Title: Clinical effectiveness and safety of transcatheter aortic valve implantation (TAVI) for aortic stenosis: a systematic review and meta-analysis

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Contributions of authors

ZL drafted the review protocol with contributions from RD, EK, SB, DB, GB, SR and CC. SB conducted the electronic database searches. ZL, RD, EK, DB and GB screened the search results and carried out study selection. EK, GB, ZL, DB and RD extracted the data from the relevant studies. Quality assessment of the studies was performed by RD and checked by ZL. Data analyses and interpretation of analyses were conducted by ZL, CC and RD. SR and MD provided clinical input; MD also contributed to the revision of the final draft. Final report was drafted by ZL with contributions from RD, EK, SB, DB, GB and CC. All authors read and approved the final version of the report.

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1 DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

AF	Atrial fibrillation
AKI	Acute kidney injury
AMI	Acute myocardial infarction
AMSTAR	Assessing the Methodological Quality of Systematic Reviews checklist
AR	Aortic regurgitation
AS	Arterial stenosis
AVR	Aortic valve replacement
AVR	Arterial valve stenosis
B&BC EAC	Birmingham & Brunel Consortium External Assessment Centre
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CE Mark	"Conformité Européene" or European Conformity Marking indicating compliance with essential requirements of the relevant European health, safety and environmental protection legislation
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
GRADE	Grading of Recommendations Assessment, Development and Evaluation
EuroSCORE	European System for Cardiac Operative Risk Evaluation. It is a method of calculating predicted operative mortality for patients undergoing cardiac surgery
EQ-5D	EuroQol five dimensions questionnaire. It is a standardized instrument for measuring generic health status.
FDA	(United States) Food and Drugs Administration
HR	Hazard ratio
HR-QoL	Health related quality of life
IPAC	Interventional Procedures Advisory Committee
IPG	Interventional procedures guidance
ITT	Intention to treat
KCCO	Kansas City Cardiomyopathy Questionnaire (range 0–100; higher better)
LogEuroSCORE	The logistic European System for Cardiac Operative Risk Evaluation. It measures patient risk at the time of surgery using a logistic-regression equation on a 0 to 100% scale (higher scores indicating greater risk; a score higher than 20% indicates very high surgical risk)
LVEF	Left ventricular ejection fraction
LVD	Left ventricular dysfunction
MD	Mean difference
MI	Myocardial infarction
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICOR	National Institute for Cardiovascular Outcomes Research
NOS	Newcastle-Ottawa Scale
NOTION trial	Nordic Aortic Valve Intervention trial
NYHA	New York Heart Association heart failure classification. It is used to classify the severity of breathlessness from class I, in which the patient has no limitation in daily physical activity, to class IV, in which the patient is breathless at rest

OR	Odds ratio
PARTNER trial	Placement of AoRTic TraNscathetER Valve Trial
PCI	Percutaneous coronary intervention
PPI	Permanent pacemaker implantation
PPM	Prosthesis-patient mismatch
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	Prospective register of systematic reviews
QoL	Quality of life
RCT	Randomised controlled trial
RR	Risk ratio or relative risk
SAVR	Surgical aortic valve replacement
SD	Standard deviation
SF-12	Short Form-12 General Health Survey
STACCATO	A Prospective, Randomised Trial of Transapical Transcatheter Aortic Valve Implantation (TAVI) vs. Surgical Aortic Valve Replacement (AVR) in Operable Elderly Patients With Aortic Stenosis
STS	Society of Thoracic Surgeons score. It is used to predict mortality risk and is on a scale of 0% to 100% with higher scores indicating greater surgical risk
SU-AVR	Sutureless surgical aortic valve replacement
TA	Transapical
TAVI	Transcatheter aortic valve implantation
TAVR	Transcatheter aortic valve replacement
TF	Transfemoral
TH	Transthoracic
TIA	Transient ischemic attack
TS	Transsubclavian
US CoreValve	Medtronic U.S. CoreValve High Risk trial
vs	versus
WMD	Weighted mean difference

2 EXECUTIVE SUMMARY

2.1 Background

Aortic stenosis is a narrowing of the aortic valve that is usually progressive, causing impaired outflow of blood from the heart to the circulation and leading to left ventricular hypertrophy and heart failure. Traditional treatment for aortic stenosis is open heart surgical aortic valve replacement (SAVR). Treatment with medications can only ease some symptoms. Transcatheter aortic valve implantation (TAVI) is a procedure for the treatment of severe aortic stenosis. It aims to provide a less invasive alternative to SAVR, avoiding the need for cardiopulmonary bypass. It may be an alternative to SAVR in patients for whom SAVR is not suitable, or who are at high risk of serious complications of SAVR.

In March 2012, based on a rapid overview of the medical literature and specialist opinion, the National Institute for Health and Clinical Excellence (NICE) issued an Interventional Procedures Guidance (IPG421) on the safety and efficacy of TAVI for patients with aortic stenosis (NICE 2012). Since the publication of IPG421, publications from clinical trials and registries have provided additional evidence regarding the indications, efficacy and safety of this procedure. Also, there have been significant developments in the technology, and new generation TAVI devices have become available for use with one or more delivery approaches to treat severe aortic stenosis, with the potential to expand the use to lower risk patient populations, such as younger and healthier patients.

2.2 Objectives

The objective of this systematic review and meta-analysis is to assess the clinical effectiveness and safety of transcatheter aortic valve implantation for patients with severe aortic stenosis, to support NICE in updating the current guidance IPG421.

2.3 Methods

The search strategy was designed to identify published literature. The Cochrane Library, CRD Centre for Reviews and Dissemination Databases (DARE, NHS EED and HTA), MEDLINE, MEDLINE in Process, EMBASE, ZETOC and PubMed were searched from March 2011 to 8th August 2016.

Published studies reporting the efficacy and safety of TAVI compared with standard therapies or no intervention for severe aortic stenosis were sought, including systematic reviews, randomised controlled trials, matched or non-matched studies. Non-comparative studies reporting longer term or important rare safety outcomes which were not covered by the comparative studies were also sought.

Double sifting was used for study selection. Quality assessment was conducted by one reviewer and checked by another. Quality of systematic reviews was assessed using the AMSTAR checklist. The Cochrane Collaboration's risk of bias tool was used to assess the quality of randomised and non-randomised controlled studies. The Newcastle-Ottawa Scale was used to assess risk of bias in cohort or case-control studies.

Data were analysed by the categories of surgical risk levels: unsuitable for SAVR; high risk but suitable for SAVR; intermediate or low risk. Meta-analyses were conducted where appropriate. Dichotomous data were expressed as risk ratio (RR), odds ratio (OR), or hazard ratio (HR) for survival data. Continuous data were expressed as weighted mean difference (WMD) between groups. The 95% confidence interval (CI) was used for these parameters.

2.4 Results

The key evidence on the efficacy and safety of TAVI for patients for whom SAVR is considered to be unsuitable was from one good quality randomised controlled trial (RCT) with 358 patients and a maximum follow-up of 5 years (PARTNER 1B). The key evidence for patients for whom SAVR is considered suitable but poses a high risk was from two good quality RCTs with a total of 1494 patients and a maximum follow-up of 5 years (PARTNER 1A; US CoreValve). For patients for whom SAVR is considered suitable and not to pose a high risk, the key evidence was from 4 recent systematic reviews with a total of 24838 patients and a maximum follow-up of 3 years (Gargiulo et al. 2016; Siemieniuk et al. 2016; Khan et al. 2016; Arora et al. 2016), two of which were considered of good quality (Gargiulo et al. 2016; Siemieniuk et al. 2016).

2.4.1 In patients for whom SAVR is considered unsuitable

One RCT (PARTNER 1B) compared TAVI with standard medical management in 358 patients considered to be unsuitable for SAVR, with longest follow-up of 5 years. The study had the following key findings.

- Compared with medical therapy, TAVI was associated with a significantly lower mortality rate of both all-cause and cardiac-cause at follow-up of 1, 2, 3 and 5 years: HR 0.58 (95% CI 0.36 to 0.92) at 1 year, HR 0.5 (95% CI 0.39 to 0.65) at 2 years, HR 0.53 (95% CI 0.41 to 0.68) at 3 years, and HR 0.5 (95% CI 0.39 to 0.65) at 5 years for all-cause mortality; HR 0.44 (95% CI 0.32 to 0.60) at 2 years, HR 0.41 (95% CI 0.30 to 0.56) at 3 years and HR 0.41 (95% CI 0.31 to 0.55) at 5 years for cardiac mortality.

- The TAVI group had a lower proportion of patients in NYHA classes III/IV at 1 and 2 years and higher proportion of patients in NYHA classes I and II at 3 and 5 years.

- TAVI was superior to medical therapy in quality of life at least for 1 year, with KCCQ summary score being 26 points higher, SF-12 physical score 5.7 points higher and SF-12 mental health 6.4 points higher than the control at 1 year ($p<0.001$ for all the three comparisons).

- There was no statistically significant differences in 30-day mortality between the two groups (TAVI vs medical therapy: 2.6% vs 5.9%, $p=0.09$).

- TAVI was associated with statistically significantly higher risk of stroke at 1 year (11.2% versus 5.5%, $p<0.001$), 2 years (HR 2.79; 95% CI 1.25 to 6.22) and 3 years (HR 2.81; 95% CI 1.26 to 6.26), with the difference becoming non-significant at 5 years.

- TAVI was associated with statistically significantly higher risk of major bleeding up to 1 year of follow-up (24.2% versus 14.9%, $p=0.04$), with the difference becoming non-significant between the treatment groups at 2 years (28.9% versus 20.1%, $p=0.09$), and then statistically significantly lower in the TAVI group at 3 years (HR 1.69; 95% CI 1.06 to 2.70).

- The risk of major vascular complications, reported for 3 years of follow-up only, was statistically significantly higher in the TAVI group than in the medical treatment group (HR 8.27; 95% CI 2.92 to 23.44).

- Patients with TAVI had a statistically significantly lower risk of re-hospitalisation due to aortic stenosis or TAVI complication at 1 year (27.0% versus 53.9%, $p<0.001$), 2 years (HR 0.41; 95%CI 0.30 to 0.58), 3 years (43.5% versus 75.5%, $p<0.0001$) and 5 years (47.6% versus 87.3%, $p<0.0001$).

- No statistically significant difference between the treatments in the risk of permanent pacemaker implantation, myocardial infarction, acute kidney injury and endocarditis at 1, 2 and 3 years.

2.4.2 In patients for whom SAVR is considered suitable but poses a high risk

Two RCTs (PARTNER 1A; US CoreValve) compared TAVI with SAVR in a total of 1494 patients. The longest follow-up was 5 years. Meta-analysis was conducted to combine results from the 2 RCTs where appropriate. The studies had the following key findings.

- A time-to-event analysis showed no statistically significant differences between TAVI and SAVR in hazard of death of any cause up to 5 years of follow-up (TAVI vs SAVR: HR 0.97; 95% CI 0.83 to 1.12).

- TAVI performed either via the transfemoral (TF) route or the transapical (TA) route, showed no statistically significant difference from SAVR in all-cause mortality at follow-up of 1, 2, and 5 years, and in cardiovascular mortality at 1 and 2 years.

- Patients who underwent TAVI had a statistically significantly better NYHA classification profile up to 6 months, which ceased at later follow-up points up to 5 years.

- Compared with SAVR, TAVI resulted in a statistically significant improvement in quality of life (QoL) as measured by summary SF-12 at 30 days but not 6 months and 1 year, and TAVI via the TF route was associated with a statistically significant improvement in QoL as measured by EQ-5D and KCCQ at 30 days, which were no longer significant at 6 months or 1 year. There were no statistically significant differences between non-TF TAVI and SAVR in QoL at any of the follow-up points.

- There were no statistically significant differences between the treatments in risk of all-cause mortality or cardiovascular mortality at 30 days, and rates of stroke, major vascular complications and myocardial infarction at all the follow-up points.

- TAVI had significantly better outcomes than SAVR in terms of the overall incidence and severity of prosthesis-patient mismatch up to 2 years of follow-up.

- There were higher rates of moderate or severe total aortic regurgitation with TAVI than SAVR at all follow-up time points up to 3 years: RR 10.07 (95% CI 4.40 to 23.02) at 30 days, RR

4.99 (95% CI 2.25 to 11.04) at 1 year, RR 15.13 (95% CI 2.02 to 113.36) at 2 years, and RR 19.93 (95% CI 1.19 to 332.48) at 3 years.

- Incidence of major bleeding reported in the PARTNER 1A trial at all the follow-up time points up to 5 years favoured the TAVI group: RR 0.48 (95% CI 0.32 to 0.71) at 30 days; RR 0.58 (95% CI 0.42 to 0.80) at 1 year; RR 0.64 (95% CI 0.48 to 0.85) at 2 years; RR 0.73 (95% CI 0.57 to 0.95) at 5 years). Whereas the US CoreValve trial showed no statistically significant differences between TAVI and SAVR at all the follow-up points up to 3 years.

- Compared with SAVR, TAVI using a self-expanding valve was associated with a statistically significantly higher risk of permanent pacemaker implantation at all the follow-up points up to 3 years: RR 3.09 (95% CI 2.01 to 4.76) at 30 days; RR 2.28 (95% CI 1.59 to 3.25) at 1 year; RR 2.33 (95% CI 1.66 to 3.25) at 2 years; RR 2.26 (95% CI 1.64 to 3.11) at 3 years. Whereas TAVI using a balloon-expanding valve had no statistically significant differences from SAVR at all the follow-up points up to 5 years.

- In the US CoreValve trial the risk of acute kidney injury was statistically significantly lower with TAVI up to 3 years: RR 0.43 (95% CI 0.27 to 0.69) at 30 days; RR 0.43 (95% CI 0.27 to 0.69) at 1 year; RR 0.45 (95% CI 0.29 to 0.72) at 2 years; RR 0.45 (95% CI 0.29 to 0.72) at 3 years. Whereas in the PARTNER 1A trial there were no statistically significant differences between the treatment groups at all the follow-up points up to 5 years.

2.4.3 In patients for whom SAVR is considered suitable and not to pose a high risk

Evidence for intermediate- or low-risk patients were based on four systematic reviews (Gargiulo et al. 2016; Khan et al. 2016; Arora et al. 2016; Siemieniuk et al. 2016) in a total of 24838 patients.

- There were no statistically significant differences between TAVI and SAVR, when not stratified by access routes, in all-cause mortality at 1 year and long-term (>1 year). Whereas when using the transfemoral route TAVI compared with SAVR was associated with a significantly lower hazard of death at 2 years (HR 0.79; 95% CI 0.66 to 0.94).

- No significant differences were found between the treatment groups with measures of quality of life.

- No significant differences were found between the treatments in 30-day all-cause mortality.

- TAVI was associated with increased risk of heart failure symptoms (OR 1.29; 95% CI 1.08 to 1.55) but shorter length of hospital stay (MD -2.23; 95% CI -5.22 to 0.76).
- There were no differences in stroke and myocardial infarction risks between the treatments.
- TAVI was associated with a reduced risk of major bleeding for both transfemoral (RR 0.39; 95% CI 0.29 to 0.54) and transapical routes (RR 0.53; 95% CI 0.42 to 0.67), a reduced risk of acute kidney injury for the transfemoral route (RR 0.38; 95% CI 0.27 to 0.54), a reduced risk of new atrial fibrillation (AF) (RR 0.43; 95% CI 0.35 to 0.52), but had an increased risk of aortic regurgitation (RR 12.22; 95% CI 5.17 to 28.88), permanent pacemaker implantation (RR 2.45; 95% CI 1.17 to 5.14), and an increased risk of aortic valve reinsertion with RR of 7.65 (95% CI 0.96 to 61.16) at 1 month, and 3.68 (95% CI 1.06 to 12.74) at 1 year.

2.5 Discussion

All evidence identified was for adult patients.

Evidence was very limited comparing TAVI with standard medical care in patients for whom SAVR is considered unsuitable, but demonstrated that TAVI was superior to medical therapy for these patients in all-cause or cardiac mortality, NYHA classification, permanent pacemaker implantation and hospitalisation, with increased risk of stroke, major bleeding, and major vascular complications up to 2 years of follow-up. Evidence for patients for whom SAVR is considered suitable but poses a high risk was from 2 RCTs; there were short-term advantages in efficacy of TAVI over SAVR and mixed evidence on safety outcomes. For patients with an intermediate or low risk for SAVR evidence was from 4 systematic reviews, and there was no consistent pattern in the evidence to suggest whether TAVI is superior or inferior to SAVR.

A strength of our review was our comprehensive search seeking comparative and non-comparative observational studies to address questions by different surgical risk levels. Studies which could not be categorised by the specific risk groups were excluded. However, evidence on the efficacy and safety of TAVI compared with SAVR for the overall population had already been reviewed by Garguilo et al. (2016), which found no statistically significant differences between TAVI and SAVR in early (≤30 days) or midterm (≤1 year) all-cause mortality, but the transfemoral route showed mortality benefits over SAVR. As with long-term follow-up (>1 year and up to 5 years), Garguilo et al. (2016) found that

data based on RCTs showed no significant differences in all-cause mortality between TAVI and SAVR, but matched studies favoured SAVR. We did not pool studies with different designs, i.e. RCTs and observational studies, to avoid methodological heterogeneity.

We explored the efficacy/safety of the TAVI approach based on transfemoral and non-transfemoral routes and also summarised data which were reported in sub-groups by LVEF, previous CABG, diabetes, prosthesis-patient mismatch and sex.

Our search was comprehensive and up to 8th August 2016. Comparative and non-comparative observational studies were sought to address our specific review questions by different surgical risk levels, in order to identify outcomes that were not covered by RCTs.

Limitations were the lack of available information comparing TAVI with SAVR using different TAVI routes, valves and delivery sheathes. There was some overlap in risk categories across the RCTs and systematic reviews included in our review. Given these overlapping and conflicting inclusion criteria, it is difficult to clearly delineate risk groups in study level systematic reviews and meta-analyses. Although RCT evidence on TAVI was available, blinding of investigators and patients was not possible and there were insufficient studies for formal assessment of publication bias. Patients in RCTs were followed for up to five years, hence there is some uncertainty concerning longer term outcomes. Greater precision on outcomes using specific routes for TAVI and on some safety outcomes in different risk populations would be desirable.

2.6 Conclusions

RCT evidence on TAVI, mostly carried out by the transfemoral route, was available for all risk groups evaluated within this review.

Overall, the evidence reviewed support the use of TAVI in patients unsuitable for SAVR. Current available evidence for this group of patients is limited to one good quality RCT with 358 patients. It found TAVI to be superior to medical management in all-cause or cardiac mortality, NYHA classification and quality of life. There was no statistically significant difference between the treatments in the risk of permanent pacemaker implantation, myocardial infarction, acute kidney injury and endocarditis up to 3 years of follow-up. However, TAVI was associated with higher rates of safety events including major bleeding up to 1 year only, stroke up to 3 years and major vascular complications at 3 years. TAVI was associated with statistically lower risk of re-hospitalisation up to 5 years.

In patients for whom SAVR is considered suitable but poses a high risk there were short-term advantages in efficacy of TAVI over SAVR and mixed evidence on safety outcomes. Key evidence for this group of patients was based on two good quality RCTs in a total of 1494 patients. There were no short or long term differences in all-cause mortality between the treatments. There were short-term advantages of TAVI over SAVR in NYHA classification and quality of life. In terms of safety outcomes, TAVI had significantly better outcomes than SAVR in terms of the overall incidence and severity of prosthesis-patient mismatch. No differences were found in the rates of stroke, major vascular complications or myocardial infarction. However, TAVI was associated with a higher rate of moderate or severe total aortic regurgitation. Incidence of major bleeding reported in the PARTNER 1A trial favoured the TAVI group, whereas the US CoreValve trial showed no statistically significant differences between TAVI and SAVR. TAVI with a self-expanding valve was associated with a higher incidence of new pacemaker implantation but lower incidence of acute kidney injury. TAVI with a balloon-expanding valve did not differ from SAVR in terms of new pacemaker implantation and acute kidney injury.

There was no consistent pattern in the evidence to suggest whether TAVI is superior or inferior to SAVR in patients with an intermediate or low risk for SAVR. Evidence for this group of patients was from four recent systematic reviews in a total of 24838 patients, two of which were considered of good quality and the others moderate quality. Overall, there were no statistically significant differences between TAVI and SAVR in all-cause mortality at long-term (>1 year) or at 2 years of follow-up. When separately analysed by TAVI routes the transfemoral route was associated with significantly reduced mortality compared to SAVR, whereas this was not the case for transapical route. TAVI was inferior to SAVR for reducing heart failure symptoms at 2 years. There were no significant differences in quality of life between the treatments up to 2 years. Compared with SAVR, there was a significantly reduced risk of major bleeding and new atrial fibrillation (AF) with TAVI regardless of TAVI access route, and acute kidney injury for the transfemoral route. There were no differences between the treatments in stroke and myocardial infarction risks. There was an increased risk for both transfemoral and transapical routes for aortic regurgitation, permanent pacemaker implantation and of aortic valve reinsertion. TAVI was associated with shorter length of hospital stay.

The main uncertainties refer to the efficacy and safety of TAVI according to different risk group stratification. This is mostly due to variations in the study criteria but also due to a level of imprecision in currently available risk scores. An individual patient data meta-analysis with sufficiently wide inclusion criteria could provide more definitive indications on the safety and efficacy of TAVI for different surgical risk groups and assist in an improved categorisation for this patient population.

3 BACKGROUND

3.1 Description of health problem

Aortic stenosis, also referred as aortic valve stenosis, is a narrowing of the aortic valve that causes impaired outflow of blood from the heart to the circulation. This restriction in blood flow increases cardiac workload and is usually progressive, leading to left ventricular hypertrophy and heart failure.

The most common cause of aortic stenosis in adults, especially in men older than 65 years and women older than 75 years of age, is the degenerative calcification of the aortic valve, where calcium deposits build up on the valve with age, causing the valve to narrow or leak (Cary & Pearce 2013; Holmes et al. 2012). Other causes include congenital heart defects where the aortic valve consists of one (unicuspid), two (bicuspid) or four (quadricuspid) instead of three leaflets, and rheumatic fever that results in scar tissue forming on the aortic valve (Cary & Pearce 2013). Aortic stenosis is not a consequence of aging alone but a dynamic process of a combination of factors (Thaden et al. 2014). Male gender, chronic renal insufficiency and cardiovascular risk factors such as diabetes, smoking and dyslipidaemia may also be associated with the progression of aortic stenosis (Kamath et al. 2008; Stewart et al. 1997).

The prevalence of aortic stenosis increases with ageing, with approximately 0.02% in people aged 18–44 years, 2% in people over the age of 65, 3.4% of people over age 75, and 4% of people over age 85. It is reported that 75.6% of people with aortic stenosis are symptomatic (Osnabrugge et al. 2013; Thaden et al. 2014). Aortic stenosis is more likely to affect men, with an approximately 1.5–2 fold excess risk in men than in women (Bonow & Greenland 2015; Stewart et al. 1997).

Prognosis is poor in symptomatic patients with aortic stenosis. The life expectancy of patients with severe, symptomatic aortic stenosis is less than five years from the onset of symptoms without aortic valve replacement (Kamath et al. 2008). It was reported that, in asymptomatic patients with mild to moderate aortic stenosis, event-free survival with end-points defined as death or aortic valve surgery was 95%, 75% and 60% at 1, 3 and 5 years, respectively (Rosenhek et al. 2004). In asymptomatic patients with very severe aortic stenosis there is a risk of rapid functional deterioration with the event-free survival being 64%, 36%, 25%, 12%, and 3% at 1, 2, 3, 4, and 6 years respectively, suggesting the requirement of early elective valve replacement surgery (Rosenhek et al. 2010).

In the UK in 2015, 2473 TAVI procedures were recorded on the National Institute for Cardiovascular Outcomes Research (NICOR) register (British Cardiovascular Intervention Society 2015), while in 2013, 4893 isolated first time aortic valve replacement procedures were carried out (The Society for Cardiothoracic Surgery in Great Britain & Ireland 2016).

3.2 Current service provision

Treatment with medications for aortic stenosis can only ease some symptoms. Surgery to repair or replace the valve is the only solution to eliminate aortic stenosis. The conventional surgical treatment for patients with severe symptomatic aortic stenosis is surgical aortic valve replacement (SAVR), which is an open cardiac surgical procedure to replace the failing aortic valve with an artificial heart valve (biological or mechanical) (Bonow et al. 2006). SAVR is performed under general anaesthesia, requires cardiopulmonary bypass and is only suitable for patients who are well enough for the surgery. Specific surgical risk of SAVR includes ischemic stroke, renal, neurological and pulmonary disease compromise, occasional need for a permanent pacemaker and sternal wound infection (Holmes, et al. 2012).

Patients may be unsuitable for SAVR because of medical co-morbidities or because of technical considerations which mean that the risks of SAVR outweigh the potential benefits. Patients who are suitable for SAVR range from those considered to be high risk to those for whom the benefits of surgery clearly outweigh the risks. For patients whose condition is unsuitable for surgery the only options have been conservative management with optimal medical care and, occasionally aortic balloon valvuloplasty, which is a procedure that widens a heart valve that is narrowed (Bonow et al. 2008; Vahanian et al. 2007; NICE 2012). The Society of Thoracic Surgeons (STS) and European System for Cardiac Operative Risk Evaluation (EuroSCORE) risk scores are used for the prediction of operative mortality following cardiac surgery which both give information concerning short-term operative risks (Holmes et al. 2012). In addition to STS and EuroSCORE risk scores other risk factors such as technical consideration are also taken into account in patient selection for surgery.

In the current NHS practice, patients with aortic valve disease and heart failure who are potentially eligible for aortic valve replacement are referred from cardiologists or other specialists in district general or specialist hospitals to cardiac surgeons or interventional cardiologists in a specialist cardiac centre.

Transcatheter aortic valve implantation (TAVI) for aortic stenosis is currently available in some cardiac centres in the NHS that meet specific standards and service specification. The use of TAVI in the NHS is stated in NICE interventional procedures guidance on transcatheter aortic valve implantation for aortic stenosis (IPG421):

- For patients with aortic stenosis who are considered to be unsuitable for surgical aortic valve replacement, TAVI may be used with normal arrangements for clinical governance, consent and audit.

- For patients with aortic stenosis for whom SAVR is considered suitable but poses a high risk, TAVI should only be used with special arrangements for clinical governance, consent and data collection or research.

- For patients with aortic stenosis for whom SAVR is considered suitable and not to pose a high risk, TAVI should only be used in the context of research.

There are relevant national guidelines on this topic:

- NICE interventional procedures guidance [IPG421]. Transcatheter aortic valve implantation for aortic stenosis. Published date: March 2012.
- NHS Commissioning Board. Clinical Commissioning Policy: Transcatheter Aortic Valve Implantation (TAVI) For Aortic Stenosis. NHSCB/A09/P/a. Published date: April 2013.
- NICE interventional procedures guidance [IPG 78]. Balloon valvuloplasty for aortic valve stenosis in adults and children. Published date: July 2004.
- NICE interventional procedures guidance [IPG 504]. Transcatheter valve-in-valve implantation for aortic bioprosthetic valve dysfunction. Published date: September 2014.
- NICE transapical transcatheter mitral valve-in-valve implantation for a failed surgically implanted mitral valve bioprosthesis in patients for whom open surgical valve implantation is unsuitable. IPG in progress. Publication date: TBC
- NICE interventional procedures guidance [IPG541]. Transapical transcatheter mitral valve-in-valve implantation for a failed surgically implanted mitral valve bioprosthesis. Published date: December 2015.

- NICE interventional procedures guidance [IPG 436]. Percutaneous pulmonary valve implantation for right ventricular outflow tract dysfunction. Published date: January 2013.
- NICE interventional procedures guidance [IPG456]. Sutureless aortic valve replacement for aortic stenosis. Published date: July 2013.
- NICE interventional procedures guidance [IPG 175]. Percutaneous fetal balloon valvuloplasty for aortic stenosis. Published date: May 2006.
- Department of Public Health. National Service Framework for Coronary Heart Disease. Published date: March 2000.
- Driver and Vehicle Licensing Agency. Guidance: Cardiovascular disorders. Advice for medical professionals for drivers with cardiovascular disorders. Assessing fitness to drive: guide for medical professionals. Available at: https://www.gov.uk/guidance/cardiovascular-disorders-assessing-fitness-to-drive#aortic-stenosis

More details about the use of TAVI procedure in the NHS are described in section 3.3 below.

3.3 Description of technology under assessment

TAVI is also referred to as transcatheter aortic valve replacement (TAVR). It is a procedure performed through a catheter, which is usually inserted into a large blood vessel (transluminal via the femoral or other large artery or vein). Through the catheter, a collapsible replacement valve is inserted to the native valve site and placed within the existing faulty valve. The catheter is sometimes inserted into the apex of the heart (transapical via apical puncture of the left ventricle by a minithoracotomy approach). The transfemoral route is the most common route whilst the transapical, transaortic, subclavian and other routes are alternative approaches usually for when it is not possible to pass the device through the common femoral or iliac arteries into the aorta (Webb et al. 2012; ECRI 2012; Bande et al. 2010). The transcatheter aortic valves are either balloon expandable or self-expanding. Balloon-expandable valves cannot be collapsed once expanded. Self-expanding valves can be partially deployed and repositioned to some extent, offering potential advantages in reducing complications from malpositioning (Holmes et al. 2012).

The TAVI procedure is carried out under either general anaesthesia or local anaesthesia with sedation. Imaging examination and guidance are required; angiography and computed tomography (CT) are needed prior to the process; fluoroscopy is used during the procedure; and

transoesophageal echocardiography is usually used throughout the procedure when a patient undergoes a general anaesthetic (whichever vascular access route is used). Preparatory balloon aortic valvuloplasty may be used to widen the heart valve during the procedure. Prophylactic antibiotics and anticoagulation medication are administered before and during the procedure. Temporary peripheral extracorporeal circulatory support (usually via the femoral vessels) is sometimes used.

As a technically challenging procedure, TAVI is performed only by clinicians and teams with special training and experience in complex endovascular cardiac interventions, with both cardiac and vascular surgical support for emergency treatment of complications being in place.

TAVI aims to provide a less invasive alternative to SAVR for the treatment of aortic stenosis, avoiding the need for cardiopulmonary bypass. It may be an alternative to treat open heart surgical valve replacement that have become narrowed in patients for whom repeat SAVR is not suitable, or who are at high risk of serious complications of SAVR.

There has been a focus on specific features related to TAVI, including aortic regurgitation, stroke, the need for a permanent pacemaker in some cases and access related complications. New generation TAVI devices have been developed to enhance this treatment option, solve the drawbacks of the early technology and improve the outcome. The key features of the newer devices include the minimisation or avoidance of aortic valve leakage, the reduction of introducer sheath diameter, the ability to reposition the valve prosthesis before final deployment, and the simplicity of device handling (Blumenstein et al. 2013).

The list below provides examples of new generation TAVI devices that are currently available to the NHS:

- LOTUS Valve System
- Direct Flow Medical (DFM) aortic valve
- Edwards SAPIEN XT valve
- Edwards SAPIEN 3 valve
- JenaValve
- CoreValve Evolut R
- Portico THV
- ACURATE TA and ACURATE TF

New generation TAVI devices are intended to be used with one or more delivery approaches. Many have the potential to be retrievable and repositionable. They may expand the use to lower risk patient populations, such as younger and healthier patients. Examples of new generation TAVI devices (Class III medical devices) that have become available since the production of NICE IPG421 are described below.

Boston Scientific announced on 16.9.2016 that they have received a CE Mark for the LOTUS Edge Valve System, the company's next generation TAVI technology. The LOTUS Edge valve system is indicated for aortic valve replacement in patients with severe aortic stenosis who are considered at high risk for SAVR. In comparison to the Lotus Valve System (CE Mark announced 28.10.2013), this next iteration incorporates a more flexible, lower profile catheter designed to improve ease of use and accommodate tortuous anatomy. Another differentiating feature of the LOTUS Edge valve system is the inclusion of Depth Guard, a design element intended to reduce the need for a permanent pacemaker (PPM).

The Direct Flow Medical Transcatheter Aortic Valve System is designed to treat aortic stenosis with minimal risk of aortic regurgitation. The system’s design includes a metal-free valve frame and flexible, low-profile delivery system, which enables repositioning and assessment of haemodynamic performance before final implantation. CE Marking was announced on 24.8.2014.

In addition to the SAPIEN TAVI available at the time of the previous IPG there have been two new generations of the device approved and released: SAPIEN XT and SAPIEN 3 (both CE marked). SAPIEN XT and SAPIEN 3 are improvements to the original SAPIEN TAVI device (no longer available) and offer improvements in terms of procedural success and reduced complications. The newer generations of TAVI devices addressed issues of usability and clinical performance. For example improved delivery devices have, it is claimed, resulted in better procedural success rates (i.e. lower incidences of “bail out” procedures or operations). For SAPIEN 3 the inclusion of a “skirt” has led to reduced paravalvular leak rates (which have been associated with post-procedural mortality and poorer outcomes). The cross-sectional profile of the devices has been reduced to facilitate easier luminal access and fewer vascular injuries. The CE marked Edwards SAPIEN 3 Transcatheter Heart Valve builds on SAPIEN technology and may be placed apically or transfemorally. The CE marked SAPIEN XT valve is available in a wider range of annulus sizes and may be used in the aortic position via transfemoral, transapical and transaortic access routes.

