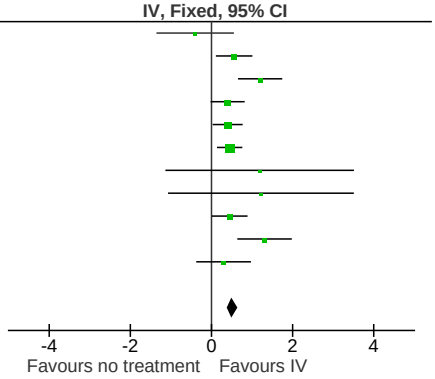

Figure 20: Total blood loss

Study or Subgroup	IV Mean	IV SD	IV Total	No treatment Mean	No treatment SD	No treatment Total	Weight	Std. Mean Difference IV, Random, 95% CI
Aguilera 2015	817.54	324.82	48	1,415.72	595.11	48	12.9%	-1.24 [-1.68, -0.80]
Digas 2015	1,086	559	30	1,455	635	30	12.7%	-0.61 [-1.13, -0.09]
Gautam 2011	266.2	83.87	14	667.5	111.48	13	9.5%	-3.97 [-5.34, -2.60]
Kim 2014-1	1,282.6	308.5	75	1,379.6	353.4	75	13.2%	-0.29 [-0.61, 0.03]
Kim 2014-2	905	299.2	90	1,018	321.3	90	13.2%	-0.36 [-0.66, -0.07]
Mehta 2019	607.9	94.37	100	1,061.3	170.06	100	12.9%	-3.28 [-3.71, -2.86]
Molloy 2007	1,225	499	50	1,415	416	50	13.0%	-0.41 [-0.81, -0.01]
Oztas 2015	898.03	298.21	30	1,263.77	298.79	30	12.6%	-1.21 [-1.76, -0.66]
Total (95% CI)			**437**			**436**	**100.0%**	**-1.33 [-2.10, -0.56]**

Heterogeneity: Tau² = 1.15; Chi² = 175.87, df = 7 (P < 0.00001); I² = 96%
Test for overall effect: Z = 3.37 (P = 0.0007)

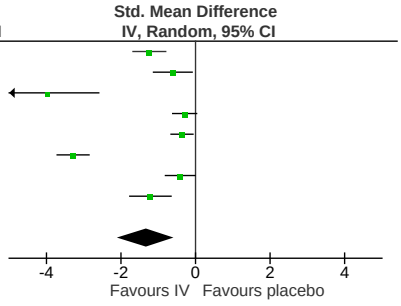

Figure 21: Surgical bleeding

Study or Subgroup	IV Mean	IV SD	IV Total	No treatment Mean	No treatment SD	No treatment Total	Weight	Std. Mean Difference IV, Random, 95% CI
Aguilera 2015	685.02	314.08	48	884.49	665.58	48	33.4%	-0.38 [-0.78, 0.02]
Digas 2015	285	26	30	277	22	30	33.1%	0.33 [-0.18, 0.84]
Mehta 2019	165.8	64.71	100	332.3	64.71	100	33.5%	-2.56 [-2.94, -2.19]
Total (95% CI)			**178**			**178**	**100.0%**	**-0.88 [-2.62, 0.86]**

Heterogeneity: Tau² = 2.32; Chi² = 100.56, df = 2 (P < 0.00001); I² = 98%
Test for overall effect: Z = 0.99 (P = 0.32)

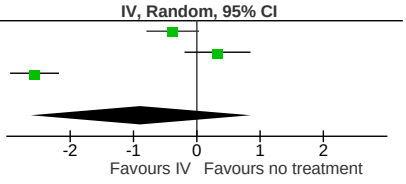

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Figure 22: Postoperative bleeding

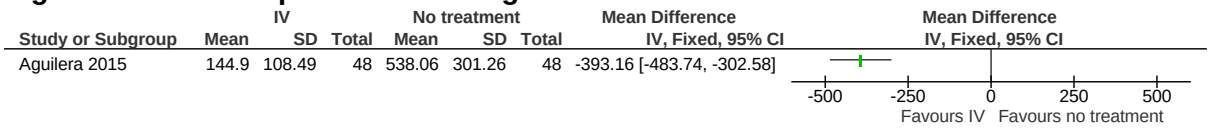
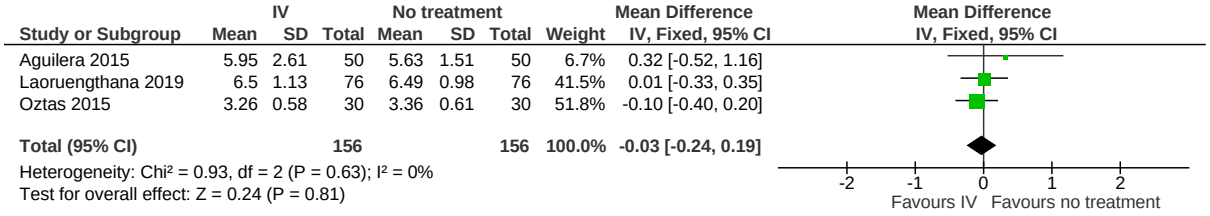


Figure 23: Length of stay



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E.41 IA/topical versus placebo

Figure 24: Mortality

Study or Subgroup	IA/topical Events	IA/topical Total	Placebo Events	Placebo Total	Risk Difference M-H, Fixed, 95% CI
Zekcer 2016	0	30	0	30	0.00 [-0.06, 0.06]

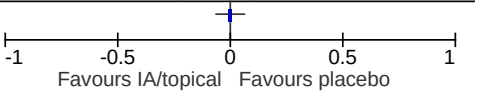

Figure 25: Quality of life

Study or Subgroup	IA/topical Mean	IA/topical SD	IA/topical Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Alshryda 2013a (#414)	0.686	0.33	47	0.715	0.3	45	41.8%	-0.03 [-0.16, 0.10]
Alshryda 2013b (#415)	0.705	0.31	52	0.78	0.24	46	58.2%	-0.08 [-0.18, 0.03]
Total (95% CI)			**99**			**91**	**100.0%**	**-0.06 [-0.14, 0.03]**

Heterogeneity: Chi² = 0.29, df = 1 (P = 0.59); I² = 0%
Test for overall effect: Z = 1.31 (P = 0.19)

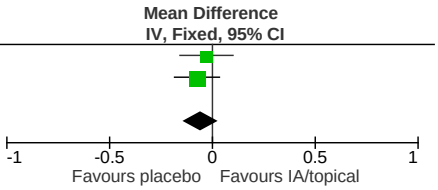

Figure 26: Transfusion

Study or Subgroup	IA/topical Events	IA/topical Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alshryda 2013a	10	80	26	81	10.2%	0.39 [0.20, 0.75]
Alshryda 2013b	1	79	13	78	5.1%	0.08 [0.01, 0.57]
Georgiadis 2013	0	50	4	51	1.8%	0.11 [0.01, 2.05]
Gillespie 2015	0	56	0	55		Not estimable
Ishida 2011	0	50	1	50	0.6%	0.33 [0.01, 7.99]
Lee 2017a	1	94	3	95	1.2%	0.34 [0.04, 3.18]
Lin 2015	1	40	6	40	2.4%	0.17 [0.02, 1.32]
Martin 2014	4	25	5	25	2.0%	0.80 [0.24, 2.64]
Prakash 2017-1	3	50	6	25	3.1%	0.25 [0.07, 0.92]
Prakash 2017-2	5	50	6	25	3.1%	0.42 [0.14, 1.23]
Roy 2012	2	25	7	25	2.8%	0.29 [0.07, 1.24]
Sa-Ngasoongsong 2011	1	24	8	24	3.1%	0.13 [0.02, 0.92]
Song 2017	1	50	7	50	2.8%	0.14 [0.02, 1.12]
Stowers 2017	1	60	2	30	1.0%	0.25 [0.02, 2.65]
Wang 2015a	2	50	9	50	3.5%	0.22 [0.05, 0.98]
Wang 2015b	0	30	7	30	3.0%	0.07 [0.00, 1.12]
Wang 2017	0	50	1	50	0.6%	0.33 [0.01, 7.99]
Wei 2014	6	102	26	100	10.3%	0.23 [0.10, 0.53]
Wong 2010-1	4	31	3	21	1.4%	0.90 [0.22, 3.63]
Wong 2010-2	0	33	3	21	1.7%	0.09 [0.01, 1.70]
Yang 2015	10	40	19	40	7.5%	0.53 [0.28, 0.99]
Yuan 2017	17	140	36	140	14.2%	0.47 [0.28, 0.80]
Yue 2014	3	52	11	49	4.5%	0.26 [0.08, 0.87]
Zekcer 2016	0	30	6	30	2.6%	0.08 [0.00, 1.31]
Zhou 2018	20	56	30	57	11.7%	0.68 [0.44, 1.04]
Total (95% CI)		**1347**		**1242**	**100.0%**	**0.36 [0.29, 0.45]**
Total events	92		245			

Heterogeneity: Chi² = 25.43, df = 23 (P = 0.33); I² = 10%
Test for overall effect: Z = 9.32 (P < 0.00001)

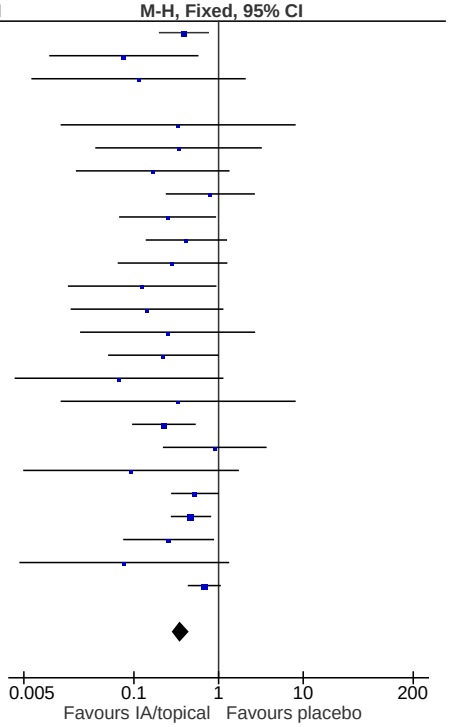

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Figure 27: Adverse events: DVT

Study or Subgroup	IA/topical Events	IA/topical Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Alshryda 2013a	2	80	2	81	6.7%	0.00 [-0.05, 0.05]
Alshryda 2013b	2	79	0	78	6.5%	0.03 [-0.02, 0.07]
Georgiadis 2013	4	50	9	51	4.2%	-0.10 [-0.23, 0.03]
Gillespie 2015	0	56	0	55	4.6%	0.00 [-0.03, 0.03]
Lin 2015	0	40	0	40	3.3%	0.00 [-0.05, 0.05]
Martin 2014	0	25	0	25	2.1%	0.00 [-0.07, 0.07]
Onodera 2012	2	50	1	50	4.1%	0.02 [-0.05, 0.09]
Prakash 2017-1	0	50	1	50	4.1%	-0.02 [-0.07, 0.03]
Prakash 2017-2	1	50	1	50	4.1%	0.00 [-0.05, 0.05]
Sa-Ngasoongsong 2011	0	24	0	24	2.0%	0.00 [-0.08, 0.08]
Song 2017	0	50	0	50	4.1%	0.00 [-0.04, 0.04]
Stowers 2017	0	60	0	30	3.3%	0.00 [-0.05, 0.05]
Wang 2015a	3	50	2	50	4.1%	0.02 [-0.07, 0.11]
Wang 2015b	0	30	0	30	2.5%	0.00 [-0.06, 0.06]
Wang 2017	0	50	0	50	4.1%	0.00 [-0.04, 0.04]
Wei 2014	1	102	0	100	8.4%	0.01 [-0.02, 0.04]
Wong 2010-1	2	31	1	35	2.7%	0.04 [-0.07, 0.14]
Wong 2010-2	1	33	1	35	2.8%	0.00 [-0.08, 0.08]
Yang 2015	0	40	0	40	3.3%	0.00 [-0.05, 0.05]
Yuan 2017	0	140	1	140	11.6%	-0.01 [-0.03, 0.01]
Yue 2014	1	52	0	49	4.2%	0.02 [-0.03, 0.07]
Zekcer 2016	1	30	4	30	2.5%	-0.10 [-0.24, 0.04]
Zhou 2018	0	56	0	57	4.7%	0.00 [-0.03, 0.03]
Total (95% CI)		**1228**		**1200**	**100.0%**	**-0.00 [-0.01, 0.01]**
Total events	20		23			

Heterogeneity: Chi² = 9.06, df = 22 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.36 (P = 0.72)

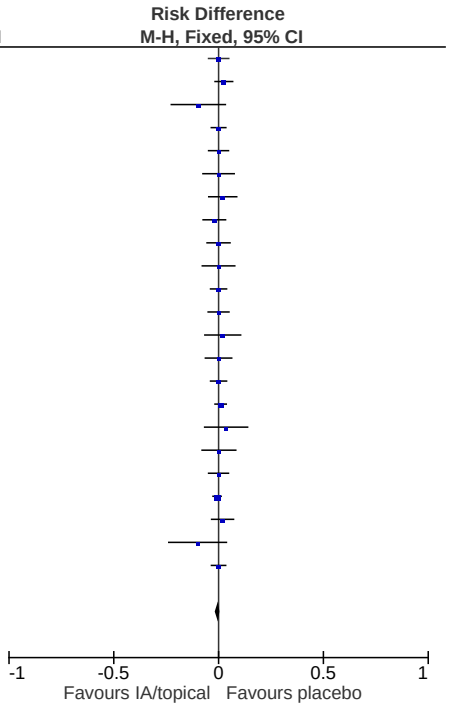

Figure 28: Blood loss via haemoglobin level after surgery

Study or Subgroup	IA/topical Mean	IA/topical SD	IA/topical Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Alshryda 2013a (#414)	10.62	1.34	80	9.78	1.45	81	5.7%	0.84 [0.41, 1.27]
Alshryda 2013b (#415)	11.52	1.33	79	10.69	1.35	78	5.8%	0.83 [0.41, 1.25]
Georgiadis 2013	-2.5	0.8	50	-3.3	1.2	51	5.9%	0.80 [0.40, 1.20]
Lin 2015	-2.4	0.9	40	-3.4	1	40	5.8%	1.00 [0.58, 1.42]
Onodera 2012	-2.2	1.11	50	-3.11	1.26	50	5.6%	0.91 [0.44, 1.38]
Prakash 2017-1	-2.1	1.2	50	-2.3	1.2	50	5.6%	0.20 [-0.27, 0.67]
Prakash 2017-2	-1.6	1.48	50	-2.3	1.48	50	5.0%	0.70 [0.12, 1.28]
Roy 2012	-1.94	0.98	25	-3.04	1.33	25	4.7%	1.10 [0.45, 1.75]
Sa-Ngasoongsong 2011	-2.1	0.9	24	-3	0.7	24	5.6%	0.90 [0.44, 1.36]
Song 2017	-2.5	1.2	50	-3.98	2.1	50	4.6%	1.48 [0.81, 2.15]
Wang 2015a (636)	-2.29	0.827	50	-3.973	1.001	50	6.1%	1.68 [1.32, 2.04]
Wang 2015b (736)	10.51	1.06	30	9.1	0.99	30	5.3%	1.41 [0.89, 1.93]
Wang 2017	-2.74	0.85	50	-4.06	0.94	50	6.1%	1.32 [0.97, 1.67]
Wong 2010-1	10	1.28	31	8.6	1.21	35	4.9%	1.40 [0.80, 2.00]
Wong 2010-2	10.1	1.03	33	8.6	1.21	35	5.2%	1.50 [0.97, 2.03]
Yang 2015	9.4	1.3	40	8.2	1.5	40	4.8%	1.20 [0.58, 1.82]
Yuan 2017	-2.92	0.42	140	-3.34	0.48	140	6.9%	0.42 [0.31, 0.53]
Yue 2014	-4.002	0.974	51	-5.327	0.479	51	6.3%	1.33 [1.03, 1.62]
Total (95% CI)			**923**			**930**	**100.0%**	**1.04 [0.80, 1.29]**

Heterogeneity: Tau² = 0.22; Chi² = 121.62, df = 17 (P < 0.00001); I² = 86%
Test for overall effect: Z = 8.44 (P < 0.00001)

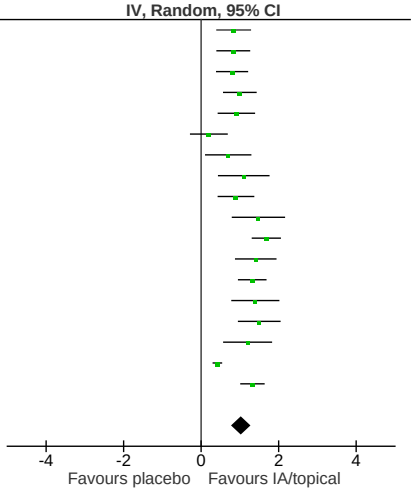

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Figure 29: Total blood loss

Study or Subgroup	IA/topical Mean	IA/topical SD	IA/topical Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Alshryda 2013a	1,617	188	56	1,981	1,007	38	6.1%	-0.55 [-0.97, -0.13]
Alshryda 2013b	919	487	64	1,725	823	61	6.4%	-1.19 [-1.57, -0.81]
Georgiadis 2013	940.2	327.1	50	1,293.1	532.7	51	6.2%	-0.79 [-1.20, -0.38]
Lin 2015	705.1	213.9	40	948.8	278.5	40	5.8%	-0.97 [-1.44, -0.51]
Onodera 2012	380.4	271.2	50	676.4	306.2	50	6.1%	-1.02 [-1.43, -0.60]
Prakash 2017-1	514.5	540	50	886.5	540	25	5.6%	-0.68 [-1.17, -0.19]
Prakash 2017-2	557.6	472	50	886.5	472	25	5.6%	-0.69 [-1.18, -0.20]
Song 2017	998.12	256.78	50	1,121.12	226.65	50	6.2%	-0.50 [-0.90, -0.11]
Stowers 2017	1,613	622	60	1,765	1,088	30	6.0%	-0.19 [-0.63, 0.25]
Wang 2015a	678.45	112.77	50	1,136.3	224.52	50	5.4%	-2.56 [-3.09, -2.02]
Wang 2015b	974.6	283.65	30	1,393.2	353.48	30	5.2%	-1.29 [-1.85, -0.73]
Wang 2017	770.3	237.3	50	1,079.9	297.4	50	6.1%	-1.14 [-1.57, -0.72]
Wei 2014	963.4	421.3	102	1,364.2	278.6	100	6.9%	-1.12 [-1.41, -0.82]
Wong 2010-1	1,295	362.2	31	1,610	389.4	18	4.9%	-0.83 [-1.44, -0.23]
Wong 2010-2	1,208	382.5	33	1,610	389.4	17	4.8%	-1.03 [-1.65, -0.41]
Yue 2014	945.5	331.7	52	1,255.5	193.5	51	6.1%	-1.13 [-1.55, -0.71]
Zhou 2018	1,211	425	56	1,464	556	57	6.4%	-0.51 [-0.88, -0.13]
Total (95% CI)			**874**			**743**	**100.0%**	**-0.94 [-1.16, -0.72]**

Heterogeneity: Tau² = 0.16; Chi² = 68.62, df = 16 (P < 0.00001); I² = 77%
Test for overall effect: Z = 8.34 (P < 0.00001)

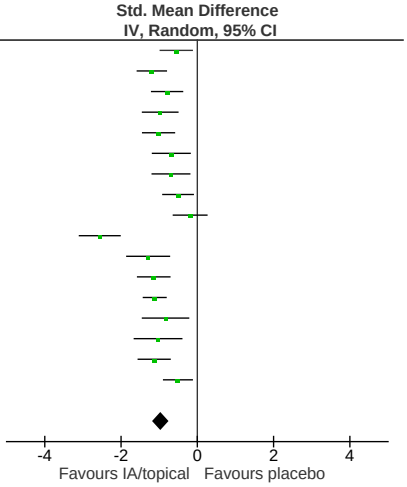


Figure 30: Surgical bleeding

Study or Subgroup	IA/topical Mean	IA/topical SD	IA/topical Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Roy 2012	109.6	71.54	25	194	79.66	25	30.4%	-1.10 [-1.70, -0.50]
Yang 2015	124	40	40	114	47	40	34.0%	0.23 [-0.21, 0.67]
Zhou 2018	404	213	56	397	239	57	35.5%	0.03 [-0.34, 0.40]
Total (95% CI)			**121**			**122**	**100.0%**	**-0.25 [-0.93, 0.44]**

Heterogeneity: Tau² = 0.31; Chi² = 13.29, df = 2 (P = 0.001); I² = 85%
Test for overall effect: Z = 0.70 (P = 0.48)

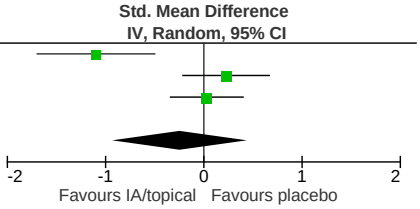


Figure 31: Postoperative bleeding

Study or Subgroup	IA/topical Mean	IA/topical SD	IA/topical Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Roy 2012	151.6	82.1	25	400	180.27	25	16.5%	-1.75 [-2.40, -1.09]
Sa-Ngasoongsong 2011	206.3	115.4	24	385.1	145.2	24	17.0%	-1.34 [-1.97, -0.71]
Yang 2015	45	13	40	55	15	40	21.1%	-0.71 [-1.16, -0.25]
Yue 2014	217.5	89.9	52	296.9	109	51	22.3%	-0.79 [-1.19, -0.39]
Zhou 2018	232	132	56	301	181	57	23.0%	-0.43 [-0.81, -0.06]
Total (95% CI)			**197**			**197**	**100.0%**	**-0.94 [-1.35, -0.53]**

Heterogeneity: Tau² = 0.16; Chi² = 14.61, df = 4 (P = 0.006); I² = 73%
Test for overall effect: Z = 4.47 (P < 0.00001)

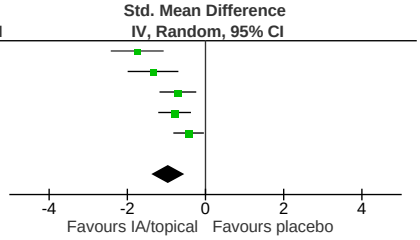
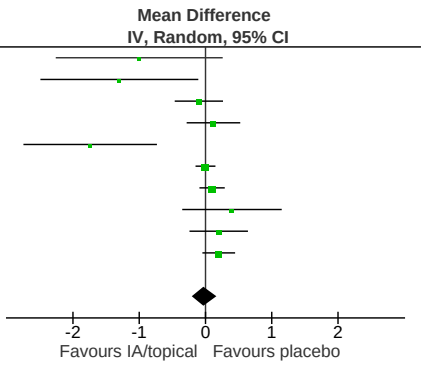