The JenaValve Pericardial Transcatheter Aortic Valve Replacement System is designed to treat symptomatic, severe aortic stenosis and symptomatic, severe aortic regurgitation using a single valve prosthesis construct. It does not require rapid pacing. It is intended to enable ease of use, reduced risks of paravalvular regurgitation and need for permanent pacing, and durability of patient haemodynamic outcomes. CE Mark approval was announce on 16.9.2013 from European regulators for its transapical TAVI system, approving it for the treatment of patients at high risk who are suitable or unsuitable for SAVR suffering from severe aortic insufficiency. This is an addition to the initial September 2011 CE Mark approval for the treatment of stenosed and calcified aortic valve diseases. According to the JenaValve website however, the JenaValve is no longer commercially available. The website reports: “the JenaValve Pericardial TAVR System is a Class III, investigational device undergoing clinical trials in the US and internationally. It is not approved for sale in any country” and adds that this new technology builds on the original CE Marked porcine root system JenaValve.

The Medtronic CoreValve Evolut R TAVI system received CE approval on 27.7.2016 to expand the indication to include patients who are at high or greater risk for SAVR or are ≥75 years of age and at intermediate risk for SAVR (Society of Thoracic Surgeons operative risk score ≥4% or with an estimated hospital mortality ≥4% as assessed by the heart team). It was CE Marked for Valve-in-Bioprosthetic Valve on 23.4.2013. The device allows controlled and accurate deployment via a self-expanding nitinol frame.

The St Jude Portico Transcatheter Aortic Heart Valve System CE Mark was first issued on 16.11.2012 and updated on 15.9.2015 to include 27mm and 29 mm valves and the 19F delivery system and loading system. The Portico valve offers ease of use and is also retrievable up to the point of final deployment. It is claimed that Portico implantations have low rates of pacemaker requirement and paravalvular leak.

The Symetis ACURATE TA system has a design featuring a two-step deployment technique. The ACURATE TA transapical aortic bioprosthesis is composed of three elements: a valve made of three non-coronary native porcine leaflets attached to a self-expanding nitinol stent and a PET skirt that is sutured onto the inner and the outer surface of the nitinol stent. The self-seating and self-sealing features, it is claimed, allow for optimal positioning of the valve, promote sealing, and reducing paravalvular leak. The ACURATE TA bioprosthesis is available in three sizes to treat patients with aortic annulus diameters from 21 mm to 27 mm.

The manufacturer of the Engager TAVI product confirmed that it is no longer commercially available, and therefore not available within the NHS or wider health care systems.

The NHS Clinical Commissioning Policy on Transcatheter aortic valve implantation (TAVI) For Aortic Stenosis stated that the number of TAVI procedures to be initially funded would equate to a level of 25 per million population across England, a total of at least 1,250 procedures (NHS Commissioning Board Clinical Reference Group for Specialised Cardiology 2013).

Information on current usage of TAVI and of SAVR replacement in the NHS can be gained from the NICOR website. NICOR collects clinical information from UK hospitals into secure registries and conducts clinical audit, comparing patient outcomes, such as case mix-adjusted survival and readmission rates. The UK TAVI Registry which is managed by NICOR collects data on all TAVI procedures performed in the UK since the introduction of the technique in 2007. In 2015 a total of 9903 procedures were recorded on the register, with 2473 registered in 2015, with the number of procedures having increased steadily since 2007 when 66 were performed (British Cardiovascular Intervention Society 2016). In 2015, 39.8 procedures were performed per million of the England population. In the same year, the mean age of patients was 81 years and 46% were female. The majority of procedures used a femoral artery approach. Tracked 30-day mortality in 2015 is awaited but was 3.7% in 2014. Over 100 UK centres carrying out percutaneous cardiac interventions took part in the register. The most commonly used devices were manufactured by Edwards (1223 procedures in 2015), Medtronic (680) and Boston Scientific (405), with other manufacturers accounting for less than 60 procedures each.

NICOR also records data on surgical cardiac procedures (The Society for Cardiothoracic Surgery in Great Britain & Ireland 2016). In 2013, 4893 isolated first time aortic valve replacement procedures were carried out, increasing from 4043 in 2007. Predicted mortality in 2013 based on the EuroSCORE was 6.81% in 2013, an increase of less than 1% since 2003 indicating a small increase in the risk of patients treated. In 2013, 1.12% of patients died before discharge from hospital. These patients were younger than those undergoing TAVI with a mean age of 69.3 years and 43% were female, with approximately 80% alive at 5 years.

4 DEFINITION OF THE CLINICAL QUESTION

In April 2011 NICE prepared a rapid overview to inform members of the Interventional Procedures Advisory Committee (IPAC) in order to make recommendations about the efficacy and safety of TAVI for patients with aortic stenosis. Based on the rapid overview of the medical literature and specialist opinion, NICE issued IPG421 on the safety and efficacy of TAVI for patients with aortic stenosis (NICE 2012), which replaced NICE IPG266, the previous guidance on the technology published in June 2008.

Since the publication of NICE IPG421 three years have elapsed and publications from clinical trials and registries have provided additional evidence regarding the indications, efficacy and safety of this procedure (Mack et al. 2015; Kapadia et al. 2015; Adams et al. 2014; Ludman et al. 2015). Also, there have been significant developments in the technology, and new generation TAVI devices have become available for use with one or more delivery approaches to treat severe aortic stenosis. They may be retrievable and repositionable and may aid the expansion of use to patients with lower risks of surgery. Thus, NICE has commissioned the Birmingham & Brunel Consortium External Assessment Centre (B&BC EAC) to carry out a systematic review of the literature published since the production of NICE IPG421.

The aim of this systematic review is to provide a comprehensive synthesis of evidence on the clinical efficacy and safety of TAVI for the treatment of aortic stenosis, in order to support NICE in updating the current guidance IPG421.

4.1 Decision problem

The systematic review aims to address the following research questions:

- What is the current evidence base for the efficacy and safety of TAVI?
- What is the comparative effectiveness and safety of TAVI compared with other treatments for aortic stenosis (including SAVR and conservative management)? The evidence is presented for the following three distinct groups of patients with aortic stenosis (as identified in NICE IPG421):

    1) Patients for whom SAVR is considered unsuitable;

2) Patients for whom SAVR is considered suitable but poses a high risk;
3) Patients for whom SAVR is considered suitable and not to pose a high risk.

The details of inclusion and exclusion criteria for the decision problem in terms of relevant population, intervention, comparator, efficacy and safety outcome, and study types are presented in Table 1 in section 5.2.

5 METHODS FOR REVIEWING EVIDENCE ON EFFICACY AND SAFETY

As the aim of this systematic review is to support NICE in updating the current guidance IPG421, the scope of the review is developed in compliance with that of the NICE rapid overview prepared in 2011 and used as the evidence base for the guidance IPG421.

A review protocol was developed to describe the rationale and planned methods of the systematic review following PRISMA-P recommendations on preparing and reporting systematic review and meta-analysis protocols (Moher et al. 2015; Shamseer et al. 2015). The protocol was registered in the registry of international prospective register of systematic reviews (PROSPERO 2016:CRD42016048396). The systematic review was conducted and reported following this protocol and the PRISMA recommendations for reporting systematic reviews (Moher et al. 2009).

Clinical experts with relevant interest were contacted for their assistance in our interpretation of the evidence and queries regarding the technology (such as types of valves and implantation technique).

5.1 Literature search

The literature search strategy was developed in accordance with the search strategy provided in Appendix C of the NICE rapid overview prepared in 2011 to identify published literature (see Appendix 1 for strategy). This strategy was then adapted to be run across each of the different databases.

Electronic databases The Cochrane Library (Wiley) (CDSR, DARE, HTA and CENTRAL), CRD Centre for Reviews and Dissemination Databases (DARE, NHS EED and HTA), MEDLINE (Ovid), MEDLINE in Process (Ovid), EMBASE (Ovid), ZETOC (British Library) and PubMed (US NLH) were

searched from March 2011 (April 19th 2011 being the date on which the electronic searches for the NICE rapid overview were conducted) to 8th August 2016.

Relevant websites were searched and experts contacted. Conference abstracts in published conference proceedings were searched to capture any unique safety events not reported in published full-text literature. Hand searching of reference lists of relevant studies was carried out. Clinical trials registers, including ClinicalTrials.gov and WHO ICTRP, were searched to locate any key trials which are emerging. Language filter was not used for the searches, although non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base. Literature search results were uploaded to and managed using EndNote X7.0.1 software.

5.2 Inclusion and exclusion criteria

The selection criteria described in Table 1 below were applied to the citations identified by the literature search.

Table 1. Inclusion and exclusion criteria

Characteristic	Criteria
Publication type	For evidence on efficacy: published systematic reviews, randomised or non-randomised controlled trials, and comparative observational studies will be included. For evidence on safety: in addition to the types of studies above-mentioned, non-comparative observational studies will be included if they report longer follow-up outcomes than those reported in comparative studies or systematic reviews for long term patient survival, and short and long term valve function/durability, or if they report important outcomes that are not covered in the included comparative studies and systematic reviews. Minimum duration of follow-up of such non-comparative observational studies will be determined following assessment of the available studies. Case reports and conference abstracts will only be included if they report important and rare safety events that are not reported in the types of aforementioned studies. Narrative reviews, editorials, laboratory studies, animal studies and unpublished material will be excluded.
Patient	Patients of any age with aortic stenosis will be included. Patients with aortic bioprosthetic valve dysfunction will be excluded.
Intervention	TAVI, including procedures performed using different types of devices and different implantation techniques. Evidence will be included on all substantial modifications directly related to the procedure such as newer devices used, new/modified approaches and delivery systems/equipment. With regard to modifications of the TAVI procedure, the review will focus on factors that are directly related to TAVI valves, delivery systems/equipment (e.g. catheter), and implantation technique including delivery route and positioning. Studies looking at the impact of ancillary variations of the TAVI procedure (such as types of anaesthetic, types of imaging examination/guidance, learning curve, etc.) rather than the above mentioned will be excluded. Transcatheter valve-in-valve implantation for aortic bioprosthetic valve dysfunction will be excluded from this systematic review as separate NICE guidance on this procedure has been published. TAVI with balloon aortic valvuloplasty will be included. TAVI in combination with any other

	surgical cardiac procedure will be excluded.
Comparator	Standard therapies (conservative management with optimal medical care and/or aortic balloon valvuloplasty; SAVR), or no intervention. Surgical replacement combined with any other surgical cardiac procedure will be excluded.
Outcome	Clinical efficacy outcomes including: mortality, cardiac function/NYHA heart failure class, quality of life, technically successful valve implantation, and reduction of symptoms. Haemodynamic performance data including mean aortic-valve area, mean aortic-valve gradients, occurrence of aortic regurgitation and ejection fraction (echocardiography or angiography) will also be extracted. Any other surrogate outcomes (such as platelet volume or other biomarkers as the indicator of any clinical outcomes) will be excluded. Safety outcomes of any complications and adverse events, including long term patient survival, and short and long term valve function/durability.
Language	Non-English-language articles will be excluded.

Abbreviation: TAVI, transcatheter aortic valve implantation; NYHA, New York Heart Association (Functional Classification); SAVR, surgical aortic valve replacement

5.3 Study selection

Two reviewers independently screened the titles and abstracts of all retrieved citations and documented the reasons for study exclusion. Where selection criteria could not be determined from the abstract, the full papers of the citation were retrieved. Full papers for studies which were deemed potentially relevant by the screening were retrieved. Any disagreements were resolved by discussion and consensus between the reviewers; where consensus was not reached a third reviewer was consulted.

5.4 Quality assessment

Quality of systematic reviews was assessed using the AMSTAR checklist (Shea et al. 2007). The Cochrane Collaboration's risk of bias tool was used to assess the quality of randomised and non-randomised controlled studies (Higgins and Green 2011). Risk of bias in the following was assessed: sequence generation, allocation concealment, blinding, any incomplete outcome data and selective outcome reporting. The Newcastle-Ottawa Scale (NOS) was used to assess risk of bias in cohort or case-control studies (Wells et al. 2016). The assessment was conducted by one reviewer and checked by a second. Any disagreement was resolved by discussion and consensus and if necessary consultation of a third reviewer. Quality of case series and case report studies was not assessed, as they were used to provide additional information and were considered inadequate to make inferences about relative effectiveness and safety due to lack of a control group.

The GRADE framework was employed to describe the quality of the key outcomes and the overall strength of the supporting evidence from the included key RCTs (Guyatt et al. 2011).

5.5 Data extraction

A data-extraction form was designed for the purposes of this review (see Appendix 2 for data fields). For each included study, data were extracted by one reviewer and checked for accuracy by a second reviewer. Any disagreements were resolved by discussion and if necessary consultation of a third reviewer.

For survival data, the hazard ratio (HR) and its variance or other data that could be used to calculate HR and variance according to the methods described by Tierney et al. (2007) were extracted from the most recent reports with the longest follow up times (Higgins and Green 2011).

5.6 Data synthesis

Studies were grouped into the following three categories according to the type of patients with aortic stenosis:

1) Patients for whom SAVR is considered unsuitable;
2) Patients for whom SAVR is considered suitable but poses a high risk;
3) Patients for whom SAVR is considered suitable and not to pose a high risk.

With regard to the TAVI procedure, the review focused on variations that are directly related to TAVI valves, delivery systems/equipment, and implantation technique including delivery route and positioning. Where appropriate, studies were further grouped by the following variations of TAVI procedures:

- characteristics of the TAVI device (type of valves, size, whether retrievable or repositionable);
- delivery routes (e.g. transfemoral, transapical, transaortic, transsubclavian, or transcarotid);
- characteristics of the delivery systems/equipment (e.g. sheath diameter).

Data were tabulated where appropriate. A narrative synthesis was employed where meta-analysis was considered unsuitable for the data identified. Meta-analyses were carried out in RevMan 5.3

where data were sufficient. The random effects model was used in the meta-analyses. Intention-to-treat methods (i.e. according to the initial treatment assignment) were adopted where appropriate. Dichotomous data were expressed as risk ratio (RR) with 95% confidence interval (CI). Continuous data were analysed by calculating the weighted mean difference (WMD) between groups and the corresponding 95% CI. For survival data, HRs were pooled using the generic inverse variance method with a fixed effect model (Higgins and Green 2011) in RevMan 5.3.

We intended to assess publication bias using a funnel plot if appropriate. However, as the number of studies included in any of the meta-analyses conducted was limited, funnel plot asymmetry testing for publication bias was not conducted. Sensitivity analyses were not conducted to explore the robustness of the meta-analyses due to limited number of relevant studies available.

5.7 Results

Our electronic databased searches resulted in a total of 12749 hits, of which 5458 were duplicates.

In total, 4 systematic reviews, 6 randomised controlled trials (RCTs) reported in 27 papers, and 10 propensity-matched comparative studies were relevant.

The study selection process was displayed in Figure 1 using a PRISMA flow diagram.

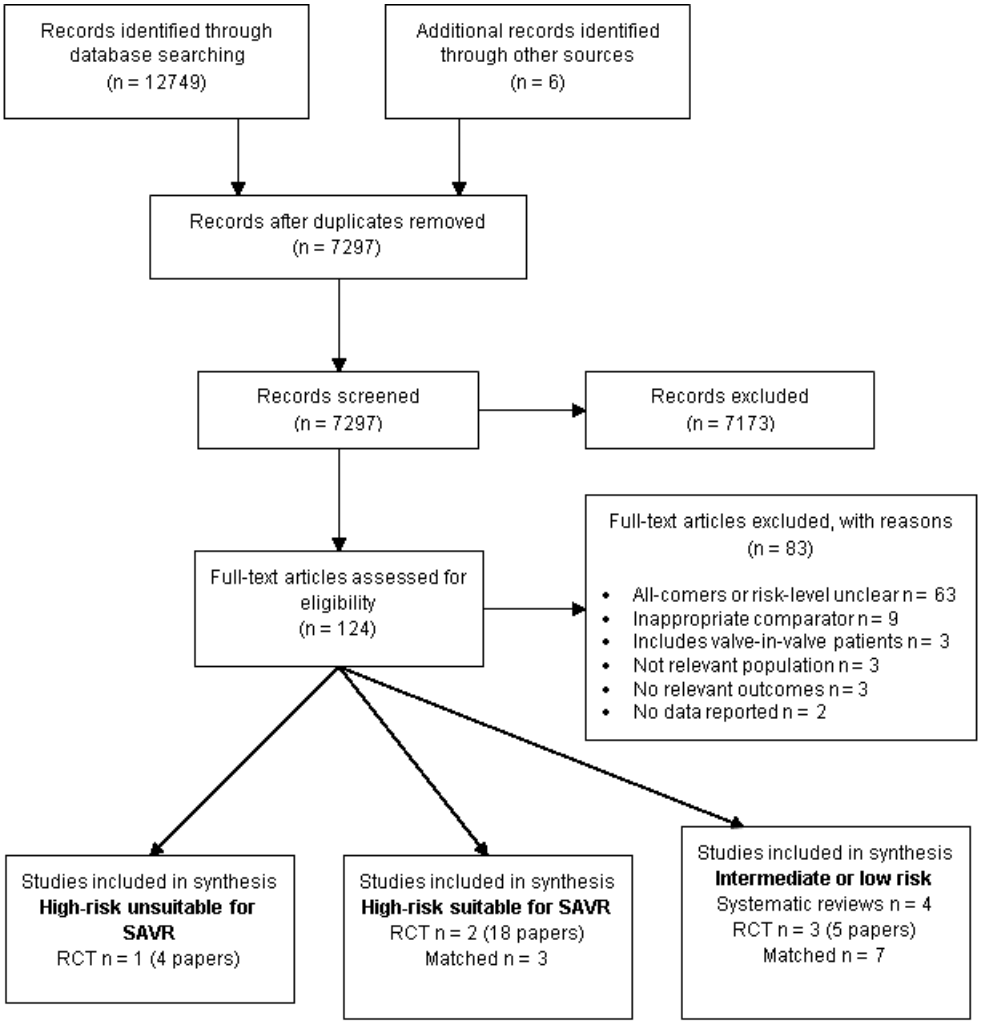

Figure 1. PRISMA flow diagram of study selection process

Table 2 maps relevant evidence identified for each of our three review questions by population risk level for surgery.

The four included systematic reviews are relevant to intermediate- or low-risk population. Of the 6 included RCTs, 1 was in patients unsuitable for SAVR, 2 in high-risk patients suitable for SAVR and 3 in intermediate- or low-risk patients. Outlines of the 6 RCTs are presented in Table 6 below. Of the 10 matched studies 3 were in high-risk patients suitable for SAVR and 7 in intermediate- or low-risk patients.

Except the study in patients unsuitable for SAVR where TAVI was compared with medical management, all the other studies compared TAVI with SAVR. All the studies were in adult patients.

A further 4 potentially relevant systematic reviews were identified. They included patients of mixed or non-specified risk levels, with no separate analyses provided for the different patient risk levels in

relation to our review questions. A number of observational studies were also identified to be relevant to the TAVI procedure, in none of which the patient risk level for surgery could be categorised to address our review question. These systematic reviews and observational studies are therefore not included for analysis in our review, as they do not answer our questions regarding population risk levels. Among the observational studies, there are non-comparative studies that reported relevant safety outcomes which had longer follow-up than those in the included systematic reviews and comparative studies and studies that may have safety outcomes which are considered as rare and not covered in the included studies in our review. Those reporting longer term follow-up safety data and those that may have data on rare safety events are presented in Appendix 3. The 4 systematic reviews, and the remaining observational studies that were considered to have reported neither longer term safety outcomes nor rare safety events, are listed in Appendix 4.

Table 2. Evidence mapping

Population risk	Systematic reviews	RCTs	Matched studies	Non-matched studies
SAVR is unsuitable	0	**1** PARTNER 1B (in 4 papers)	0	0
SAVR is suitable but poses a high risk	0	**2** US CoreValve PARTNER 1A (in 18 papers)	**3**	0
SAVR is suitable and not to pose a high risk (Intermediate or low risk)	**4** Gargiulo et al. 2016 Khan et al. 2016 Arora et al. 2016 Siemieniuk et al. 2016	**3** PARTNER 2A STACCATO NOTION (in 5 papers)	**7**	0

5.7.1 Systematic reviews included in the report

Four systematic reviews were identified to be relevant, all comparing TAVI against SAVR in patients with an intermediate or low surgical risk. Table 3 and Table 4 display the characteristics and studies included in these systematic reviews. No systematic reviews were identified to be relevant to specifically either patients who are considered unsuitable for SAVR or patients for whom SAVR is considered suitable but poses a high risk.

Table 3. Systematic reviews included in the report (intermediate or low risk)

Systematic reviews	Population risk level	Comparison	Key outcomes and follow-up length	Searches	Studies included	Note
Gargiulo et al. 2016	Suitable for SAVR but with a high risk; low to intermediate risk (pre-specified in included studies)	TAVI vs SAVR Subgroup analysis: · By TAVI route: TF vs SAVR, TA vs SAVR; · By risk level: overall population; low- to intermediate-risk · By study type: RCTs and matched studies	All-cause mortality (≤30-day, ≤1-year, >1-yr). Longest follow-up: 5 yrs.	Medline, Cochrane, and Scopus databases (without language restrictions) from April 2002 to 5 April 2016; multiple registries and Web sites; scientific meeting presentations.	5 RCTs (NOTION, PARTNER 1A, PARTNER 2A, STACCATO, US CoreValve) and 31 observational matched studies	Analyses were conducted separately for all patients (of any risk levels) and those of low- to intermediate-risk. PARTNER 1A included patients with a high risk but suitable for SAVR. Analysis was not conducted for this group.
Khan et al. 2016	Intermediate surgical risk	TAVI vs SAVR	All-cause mortality (30-day, 1yr); incidence of stroke, vascular access complications, life threatening bleeding, safety.	Pub Med, Embase, Cochrane Central Register of Controlled Trials, ISI Web of Science, and Scopus. From inception up to February 25, 2015.	1 RCT (STACCATO), 6 observational studies	Excluded studies with low-risk patients
Arora et al. 2016	Intermediate surgical risk (STS <8%, EuroSCORE mean<20% if no STS score was available)	TAVI vs SAVR	30day and 1yr mortality, neurological events and myocardial infarction, post-procedural acute renal failure and pacemaker implantations. Follow-up up to 1yr.	Medline, Embase, Google Scholar, Web of Science and Cochrane. Search date not stated	1 RCT (NOTION), 5 propensity score matched observational studies (1 case control study and 4 prospective cohort studies)	
Siemieniuk et al. 2016	Low and intermediate surgical risk (risk score of 8% or less)	TAVI vs SAVR	Mortality, stroke, life-threatening bleeding, AF, AKI, short term aortic valve re-intervention, PPI, moderate or severe symptoms of heart failure, structural valve deterioration. Longest follow-up: median 2 yrs	Medline, Embase, and Cochrane CENTRAL	4 RCTs (NOTION, PARTNER 2A, STACCATO, US CoreValve), 5 secondary reports with eligible data	No sub-group analyses were conducted separately for low and intermediate risk groups

Abbreviation: AF, Atrial fibrillation; AKI; acute kidney injury; PPI, permanent pacemaker implantation; TA: transapical; TF: transfemoral; n, number (of patients); yr, year

Table 4. Characteristics of studies included in systematic reviews (intermediate or low risk)

					Data supporting risk categorisation		Systematic review			
Study	Paper	Description	No. patients	Surgical mortality risk	TAVI	Comparator	Gargiulo et al. 2016 *	Arora et al. 2016	Khan et al. 2016	Siemieniuk et al. 2016
NOTION	Thyregod et al. 2015; Sondergaard et al. 2016; Thyregod et al. 2016	RCT	280	Open to all-comers	STS 2.9 ± 1.6 Logistic EuroSCORE 8.4±4.0	STS 3.1±1.7 Logistic EuroSCORE 8.9±5.5	Included	Included	Not included	Included
PARTNER 2A	Leon et al. 2016	RCT	2032	Intermediate STS scores 4% to 8% or <4% with additional comorbidities	STS 5.8±2.1	STS 5.8±1.9	Included	Not included	Not included	Included
STACCATO trial	Nielsen et al. 2012	RCT. Prematurely terminated due to adverse events in TAVI arm	70	Planned for lower risk	STS 3.1±1.5 Logistic EuroSCORE 9.4±3.9	STS scores 3.4±1.2 Logistic EuroSCORE 10.3±5.8	Not included	Not included	Included	Included
US CoreValve	Adams et al. 2014; Arnold et al. 2015; Reardon et al. 2015; Deeb et al. 2016	RCT	795	Increased risk (estimated as ≥15%)	STS 7.3±3.0 Logistic EuroSCORE 17.6±13	STS 7.5±3.2 Logistic EuroSCORE 18.4±12.8	Not included	Not included	Not included	Included
	Biancari et al. 2015	Propensity score matched. SU-AVR vs TAVI	288		EuroSCORE II 3.6±2.6	EuroSCORE II 4.1±3.2	Not included	Not included	Not included	Not included
OBSERVANT	D'Errigo et al. 2013	Propensity matched	266	Intermediate	Logistic EuroSCORE 8.8±9.5	Logistic EuroSCORE 9.4±10.4	Included	Included	Include	Not included
	Tamburino et al. 2015	Propensity matched	1300	Low to intermediate	Logistic EuroSCORE 9.5±7.1	Logistic EuroSCORE 10.2±9.2				
	Fraccaro et al. 2016	Propensity matched	830	Intermediate	Logistic EuroSCORE 14.9±11.8	Logistic EuroSCORE 8.0±5.7				
	Rosato et al. 2016	Propensity matched	710	Low	Logistic EuroSCORE 6.3±2.7	Logistic EuroSCORE 6.3±3.0				
	Latib et al. 2012	Propensity matched	222	Moderate to high	STS 4.57±2.28 Logistic EuroSCORE 23.2±15.1	STS 4.60±2.63 Logistic EuroSCORE 24.4±13.4	Included	Included	Not included	Not included
	Macon et al. 2014	Low STS scores but	72	Low to intermediate	STS 4.24 ±2.3	STS 4.84 ±2.2	Not included	Not included	Included	Not included

		deemed unsuitable for SAVR for technical reasons compared to SAVR patients with similar STS scores								
	Muneretto et al. 2015	Propensity matched	612	Intermediate- to high	STS 8.2 ±4.2 Logistic EuroSCORE 19.5±6.7	SAVR STS 8.3±4.4 Logistic EuroSCORE 19.2±7.4 SU-AVR STS 7.9±3.2 Logistic EuroSCORE 18.9±5.9	Not included	Included	Not included	Not included
	Osnabrugge et al. 2012	Propensity matched	84	Intermediate	Logistic EuroSCORE 12.9±6.8	Logistic EuroSCORE 12.5±6.4	Included	Not included	Included	Not included
	Piazza et al. 2013	Propensity matched	510	Intermediate	Logistic EuroSCORE 17.1±10.7	Logistic EuroSCORE 17.5 ±12.1	Included	Included	Included	Not included
	Schymik et al. 2015	Propensity matched	432	“less than high”	Logistic EuroSCORE 8.7±2.7	Logistic EuroSCORE 8.8±2.8	Included	Included	Not included	Not included
	Thourani et al. 2016	Observational data of TAVI in PARTNER 2 SAPIEN 3 vs surgical arm in PARTNER 2A. Propensity matched	2021	Intermediate. STS scores 4% to 8% or <4% with additional comorbidities	STS median (IQR) 5.2 (4.3-6.3)	STS median (IQR) 5.4 (4.4-6.7)	Included	Not included	Not included	Not included
	Wenaweser et al. 2011	Registry data, unmatched patients.	442	Increased surgical risk. Logistic EuroSCORE >15%	STS 6.4±5.0 Logistic EuroSCORE 24.7±24.9	SAVR STS 4.8±5.3 Logistic EuroSCORE 12.5±8.2 MT STS 6.5±4.1 Logistic EuroSCORE 27.9±14.5	Not included	Not included	Included	Not included

* Low- to intermediate-risk subgroup analyses
Abbreviation: MT, medical treatment; RCT, randomised controlled trial; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; SU-AVR, sutureless aortic valve replacement; TAVI, transcatheter aortic valve implantation

The AMSTAR checklist (Shea et al. 2007) was used to assess the quality of the 4 systematic reviews (Table 5).

Table 5. Systematic reviews comparing TAVI with SAVR (intermediate or low risk)

	Arora et al. 2016	Gargiulo et al. 2016	Khan et al. 2016	Siemieniuk et al. 2016
1. Was an 'a priori' design provided?	No	Yes	No	Yes
2. Was there duplicate study selection and data extraction?	Yes	Yes	Yes	Yes
3. Was a comprehensive literature search performed?	Cannot answer	Yes	Yes	Yes
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Cannot answer	Cannot answer	Yes	Yes
5. Was a list of studies (included and excluded) provided? *Lists of excluded studies not provided*	No	No	No	No
6. Were the characteristics of the included studies provided?	Yes	Yes	Yes	Yes
7. Was the scientific quality of the included studies assessed and documented?	No	Yes	Yes	Yes
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	No	Yes	Yes	Yes
9. Were the methods used to combine the findings of studies appropriate?	Yes	Yes	Yes	Yes
10. Was the likelihood of publication bias assessed?	No	Yes	Yes	No
11. Was the conflict of interest included?	No	No	No	Yes

Neither Arora et al. (2016) nor Khan et al. (2016) appeared to have a pre-specified design or protocol and the former did not assess the quality of included studies. None of the reviews listed the studies that were excluded. All reported the characteristics of the included studies. Given that two recent and relatively high quality systematic reviews were available (Gargiulo et al. 2016; Siemieniuk et al. 2016), the evidence synthesis from these reviews has been used in this report.

Gargiulo et al. (2016) asked clear questions. A published protocol was followed; appropriate databases, registries, web sites and scientific meeting presentations were searched, applying no language limits. Two people independently extracted data and assessed risk of bias using the Cochrane tool for RCTs and NOS for observational studies. The authors conducted a sub-analysis of studies with patients with low- to intermediate-risk for surgery.

Siemieniuk et al. (2016) was registered on the PROSPERO database, had well described searches and selection procedures and assessed study quality and rated the quality of the evidence. This review included the CoreValve RCT as the mean STS score was below 8. However in our systematic review we have included the CoreValve trial as a high risk, not an intermediate risk study, as the study protocol specified higher risk patients (with STS of at least 15%).

5.7.2 Randomised controlled trials included in the report

Six RCTs were identified to be relevant: PARTNER 1A, PARTNER 1B, PARTNER 2A, US CoreValve, NOTION, and STACCATO, all included adult patients. One of them compared TAVI with standard care (medical therapy) in patients who were considered unsuitable for SAVR (PARTNER 1B), two compared TAVI with SAVR in patients for whom SAVR was considered suitable but would pose a high risk (PARTNER 1A and US CoreValve), and the remaining (PARTNER 2A; NOTION; STACCATO) compared TAVI with SAVR in patients for whom SAVR was considered suitable and not to pose a high risk (intermediate or low risk).

The PARTNER 1B trial was initially published with 1-year follow-up data in 2010 (Leon et al. 2010). As our systematic review is to support NICE in updating the current guidance IPG421 with the search date starting from March 2011, the Leon et al (2010) paper is not included in this systematic review.

The GRADE framework was employed to describe the key findings and the overall strength of the supporting evidence from the included key RCTs (Guyatt et al. 2011). The results are presented in Appendix 6.

5.7.2.1 Characteristics

Table 6 presents the outline of RCTs and Table 7 presents baseline patient characteristics of the 6 RCTs.

5.7.2.2 Quality and risk of bias

Among the 6 RCTs randomisation methods were not clearly described for the NOTION trial, but only in this trial allocation concealment was stated. Due to the nature of the interventions, blinding of the patients and personnel was impossible. Blinding of the outcome assessment was applied in all the trials. Overall, the PARTNER 1B trial in patients unsuitable for SAVR and the PARTNER 1A and US CoreValve trials in patients with a high risk suitable for SAVR are of good quality. Of the trials in intermediate- or low-risk patients PARTNER 2A is of good quality, the NOTION trial is of reasonable quality and there are more quality issues in STACCATO. Risk of bias of the RCTs is presented in Figure 2. Further information about risk of bias of the RCTs can be found in Appendix 5.