Figure 32: Length of stay

Study or Subgroup	IA/topical Mean	IA/topical SD	IA/topical Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Alshryda 2013a (#414)	5.2	3.6	79	6.2	4.4	80	2.1%	-1.00 [-2.25, 0.25]
Alshryda 2013b (#415)	4.8	2.3	77	6.1	4.6	72	2.3%	-1.30 [-2.48, -0.12]
Georgiadis 2013	2.7	1	50	2.8	0.8	51	12.4%	-0.10 [-0.45, 0.25]
Onodera 2012	3.36	1.16	50	3.24	0.82	50	11.2%	0.12 [-0.27, 0.51]
Wang 2015b (736)	6.43	0.68	30	8.17	2.7	30	3.1%	-1.74 [-2.74, -0.74]
Wang 2017	7	0.3	50	7	0.4	50	19.3%	0.00 [-0.14, 0.14]
Wei 2014	5	0.7	102	4.9	0.6	100	18.0%	0.10 [-0.08, 0.28]
Wong 2010-1	4.7	1.85	31	4.3	1.06	35	5.1%	0.40 [-0.34, 1.14]
Wong 2010-2	4.5	0.73	33	4.3	1.06	35	10.3%	0.20 [-0.23, 0.63]
Yue 2014	5.1	0.5	52	4.9	0.7	51	16.2%	0.20 [-0.04, 0.44]
Total (95% CI)			**554**			**554**	**100.0%**	**-0.01 [-0.20, 0.18]**

Heterogeneity: Tau² = 0.04; Chi² = 24.60, df = 9 (P = 0.003); I² = 63%
Test for overall effect: Z = 0.14 (P = 0.89)



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E.51 IV versus placebo

Figure 33: Mortality

Study or Subgroup	IV Events	IV Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Clave 2019-1	0	76	0	38	38.5%	0.00 [-0.04, 0.04]
Clave 2019-2	0	78	0	38	38.8%	0.00 [-0.04, 0.04]
Zekcer 2016	0	30	0	30	22.8%	0.00 [-0.06, 0.06]
Total (95% CI)		**184**		**106**	**100.0%**	**0.00 [-0.03, 0.03]**
Total events	0		0			

Heterogeneity: Chi² = 0.00, df = 2 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)

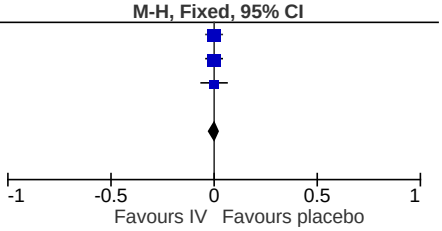

Figure 34: Transfusion

Study or Subgroup	IV Events	IV Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Almeida 2018	0	51	6	50	0.5%	0.08 [0.00, 1.30]
Barrachina 2016-1	8	35	7	18	3.0%	0.59 [0.25, 1.36]
Barrachina 2016-2	4	36	7	19	2.2%	0.30 [0.10, 0.90]
Benoni 1996	8	43	24	43	3.5%	0.33 [0.17, 0.66]
Benoni 2001	4	18	8	20	2.4%	0.56 [0.20, 1.54]
Bidolegui 2014	0	0	0	0		Not estimable
Camarasa 2006	1	35	23	60	1.0%	0.07 [0.01, 0.53]
Chen 2016a	36	60	58	60	5.2%	0.62 [0.50, 0.77]
Claeys 2007	1	20	6	20	0.9%	0.17 [0.02, 1.26]
Clave 2019-1	2	70	5	32	1.4%	0.18 [0.04, 0.89]
Clave 2019-2	4	70	5	32	1.9%	0.37 [0.11, 1.27]
Cvetanovich 2018	0	52	0	56		Not estimable
Ekback 2000	1	20	1	20	0.6%	1.00 [0.07, 14.90]
Garneti 2004	14	25	16	25	4.4%	0.88 [0.56, 1.38]
Gautam 2011	7	20	15	20	3.6%	0.47 [0.24, 0.89]
Good 2003	3	27	14	24	2.2%	0.19 [0.06, 0.58]
Husted 2003	2	20	7	20	1.6%	0.29 [0.07, 1.21]
Kazemi 2010	4	32	11	32	2.4%	0.36 [0.13, 1.02]
Kundu 2015	3	30	24	30	2.3%	0.13 [0.04, 0.37]
Lee 2013a	9	34	20	34	3.7%	0.45 [0.24, 0.84]
Lee 2013b	4	36	15	36	2.5%	0.27 [0.10, 0.73]
Lemay 2004	0	20	8	19	0.5%	0.06 [0.00, 0.91]
Lin 2012-1	3	49	6	27	1.8%	0.28 [0.07, 1.01]
Lin 2012-2	2	52	6	27	1.4%	0.17 [0.04, 0.80]
Malhotra 2011	6	25	18	25	3.3%	0.33 [0.16, 0.70]
Niskanen 2005	5	19	8	20	2.7%	0.66 [0.26, 1.66]
Orpen 2006	1	15	3	14	0.8%	0.31 [0.04, 2.65]
Pauzenberger 2017	0	27	0	27		Not estimable
Prakash 2017-1	3	50	12	50	2.0%	0.25 [0.08, 0.83]
Shinde 2015-1	1	14	9	14	1.0%	0.11 [0.02, 0.76]
Shinde 2015-2	2	14	14	14	2.1%	0.17 [0.06, 0.54]
Song 2017	0	50	7	50	0.5%	0.07 [0.00, 1.14]
Stowers 2017	0	60	2	30	0.5%	0.10 [0.01, 2.05]
Tanaka 2001-1	17	22	9	9	5.1%	0.80 [0.61, 1.05]
Tanaka 2001-2	16	24	9	9	4.9%	0.69 [0.51, 0.95]
Tanaka 2001-3	14	27	9	9	4.7%	0.55 [0.37, 0.80]
Vara 2017	3	53	7	49	1.8%	0.40 [0.11, 1.45]
Veien 2002	0	15	2	15	0.5%	0.20 [0.01, 3.85]
Wang 2016-1	8	39	5	19	2.6%	0.78 [0.29, 2.06]
Wang 2016-2	1	42	5	19	0.9%	0.09 [0.01, 0.72]
Wang 2017	1	50	1	50	0.5%	1.00 [0.06, 15.55]
Wei 2014	6	101	26	100	3.0%	0.23 [0.10, 0.53]
Yi 2016	8	50	19	50	3.4%	0.42 [0.20, 0.87]
Yuan 2017	15	140	36	140	4.0%	0.42 [0.24, 0.73]
Zekcer 2016	0	30	6	30	0.5%	0.08 [0.00, 1.31]
Zhao 2018	2	40	8	40	1.5%	0.25 [0.06, 1.11]
Zhou 2018	24	57	30	57	4.6%	0.80 [0.54, 1.18]
Total (95% CI)		**1819**		**1564**	**100.0%**	**0.39 [0.32, 0.49]**
Total events	253		537			

Heterogeneity: Tau² = 0.21; Chi² = 113.89, df = 43 (P < 0.00001); I² = 62%
Test for overall effect: Z = 8.61 (P < 0.00001)

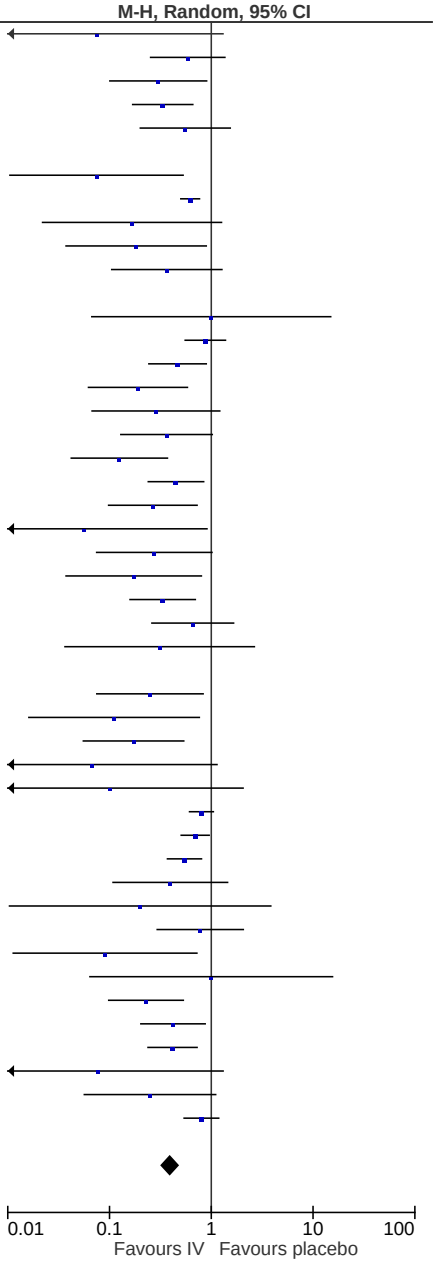

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Figure 35: Adverse events: DVT

Study or Subgroup	IV Events	IV Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Barrachina 2016-1	1	35	2	34	2.1%	-0.03 [-0.13, 0.07]
Benoni 1996	4	43	3	43	2.6%	0.02 [-0.09, 0.14]
Benoni 2001	0	18	0	20	1.2%	0.00 [-0.10, 0.10]
Bidolegui 2014	0	25	0	25	1.5%	0.00 [-0.07, 0.07]
Camarasa 2006	0	35	0	60	2.7%	0.00 [-0.04, 0.04]
Chen 2016a	0	60	0	60	3.7%	0.00 [-0.03, 0.03]
Claeys 2007	3	17	0	18	1.1%	0.18 [-0.02, 0.37]
Clave 2019-1	0	76	0	38	3.1%	0.00 [-0.04, 0.04]
Clave 2019-2	0	78	0	38	3.1%	0.00 [-0.04, 0.04]
Cvetanovich 2018	0	52	1	56	3.3%	-0.02 [-0.07, 0.03]
Ekback 2000	1	20	1	20	1.2%	0.00 [-0.14, 0.14]
Good 2003	2	27	2	24	1.6%	-0.01 [-0.16, 0.14]
Hsu 2015	0	30	0	30	1.8%	0.00 [-0.06, 0.06]
Husted 2003	0	20	0	20	1.2%	0.00 [-0.09, 0.09]
Kakar 2009-1	0	12	0	12	0.7%	0.00 [-0.15, 0.15]
Kakar 2009-2	0	13	0	13	0.8%	0.00 [-0.14, 0.14]
Kazemi 2010	0	32	1	32	2.0%	-0.03 [-0.11, 0.05]
Kundu 2015	3	30	2	30	1.8%	0.03 [-0.11, 0.17]
Lee 2013a	0	34	0	34	2.1%	0.00 [-0.06, 0.06]
Lee 2013b	3	36	4	36	2.2%	-0.03 [-0.16, 0.11]
Lemay 2004	0	20	0	19	1.2%	0.00 [-0.09, 0.09]
Lin 2012-1	1	49	0	25	2.0%	0.02 [-0.05, 0.09]
Lin 2012-2	0	52	0	25	2.1%	0.00 [-0.06, 0.06]
Malhotra 2011	0	25	0	25	1.5%	0.00 [-0.07, 0.07]
Motififard 2015	0	45	0	45	2.8%	0.00 [-0.04, 0.04]
Orpen 2006	0	15	0	14	0.9%	0.00 [-0.12, 0.12]
Prakash 2017-1	0	50	1	50	3.1%	-0.02 [-0.07, 0.03]
Shinde 2015-1	2	14	0	14	0.9%	0.14 [-0.07, 0.35]
Shinde 2015-2	1	14	2	14	0.9%	-0.07 [-0.30, 0.16]
Song 2017	0	50	0	50	3.1%	0.00 [-0.04, 0.04]
Stowers 2017	0	60	0	60	3.7%	0.00 [-0.03, 0.03]
Tanaka 2001-1	0	22	0	9	0.8%	0.00 [-0.15, 0.15]
Tanaka 2001-2	0	24	0	9	0.8%	0.00 [-0.15, 0.15]
Tanaka 2001-3	0	27	0	8	0.8%	0.00 [-0.16, 0.16]
Vara 2017	0	53	0	49	3.1%	0.00 [-0.04, 0.04]
Veien 2002	0	15	0	15	0.9%	0.00 [-0.12, 0.12]
Wang 2016-1	1	39	0	19	1.6%	0.03 [-0.06, 0.12]
Wang 2016-2	0	42	0	19	1.6%	0.00 [-0.08, 0.08]
Wang 2017	0	50	0	50	3.1%	0.00 [-0.04, 0.04]
Wei 2014	1	101	0	100	6.2%	0.01 [-0.02, 0.04]
Yi 2016	2	50	1	50	3.1%	0.02 [-0.05, 0.09]
Yuan 2017	2	140	1	140	8.6%	0.01 [-0.02, 0.03]
Zekcer 2016	0	30	4	30	1.8%	-0.13 [-0.27, -0.00]
Zhao 2018	0	40	0	40	2.4%	0.00 [-0.05, 0.05]
Zhou 2018	0	57	0	57	3.5%	0.00 [-0.03, 0.03]
Total (95% CI)		**1777**		**1579**	**100.0%**	**0.00 [-0.01, 0.01]**
Total events	27		25			

Heterogeneity: Chi² = 13.49, df = 44 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.13 (P = 0.90)

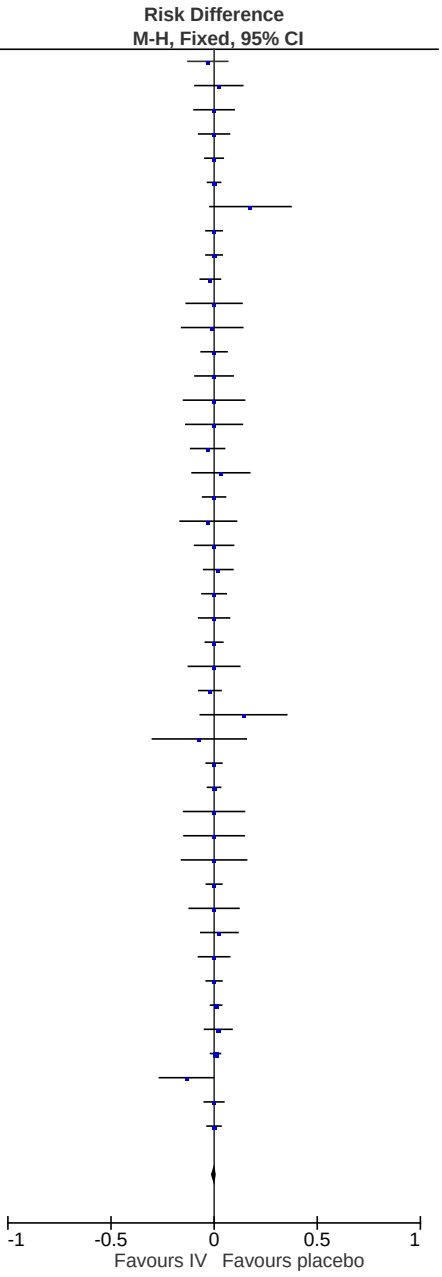

Figure 36: Acute coronary syndrome

Study or Subgroup	IV Events	IV Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Clave 2019-1	0	76	0	38	49.8%	0.00 [-0.04, 0.04]
Clave 2019-2	1	78	0	38	50.2%	0.01 [-0.03, 0.06]
Total (95% CI)		**154**		**76**	**100.0%**	**0.01 [-0.02, 0.04]**
Total events	1		0			

Heterogeneity: Chi² = 0.17, df = 1 (P = 0.68); I² = 0%
Test for overall effect: Z = 0.40 (P = 0.69)

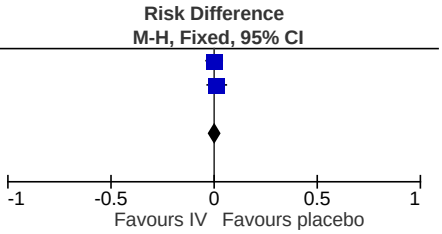

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Figure 37: Blood loss via haemoglobin level after surgery

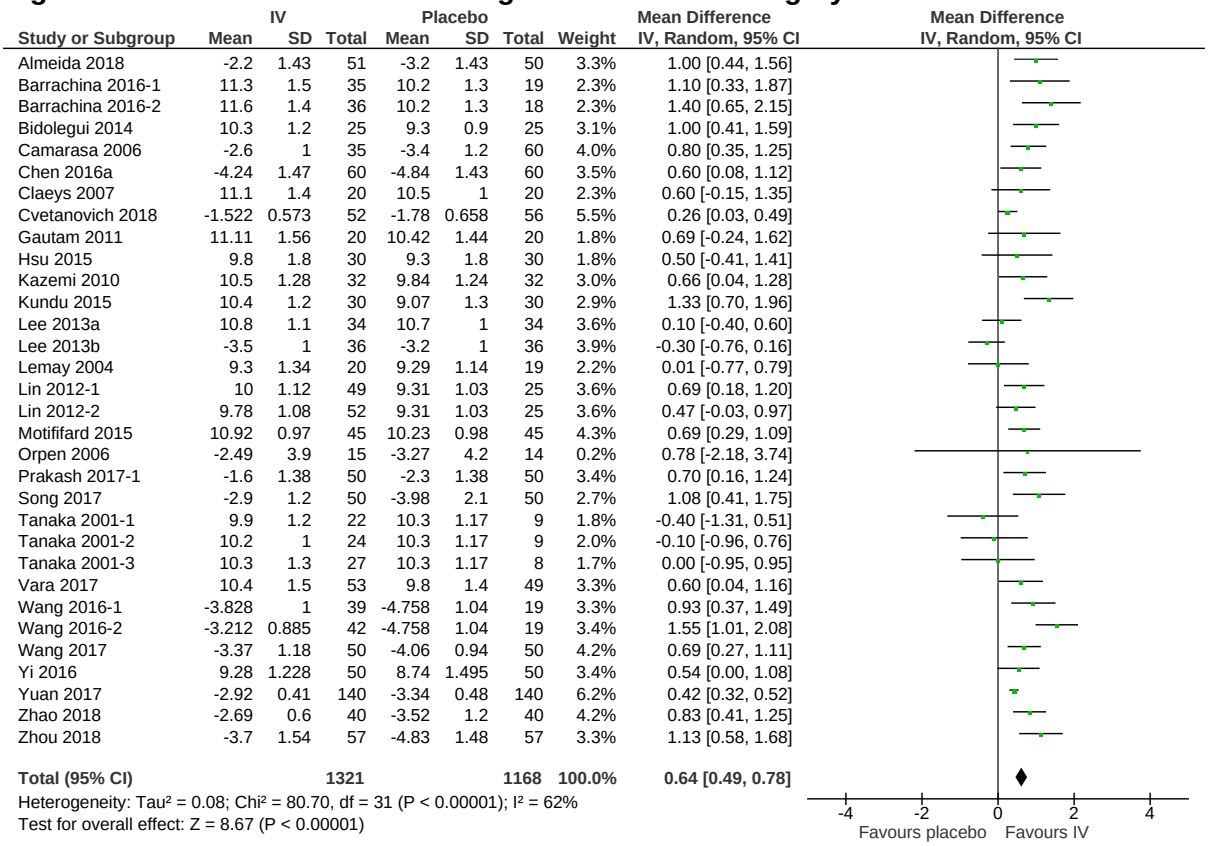

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Figure 38: Total blood loss

Study or Subgroup	IV Mean	IV SD	IV Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Almeida 2018	800	678	51	1,200	678	50	3.4%	-0.59 [-0.98, -0.19]
Barrachina 2016-1	1,377	689	35	2,215	1,136	19	2.7%	-0.95 [-1.54, -0.36]
Barrachina 2016-2	1,308	641	36	2,215	1,136	18	2.7%	-1.07 [-1.67, -0.47]
Benoni 1996	730	280	43	1,410	480	43	3.1%	-1.72 [-2.21, -1.22]
Camarasa 2006	1,095	473	35	1,784	660	60	3.2%	-1.14 [-1.59, -0.69]
Chen 2016a	1,739.5	609.1	60	2,392.9	538.8	60	3.5%	-1.13 [-1.52, -0.74]
Claeys 2007	801	244	20	1,038	289	20	2.5%	-0.87 [-1.52, -0.22]
Clave 2019-1	807.8	506.7	74	1,361.6	861.5	35	3.4%	-0.86 [-1.28, -0.44]
Clave 2019-2	833.1	584.1	74	1,361.6	861.5	35	3.4%	-0.77 [-1.18, -0.35]
Cvetanovich 2018	1,100.9	367.4	52	1,274.5	460	56	3.5%	-0.41 [-0.79, -0.03]
Garneti 2004	1,443	809	25	1,340	665	25	2.8%	0.14 [-0.42, 0.69]
Gautam 2011	427.6	129.56	20	911.5	261.08	20	2.0%	-2.30 [-3.12, -1.49]
Hsu 2015	1,070	345	30	1,337	345	30	3.0%	-0.76 [-1.29, -0.24]
Husted 2003	814	1,351	20	1,231	1,727	20	2.6%	-0.26 [-0.89, 0.36]
Lee 2013a	674.2	216.4	34	1,362.2	347.8	34	2.6%	-2.35 [-2.97, -1.72]
Lee 2013b	306	214	36	590	287	36	3.1%	-1.11 [-1.61, -0.61]
Lemay 2004	1,308	462	20	1,469	405	19	2.6%	-0.36 [-1.00, 0.27]
Lin 2012-1	986	297	49	1,222	261	25	3.0%	-0.82 [-1.32, -0.32]
Lin 2012-2	1,035	259	52	1,222	261	25	3.1%	-0.71 [-1.20, -0.22]
Niskanen 2005	792	386	19	1,102	495	20	2.5%	-0.68 [-1.33, -0.03]
Orpen 2006	660	324	15	726	340	14	2.3%	-0.19 [-0.92, 0.54]
Pauzenberger 2017	871	472.8	27	1,248.2	550.2	27	2.9%	-0.72 [-1.28, -0.17]
Prakash 2017-1	580.6	370	50	886.5	370	50	3.4%	-0.82 [-1.23, -0.41]
Song 2017	972.29	268.8	50	1,121.12	226.65	50	3.4%	-0.59 [-0.99, -0.19]
Stowers 2017	1,807	893	60	1,765	1,242	30	3.3%	0.04 [-0.40, 0.48]
Vara 2017	1,122.4	411.6	53	1,472.6	475.4	49	3.4%	-0.78 [-1.19, -0.38]
Wang 2016-1	1,000.1	252.9	39	1,228.9	296.3	19	2.8%	-0.84 [-1.41, -0.27]
Wang 2016-2	871.1	244.9	42	1,228.9	296.3	19	2.7%	-1.35 [-1.95, -0.75]
Wang 2017	919.7	327.7	50	1,079.9	297.4	50	3.4%	-0.51 [-0.91, -0.11]
Wei 2014	958.5	422.1	101	1,364.2	278.6	100	3.8%	-1.13 [-1.43, -0.83]
Yi 2016	1,002.62	366.85	50	1,221.11	386.25	50	3.4%	-0.58 [-0.98, -0.18]
Zhao 2018	692.7	172.7	40	948.5	193.4	40	3.1%	-1.38 [-1.87, -0.89]
Zhou 2018	1,125	514	57	1,464	556	57	3.5%	-0.63 [-1.01, -0.25]
Total (95% CI)			**1419**			**1205**	**100.0%**	**-0.84 [-1.00, -0.68]**

Heterogeneity: Tau² = 0.15; Chi² = 113.31, df = 32 (P < 0.00001); I² = 72%
Test for overall effect: Z = 10.40 (P < 0.00001)

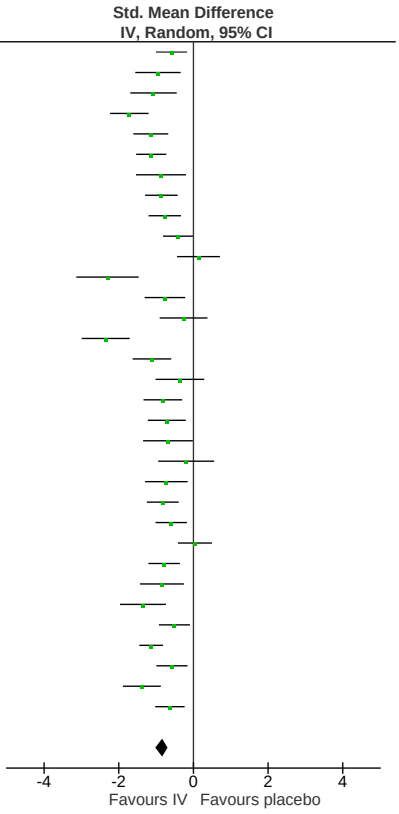

Figure 39: Surgical bleeding

Study or Subgroup	IV Mean	IV SD	IV Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Barrachina 2016-1	470	283	35	435	217	19	7.9%	0.13 [-0.43, 0.69]
Barrachina 2016-2	421	199	36	435	217	18	7.9%	-0.07 [-0.63, 0.50]
Claeys 2007	423	174	20	516	167	20	7.5%	-0.53 [-1.17, 0.10]
Hsu 2015	441	327	30	615	327	30	8.1%	-0.53 [-1.04, -0.01]
Kundu 2015	40.83	25.87	30	139.67	57.28	30	7.4%	-2.20 [-2.84, -1.55]
Lee 2013a	234.9	93.9	34	251.8	109.9	34	8.3%	-0.16 [-0.64, 0.31]
Motififard 2015	268.66	116.68	45	478.11	254.19	45	8.5%	-1.05 [-1.49, -0.61]
Niskanen 2005	626	299	19	790	436	20	7.5%	-0.43 [-1.06, 0.21]
Orpen 2006	220	174	15	169	201	14	7.0%	0.26 [-0.47, 1.00]
Shinde 2015-1	142	80	14	310	149	14	6.4%	-1.36 [-2.20, -0.53]
Shinde 2015-2	282	64	14	425	108	14	6.3%	-1.56 [-2.43, -0.70]
Zhao 2018	132.5	17.7	40	156.3	35.9	40	8.4%	-0.83 [-1.29, -0.37]
Zhou 2018	402	229	57	397	239	57	8.8%	0.02 [-0.35, 0.39]
Total (95% CI)			**389**			**355**	**100.0%**	**-0.61 [-0.97, -0.25]**

Heterogeneity: Tau² = 0.35; Chi² = 65.13, df = 12 (P < 0.00001); I² = 82%
Test for overall effect: Z = 3.31 (P = 0.0009)

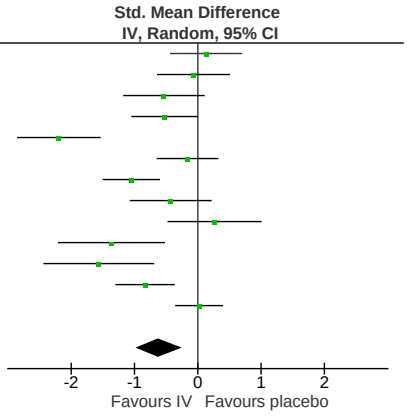

Figure 40: Postoperative bleeding

Study or Subgroup	IV Mean	IV SD	IV Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Garneti 2004	411	220	25	353	311	25	8.0%	0.21 [-0.34, 0.77]
Gautam 2011	272.5	122.51	20	685	118.21	20	6.5%	-3.36 [-4.35, -2.37]
Hsu 2015	285	128	30	392	128	30	8.1%	-0.83 [-1.35, -0.30]
Husted 2003	334	703	20	609	1,104	20	7.8%	-0.29 [-0.91, 0.33]
Kundu 2015	105.16	24.9	30	438	151.72	30	7.4%	-3.02 [-3.78, -2.27]
Lee 2013a (#626)	439.3	171.6	34	1,074.4	287.1	34	7.7%	-2.65 [-3.32, -1.99]
Orpen 2006	95	76	15	218	158	14	7.3%	-0.98 [-1.75, -0.20]
Shinde 2015-1	295	218	14	482	186	14	7.3%	-0.90 [-1.68, -0.11]
Shinde 2015-2	596	235	14	1,349	412	14	6.6%	-2.18 [-3.14, -1.22]
Vara 2017	221	126	53	372	166	49	8.4%	-1.02 [-1.44, -0.61]
Wang 2016-1	271.5	111.7	39	399.5	147.7	38	8.3%	-0.97 [-1.44, -0.50]
Wang 2016-2	213.57	65.32	42	399.5	147.7	38	8.2%	-1.64 [-2.15, -1.13]
Yi 2016	126.8	91.91	50	244.4	146.14	50	8.4%	-0.96 [-1.37, -0.54]
Total (95% CI)			**386**			**376**	**100.0%**	**-1.38 [-1.87, -0.89]**

Heterogeneity: Tau² = 0.69; Chi² = 104.60, df = 12 (P < 0.00001); I² = 89%
Test for overall effect: Z = 5.55 (P < 0.00001)

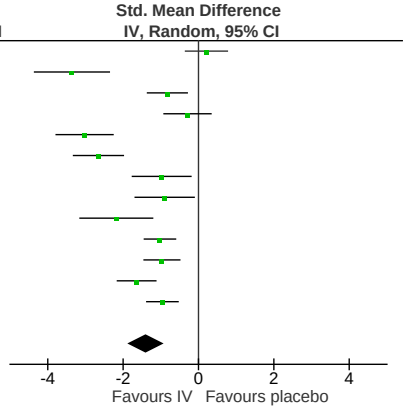

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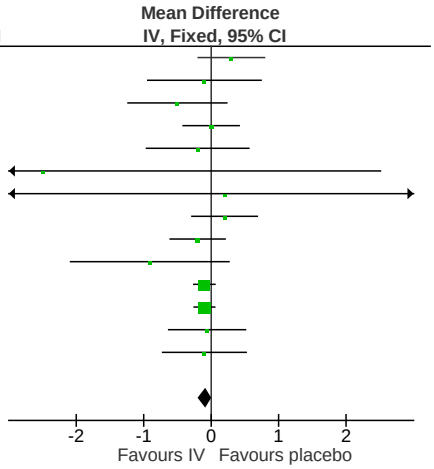
Figure 41: Length of stay

Study or Subgroup	IV Mean	IV SD	IV Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Bidolegui 2014	4.1	0.83	25	3.8	0.94	25	3.6%	0.30 [-0.19, 0.79]
Clave 2019-1	4.7	2.86	76	4.8	1.7	38	1.2%	-0.10 [-0.94, 0.74]
Clave 2019-2	4.3	2.06	78	4.8	1.8	38	1.6%	-0.50 [-1.23, 0.23]
Cvetanovich 2018	1.8	1	52	1.8	1.2	56	5.0%	0.00 [-0.42, 0.42]
Hsu 2015	5.66	1.5	30	5.86	1.5	30	1.5%	-0.20 [-0.96, 0.56]
Kazemi 2010	13	12.4	32	15.5	7.44	32	0.0%	-2.50 [-7.51, 2.51]
Lee 2013a	15.4	3.3	4	15.2	3.1	34	0.1%	0.20 [-3.20, 3.60]
Lin 2012-1	5.7	1.11	49	5.5	0.95	25	3.7%	0.20 [-0.29, 0.69]
Lin 2012-2	5.3	0.61	52	5.5	0.95	25	5.2%	-0.20 [-0.61, 0.21]
Motififard 2015	6.02	2.97	45	6.93	2.71	45	0.6%	-0.91 [-2.08, 0.26]
Wang 2017	6.9	0.4	50	7	0.4	50	35.3%	-0.10 [-0.26, 0.06]
Wei 2014	4.8	0.5	101	4.9	0.6	100	37.2%	-0.10 [-0.25, 0.05]
Yi 2016	6.52	1.2	50	6.58	1.67	50	2.7%	-0.06 [-0.63, 0.51]
Zhao 2018	2.8	0.63	40	2.9	1.9	40	2.3%	-0.10 [-0.72, 0.52]
Total (95% CI)			**684**			**588**	**100.0%**	**-0.09 [-0.18, 0.01]**

Heterogeneity: Chi² = 8.37, df = 13 (P = 0.82); I² = 0%
Test for overall effect: Z = 1.84 (P = 0.07)



E.6 1 Oral versus placebo

Figure 42: Transfusion

Study or Subgroup	Oral Events	Oral Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bradshaw 2012	0	26	1	20	3.7%	0.26 [0.01, 6.05]
Yuan 2017	15	140	36	140	78.8%	0.42 [0.24, 0.73]
Zhao 2018	1	40	8	40	17.5%	0.13 [0.02, 0.95]
Total (95% CI)		**206**		**200**	**100.0%**	**0.36 [0.21, 0.61]**
Total events	16		45			

Heterogeneity: Chi² = 1.35, df = 2 (P = 0.51); I² = 0%
Test for overall effect: Z = 3.82 (P = 0.0001)

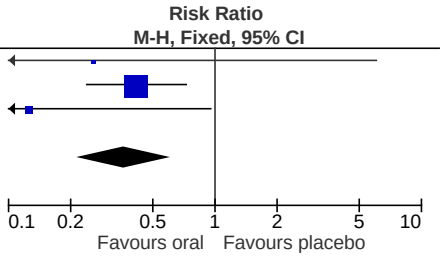


Figure 43: Adverse events: DVT

Study or Subgroup	Oral Events	Oral Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Bradshaw 2012	0	26	1	20	11.2%	-0.05 [-0.17, 0.07]
Yuan 2017	1	140	1	140	69.1%	0.00 [-0.02, 0.02]
Zhao 2018	0	40	0	40	19.7%	0.00 [-0.05, 0.05]
Total (95% CI)		**206**		**200**	**100.0%**	**-0.01 [-0.03, 0.02]**
Total events	1		2			

Heterogeneity: Chi² = 0.88, df = 2 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.50 (P = 0.62)

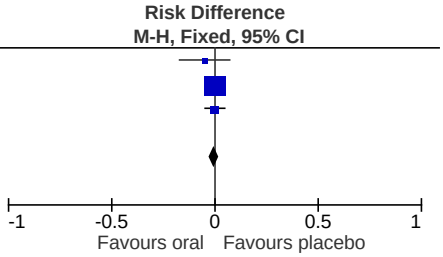


Figure 44: Blood loss via haemoglobin level after surgery

Study or Subgroup	Oral Mean	Oral SD	Oral Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Bradshaw 2012	-1.75	1.02	26	-2.47	1.02	20	2.9%	0.72 [0.13, 1.31]
Yuan 2017	-2.9	0.43	140	-3.34	0.48	140	91.1%	0.44 [0.33, 0.55]
Zhao 2018	-2.75	0.6	40	-3.52	1.2	40	6.0%	0.77 [0.35, 1.19]
Total (95% CI)			**206**			**200**	**100.0%**	**0.47 [0.37, 0.57]**

Heterogeneity: Chi² = 2.98, df = 2 (P = 0.23); I² = 33%
Test for overall effect: Z = 9.01 (P < 0.00001)

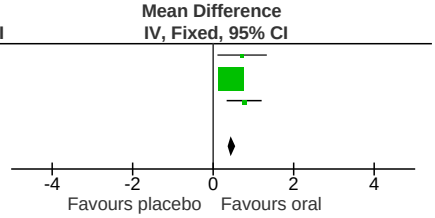


Figure 45: Total blood loss

Study or Subgroup	Oral Mean	Oral SD	Oral Total	Placebo Mean	Placebo SD	Placebo Total	Mean Difference IV, Fixed, 95% CI
Zhao 2018	694.1	142.3	40	948.5	193.4	40	-254.40 [-328.81, -179.99]

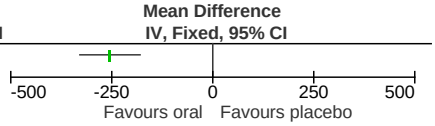


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Figure 46: Surgical bleeding

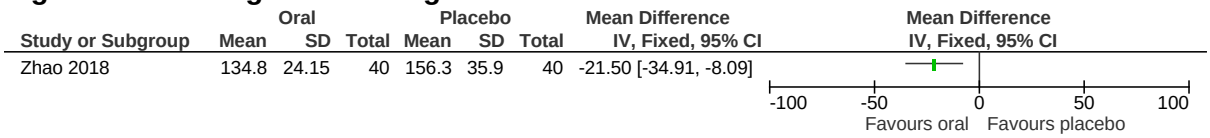
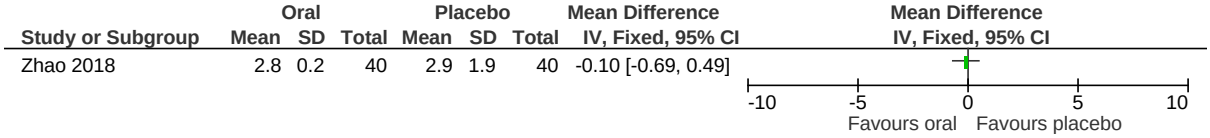


Figure 47: Length of stay



E.71 IV plus IA/topical versus placebo

Figure 48: Transfusion

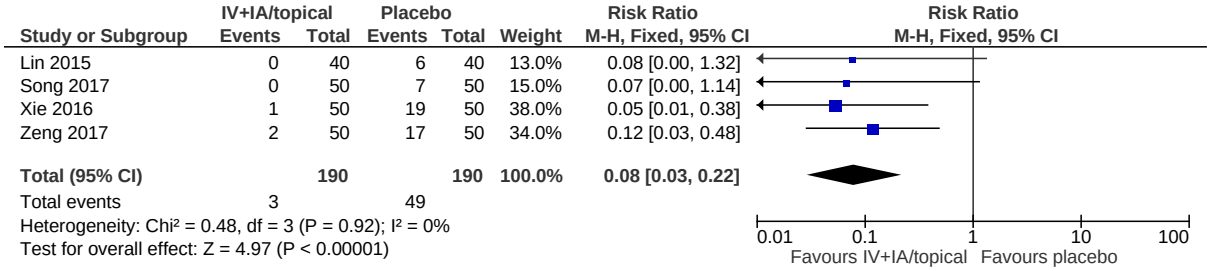
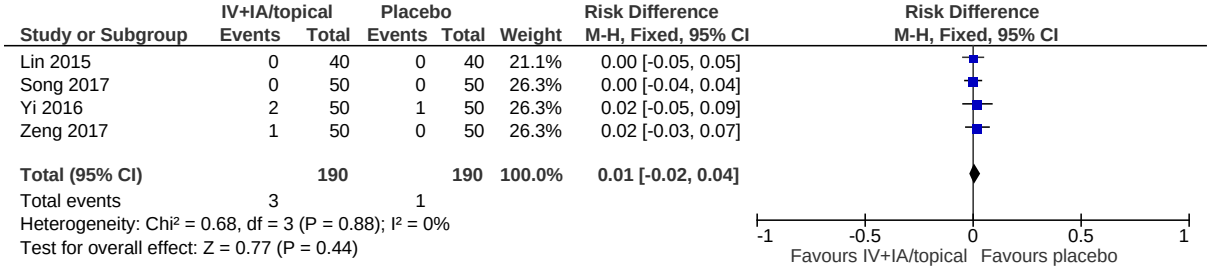
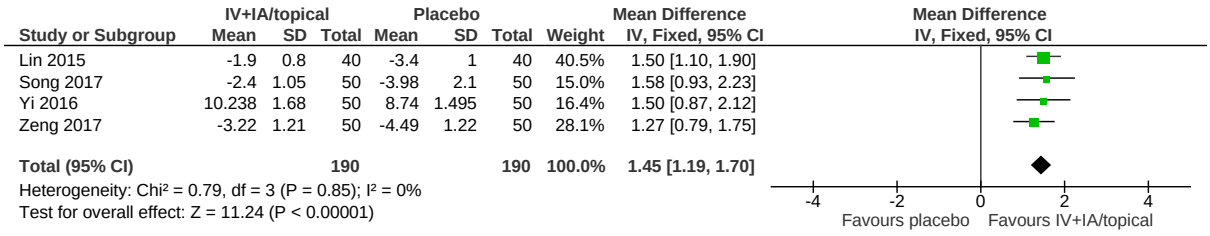


Figure 49: Adverse events: DVT



2 **Figure 50: Blood loss via haemoglobin level after surgery**



3

Figure 51: Total blood loss

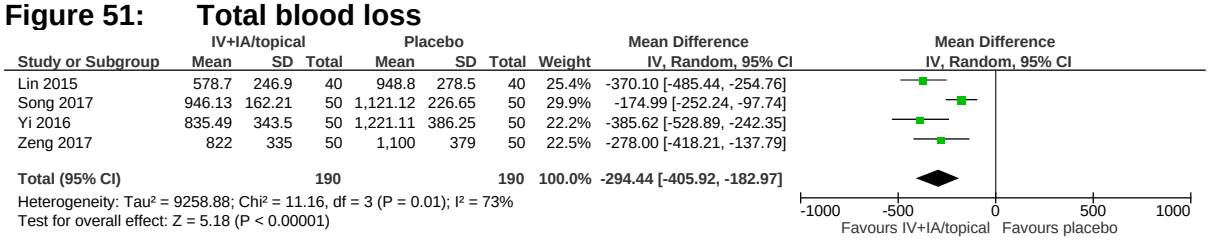


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Figure 52: Surgical bleeding

Study or Subgroup	IV+IA/topical Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Zeng 2017	193.8	90	50	288.2	105.2	50	-94.40 [-132.77, -56.03]

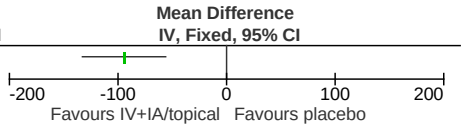


Figure 53: Postoperative bleeding

Study or Subgroup	IV+IA/topical Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Yi 2016	127.2	113.52	50	244.4	146.14	50	50.3%	-0.89 [-1.30, -0.48]
Zeng 2017	118.8	94.9	50	242.4	155.4	50	49.7%	-0.95 [-1.37, -0.54]
Total (95% CI)			**100**			**100**	**100.0%**	**-0.92 [-1.21, -0.63]**

Heterogeneity: Chi² = 0.05, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 6.18 (P < 0.00001)

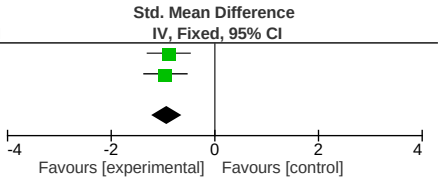
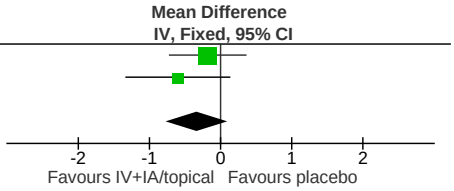


Figure 54: Length of stay

Study or Subgroup	IV+IA/topical Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Yi 2016	6.4	0.97	50	6.58	1.67	50	64.9%	-0.18 [-0.72, 0.36]
Zeng 2017	6.2	1.7	50	6.8	2	50	35.1%	-0.60 [-1.33, 0.13]
Total (95% CI)			**100**			**100**	**100.0%**	**-0.33 [-0.76, 0.10]**

Heterogeneity: Chi² = 0.83, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 1.49 (P = 0.14)



E.8.1 IA/topical versus IV

Figure 55: Mortality

Study or Subgroup	IA/topical Events	Total	IV Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Patel 2014	1	47	0	42	33.0%	0.02 [-0.04, 0.08]
Wang 2018b	0	60	0	60	44.7%	0.00 [-0.03, 0.03]
Zekcer 2016	0	30	0	30	22.3%	0.00 [-0.06, 0.06]
Total (95% CI)		**137**		**132**	**100.0%**	**0.01 [-0.02, 0.04]**
Total events	1		0			

Heterogeneity: Chi² = 0.46, df = 2 (P = 0.79); I² = 0%
Test for overall effect: Z = 0.48 (P = 0.63)

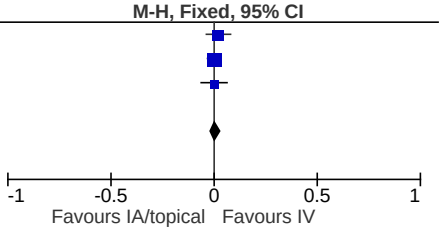


Figure 56: Quality of life: SF-36 MCS

Study or Subgroup	IA/topical Mean	SD	Total	IV Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Zhang 2019	60.8	9.76	50	63.3	12.37	50	-2.50 [-6.87, 1.87]

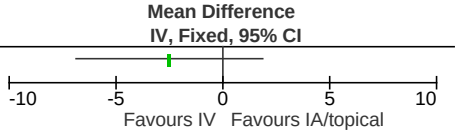


Figure 57: Quality of life: SF-36 PCS

Study or Subgroup	IA/topical Mean	SD	Total	IV Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Zhang 2019	55.02	8.85	50	57.28	11.05	50	-2.26 [-6.18, 1.66]