Table 6. Outline of the RCTs identified (TAVI vs SAVR or medical therapy)

Trial	Location	Surgical risk category	Comparison and n. of patients [a]	TAVI valve	TAVI route	Primary outcome	Secondary outcome	Longest follow-up	Paper reported relevant outcomes
PARTNER 1B	Multi-centres in the US, Canada and Germany	Unsuitable for SAVR	TAVI (n=179) vs medical therapy which could include aortic valvuloplasty (n=179)	Edwards SAPIEN heart-valve balloon expanding	TF	All-cause mortality, over the duration of the trial	Cardiovascular mortality, stroke, vascular complications, major bleeding, functional status (including first occurrence of re-hospitalisation for valve or procedure-related clinical deterioration)	5 years	Makkar et al. 2012 Kapadia et al. 2014 Kapadia et al. 2015 Reynolds et al. 2011
PARTNER 1A	Multi-centres in the US, Canada and Germany	Suitable for SAVR but with a high risk	TAVI (n=348) vs SAVR (n=351)	Edwards SAPIEN heart-valve balloon expanding	TF (n=244), TA (n=104)	All-cause mortality at 1 year	Cardiovascular mortality, stroke, re-hospitalisation, AKI, vascular complications, bleeding events, and NYHA functional class. Two-year follow-up with annual visits and assessments	5 years	Smith et al. 2011 Reynolds et al. 2012 Genereux et al. 2014 Kodali et al. 2012 Mack et al. 2015 Miller et al. 2012 Hahn et al. 2013 Elmariah et al. 2013 Greason et al. 2014 Lindman et al. 2014 Pibarot et al. 2014 Williams et al. 2014
US CoreValve	Multi-centres in the US	Suitable for SAVR but with a high risk	TAVI (n=394) vs SAVR (n=401)	Medtronic CoreValve self-expanding	TF (n=330), non-TF [b] (n=64)	All-cause mortality rate at 1 year	The composite of major adverse cardiovascular and cerebrovascular events (defined as a composite of death from any cause, myocardial infarction, any stroke, or re-intervention) at 30 days and 1 year, as well as the individual components of this composite	3 years	Adams et al. 2014 Reardon et al. 2015 Deeb et al. 2016 Skelding et al. 2016 Zorn et al. 2016 Arnold et al. 2015
PARTNER 2A	Multi-centres in the US and Canada	Intermediate risk	TAVI (n=1011) vs SAVR (n=1021)	Edwards SAPIEN XT balloon expanding	TF, TH	Death from any cause or disabling stroke at 2 years (analysed also by route)	Aortic-valve areas, AKI, severe bleeding, new-onset AF, major vascular complications, paravalvular aortic regurgitation	2 years	Leon et al. 2016
STACCATO [c]	Multi-centres in the Nordic region	Low risk	Randomised: 72 Analysed: TAVI (n=34) vs SAVR (n=36)	Edwards SAPIEN heart-valve balloon expanding	TA	The composite of 30-day all-cause mortality, major stroke, and renal failure requiring dialysis at 30 days	All-cause death, cardiac death, stroke, myocardial infarction, NYHA function class, SF-36 composite physical and mental functional scores, echocardiographic parameters, operation for bleeding, and PPI. Follow-up duration 3 months.	3 months	Nielsen et al. 2012
NOTION	Multi-centres	All-comers,	TAVI (n=145)	Medtronic	TF, TS	The composite	Rate of cardiovascular death or	2 years	Thyregod et al. 2015

Trial	Location	Surgical risk category	Comparison and n. of patients [a]	TAVI valve	TAVI route	Primary outcome	Secondary outcome	Longest follow-up	Paper reported relevant outcomes
	in Denmark and Sweden	81.8% being low-risk	vs SAVR (n=135)	CoreValve self-expanding		rate of death from any cause, stroke, or myocardial infarction at 1 year	prosthesis re-intervention, PPI, effective orifice area, total aortic valve regurgitation, NYHA functional class, major bleeding, cardiogenic shock, AKI, and new-onset or worsening AF.		Thyregod et al. 2016 Sondergaard et al. 2016

Abbreviation: AF, atrial fibrillation; AKI, acute kidney injury; NYHA, New York Heart Association; PPI, permanent pacemaker implantation; RCT, randomised controlled trial; SAVR, surgical aortic valve replacement; TA, transapical; TF, transfemoral; TH, transthoracic; TS, Transsubclavian; vs, versus.
[a] Number randomised unless otherwise specified. [b] Non-TF included subclavian artery or direct aortic approach. [c] The study was terminated prematurely after a total of 72 patients were randomised due to three severe adverse events in the TA TAVI group; two of the randomised patients were excluded and it was unclear from which group the 2 patients were excluded.

Table 7. Baseline patient characteristics of the RCTs

Study	Female (%)	Age (year), mean (SD)	NYHA III/IV (%)	Risk level, % or mean (SD)		CAD, (%)	AF, (%)	Diabetes (%)	Kidney disease (%)	COPD (%)	Previous cardiac surgery (%)
				Logistic EuroSCORE, %	STS, mean						
PARTNER 1B (***unsuitable for SAVR)***											
• TAVI	54.2	83.1 (8.6)	92.2	NR	11.2 (5.8)	27.4	32.9	NR	5.6	41.3	PCI: 30.5; CABG: 37.4
• Medical therapy	53.1	83.2 (8.3)	93.9	NR	12.1 (6.1)	27.5	48.8	NR	9.6	52.5	PCI: 24.8; CABG: 45.6
PARTNER 1A (***SAVR is suitable but poses a high risk)***											
• TAVI	42.2	83.6 (6.8)	94.3	29.3 (16.5)	11.8 (3.3)	74.9	40.8	NR	11.1	43.4	PCI: 34.0; CABG: 42.6
• SAVR	43.3	84.5 (6.4)	94.0	29.2 (15.6)	11.7 (3.5)	76.9	42.7	NR	7.0	43.0	PCI: 32.5; CABG: 44.2
US CoreValve (***SAVR is suitable but poses a high risk)***											
• TAVI	46.4	83.2 (7.1)	80.7	17.6 (13.0)	7.3 (3.0)	75.4	40.0	34.9	12.3 (stage 4/5)	13.3	PCI: 33.8; CABG: 29.7
• SAVR	47.1	83.5 (6.3)	86.8	18.4 (12.8)	7.5 (3.2)	76.3	47.5	45.4	13.1 (stage 4/5)	9	PCI: 37.9; CABG: 30.2
PARTNER 2A (***intermediate or low risk)***											
• TAVI	45.8	81.5 (6.7)	77.3	NR	5.8 (2.1)	69.2	30.1	37.7	5.0	31.8	PCI: 27.1; CABG: 23.6
• SAVR	45.2	81.7 (6.7)	76.1	NR	5.8 (1.9)	66.5	35.2	34.2	5.2	30.0	PCI: 27.6; CABG: 25.6
STACCATO (***intermediate or low risk)***											
• TAVI	83.5	80 (3.6)	NR	9.4 (3.9)	3.1 (1.5)	NR	NR	2.9	2.9	2.9	PCI: NR; CABG: NR
• SAVR	66.7	82 (4.4)	NR	10.3 (5.8)	3.4 (1.2)	NR	NR	8.3	0.0	2.8	PCI: NR; CABG: NR
NOTION (***intermediate or low risk)***											
• TAVI	46.2	79.2 (4.9)	48.61	8.4 (4.0)	2.9 (1.6)	NR	27.8	17.9	1.4	11.7*	PCI: 7.6; CABG: NR
• SAVR	47.4	79.0 (4.7)	45.5	8.9 (5.5)	3.1 (1.7)	NR	26.5	20.7	0.7	11.9*	PCI: 8.9; CABG: NR

Abbreviation: AF, atrial fibrillation; CAB, coronary artery bypass; CABG, coronary artery bypass grafting; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation; NR, not reported; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgeons (predictor risk of mortality). * Chronic lung disease.

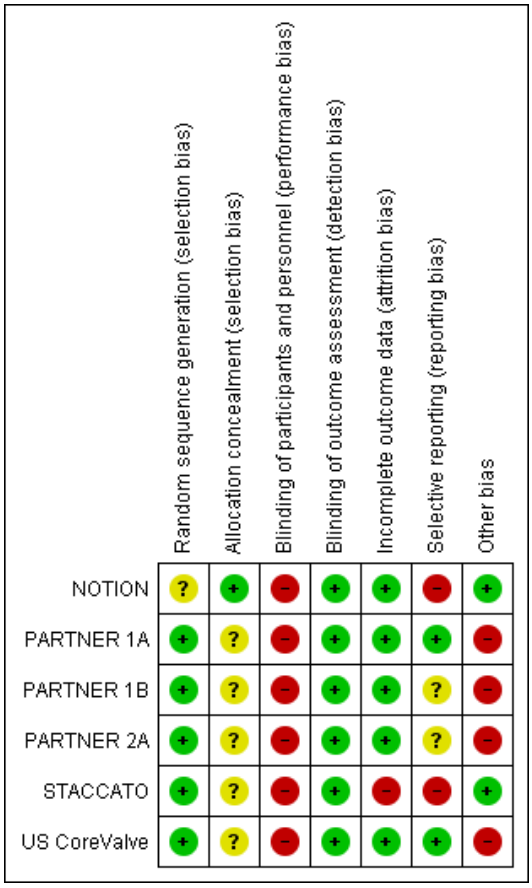

Figure 2. Risk of bias of the 6 RCTs

5.7.3 Matched comparative studies included in the report

The 10 propensity-matched comparative studies were included in this report, 3 of which were in patients for whom SAVR was considered suitable but would pose a high risk and 7 in patients with an intermediate or low risk.

An outline of the 3 studies in patients for whom SAVR was considered suitable but would pose a high risk and baseline patient characteristics are presented in Table 8 and Table 9. Quality assessment of these 3 studies in high-risk patients suitable for SAVR is presented in Table 10.

The 7 studies in intermediate- or low-risk patients were already included in the 4 systematic reviews identified for intermediate- to low-risk patients, thus the characteristics and quality of these studies were not described here.

Table 8. Propensity-matched comparative studies (SAVR is suitable but poses a high risk)

Study	Patients and comparison	Key outcomes	Follow-up
Onorati et al. 2013	Females, 194 in TAVI and 194 in SAVR	Hospital mortality, transfusion, incidence of low cardiac output state, AKI, transprosthetic gradients, postprocedural aortic regurgitation, stroke, major vascular complications, emergent percutaneous coronary intervention, MI	30-day
D'Onofrio et al. 2012	Females 468 in TA-TAVI and 51 in SU-AVR	Hospital mortality, stroke, MI, PPI, dialysis required, pre-discharge echocardiographic data (incidence of paravalvular leak, mean transprosthetic gradient)	30-day*
Higgins et al. 2011	46 in TAVI and 46 in SAVR	Mortality and in-hospital postoperative complication	30-day

Abbreviation: AKI, acute kidney injury; MI, myocardial infarction; PPI, permanent pacemaker implantation; SU-AVR: sutureless aortic valve replacement; TA-TAVI, transapical aortic valve implantation.
* Follow-up length was not very clearly reported. Presumably it was 30 days.

Table 9. Baseline patient characteristics of matched studies (SAVR is suitable but poses a high risk)

Study	Female (%)	Age (year), mean (SD)	NYHA III/IV (%)	Risk level, % or mean (SD)		CAD, (%)	AF, (%)	Diabetes (%)	Kidney disease (%)	COPD (%)	Previous cardiac surgery (%)
				Logistic EuroSCORE, %	STS, mean						
Onorati et al. 2013											
• TAVI	100	79.7 (6.9)	55.2	11.7 (15.4)*	NR	16.5**	NR	38 (19.6)	Reported	11.3	PCI: 11.3; CABG: NR
• Medical therapy	100	80.02 (5.5)	54.1	11.4 (14.0)*	NR	20.6**	NR	48 (24.7)	creatinine level	13.9	PCI: 13.4; CABG: NR
D'Onofrio et al. 2012											
• TAVI	60	82 (76-86)	84.1	26 (14.4)	NR	24.6	21.3	26.9	Dialysis 1.3	32.1	PCI: 34.0; CABG: 42.6
• SU-AVR	12	80(76-83)	58.9	14.2 (8.1)	NR	25.5	11.8	25.5	Dialysis 2	13.7	PCI: 32.5; CABG: 44.2
Higgins et al. 2011											
• TAVI	63	81 (12)	96	NR	NR	51	NR	34	57	51	PCI: 35; CABG: NR
• SAVR	44	69 (12)	41	NR	NR	19	NR	19	15	19	PCI: 6; CABG: NR

Abbreviation: AF, atrial fibrillation; CAB, coronary artery bypass; CABG, coronary artery bypass grafting; CAD, coronary artery disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation; NR, not reported; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgeons (predictor risk of mortality). * EuroSCORE. **1-3 vessels.

Table 10. Quality assessment of matched studies (SAVR is suitable but poses a high risk)

Study ID	Selection	Comparability	Outcome
	Points (max 4)	Points (max 2)	Points (max 3)
D'Onofrio et al. 2012	4	2	3
Higgins et al. 2011	4	2	3
Onorati et al. 2013	4	2	3

Note: the score for each item ranges between 0 (indicating lowest quality) and the maximum value (indicating highest quality).

6 ASSESSMENT OF EFFICACY

Clinical efficacy outcomes such as mortality at longer than 30 days of follow-up, quality of life and change in cardiac function measured by the New York Heart Association (NYHA) classification are presented in this section. Haemodynamic performance data regarding clinical efficacy (including mean aortic-valve area, mean aortic-valve gradients and ejection fraction) are presented in Appendix 8. Evidence is presented separately for patients unsuitable for SAVR, patients with a high surgical risk but suitable for SAVR and those with an intermediate or low surgical risk.

6.1 In patients for whom SAVR is considered unsuitable

No recent systematic reviews comparing TAVI with SAVR in patients for whom SAVR is considered unsuitable were identified.

Only one RCT (PARTNER 1B trial) reported in 4 papers (Kapadia et al. 2015; Kapadia et al. 2014; Makkar et al. 2012; Reynolds et al. 2011) was identified comparing TAVI with medical management in patients unsuitable for SAVR. Some data based on TAVI access route were reported. No sub-group analyses based on TAVI valve size or delivery sheath type or size were available. No matched or non-matched comparative studies reporting efficacy outcomes were identified for TAVI compared with medical management in patients unsuitable for SAVR. The papers reporting relevant outcomes of this trial are presented in Table 11.

The study characteristics, baseline patient characteristics and risk of bias of the PARTNER 1B trial and outline of the 3 papers reporting this trial were previously described in section 5.7.2.

Table 11. Papers reporting the PARTNER 1B trial (TAVI vs medical management in patients unsuitable for SAVR)

Papers	Number of patients analysed	Key relevant outcome
Makkar et al. 2012	179 with TAVI and 179 with control	Two-year clinical outcomes including mortality, NYHA classification, adverse events, and echocardiographic findings
Kapadia et al. 2014	179 with TAVI and 179 with control	Major clinical outcomes at 3 years including death, cardiac death, stroke, major vascular complications, major bleeding, renal failure, new pacemaker, endocarditis, myocardial infarction, aortic valvuloplasty, re-hospitalisation, and

		NYHA I/II; haemodynamic up to 3 years.
Kapadia et al. 2015	179 with TAVI and 179 with control	Mortality, NYHA classification and haemodynamic performance at 5 years of follow-up.
Reynolds et al. 2011	179 with TAVI and 179 with control	Health-related quality of life (KCCQ, SF-12) up to 1 year of follow-up.

Abbreviation: KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association; SF-12, Short Form-12 General Health Survey; vs, versus.

6.1.1 Mortality (patients unsuitable for SAVR)

In patients who are considered to be unsuitable for SAVR, TAVI had a significantly lower mortality rate of both all-cause and cardiac-cause compared with standard medical therapy at follow-up of 1, 2, 3 and 5 years (Table 12). Makkar et al. (2012) stratified the analysis of 2-year all-cause mortality according to STS categories, which showed a significant association between the outcome of TAVI and STS score, with the survival benefit of TAVI diminishing with a higher STS score (p=0.01, log-rank test) but no significant association between the STS score and the poor outcomes of standard therapy (p=0.67, log-rank test). This finding is considered to have moderate quality by our GRADE assessment (Appendix 6).

Table 12. Mortality of TAVI vs medical therapy (unsuitable for SAVR)

Follow-up	Reference paper	TAVI (n=179)	Medical therapy (n=179)	Analysis (HR (95% CI))
At 1-year:	Makkar et al. 2012			
• All-cause		30.7%	50.7%	0.58 (0.36 to 0.92), p=0.02
At 2-year:	Makkar et al. 2012			
• All-cause		43.3%	68.0%	0.56 (0.43 to 0.73), p<0.001
○ STS <5%*		-	-	0.37 (0.13 to 1.01), p=0.04
○ STS 5 to 14.9%*		-	-	0.58 (0.41 to 0.81), p=0.002
○ STS ≥15%*		-	-	0.77 (0.46 to 1.28), p=0.31
• Cardiac cause		31.0%	62.4%	0.44 (0.32 to 0.60), p<0.001
At 3-year:	Kapadia et al. 2014			
• All-cause		54.1%	80.9%	0.53 (0.41 to 0.68), p<0.0001
• Cardiac cause		41.4%	74.5%	0.41 (0.30 to 0.56), p<0.0001
At 5-year:	Kapadia et al. 2015			
• All-cause		71.8%	93.6%	0.5 (0.39 to 0.65), p<0.0001
• Cardiac cause		57.5%	85.9%	0.41 (0.31 to 0.55)

Abbreviation: CI, confidence interval; HR, hazard ratio; vs, versus. Note: percentages shown are Kaplan–Meier estimates. * Stratification according to STS categories <5%, 5 to 14.9%, and ≥15% (on a scale of 0% to 100%, with higher scores indicating greater surgical risk).

6.1.2 NYHA classification (patients unsuitable for SAVR)

At both 1 year and 2 years of follow-ups there were fewer patients in the TAVI arm than in the medical therapy arm in NYHA classes III/IV (Makkar et al. 2012). Reporting of follow-up data was not

presented consistently across years. Kapadia et al. (2014) reported a higher proportion of patients in the TAVI arm in NYHA classes I and II both at follow-ups of 3 years and 5 years (Table 13).

Table 13. NYHA classification: TAVI vs medical therapy (patients unsuitable for SAVR)

Follow-up	Reference	TAVI n/N (%)	Medical therapy n/N (%)	Analysis
1-year (NYHA class III/IV)	Makkar et al. 2012	23.7% (28/118)	60.8% (48/79)	p<0.001
2-year (NYHA class III/IV)	Makkar et al. 2012	16.8% (16/95)	57.5% (23/40)	p<0.001
3-year (NHYA class I/II)	Kapadia et al. 2014	29.7%*	4.8%*	p<0.001
5-year (NHYA class I/II)	Kapadia et al. 2015	86% (42/49 survivors)	60% (3/5 survivors)	p<0.0001

Abbreviation: n, number of patients; NYHA, New York Heart Association (class); vs, versus. * ITT analysis based on 179 patients randomised in each group.

6.1.3 Quality of life (patients unsuitable for SAVR)

Reynolds et al. (2011) reported on quality of life (QoL) in patients who were considered unsuitable for SAVR from the PARTNER 1B trial. Health-related QoL was assessed at baseline and at 1, 6, and 12 months with the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the 12-item Short Form-12 General Health Survey (SF-12). The primary end point was the KCCQ overall summary score. There were no statistically significantly differences between the treatments at baseline in these measures, The KCCQ summary score improved from markedly depressed at baseline in both groups, the extent of improvement was statistically significantly greater with TAVI than with control at 1 month (mean difference between groups (MD) 13, 95% CI 7.6 to 19.0; p<0.001) with larger benefits at 6 months (MD 21, 95% CI 15 to 27; p<0.001) and 12 months (MD 26, 95% CI 19 to 33; p<0.001). At 12 months, the TAVI group also had higher SF-12 physical and mental health scores with mean differences compared with the control group of 5.7 and 6.4 points, respectively (p<0.001 for both comparisons).

Table 14. Quality of life: TAVI vs medical therapy (patients unsuitable for SAVR)

Scale	Mean difference: TAVI (n=179) - SAVR (n=179)	Analysis
KCCQ summary		
• 1-month	13.3	95% CI 7.6 to 19.0, p<0.001
• 6-month	20.8	95% CI 14.7 to 27.0, p<0.001
• 12-month	26.0	95% CI 18.7 to 33.3, p<0.001
KCCQ quality of life		
• 1-month	14.5	95% CI 8.6 to 21.0, p<0.001
• 6-month	24.2	95% CI 17.4 to 31.0, p<0.001
• 12-month	30.5	95% CI 22.3 to 38.7, p<0.001
SF-12 physical		
• 1-month	4.5	95% CI 2.5 to 6.6, p<0.001
• 6-month	5.5	95% CI 3.0 to 7.9, p<0.001
• 12-month	5.7	95% CI 2.8 to 8.5, p<0.001
SF-12 mental		
• 1-month	0.6	95% -1.6 to 2.6, p=0.61

• 6-month	3.2	95% CI 1.1 to 5.3, p=0.003
• 12-month	6.4	95% CI 3.5 to 9.4, p<0.001

Abbreviation: CI, confidence interval; KCCQ, Kansas City Cardiomyopathy Questionnaire; SF-12, Short Form-12 General Health Survey; vs, versus. Note: positive values indicate better health status with TAVI.

6.2 Summary of efficacy outcomes in patients for whom SAVR is considered unsuitable

No systematic reviews evaluating the efficacy of TAVI in patients for whom SAVR is considered unsuitable were identified. One good quality RCT (PARTNER 1B) comparing TAVI with standard care (medical therapy) reported outcomes up to 5 years of follow-up. At all the follow-up points, TAVI demonstrated superiority over medical therapy for all-cause or cardiac mortality and NYHA classification. Compared with medical therapy, TAVI resulted in significant improvements in health-related quality of life that were maintained for at least 1 year. The evidence suggests TAVI to be more effective than medical management for patients for whom SAVR is considered unsuitable.

6.3 In patients for whom SAVR is considered suitable but poses a high risk

No systematic reviews were identified comparing TAVI with SAVR that focused specifically on patients for whom SAVR is considered suitable but poses a high risk.

Two RCTs (US CoreValve and PARTNER 1A) compared TAVI with SAVR in patients for whom SAVR was considered suitable but would pose a high risk. Six papers reported the US CoreValve trial and 12 papers reported the PARTNER 1A trial. The outlines and the baseline patient characteristics of the two trials were previously described in section 5.7.2. The papers reporting relevant outcomes of the two trials are presented in Table 15.

Three propensity-matched comparative studies also compared TAVI with SAVR in patients for whom SAVR was considered suitable but would pose a high risk. The characteristics of these 3 studies are described in Table 8 in section 5.7.3.

Table 15. Papers reporting RCTs (SAVR is suitable but poses a high risk)

Papers	Number of patients analysed	Key outcome	Follow-up
US CoreValve			
Adams et al. 2014	795	Mortality at 30 days and 1 yr	1 yr
Arnold et al. 2015	795	Health status up to 1yr	1 yr
Skelding et al. 2016	353 women of randomised	1-yr survival, composite all-cause mortality or major stroke rate, major stroke, quality of life	1 yr
Zorn et al. 2016	TAVI=389; SAVR=353	Postoperative prosthesis–patient mismatch	1 year
Reardon et al. 2015	797	Clinical and echocardiographic outcomes	2 yrs
Deeb et al. 2016	797	3-yr all-cause mortality or stroke, major adverse cardiovascular or cerebrovascular events, aortic valve haemodynamic, valve thrombosis	3 yrs
PARTNER 1A			
Smith et al. 2011	699	All-cause mortality; cardiovascular mortality, NYHA functional class, re-hospitalisation, MI, stroke, AKI, vascular complications, bleeding, 6-minute walk distance, valve performance	Up to 1 yr
Généreux et al. 2014	699. Data analysed by TAVI route	Bleeding complications	Up to 1 yr
Reynolds et al. 2012	628 who completed baseline questionnaires. Stratified by TAVI route	Health-related quality of life	Up to 1 yr
Lindman et al. 2014	275 with diabetes of those underwent treatment	All-cause mortality, stroke, renal failure requiring dialysis	1 yr
Elmariah et al. 2013	699. Stratified by the presence of left ventricular ejection fraction <50%	All-cause mortality, cardiovascular mortality, stroke, re-hospitalisation, AKI, vascular complications, bleeding, NYHA functional class	1 yr
Pibarot et al. 2014		Incidence of PPM	2 yrs
Hahn et al. 2013	699	Echocardiographic findings	Up to 2 yrs
Kodali et al. 2012	699	All-cause mortality, cardiovascular mortality, stroke, re-hospitalisation, AKI, vascular complications, bleeding events, NYHA functional class	Up to 2 yrs
Williams et al. 2014	699	Procedural mortality by sex	Up to 2 yrs
Greason et al. 2014	288 with a history of CABG	Operative death, stroke, MI, paravalvular regurgitation; all-cause mortality, re-hospitalisation	2 yrs
Miller et al. 2012	699	Neurologic events	2 yrs
Mack et al. 2015	699	All-cause mortality; cardiovascular mortality, stroke, re-hospitalisation, AKI, vascular complications, bleeding, and NYHA class.	5 yrs

Abbreviation: AKI, acute kidney injury; CABG, coronary-artery bypass grafting; MI, myocardial infarction; NYHA, New York Heart Association; PPM, prosthesis-patient mismatch; vs, versus; yr, year.

6.3.1 Mortality in patients for whom SAVR is considered suitable but poses a high risk

6.3.1.1 All-cause mortality

Pooled data from the PARTNER 1A and the US CoreValve trials based on intention-to-treat (ITT) analysis showed a statistically non-significantly lower all-cause mortality rate at 30 days, 1 year (Smith et al. 2011; Adams et al. 2014) and 2 years (Kodali et al. 2012; Reardon et al. 2015) with TAVI than with SAVR, and the difference tended to be smaller over time. Based on ITT analysis the TAVI group had a statistically significantly higher all-cause mortality than the SAVR group at 5 years (Figure 3).

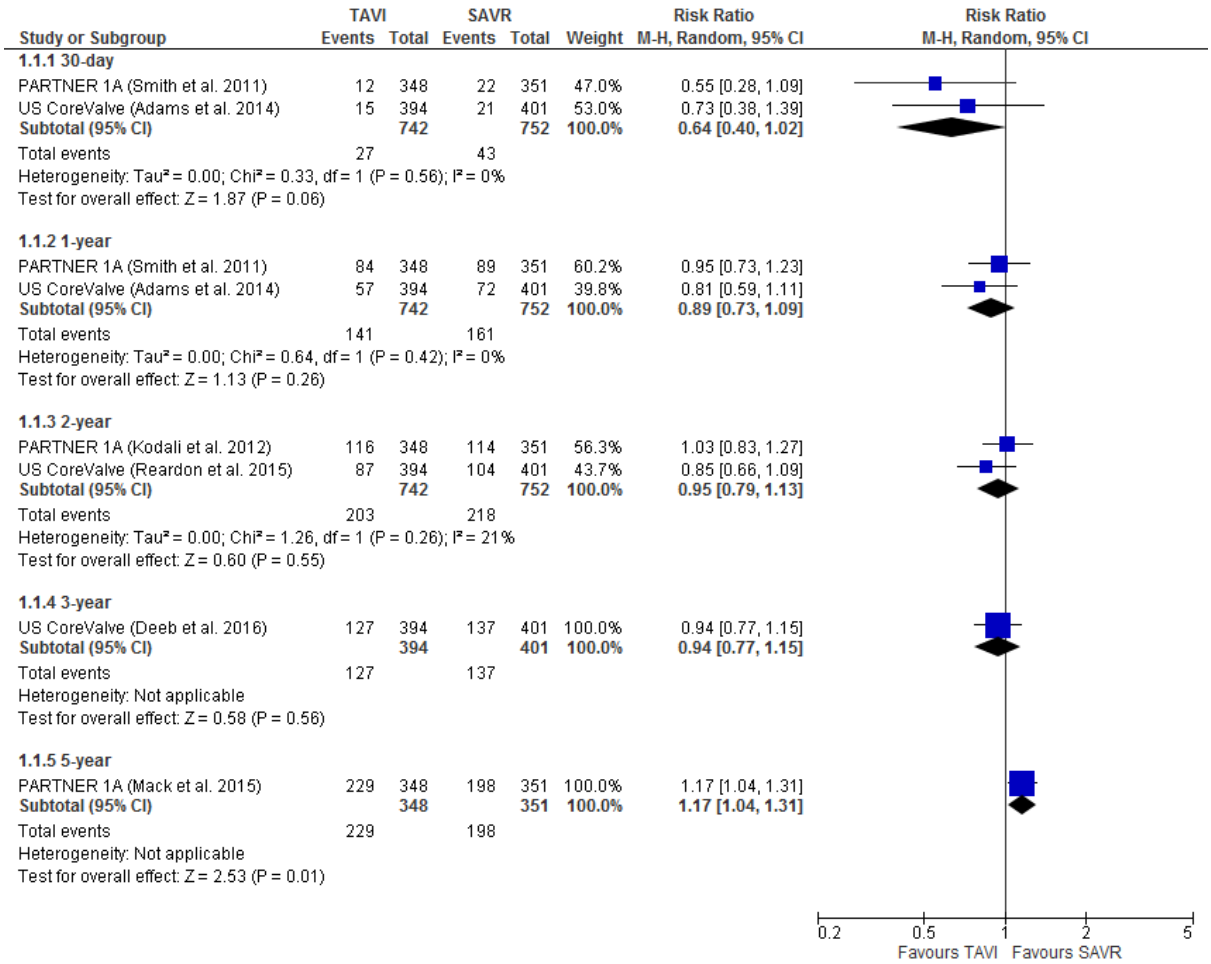

Figure 3. All-cause mortality up to 5 years: ITT analysis (SAVR is suitable but poses a high risk)

A Kaplan-Meier cumulative probability analysis for all-cause mortality up to 3 years of follow-up was reported in the US CoreValve trial. A Kaplan-Meier probability analysis for all-cause mortality up to 5 years of follow up was reported in the PARTNER 1A trial. Individual and pooled hazard ratios showed no statistically significant differences between TAVI and SAVR in hazard of death (Figure 4).

The quality of all-cause mortality outcome is graded as low (Appendix 6).

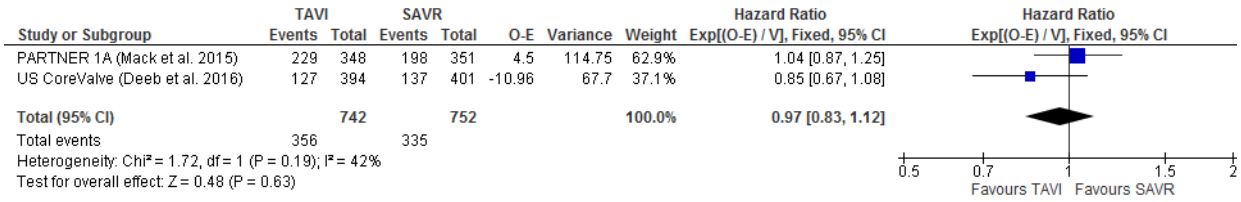

Figure 4. All-cause mortality up to 5 years: time to event (SAVR is suitable but poses a high risk)

6.3.1.2 Cardiovascular mortality

There were no statistically significant differences in individual or pooled cardiovascular mortality at 30 days, 1 years, 2 years and 5 years based on ITT analysis, although it tended to favour SAVR at 5 years (Figure 5).

6.3.1.3 Mortality by TAVI vascular access route

Data on mortality by TAVI vascular access route were only available from the PARTNER 1A study. There was no statistically significant difference between TAVI, performed either via the transfemoral route or the transapical route, and SAVR, in all-cause mortality at follow-up of 1, 2, and 5 years, and in cardiovascular mortality at 1 and 2 years (Table 16).