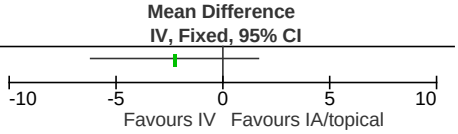


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Figure 58: Transfusion

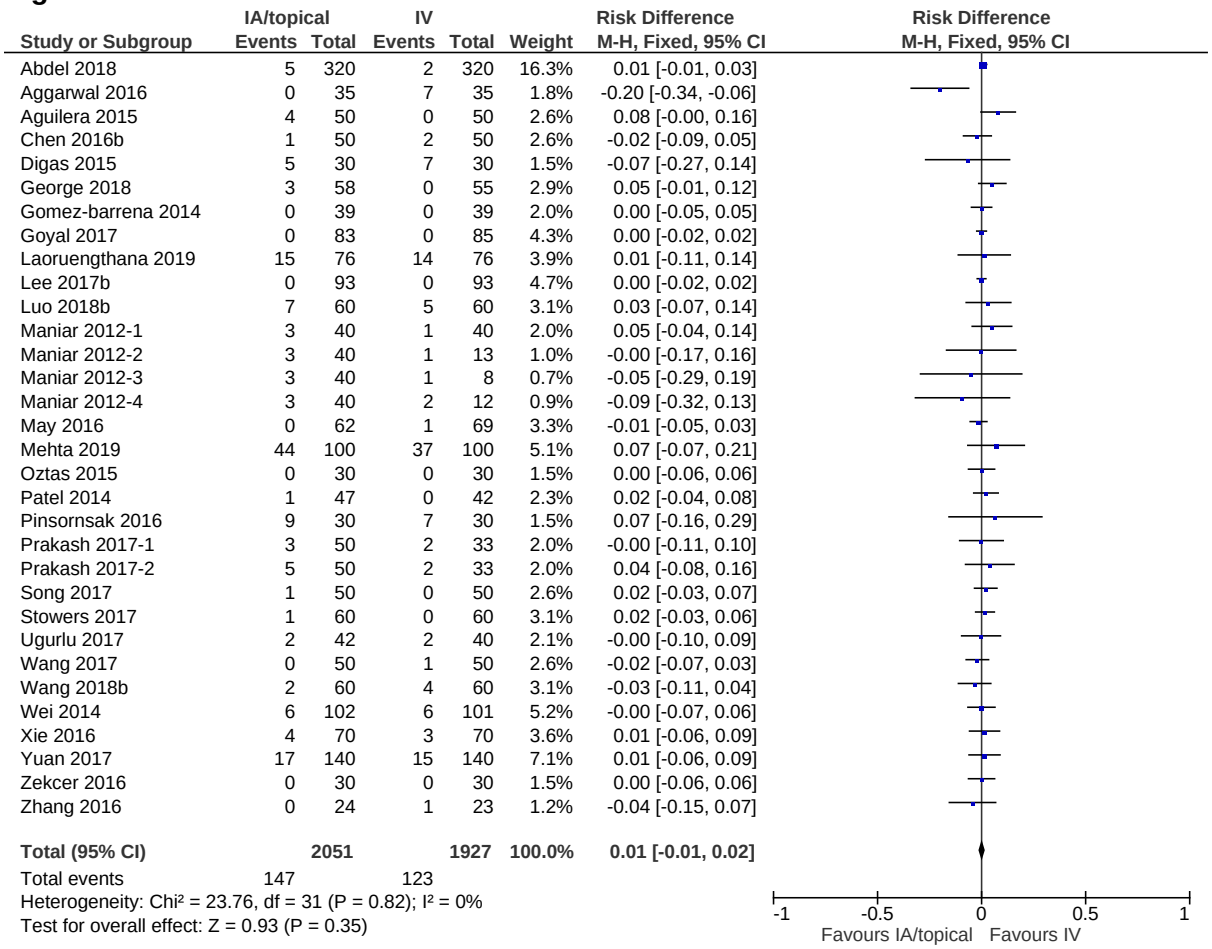

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Figure 59: Adverse events: DVT

Study or Subgroup	IA/topical Events	IA/topical Total	IV Events	IV Total	Weight	Risk Difference M-H, Fixed, 95% CI
Abdel 2018	2	320	4	320	16.7%	-0.01 [-0.02, 0.01]
Aggarwal 2016	0	35	0	35	1.8%	0.00 [-0.05, 0.05]
Chen 2016b	0	50	0	50	2.6%	0.00 [-0.04, 0.04]
Digas 2015	0	30	1	30	1.6%	-0.03 [-0.12, 0.05]
George 2018	0	58	0	55	3.0%	0.00 [-0.03, 0.03]
Gomez-barrena 2014	1	39	0	39	2.0%	0.03 [-0.04, 0.09]
Goyal 2017	3	83	2	85	4.4%	0.01 [-0.04, 0.06]
Lacko 2017	0	30	0	30	1.6%	0.00 [-0.06, 0.06]
Lee 2017b	0	93	0	93	4.9%	0.00 [-0.02, 0.02]
Luo 2018b	0	60	0	60	3.1%	0.00 [-0.03, 0.03]
Maniar 2012-1	0	40	0	40	2.1%	0.00 [-0.05, 0.05]
May 2016	1	62	2	69	3.4%	-0.01 [-0.06, 0.04]
Mehta 2019	0	100	0	100	5.2%	0.00 [-0.02, 0.02]
Oztas 2015	0	30	0	30	1.6%	0.00 [-0.06, 0.06]
Pinsornsak 2016	0	30	0	30	1.6%	0.00 [-0.06, 0.06]
Prakash 2017-1	0	50	0	25	1.7%	0.00 [-0.06, 0.06]
Prakash 2017-2	0	50	1	50	2.6%	-0.02 [-0.07, 0.03]
Song 2017	0	50	0	50	2.6%	0.00 [-0.04, 0.04]
Stowers 2017	0	60	0	60	3.1%	0.00 [-0.03, 0.03]
Ugurlu 2017	1	42	1	40	2.1%	-0.00 [-0.07, 0.07]
Wang 2017	0	50	0	50	2.6%	0.00 [-0.04, 0.04]
Wang 2018b	0	60	1	60	3.1%	-0.02 [-0.06, 0.03]
Wei 2014	1	102	1	101	5.3%	-0.00 [-0.03, 0.03]
Wei 2018	0	32	0	32	1.7%	0.00 [-0.06, 0.06]
Xie 2016	0	70	1	70	3.7%	-0.01 [-0.05, 0.02]
Yuan 2017	0	140	2	140	7.3%	-0.01 [-0.04, 0.01]
Zekcer 2016	1	30	0	30	1.6%	0.03 [-0.05, 0.12]
Zhang 2016	0	25	1	25	1.3%	-0.04 [-0.14, 0.06]
Zhang 2019	8	50	9	50	2.6%	-0.02 [-0.17, 0.13]
Zhou 2018	0	56	0	57	3.0%	0.00 [-0.03, 0.03]
Total (95% CI)		**1927**		**1906**	**100.0%**	**-0.00 [-0.01, 0.00]**
Total events	18		26			

Heterogeneity: Chi² = 5.48, df = 29 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.98 (P = 0.33)

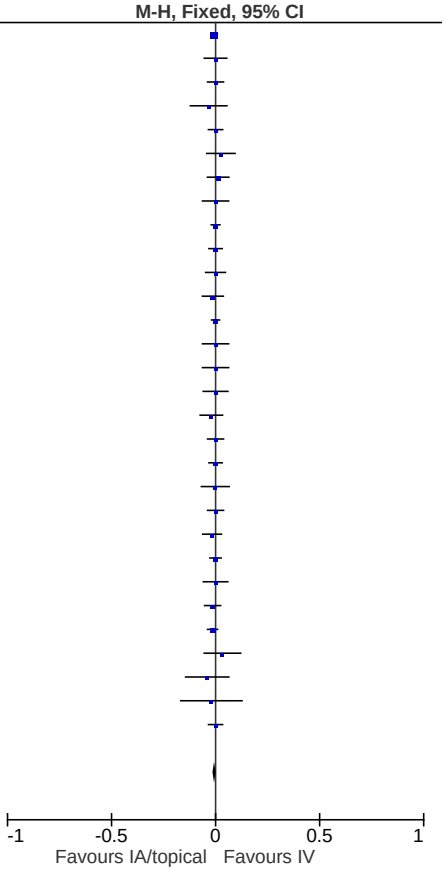

Figure 60: Adverse events: acute myocardial infarction

Study or Subgroup	IA/topical Events	IA/topical Total	IV Events	IV Total	Peto Odds Ratio Peto, Fixed, 95% CI
Patel 2014	1	47	0	42	6.64 [0.13, 336.89]

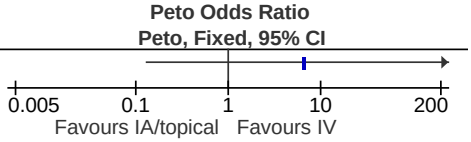

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Figure 61: Blood loss via haemoglobin level after surgery

Study or Subgroup	IA/topical Mean	SD	Total	IV Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Aggarwal 2016	9.66	1.47	35	10.3	1.11	35	2.5%	-0.64 [-1.25, -0.03]
Aguilera 2015	9	2.39	50	9.2	2.74	50	1.1%	-0.20 [-1.21, 0.81]
Digas 2015	-2.24	0.93	30	-2.26	0.99	30	3.4%	0.02 [-0.47, 0.51]
Gomez-barrena 2014	-3.4	0.9	39	-3.1	1	39	4.0%	-0.30 [-0.72, 0.12]
Goyal 2017	-2.5	0.8	83	-2.4	0.9	85	6.3%	-0.10 [-0.36, 0.16]
Lee 2017b	-2.9	0.9	93	-2.4	0.8	93	6.5%	-0.50 [-0.74, -0.26]
Luo 2018b	-3.58	1.07	60	-3.66	1.26	60	4.1%	0.08 [-0.34, 0.50]
May 2016	10.2	1.4	69	10.7	1.5	62	3.3%	-0.50 [-1.00, -0.00]
Mehta 2019	1.041	0.117	100	1.041	0.1	100	9.5%	0.00 [-0.03, 0.03]
Patel 2014	-3.06	1.02	42	-3.42	1.07	47	3.9%	0.36 [-0.07, 0.79]
Pinsornsak 2016	-1.85	0.95	30	-1.87	1.37	30	2.6%	0.02 [-0.58, 0.62]
Prakash 2017-1	-1.6	1	50	-1.6	1	25	3.4%	0.00 [-0.48, 0.48]
Prakash 2017-2	-1.6	1	50	-2.1	1	25	3.4%	0.50 [0.02, 0.98]
Song 2017	-2.9	1.2	50	-2.5	1.2	50	3.5%	-0.40 [-0.87, 0.07]
Ugurlu 2017	10.96	1.65	40	10.52	1.24	42	2.3%	0.44 [-0.19, 1.07]
Wang 2017	-2.74	0.85	50	-3.37	1.18	50	4.2%	0.63 [0.23, 1.03]
Wang 2018b	-2.99	1.03	60	-3.13	0.89	60	5.0%	0.14 [-0.20, 0.48]
Wei 2018	-2.84	0.68	32	-2.66	0.6	32	5.4%	-0.18 [-0.49, 0.13]
Xie 2016	-3.36	0.78	70	-3.89	0.72	70	6.5%	0.53 [0.28, 0.78]
Yuan 2017	-2.92	0.41	140	-2.92	0.42	140	8.9%	0.00 [-0.10, 0.10]
Zhang 2016	8.5	0.9	23	8.9	1.1	24	2.7%	-0.40 [-0.97, 0.17]
Zhang 2019	-2.214	1.09	50	-2.734	0.941	50	4.3%	0.52 [0.12, 0.92]
Zhou 2018	4.02	1.33	56	3.7	1.54	57	3.0%	0.32 [-0.21, 0.85]
Total (95% CI)			**1302**			**1256**	**100.0%**	**0.03 [-0.09, 0.14]**

Heterogeneity: Tau² = 0.03; Chi² = 76.86, df = 22 (P < 0.00001); I² = 71%
Test for overall effect: Z = 0.45 (P = 0.65)

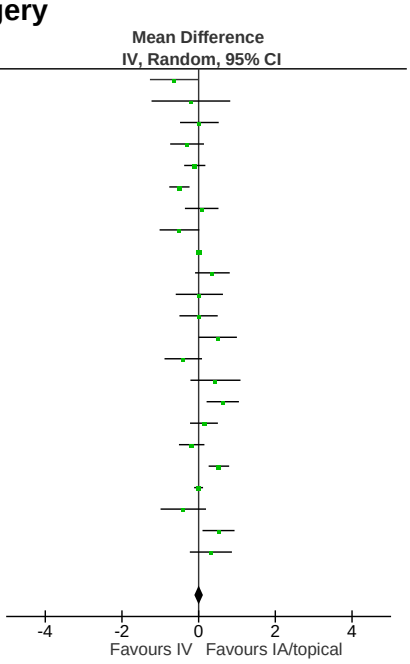

Figure 62: Total blood loss

Study or Subgroup	IA/topical Mean	SD	Total	IV Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Abdel 2018	560	336	320	456	336	320	5.2%	0.31 [0.15, 0.47]
Aggarwal 2016	543	264	35	1,039	483	35	3.4%	-1.26 [-1.78, -0.74]
Aguilera 2015	1,021.57	481.09	47	817.54	324.82	48	4.0%	0.49 [0.09, 0.90]
Chen 2016b	799	909	50	730	725	50	4.1%	0.08 [-0.31, 0.48]
Digas 2015	943	477	30	1,086	559	30	3.4%	-0.27 [-0.78, 0.24]
George 2018	672.2	368	58	666.1	368	55	4.2%	0.02 [-0.35, 0.39]
Gomez-barrena 2014	1,574.5	542.9	39	1,626	519.2	39	3.8%	-0.10 [-0.54, 0.35]
Lee 2017b	633	205	93	764	217	93	4.6%	-0.62 [-0.91, -0.32]
Luo 2018b	1,064	410	60	1,032	350	60	4.2%	0.08 [-0.27, 0.44]
Maniar 2012-1	809	341.1	40	688	308.2	10	2.6%	0.36 [-0.34, 1.05]
Maniar 2012-2	809	341.1	40	782	233.1	10	2.6%	0.08 [-0.61, 0.78]
Maniar 2012-3	809	341.1	40	824	226.8	10	2.6%	-0.05 [-0.74, 0.65]
Maniar 2012-4	809	341.1	40	864	315	10	2.6%	-0.16 [-0.85, 0.53]
May 2016	977.7	342.6	62	1,075.5	419	69	4.3%	-0.25 [-0.60, 0.09]
Mehta 2019	614.15	128.73	100	607.9	94.37	100	4.7%	0.06 [-0.22, 0.33]
Oztas 2015	823.64	224.33	30	898.03	298.21	30	3.4%	-0.28 [-0.79, 0.23]
Prakash 2017-1	514.5	1,000	50	580.6	1,000	25	3.6%	-0.07 [-0.55, 0.41]
Prakash 2017-2	557.6	996	50	580.6	996	25	3.6%	-0.02 [-0.50, 0.46]
Song 2017	998.12	256.78	50	972.29	268.8	50	4.1%	0.10 [-0.29, 0.49]
Stowers 2017	1,613	622	30	1,807	893	60	3.8%	-0.24 [-0.68, 0.20]
Wang 2017	770.3	237.3	50	919.7	327.7	50	4.0%	-0.52 [-0.92, -0.12]
Wang 2018b	1,059.37	422.99	60	1,108.31	392.11	60	4.2%	-0.12 [-0.48, 0.24]
Wei 2014	963.4	421.3	102	958.5	422.1	101	4.7%	0.01 [-0.26, 0.29]
Xie 2016	905.07	237.7	70	878.03	210	70	4.4%	0.12 [-0.21, 0.45]
Zhang 2019	501.34	106.79	50	621.44	102.4	50	3.9%	-1.14 [-1.56, -0.72]
Zhou 2018	1,211	425	56	1,125	514	57	4.2%	0.18 [-0.19, 0.55]
Total (95% CI)			**1652**			**1517**	**100.0%**	**-0.12 [-0.27, 0.04]**

Heterogeneity: Tau² = 0.11; Chi² = 103.40, df = 25 (P < 0.00001); I² = 76%
Test for overall effect: Z = 1.50 (P = 0.13)

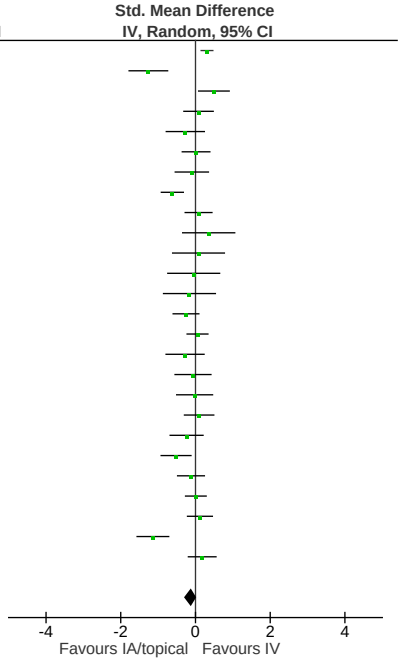

Figure 63: Surgical bleeding

Study or Subgroup	IA/topical Mean	SD	Total	IV Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Abdel 2018	324	238	320	271	238	320	17.3%	0.22 [0.07, 0.38]
Aguilera 2015	851.64	464.71	47	685.02	314.08	48	16.7%	0.42 [0.01, 0.82]
Digas 2015	235	23	30	285	26	30	15.8%	-2.01 [-2.64, -1.38]
Mehta 2019	317.8	86.15	100	165.8	49.75	100	16.9%	2.15 [1.80, 2.50]
Wei 2018	109.06	33.38	32	122.81	41.6	32	16.4%	-0.36 [-0.85, 0.13]
Zhou 2018	404	213	56	402	229	57	16.8%	0.01 [-0.36, 0.38]
Total (95% CI)			**585**			**587**	**100.0%**	**0.10 [-0.73, 0.92]**

Heterogeneity: Tau² = 1.01; Chi² = 170.15, df = 5 (P < 0.00001); I² = 97%
Test for overall effect: Z = 0.23 (P = 0.82)

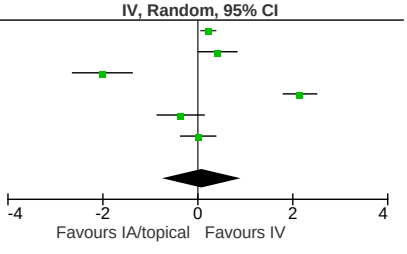

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Figure 64: Postoperative bleeding

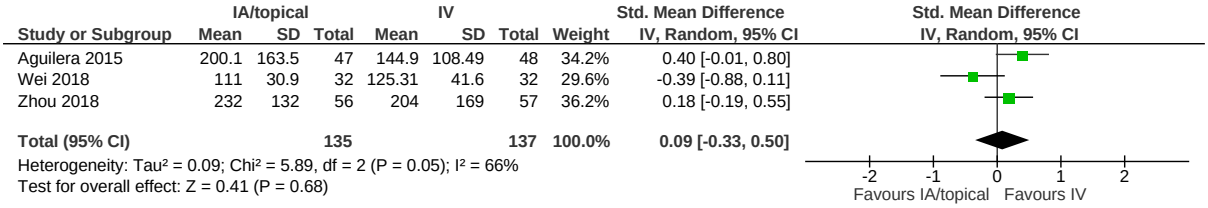
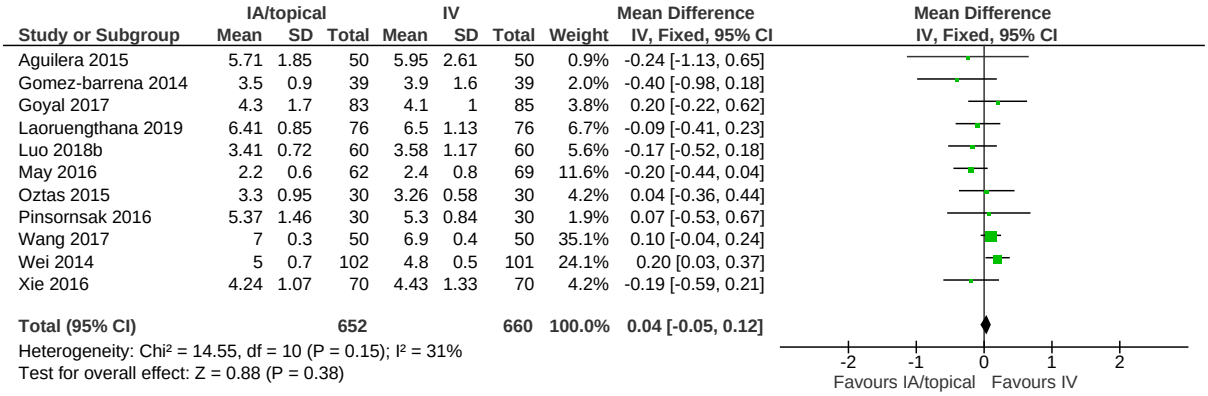


Figure 65: Length of stay



E.91 Oral versus IV

Figure 66: Mortality

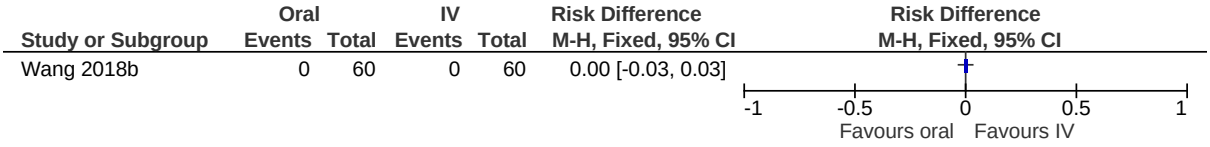


Figure 67: Transfusion

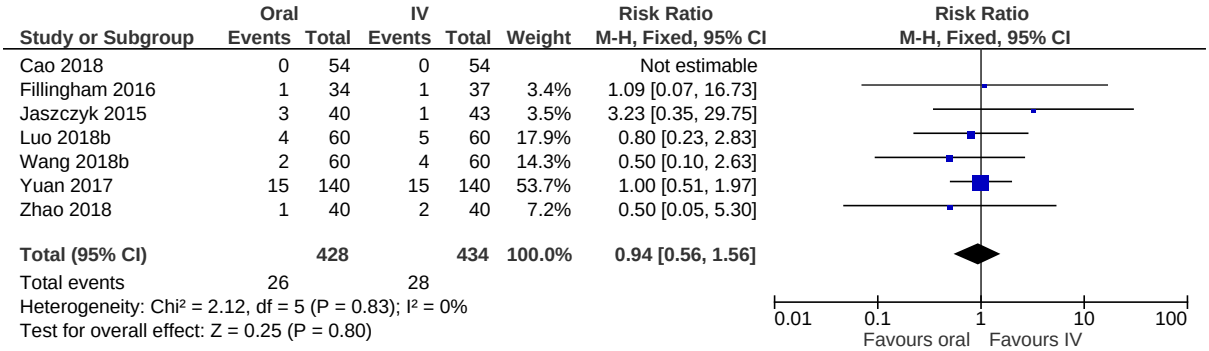


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Figure 68: Adverse events: DVT