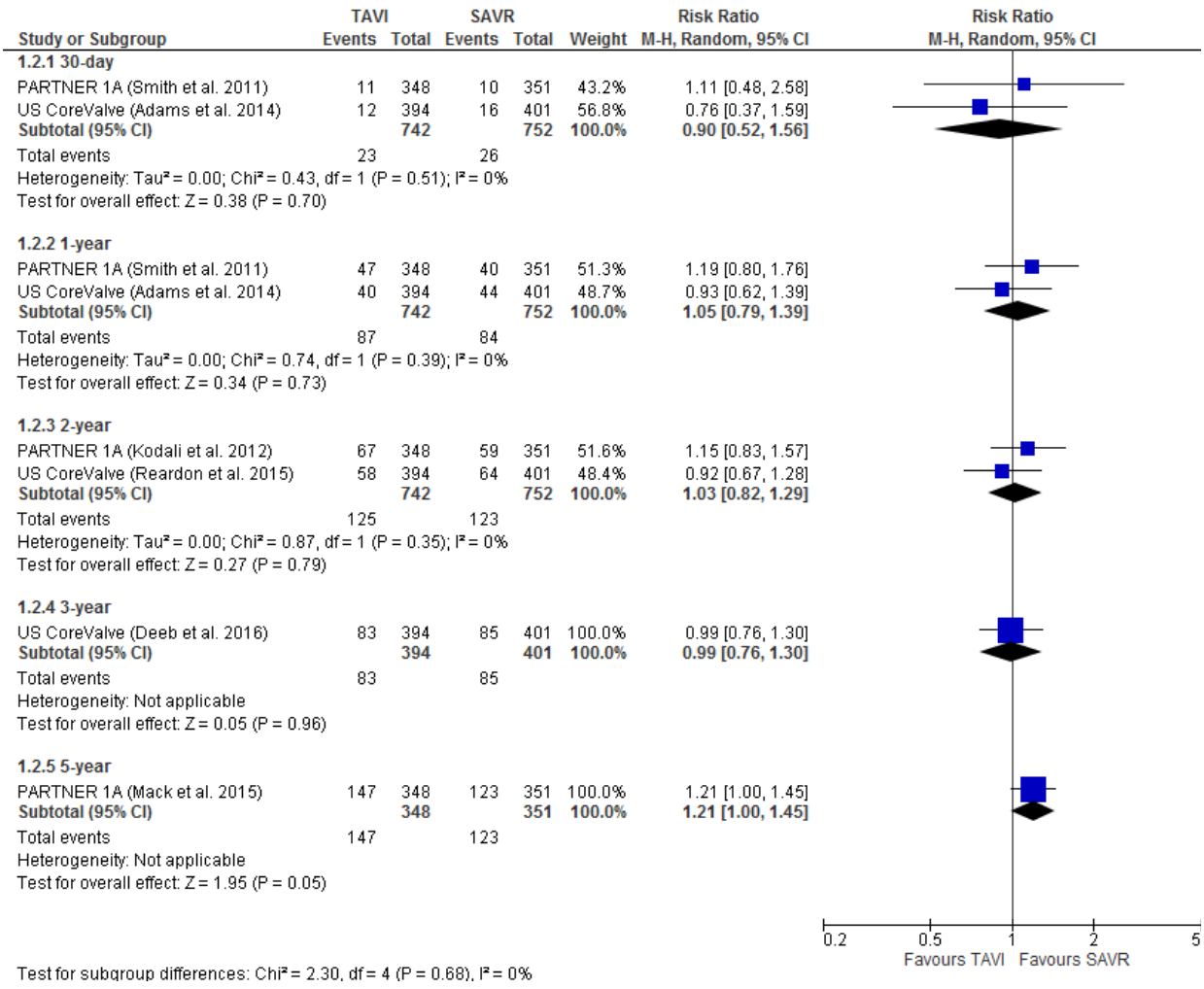

Figure 5. Cardiovascular mortality (SAVR is suitable but poses a high risk)

Table 16. Mortality by TAVI vascular access route (SAVR is suitable but poses a high risk)

Follow-up	Reference for PARTNER 1A	**TF-TAVI** (n=244)	SAVR (n=248)	Analysis
All-cause				
• 1-year	Smith et al. 2011; Kodali et al. 2012	22.2%	26.4%	p=0.29
• 2-year	Kodali et al. 2012	30.9%	34.6%	p=0.38
• 5-year	Mack et al. 2015	64.38%	70.21%	HR 0.91 (95% CI 0.72 to 1.14), p=0.41
Cardiovascular cause				
• 1-year	Smith et al. 2011; Kodali et al. 2012	12.6%	13.3%	p=0.83
• 2-year	Kodali et al. 2012	19.5%	20.6%	p=0.60
Follow-up	Reference	**TA-TAVI** (n=104)	SAVR (n=103)	Analysis
All-cause				
• 1-year	Smith et al. 2011; Kodali et al. 2012	29.0%	27.9%	p=0.85
• 2-year	Kodali et al. 2012	41.1%	35.7%	p=0.44
• 5-year	Mack et al. 2015	85.73%	67.46%	HR 1.37 (95% CI 0.98 to 1.92), p=0.07
Cardiovascular cause				
• 1-year	Smith et al. 2011; Kodali et al. 2012	18.5%	12.3%	p=0.24
• 2-year	Kodali et al. 2012	26.0%	20.5%	p=0.40

Abbreviation: CI, confidence interval; HR, hazard ratio; n, number of patient; TA-TAVI, Transcatheter aortic valve implantation; TF-TAVI, transfemoral aortic valve implantation; SAVR, surgical aortic valve replacement.
* All based on intention-to-treat analysis. Percentages are Kaplan-Meier estimates at the specific time point; p-values are for between-group comparisons of the frequency of the event at each time point (except for the 5-year follow-ups).

6.3.1.4 Reported sub-group analyses of mortality

Elmariah et al. (2013) analysed all-cause mortality in the PARTNER 1A trial by stratifying the data based on left ventricular ejection fraction (LVEF) <50% or ≥50%. All-cause mortality was similar for TAVI and SAVR at 1 year regardless of baseline left ventricular function and valve replacement technique (Table 17). Time-to-event curves for risk of all-cause death for TAVI and SAVR stratified by baseline LVEF showed no difference in 2-year survival between any of the treatment groups (p=0.826).

Table 17. Mortality by LVEF (SAVR is suitable but poses a high risk)

PARTNER 1A (Elmariah et al. 2013)	TAVI (n=108)	SAVR (n=95)	Analysis
LVEF <50%			
• All-cause mortality at 1-year, n (%)	25.9%	23.3%	p=0.648*
• Cardiac mortality at 1-year, n (%)	9.0%	9.8%	p=0.775*
LVEF ≥50%	TAVI (n=224)	SAVR (n=209)	
• All-cause mortality at 1-year, n (%)	22.9%	25.2%	p=0.606*
• Cardiac mortality at 1-year, n (%)	8.9%	5.9%	p=0.187*

Abbreviation: LVEF, left ventricular ejection fraction; n, number of patient. Note: the event rates were Kaplan-Meier estimates. *Calculated by the authors of the current review.

Greason et al. (2014) conducted a subgroup analysis of mortality in the patients with a history of coronary artery bypass grafting (CABG) in the PARTNER 1A trial, and found no statistically significant difference in mortality (both all-cause and cardiovascular cause) between the treatment groups at 1 year and 2 years (Table 18). A similar pattern was seen in patients with previous CABG at 1-year follow-up in the US CoreValve trial (HR 0.50, 95% CI 0.24 to 1.04).

Table 18. Mortality in patients with a history of CABG (SAVR is suitable but poses a high risk)

PARTNER 1A (Greason et al. 2014)	TAVI (n=148)	SAVR (n=140)	Analysis
Any cause, n (%)			
• 1-year	25.0%	18.0%	p=0.19
• 2-year	36.1%	24.7%	p=0.052
Cardiovascular cause, n (%)			
• 1-year	9.5%	6.7%	p=0.47
• 2-year	13.1%	10.2%	p=0.5

Abbreviation: CABG, coronary artery bypass grafting; n, number of patient. Note: the percentages are time-to-event data.

Lindman et al. (2014) analysed all-cause mortality and cardiovascular mortality at 60 days, 1 year and 2 years in patients with diabetes in the PARTNER 1A trial, for whom SAVR was considered suitable but would pose a high risk. Compared with the SAVR group, the TAVI group had a statistically significantly lower hazard of all-cause deaths at 60 days, and the survival benefit just reached significance at 1 year but was no longer significant at 2 years. The analyses by either the

transfemoral route or the transapical route showed no statistically significant differences between TAVI and SAVR at 1 year and 2 years. No statistically significant differences were found in cardiovascular mortality at 1 year of follow-up between the treatment groups (Table 19). Reported in the US CoreValve trial (Adams et al. 2014), the hazard of all-cause deaths at 1 year in patients with diabetes did not differ significantly between the treatment groups (HR 0.72, 95% CI 0.38 to 1.37).

Table 19. Mortality in patients with diabetes (SAVR is suitable but poses a high risk)

PARTNER 1A (Lindman et al. 2014)	TAVI (n=145)	SAVR (n=130)	Analysis, HR (95% CI)
All-cause			
• 60-day	10.3%	23.4%;	0.41 (0.22 to 0.76), p=0.003
• 1-year	18%	27.4%	0.60 (0.36 to 0.99), p=0.044
– TF cohort	16.7%	24.4%	0.61 (0.32 to 1.17), p=0.13
– TA cohort	21.4%	33.6%	0.59 (0.26 to 1.37), p=0.22
• 2-year	26.6%	31.4%	0.76 (0.49 to 1.19), p=0.23
– TF cohort	29.2%	24.8%	0.76 (0.44 to 1.32)
– TA cohort	31.1%	36.0%	0.79 (0.38 to 1.66)
Cardiovascular at 1-year	8.0%	8.3%	0.89 (0.38 to 2.11), p=0.80

Abbreviations: CI, confidence interval; HR, hazard ratio; n, number of patient; TA, transapical; TF, transfemoral. Note: the events rates are time-to-event data.

6.3.2 NYHA classification in patients for whom SAVR is considered suitable but poses a high risk

Two RCTs (US CoreValve and PARTNER 1A) compared TAVI with SAVR for the improvement in symptoms as measured by NYHA class. These two studies reported the proportion of individuals in each NYHA class (where class I and II means no or moderate impairment and III and IV marked or severe impairment). Both at 1 and 6 months in the US CoreValve study a greater proportion of individuals in the SAVR arm were in either class I or II than TAVI. Whereas at 12 months there were no significant differences between the treatment groups (Adams et al. 2014). The proportion of individuals in class I or II were not statistically significant between TAVI and SAVR in the PARTNER A trial at 12 months (Mack et al. 2015).Outcomes at 24 and 36 months were reported for the US CoreValve trial (Reardon et al. 2015; Deeb et al. 2016). At both time points the proportion of individuals in each arm surviving in classes I and II were not statistically significantly different between the treatment arms. Five-year follow-up statistics were provided for PARTNER IA and outcomes for TAVI and SAVR were not statistically significantly different between the treatment groups (Mack et al. 2015). See Table 20 for details.

Table 20. Proportion of patients in NYHA classes (SAVR is suitable but poses a high risk)

Follow-up	Trial	TAVI		SAVR		Analysis
		n. analysed	n (%)	n. analysed	n (%)	
1-month						
• NYHA class I	US CoreValve (Adams el al. 2014)	337	13.4%	331	32.6%	p<0.01*
• NYHA class II	US CoreValve (Adams el al. 2014)	376	39.4%	331	40.8%	
• NYHA class III	US CoreValve (Adams el al. 2014)	376	13.0%	331	18.4%	
• NYHA class IV	US CoreValve (Adams el al. 2014)	376	0.3%	331	4.2%	
6-month						
• NYHA class I	US CoreValve (Adams el al. 2014)	363	5.23%	315	42.5%	p=0.04*
• NYHA class II	US CoreValve (Adams el al. 2014)	363	31.4%	315	33.7%	
• NYHA class III	US CoreValve (Adams el al. 2014)	363	6.1%	315	4.4%	
• NYHA class IV	US CoreValve (Adams el al. 2014)	363	0.3%	315	0.6%	
12-month						
• NYHA class I	US CoreValve (Adams el al. 2014)	365	48.2%	304	44.1%	p=0.10 *
• NYHA class II	US CoreValve (Adams el al. 2014)	365	30.7%	304	28.3%	
• NYHA class III	US CoreValve (Adams el al. 2014)	365	4.7%	304	4.6%	
• NYHA class IV	US CoreValve (Adams el al. 2014)	365	0	304	0.7%	
• NYHA class I/II	PARTNER 1A (Mack et al. 2015)	250	84.8%	226	86.7%	
• NYHA class III/IV	PARTNER 1A (Mack et al. 2015)	250	15.2%	226	13.3%	
24-month						
• NYHA class I	US CoreValve (Reardon et al. 2015)	252	62.7%	190	57.9%	p =0.66**
• NYHA class II	US CoreValve (Reardon et al. 2015)	252	29.4%	190	32.6%	
• NYHA class III	US CoreValve (Reardon et al. 2015)	252	7.5%	190	8.4%	
• NYHA class IV	US CoreValve (Reardon et al. 2015)	252	0.4%	190	1.1%	
36-month						
• NYHA class I	US CoreValve (Deeb et al. 2016)	195	52.3%	146	55.5%	p=0.65**
• NYHA class II	US CoreValve (Deeb et al. 2016)	195	40.0%	146	35.6%	
• NYHA class III	US CoreValve (Deeb et al. 2016)	195	6.2%	146	8.2%	
• NYHA class IV	US CoreValve (Deeb et al. 2016)	195	1.5%	146	0.7%	
60-month						
• NYHA class I/II	PARTNER 1A (Mack et al. 2015)	100	85.0%	97	81.4%	p=0.85**
• NYHA class III/IV	PARTNER 1A (Mack et al. 2015)	100	15.0%	97	18.6%	

Abbreviation: n, number of patient; NYHA, New York Heart Association. * p value for the comparison of TAVI versus SAVR for the overall group of NYHA class I, II, III and IV. ** Calculated by the authors of the current review.

Subgroup analyses of NYHA classification were produced for both the CoreValve and the PARTNER 1A trials. Elmariah et al. (2013) provided separate analyses for patients in the PARTNER 1A trial with a baseline LVEF≤50%. At 30-days, for those with left ventricular dysfunction (defined as LVEF<50%) at baseline, the proportion of patients with NYHA class III/IV or dead was significantly lower in the TAVI than in the SAVR group; whereas there were no significant differences between the treatment groups at both 6 months and 1 year (Table 21).

Table 21. Patients with NYHA class III/IV or dead in those with LVD at baseline (SAVR is suitable but poses a high risk)

PARTNER 1A (Elmariah et al. 2013)	TAVI (n=108)	SAVR (n=95)	Analysis
• 30-day	24%	38%	p=0.04
• 6-month	39%	28%	p=0.97
• 1-year	41%	32%	p=0.37

Abbreviation LVD, left ventricular dysfunction; n, number of patient; NYHA, New York Heart Association.

Greason et al. (2014) reported NYHA classification at 30 days, 6 months, 1 year and 2 years respectively for patients who previously had a CABG in the PARTNER 1A trial. No statistically significant differences were found between the treatment groups at all the follow-up points (Table 22).

Table 22. Patients with NYHA class III/IV in those with a history of CABG (SAVR is suitable but poses a high risk)

PARTNER 1A (Greason et al. 2014), % (n/total n)	TAVI (n=148)	SAVR (n=140)	Analysis, RR (95% CI)
• 30-day	22.2% (30/135)	31.7% (38/120)	0.70 (0.47 to 1.06), p=0.09
• 6-month	18.2% (22/121)	12.4% (13/105)	1.47 (0.78 to 2.77), p=0.23
• 1-year	11.4% (12/105)	12.6% (14/111)	0.91 (0.44 to 1.87), p=0.79
• 2-year	23.6% (21/89)	12.2% (11/90)	1.93 (0.99 to 3.77), p=0.05

Abbreviation: CABG, coronary artery bypass grafting; CI, confidence interval; n, number of patients; NYHA, New York Heart Association; RR, relative risk.

Lindman et al. (2014) reported the percentage of patients in NYHA class III/IV at discharge, 30 days, 6 months and 1 year for patients with diabetes in the PARTNER 1A trial. At both discharge and 30 days there were significantly lower proportions of patients in NYHA class III/IV in the TAVI than in the SAVR group, and the significance did not last at 6 months and 1 year (Table 23).

Table 23. Patients with NYHA class III/IV in those with diabetes (SAVR is suitable but poses a high risk)

PARTNER 1A (Lindman et al. 2014)	TAVI (n=145)	SAVR (n=130)	Analysis
• Discharge/7-day	40%	60%	p=0.003
• 30-day	21%	40%	p=0.002
• 6-month	18%	11%	p=0.18
• 1-year	13%	10%	p=0.58

Abbreviation: n, number of patients; NYHA, New York Heart Association (Functional Classification).

Skelding et al. (2016) reported the proportion of patients with NYHA class I, II, III and IV in women for whom SAVR was considered suitable but would pose a high risk in the US CoreValve trial. No

statistically significant differences were observed between the two treatment groups at 30 days and 1 year (Table 24).

Table 24. Patients with NYHA class I, II, III and IV and dead in women (SAVR is suitable but poses a high risk)

US CoreValve (Skelding et al. 2016)	TAVI		SAVR		Analysis
	n. analysed	n (%) in the class	n. analysed	n (%) in the class	
30-day	175		155		
• NYHA class I		64 (36.6)		43 (27.7)	p=0.124*
• NYHA class II		74 (42.3)		66 (42.6)	
• NYHA class III		29 (16.6)		33 (21.3)	
• NYHA class IV		1 (0.6)		6 (3.9)	
• Dead		7 (4.0)		7 (4.5)	
1- year	166		143		
• NYHA class I		73 (44.0)		63 (44.1)	p=0.102*
• NYHA class II		61 (36.7)		39 (27.3)	
• NYHA class III		7 (4.2)		4 (2.8)	
• NYHA class IV		0 (0.0)		1 (0.7)	
• Dead		25 (15.1)		36 (25.2)	

Abbreviation: n, number of patients; NYHA, New York Heart Association (Functional Classification). * Calculated by the authors of the current review.

Zorn et al. (2016) reported the proportions of patients in different NYHA classifications at 1, 6 and 12 months respectively in patients who had a prosthesis-patient mismatch (PPM) in the US CoreValve trial. In those without severe PPM there was a significantly higher proportion of patients with NYHA III or IV at 1 month, 6 months and 1 year; whereas the differences were insignificant at any of these follow-ups in those with severe PPM (accepting small numbers for analysis) (Table 25).

Table 25. Patients with NYHA III/ IV who had PPM (SAVR is suitable but poses a high risk)

US CoreValve (Zorn et al. 2016)	TAVI		SAVR		Analysis
	n. analysed	n (%) in the class	n. analysed	n. (%) in the class	
1-month					
• Severe PPM	23	2 (21.7)	65	18 (27.7)	p=0.061*
• No severe PPM	331	42 (12.7)	240	52 (21.7)	p=0.004*
6-month					
• Severe PPM	19	2 (10.5)	65	18 (27.7)	p=0.122*
• No severe PPM	305	20 (6.6)	240	52 (21.7)	p <0.05*
1-year					
• Severe PPM	19	1 (5.3)	48	5 (10.4)	p=0.505*
• No severe PPM	282	15 (5.3)	183	19 (5.5)	p=0.040*

Abbreviation: n, number of patients; NYHA, New York Heart Association (Functional Classification); PPM, prosthesis-patient mismatch. Note: severe PPM was defined as the effective orifice area index (EOAi) ≤0.65 cm^2/m^2; no severe PPM was defined as EOAi >0.65 cm^2/m^2. * Calculated by the authors of the current review.

6.3.3 Quality of life in patients for whom SAVR is considered suitable but poses a high risk

Health related quality of life (QoL) was measured by EuroQol five dimensions questionnaire (EQ-5D), SF-12, and KCCQ in both the PARTNER 1A (Reynolds et al. 2012) and the US CoreValve (Arnold et al. 2015) trials. Mean changes in EQ-5D, SF-12, and KCCQ from baseline at 1 month, 2 month and

12 month follow-ups were presented for TAVI compared with SAVR by TAVI route in the categories of transfemoral, transapical and non-transfemoral.

6.3.3.1 EQ-5D

At 1-month follow-up patients receiving TAVI using the transfemoral route reported on average a statistically significantly greater improvement in QoL than patients randomised to the SAVR procedure when measured using EQ-5D in both the PARTNER 1A (Reynolds et al. 2012) and the US CoreValve (Arnold et al. 2015) trials. At 6 and 12 months the difference between those who had TAVI and SAVR had been reduced in both trials and was no longer statistically significant (Table 26). Comparing TAVI using either the transapical or non-transfemoral access with SAVR, the EQ-5D scores showed no statistically significant differences at 1, 6 and 12 months (Table 26).

Figure 6 displays the pooled EQ-5D data from these two trials on the mean differences between the transfemoral TAVI and the SAVR groups in mean changes from baseline at 1 month, 6 months and 1 year. The overall estimates favoured TAVI significantly at 1 month, whereas the differences were insignificant at 6 months and 1 year.

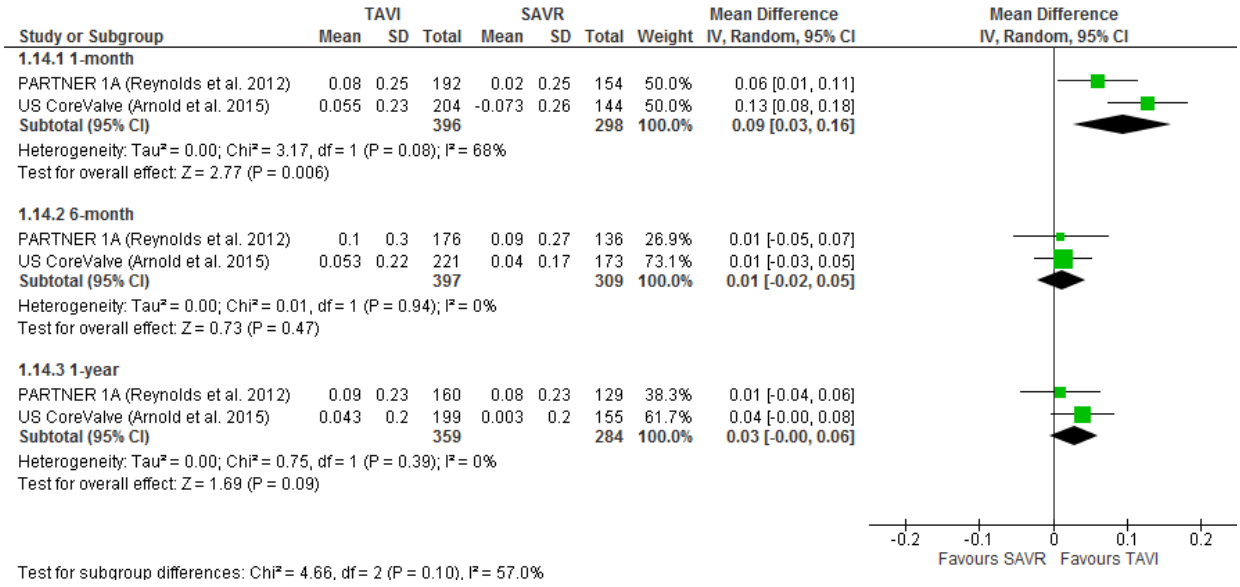

Figure 6. EQ-5D: mean change from baseline – TF TAVI vs SAVR (SAVR is suitable but poses a high risk)

(Standard deviations were calculated for the meta-analysis by the authors of the current review)

Figure 7 displays the pooled EQ-5D data on transapical TAVI versus SAVR from the PARTNER 1A trial and EQ-5D data on non-transfemoral TAVI versus SAVR from the US CoreValve trial. The overall estimates for EQ-5D showed no statistically significant differences between the TAVI and SAVR groups in mean changes from baseline at 1 month, 6 months and 1 year.

The quality of this finding is graded as moderate (Appendix 6).

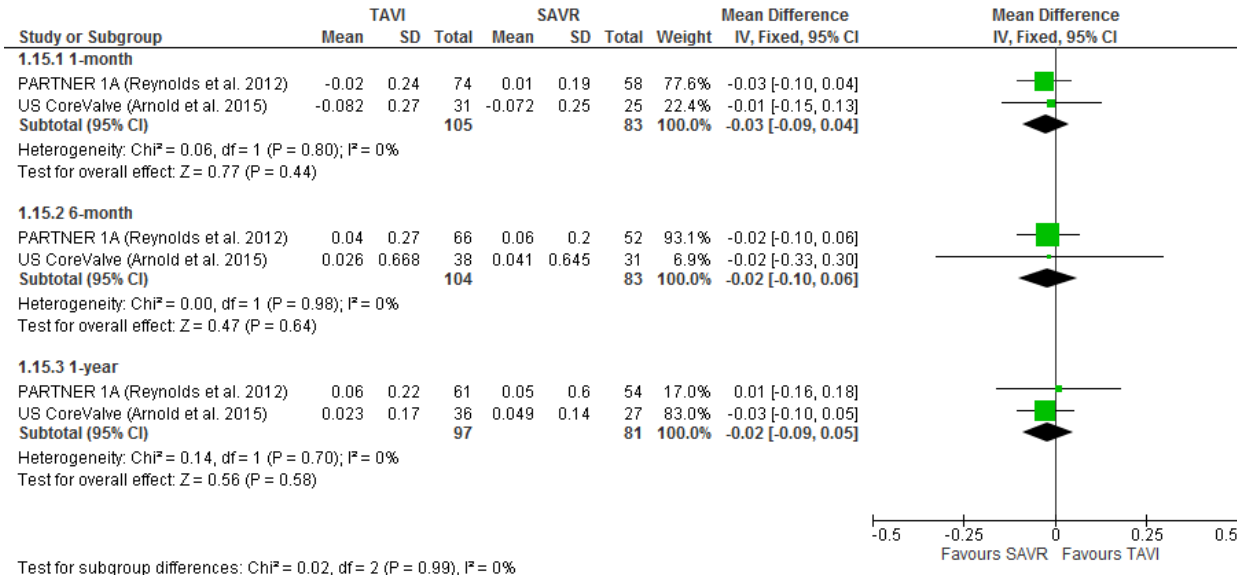

Figure 7. EQ-5D: mean change from baseline: non-TF TAVI vs SAVR (SAVR is suitable but poses a high risk)

(For TAVI the route was transapical in the PARTNER 1A trial and non-transfemoral in the US CoreValve trial. Standard deviations were calculated for the meta-analysis by the authors of the current review)

6.3.3.2 SF-12

Comparing TAVI using transfemoral route with SAVR on SF-12 scores, both the PARTNER 1A (Reynolds et al. 2012) and the US CoreValve (Arnold et al. 2015) trials reported a greater improvement on SF-12 in the TAVI group than in the SAVR group in both physical and mental scores at 1 month follow-up. At 6 months, the only statistically significant difference was reported in the US CoreValve trial (Arnold et al. 2015) for the mental score improvement in the TAVI group compared with the SAVR group. There were no statistically significant differences between TAVI using either the transfemoral or non-transfemoral route and SAVR at 1 year on both physical and mental scores (Table 27).

6.3.3.3 KCCQ

Statistically significant differences in favour of TAVI were reported on the KCCQ quality of life subscale at 1 month follow up for patients where transfemoral access route was used in both PARTNER 1A and US CoreValve studies but no longer significant at 6 months and 1 year (Reynolds et al. 2012; Arnold et al. 2015). There were no statistically significant differences in mean change in KCCQ QoL scores for patients who had received TAVI using either the transapical route in

PARTNER 1A study or non-transfemoral routes in US CoreValve study compared to patients who had received SAVR (Table 28).

At 1 month follow-up the mean differences data from both the individual studies or the pooled estimate showed a statistically significant improvement from baseline in the TAVI group compared with the SAVR group in the mean KCCQ scores (Figure 8).

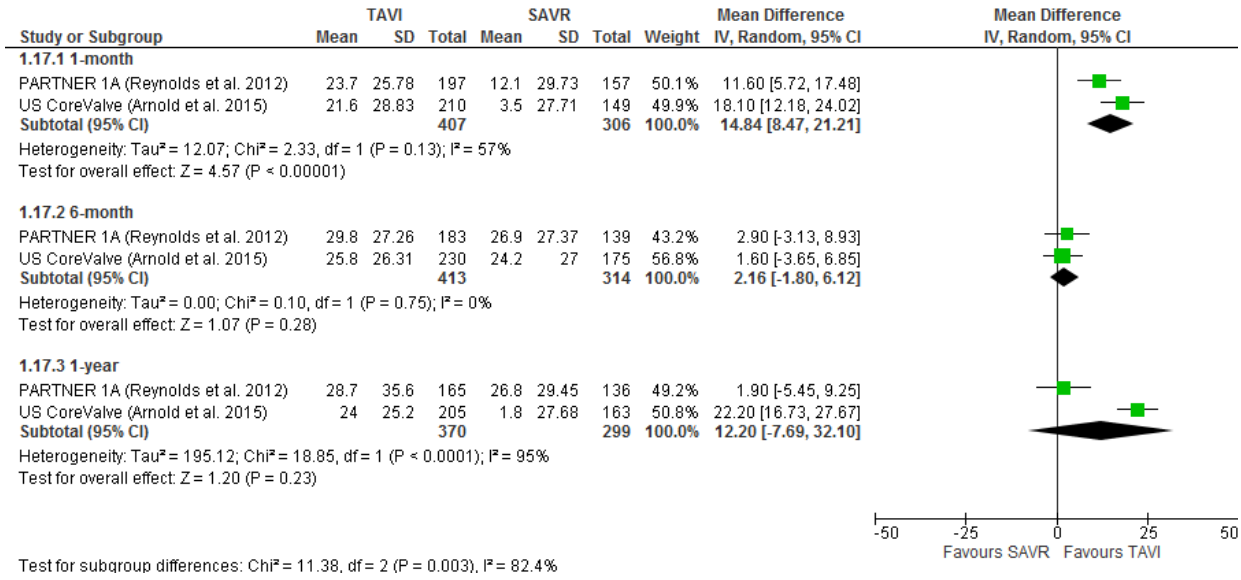

Figure 8. Transfemoral TAVI vs SAVR for KCCQ (SAVR is suitable but poses a high risk)
(Standard deviations were calculated for the meta-analysis by the authors of the current review)

KCCQ scores for transapical TAVI versus SAVR from the PARTNER 1A trial and for non-transfemoral TAVI versus SAVR from the US CoreValve trial were pooled and displayed in Figure 9. The overall estimates showed no statistically significant differences between the TAVI and SAVR groups in mean changes on KCCQ scores from baseline at 1 month, 6 months and 1 year.

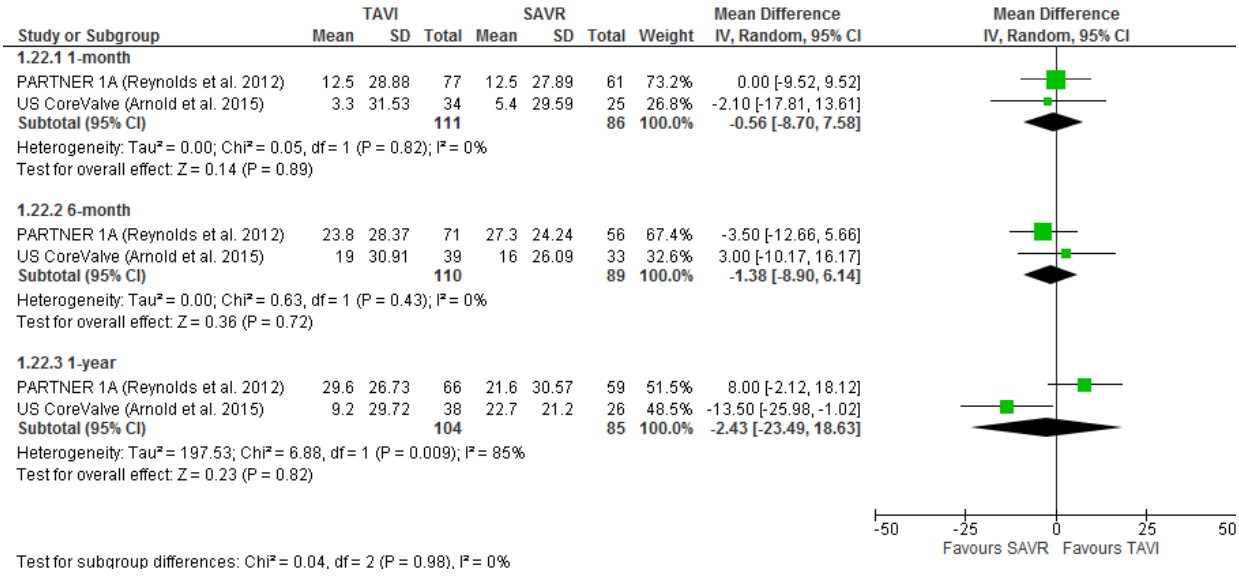

Figure 9. Non-transfemoral TAVI vs SAVR for KCCQ (SAVR is suitable but poses a high risk)

(For TAVI the route was transapical in the PARTNER 1A trial and non-transfemoral in the US CoreValve trial. Standard deviations were calculated for the meta-analysis by the authors of the current review)

Table 26. Mean change (95% CI) in EQ-5D from baseline (SAVR is suitable but poses a high risk)

Follow-up	Trial	TAVI		SAVR		Adjusted mean difference (95% CI)
		TAVI – transfemoral		**SAVR**		
		n	Mean change	n	Mean change	
1-month	PARTNER 1A (Reynolds et al. 2012)	192	0.08	154	0.02	0.06 (0.02 to 0.10), p=0.008
	US CoreValve (Arnold et al. 2015)	204	0.055	144	-0.073	0.117 (0.075 to 0.159), p<0.001
6-month	PARTNER 1A (Reynolds et al. 2012)	176	0.10	136	0.09	0.01 (-0.03 to 0.05), p=0.57
	US CoreValve (Arnold et al. 2015)	221	0.053	173	0.040	0.012 (-0.012 to 0.045), p=0.486
1-year	PARTNER 1A (Reynolds et al. 2012)	180	0.09	129	0.08	0.03 (-0.02 to 0.07), p=0.23
	US CoreValve (Arnold et al. 2015)	199	0.043	155	0.003	0.016 (-0.019 to 0.050), p=0.378
		TAVI – transapical		**SAVR**		
	PARTNER 1A (Reynolds et al. 2012)	n	Mean change	n	Mean change	
1-month		74	-0.02	58	0.03	-0.06 (-0.13 to 0.02), p=0.13
6-month		66	0.04	52	0.06	-0.07 (-0.13 to 0.0), p=0.05
1-year		61	0.06	54	0.05	-0.05 (-0.12 to 0.02), p=0.17
		TAVI – non-transfemoral		**SAVR**		
	US CoreValve (Arnold et al. 2015)	n	Mean change	n	Mean change	
1-month		31	-0.082	25	-0.072	0.042 (-0.051 to 0.136), p=0.375
6-month		38	0.026	31	0.041	-0.004 (-0.0115 to 0.026), p=0.219
1-year		35	0.023	27	0.049	-0.018 (-0.100 to 0.064), p=0.667

Abbreviation: CI, confidence interval; EQ-5D, EuroQol five dimensions questionnaire; n, number of patients. Note: 95% CIs but not standard deviations were reported for the mean changes in the papers.