Study or Subgroup	Oral Events	Oral Total	IV Events	IV Total	Weight	Risk Difference M-H, Fixed, 95% CI
Cao 2018	0	54	2	54	11.4%	-0.04 [-0.10, 0.02]
Fillingham 2016	0	34	0	37	7.5%	0.00 [-0.05, 0.05]
Jaszczyk 2015	0	40	0	43	8.8%	0.00 [-0.05, 0.05]
Kayupov 2017	0	40	0	43	8.8%	0.00 [-0.05, 0.05]
Luo 2018b	0	60	0	60	12.7%	0.00 [-0.03, 0.03]
Wang 2018b	0	60	1	60	12.7%	-0.02 [-0.06, 0.03]
Yuan 2017	1	140	2	140	29.6%	-0.01 [-0.03, 0.02]
Zhao 2018	0	40	0	40	8.5%	0.00 [-0.05, 0.05]
Total (95% CI)		**468**		**477**	**100.0%**	**-0.01 [-0.02, 0.01]**
Total events	1		5			

Heterogeneity: Chi² = 1.74, df = 7 (P = 0.97); I² = 0%
Test for overall effect: Z = 1.12 (P = 0.26)

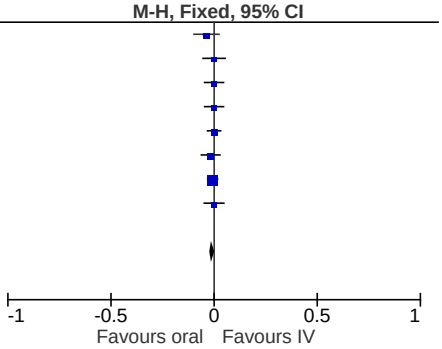


Figure 69: Blood loss via haemoglobin level after surgery

Study or Subgroup	Oral Mean	Oral SD	Oral Total	IV Mean	IV SD	IV Total	Weight	Mean Difference IV, Fixed, 95% CI
Cao 2018	-2.48	0.88	54	-2.56	1.2	54	4.1%	0.08 [-0.32, 0.48]
Fillingham 2016	-3.45	0.93	34	-3.31	0.95	37	3.4%	-0.14 [-0.58, 0.30]
Jaszczyk 2015	-3.67	1.2	40	-3.53	1.2	43	2.4%	-0.14 [-0.66, 0.38]
Kayupov 2017	-3.67	1.2	40	-3.53	1.2	43	2.4%	-0.14 [-0.66, 0.38]
Luo 2018b	-3.48	1.32	60	-3.58	1.07	60	3.5%	0.10 [-0.33, 0.53]
Wang 2018b	-2.91	1.13	60	-3.13	0.89	60	4.9%	0.22 [-0.14, 0.58]
Yuan 2017	-2.9	0.4	140	-2.92	0.42	140	70.0%	0.02 [-0.08, 0.12]
Zhao 2018	-2.75	0.6	40	-2.69	0.6	40	9.3%	-0.06 [-0.32, 0.20]
Total (95% CI)			**468**			**477**	**100.0%**	**0.01 [-0.07, 0.09]**

Heterogeneity: Chi² = 2.97, df = 7 (P = 0.89); I² = 0%
Test for overall effect: Z = 0.35 (P = 0.73)

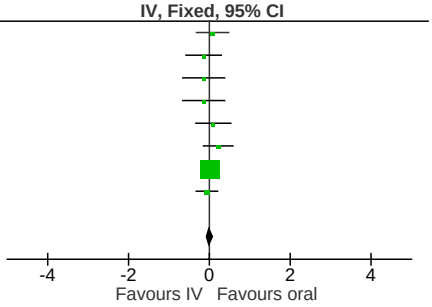


Figure 70: Total blood loss

Study or Subgroup	Oral Mean	Oral SD	Oral Total	IV Mean	IV SD	IV Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Cao 2018	728.4	302	54	703.6	480	54	16.3%	0.06 [-0.32, 0.44]
Fillingham 2016	1,281	265	34	1,231	253	37	10.6%	0.19 [-0.28, 0.66]
Jaszczyk 2015	1,339	375	40	1,301	424	43	12.5%	0.09 [-0.34, 0.52]
Kayupov 2017	1,339	375	40	1,301	424	43	12.5%	0.09 [-0.34, 0.52]
Luo 2018b	1,004	415	60	1,032	350	60	18.1%	-0.07 [-0.43, 0.29]
Wang 2018b	1,003.99	414.44	60	1,108.31	392.11	60	17.9%	-0.26 [-0.62, 0.10]
Zhao 2018	694.1	142.3	40	692.7	172.2	40	12.1%	0.01 [-0.43, 0.45]
Total (95% CI)			**328**			**337**	**100.0%**	**-0.00 [-0.16, 0.15]**

Heterogeneity: Chi² = 3.23, df = 6 (P = 0.78); I² = 0%
Test for overall effect: Z = 0.06 (P = 0.95)

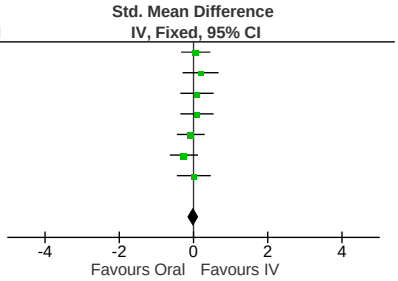


Figure 71: Surgical bleeding

Study or Subgroup	Oral Mean	Oral SD	Oral Total	IV Mean	IV SD	IV Total	Weight	Mean Difference IV, Fixed, 95% CI
Wang 2018b	147.12	25.64	60	148.92	31.43	60	45.0%	-1.80 [-12.06, 8.46]
Zhao 2018	134.8	24.15	40	132.5	17.7	40	55.0%	2.30 [-6.98, 11.58]
Total (95% CI)			**100**			**100**	**100.0%**	**0.46 [-6.43, 7.34]**

Heterogeneity: Chi² = 0.34, df = 1 (P = 0.56); I² = 0%
Test for overall effect: Z = 0.13 (P = 0.90)

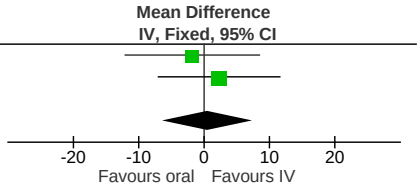
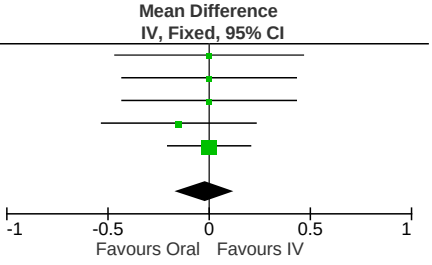


Figure 72: Length of stay

Study or Subgroup	Oral Mean	Oral SD	Oral Total	IV Mean	IV SD	IV Total	Weight	Mean Difference IV, Fixed, 95% CI
Fillingham 2016	3	1	34	3	1	37	10.0%	0.00 [-0.47, 0.47]
Jaszczyk 2015	2	1	40	2	1	43	11.7%	0.00 [-0.43, 0.43]
Kayupov 2017	2	1	40	2	1	43	11.7%	0.00 [-0.43, 0.43]
Luo 2018b	3.43	0.95	60	3.58	1.17	60	14.9%	-0.15 [-0.53, 0.23]
Zhao 2018	2.8	0.2	40	2.8	0.63	40	51.7%	0.00 [-0.20, 0.20]
Total (95% CI)			**214**			**223**	**100.0%**	**-0.02 [-0.17, 0.12]**

Heterogeneity: Chi² = 0.51, df = 4 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.30 (P = 0.77)



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E.102 IA/topical versus oral

Figure 73: Mortality

Study or Subgroup	IA/topical Events	IA/topical Total	Oral Events	Oral Total	Weight	Risk Difference M-H, Fixed, 95% CI
Luo 2018a	0	58	0	59	30.5%	0.00 [-0.03, 0.03]
Wang 2018a	0	74	0	73	38.3%	0.00 [-0.03, 0.03]
Wang 2018b	0	60	0	60	31.3%	0.00 [-0.03, 0.03]
Total (95% CI)		**192**		**192**	**100.0%**	**0.00 [-0.02, 0.02]**
Total events	0		0			

Heterogeneity: Chi² = 0.00, df = 2 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)

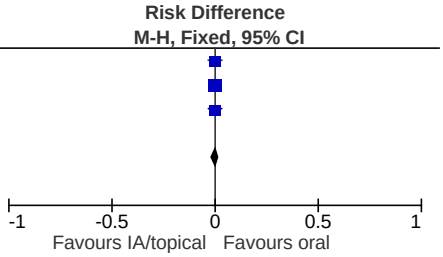


Figure 74: Transfusion

Study or Subgroup	IA/topical Events	IA/topical Total	Oral Events	Oral Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Luo 2018a	2	58	1	59	4.0%	2.03 [0.19, 21.83]
Luo 2018b	7	60	4	60	16.0%	1.75 [0.54, 5.67]
Wang 2018a	4	75	3	75	12.0%	1.33 [0.31, 5.75]
Wang 2018b	2	60	2	60	8.0%	1.00 [0.15, 6.87]
Yuan 2017	17	140	15	140	60.0%	1.13 [0.59, 2.18]
Total (95% CI)		**393**		**394**	**100.0%**	**1.28 [0.78, 2.11]**
Total events	32		25			

Heterogeneity: Chi² = 0.62, df = 4 (P = 0.96); I² = 0%
Test for overall effect: Z = 0.97 (P = 0.33)

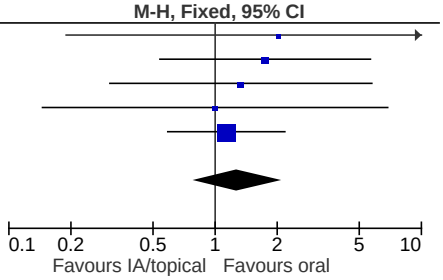
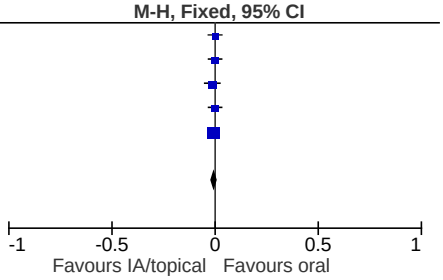


Figure 75: Adverse events: DVT

Study or Subgroup	IA/topical Events	IA/topical Total	Oral Events	Oral Total	Weight	Risk Difference M-H, Fixed, 95% CI
Luo 2018a	0	58	0	59	14.9%	0.00 [-0.03, 0.03]
Luo 2018b	0	60	0	60	15.3%	0.00 [-0.03, 0.03]
Wang 2018a	0	73	1	74	18.7%	-0.01 [-0.05, 0.02]
Wang 2018b	0	60	0	60	15.3%	0.00 [-0.03, 0.03]
Yuan 2017	0	140	1	140	35.7%	-0.01 [-0.03, 0.01]
Total (95% CI)		**391**		**393**	**100.0%**	**-0.01 [-0.02, 0.01]**
Total events	0		2			

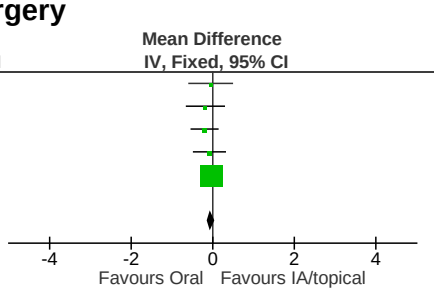
Heterogeneity: Chi² = 0.53, df = 4 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.76 (P = 0.45)



3 **Figure 76: Blood loss via haemoglobin level after surgery**

Study or Subgroup	IA/topical Mean	IA/topical SD	IA/topical Total	Oral Mean	Oral SD	Oral Total	Weight	Mean Difference IV, Fixed, 95% CI
Luo 2018a	-3.12	1.49	58	-3.07	1.44	59	2.8%	-0.05 [-0.58, 0.48]
Luo 2018b	-3.66	1.26	60	-3.48	1.32	60	3.7%	-0.18 [-0.64, 0.28]
Wang 2018a	-2.4	1.1	73	-2.2	0.9	74	7.6%	-0.20 [-0.53, 0.13]
Wang 2018b	-2.99	1.03	60	-2.91	1.13	60	5.3%	-0.08 [-0.47, 0.31]
Yuan 2017	-2.92	0.42	140	-2.9	0.43	140	80.5%	-0.02 [-0.12, 0.08]
Total (95% CI)			**391**			**393**	**100.0%**	**-0.04 [-0.13, 0.05]**

Heterogeneity: Chi² = 1.47, df = 4 (P = 0.83); I² = 0%
Test for overall effect: Z = 0.96 (P = 0.34)



4

Figure 77: Total blood loss

Study or Subgroup	IA/topical Mean	IA/topical SD	IA/topical Total	Oral Mean	Oral SD	Oral Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Luo 2018a	902	418	58	863	432	59	23.3%	0.09 [-0.27, 0.45]
Luo 2018b	1,064	410	60	1,004	415	60	23.8%	0.14 [-0.21, 0.50]
Wang 2018a	872.4	393.1	73	788.8	349.1	74	29.1%	0.22 [-0.10, 0.55]
Wang 2018b	1,059.37	422.99	60	1,003.99	414.44	60	23.8%	0.13 [-0.23, 0.49]
Total (95% CI)			**251**			**253**	**100.0%**	**0.15 [-0.02, 0.33]**

Heterogeneity: Chi² = 0.31, df = 3 (P = 0.96); I² = 0%
Test for overall effect: Z = 1.70 (P = 0.09)

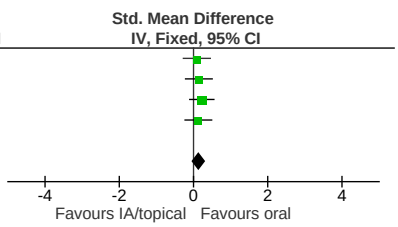


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Figure 78: Surgical bleeding

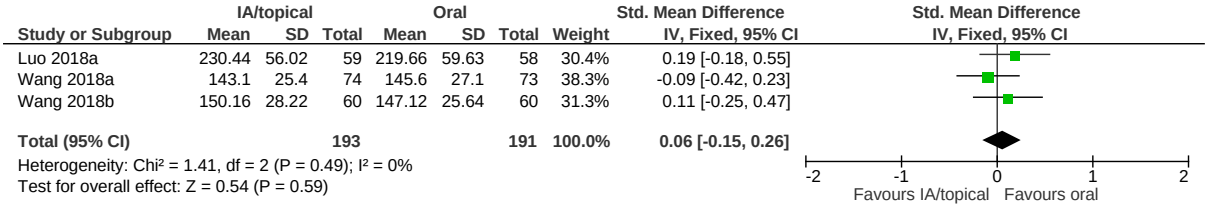
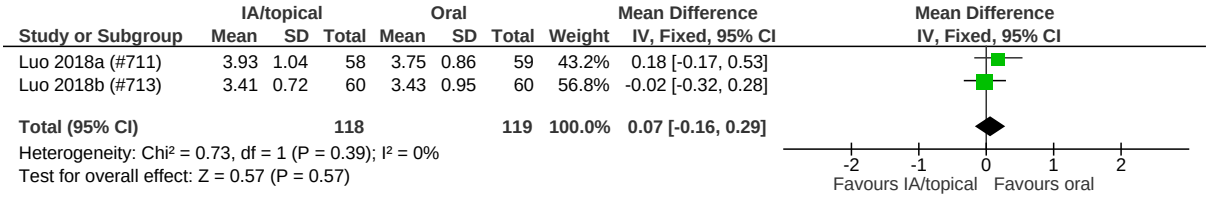


Figure 79: Length of stay



1

E.11.2 IV plus IA/topical versus IV

Figure 80: Quality of life: SF-36 MCS

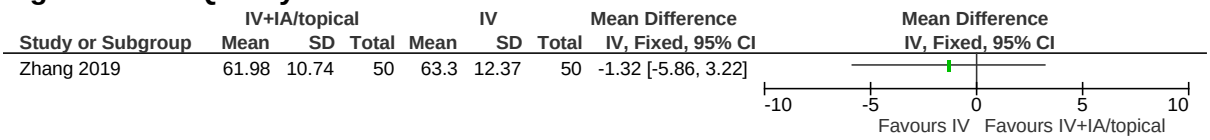


Figure 81: Quality of life: SF-36 PCS

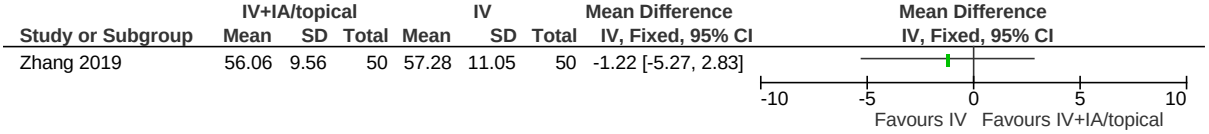


Figure 82: Transfusion

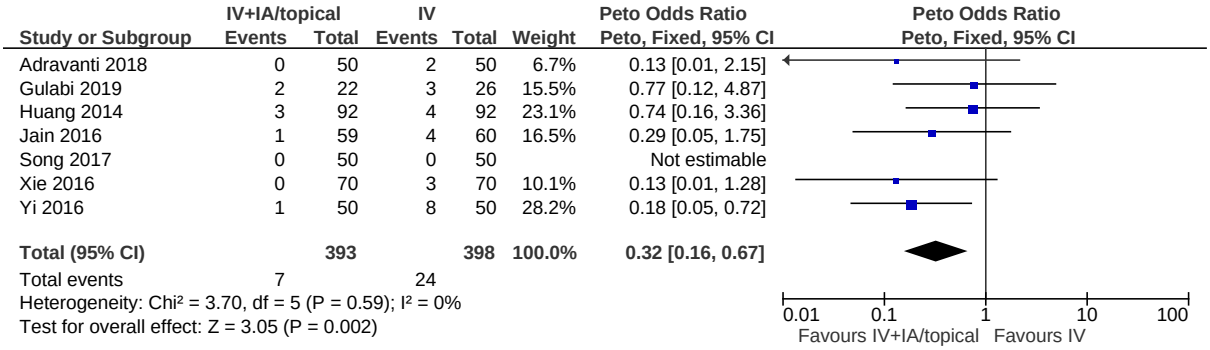


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Figure 83: Adverse events: DVT

Study or Subgroup	IV+IA/topical Events	Total	IV Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Adravanti 2018	0	50	0	50	11.2%	0.00 [-0.04, 0.04]
Gulabi 2019	2	22	2	26	5.4%	0.01 [-0.14, 0.17]
Huang 2014	0	92	1	92	20.7%	-0.01 [-0.04, 0.02]
Jain 2016	0	59	1	60	13.4%	-0.02 [-0.06, 0.03]
Song 2017	0	50	0	50	11.2%	0.00 [-0.04, 0.04]
Xie 2016	2	70	1	70	15.7%	0.01 [-0.03, 0.06]
Yi 2016	2	50	2	50	11.2%	0.00 [-0.08, 0.08]
Zhang 2019	10	50	9	50	11.2%	0.02 [-0.13, 0.17]
Total (95% CI)		**443**		**448**	**100.0%**	**0.00 [-0.02, 0.03]**
Total events	16		16			

Heterogeneity: Chi² = 1.56, df = 7 (P = 0.98); I² = 0%
Test for overall effect: Z = 0.06 (P = 0.95)

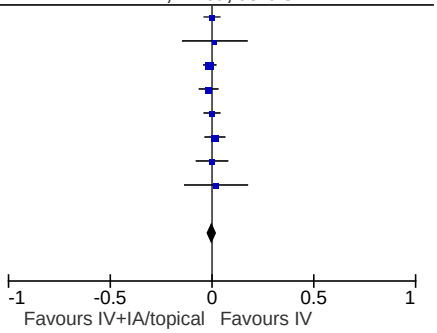


Figure 84: Blood loss via haemoglobin level after surgery

Study or Subgroup	IV+IA/topical Mean	SD	Total	IV Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Adravanti 2018	10.4	1.3	50	11.1	1.2	50	11.0%	-0.70 [-1.19, -0.21]
Gulabi 2019	2.87	0.98	22	3.16	0.82	26	10.7%	-0.29 [-0.81, 0.23]
Huang 2014	-2.73	0.55	92	-2.56	0.53	92	14.9%	-0.17 [-0.33, -0.01]
Jain 2016	-1.82	0.6	60	-1.14	0.5	59	14.6%	-0.68 [-0.88, -0.48]
Song 2017	-2.9	1.2	50	-2.4	1.05	50	11.7%	-0.50 [-0.94, -0.06]
Xie 2016	-3.36	0.78	70	-2.98	0.78	70	14.0%	-0.38 [-0.64, -0.12]
Yi 2016	10.238	1.68	50	9.28	1.228	50	9.9%	0.96 [0.38, 1.53]
Zhang 2019	-2.734	0.941	50	-1.682	0.65	50	13.3%	-1.05 [-1.37, -0.73]
Total (95% CI)			**444**			**447**	**100.0%**	**-0.39 [-0.69, -0.09]**

Heterogeneity: Tau² = 0.15; Chi² = 55.33, df = 7 (P < 0.00001); I² = 87%
Test for overall effect: Z = 2.52 (P = 0.01)