Table 27. Mean change in SF-12 from baseline (SAVR is suitable but poses a high risk)

Follow-up	Trial	TAVI			SAVR			Adjusted mean difference (95% CI)	
		Transfemoral			SAVR			Physical summary	Mental summary
		n	Physical summary	Mental summary	n	Physical summary	Mental summary		
1-month	PARTNER 1A (Reynolds et al. 2012)	184	5.0	4.3	149	2.6	-0.3	2.0 (0.1 to 3.9), p=0.04	5.4 (3.1 to 7.7), p<0.001
	US CoreValve (Arnold et al. 2015)	186	5.4	3.5	137	0	-2.9	4.9 (3.1 to 6.7), p<0.001	6.1 (3.8 to 8.5), p<0.001
6-month	PARTNER 1A (Reynolds et al. 2012)	149	6.7	5.1	134	7.2	4.0	-0.9 (-3.0 to 1.2), p=0.41	1.2 (-1.0 to 3.5), p=0.28
	US CoreValve (Arnold et al. 2015)	210	6.3	5.2	159	6.8	2.7	-0.3 (-2.1 to 1.4), p=0.721	2.2 (0.3 to 4.1), p=0.026
1-year	PARTNER 1A (Reynolds et al. 2012)	187	6.3	5.3	147	6.1	4.7	0.41 (-2.8 to 2.0), p=0.77	0.4 (-1.8 to 2.7), p=0.69
	US CoreValve (Arnold et al. 2015)	67	5.9	4.8	57	5.1	2.9	0.1 (-2.0 to 2.2), p=0.927	0.8 (-1.3 to 3.0), p=0.456
		Transapical			SAVR				
	PARTNER 1A (Reynolds et al. 2012)	n	Physical summary	Mental summary	n	Physical summary	Mental summary		
1-month		76	2.8	-0.8	61	0.5	1.7	-5.8 (-17.9 to 6.4), p=0.35	0.3 (-2.7 to 3.3), p=0.85
6-month		70	5.2	3.3	57	5.7	3.7	-3.8 (-15.1 to 7.5), p=0.51	-3.3 (-6.7 to 0.0), p=0.05
1-year		66	7.1	3.6	58	4.5	3.9	6.1 (5.9 to 18.1), p=0.32	0.2 (-3.5 to 3.8), p=0.92
		Non-transfemoral			SAVR				
	US CoreValve (Arnold et al. 2015)	n	Physical summary	Mental summary	n	Physical summary	Mental summary		
1-month		29	1.7	-2.8	21	-1.0	0.4	3.2 (-0.09 to 7.4), p=0.126	-0.1 (-5.4 to 5.1), p=0.957
6-month		38	6.3	0.026	32	3.4	2.8	0.1 (-0.35 to 3.7), p=0.975	-1.0 (-5.0 to 2.9), p=0.609
1-year		36	6.6	0.023	25	6.1	4.8	2.9 (-1.9 to 7.8), p=0.237	1.3 (-3.7 to 6.3), p=0.610

Abbreviation: CI, confidence interval; n, number of patients, SF-12, Short Form-12 General Health Survey. Note: 95% confidence intervals but not standard deviations were reported for the mean changes in the papers.

Table 28. Mean change in KCCQ from baseline (SAVR is suitable but poses a high risk)

Follow-up	Trial	TAVI		SAVR		Adjusted mean difference (95% CI)
		Transfemoral				
		n	Mean change	n	Mean change	
1-month	PARTNER 1A (Reynolds et al. 2012)	196	31.5	154	18.9	9.8 (4.0 to 15.6) p=0.001
	US CoreValve (Arnold et al. 2015)	207	30.3	147	10.2	19.0 (13.7 to 24.3) p<0.001
6-month	PARTNER 1A (Reynolds et al. 2012)	182	38.2	137	34.0	0.3 (-5.2 to 5.7) p=0.93
	US CoreValve (Arnold et al. 2015)	224	36.5	172	32.4	4.1 (-0.5 to 8.6) p=0.078
1-year	PARTNER 1A (Reynolds et al. 2012)	165	38.1	130	22.3	-1.9 (-7.6 to 3.7) p=0.50
	US CoreValve (Arnold et al. 2015)	202	34.2	135	33.6	0.2 (-4.5 to 4.9) p=0.948
		Transapical		**SAVR**		
	PARTNER 1A (Reynolds et al. 2012)	n	Mean change	n	Mean change	
1-month		77	22.1	61	20.9	-4.7 (-13.9 to 4.5) p=0.32
6-month		71	32.1	56	34.8	-8.4 (-17.0 to 0.2) p=0.06
1-year		65	41.7	58	29.5	4.8 (-4.0 to 13.17) p=0.28
		Non-transfemoral		**SAVR**		
	US CoreValve (Arnold et al. 2015)	n	Mean change	n	Mean change	
1-month		34	12.6	25	11.3	8.3 (-3.5 to 20.2) p=0.169
6-month		39	27.4	31	23.1	-2.3 (-11.8 to 7.2) p=0.638
1-year		36	22.8	26	31.1	-1.1 (-12.2 to 10.1) p=0.853

Abbreviation: CI, confidence interval; KCCQ, Kansas City Cardiomyopathy Questionnaire; n, number of patients. Note: 95% confidence intervals but not standard deviations were reported for the mean changes in the papers.

6.4 *Summary of efficacy outcomes in patients for whom SAVR is considered suitable but poses a high risk*

Two good quality RCTs (US CoreValve and PARTNER 1A) compared TAVI with SAVR in the patient group for whom SAVR is considered suitable but poses a high risk, with follow-up up to 3 years and 5 years. A total of 18 papers reported findings resulting from these two trials.

Although ITT analysis showed a statistically significantly higher all-cause mortality in the TAVI group at 5 years, time-to-event analysis indicated no statistically significant differences in all-cause mortality between TAVI and SAVR up to 5 years of follow-up. No significant differences were observed in cardiovascular mortality at all follow-up points up to 5 years.

TAVI performed either via the transfemoral route or the transapical route, showed no statistically significant difference from SAVR in all-cause mortality at follow-up of 1, 2, and 5 years, and in cardiovascular mortality at 1 and 2 years.

Subgroup analyses of the two RCTs by LVEF or previous CABG for mortality found no statistically significant differences up to 2 years. For patients with diabetes a statistically significantly higher hazard rate for mortality was observed in the SAVR group at 60 days of follow-up but the significance did not remain beyond this follow-up.

Patients who underwent TAVI had a statistically significantly better NYHA classification profile at short term follow-up, and the statistical significance in differences ceased at longer follow-up. Subgroup analyses on this outcome measure by LVEF, previous CABG, diabetes, patient-prosthesis mismatch (PPM) or sex found a similar pattern, except for patients without severe PPM, for which the SAVR group had a statistically significantly higher rate of patients with NYHA class III/IV.

A statistically significant improvement in quality of life as measured by EQ-5D and KCCQ was observed at 30 days for patients undergoing transfemoral TAVI when compared with SAVR. These differences were not significant at 6 months or 1 year. No statistically significant differences were observed at any of the follow-up points for patients undergoing non-transfemoral TAVI. There was a significant improvement in summary SF-12 in the TAVI group when compared with the SAVR group at 1 months but not 6 months and 1 year.

6.5 In patients for whom SAVR is considered suitable and not to pose a high risk (intermediate or low risk)

As 4 very recent systematic reviews were identified for the patient group for whom SAVR is considered suitable and not to pose a risk (Gargiulo et al. 2016; Siemieniuk et al. 2016; Khan et al. 2016; Arora et al. 2016), and these systematic reviews included the 3 RCTs in patients with an intermediate or low risk (PARTNER 2A; NOTION; STACCATO), key evidence for these patients is drawn from the systematic reviews only. See more details about the 4 systematic reviews and the 3 RCTs in section 5.7.1 and 5.7.2.

In the Siemieniuk et al. (2016) review the authors also evaluated the quality of the key outcomes using the GRADE framework (Table 29).

Table 29. GRADE summary of findings for outcomes (adapted from Siemieniuk et al. 2016)

Outcome (timeframe*)	Study results (95% CI) and measurements	Absolute effect estimates (per 1000)†		Difference (95% CI)	Certainty in effect estimates (quality of evidence)	Summary
		SAVR	TAVI			
Transfemoral TAVI						
Mortality‡ (2 years)	HR 0.79 (0.66 to 0.94). Based on data from 2576 patients in 3 studies; follow up 2 years	152	122	−30 (−49 to −8)	Moderate (serious imprecision)	Probably reduces risk
Stroke (2 years)	RR 0.80 (0.63 to 1.01). Based on data from 2576 patients in 3 studies; follow up 2 years	99	79	−20 (−37 to 1)	Moderate (serious imprecision)	Probably reduces risk
Acute kidney injury (2 years)	RR 0.38 (0.27 to 0.54). Based on data from 2576 patients in 3 studies; follow-up 2 years	85	32	−53 (−62 to −39)	High	Reduces risk
Life threatening or disabling bleeding (2 years)	RR 0.39 (0.29 to 0.54). Based on data from 2576 patients in 3 studies; follow-up 2 years	413	161	−252 (−293 to −190)	High	Reduces risk
Transapical TAVI						
Mortality‡ (2 years)	HR 1.34 (0.91 to 1.97). Based on data from 552 patients in 2 studies; follow up 2 years	196	253	57 (−16 to 153 more)	Moderate (borderline inconsistency and serious imprecision: I^2=45%, wide CI)	Might increase risk
Stroke (2 years)	RR 1.67 (0.97 to 2.87). Based on data from 552 patients in 2 studies; follow up 2 years	67	112	45 (−2 to 125)	Moderate (serious imprecision: wide CI)	Probably increases risk
Acute kidney injury (2 years)	RR 1.54 (0.77 to 3.07). Based on data from 552 patients in 2 studies; follow up 2 years	43	66	23 (−10 to 89)	Low (serious imprecision and inconsistency)	Might increase risk
Life threatening or disabling bleeding (2 years)	RR 0.53 (0.42 to 0.67). Based on data from 552 patients in 2 studies; follow up 2 years	413	219	−194 (−240 to −136)	High	Reduces risk
TAVI *versus* SAVR (outcomes consistent for both TAVI approaches)						
Atrial fibrillation (2 years)	RR 0.43 (0.35 to 0.52). Based on data from 3058 patients in 3 studies; follow-up 2 years	312	134	−178 (−203 to −150)	High	Reduces risk of new onset
Heart failure symptoms (NYHA ≥II) (2 years)	OR 1.29 (1.08 to 1.55). Based on data from 2146 patients in 4 studies; follow-up 2 years	330	389	59 (17 to 103)	High	Increases risk
Moderate/severe heart failure	OR 1.29 (1.08 to 1.55). Based on	69	87	18 (5 to 34)	Moderate (serious imprecision)	Increases risk

Outcome (timeframe*)	Study results (95% CI) and measurements	Absolute effect estimates (per 1000)†		Difference (95% CI)	Certainty in effect estimates (quality of evidence)	Summary
		SAVR	TAVI			
symptoms (NYHA ≥III) (2 years)	data from 2146 patients in 4 studies; follow-up 2 years					
Aortic valve reintervention (2 years)	RR 3.25 (1.29 to 8.14). Based on data from 3058 patients in 3 studies; follow-up 2 years	3	10	7 (1 to 21)	Moderate (serious imprecision: wide CI. Rated down for indirectness because follow-up period not long enough)	Probably increases risk
Permanent pacemaker insertion (2 years)	RR 2.46 (1.17 to 5.15). Based on data from 3128 patients in 4 studies; follow-up 2 years	92	226	134 (16 to 382)	High (I^2=88% but not rated down because all studies suggested benefit)	Increases risk
Myocardial infarction (2 years)	RR 0.87 (0.59 to 1.29). Based on data from 3128 patients in 4 studies; follow-up 2 years	36	31	−5 (−15 to 10)	Moderate (serious risk of bias: inadequate blinding of outcome assessors)	Might have little or no impact
Health related quality of life (2 years)	Measured by: difference from baseline in KCCQ score. Minimal important difference 5 points. Scale: 0-100 (high better). Based on data from 797 patients in 1 study (US Pivotal); follow-up 2 years	Mean 18.7 points	Mean 22.2 points	3.5 (−1.9 to 8.9)	Low (serious risk of bias and serious imprecision)	Might have little or no impact
Length of index admission§	Measured by scale (lower better). Based on data from 2032 patients in 1 study	Median 12.0 days	Median 8.0 days	−4.0 (−5 to −3)	High	Reduces length of stay

Abbreviation: CI, confidence interval; HR, hazard ratio; RR, relative risk; OR, odds ratio; NYHA, New York Heart Association; KCCQ, Kansas City Cardiomyopathy Questionnaire.
*Median follow-up
†Unless otherwise specified.
‡Age adjusted baseline risk of death for ages 75-85, calculated from baseline risk of death with SAVR in a linked meta-analysis of observational studies
§Calculated from baseline risk of death with SAVR in linked meta-analysis of observational studies

6.5.1 Mortality in patients for whom SAVR is considered suitable and not to pose a high risk

The sub-analyses by Gargiulo et al. (2016) for patients in the intermediate or low risk population included 2 RCTs and 6 observational studies. They showed a non-significant difference in all-cause mortality for TAVI compared to SAVR at 30 days (OR 0.67; 95% CI 0.42 to 1.07), midterm i.e. up to 1 year (OR 0.91; 95% CI 0.67 to 1.23) and at a long-term follow-up (>1 year) (OR 1.06; 95% CI 0.59 to 1.91). Outcomes at 30 days and midterm showed moderate heterogeneity.

Siemieniuk et al. (2016) included 4 RCTs, including the CoreValve trial, in which patients had a mean STS risk score of 7% (standard deviation (SD) 3.1). The findings of this systematic review are summarised in the GRADE table as a whole and as transapical and transfemoral sub-groups (Table 29). TAVI was associated with a lower hazard of death at 2 years compared with SAVR when carried out by the transfemoral but not transapical route. Transfemoral TAVI was associated with a 3% reduced risk in mortality at 2 years (HR 0.79; 95% CI 0.66 to 0.94; risk difference -3.0, 95% CI -0.8 to -4.9). Mortality outcome was graded by the authors as to have a moderate quality.

As the quality of the Arora et al. (2016) and Khan et al. (2016) reviews were considered poorer than the above mentioned systematic reviews and they were equally evaluating TAVI for intermediate or low risk, the findings of Arora et al. (2016) and Khan et al. (2016) are only mentioned briefly. Arora et al. (2016) reviewed data for intermediate risk only. They included 1 RCT and 5 observational studies. Their results were similar to Gargiulo et al. (2016), with a non-statistically significant reduction in 30-day mortality with TAVI (OR 0.85; 95% CI 0.57 to 2.45) and no difference at 12 months (OR 0.96; 95% CI 0.75 to 1.23).

Khan et al. (2016) included 1 RCT and 6 observational studies with intermediate-risk patients. They also found no evidence of effect on mortality at 30 days (RR 1.02; 95% CI 0.63 to 1.63) or 1 year (RR 0.99; 95% CI 0.81 to 1.21).

6.5.2 NYHA classification in patients for whom SAVR is considered suitable and not to pose a high risk

Siemieniuk et al. (2016), based on data from 2146 patients in 4 studies with 2 years of follow-up, found that TAVI was associated with an increased risk of heart failure symptoms (NYHA ≥II)

compared to SAVR, OR 1.29 (95% CI 1.08 to 1.55), and graded the quality of this finding as high. The OR for moderate/severe heart failure symptoms (NYHA ≥III) was 1.29 (95% CI 1.08 to 1.55) and the quality of this finding was graded as moderate (serious imprecision).

6.5.3 Quality of life in patients for whom SAVR is considered suitable and not to pose a high risk

Siemieniuk et al. (2016) reported on health related quality of life as measured by: difference from baseline in KCCQ score (minimal important difference 5 points, on a scale of 0-100, higher better). Based on data from 797 patients in 1 study (US CoreValve) with follow-up of 2 years, the mean score for SAVR patients was 18.7 points and the mean for TAVI 22.2 points, the mean difference being 3.5 (95% CI -1.9 to 8.9). This finding was not statistically significant and was graded as of low quality (serious risk of bias and serious imprecision).

6.5.4 Length of index admission in patients for whom SAVR is considered suitable and not to pose a high risk

Siemieniuk et al. (2016) found two RCTs (Leon et al. 2016; Thyregod et al. 2015) that reported length of hospital stay, both reporting statistically significantly shorter length of stay for TAVI (about 33%). The authors were unable to pool the data but, based on 2032 patients in 1 study, TAVI reduced the length of index admission by a median of 4 days (95% CI 3 to 5), with a median of 12 days for SAVR and 8 days for TAVI. This finding was graded as having a high quality. Khan et al. (2016) reported no difference in length of stay between TAVI and SAVR (MD -2.23, 95% CI -5.22 to 0.76).

6.6 Summary of efficacy outcomes in patients in whom SAVR is considered suitable and not to pose a high risk (intermediate or low risk)

When TAVI was compared with SAVR for patients with an intermediate or low risk in the systematic review and meta-analysis by Gargiulo et al. (2016), which included 2 RCTs and 6 observational studies, there were no differences in all-cause mortality at 30 days, 1 year and long-term (>1 year). Siemieniuk et al. (2016) found that TAVI was associated with a lower hazard of death at two years

compared with SAVR when carried out by the transfemoral but not transapical route. Transfemoral TAVI was associated with a 3% reduced risk in mortality at 2 years.

Siemieniuk et al. (2016) found that TAVI compared to SAVR was associated with an increased risk of heart failure symptoms. No statistically significant differences were observed for quality of life.

Siemieniuk et al. (2016) reported on the findings of 2 RCTs showing a statistically significantly shorter length of hospital stay favouring TAVI when compared with SAVR.

6.7 Discussion on efficacy outcomes

RCT evidence on the efficacy of TAVI was available for all risk groups evaluated within this review. In most of the patients TAVI was carried out via the transfemoral route.

TAVI was superior to standard care with medical therapy for patients for whom SAVR is considered unsuitable in all-cause or cardiac mortality and NYHA classification up to 5 years and quality of life at least for 1 year. The key evidence on the efficacy of TAVI for these patients was from one good quality RCT (PARTNER 1B) with a follow-up of 5 years.

For patients for whom SAVR is considered suitable but poses a high risk there were no significant differences between TAVI and SAVR for all-cause and cardiovascular mortality up to 5 years of follow-up. Separate analyses of patients considered suitable for transfemoral TAVI or non-transfemoral TAVI found no statistically significant differences between TAVI and SAVR for all-cause mortality. Although efficacy outcomes such as NYHA classification and quality of life favoured TAVI at shorter follow-ups, the differences ceased to be significant in the long-term. The key evidence for patients with this category of risk was from two good quality RCTs (US CoreValve and PARTNER 1A), with follow-up durations of 3 and 5 years respectively. As there were only two studies included in any of the meta-analyses conducted for the efficacy outcomes, testing for publication bias using funnel plot and testing for robustness of the findings using subgroup analysis could not be conducted.

For patients for whom SAVR is considered suitable and not to pose a high risk (intermediate or low risk) TAVI was associated with a lower hazard of death at 2 years when using the transfemoral route. No significant differences were found with TAVI compared to SAVR for all-cause mortality at 30 days or long-term follow-up or for measures of quality of life. TAVI was associated with an increased risk of heart failure symptoms but shorter length of hospital stay. Evidence on efficacy for these patients has been summarised from 4 systematic reviews, two of which were of higher methodological quality.

A caveat around these findings is that some overlap in risk categories between studies was observed in the RCTs and systematic reviews included. If, the inclusion of “medium” or “intermediate” risk is relaxed to include data from the CoreValve trial, as done in the systematic review of Siemienuik et al. (2016), then 2 year mortality is improved by 3% when transfemoral TAVI is compared to SAVR. However, the CoreValve study (Adams et al. 2014) recruited patients with “increased risk” (at least 15%) of mortality but was eligible for this systematic review as the mean STS score was less than 8.

Hence results from Siemienuik et al. (2016) may not be generalisable to lower-risk populations or sub-groups. The CoreValve study has been included in the systematic review of TAVI in high risk patients presented in this report. Given these overlapping and conflicting inclusion criteria, it is difficult to clearly delineate risk groups in study level systematic reviews and meta-analyses. An individual patient data meta-analysis with sufficiently wide inclusion criteria might be better able to quantify outcomes for clearly defined surgical risk groups.

7 ASSESSMENT OF SAFETY

Clinical safety data such as mortality up to 30 days of follow-up, stroke, major bleeding, major vascular complications, acute kidney injury, myocardial infarction, permanent pacemaker implantation and prosthesis-patient mismatch, are reported in this section. Haemodynamic performance data regarding safety, i.e. aortic regurgitation, are also presented in this section. Evidence is presented separately for patients for whom SAVR is considered unsuitable, patients for whom SAVR is considered suitable but poses a high risk, and those for whom SAVR is considered suitable and not to pose a high risk.

7.1 Safety events in patients for whom SAVR is considered unsuitable

No recent systematic reviews comparing TAVI with SAVR in patients for whom SAVR is considered unsuitable were identified.

One RCT (PARTNER 1B trial) reported in 3 papers (Makkar et al. 2012; Kapadia et al. 2014; Kapadia et al. 2015) was identified comparing TAVI with standard medical therapy in patients for whom SAVR is considered unsuitable. Details of the baseline characteristics and risk of bias of the PARTNER 1B trial and the papers reporting this trial were previously described in section 5.7.2.

Mortality at 30 days of follow-up showed no statistically significant difference between the TAVI group and the standard medical therapy group (2.6% versus 5.9%, p=0.09) (Kapadia et al. 2014). The quality of this finding is graded as moderate (Appendix 6).

The hazard of stroke in the TAVI group up to 1, 2 and 3 years were all statistically significantly higher than in the standard medical therapy group. Then the significance did not maintain up to 5 years (Table 30).

Table 30. All stroke: TAVI vs medical therapy (unsuitable for SAVR)

Follow-up	Reference	TAVI (n=179)	Medical therapy (n=179)	Analysis, HR (95% CI)
1-year	PARTNER 1B (Makkar et al. 2012)	11.2%	5.5%	p<0.001
2-year	PARTNER 1B (Makkar et al. 2012)	13.8%	5.5%	2.79 (1.25 to 6.22), p=0.009
3-year	PARTNER 1B (Kapadia et al. 2014)	15.7%	5.5%	2.81 (1.26 to 6.26), p=0.012
5-year	PARTNER 1B (Kapadia et al. 2015)	16%	18.2%	1.39 (0.62 to 3.11), p=0.555

Abbreviation: CI, confidence interval; HR, hazard ratio; n, number of patients; vs, versus. Note: all estimates represent Kaplan–Meier estimates.

TAVI was associated with statistically significantly higher risk of major bleeding up to 1 year, with the difference becoming non-significant between the treatment groups at 2 years, and then statistically significantly lower in the TAVI group at 3 years (Table 31). The quality of this finding is graded as moderate (Appendix 6).

Table 31. Major bleeding: TAVI vs medical therapy (unsuitable for SAVR)

Follow-up	Reference	TAVI (n=179)	Medical therapy (n=179)	Analysis
1-year	PARTNER 1B (Makkar et al. 2012)	24.2%	14.9%	p=0.04
2-year	PARTNER 1B (Makkar et al. 2012)	28.9%	20.1%	p=0.09
3-year	PARTNER 1B (Kapadia et al. 2014)	32.0%	32.9%	HR 1.69 (95% CI 1.06 to 2.70), p=0.03*

Abbreviation: CI, confidence interval; HR, hazard ratio; n, number of patients; vs, versus. Note: percentages shown are Kaplan–Meier estimates. * There was some discrepancy in the paper: the p value reported in the table 1 in the paper was 0.92 while in the text was 0.03; according to the 95% CI the p value of 0.92 should be incorrect.

The hazard rate of major vascular complications at 3 years of follow-up was statistically significantly higher in the TAVI group (Table 32).

Table 32. Major vascular complications: TAVI vs medical therapy (unsuitable for SAVR)

Follow-up	Reference	TAVI (n=179)	Medical therapy (n=179)	Analysis
3-year	PARTNER 1B (Kapadia et al. 2014)	17.4%	2.8%	HR 8.27 (95% CI 2.92 to 23.44), p<0.0001

Abbreviation: CI, confidence interval; HR, hazard ratio; n, number of patients; vs, versus.

There were no statistically significant differences between TAVI and medical management in the risk of permanent pacemaker implantation (PPI) (Table 33), myocardial infarction (MI) (Table 34), acute kidney injury (AKI) (Table 35) and endocarditis (Table 36) at 1, 2 and 3 years. The quality of this finding is graded as moderate (Appendix 6).

Table 33. PPI: TAVI vs medical therapy (unsuitable for SAVR)

Follow-up	Reference	TAVI (n=179)	Medical therapy (n=179)	Analysis
1-year	PARTNER 1B (Makkar et al. 2012)	4.7%	8.6%	p=0.15
2-year	PARTNER 1B (Makkar et al. 2012)	6.4%	8.6%	p=0.47
3-year	PARTNER 1B (Kapadia et al. 2014)	7.6%	8.6%	p=0.75

Abbreviation: PPI, permanent pacemaker implantation; n, number of patients; vs, versus. Note: percentages are Kaplan-Meier estimates.

Table 34. Myocardial infarctions: TAVI vs medical therapy (unsuitable for SAVR)

Follow-up	Reference	TAVI (n=179)	Medical therapy (n=179)	Analysis
1-year	PARTNER 1B (Makkar et al. 2012)	0.8%	0.7%	p=0.91
2-year	PARTNER 1B (Makkar et al. 2012)	1.6%	2.5%	p=0.69
3-year	PARTNER 1B (Kapadia et al. 2014)	4.1%	2.5%	p=0.59

Abbreviation: n, number of patients; vs, versus. Note: percentages are Kaplan-Meier estimates.

Table 35. Renal failure: TAVI vs medical therapy (unsuitable for SAVR)

Follow-up	Reference	TAVI (n=179)	Medical therapy (n=179)	Analysis
1-year	PARTNER 1B (Makkar et al. 2012)	2.3%	4.7%	p=0.26
2-year	PARTNER 1B (Makkar et al. 2012)	3.2%	7.6%	p=0.15
3-year	PARTNER 1B (Kapadia et al. 2014)	3.2 %	11.1%	p=0.08

Abbreviation: n, number of patients; vs, versus. Note: percentages shown are Kaplan-Meier estimates.

Table 36. Endocarditis: TAVI vs medical therapy (unsuitable for SAVR)

Follow-up	Reference	TAVI (n=179)	Medical therapy (n=179)	Analysis
1-year	PARTNER 1B (Makkar et al. 2012)	1.4%	0.8%	p=0.62
2-year	PARTNER 1B (Makkar et al. 2012)	2.3%	0.8%	p=0.32
3-year	PARTNER 1B (Kapadia et al. 2014)	2.3%	0.8%	p=0.32

Abbreviation: n, number of patients; vs, versus. Note: percentages shown are Kaplan–Meier estimates.

TAVI had a statistically significantly lower hazard rate of repeat hospitalisation due to aortic stenosis or TAVI complications at 1, 2, 3 and 5 years (Table 37). The quality of this finding is graded as moderate (Appendix 6).

Table 37. Re-hospitalisation due to AS or TAVI complication: TAVI vs medical therapy (unsuitable for SAVR)

Follow-up	Reference	TAVI (n=179)	Medical therapy (n=179)	Analysis
1-year	PARTNER 1B (Makkar et al. 2012)	27.0%	53.9%	p<0.001
2-year	PARTNER 1B (Makkar et al. 2012)	35%	72.5%	HR 0.41 (95% CI 0.30 to 0.58), p<0.001
3-year	PARTNER 1B (Kapadia et al. 2014)	43.5%	75.5%	p<0.0001
5-year	PARTNER 1B (Kapadia et al. 2015)	47.6%	87.3%	p<0.0001

Abbreviation: AS, aortic stenosis; CI, confidence interval; HR, hazard ratio; n, number of patients; vs, versus. Note: percentages shown are Kaplan–Meier estimates.

Data on aortic regurgitation were reported only for patients undergoing TAVI in the PARTNER 1B trial. They are presented in Appendix 8.

7.2 Summary of safety outcomes in patients for whom SAVR is considered unsuitable

Evidence on safety outcomes in patients for whom SAVR is considered unsuitable was from one good quality RCT (PARTNER 1B) comparing TAVI with standard care (medical therapy) for follow-up points of 1, 2, 3 and 5 years. No statistically significant differences were found between the treatment groups in 30-day mortality. Compared with patients receiving medical therapy, patients with TAVI had a statistically significantly higher risk of stroke up to 3 years. TAVI was associated with a statistically significantly higher risk of major bleeding up to 1 year, with the difference becoming non-significant between the treatment groups at 2 years, and then statistically significantly lower in the TAVI group at 3 years. The risk of major vascular complications was only reported for 3 years of follow-up and showed over 8 times more frequent in the TAVI than in the medical therapy group with the difference being statistically significant. There was no statistically significant difference between the treatments in the risk of permanent pacemaker implantation, myocardial infarction, acute kidney injury and endocarditis at 1, 2 and 3 years. Patients with TAVI had a statistically significantly lower risk of re-hospitalisation due to aortic stenosis or TAVI complication at 1, 2, 3 and 5 years.

7.3 Safety events in patients for whom SAVR is considered suitable but poses a high risk

No systematic reviews were identified comparing TAVI with SAVR that focused specifically on patients for whom SAVR is considered suitable but poses a high risk.

Two RCTs (US CoreValve and PARTNER 1A) reported in a number of papers, and 3 matched comparative studies were identified comparing TAVI with SAVR in patients for whom SAVR is considered suitable but poses a high risk. They were described previously in section 5.7.2. An outline and quality assessment of the matched studies was described in section 5.7.3.

7.3.1 Mortality at 30 days in patients for whom SAVR is considered suitable but poses a high risk

Both individual and pooled mortality rates at 30 days although tended to favour the TAVI group than the SAVR group showed no statistically significant differences between the two treatment groups (Figure 10).

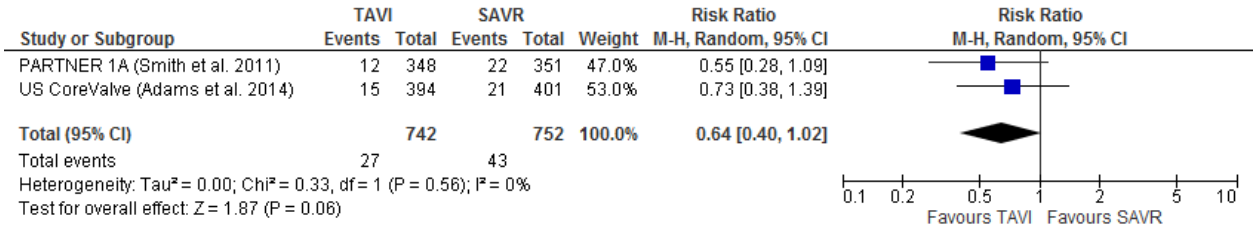

Figure 10. All-cause mortality at 30 days (SAVR is considered suitable but poses a high risk)

Data on mortality at 30 days by TAVI vascular access route were available from the PARTNER 1A study. There were no statistically significant differences in 30-day mortality between TAVI, either via the transfemoral route or via the transapical route, and SAVR (Table 38). The quality of this finding is graded as moderate (Appendix 6).

Table 38. Mortality at 30 days by TAVI route (SAVR is suitable but poses a high risk)

PARTNER 1A (Smith et al. 2011)	TF-TAVI (n=244)	SAVR (n=248)	Analysis
• All-cause	3.3%	6.2%	p=0.13
• Cardiac	3.3%	3.0%	p=0.85
PARTNER 1A (Smith et al. 2011)	TA-TAVI (n=104)	SAVR (n=103)	Analysis
• All-cause	3.8%	7.0%	p=0.32
• Cardiac	2.9%	3.0%	p=0.95

Abbreviations: n, number of patients; TA, transapical; TF, transfemoral. Note: event rates are time-to-event data.

Data on mortality at 30 days in the PARTNER 1A trial were also analysed by left ventricular fraction (

Table 39), in patients with a history of coronary artery bypass grafting (Table 40), and in patients with diabetes (Table 41). No statistically significant differences were observed between the TAVI group and the SAVR group.

Table 39. Mortality at 30 days by LVEF (SAVR is suitable but poses a high risk)

PARTNER 1A (Elmariah et al. 2013)	TAVI (n=108)	SAVR (n=95)	Analysis
LVEF <50%			
• All-cause mortality	6 (5.6)	9 (9.5)	p=0.287*
• Cardiac mortality	4 (3.7)	6 (6.4)	p=0.391*
LVEF ≥50%	TAVI (n=224)	SAVR (n=209)	
• All-cause mortality	12 (5.4)	16 (7.7)	p=0.331*
• Cardiac mortality	9 (4.0)	3 (1.5)	

Abbreviation: n, number of patients; LVEF, left ventricular ejection fraction; n, number of patients. *Calculated by the authors of the current review.

Table 40. Mortality at 30 days or at hospital discharge in patients with a history of CABG (SAVR is suitable but poses a high risk)

PARTNER 1A (Greason et al. 2014)	TAVI (n=148)	SAVR (n=140)	Analysis
• Aall cause	6.8 %	5.7%	p=0.71
• Cardiovascular cause	3.4%	2.9%	p=1

Abbreviation: CABG, coronary artery bypass grafting. Note: the percentages are time-to-event data.

Table 41. Mortality at 30 days in patients with diabetes (SAVR is suitable but poses a high risk)

PARTNER 1A (Lindman et al. 2014)	TAVI (n=145)	SAVR (n=130)	Analysis, HR (95% CI)
• Any cause	3.4%	6.2%	0.56 (0.18 to 1.70), p=0.29
– TF cohort	1.9%	6.9%	0.28 (0.06 to 1.39), p=0.09
– TA cohort	7.1%	4.8%	1.51 (0.25 to 9.07), p=0.65
• Cardiovascular	1.4%	3.2%	0.44 (0.08 to 2.42), p=0.33

Abbreviation: CI, confidence interval; HR, hazard ratio; n, number of patients; TA, transapical; TF, transfemoral. Note: the events rates are time-to-event data.

A small study (Higgins et al. 2011) compared all-cause mortality at 30 days in 46 patients for whom SAVR was considered suitable but would pose a high risk and who had undergone TAVI with that in 46 matched patients within the same risk category who had undergone SAVR. No significantly significant difference was found between the TAVI (13.0%) group and the SAVR group (11.0%).

Hospital mortality in women for whom SAVR is considered suitable but poses a high risk was reported in a propensity-matched study comparing TAVI with sutureless aortic valve replacement (SU-AVR) (D'Onofrio et al. 2012) and another matched study comparing TAVI with SAVR (Onorati et al. 2013) in a registry. No statistically significant difference was found in both studies. There is a discrepancy between the numbers of death and the death rates reported in the Onorati et al. (2013) paper, with the reported hospital mortality being 3.1% (17 deaths in 194 patients) for the TAVI group and 4.1% (9 deaths in 194 patients) for the SAVR group.

7.3.2 Stroke or transient ischemic attack in patients for whom SAVR is considered suitable but poses a high risk

Both pooled and individual risk ratios from the PARTNER 1A and US CoreValve trials showed no statistically significant differences in the incidence of all stroke in 30 days, 1 year, 2 years, 3 years and 5 years (Figure 11). A similar pattern was shown on both the incidence of major stroke and minor stroke at 30 days, 1 year, 2 years and 3 years (Figure 12 and Figure 13). The quality of the finding on all stroke is graded as very low (Appendix 6).

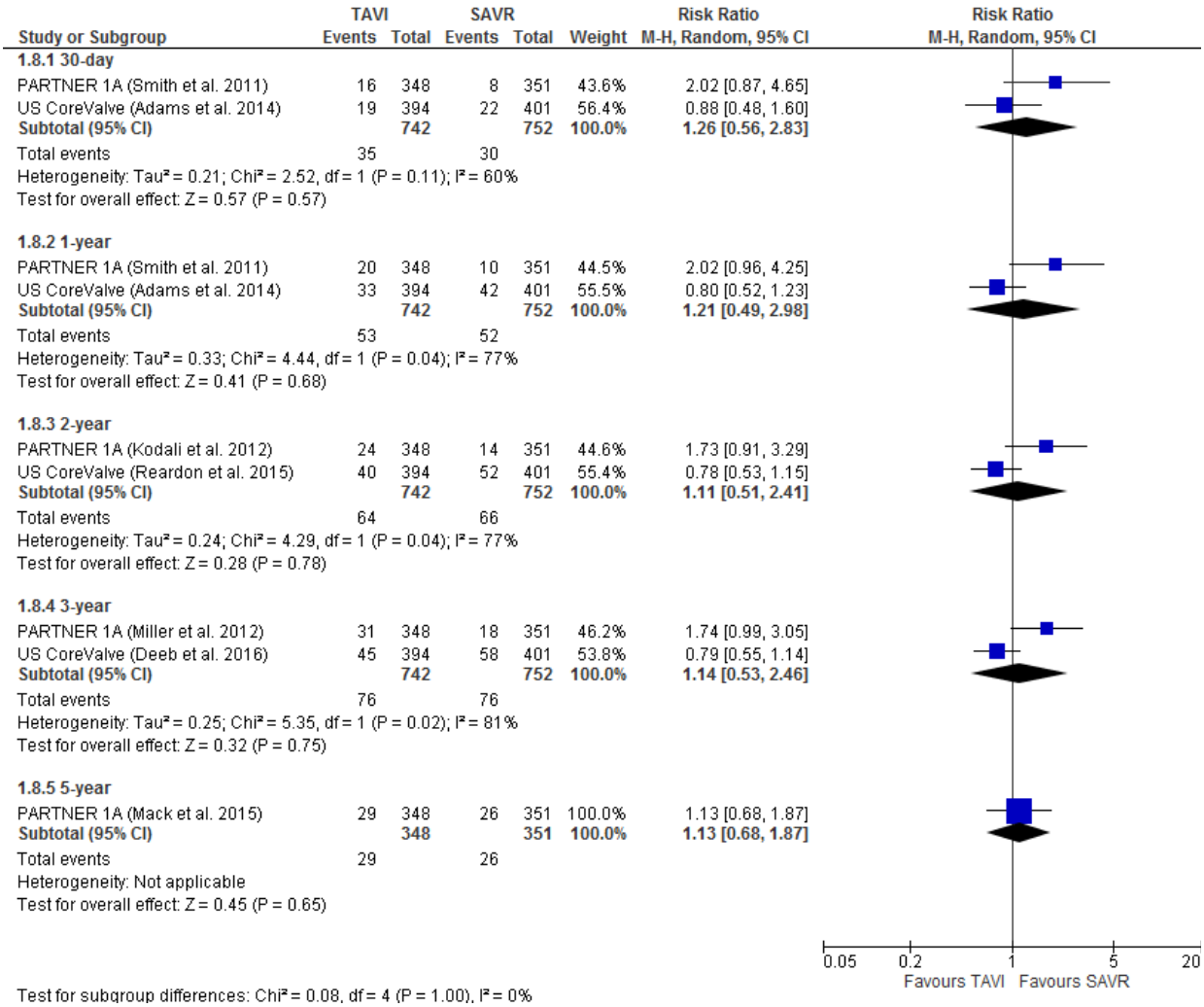

Figure 11. All stroke (SAVR is suitable but poses a high risk)

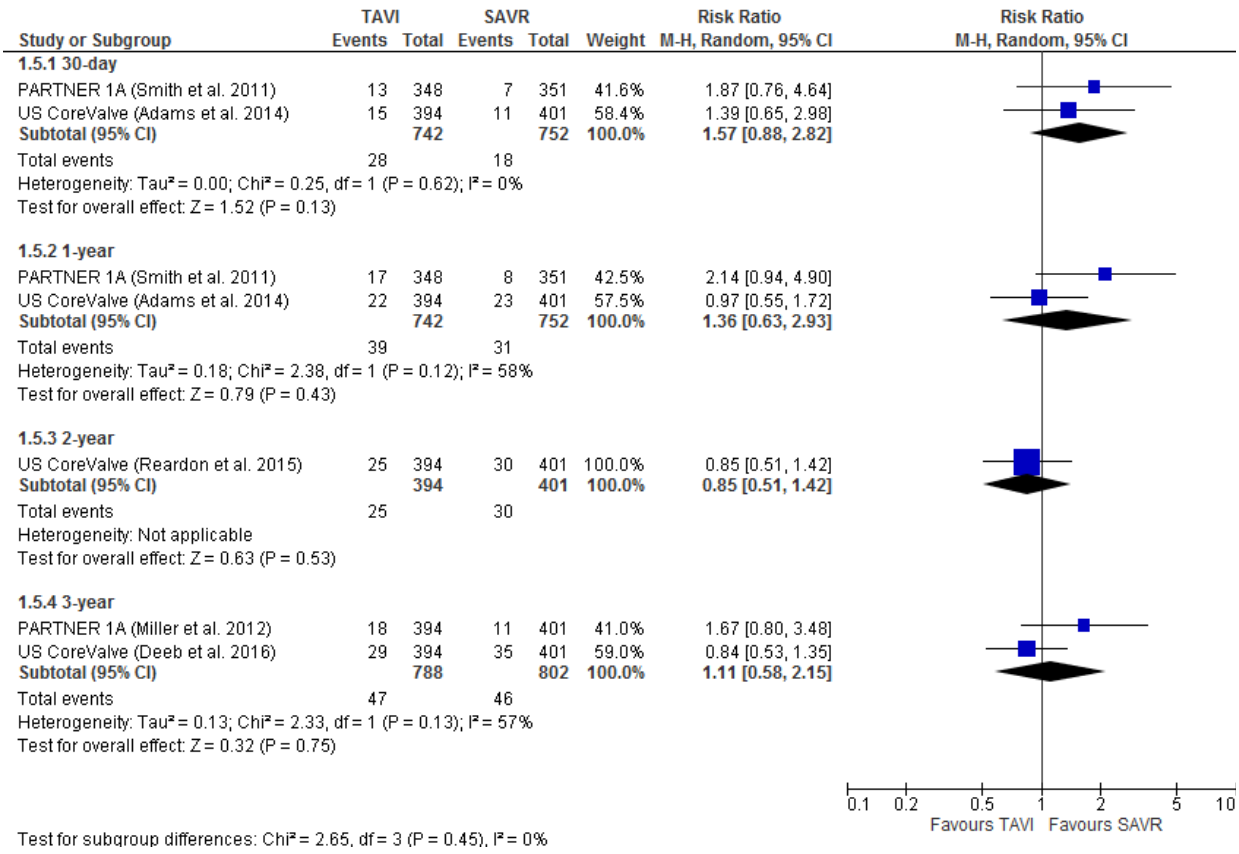

Figure 12. Major stroke (SAVR is suitable but poses a high risk)

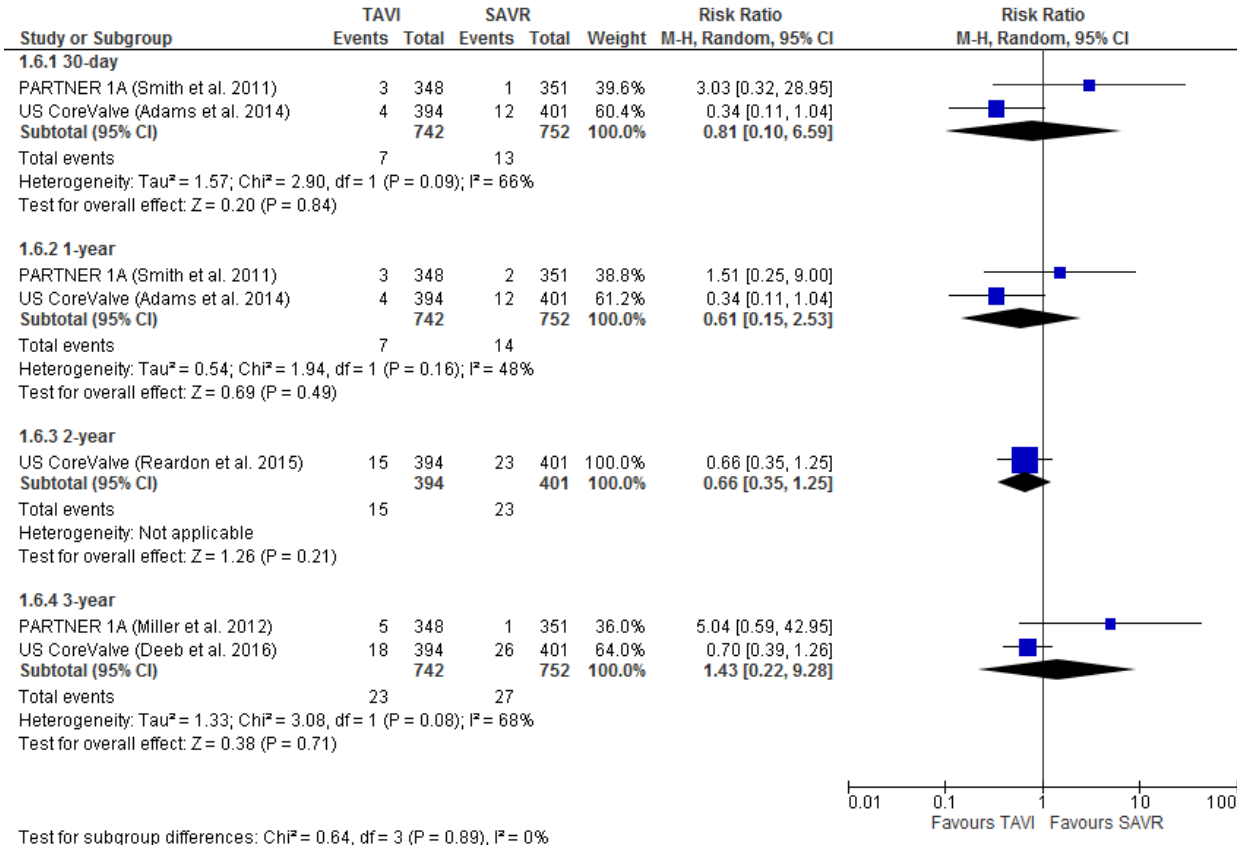

Figure 13. Minor stroke (SAVR is suitable but poses a high risk)

Based on ITT analysis, both pooled and individual risk ratios for transient ischemic attack (TIA) from the PARTNER 1A and US CoreValve trials showed no statistically significant differences at 30 days, 1 year, 2 years, 3 years and 5 years, although at all these time points the results tended to favour the SAVR group (Figure 14).

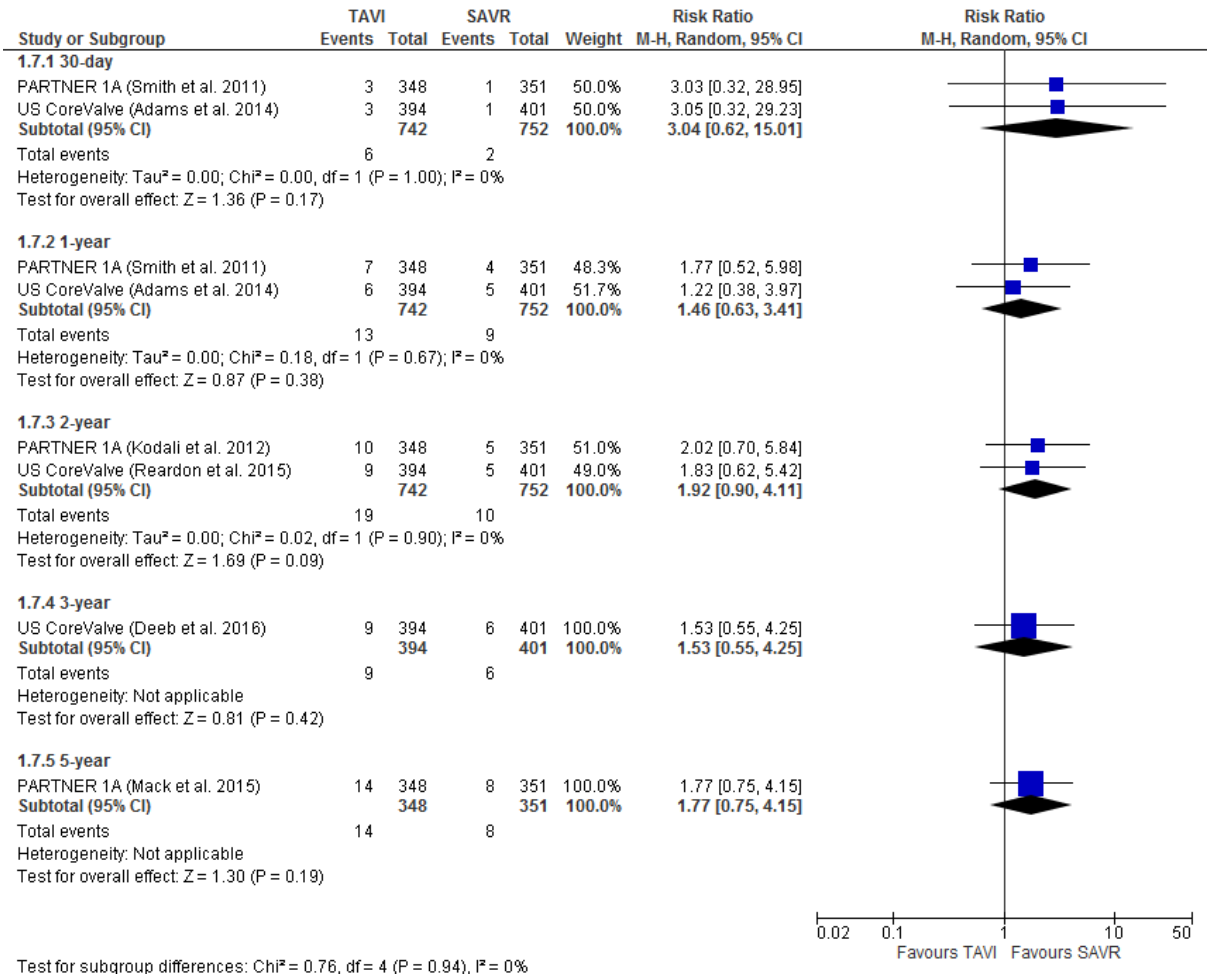

Figure 14. Transient ischemic attack (SAVR is suitable but poses a high risk)

Subgroup analyses of the PARTNER 1A trial were reported for the incidence of stroke comparing TAVI with SAVR in patients with diabetes (Lindman et al. 2014), with left ventricular dysfunction (Elmariah et al. 2013), with a history of coronary artery bypass grafting (Greason et al. 2014), or by sex (Williams et al. 2014).

Lindman et al. (2014) found no statistically significant differences in the hazard of stroke at 30 days and 1 year in patients with diabetes who received TAVI compared with those received SAVR (Table 42).

Table 42. Incidence of stroke in patients with diabetes (SAVR is suitable but poses a high risk)

PARTNER 1A (Lindman et al. 2014)	TAVI (n=145)	SAVR (n=130)	Analysis, HR (95% CI)
Stroke, n (%)			
• 30-day	3.5%	2.4%	1.5 (0.36 to 6.27), p=0.58
• 1-year	3.5%	3.5%	1.11 (0.30 to 4.12), p=0.88

Abbreviation: CI, confidence interval; HR, hazard ratio; n, number of patients. Note: the event rates were of Kaplan-Meier estimates.

Elmariah et al. (2013) reported no significant differences between the treatment groups in the incidence of stroke or TIA in high-risk patients with either LVEF<50% or LVEF≥50% at 30 days and 1 year (Table 43).

Table 43. Incidence of stroke or TIA patients with left ventricular dysfunction (SAVR is suitable but poses a high risk)

PARTNER 1A (Elmariah et al. 2013)	TAVI	SAVR	Analysis
LVEF <50%	n=108	n=95	
Stroke, n (%)			
• 30-day	2 (1.9)	2 (2.1)	p=0.897*
• 1-year	1 (0.9)	0 (0.0)	p=0.347*
TIA, n (%)			
• 30-day	1 (0.9)	0 (0.0)	p=0.347*
• 1-year	9 (9.0)	9 (9.8)	p=0.133*
LVEF ≥50%	n=224	n=209	
Stroke, n (%)			
• 30-day	12 (5.4)	5 (2.4)	p=0.133*
• 1-year	15 (7)	5 (2.4)	p=0.396 *
TIA, n (%)			
• 30-day	1 (0.5)	1 (0.5)	p=0.927*
• 1-year	5 (2.6)	4 (2.3)	p=0.885*

Abbreviation: LVEF, Left ventricular ejection fraction; TIA, transient ischemic attack; n, number of patients.
* Calculated by the authors of the current review.

Greason et al. (2014) found there were no significant differences between TAVI and SAVR in the incidence of stroke or TIA at 30 days, 1 year and 2 years in patients with a history of coronary artery bypass grafting (Table 44).

Table 44. Stroke or TIA rates in patients with a history of CABG (SAVR is suitable but poses a high risk)

PARTNER 1A (Greason et al. 2014)	TAVI (n=148)	SAVR (n=140)	Analysis
Stroke or TIA			
• 30-day or hospital discharge adjudicated	4.7%	3.6%	p=0.62
• 1-year	9.8%	6.2%	p=0.3
• 2-year	13.7%	9.0%	p=0.25
Major stroke			
• 30-day or hospital discharge adjudicated	1.4%	0.7%	p=1
• 1-year	1.4%	0.7%	p=0.59
• 2-year	2.3%	0.7%	p=0.33
Minor stroke			
• 30-day or hospital discharge adjudicated	3.4%	2.9%	p=1
• 1-year	5.1%	3.8%	p=0.62
• 2-year	7.1%	4.7%	p=0.46
TIA			
• 30-day or hospital discharge adjudicated	0	0	NA
• 1-year	3.3%	1.7%	p=0.43
• 2-year	4.4%	3.6%	p=0.72

Abbreviation: CABG, coronary artery bypass grafting; n, number of patients; NA, not applicable; TIA, transient ischemic attack. Note: the percentages for 1-year and 2-year are time-to-event data.

Williams et al. (2014) found that in women for whom SAVR was suitable but would pose a high risk there was a statistically significantly higher risk of all stroke or TIA at 30 days in the TAVI than in the SAVR group; whereas no significant differences were found between the two treatment groups in

male patients. However, for TIA alone there were no significant differences between the treatment groups at 30 days both in female and male patients (Table 45).

Table 45. Incidence of 30-days or in-hospital stroke or TIA by sex (SAVR is suitable but poses a high risk)

PARTNER 1A (Williams et al. 2014)	TAVI (n=348)	SAVR (n=349)	Analysis
Female, n (%)	**n=147**	**n=151**	
• All Stroke or TIA	6.8%	0.7%	p<0.01
• All stroke	5.4%	0.7%	p=0.02
• TIA	1.4%	0.0%	p=0.24
Male, n (%)	**n=201**	**n=198**	
• All Stroke or TIA	4.5%	4.0%	p=0.98
• All stroke	4.0%	4.0%	p=0.98
• TIA	0.5%	0.5%	p=1.00

Abbreviation: n, number of patients; TIA, transient ischemic attack.

A propensity score matched study by Onorati et al. (2013) reported stroke at 30 days in female patients, for whom SAVR was suitable but would pose a high risk and who had undergone TAVI or SAVR recorded in a registry. The risk of stroke was statistically significantly higher in the patients with TAVI than those with SAVR (7.7% versus 2.5%, p=0.037).

7.3.3 Major bleeding in patients for whom SAVR is considered suitable but poses a high risk

Pooled risk ratios from the PARTNER 1A and US CoreValve trials on major bleeding at 30 days, 1 year and 2 years all tended to favour TAVI but the differences were not statistically significant. Individual risk ratios at 3 years showed a similar pattern, but at 5 years the risk of major bleeding was significantly lower in the TAVI than the SAVR group (Figure 15). The quality of this finding is graded as moderate (Appendix 6).

Major bleeding rates by TAVI route at 30 days after the procedures in the PARTNER 1A trial were reported by Genereux et al. (2014), which were significantly more frequent with SAVR (22.7%) than either TF-TAVI (11.3%) or TA-TAVI (8.8%) (p=0.0004 for TF-TAVI versus SAVR; p=0.002 for TA-TAVI versus SAVR).

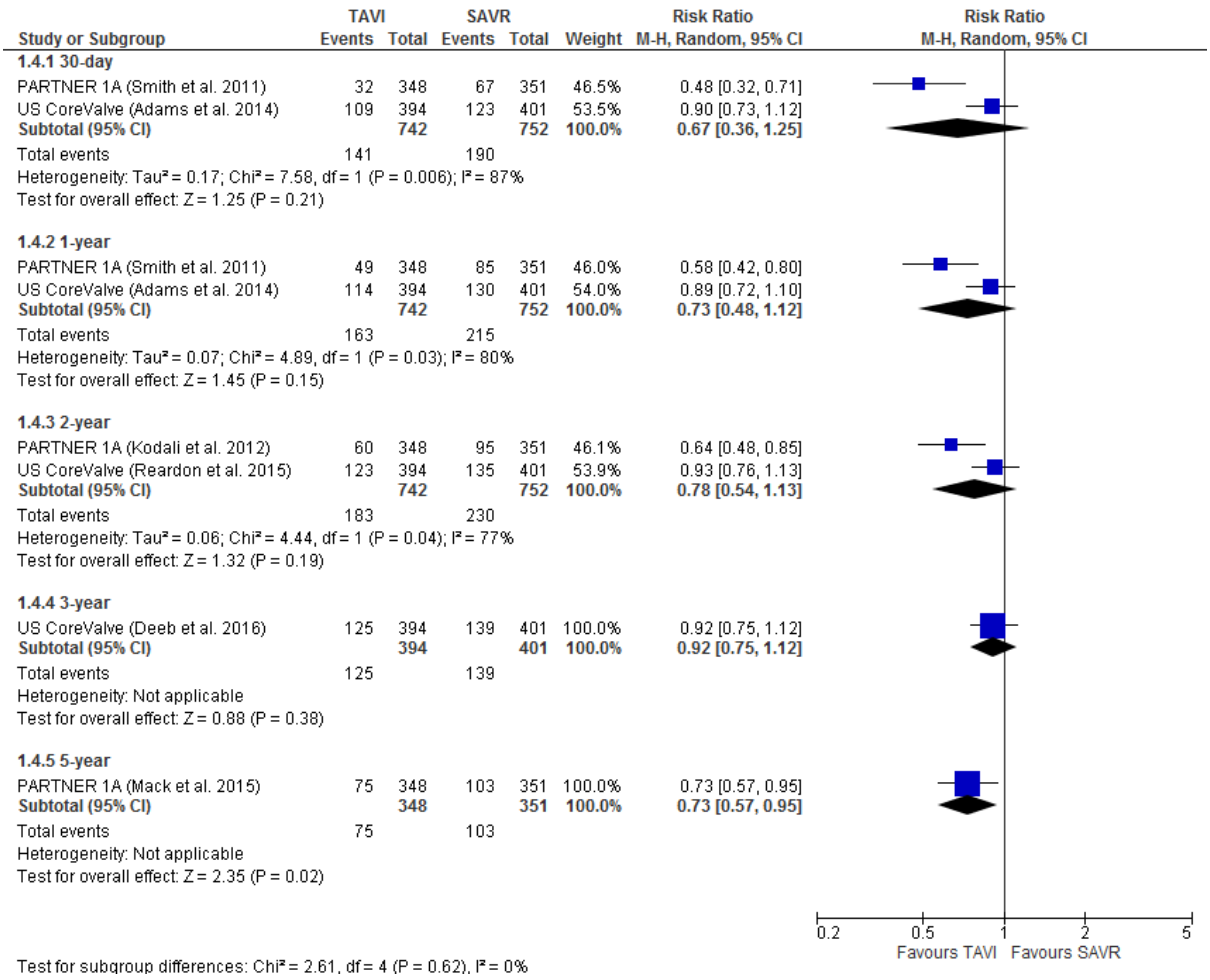

Figure 15. Major bleeding (SAVR is suitable but poses a high risk)

Separate analyses were provided for both patients with diabetes (Lindman et al. 2014) and those who had a history of CABG (Greason et al. 2014) in the PARTNER 1A trial. Lindman et al. (2014) reported a lower incidence of major bleeding in patients who received TAVI than those who received SAVR in 275 patients with diabetes (Table 46). Similarly Greason et al. (2014) reported a lower incidence of major bleeding for patients who received TAVI with a history of CABG (Table 47).

Table 46. Incidence of major bleeding in patients with diabetes (SAVR is suitable but poses a high risk)

PARTNER 1A (Lindman et al. 2014)	TAVI (n=145)	SAVR (n=130)	Analysis, HR (95% CI)
• At 30 days	11.1%	22.3%	0.48 (0.26 to 0.88), p=0.01
• At 1 year	15.1%	26.9%	0.52 (0.30 to 0.89), p=0.01

Abbreviation: CI, confidence interval; HR, hazard ratio; n, number of patients. Note: the event rates are Kaplan-Meier estimates.

Table 47. Hazard of major bleeding in patients with a history of CABG (SAVR is suitable but poses a high risk)

PARTNER 1A (Greason et al. 2014)	TAVI (n=148)	SAVR (n=140)	Analysis
Major bleeding, n (%)			
• 30-day or hospital discharge adjudicated	8.1%	25.7%	p<0.0001
• 1-year	13.6%	32.2%	p=0.0001
• 2-year	19.1%	33.9%	p=0.002

Abbreviation: CABG, coronary artery bypass grafting; n, number of patients. Note: the percentages are time-to-event data.

7.3.4 Aortic regurgitation in patients for whom SAVR is considered suitable but poses a high risk

Total aortic regurgitation (paravalvular and transvalvular regurgitation) in patients for whom SAVR is considered suitable but poses a high risk was reported in the PARTNER 1A and US CoreValve trials, based on patients who had echocardiography studies.

Pooled data and individual study data on moderate or severe total aortic regurgitation favoured SAVR over TAVI at all the follow-up points up to 3 years (Figure 16).

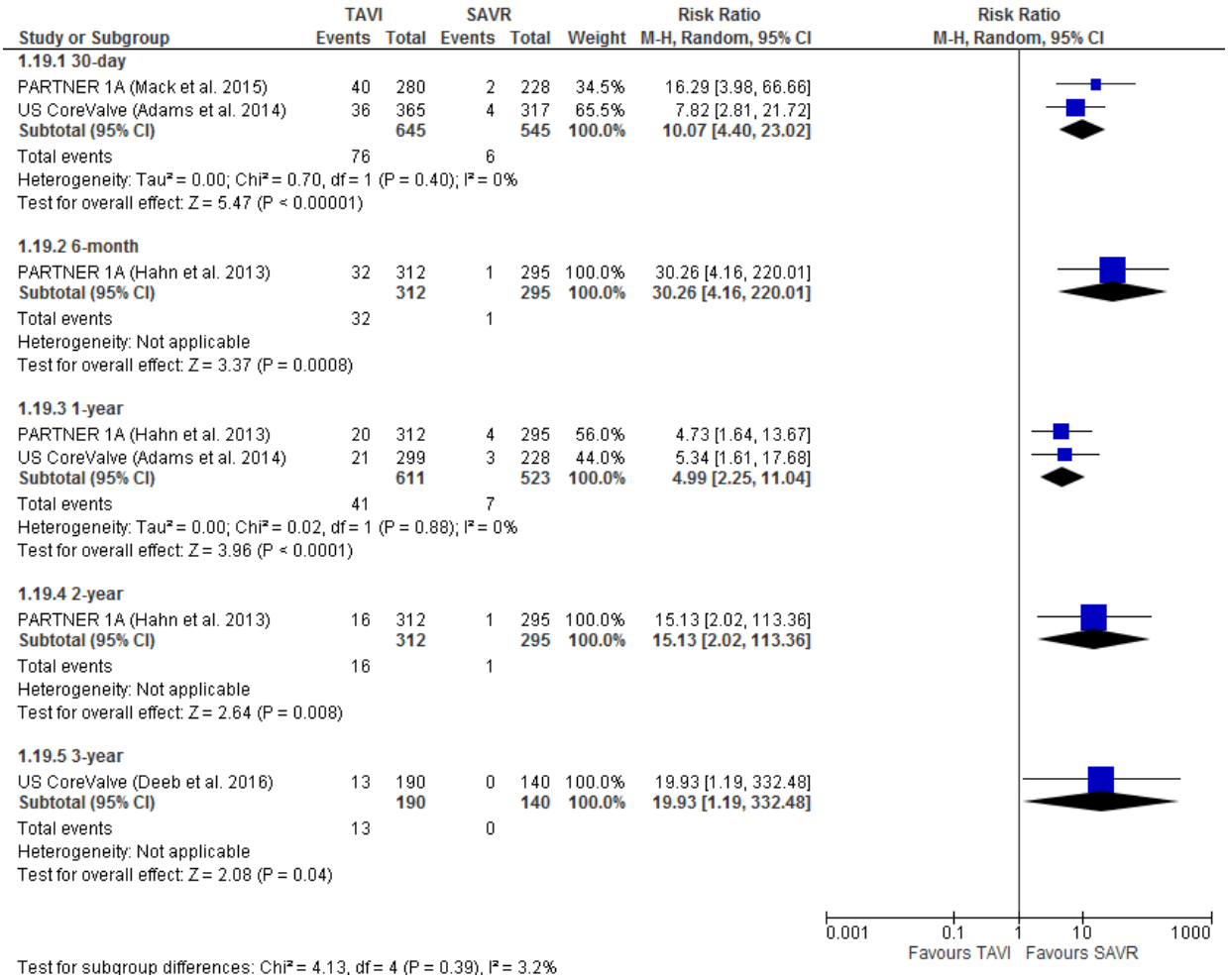

Figure 16. Moderate or severe aortic regurgitation (SAVR is suitable but poses a high risk)
(based on number of patients in each treatment group who had echocardiography study)

In a subgroup of 275 patients with diabetes in the PARTNER 1A trial (Lindman et al. 2014), the proportion of patients with moderate or severe aortic regurgitation was significantly lower in the SAVR group than in the TAVI group at 30 days, but the difference was not statistically significant at 6 months (Table 48).