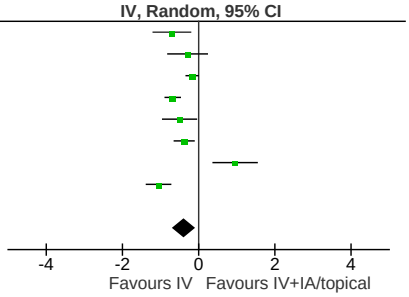


Figure 85: Total blood loss

Study or Subgroup	IV+IA/topical Mean	SD	Total	IV Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Gulabi 2019	772.22	322.07	22	848.871	224.1	26	15.5%	-0.28 [-0.85, 0.29]
Huang 2014	867	374	92	957	285	92	17.5%	-0.27 [-0.56, 0.02]
Jain 2016	385.368	182.5	59	590.69	191.1	60	16.9%	-1.09 [-1.48, -0.71]
Song 2017	946.13	162.21	50	972.29	268.8	50	16.9%	-0.12 [-0.51, 0.28]
Xie 2016	776.75	188.95	70	878.03	210	70	17.2%	-0.50 [-0.84, -0.17]
Zhang 2019	394.44	86.94	50	621.44	102.4	50	16.0%	-2.37 [-2.89, -1.86]
Total (95% CI)			**343**			**348**	**100.0%**	**-0.76 [-1.33, -0.19]**

Heterogeneity: Tau² = 0.47; Chi² = 63.78, df = 5 (P < 0.00001); I² = 92%
Test for overall effect: Z = 2.59 (P = 0.010)

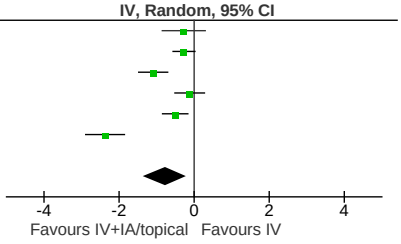


Figure 86: Postoperative bleeding

Study or Subgroup	IV+IA/topical Mean	SD	Total	IV Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Adravanti 2018	746.2	291.5	50	853.9	294.2	50	49.6%	-0.36 [-0.76, 0.03]
Yi 2016	127.2	113.52	50	126.8	91.91	50	50.4%	0.00 [-0.39, 0.40]
Total (95% CI)			**100**			**100**	**100.0%**	**-0.18 [-0.46, 0.10]**

Heterogeneity: Chi² = 1.69, df = 1 (P = 0.19); I² = 41%
Test for overall effect: Z = 1.26 (P = 0.21)

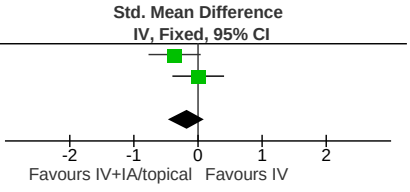
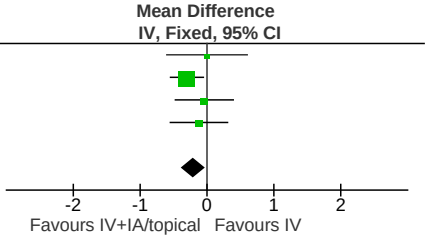


Figure 87: Length of stay

Study or Subgroup	IV+IA/topical Mean	SD	Total	IV Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Gulabi 2019	4.46	0.91	22	4.46	1.21	26	9.2%	0.00 [-0.60, 0.60]
Huang 2014	6.9	0.9	92	7.2	0.8	92	54.9%	-0.30 [-0.55, -0.05]
Xie 2016	4.39	1.28	70	4.43	1.33	70	17.8%	-0.04 [-0.47, 0.39]
Yi 2016	6.4	0.97	50	6.52	1.2	50	18.2%	-0.12 [-0.55, 0.31]
Total (95% CI)			**234**			**238**	**100.0%**	**-0.19 [-0.38, -0.01]**

Heterogeneity: Chi² = 1.72, df = 3 (P = 0.63); I² = 0%
Test for overall effect: Z = 2.08 (P = 0.04)



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E.12.1 IA/topical plus oral versus IA/topical

Figure 88: Transfusion

Study or Subgroup	IA/topical+oral Events	Total	IA/topical Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Cankaya 2017	0	50	3	50	0.13 [0.01, 1.28]

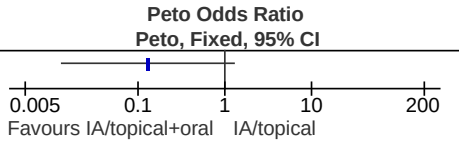


Figure 89: Adverse events: DVT

Study or Subgroup	IA/topical+oral Events	Total	IA/topical Events	Total	Risk Difference M-H, Fixed, 95% CI
Cankaya 2017	0	50	0	50	0.00 [-0.04, 0.04]

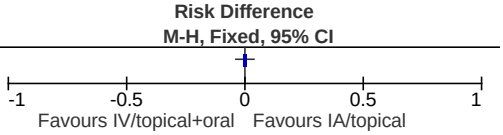


Figure 90: Blood loss via haemoglobin level after surgery

Study or Subgroup	IA/topical+oral Mean	SD	Total	IA/topical Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Cankaya 2017	10.8	1.4	50	9.9	1.3	50	0.90 [0.37, 1.43]

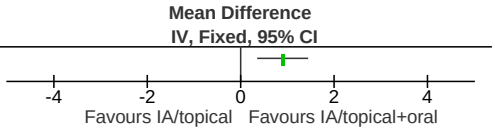


Figure 91: Total blood loss

Study or Subgroup	IA/topical+oral Mean	SD	Total	IA/topical Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Cankaya 2017	628	156	50	731	180	50	-103.00 [-169.02, -36.98]

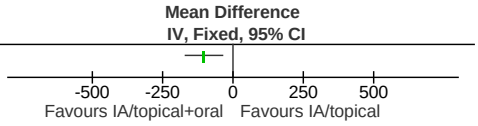
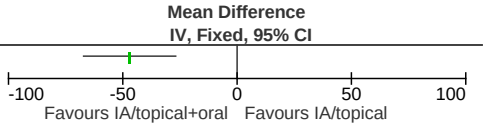


Figure 92: Postoperative bleeding

Study or Subgroup	IA/topical+oral Mean	SD	Total	IA/topical Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Cankaya 2017	81	38	50	128	62	50	-47.00 [-67.16, -26.84]



E.13.2 IV plus IA/topical versus IA/topical

Figure 93: Quality of life: SF-36 MCS

Study or Subgroup	IV+IA/topical Mean	SD	Total	IA/topical Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Zhang 2019	61.98	10.74	50	60.8	9.76	50	1.18 [-2.84, 5.20]

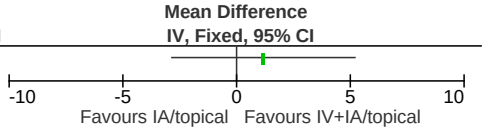


Figure 94: Quality of life: SF-36 PCS

Study or Subgroup	IV+IA/topical Mean	SD	Total	IA/topical Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Zhang 2019	56.06	9.56	50	55.02	8.85	50	1.04 [-2.57, 4.65]

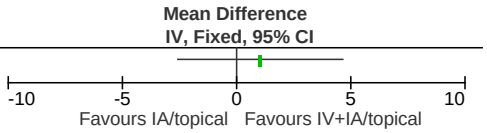


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Figure 95: Transfusion

Study or Subgroup	IV+IA/topical Events	Total	IA/topical Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Lin 2015	0	40	1	40	16.9%	0.14 [0.00, 6.82]
Song 2017	0	50	1	50	16.9%	0.14 [0.00, 6.82]
Xie 2016	0	70	4	70	66.2%	0.13 [0.02, 0.94]
Total (95% CI)		**160**		**160**	**100.0%**	**0.13 [0.03, 0.66]**
Total events	0		6			

Heterogeneity: Chi² = 0.00, df = 2 (P = 1.00); I² = 0%
Test for overall effect: Z = 2.47 (P = 0.01)

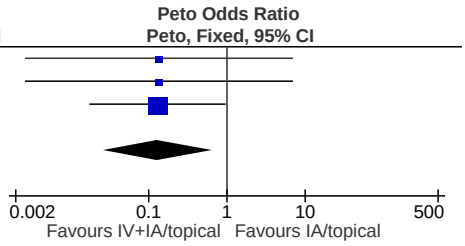


Figure 96: Adverse events: DVT

Study or Subgroup	IV+IA/topical Events	Total	IA/topical Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Lin 2015	0	40	0	40	19.0%	0.00 [-0.05, 0.05]
Song 2017	0	50	0	50	23.8%	0.00 [-0.04, 0.04]
Xie 2016	2	70	0	70	33.3%	0.03 [-0.02, 0.08]
Zhang 2019	10	50	8	50	23.8%	0.04 [-0.11, 0.19]
Total (95% CI)		**210**		**210**	**100.0%**	**0.02 [-0.02, 0.06]**
Total events	12		8			

Heterogeneity: Chi² = 1.80, df = 3 (P = 0.61); I² = 0%
Test for overall effect: Z = 0.90 (P = 0.37)

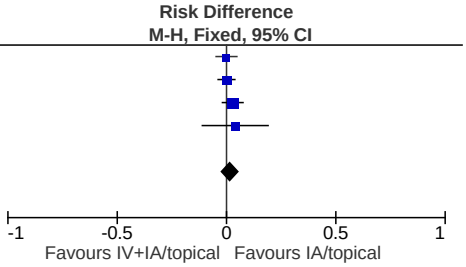


Figure 97: Blood loss via haemoglobin level after surgery

Study or Subgroup	IV+IA/topical Mean	SD	Total	IA/topical Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Lin 2015	-1.9	0.8	40	-2.4	0.9	40	24.2%	0.50 [0.13, 0.87]
Song 2017	-2.4	1.05	50	-2.5	1.2	50	21.6%	0.10 [-0.34, 0.54]
Xie 2016	-2.98	0.78	70	-3.89	0.72	70	29.1%	0.91 [0.66, 1.16]
Zhang 2019	-1.682	0.65	50	-2.214	1.09	50	25.1%	0.53 [0.18, 0.88]
Total (95% CI)			**210**			**210**	**100.0%**	**0.54 [0.21, 0.87]**

Heterogeneity: Tau² = 0.08; Chi² = 11.16, df = 3 (P = 0.01); I² = 73%
Test for overall effect: Z = 3.18 (P = 0.001)

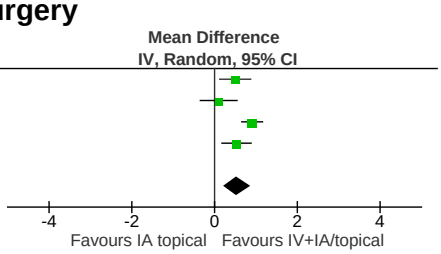


Figure 98: Total blood loss

Study or Subgroup	IV+IA/topical Mean	SD	Total	IA/topical Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Lin 2015	578.7	246.9	40	705.1	213.5	40	19.4%	-0.54 [-0.99, -0.10]
Song 2017	946.13	162.21	50	998.12	256.78	50	25.0%	-0.24 [-0.63, 0.15]
Xie 2016	776.75	188.95	70	905.07	237.7	70	33.7%	-0.59 [-0.93, -0.26]
Zhang 2019	394.44	86.94	50	501.34	106.79	50	21.8%	-1.09 [-1.51, -0.67]
Total (95% CI)			**210**			**210**	**100.0%**	**-0.60 [-0.80, -0.41]**

Heterogeneity: Chi² = 8.46, df = 3 (P = 0.04); I² = 65%
Test for overall effect: Z = 6.01 (P < 0.00001)

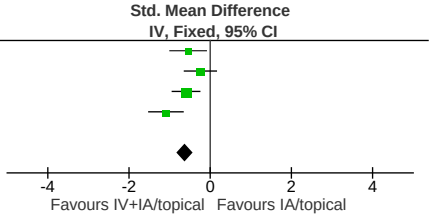
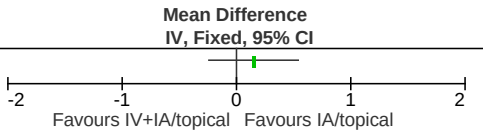


Figure 99: Length of stay

Study or Subgroup	IV+IA/topical Mean	SD	Total	IA/topical Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Xie 2016	4.39	1.28	70	4.24	1.07	70	0.15 [-0.24, 0.54]



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Appendix F: GRADE tables

Table 27: Clinical evidence profile: IA/topical versus no treatment

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IA/topical tranexamic acid	No treatment	Relative (95% CI)	Absolute		
Transfusion (follow-up ranged from while admitted in hospital to 2 months after surgery)												
10	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	88/539 (16.3%)	195/539 (36.2%)	RR 0.46 (0.37 to 0.56)	195 fewer per 1000 (from 159 fewer to 228 fewer)	⊕⊕⊕O MODERATE	CRITICAL
DVT (follow-up ranged from in hospital period to 1 year after surgery)												
8	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/394 (0.25%)	3/396 (0.76%)	See comment[2]	8 fewer per 1000 (from 8 more to 8 more)[3]	⊕⊕⊕O MODERATE	CRITICAL
Blood loss via haemoglobin level after surgery (follow-up ranges from 12 hours to 5 days after surgery; Better indicated by higher values)												
9	randomised trials	serious[1]	very serious[4]	no serious indirectness	serious[5]	none	453	453	-	MD 0.43 higher (0.11 lower to 0.97 higher)	⊕OOO VERY LOW	CRITICAL

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Total blood loss (follow-up ranges from 1 to 5 days after surgery; Better indicated by lower values)												
6	randomised trials	very serious[1]	very serious[4]	no serious indirectness	serious[5]	none	352	357	-	SMD 1.5 lower (2.3 to 0.71 lower)	⊕OOO VERY LOW	CRITICAL
Surgical bleeding (Better indicated by lower values)												
3	randomised trials	serious[1]	very serious[4]	no serious indirectness	very serious[5]	none	177	178	-	SMD 0.65 lower (1.51 lower to 0.2 higher)	⊕OOO VERY LOW	CRITICAL
Postoperative bleeding (follow-up 24 hours after surgery; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	47	48	-	MD 337.96 lower (435.16 to 240.76 lower)	⊕⊕⊕⊕ HIGH	IMPORTANT
Length of stay (Better indicated by lower values)												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	156	156	-	MD 0.06 lower (0.28 lower to 0.17 higher)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Risk difference used to analyse data due to very low event rates
[3] Risk difference utilised to calculate absolute effect
[4] Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects (DerSimonian and Laird) model was employed.
[5] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

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1 **Table 28: Clinical evidence profile: Oral versus no treatment**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral tranexamic acid	No treatment	Relative (95% CI)	Absolute		
Mortality at 30 days (follow-up 30 days after surgery)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/94 (0%)	0/95 (0%)	See comment[3]	0 fewer per 1000 (from 20 fewer to 20 more)[4]	⊕⊕OO LOW	CRITICAL
Transfusion (follow-up unclear)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	1/94 (1.1%)	3/95 (3.2%)	RR 0.34 (0.04 to 3.18)	21 fewer per 1000 (from 30 fewer to 69 more)	⊕OOO VERY LOW	CRITICAL
DVT (follow-up within 7 days of surgery)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	1/94 (1.1%)	0/95 (0%)	Peto OR 7.47 (0.15 to 376.39)	10 more per 1000 (from 20 fewer to 40 more)[4]	⊕OOO VERY LOW	CRITICAL
Blood loss via haemoglobin level after surgery (follow-up unclear; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	94	95	-	MD 0.8 higher (0.56 to 1.04 higher)	⊕⊕⊕O MODERATE	CRITICAL

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Total blood loss (follow-up unclear; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	94	95	-	MD 228 lower (293.22 to 162.78 lower)	⊕⊕⊕O MODERATE	CRITICAL
Length of stay (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	94	95	-	MD 0.1 higher (0.46 lower to 0.66 higher)	⊕⊕⊕O MODERATE	

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded one increment for imprecision as it is a small study with no events.
[3] Analysis via risk difference due to low event rate
[4] Absolute effect calculated using risk difference
[5] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 29: Clinical evidence profile: IV versus no treatment

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IV tranexamic acid**	**No treatment**	**Relative (95% CI)**	**Absolute**		
Mortality at 30 days (follow-up within 90 days of surgery)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	0/50 (0%)	0/50 (0%)	See comment[4]	0 fewer per 1000 (from 40 fewer to 40 more)[5]	⊕OOO VERY LOW	CRITICAL

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Transfusion (follow-up ranged from in-hospital period to 90 days after surgery)												
15	randomised trials	very serious[1]	very serious[6]	no serious indirectness	no serious imprecision	none	74/699 (10.6%)	192/625 (30.7%)	See comment[4]	140 fewer per 1000 (from 210 fewer to 80 fewer)[5]	⊕OOO VERY LOW	CRITICAL
DVT (follow-up ranged from 2 days to 1 year after surgery)												
14	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	13/571 (2.3%)	7/504 (1.4%)	See comment[4]	0 fewer per 1000 (from 20 fewer to 20 more)[5]	⊕⊕⊕O MODERATE	CRITICAL
Blood loss via haemoglobin level after surgery (follow-up ranges from 1 to 5 days after surgery; Better indicated by higher values)												
11	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[7]	none	526	512	-	MD 0.53 higher (0.38 to 0.67 higher)	⊕⊕OO LOW	CRITICAL
Total blood loss (follow-up either unclear or 3 days after surgery; Better indicated by lower values)												
8	randomised trials	serious[1]	very serious[6]	no serious indirectness	no serious imprecision	none	437	436	-	SMD 1.33 lower (2.1 to 0.56 lower)	⊕OOO VERY LOW	CRITICAL
Surgical bleeding (Better indicated by lower values)												
3	randomised trials	serious[1]	very serious[6]	no serious indirectness	very serious[7]	none	178	178	-	SMD 0.88 lower (2.62 lower to 0.86 higher)	⊕OOO VERY LOW	CRITICAL
Postoperative bleeding (follow-up 24 hours after surgery; Better indicated by lower values)												

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1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	48	48	-	MD 393.16 lower (483.74 to 302.58 lower)	⊕⊕⊕⊕ HIGH	IMPORTANT
Length of stay (Better indicated by lower values)												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	156	156	-	MD 0.03 lower (0.24 lower to 0.19 higher)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Considered indirect due to the study follow-up period extending beyond 30 days
[3] Study considered imprecise because it is small and there were no events in either treatment group
[4] Results analysed using risk difference due to low event rates
[5] Risk difference utilised to calculate absolute effect
[6] Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects (DerSimonian and Laird) model was employed.
[7] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 30: Clinical evidence profile: IA/topical versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IA/topical tranexamic acid**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Mortality at 30 days (follow-up 15 days after surgery)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/30 (0%)	0/30 (0%)	See comment[3]	0 fewer per 1000 (from 60 fewer to 60 more)[4]	⊕OOO VERY LOW	CRITICAL
Quality of life within 6 weeks (follow-up 3 months after surgery; measured with: EuroQol Index (EQ-5D); Better indicated by higher values)												

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2	randomised trials	very serious[1]	no serious inconsistency	serious[5]	no serious imprecision	none	99	91	-	MD 0.06 lower (0.14 lower to 0.03 higher)	⊕OOO VERY LOW	CRITICAL
Transfusion (follow-up ranged from 3 days to 3 months of surgery)												
24	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	92/1347 (6.8%)	245/1242 (19.7%)	RR 0.36 (0.29 to 0.45)	126 fewer per 1000 (from 108 fewer to 140 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
DVT (follow-up ranged from 5 days to 3 months after surgery)												
23	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[6]	none	20/1228 (1.6%)	23/1200 (1.9%)	See comment[3]	0 fewer per 1000 (from 10 fewer to 10 more)[4]	⊕OOO VERY LOW	CRITICAL
Blood loss via haemoglobin level after surgery (follow-up ranges from 24 hours to 5 days after surgery; Better indicated by higher values)												
18	randomised trials	serious[1]	very serious[7]	no serious indirectness	no serious imprecision	none	923	930	-	MD 1.04 higher (0.8 to 1.29 higher)	⊕OOO VERY LOW	CRITICAL
Total blood loss (follow-up ranges from 1 to 5 days after surgery or until hospital discharge; Better indicated by lower values)												
17	randomised trials	serious[1]	serious[7]	no serious indirectness	no serious imprecision	none	874	743	-	SMD 0.94 lower (1.16 to 0.72 lower)	⊕⊕OO LOW	CRITICAL
Surgical bleeding (Better indicated by lower values)												
3	randomised trials	no serious risk of bias	very serious[7]	no serious indirectness	serious[6]	none	121	122	-	SMD 0.25 lower (0.93 lower to 0.44	⊕OOO VERY LOW	CRITICAL

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										higher)		
Postoperative bleeding (follow-up ranges from 36 hours to 4 days after surgery; Better indicated by lower values)												
5	randomised trials	no serious risk of bias	serious[7]	no serious indirectness	no serious imprecision	none	197	197	-	SMD 0.94 lower (1.35 to 0.53 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Length of stay (Better indicated by lower values)												
10	randomised trials	serious[1]	serious[7]	no serious indirectness	no serious imprecision	none	554	554	-	MD 0.01 lower (0.2 lower to 0.18 higher)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Study considered imprecise because it is small and there were no events in either treatment group
[3] Results analysed using risk difference due to low event rates
[4] Risk difference used to calculate absolute effect
[5] Considered indirect evidence as the outcome was outside of the specified timepoint
[6] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[7] Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects (DerSimonian and Laird) model was employed.