Table 48. Moderate/severe AR in patients with diabetes (SAVR is suitable but poses a high risk)

PARTNER 1A (Lindman et al. 2014)	TAVI (n=145)	SAVR (n=130)	Analysis
• Baseline	6.4%	13.6%	p=0.05
• 30-day	9.8%	1.0%	p=0.007
• 6-month	9.0%	1.4%	p=0.052

Abbreviation: AR, aortic regurgitation; n, number of patients..

7.3.5 Major vascular complications in patients for whom SAVR is considered suitable but poses a high risk

Major vascular complications were reported in the PARTNER 1A trial and the US CoreValve trial. Although the SAVR group tended to have a lower rate at all the follow-up points, there were no statistically significant differences between the treatments in either pooled estimates at 30 days, 1 year or 2 years of follow-up, or in the findings of a single trial at 3 years or 5 years (Figure 17).

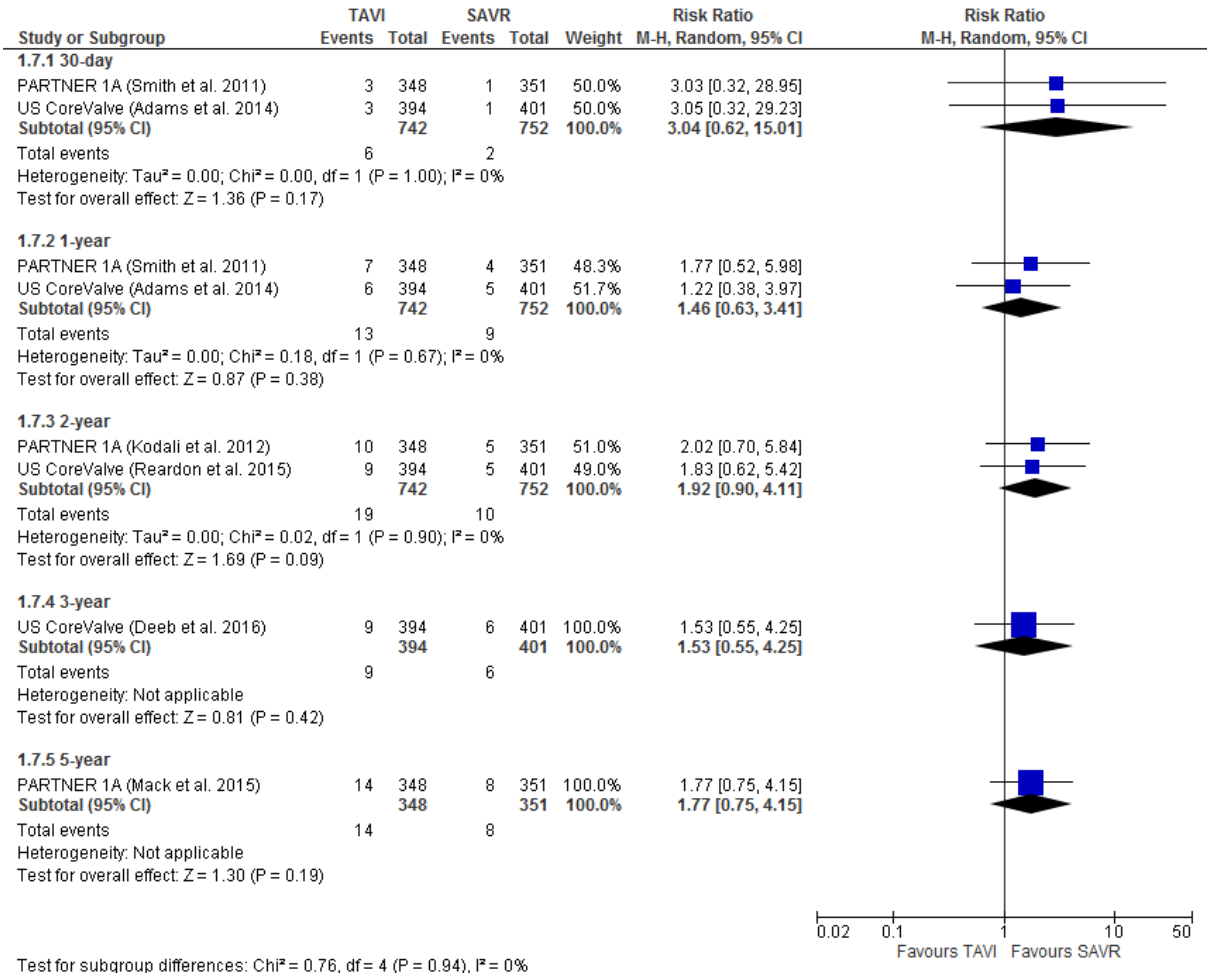

Figure 17. Major vascular complications (SAVR is suitable but poses a high risk)

Subgroup analyses of the PARTNER 1A trial were reported for the hazard ratios of major vascular complications in patients with diabetes (Lindman et al. 2014), those with a history of coronary artery bypass grafting (Greason et al. 2014), and by sex (Williams et al. 2014).

Lindman et al. (2014) reported statistically significantly higher rates of major vascular complications in the TAVI than in the SAVR group in patients of this risk category and with diabetes, both at 30 days and 1 year (Table 49).

Table 49. Major vascular complications in patients with diabetes (SAVR is suitable but poses a high risk)

PARTNER 1A (Lindman et al. 2014)	TAVI (n=145)	SAVR (n=130)	Analysis
• 30-day	11.7%	2.3%	HR 5.1 (95% CI 1.50 to 17.4), p=0.003
• 1-year	11.7%	2.3%	HR 5.1 (95% CI 1.50 to 17.4), p=0.003

Abbreviation: CI, confidence interval; HR, hazard ratio; n, number of patients. Note: the event rates were based on Kaplan-Meier methods.

Greason et al. (2014) also reported a statistically significantly higher incidence of major vascular complications in the TAVI than in the SAVR group in patients with a history of coronary artery bypass grafting, at hospital discharge or at 30 days, 1 year and 2 years (Table 50).

Table 50. Major vascular complications in patients with a history of CABG (SAVR is suitable but poses a high risk)

PARTNER 1A (Greason et al. 2014)	TAVI (n=148)	SAVR (n=140)	Analysis
• 30-day or hospital discharge adjudicated	9.5%	3.6%	p=0.04
• 1-year	9.5%	3.6%	p=0.04
• 2-year	9.5%	3.6%	p=0.04

Abbreviation: CABG, coronary artery bypass grafting; n, number of patients.

Williams et al. (2014) found that both in women and men there was a statistically significantly higher proportion of patients with major vascular complications at 30 days in the TAVI than in the SAVR group (Table 51).

Table 51. Major vascular complications at 30 days by sex (SAVR is suitable but poses a high risk)

PARTNER 1A (Williams et al. 2014)	TAVI (female 147; male 201)	SAVR (female 151; male 198)	Analysis
Female	15.0%	4.6%	p<0.01
Male	8.0%	2.5%	p=0.02

A propensity score matched study (Onorati et al. 2013) also reported the incidence of major vascular complications at 30 days in female patients, for whom SAVR was considered suitable but would pose a high risk, who underwent TAVI or SAVR in a registry study. The findings were similar to that in the subgroups (9.3% vs 1 0.5%, p<0.001).

7.3.6 Incidence of prosthesis-patient mismatch in patients for whom SAVR is considered suitable but poses a high risk

The incidence of prosthesis-patient mismatch (PPM) in patients for whom SAVR is considered suitable but poses a high risk was reported in the PARTNER 1A trial by Hahn et al. (2013). The TAVI group had significantly better outcomes in terms of the overall incidence and severity of PPM than in the SAVR group at 30 days and 6, 12, and 24 months (Table 52). Pibarot et al. (2014) reported similar findings on PPM from the PARTNER 1A trial, with the incidence of PPM being 46.4% (severe 19.7%) in the TAVI group and 60.0% (severe 28.1%) in the SAVR group (p<0.001) assessed at the

first postoperative echocardiogram, and 42% in the TAVI versus 57% in the SAVR (p<0.001) at 30 days.

Table 52. Incidence and severity of PPM (SAVR is suitable but poses a high risk)

PARTNER 1A (Hahn et al. 2013)	TAVI		SAVR		Analysis
	n. analysed	% of patients	n. analysed	% of patients	
30-day	259		201		p=0.0079
• Insignificant		58.3		43.8	
• Moderate		27.8		38.3	
• Severe		13.9		17.9	
6-month	217		156		p=0.0194
• Insignificant		53.9		39.1	
• Moderate		30.0		39.7	
• Severe		16.1		21.2	
1-year	203		142		p=0.0147
• Insignificant		51.2		35.9	
• Moderate		26.6		34.5	
• Severe		20.2		29.6	
2-year	134		102		p=0.0193
• Insignificant		47.0		29.4	
• Moderate		33.6		48.0	
• Severe		19.4		22.5	

Abbreviations: n, number of patients; PPM, prosthesis-patient mismatch.

7.3.7 New permanent pacemaker implantation in patients for whom SAVR is considered suitable but poses a high risk

Pooled estimates of new permanent pacemaker implantation (PPI) in patients for whom SAVR was considered suitable but would pose a high risk in the PARTNER 1A trial and the US CoreValve trial at 30 days, 1 year and 2 years all tended to favour the SAVR group, however the differences were not statistically significant. There is a clear pattern that, in the US CoreValve trial where a self-expanding valve was used, the risk of patients requiring a new PPI was statistically significantly higher in the TAVI group than in the SAVR group at all the follow-up time points from 30 days to 3 years. Whilst in the PARTNER 1A trial where a balloon-expanding valve was used, there were no statistically significant differences between the TAVI group and the SAVR group in the risk of patients requiring a new PPI at all the follow-up time points from 30 days to 5 years (Figure 18).

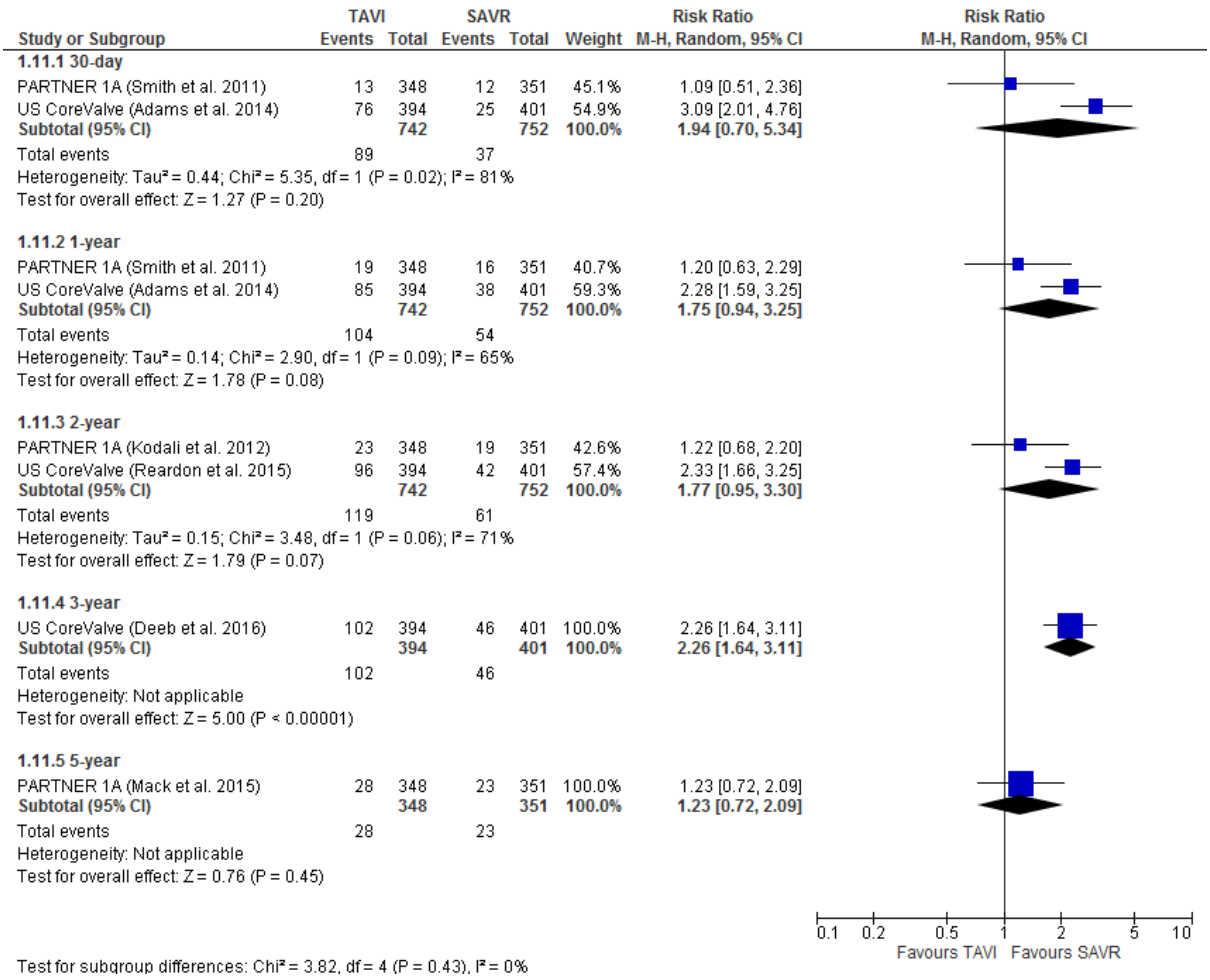

Figure 18. Permanent pacemaker implantation (SAVR is suitable but poses a high risk)

Subgroup analyses on PPI were reported in the PARTNER 1A trial for patients with a history of CABG (Greason et al. 2014), by sex (Williams et al. 2014), and in the US CoreValve trial for women (Skelding et al. 2016).

In the PARTNER 1A trial (Greason et al. 2014) where a balloon-expanding valve was used there were no statistically significant differences between TAVI and SAVR for new PPI in patients with a history of CABG at 30 days, 1 year and 2 years of follow-up points or across these time points (Table 53).

Table 53. New PPI in patients with a history of CABG (SAVR is suitable but poses a high risk)

PARTNER 1A (Greason et al. 2014)	TAVI (n=148)	SAVR (n=140)	
• 30-day or hospital discharge adjudicated	3.4%	2.9%	p=1
• 1-year	3.4%	2.9%	p=0.8
• 2-year	3.4%	2.9%	p=0.8

Abbreviation: CABG, coronary artery bypass grafting; n, number of patients; PPI, permanent pacemaker implantation

In the US CoreValve trial (Skelding et al. 2016) where a self-expanding valve was used there was a statistically significantly higher proportion of females with PPI in the TAVI group compared with the

SAVR group at both 30 days and 1 year. Whereas in the PARTNER 1A trial (Williams et al. 2014) where a balloon-expanding valve was used there were no statistically significant differences between the treatment groups both in women and men at 30 days (Table 54).

Table 54. Incidence of new PPI by sex (SAVR is suitable but poses a high risk)

US CoreValve (Skelding et al. 2016)	TAVI	SAVR	Analysis
Female	(n=183)	(n=170)	
• 30-day	20.7% (37/183)	7.2% (12/170)	p<0.001
• 12-month	22.5% (40/183)	10.7% (17/170)	p=0.001
PARTNER 1A (Williams et al. 2014)	TAVI	SAVR	Analysis
By sex at 30-day	(n=348)	(n=349)	
• Female	4.8% (7/147)	6.5% (10/151)	p=0.51
• Male	4.0% (8/201)	1.0% (2/198)	p=0.11

Abbreviation: n, number of patients; PPI, permanent pacemaker implantation.

Incidence of PPI at 30 days reported by a matched study in women patients, for whom SAVR was considered suitable but would pose a high risk (Onorati et al. 2013), found a statistically significantly higher incidence of PPI in the TAVI group (12.6% compared with 6.2%, p=0.04). In the study 44% of the vales used were a self-expanding CoreValve.

A small matched study (D'Onofrio et al. 2012) comparing TAVI with sutureless SAVR found no significant difference in PPI at 30 days (5.3% versus 5.3%, p=1.0).

7.3.8 Acute kidney injury in patients for whom SAVR is suitable but poses a high risk

Both the PARTNER 1A and the US CoreValve trials reported on acute kidney injury (AKI) comparing TAVI with SAVR in patients for whom SAVR was considered suitable but would pose a high risk. Based on an ITT analysis, the risk ratio from the individual US CoreValve study significantly favoured the TAVI group at 30 days and 1, 2 and 3 years. Whereas in the PARTNER 1A trial there were no statistically significant differences between the treatment groups at all the follow-up points up to 5 years. Pooled results of the two trials favoured the TAVI group at 30 days and 3 years (Figure 19). The quality of this finding is graded as low (Appendix 6).

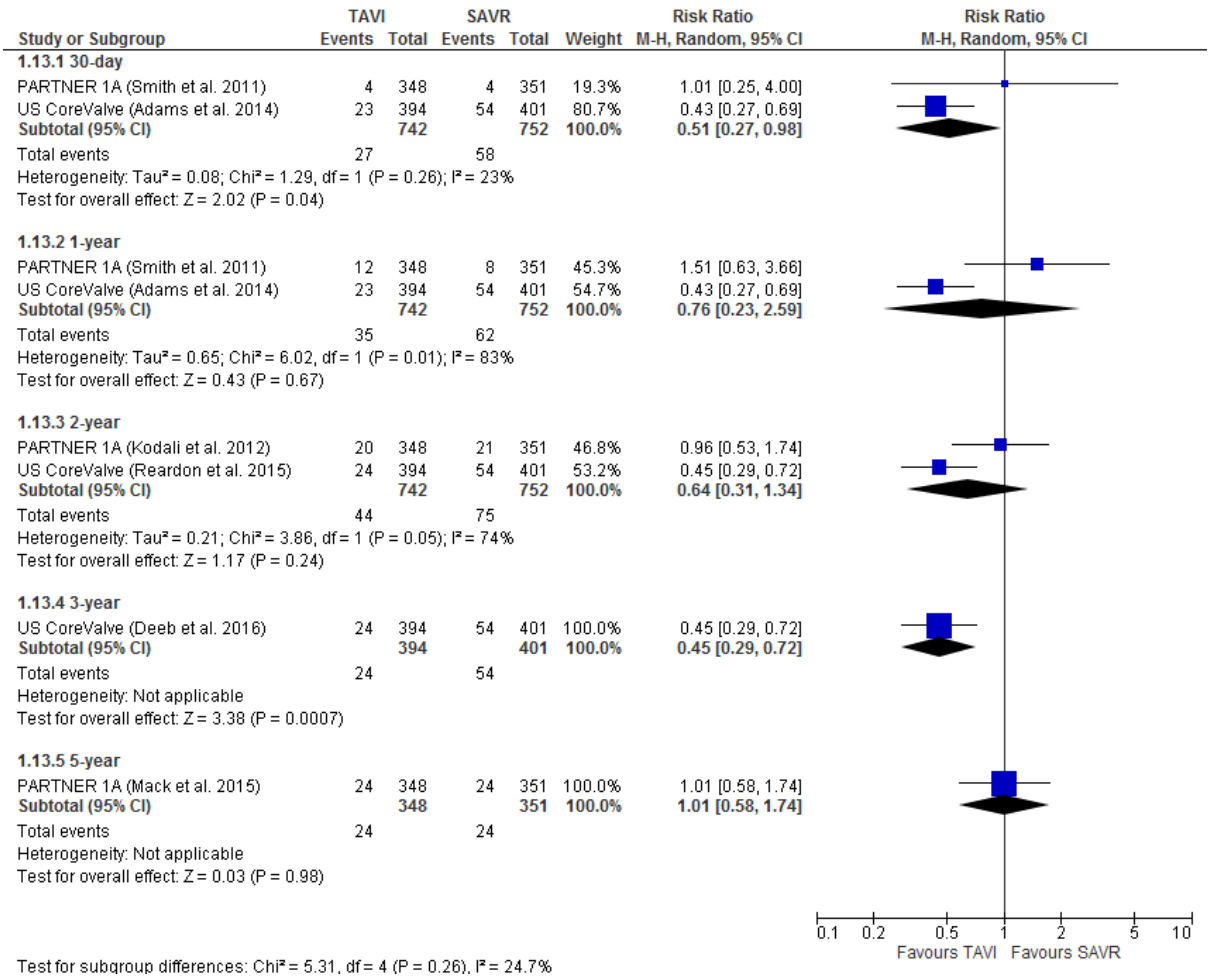

Figure 19. Acute kidney injury (SAVR is suitable but poses a high risk)

The PARTNER 1A trial (Smith et al. 2011) reported acute kidney injury at 30-day and 1-year, with data separately for those with creatinine >3 mg/dl and those with renal-replacement therapy. Only data on creatinine >3 mg/dl were included in this meta-analysis.

Subgroup analyses of the PARTNER 1A trial on acute renal injury (ARI) were reported for patients with a history of CABG (Greason et al. 2014), patients with diabetes (Lindman et al. 2014), and by sex (Williams et al. 2014). Subgroup analyses were also reported for the US CoreValve trial for female patients (Skelding et al. 2016) and for patients with prosthesis-patient mismatch (Zorn et al. 2016).

Greason et al. (2014) reported no significant differences in the occurrence of renal failure between the TAVI and SAVR treatments in patients with a history of CABG (Table 55).

Table 55. Renal failure in patients with a history of CABG (SAVR is suitable but poses a high risk)

PARTNER 1A (Greason et al. 2014)	TAVI (n=148)	SAVR (n=140)	
Renal failure			
• 30-day or hospital discharge adjudicated	4.1%	4.3%	p=0.92
• 1-year	4.9%	6.0%	p=0.69
• 2-year	5.9%	6.9%	p=0.72

Abbreviation: CABG, coronary-artery bypass grafting; n, number of patients. Note: the percentages for 1-year and 2-year are time-to-event data.

Lindman et al. (2014) also found no statistically significant differences between the treatment groups in patients with diabetes in terms of renal failure requiring dialysis at both 30 days and 1 year (Table 56).

Table 56. Renal failure requiring dialysis in patients with diabetes (SAVR is suitable but poses a high risk)

PARTNER 1A (Lindman et al. 2014)	TAVI (n=145)	SAVR (n=130)	Analysis, HR (95% CI)
Follow-up			
• 30-days	3.5%	7.8%	0.44 (0.15 to 1.03), p=0.12
• 1-year	4.2%	10.6%	0.39 (0.15 to 1.03), p=0.05

Abbreviation: CI, confidence interval; HR, hazard ratio. Note: the event rates were based on Kaplan-Meier methods.

Zorn et al. (2016) reported the incidence of AKI in patients with PPM in the US CoreValve trial. In patients with a severe PPM there were no significant differences between the treatment groups (albeit with low numbers for analysis). The TAVI group had a statistically significantly lower incidence of AKI in patients without severe PPM (Table 57).

Table 57. AKI rates in patients with PPM (SAVR is suitable but poses a high risk)

US CoreValve (Zorn et al. 2016)	TAVI	SAVR	Analysis
• Severe PPM	3/24 (12.5%)	16/75 (21.3%)	p=0.339*
• No severe PPM	19/343 (5.5%)	32/259 (12.4%)	p=0.002*

Abbreviation: AKI, acute kidney injury; PPM, prosthesis-patient mismatch. Note: severe PPM was defined as the effective orifice area index (EOAi) ≤0.65 cm^2/m^2; no severe PPM was defined as EOAi >0.65 cm^2/m^2. * Calculated by the authors of the current review.

In female patients in the US CoreValve trial (Skelding et al. 2016) there were statistically significantly higher proportion of patients with acute kidney injury in the SAVR group than in the TAVI group both at 30 days and 1 year. Whereas in the PARTNER 1A trial (Williams et al. 2014) there were no statistically significant differences between the treatment groups in renal failure requiring dialysis either in male or female patients (Table 58).

Table 58. AKI and renal failure by sex (SAVR is suitable but poses a high risk)

	Reference	TAVI	SAVR	Analysis
AKI in female patients	US CoreValve (Skelding et al. 2016)	n=183	n=170	
• 30-day		2.8%	17.6%	p<0.001
• 1-year		2.8%	17.6%	p<0.001
Renal failure requiring dialysis	PARTNER 1A (Williams et al. 2014)	Male 201, female 147	Male 198, female 151	
• 30-days, Female		3.4%	6.5%	p=0.23
• 30-days, Male		5.0%	3.5%	p=0.48

Abbreviation: AKI, acute kidney injury; n, number of patients. Note: the percentages for the Skelding et al. 2016 study are Kaplan-Meier estimates.

One propensity-matched study reported on acute renal failure at 30-day follow-up in female patients for whom SAVR was suitable but would pose a high risk (Onorati et al. 2013), and found no statistically significant differences between the treatment groups.

Another matched study (D'Onofrio et al. 2012) study comparing TAVI (n=38) with sutureless aortic valve replacement (n=38) also found no statistically significant difference in AKI at 30 days.

7.3.9 Myocardial infarction in patients for whom SAVR is considered suitable but poses a high risk

Myocardial infarction (MI) in patients for whom SAVR is considered suitable but poses a high risk was measured in the PARTNER 1A trial and the US CoreValve trial. There were no statistically significant differences between the treatment groups in MI in either the pooled estimate at the 30 day, 1 year or 2 year follow-up, or the finding reported in the single studies at the 3 year or 5 year follow-up, based on an ITT analysis (Figure 20).

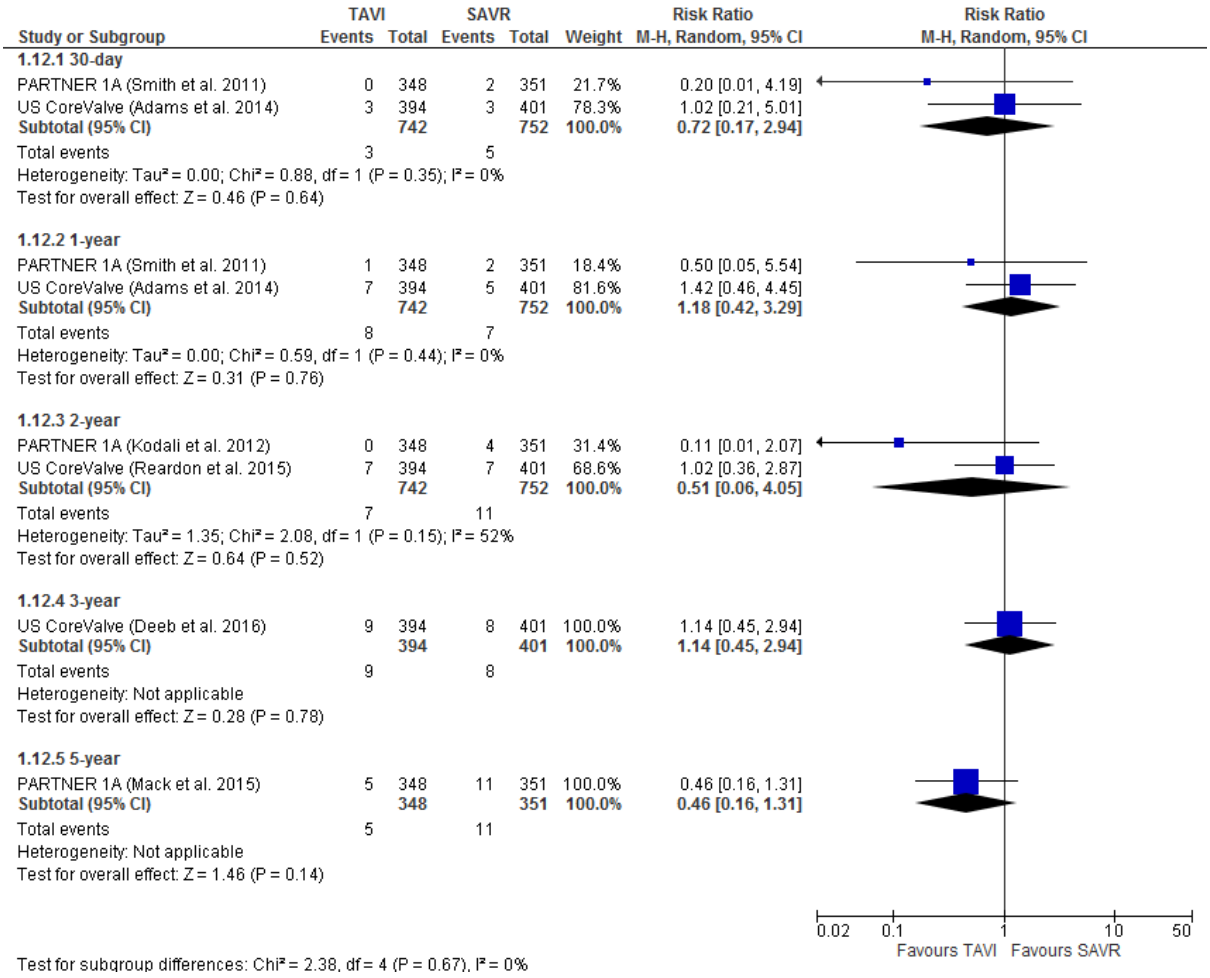

Figure 20. Myocardial infarction (SAVR is suitable but poses a high risk)

Subgroup analyses of the PARTNER 1A trial on MI were reported in patients with left ventricular dysfunction (Elmariah et al. 2013), with diabetes (Lindman et al. 2014), and with PPM (Zorn et al. 2016). Skelding et al. (2014) also reported MI in female patients for whom SAVR was considered

suitable but would pose a high risk in the US CoreValve trial. The quality of this finding is graded as very low (Appendix 6).

Stratified analyses of the patients with left ventricular ejection fraction (LVEF) <50% showed no statistical significantly differences in MI at both 30 days and 1 year between the two treatments. There was no MI event with either treatment in patients with LVEF ≥50% both at 30 day and 1 year (Table 59). There were no statistically significant differences between the treatment groups in the proportion of patients with MI both at 30 days and 1 year, either in those patients with diabetes (Table 60) or in women (Table 61). In patients with PPM there were no statistically significant differences in the incidence of MI (Table 62).

Table 59. Incidence of MI by LVEF (SAVR is suitable but poses a high risk)

PARTNER 1A (Elmariah et al. 2013)	TAVI	SAVR	Analysis
In those with LVEF <50%, n (%)	n=108	n=95	
• 30-day	0 (0.0)	1 (1.1)	p=0.47*
• 1-year	0 (0.0)	1 (1.1)	p=0.47*
In those with LVEF ≥50%, n (%)	n=224	n=209	
• 30-day	0 (0.0)	0 (0.0)	
• 1-year	0 (0.0)	0 (0.0)	

Abbreviation: LVEF, left ventricular ejection fraction; MI, myocardial infarction; n, number of patients.
* Calculated by the authors of the current review.

Table 60. MI in patients with diabetes (SAVR is suitable but poses a high risk)

PARTNER 1A (Lindman et al. 2014)	TAVI (n=145)	SAVR (n=130)	Analysis
Myocardial infarction (%)			
• 30-day	0.0%	0.8%	p=0.29
• 1-year	0.0%	0.8%	p=0.29

Abbreviation: MI, myocardial infarction; n, number of patients. Note: the event rates are based on Kaplan-Meier estimates.

Table 61. MI in women (SAVR Is suitable but poses a high risk)

US CoreValve (Skelding et al. 2016)	TAVI (n=183)	SAVR (n=170)	Analysis
Myocardial infarction			
• 30-day	1.6%	0.6%	p=0.35
• 1-year	2.2%	2.0%	p=0.79

Abbreviation: MI, myocardial infarction; n, number of patients. Note: the event rates are based on Kaplan-Meier estimates.

Table 62. MI in patients with PPM (SAVR is suitable but poses a high risk)

PARTNER 1A (Zorn et al. 2016)	TAVI	SAVR	Analysis
Myocardial infarction, n (%)			
• Severe PPM	0.0 (0/24)	0 (0/75)	
• No Severe PPM	1.8% (6/343)	1.6% (4/259)	p=0.459*

Abbreviation: MI, myocardial infarction; n, number of patients; PPM, prosthesis-patient mismatch. Note: severe PPM was defined as the effective orifice area index (EOAi) ≤0.65 cm^2/m^2; no severe PPM was defined as EOAi >0.65 cm^2/m^2. * Calculated by the authors of the current review.