Table 31: Clinical evidence profile: IV versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IV tranexamic acid**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Mortality at 30 days (follow-up either during hospital stay or within 15 days of surgery)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	0/184 (0%)	0/106 (0%)	See comment[2]	0 fewer per 1000 (from 30 fewer to 30	⊕⊕⊕O MODERATE	CRITICAL

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										more)[3]		
Transfusion (follow-up ranged from 24 hours to 6 months after surgery)												
44	randomised trials	serious[4]	serious[5]	no serious indirectness	no serious imprecision	none	253/1819 (13.9%)	537/1564 (34.3%)	RR 0.39 (0.32 to 0.49)	209 fewer per 1000 (from 175 fewer to 233 fewer)	⊕⊕OO LOW	CRITICAL
DVT (follow-up ranged from in hospital period to 6 months after surgery)												
45	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	28/1777 (1.6%)	26/1579 (1.6%)	See comment[2]	0 fewer per 1000 (from 10 fewer to 10 more)[3]	⊕⊕⊕O MODERATE	CRITICAL
Acute coronary syndrome (follow-up during hospital stay)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	1/154 (0.65%)	0/76 (0%)	RD 0 (-0.02 to 0.04)[2]	10 more per 1000 (from 20 fewer to 40 more)[3]	⊕⊕⊕O MODERATE	CRITICAL
Blood loss via haemoglobin level after surgery (follow-up ranges from 1 day after surgery to discharge from hospital; Better indicated by lower values)												
32	randomised trials	serious[4]	serious[5]	no serious indirectness	serious[7]	none	1321	1168	-	MD 0.64 higher (0.49 to 0.78 higher)	⊕OOO VERY LOW	CRITICAL
Total blood loss (follow-up ranges from 1 to 6 days after surgery or until hospital discharge; Better indicated by lower values)												
33	randomised trials	serious[4]	serious[5]	no serious indirectness	no serious imprecision	none	1419	1205	-	SMD 0.84 lower (1 to 0.68 lower)	⊕⊕OO LOW	CRITICAL

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Surgical bleeding (Better indicated by lower values)												
13	randomised trials	serious[4]	very serious[5]	no serious indirectness	serious[7]	none	389	355	-	SMD 0.61 lower (0.97 to 0.25 lower)	⊕OOO VERY LOW	CRITICAL
Postoperative bleeding (follow-up ranges from 48 hours of surgery to in-hospital period; Better indicated by lower values)												
13	randomised trials	serious[4]	very serious[5]	no serious indirectness	no serious imprecision	none	386	376	-	SMD 1.38 lower (1.87 to 0.89 lower)	⊕OOO VERY LOW	IMPORTANT
Length of stay (Better indicated by lower values)												
14	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	684	588	-	MD 0.09 lower (0.18 to 0.01 lower)	⊕⊕⊕⊕ HIGH	IMPORTANT

[1] Outcome considered imprecise due to low event rate
[2] Analysis by risk difference due to low events rate
[3] Absolute effect calculated using risk difference
[4] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[5] Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects (DerSimonian and Laird) model was employed.
[6] No explanation was provided
[7] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 32: Clinical evidence profile: Oral versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oral tranexamic acid**	**Placebo**	**Relative (95% CI)**	**Absolute**		

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Transfusion (follow-up ranged from in hospital period to 3 months after surgery)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	17/206 (8.3%)	45/200 (22.5%)	RR 0.38 (0.23 to 0.64)	139 fewer per 1000 (from 81 fewer to 173 fewer)	⊕⊕⊕O MODERATE	CRITICAL
DVT (follow-up ranged from 2 weeks to 3 months after surgery)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/206 (0.49%)	2/200 (1%)	See comment[2]	10 fewer per 1000 (from 30 fewer to 20 more)[3]	⊕⊕⊕O MODERATE	CRITICAL
Blood loss via haemoglobin level after surgery (follow-up ranges from 1 to 3 days after surgery; Better indicated by lower values)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	206	200	-	MD 0.47 higher (0.37 to 0.57 higher)	⊕⊕OO LOW	CRITICAL
Total blood loss (follow-up 3 days after surgery; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	66	60	-	SMD 1.13 lower (1.51 to 0.75 lower)	⊕⊕⊕O MODERATE	CRITICAL
Surgical bleeding (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	40	40	-	MD 21.5 lower (34.91 to 8.09 lower)	⊕⊕OO LOW	CRITICAL
Length of stay (Better indicated by lower values)												

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1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	40	40	-	MD 0.1 lower (0.69 to 0.49 lower)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Analysed using risk difference due to low events rates
[3] Absolute effect calculated using risk difference
[4] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 33: Clinical evidence profile: IV plus IA/topical versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IV+IA/topical tranexamic acid**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Transfusion (follow-up while admitted in hospital)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/190 (1.6%)	49/190 (25.8%)	RR 0.08 (0.03 to 0.22)	237 fewer per 1000 (from 201 fewer to 250 fewer)	⊕⊕⊕O MODERATE	CRITICAL
DVT (follow-up ranged from 2 weeks to 6 months after surgery)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/190 (1.6%)	1/190 (0.53%)	See comment[2]	10 more per 1000 (from 20 fewer to 40 more)[3]	⊕⊕⊕O MODERATE	CRITICAL
Blood loss via haemoglobin level after surgery (follow-up 3 days after surgery; Better indicated by lower values)												
4	randomised	serious[1]	no serious	no serious	no serious	none	190	190	-	MD 1.45 higher (1.19	⊕⊕⊕O	CRITICAL

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	trials		inconsistency	indirectness	imprecision					to 1.7 higher)	MODERATE	
Total blood loss (follow-up 3 days after surgery or in-hospital period; Better indicated by lower values)												
4	randomised trials	serious[1]	serious[4]	no serious indirectness	no serious imprecision	none	190	190	-	MD 294.44 lower (405.92 to 182.97 lower)	⊕⊕OO LOW	CRITICAL
Surgical bleeding (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	50	-	MD 94.4 lower (132.77 to 56.03 lower)	⊕⊕⊕O MODERATE	CRITICAL
Postoperative bleeding (follow-up 3 days after surgery; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	100	100	-	SMD 0.92 lower (1.21 to 0.63 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Length of stay (Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	100	100	-	MD 0.33 lower (0.76 lower to 0.1 higher)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Analysed via risk difference due to low event rates
[3] Absolute effect calculated using risk difference
[4] Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects (DerSimonian and Laird) model was employed.

Table 34: Clinical evidence profile: IA/topical versus IV

Quality assessment							No of patients		Effect	Quality	Importance

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No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IA/topical tranexamic acid**	**IV tranexamic acid**	**Relative (95% CI)**	**Absolute**		
Mortality at 30 days (follow-up ranged from 15 to 30 days after surgery)												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1/137 (0.73%)	0/132 (0%)	See comment[3]	10 more per 1000 (from 20 fewer to 40 more)[4]	⊕OOO VERY LOW	CRITICAL
Quality of life (mental component score) within 6 weeks (follow-up unclear; measured with: SF-36 ; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	50	50	-	MD 2.5 lower (6.87 lower to 1.87 higher)	⊕⊕OO LOW	CRITICAL
Quality of life (physical component score) within 6 weeks (follow-up unclear; measured with: SF-36 ; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	50	50	-	MD 2.26 lower (6.18 lower to 1.66 higher)	⊕⊕OO LOW	CRITICAL
Transfusion (follow-up ranged from in hospital period to 3 months after surgery)												
32	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	147/2051 (7.2%)	123/1927 (6.4%)	See comment[3]	10 more per 1000 (from 10 fewer to 20 more)[4]	⊕⊕⊕⊕ HIGH	CRITICAL
DVT (follow-up ranged from within 96 hours of surgery to 1 year after surgery)												

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29	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/1897 (0.95%)	26/1876 (1.4%)	See comment[3]	0 fewer per 1000 (from 10 fewer to 0 more)[4]	⊕⊕⊕⊕ HIGH	CRITICAL
Acute myocardial infarction (follow-up unclear)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	1/47 (2.1%)	0/42 (0%)	Peto OR 6.64 (0.13 to 336.89)	-	⊕OOO VERY LOW	CRITICAL
Blood loss via haemoglobin level after surgery (follow-up ranges from 12 hours to 5 days after surgery; Better indicated by lower values)												
19	randomised trials	serious[1]	serious[6]	no serious indirectness	no serious imprecision	none	1302	1256	-	MD 0.03 higher (0.09 lower to 0.14 higher)	⊕⊕OO LOW	CRITICAL
Total blood loss (follow-up ranges from 1 to 5 days after surgery; Better indicated by lower values)												
26	randomised trials	serious[1]	serious[6]	no serious indirectness	no serious imprecision	none	1386	1420	-	SMD 0.12 lower (0.27 lower to 0.04 higher)	⊕⊕OO LOW	CRITICAL
Surgical bleeding (Better indicated by lower values)												
6	randomised trials	serious[1]	very serious[6]	no serious indirectness	very serious[5]	none	585	587	-	SMD 0.1 higher (0.73 lower to 0.92 higher)	⊕OOO VERY LOW	CRITICAL
Postoperative bleeding (follow-up ranges from 24 to 96 hours after surgery; Better indicated by lower values)												

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3	randomised trials	no serious risk of bias	serious[6]	no serious indirectness	serious[5]	none	135	137	-	SMD 0.09 higher (0.33 lower to 0.5 higher)	⊕⊕OO LOW	IMPORTANT
Length of stay (Better indicated by lower values)												
11	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	652	660	-	MD 0.04 higher (0.05 lower to 0.12 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Outcome considered imprecise because of the small number of participants and a single event
[3] Results analysed using risk difference due to low event rates
[4] Absolute effect calculated using risk difference
[5] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[6] Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects (DerSimonian and Laird) model was employed.

Table 35: Clinical evidence profile: Oral versus IV

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oral tranexamic acid**	**IV tranexamic acid**	**Relative (95% CI)**	**Absolute**		
Mortality at 30 days (follow-up 30 days after surgery)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	0/60 (0%)	0/60 (0%)	Not estimable[2]	0 fewer per 1000 (from 30 fewer to 30 more)[3]	⊕⊕⊕O MODERATE	CRITICAL
Transfusion (follow-up ranged from in hospital period to 1 month after surgery)												

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7	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	26/428 (6.1%)	28/434 (6.5%)	RR 0.94 (0.56 to 1.56)	4 fewer per 1000 (from 28 fewer to 36 more)	⊕OOO VERY LOW	CRITICAL
DVT (follow-up ranged from 30 days to 3 months after surgery)												
7	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/468 (0.21%)	5/477 (1%)	See comment[2]	10 fewer per 1000 (from 20 fewer to 10 more)[3]	⊕⊕⊕O MODERATE	CRITICAL
Blood loss via haemoglobin level after surgery (follow-up ranges from 1 day after surgery to hospital discharge; Better indicated by lower values)												
8	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	468	477	-	MD 0.01 higher (0.07 lower to 0.09 higher)	⊕⊕⊕O MODERATE	CRITICAL
Total blood loss (follow-up ranges from 1 to 3 days after surgery or until hospital discharge; Better indicated by lower values)												
7	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	328	337	-	SMD 0.0 higher (0.16 lower to 0.15 higher)	⊕⊕⊕O MODERATE	CRITICAL
Surgical bleeding (Better indicated by lower values)												
2	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	100	100	-	MD 0.46 higher (6.43 lower to 7.34 higher)	⊕⊕⊕O MODERATE	CRITICAL
Length of stay (Better indicated by lower values)												

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5	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	214	223	-	MD 0.02 lower (0.17 lower to 0.12 higher)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Results considered imprecise due to zero events in both intervention groups
[2] Analysis using risk difference due to low event rates
[3] Absolute effect calculate through risk difference
[4] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[5] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 36: Clinical evidence profile: IA/topical versus oral

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IA/topical tranexamic acid**	**Oral tranexamic acid**	**Relative (95% CI)**	**Absolute**		
Mortality at 30 days (follow-up 30 days after surgery)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	0/192 (0%)	0/192 (0%)	See comment[2]	0 fewer per 1000 (from 20 fewer to 20 more)[3]	⊕⊕⊕O MODERATE	CRITICAL
Transfusion (follow-up ranged from in hospital period to 2 weeks after surgery)												
5	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	32/393 (8.1%)	25/394 (6.3%)	RR 1.28 (0.78 to 2.11)	18 more per 1000 (from 14 fewer to 70 more)	⊕OOO VERY LOW	CRITICAL
DVT (follow-up ranged from 2 weeks to 3 months after surgery)												

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5	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[6]	none	0/391 (0%)	2/393 (0.51%)	See comment[2]	10 fewer per 1000 (from 20 fewer to 10 more)[3]	⊕⊕OO LOW	CRITICAL
Blood loss via haemoglobin level after surgery (follow-up ranges from 2 days after surgery until hospital discharge; Better indicated by lower values)												
5	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	391	393	-	MD 0.04 lower (0.13 lower to 0.05 higher)	⊕⊕⊕O MODERATE	CRITICAL
Total blood loss (follow-up ranges from 3 days after surgery or until hospital discharge; Better indicated by lower values)												
4	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	251	253	-	SMD 0.15 higher (0.02 lower to 0.33 higher)	⊕⊕⊕O MODERATE	CRITICAL
Surgical bleeding (Better indicated by lower values)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	193	191	-	SMD 0.06 higher (0.15 lower to 0.26 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Length of stay (Better indicated by lower values)												
2	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	118	119	-	MD 0.07 higher (0.16 lower to 0.29 higher)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Outcome considered very imprecise because of the small number of participants and zero events
[2] Analysis via risk difference due to low event rates
[3] Absolute effect calculated using risk difference
[4] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

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[5] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[6] Outcome considered imprecise because of the small number of participants and two events

Table 37: Clinical evidence profile: IV plus IA/topical versus IV

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV+IA/topical tranexamic acid	IV tranexamic acid	Relative (95% CI)	Absolute		
Quality of life (mental component score) within 6 weeks (follow-up unclear; measured with: SF-36; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	50	50	-	MD 1.32 lower (5.86 lower to 3.22 higher)	⊕⊕OO LOW	CRITICAL
Quality of life (physical component score) within 6 weeks (follow-up unclear; measured with: SF-36; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	50	50	-	MD 1.22 lower (5.27 lower to 2.83 higher)	⊕⊕OO LOW	CRITICAL
Transfusion (follow-up ranged from while admitted in hospital to 6 weeks after surgery)												
7	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/393 (1.8%)	24/398 (6%)	Peto OR 0.32 (0.16 to 0.67)	41 fewer per 1000 (from 20 fewer to 51 fewer)	⊕⊕⊕O MODERATE	CRITICAL
DVT (follow-up ranged from in hospital period to 6 months after surgery)												

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8	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	16/443 (3.6%)	16/448 (3.6%)	See comment[3]	0 fewer per 1000 (from 20 fewer to 30 more)[4]	⊕⊕⊕O MODERATE	CRITICAL
Blood loss via haemoglobin level after surgery (follow-up ranges from 3 to 5 days after surgery; Better indicated by lower values)												
8	randomised trials	serious[1]	very serious[5]	no serious indirectness	serious[2]	none	444	447	-	MD 0.39 lower (0.69 to 0.09 lower)	⊕OOO VERY LOW	CRITICAL
Total blood loss (follow-up ranges from 3 to 5 days after surgery; Better indicated by lower values)												
6	randomised trials	serious[1]	very serious[5]	no serious indirectness	serious[2]	none	343	348	-	SMD 0.76 lower (1.33 to 0.19 lower)	⊕OOO VERY LOW	CRITICAL
Postoperative bleeding (follow-up ranges from within 3 days of surgery to during in hospital period; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	100	100	-	SMD 0.18 lower (0.46 lower to 0.1 higher)	⊕⊕OO LOW	IMPORTANT
Length of stay (Better indicated by lower values)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	234	238	-	MD 0.19 lower (0.38 to 0.01 lower)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[3] Data analysed using risk difference due to low event rates

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[4] Absolute effect calculated using risk difference
[5] Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects (DerSimonian and Laird) model was employed.

Table 38: Clinical evidence profile: IA/topical plus oral versus IA/topical

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IA/topical+oral tranexamic acid	IA/topical tranexamic acid	Relative (95% CI)	Absolute		
Transfusion (follow-up within 3 days of surgery)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/50 (0%)	3/50 (6%)	OR 0.13 (0.01 to 1.28)	52 fewer per 1000 (from 59 fewer to 16 more)	⊕OOO VERY LOW	CRITICAL
DVT (follow-up 1 year after surgery)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	0/50 (0%)	0/50 (0%)	See comment[4]	0 fewer per 1000 (from 40 fewer to 40 more)[5]	⊕⊕OO LOW	CRITICAL
Blood loss via haemoglobin level after surgery (follow-up 3 days after surgery; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	50	50	-	MD 0.9 higher (0.37 to 1.43 higher)	⊕⊕OO LOW	CRITICAL
Total blood loss (follow-up 3 days after surgery; Better indicated by lower values)												

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1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	50	50	-	MD 103 lower (169.02 to 36.98 lower)	⊕⊕OO LOW	CRITICAL
Postoperative bleeding (follow-up 3 days after surgery; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	50	50	-	MD 47 lower (67.16 to 26.84 lower)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[3] Outcome considered imprecise because of the small number of participants and zero events
[4] Analysed via risk difference due to low event rate
[5] Absolute effect calculated using risk difference

Table 39: Clinical evidence profile: IV plus IA/topical versus IA/topical

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IV+IA/topical tranexamic acid**	**IA/topical tranexamic acid**	**Relative (95% CI)**	**Absolute**		
Quality of life (mental component score) within 6 weeks (follow-up unclear; measured with: SF-36; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	50	50	-	MD 1.18 higher (2.84 lower to 5.2 higher)	⊕⊕OO LOW	CRITICAL
Quality of life (physical component score) within 6 weeks (follow-up unclear; measured with: SF-36; range of scores: 0-100; Better indicated by higher values)												

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1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	50	50	-	MD 1.04 higher (2.57 lower to 4.65 higher)	⊕⊕OO LOW	CRITICAL
Transfusion (follow-up while admitted in hospital or within 5 days of surgery)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/160 (0%)	6/160 (3.8%)	OR 0.13 (0.03 to 0.66)	32 fewer per 1000 (from 12 fewer to 36 fewer)	⊕⊕⊕O MODERATE	CRITICAL
DVT (follow-up 3 or 6 months after surgery)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	12/210 (5.7%)	8/210 (3.8%)	See comment[4]	20 more per 1000 (from 20 fewer to 60 more)[5]	⊕⊕OO LOW	CRITICAL
Blood loss via haemoglobin level after surgery (follow-up ranges from 3 to 5 days after surgery; Better indicated by lower values)												
3	randomised trials	serious[1]	very serious[6]	no serious indirectness	serious[2]	none	210	210	-	MD 0.54 higher (0.21 to 0.87 higher)	⊕OOO VERY LOW	CRITICAL
Total blood loss (follow-up ranges from 3 to 5 days after surgery or until hospital discharge; Better indicated by lower values)												
3	randomised trials	serious[1]	serious[6]	no serious indirectness	serious[2]	none	210	210	-	SMD 0.60 lower (0.8 to 0.41 lower)	⊕OOO VERY LOW	CRITICAL
Length of stay (Better indicated by lower values)												
1	randomised	serious[1]	no serious	no serious	very serious[2]	none	70	70	-	MD 0.15 higher (0.24 lower to	⊕OOO	IMPORTANT

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	trials		inconsistency	indirectness						0.54 higher)	VERY LOW	

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[3] Outcome considered imprecise due to small number of participants and low event rate
[4] Analysis using risk difference due to low event rate
[5] Absolute effect calculated using risk difference
[6] Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects (DerSimonian and Laird) model was employed.

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Appendix G: Health economic evidence selection

Figure 100: Flow chart of health economic study selection for the guideline

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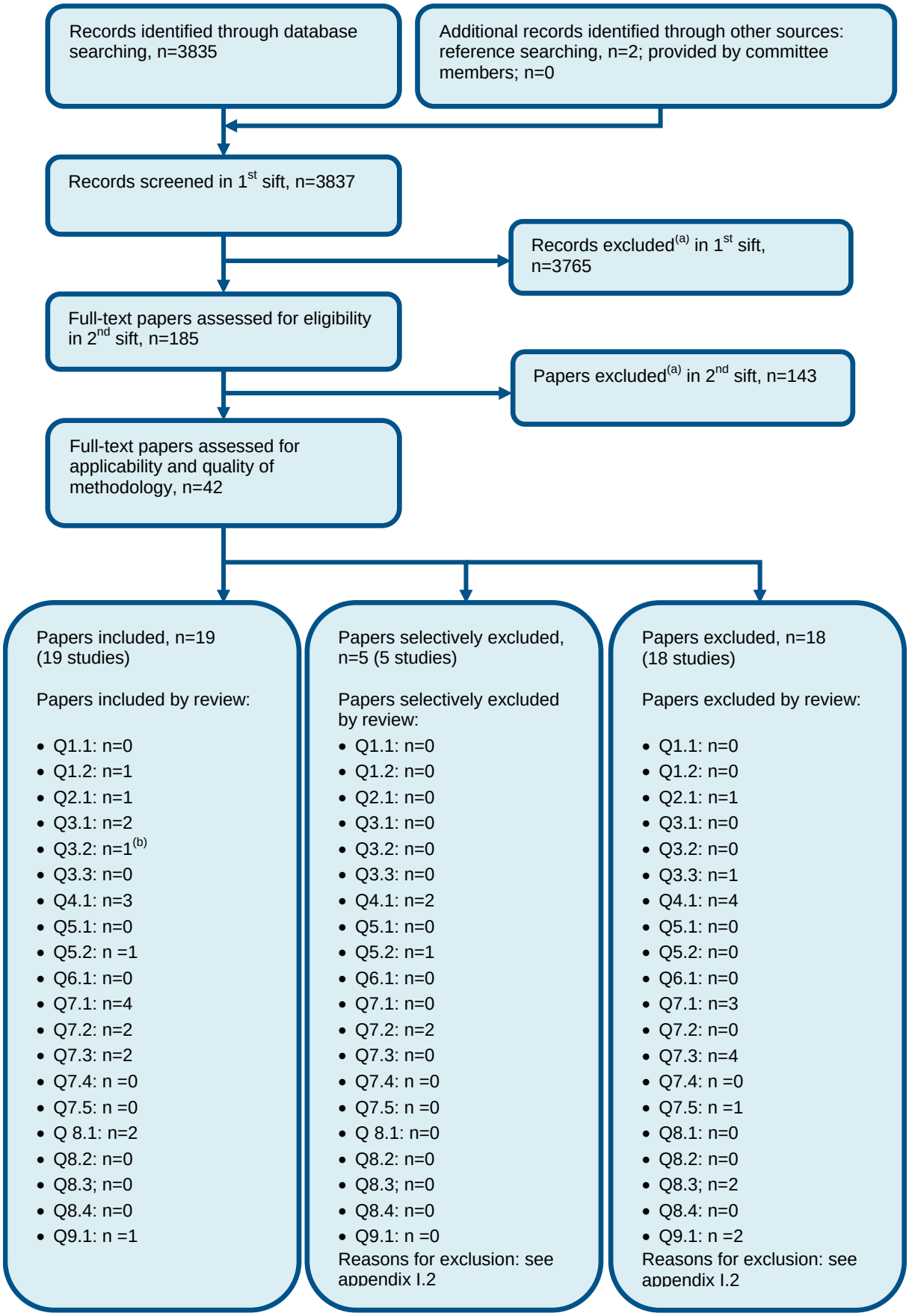

a) Non-relevant population, intervention, comparison, design or setting; non-English language
b) One study was applicable to both Q3.1 and Q3.2

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Appendix H: Health economic evidence tables

Study	Alshryda 2013[13]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost utility analysis **Study design:** Within-trial analysis (TRANX-K RCT) **Approach to analysis:** Analysis of individual level outcomes (transfusion, OKS and EQ-5D) and resource use. Unit costs applied. Logistic regression model **Perspective:** UK NHS **Follow-up**: 3months **Discounting:** Costs: N/A; Outcomes: N/A	**Population:** People undergoing primary unilateral cemented TKR **Patient characteristics:** **N** = 157 **Mean age** of; Intervention 1 = 67.1(SD:10.2) Intervention 2 = 65.5(SD:9.6) **Male percentage** of; Intervention 1 = 56% Intervention 2 = 38% **Intervention 1:** Placebo **Intervention 2:** Topical (intra-articular tranexamic acid)	**Total costs (mean per patient):** Intervention 1: £1450 Intervention 2: £1117 Incremental (2−1): Tranexamic acid saves £333 (95% CI: -630 to -37; p=0.028) **Currency & cost year:** Reported and presented here as British Pound Sterling 2008 **Cost components incorporated:** Blood transfusions, length of stay, tranexamic acid	**QoL[(a)] (mean per patient):** Baseline,3 months and difference between time points: Intervention 1: 0.431, 0.780 and 0.349 Intervention 2: 0.377, 0.705 and 0.328 Incremental improvement over time (2−1): Tranexamic acid gave 0.021 fewer per person Incremental QALYs (mean per patient) (2-1): [(b)] Tranexamic acid gave 0.0053 fewer per person	**ICER (Intervention 1 versus Intervention 2) Placebo cost £63,429 per QALY gained compared to tranexamic acid[(b)]** **Analysis of uncertainty:** Costs were bootstrapped due to skewness of the cost data. The results showed a similar cost saving of £333 for the use of tranexamic acid. A logistic regression model was run to control for the baseline difference in sex. Sex did not improve the model fit.
Data sources				
Health outcomes: Outcomes of individual participants recorded during the trial **Quality-of-life weights:** EQ-5D was recorded as an outcome but not used in any cost-effectiveness calculations **Cost sources:** Not referenced but may be hospital level data				
Comments				
Source of funding: Department of Trauma and Orthopaedics and the Department of Research and Development, University Hospitals of North Tees and Hartlepool **Limitations:** Costs of complications during the trial were not accounted for; unit costs are not referenced; outcomes are from a single RCT rather than a systematic review; large difference in baseline EQ-5D values between arms				
Overall applicability:[(c)] Partially applicable **Overall quality:**[(d)] Potentially serious limitations				

Abbreviations: EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; OKS: Oxford Knee Score; QALYs: quality-adjusted life years; RCT: randomised control trial; TRANX-K: Topical (intra-articular) tranexamic acid reduces blood loss and transfusion rates following total knee replacement: a randomized controlled trial

(a) Measured from EQ-5D. Baseline values are different so conclusions about QoL should be treated with caution

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(b) ICER was not reported in the study. ICER calculated here has been adjusted for the 3 month time horizon by dividing the incremental QoL by 4
(c) Directly applicable / Partially applicable / Not applicable
(d) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**Alshryda 2013[12]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost utility analysis **Study design:** Within-trial analysis (TRANX-H RCT) **Approach to analysis:** Analysis of individual level outcomes (transfusion, OHS and EQ-5D) and resource use. Unit costs applied. Logistic regression model **Perspective:** UK NHS **Follow-up**: 3months **Discounting:** Costs: N/A; Outcomes: N/A	**Population:** People undergoing primary unilateral THR **Patient characteristics:** **N** = 161 **Mean age** of; Intervention 1 = 63(SD:11) Intervention 2 = 66(SD:9) **Male percentage** of; Intervention 1 = 41% Intervention 2 = 38% **Intervention 1:** Placebo **Intervention 2:** Topical (intra-articular tranexamic acid	**Total costs (mean per patient):** Intervention 1: £1526 Intervention 2: £1221 Incremental (2−1): Tranexamic acid saves £305 per person (95% CI -610 to 0; p=0.05) **Currency & cost year:** Reported and presented here as British Pound Sterling 2010 **Cost components incorporated:** Blood transfusions, length of stay, tranexamic acid	**QoL[(a)] (mean per patient):** Baseline, 3 months and difference between time points: Intervention 1: 0.205, 0.686 and 0.481 Intervention 2: 0.340, 0.715 and 0.375 Incremental improvement over time (2−1): Tranexamic acid gave 0.106 fewer per person Incremental QALYs (mean per patient) (2-1): [(b)] Tranexamic acid gave 0.0265 fewer per person	**ICER (Intervention 1 versus Intervention 2) Placebo cost £11,509 per QALY gained compared to tranexamic acid[(b)]** **Analysis of uncertainty:** Costs were bootstrapped due to skewness of the cost data. The results showed a similar cost saving of £305 for the use of tranexamic acid. A logistic regression model showed that the difference in pre-operative haemoglobin levels was likely to overestimate the effect of tranexamic acid in reducing transfusions.
Data sources				
Health outcomes: Outcomes of individual participants recorded during the trial **Quality-of-life weights:** EQ-5D was recorded as an outcome but not used in any cost-effectiveness calculations **Cost sources:** Not referenced but may be hospital level data				
Comments				
Source of funding: Department of Trauma and Orthopaedics and the Department of Research and Development, University Hospitals of North Tees and Hartlepool **Limitations:** Costs of complications during the trial were not accounted for; unit costs are not referenced; outcomes are from a single RCT rather than a systematic review; large difference in baseline EQ-5D values between arms.				
Overall applicability:[(c)] Partially applicable		**Overall quality:**[(d)] Potentially serious limitations		

Abbreviations: EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; OHS: Oxford Hip Score; QALYs: quality-adjusted life years; RCT: randomised control trial; TRANX-H: Topical (intra-articular) tranexamic acid reduces blood loss and transfusion rates following total hip replacement: a randomized controlled trial

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(a) Measured from EQ-5D. Baseline values are different so conclusions about QoL should be treated with caution.
(b) ICER was not reported in the study. ICER calculated here has been adjusted for the 3 month time horizon by dividing the incremental QoL by 4
(c) Directly applicable / Partially applicable / Not applicable
(d) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**Davies 2018[50]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost comparison **Study design:** Retrospective cohort analysis with multivariate regression **Approach to analysis:** Individual patient data on resource use and outcomes were taken from hospital databases **Perspective:** Welsh NHS **Follow-up** 90 days **Discounting:** Costs: N/A; Outcomes: N/A	**Population:** All primary hip or knee replacement procedures by a single surgeon **Patient characteristics:** N: 673 Median age: 68 years Male: 43.7% **Intervention 1:** No tranexamic acid **Intervention 2:** Intravenous tranexamic acid	**Total costs (mean per patient):** Intervention 1: £947 (min)[(a)], £2749.09 (max) Intervention 2: £879.11 (min), £2593.19 (max) Incremental (2−1): Tranexamic acid saves £67.89 (min) and £155.90 (max) (95% CI: NR; p=NR) **Currency & cost year:** Year is not explicitly stated but 'most up-to-date estimates were used' in pounds sterling and study was published in 2018. **Cost components incorporated:** Maximum and minimum bed days, blood transfusion, tranexamic acid.	**Median drop in haemoglobin from before to after surgery (g/L):** Intervention 1: 26 Intervention 2: 21 Incremental (2-1): Tranexamic acid saves 5g/L of haemoglobin **Blood transfusion after surgery:** Intervention 1: 17.6% Intervention 2: 6.3% Incremental (2-1): 11.3% fewer transfusions with tranexamic acid	Tranexamic acid is cost saving for hip and knee replacements. **Analysis of uncertainty:** Two estimates of cost difference are given to account for the minimum and maximum cost of a bed day. Tranexamic acid was cost saving in both analyses.
Data sources				
Health outcomes: Only used as part of cost calculations; sourced retrospectively from hospital databases. **Quality-of-life weights:** N/A. **Cost sources:** British National Formulary, National Health Service Wales Informatics Service.				
Comments				
Source of funding: No specific grant or funding received **Limitations:** Observational data from a single study used, although data is adjusted; no health outcomes or adverse events are factored into cost calculations.				
Overall applicability:[(b)] Partially applicable **Overall quality:**[(c)] Potentially serious limitations				

Abbreviations: g/L: grams per litre; max: maximum; min: minimum; NR: not reported; N/A: not applicable; 95% CI: 95% confidence interval;

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(a) A minimum and maximum cost estimate is given as a sensitivity analysis to the cost of a bed day
(b) Directly applicable / Partially applicable / Not applicable
(c) Minor limitations / Potentially serious limitations / Very serious limitations

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Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 40: Studies excluded from the clinical review

Study	Exclusion reason
Abildgaard 2016[2]	Incorrect study design
Abrisham 2018[3]	Not in English
Abrishami 2009[4]	Unclear whether the population was people having primary joint replacement surgery
Ahmed 2018[8]	Unclear whether the population was people having primary joint replacement surgery
Akgul 2016[9]	Incorrect study design
Alipour 2013[10]	Unclear if the population is undergoing primary joint replacement surgery
Alshryda 2011[14]	Systematic review does not include shoulder joint replacement. Included studies checked for this review.
Alshryda 2014[15]	Systematic review does not include shoulder joint replacement. Included studies checked for this review.
Alvarez 2008[17]	Unclear if the population is undergoing primary joint replacement surgery
Alvarez 2019[16]	Not in English
Arora 2018[19]	Incorrect study design
Bagsby 2015[20]	Incorrect study design
Balasubramanian 2016[21]	Unclear if the population is undergoing primary joint replacement surgery
Box 2018[26]	Systematic review does not include knee or hip joint replacement. Included studies checked for this review.
Cao 2015[32]	Not in English
Cao 2018[31]	Incorrect interventions
Castro-menendez 2016[33]	Incorrect study design
Çavuşoğlu 2015[34]	Not in English
Chai 2015[35]	Not in English
Charoencholvanich 2011[36]	Unclear whether the population was people having primary joint replacement surgery
Chen 2016[40]	Systematic review does not include knee or shoulder joint replacement. Included studies checked for this review.
Chen 2016[43]	Systematic review does not include knee or shoulder joint replacement. Included studies checked for this review.
Chen 2017[41]	Systematic review does not include hip or shoulder joint replacement. Included studies checked for this review.
Chen 2018[37]	Not in English
Cui 2015[47]	Not in English
Dai 2018[49]	Systematic review does not include hip or shoulder joint replacement. Included studies checked for this review.
De Napoli 2016[51]	Unable to acquire

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Study	Exclusion reason
Dhillon 2011[52]	Inappropriate comparison
Drosos 2016[57]	Unclear whether the population was people having primary joint replacement surgery
Duan 2017[58]	Not in English
Durgut 2019[59]	Incorrect study design
Ellis 2004[61]	Unclear whether the population was people having primary joint replacement surgery
Engel 2001[62]	Unclear whether the population was people having primary joint replacement surgery
Fernandez-cortinas 2017[63]	Not in English
Fillingham 2018[65]	Systematic review does not include shoulder joint replacement. Included studies checked for this review.
Fillingham 2018[66]	Systematic review does not include shoulder joint replacement. Included studies checked for this review.
Franchini 2018[67]	Systematic with a different population. Included studies checked for this review.
Fraval 2017[68]	Unclear whether the population was people having primary joint replacement surgery
Friedman 2016[69]	Incorrect study design
Fu 2013[70]	Systematic review does not include hip or shoulder joint replacement. Included studies checked for this review.
Fu 2016[71]	Systematic review does not include hip or shoulder joint replacement. Included studies checked for this review.
Gandhi 2013[72]	Systematic review does not include shoulder joint replacement. Included studies checked for this review.
Gao 2015[73]	incorrect comparison
Georgiev 2018[80]	Systematic review does not include shoulder joint replacement. Included studies checked for this review.
Ghijselings 2015[81]	Unable to acquire
Gianakos 2018[82]	Systematic review does not include shoulder joint replacement. Included studies checked for this review.
Gill 2009[83]	Not review population
Gomez-barbero 2019[86]	Not in English
Guo 2018[93]	Systematic review does not include hip or shoulder joint replacement. Included studies checked for this review.
Hanna 2016[94]	Systematic review does not include shoulder or knee joint replacement. Included studies checked for this review.
He 2015[96]	Systematic review does not include hip or shoulder joint replacement. Included studies checked for this review.
He 2017[95]	Systematic review does not include hip or knee joint replacement. Included studies checked for this review.
Hegde 2013[97]	Incorrect study design
Hiippala 1995[98]	Unclear how tranexamic acid was administered
Hiippala 1997[99]	Unclear whether the population was people having primary joint replacement surgery
Hill 2018[100]	Study protocol
Ho 2003[101]	Systematic review does not include shoulder joint replacement. Included studies checked for this review.
Hou 2017[102]	Not in English
Hourlier 2015[103]	Inappropriate comparison

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Study	Exclusion reason
Hu 2018[105]	Not in English
Huang 2015[108]	Not in English
Huang 2016[106]	Unclear whether the population was people having primary joint replacement surgery
Hynes 2003[110]	Incorrect study design
Iseki 2018[113]	Incorrect study design
Ishii 2015[115]	Incorrect study design
Jansen 1999[117]	Unclear how tranexamic acid was administered
Jiang 2016[119]	Systematic review does not include hip or shoulder joint replacement. Included studies checked for this review.
Johansson 2005[120]	Unclear whether the population was people having primary joint replacement surgery
Jordan 2019[121]	Unclear whether the population was people having primary joint replacement surgery
Kang 2017[123]	Incorrect study design
Karaaslan 2014[124]	Abstract
Karam 2014[125]	Incorrect study design
Kelley 2014[128]	Incorrect study design
Kim 2017[133]	Incorrect study design
Kim 2017[130]	Incorrect study design
Kim 2018[132]	All people received both interventions randomised by knee
Konig 2013[134]	Incorrect study design
Kuo 2018[136]	Systematic review does not include hip or knee joint replacement. Included studies checked for this review.
Kwok 2018[137]	Incorrect study design
Lanoiselee 2018[139]	Inappropriate comparison
Lee 2017[141]	Incorrect study design
Lei 2017[146]	Not review population
Li 2016[149]	Systematic review does not include knee or shoulder joint replacement. Included studies checked for this review.
Li 2017[148]	Systematic review does not include shoulder joint replacement. Included studies checked for this review.
Li 2017[150]	Systematic review does not include shoulder joint replacement. Included studies checked for this review.
Li 2017[151]	Not in English
Lin 2011[153]	Incorrect study design
Lin 2016[152]	Systematic review does not include hip or shoulder joint replacement. Included studies checked for this review.
Liu 2017[157]	Systematic review does not include knee or shoulder joint replacement. Included studies checked for this review.
Liu 2017[158]	Systematic review does not include hip or shoulder joint replacement. Included studies checked for this review.
Liu 2018[156]	Unclear whether the population was people having primary joint replacement surgery
Lopez-hualda 2018[159]	Not in English
Lopez-picado 2017[160]	Incorrect study design
Ma 2014[163]	Not in English
Macgillivray 2011[164]	Unclear whether the population was people having primary joint

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Study	Exclusion reason
	replacement surgery
Machin 2014[165]	Incorrect study design
March 2013[168]	Incorrect study design
Marra 2016[169]	Incorrect study design
Meena 2017[174]	Systematic review does not include hip or shoulder joint replacement. Included studies checked for this review.
Mi 2017[178]	Systematic review does not include hip or shoulder joint replacement. Included studies checked for this review.
Mi 2017[177]	Systematic review does not include hip or shoulder joint replacement. Included studies checked for this review.
Min 2015[179]	Not in English
Moskal 2016[181]	Systematic review does not include knee or shoulder joint replacement. Included studies checked for this review.
Moskal 2018[182]	Systematic review does not include hip or shoulder joint replacement. Included studies checked for this review.
Mutsuzaki 2012[184]	Incorrect study design
Ni 2016[189]	Not in English
Nielsen 2016[190]	Unclear whether the population was people having primary joint replacement surgery
Oremus 2014[194]	Incorrect interventions
Panteli 2013[199]	Systematic review does not include shoulder or hip joint replacement. Included studies checked for this review.
Peng Zhang 2017[202]	Systematic review does not include shoulder joint replacement. Included studies checked for this review.
Perreault 2017[204]	Incorrect study design
Pertlíček 2015[205]	Not in English
Pinzon-florez 2015[207]	Not in English
Pongcharoen 2016[208]	Incorrect study design
Prabhu 2015[209]	Unclear how tranexamic acid was administered
Prakash 2018[211]	Unclear whether the population was people having primary joint replacement surgery
Rajesparan 2009[212]	Incorrect study design
Raviraj 2012[213]	Unclear whether the population was people having primary joint replacement surgery
Sadigursky 2016[216]	Incorrect study design
Sadigursky 2018[217]	Literature review. Studies checked for inclusion in this review.
Sanz-reig 2018[218]	Incorrect study design
Sarzaeem 2014[219]	Unclear whether the population was people having primary joint replacement surgery
Seo 2013[220]	Unclear whether the population was people having primary joint replacement surgery
Seol 2016[221]	Incorrect study design
Shang 2016[222]	Systematic review does not include shoulder joint replacement. Included studies checked for this review.
Shen 2015[223]	Unclear whether the population was people having primary joint replacement surgery
Shin 2017[224]	Systematic review does not include hip or shoulder joint replacement. Included studies checked for this review.
Singh 2010[226]	Incorrect study design

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Study	Exclusion reason
Soni 2014[228]	Unclear whether the population was people having primary joint replacement surgery
Sridharan 2017[229]	Systematic review does not include knee or shoulder joint replacement. Included studies checked for this review.
Sridharan 2018[230]	NMA does not include knee or shoulder joint replacement. Included studies checked for this review.
Sridharan 2018[231]	NMA does not include hip or shoulder joint replacement. Included studies checked for this review.
Subramanyam 2018[234]	Unclear whether the population was people having primary joint replacement surgery
Sukeik 2011[235]	Systematic review does not include knee or shoulder joint replacement. Included studies checked for this review.
Sun 2016[237]	Not in English
Sun 2016[238]	Systematic review does not include shoulder or knee joint replacement. Included studies checked for this review.
Sun 2017[236]	Systematic review does not include knee or hip joint replacement. Included studies checked for this review.
Sun 2017[239]	Systematic review does not include shoulder or knee joint replacement. Included studies checked for this review.
Tan 2013[240]	Systematic review does not include hip or shoulder joint replacement. Included studies checked for this review.
Tavares Sanchez-monge 2018[242]	Not English language
Thipparampall 2017[243]	Not review population
Tzatzairis 2016[244]	Unclear whether the population was people having primary joint replacement surgery
Ueno 2016[245]	Incorrect study design
Volquind 2016[250]	Inclusion included those with RA
Wang 2014[257]	Systematic review does not include shoulder or hip joint replacement. Included studies checked for this review.
Wang 2015[258]	Systematic review does not include shoulder or hip joint replacement. Included studies checked for this review.
Wang 2015[260]	Not in English
Wang 2015[252]	Systematic review does not include shoulder or knee joint replacement. Included studies checked for this review.
Wang 2017[262]	Systematic review does not include shoulder or hip joint replacement. Included studies checked for this review.
Wang 2017[261]	Systematic review does not include hip or shoulder joint replacement. Included studies checked for this review.
Wei 2015[265]	Systematic review does not include shoulder joint replacement. Included studies checked for this review.
Weng 2016[266]	Systematic review does not include shoulder or hip joint replacement. Included studies checked for this review.
Wind 2013[267]	Incorrect study design
Wind 2014[268]	Incorrect study design
Wong 2009[269]	Unclear whether the population was people having primary joint replacement surgery
Wu 2015[272]	Systematic review does not include hip or shoulder joint replacement. Included studies checked for this review.
Wu 2017[271]	Systematic review does not include shoulder or knee joint replacement. Included studies checked for this review.

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Study	Exclusion reason
Wu 2017[273]	Systematic review does not include hip or shoulder joint replacement. Included studies checked for this review.
Wu 2018[274]	Incorrect interventions
Xie 2017[275]	Systematic review does not include shoulder joint replacement. Included studies checked for this review.
Xu 2015[277]	Systematic review does not include shoulder or knee joint replacement. Included studies checked for this review.
Yamasaki 2005[278]	Unclear whether the population was people having primary joint replacement surgery
Yang 2012[281]	Systematic review does not include hip or shoulder joint replacement. Included studies checked for this review.
Yang 2017[279]	Systematic review does not include shoulder joint replacement. Included studies checked for this review.
Yu 2015[284]	Systematic review does not include shoulder or hip joint replacement. Included studies checked for this review.
Yu 2017[283]	Systematic review does not include knee or hip joint replacement. Included studies checked for this review.
Yuan 2016[286]	Systematic review does not include shoulder or hip joint replacement. Included studies checked for this review.
Yue 2015[288]	Systematic review does not include shoulder or hip joint replacement. Included studies checked for this review.
Zhang 2007[293]	Not in English
Zhang 2014[301]	Systematic review does not include shoulder or hip joint replacement. Included studies checked for this review.
Zhang 2015[292]	Not in English
Zhang 2016[298]	Systematic review does not include shoulder or knee joint replacement. Included studies checked for this review.
Zhang 2017[295]	Systematic review does not include shoulder or hip joint replacement. Included studies checked for this review.
Zhang 2017[299]	Systematic review does not include shoulder or knee joint replacement. Included studies checked for this review.
Zhang 2017[300]	Systematic review with different interventions. Included studies checked for this review.
Zhang 2017[296]	Systematic review does not include shoulder joint replacement. Included studies checked for this review.
Zhang 2017[297]	Not review population
Zhang 2017[294]	Systematic review does not include shoulder or knee joint replacement. Included studies checked for this review.
Zhao-Yu 2014[304]	Systematic review does not include shoulder or hip joint replacement. Included studies checked for this review.
Zhao 2016[306]	Not in English
Zhou 2013[308]	Systematic review does not include knee or shoulder joint replacement. Included studies checked for this review.
Zhu 2017[309]	Systematic review does not include knee or shoulder joint replacement. Included studies checked for this review.
Zohar 2004[310]	Unclear whether the population was people having primary joint replacement surgery

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I.21 Excluded health economic studies

2 **Table 41: Studies excluded from the health economic review**

Reference	Reason for exclusion
Irisson 2012[112]	More applicable UK analyses were available, [12 13 50] so this study was selectively excluded.
Vigna-Taglianti 2014[249]	More applicable UK analyses were available, [12 13 50] so this study was selectively excluded.
Chen 2015[39]	Inadequate adjustment of data
Goyal 2016[89]	Inadequate adjustment of data
McGoldrick 2015[173]	Inadequate adjustment of data
Panchmatia 2012[198]	Inadequate adjustment of data

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