One propensity-matched study also reported on incidence of myocardial infarction in female patients for whom SAVR was considered suitable but would pose a high risk (Onorati et al. 2013). No statistically significant differences were observed between TAVI and SAVR in the incidence of perioperative MI, with 7.7% (15/194) for TAVI and 5.7% (11/194) for SAVR (p=0.417, calculated by the authors of the current review).

Another propensity-matched study (D'Onofrio et al. 2012) comparing TAVI (n=38) with sutureless SAVR (n=38) found no events of MI in both treatment groups at the 30 days of follow-up.

7.4 Summary of safety outcomes in patients for whom SAVR is considered suitable but poses a high risk

Safety outcomes in patients for whom SAVR is considered suitable but poses a high risk were from two good quality RCTs (PARTNER 1A and US CoreValve) with follow-up points up to 5 years and three small propensity matched studies.

No statistically significant differences were observed in 30-day mortality between the TAVI group and the SAVR group. Sub-group analyses found no statistically significant differences in 30-day mortality between the treatment groups either by TAVI access route (via the transfemoral or the transapical route), by LVEF, in patients with a history of CABG, or in patients with diabetes.

No statistically significant differences were observed for all stroke, major stroke, minor stroke or TIA, either based on pooled analyses or from individual studies at the different follow-up points. Subgroup analyses based on patients with diabetes, by level of left-ventricular dysfunction, and in patients with previous CABG also revealed no significant differences in stroke or TIA at all the follow-up points up to 2 years. Subgroup analysis by sex at 30 days showed statistically significantly higher rates of all stroke or TIA in female patients with TAVI.

The PARTNER 1A trial showed statistically significantly lower risks of major bleeding at all the follow-up points up to 5 years in favour of TAVI, whereas no significant differences were observed in the US CoreValve trial. Pooled analyses up to 2 years demonstrated no significant differences. Subgroup analyses by presence of diabetes or previous CABG found statistically significantly lower rates of major bleeding for patients receiving TAVI up to 2 years of follow up.

In both individual RCTs and pooled analyses the moderate or severe total aortic regurgitation rates were statistically significantly higher for patients undergoing TAVI than SAVR up to 3 years of follow up.

No statistically significant differences were observed for major vascular complications up to 5 years. Subgroup analyses based on patients with diabetes, in patients with previous CABG and by sex showed statistically significantly lower major vascular complications in patients who had SAVR than TAVI at all the follow-ups reported in the studies up to 2 years.

TAVI had significantly better outcomes than SAVR in terms of the overall incidence and severity of PPM at all the follow-up points up to 2 years.

Incidence of major bleeding reported in the PARTNER 1A trial favoured the TAVI group, whereas the US CoreValve trial showed no statistically significant differences between TAVI and SAVR.

The rates of a new PPI were statistically significantly higher with TAVI using a self-expanding valve than with SAVR at all the follow-up points up to 3 years. Subgroup analysis in female patients up to 1 year of follow-up showed a similar pattern. Whilst there were no statistically significant differences between the treatment groups when a balloon-expanding valve was used for TAVI at all the follow-up points up to 5 years. Subgroup analysis in patients with a history of CABG up to 2 years or by gender at 30 days had a similar pattern. No significant differences were observed for the incidence of PPI between TAVI and sutureless SAVR at 30 days in a matched study.

Risk of AKI reported in the US CoreValve trial was statistically significantly lower at all follow-up points up to 3 years in the TAVI than the SAVR group. Pooled analyses and results of the PARTNER 1A trial indicated no significant differences at all the follow-up points up to 5 years.

No statistically significant differences between the treatment groups in the risk of MI up to 5 year follow-up.

7.5 Safety events in patients for whom SAVR is considered suitable and not to pose a high risk (intermediate or low risk)

As 4 very recent systematic reviews were identified for the patient group for whom SAVR is considered suitable and not to pose a risk (Gargiulo et al. 2016; Siemieniuk et al. 2016; Khan et al.

2016; Arora et al. 2016), and these systematic reviews included the 3 trials in patients with an intermediate or low risk (PARTNER 2A; NOTION; STACCATO), key evidence for these patients is drawn from the systematic reviews only. The Siemieniuk et al. (2016) review also included the US CoreValve trial, which is considered with high-risk patients in our systematic review. See more details about the 4 systematic reviews and the 3 trials in section 5.7.1 and 5.7.2. In the Siemieniuk et al. (2016) review the authors also evaluated the quality of the key outcomes using the GRADE framework (Table 29).

7.5.1 Mortality at 30 days in patients with an intermediate or low risk

The sub-analyses by Gargiulo et al. (2016) for patients in the intermediate or low risk population included 2 RCTs and 6 observational studies. They showed a non-significantly lower all-cause mortality up to 30 days for TAVI compared to SAVR (OR 0.67; 95% CI 0.42 to 1.07). Khan et al. (2016) included 1 RCT and 6 observational studies with intermediate-risk patients. They, too, found no evidence of effect on mortality at 30 days (RR 1.02; 95% CI 0.63 to 1.63). Outcomes at 30 days showed moderate heterogeneity.

7.5.2 Stroke or transient ischaemic attack in patients with an intermediate or low risk

Siemieniuk et al. (2016) found a non-significant reduction in stroke rates (RR 0.80; 95% CI 0.63 to 1.01) up to 3 years of follow-up for transfemoral TAVI compared with SAVR. This was based on data from 2576 patients in 3 studies, and was graded as having moderate quality (serious imprecision). Comparing transpical TAVI with SAVR up to 2 years of follow-up, the RR was 1.67 (95% CI 0.97 to 2.87). This was based on data from 552 patients in 2 studies and graded by the authors as having moderate quality.

Arora et al. (2016) reviewed data for intermediate risk only. They included 1 RCT and 5 observational studies. Differences in 30-day outcomes for stroke were non-significant (OR 0.61; 95% CI 0.31 to 1.20) as was the case for adverse neurological events (OR 0.63; 95% CI 0.35 to 1.14).

Khan et al. (2016) found a non-significant increase in stroke with TAVI (RR 2.96; 95% CI 0.87 to 10.09).

7.5.3 Major bleeding in patients with an intermediate or low risk

Siemieniuk et al. (2016) found that up to 3 years of follow-up, transfemoral TAVI was associated with a statistically significant reduction in life threatening or disabling bleeding (RR 0.39; 95% CI 0.29 to 0.54). This was based on data from 2576 patients in 3 studies and the finding was graded as having high quality. Compared to SAVR, transapical TAVI up to 2 years of follow also had a reduced risk (RR 0.53; 0.42 to 0.67) based on data from 552 patients in 2 studies, also graded as high quality.

Khan et al. (2016) included 1 RCT and 6 observational studies with intermediate-risk patients. They found a higher incidence of major or life threatening bleeding in SAVR when compared to TAVI (RR 1.36; 95% CI 1.04 to 1.80).

7.5.4 Aortic regurgitation in patients with an intermediate or low risk

Siemieniuk et al. (2016) found that moderate or severe aortic regurgitation occurred more often up to 3 years of follow-up in TAVI than in SAVR patients. This was based on 3 trials (RR 12.22; 95% CI 5.17 to 28.88), with no heterogeneity. This finding was graded as having moderate quality.

Khan et al. (2016) reported a significantly higher risk of aortic regurgitation for TAVI compared with SAVR for all grades of aortic regurgitation (RR 3.59; 95% CI 2.13 to 6.05), for mild aortic regurgitation (RR 7.20; 95% CI 0.91 to 57.14), and moderate or severe aortic regurgitation (RR 2.53; 95% CI 0.91 to 7.0) based on 1 RCT and 1 observational study.

7.5.5 New permanent pacemaker implantation in patients with an intermediate or low risk

Siemieniuk et al. (2016) found an increased risk of a new permanent pacemaker implantation (PPI) for patients undergoing TAVI when compared with SAVR (RR 2.45; 95% CI 1.17 to 5.14) based on data from 3128 patients in 4 studies at follow-up of up to 3 years. This pooled result was based on 4 RCTs (NOTION; US CoreValve; STACCATO; PARTNER 2A). In the NOTION and US CoreValve trials where the self-expanding CoreValve was used for TAVI, there were statistically significantly higher risks of PPI in the TAVI group than in the SAVR group (RR 10.35 with 95% CI 4.28 to 25.04 for the NOTION trial; RR 1.93 with 95% CI 1.41 to 2.64 for the US CoreValve trial). Whereas in the STACCATO and PARTNER 2A trials where the Edwards balloon-expanding valve was used there

were no statistically significant differences between the treatment group in new PPI (RR 2.12 with 95% CI 0.20 to 22.30 for the STACCATO trial and RR 2.45 with 95% CI 1.17 to 5.14 for the PARTNER 2A trial). Subgroup analysis comparing a self-expanding valve and a balloon-expanding valve showed no statistically significant differences; this is due to the imprecision of the effect estimates with very wide confidence intervals in the STACCATO trial and the NOTION trial. The authors graded this outcome as having high quality despite high degree of heterogeneity in the results.

Arora et al. (2016) found risk of PPI increased sixfold with TAVI at 30 days (OR 6.51; 95% CI 3.23 to 13.12). The meta-analysis included patients receiving both balloon-expandable and self-expanding valves from 5 studies; in all the 5 studies the risk of PPI favoured the SAVR treatment. However, only 1 of the 5 studies was an RCT (the NOTION trial) in which a CoreValve self-expanding valve was used, the other studies were observational studies.

Khan et al. (2016) also found an increased risk of PPI (OR 6.53; 95% CI 1.91 to 22.32). It was not clear at what follow-up time point the PPI was measured. Only 1 of the 3 studies included in this meta-analysis was an RCT (STACCATO trial reported by Nielsen et al. 2012) which used a self-expanding valve and in which the risk of PPI showed no statistically significant differences between the TAVI group and the SAVR group. It is not totally clear as to what aortic valve was used in the other two included observational studies.

7.5.6 Acute kidney injury in patients with an intermediate or low risk

Siemieniuk et al. (2016) found a RR of AKI of 0.38 (95% CI 0.27 to 0.54) for transfemoral TAVI compared with SAVR with follow up of up to 3 years based on data from 2576 patients in 3 studies. For transapical TAVI the RR was 1.54 (95% CI 0.77 to 3.07) with follow up of up to 2 years. The quality of this finding in transfemoral TAVI was graded as high but was graded as low for transapical TAVI.

Arora et al. (2016) reported that the risk of acute renal failure at 30 days was significantly lower in the TAVI group (OR 0.51; 95% CI 0.27 to 0.99).

7.5.7 Myocardial infarction in patients with an intermediate or low risk

Siemieniuk et al. (2016) found no differences between the treatment groups for MI (RR 0.87; 95% CI 0.59 to 1.29) up to 3 years of follow-up based on data from 3128 patients in 4 studies. The quality of this finding was graded as moderate by the authors.

Arora et al. (2016) reported 30-day outcomes for MI in TAVI compared with SAVR, OR 0.61 (95% CI 0.31 to 1.20).

7.5.8 Atrial fibrillation in patients with an intermediate or low risk

Sieminieniuk et al. (2016) found that the RR for new onset AF at up to 3 years of follow-up was 0.43 (95% CI 0.35 to 0.52) for TAVI compared with SAVR. This was based on data from 3058 patients in 3 studies and the quality of this outcome was graded as high.

7.5.9 Aortic valve reintervention in patients with an intermediate or low risk

Based on data from 3058 patients in 3 studies the Siemieniuk et al. (2016) found that the risk for aortic valve reintervention with up to 3 years of follow-up was statistically significantly higher for patients with TAVI than SAVR (RR 3.25; 95% CI 1.29 to 8.14). However, the relative risk of aortic valve reintervention based subgroup analyses by time points was 7.65 (95% CI 0.96 to 61.16) at 1 month, and 3.68 (95% CI 1.06 to 12.74) at 1 year. The authors considered the findings to be of moderate quality.

7.5.10 Vascular access complications in patients with an intermediate or low risk

Khan et al. (2016) reported a nonsignificant increase in vascular access complications with TAVI than with SAVR (RR 3.84; 95% CI 0.65-22.76).

7.6 Summary of safety outcomes in patients for whom SAVR is considered suitable and not to pose a high risk

Evidence on safety events in patients with an intermediate or low risk is drawn from 4 systematic reviews (Gargiulo et al. 2016; Siemieniuk et al. 2016; Khan et al. 2016; Arora et al. 2016).

No statistically significant differences were identified in all-cause mortality up to 30 days for TAVI compared to SAVR.

No statistically significant differences in stroke rates were identified in the systematic reviews. Sub-group analyses by TAVI route did not find a reduction in stroke rate.

Significant reductions in major bleeding were observed for patients receiving TAVI when compared with SAVR. Sub-group analysis for transfemoral and transapical TAVI compared with SAVR were associated with a significant reduction in life threatening or disabling bleeding.

One systematic review observed a statistically significantly higher incidence of moderate or severe aortic regurgitation for TAVI when compared with SAVR. Another systematic review observed a statistically significantly higher incidence of all aortic regurgitation in TAVI compared with SAVR but this difference was not significant when evaluating mild regurgitation and moderate or severe regurgitation.

Pooled results showed a statistically significantly increased risk of a new PPI with TAVI when compared with SAVR at a maximum follow-up of 3 years. However, in individual RCTs where a self-expanding valve was used the risk of a new PPI was statistically significantly higher with TAVI; whereas where a balloon-expandable valve was used the differences between the treatments were not statistically significant.

Acute renal failure at 30 days was found to be statistically significantly lower in patients with TAVI. Transfemoral TAVI compared with SAVR had a statistically significantly lower risk of AKI at a 3-year maximum follow-up. For transapical TAVI the difference was not statistically different up to 2 years follow-up.

No differences between TAVI and SAVR were found for rates of MI at the different follow-up by all 3 systematic reviews.

TAVI had a statistically significantly lower onset AF when compared with SAVR up to 3 years follow-up.

There was an increased risk of aortic valve reintervention with TAVI compared to SAVR at up to 3 years of follow-up. However, this risk occurred mainly within the first month after the operation, with the RR of 7.65 (95% CI 0.96 to 61.16) at 1 month, and 3.68 (95% CI 1.06 to 12.74) at 1 year.

No significant differences between TAVI and SAVR were found for vascular access complication rates.

7.7 Discussion on safety outcomes

RCT evidence on the safety of TAVI was available for all risk groups evaluated within this review. In most of the patients TAVI was carried out via the transfemoral route.

The key evidence on the safety of TAVI for patients for whom SAVR is considered unsuitable was from one good quality RCT (PARTNER 1B) with a follow-up of 5 years. In these patients, TAVI when compared to standard medical therapy was associated with higher rates of safety events including stroke, major bleeding, major vascular complications, but lower risk of PPI up to 2 years follow-up, with the differences becoming non-significant at 3 years. A lower risk of re-hospitalisation favoured TAVI at all follow-ups up to 5 years. No differences between TAVI and medical therapy were found for the other safety events reported.

The key evidence on the safety of TAVI for patients for whom SAVR is suitable but poses a high risk was from two good quality RCTs (US CoreValve and PARTNER 1A), with follow-up durations of 3 and 5 years respectively. As there were only two studies included in any of the meta-analyses conducted for the safety outcomes, publication bias using funnel plot testing cannot be conducted. For patients for whom SAVR is suitable but poses a high risk, no differences were found in the rates of stroke, major bleeding or major vascular complications. Rates of aortic regurgitation were found to be higher in TAVI. TAVI had a lower proportion of patients with moderate or severe PPM. Discrepant findings were observed for risk of AKI with the US CoreValve trial reporting a statistically significantly higher risk of AKI for patients receiving TAVI, whereas the PARTNER 1A trial did not observe significant differences in the risk for the event. Although the evidence is from RCTs, safety evidence was graded as moderate or low, indicating imprecision in the results.

Evidence on safety for patients with an intermediate or low risk for surgery was summarised from 4 systematic reviews. When compared with SAVR, TAVI was associated with a reduced risk of major bleeding for both the transfemoral and transapical routes, a reduced risk of AKI for the transfemoral route, a reduce risk of new AF, but had an increased risk of aortic regurgitation, PPI and of aortic valve reinsertion. There were no differences in the risk of stroke and the risk of MI between the

treatment groups. The quality of some safety evidence was graded as moderate with reduced certainty.

Some overlap in risk categories between studies was observed in the RCTs and systematic reviews included. If the inclusion of “medium” or “intermediate” risk is relaxed to include data from the CoreValve trial, as done in the systematic review of Siemienuik et al. (2016), then 2 year mortality is improved by 3% when transfemoral TAVI is compared to SAVR. However, the CoreValve study (Adams et al. 2014) recruited patients with “increased risk” (at least 15%) of mortality but was eligible for this systematic review as the mean STS score was less than 8. Hence results from Siemienuik et al. (2016) may not be generalisable to lower-risk populations. The CoreValve study has been included in the systematic review of TAVI in high risk patients presented in this report. Given these overlapping and conflicting inclusion criteria, it is difficult to clearly delineate risk groups in study level systematic reviews and meta-analyses. An individual patient data meta-analysis with sufficiently wide inclusion criteria might be better able to quantify outcomes for surgical risk groups.

No analyses based on TAVI valve type/size or delivery sheath type/size were reported.

8 ASSESSMENT OF FACTORS RELEVANT TO THE NHS AND OTHER PARTIES

If the numbers of TAVI procedures carried out in the NHS continues to rise, this may have implications for the organisation of specialised interventional cardiology services. No factors outside the remit of this systematic review were evaluated.

9 DISCUSSION

9.1 Statement of principal findings

The key evidence on the efficacy and safety of TAVI for patients for whom SAVR is considered unsuitable was from one good quality randomised controlled trial (RCT) comparing TAVI with standard care (medical therapy) with 358 patients and a maximum follow-up of 5 years. The key evidence for patients for whom SAVR is considered suitable but poses a high risk was from two good quality RCTs with a total of 1494 patients and a maximum follow-up of 5 years. For patients for whom

SAVR is considered suitable and not to pose a high risk, the key evidence was from 4 recent systematic reviews with a total of 24838 patients and a maximum follow-up of 3 years, two of which were considered of good quality. Meta-analysis was conducted where appropriate.

9.1.1 TAVI versus medical therapy in patients for whom SAVR is considered unsuitable

- TAVI was associated with a statistically significantly lower mortality rate of both all-cause and cardiac-cause at follow-up of 1, 2, 3 and 5 years: HR 0.58 (95% CI 0.36 to 0.92) at 1 year, HR 0.5 (95% CI 0.39 to 0.65) at 2 years, HR 0.53 (95% CI 0.41 to 0.68) at 3 years, and HR 0.5 (95% CI 0.39 to 0.65) at 5 years for all-cause mortality; HR 0.44 (95% CI 0.32 to 0.60) at 2 years, HR 0.41 (95% CI 0.30 to 0.56) at 3 years and HR 0.41 (95% CI 0.31 to 0.55) at 5 years for cardiac mortality.

- Compared with medical therapy, the TAVI group had a lower proportion of patients in NYHA classes III/IV at 1 and 2 years and higher proportion of patients in NYHA classes I and II at 3 and 5 years.

- TAVI was superior to medical therapy in QoL at least for 1 year, with KCCQ summary score being 26 points higher, SF-12 physical score 5.7 points higher and SF-12 mental health 6.4 points higher than the control at 1 year ($p<0.001$ for all the three comparisons).

- TAVI was associated with statistically significantly higher risk of stroke at 1 year (11.2% versus 5.5%, $p<0.001$), 2 years (HR 2.79; 95% CI 1.25 to 6.22) and 3 years (HR 2.81; 95% CI 1.26 to 6.26), with the difference becoming non-significant at 5 years.

- TAVI was associated with statistically significantly higher risk of major bleeding up to 1 year of follow-up (24.2% versus 14.9%, $p=0.04$), with the difference becoming non-significant between the treatment groups at 2 year (28.9% versus 20.1%, $p=0.09$), and then statistically significantly lower in the TAVI group at 3 years (HR 1.69; 95% CI 1.06 to 2.70).

- The risk of major vascular complications, reported for 3 years of follow-up only, was statistically significantly higher in the TAVI than in the medical treatment group (HR 8.27; 95% CI 2.92 to 23.44).

- Patients with TAVI had a statistically significantly lower risk of re-hospitalisation due to aortic stenosis or TAVI complication at 1 year (27.0% versus 53.9%, p<0.001), 2 years (HR 0.41; 95%CI 0.30 to 0.58), 3 years (43.5% versus 75.5%, p<0.0001) and 5 years (47.6% versus 87.3%, p<0.0001).

- No statistically significant difference between the treatments in the risk of PPI, MI, AKI and endocarditis at 1, 2 and 3 years.

9.1.2 In patients for whom SAVR is considered suitable but poses a high risk

- Based on a time-to-event analysis there was no statistically significant differences between TAVI and SAVR in hazard of death of any cause up to 5 years of follow-up.

- TAVI performed either via the transfemoral route or the transapical route, showed no statistically significant difference from SAVR in all-cause mortality up to 5 years of follow-up, and in cardiovascular mortality up to 2 years.

- Patients who underwent TAVI had a statistically significantly better NYHA classification profile up to 6 months, which ceased at later follow-up points up to 5 years.

- Compared with SAVR, TAVI resulted in a statistically significant improvement in QoL as measured by summary SF-12 at 30 days but not 6 months and 1 year, and TAVI via the TF route was associated with a statistically significant improvement in QoL as measured by EQ-5D and KCCQ at 30 days, which were no longer significant at 6 months or 1 year. There were no statistically significant differences between non-TF TAVI and SAVR in QoL at any of the follow-up points.

- There were no statistically significant differences between the treatments in pooled risk of all-cause mortality or cardiovascular mortality at 30 days. No differences were found in the rates of stroke, major vascular complications or MI.

- TAVI had significantly better outcomes than SAVR in terms of the overall incidence and severity of PPM up to 2 years of follow-up.

- TAVI had higher rates of moderate or severe total aortic regurgitation than SAVR up to 3 years.

- Incidence of major bleeding reported in the PARTNER 1A trial at all the follow-up time points up to 5 years favoured the TAVI group: RR 0.48 (95% CI 0.32 to 0.71) at 30 days; RR 0.58 (95% CI 0.42 to 0.80) at 1 year; RR 0.64 (95% CI 0.48 to 0.85) at 2 years; RR 0.73 (95% CI 0.57 to 0.95) at 5 years). Whereas the US CoreValve trial showed no statistically significant differences between TAVI and SAVR at all the follow-up points up to 3 years.

- Compared with SAVR, TAVI using a self-expanding valve was associated with a statistically significantly higher risk of PPI at all the follow-up points up to 3 years; while TAVI using a balloon-expanding valve had no statistically significant differences from SAVR at all the follow-up points up to 5 years.

- In the US CoreValve trial the risk of AKI was statistically significantly lower with TAVI at 30 days and 1, 2 and 3 years. Whereas in the PARTNER 1A trial there were no statistically significant differences between the treatment groups at all the follow-up points up to 5 years.

9.1.3 In patients for whom SAVR is considered suitable and not to pose a high risk

- There were no statistically significant differences between TAVI, when not stratified by access routes, and SAVR, in all-cause mortality at 1 year and long-term (>1 year). Whereas when using the transfemoral route TAVI compared with SAVR was associated with a significantly lower hazard of death at 2 years (HR 0.79; 95% CI 0.66 to 0.94).

- No significant differences were found between the treatment groups with measures of QoL.

- No significant differences were found between the treatments in 30-day all-cause mortality.

- TAVI was associated with an increased risk of heart failure symptoms (OR 1.29; 95% CI 1.08 to 1.55) but shorter length of hospital stay (MD -2.23; 95% CI -5.22 to 0.76).

- There were no differences in the risk of stroke and MI between the two treatments.

- TAVI was associated with a reduced risk of major bleeding for both transfemoral (RR 0.39; 95% CI 0.29 to 0.54) and transapical routes (RR 0.53; 95% CI 0.42 to 0.67), a reduced risk of acute kidney injury for the transfemoral route (RR 0.38; 95% CI 0.27 to 0.54), a reduced risk of new AF (RR 0.43; 95% CI 0.35 to 0.52), but had an increased risk of aortic regurgitation

(RR 12.22; 95% CI 5.17 to 28.88), PPI (RR 2.45; 95% CI 1.17 to 5.14) and of aortic valve reinsertion (RR 3.25; 95% CI 1.29 to 8.14).

9.2 Strengths and limitations of the assessment

We investigated the efficacy and safety of TAVI for aortic stenosis specifically by surgical risk levels (patients for whom SAVR is considered unsuitable; patients for whom SAVR is considered suitable but poses a high risk; patients for whom SAVR is considered suitable and not to pose a risk), in order to answer clinically important questions that have not been addressed such as the beneficial outcomes and safety of TAVI in patients for whom SAVR is suitable but poses a high risk.

We included evidence and analysed data based on surgical risk levels, and excluded studies which could not be categorised by the specific risk groups in our review question. However, evidence on the safety and efficacy of TAVI compared with SAVR for the overall population has already been provided by the systematic review and meta-analysis by Gargiulo et al. (2016). Based on analyses of the overall population of 16638 patients, it found that there were no statistically significant differences between TAVI and SAVR in early (≤30 days) or midterm (≤1 year) all-cause mortality, while separate analysis for TAVI with the transfemoral route showed mortality benefits over SAVR. Long-term follow-up (>1 year and up to 5 years) based on RCTs showed no significant differences in all-cause mortality between TAVI and SAVR, while results from matched studies favoured SAVR.

We explored the efficacy/safety of the TAVI approach based on transfemoral and non-transfemoral routes and also summarised data which were reported in sub-groups by LVEF, previous CABG, diabetes, prosthesis-patient mismatch and sex.

Our search was comprehensive and up to 8th August 2016. Comparative and non-comparative observational studies were sought to address our specific review questions by different surgical risk levels, in order to identify outcomes that were not covered by the included trials.

We did not pool studies with different design, i.e. RCTs and observational studies, to avoid methodological heterogeneity.

There is limited available information comparing TAVI with SAVR using different TAVI routes, valves and delivery sheathes. Evidence on which TAVI route, valve and delivery sheath may be superior could be derived from direct comparisons between TAVI procedures performed using such devices.

Our review aimed to evaluate the relative efficacy and safety of TAVI when compared to medical management or SAVR and not studies comparing different TAVI procedures.

With regard to modifications of the TAVI procedure, our review did not look at the impact of ancillary variations of the TAVI procedure (such as types of anaesthetic, types of imaging examination / guidance, learning curve, etc.). However, these factors may have influenced the outcomes, for example, local anaesthesia which is possible with TAVI, may have associated with more rapid recovery and shorter length of stay than general anaesthesia. Similarly, we did not look at SAVR combined with any other surgical cardiac procedure, despite that some patients would be treated by coronary artery bypass graft and SAVR at surgery but would either only undergo TAVI or would undergo percutaneous coronary intervention first followed by TAVI.

Studies that could not be categorised according to the surgical risk groups were excluded from our review.

There was some overlap in risk categories across the RCTs and systematic reviews included in our review. Given these overlapping and conflicting inclusion criteria, it is difficult to clearly delineate risk groups in study level systematic reviews and meta-analyses. There was also overlap in RCTs included the four systematic reviews for the intermediate- or low-risk group of patients.

9.3 Uncertainties

In all risk groups RCT evidence on the efficacy of TAVI was available, although given the nature of TAVI and the comparator treatments, blinding of investigators and patients was not possible. There were insufficient studies for formal assessment of publication bias.

Patients in RCTs were followed for up to five years, hence there is some uncertainty concerning longer term outcomes of TAVI. Patients who are candidates for TAVI however have a poor prognosis and RCT populations had a high mean age, so competing risks of death will become more prominent should longer term follow up data become available.

The included evidence did not conduct sub-group analyses comparing TAVI valves from different manufacturers. Moreover, these devices and delivery systems are subject to incremental innovation and newer valve devices are now marketed. The UK TAVI register collects information on the device manufacturer and might be a future source of information.

While there was some RCT evidence on TAVI using the transfemoral route and less on the transapical route, greater precision on outcomes using specific routes in different risk populations would be desirable. Likewise, greater precision in the quantification of some safety outcomes would facilitate the characterisation of the risk and benefit profiles of SAVR and TAVI.

There is some uncertainty around the risk stratification of studies, given that RCTs have overlapping patient populations to a certain degree. This particularly applies to the US CoreValve RCT which given the inclusion criteria and baseline patient characteristics has been included within our review in the high risk group but also in systematic reviews of intermediate and low risk patient populations. This problem cannot be addressed in study level meta-analysis. Individual patient data meta-analysis, should RCT sponsors agree to release trial data, would be required to more fully explore the effectiveness and safety of TAVI based on surgical risk stratification.

9.4 Ongoing research

A considerable volume of research concerning TAVI is in progress (Appendix 7). RCTs comparing TAVI with SAVR or other comparators will add to the evidence reported here. RCTs comparing newer TAVI devices with established devices are also in progress, while cohort studies are addressing questions concerned with complications and access routes.

Eight ongoing RCTs comparing TAVI with SAVR were identified. The United Kingdom Transcatheter Aortic Valve Implantation (UK TAVI) trial is a multi-centre RCT to assess the clinical effectiveness and cost utility of TAVI (any commercially available device), compared with SAVR, in patients with severe symptomatic aortic stenosis at intermediate or high operative risk. With a sample size of 808 patients, this RCT investigates whether TAVI is non-inferior to SAVR in patients at intermediate or high operative risk over a 5-year period and will probably end recruitment in 2017. SURTAVI is an RCT of CoreValve in intermediate risk patients with a planned sample size of 2500 patients which should reach the primary endpoint in October 2016.

Further RCTs planned, recruiting or active are expected to reach endpoints between 2018 and 2027. The PARTNER 3 RCT will use the SAPIEN 3 valve in low risk patients with severe calcified aortic stenosis with a planned sample size of 1228 patients. The Medtronic CoreValve Evolut R System TAVI trial is recruiting 1250 low risk patients. The NOTION-2 RCT will recruit 992 younger patients with low surgical risk. TAVR UNLOAD RCT is in 600 patients with advanced heart failure comparing

TAVI with optimum heart failure treatment. The TRANSIT RCT is in 600 all-comers with severe aortic stenosis.

Four RCTs in progress comparing different TAVI devices were found.

Relevant cohort studies were the SOLACE-AU cohort which will be compared to cohort A of the PARTNER 2 RCT; a retrospective analysis of periprocedural stroke rates in the UK TAVI register; a study of direct aortic versus subclavian access for TAVI also in collaboration with the national register; a prospective study examining criteria for pacing following TAVI in 165 patients; a prospective study of the feasibility of early discharge following transfemoral TAVI.

9.5 Other relevant factors

If the numbers of TAVI procedures carried out in the NHS continues to rise, this may have implications for the organisation of specialised interventional cardiology services. No factors outside the remit of this systematic review were evaluated.

10 CONCLUSIONS

10.1 Synthesis of results to inform IPAC decision making

RCT evidence on the efficacy of TAVI was available for all risk groups evaluated within this review. In most of the patients TAVI was carried out via the transfemoral route.

TAVI was superior to medical therapy for patients unsuitable for SAVR in all-cause or cardiac mortality, NYHA classification and quality of life at follow-up. TAVI, when compared to medical therapy, was associated with higher rates of safety events including stroke, major bleeding and major vascular complications, but a lower risk of permanent pacemaker implantation up to 2 years follow-up, with the differences becoming non-significant at 3 years. The TAVI group had a lower risk of re-hospitalisation at all follow-ups up to 5 years. No differences between TAVI and medical therapy were found for the other safety events reported.

For patients for whom SAVR is suitable but poses a high risk, there were no significant differences between TAVI and SAVR for all-cause mortality and cardiovascular mortality up to 5 years of follow-

up. TAVI performed either via the transfemoral route or the transapical route, showed no statistically significant difference from SAVR in all-cause mortality at follow-up of 1, 2, and 5 years, and in cardiovascular mortality at 1 and 2 years. Although efficacy outcomes such as NYHA classification at follow-up and quality of life favoured TAVI at shorter follow-ups, the differences ceased to be significant in the long-term. No differences were found in the rates of death at 30 days, stroke, major vascular complications or myocardial infarction. Rates of moderate or severe total aortic regurgitation were found to be higher with TAVI. The TAVI group had a lower proportion of patients with moderate or severe prosthesis-patient mismatch. Incidence of major bleeding reported in the PARTNER 1A trial at all the follow-up time points up to 5 years favoured the TAVI group, whereas the US CoreValve trial showed no statistically significant differences between TAVI and SAVR up to 3 years. Compared with SAVR, TAVI using a self-expanding valve resulted in an increased risk of permanent pacemaker implantation (PPI) at all the follow-up points up to 3 years; whereas there were not significant differences when TAVI was performed using a balloon-expanding valve up to 5 years. In the US CoreValve trial TAVI was associated with a significantly lower risk of acute kidney injury at all the follow-up points, whereas in the PARTNER 1A trial there were no statistically significant differences between the treatments. Although the evidence is from RCTs, quality of the safety evidence was graded as moderate or very low, indicating serious imprecision in the results.

For patients with an intermediate or low risk, TAVI compared with SAVR was associated with a statistically significantly lower hazard of death at 2 years when using the transfemoral route. No statistically significant differences were found in measures of quality of life. No significant differences were found between the treatments for all-cause mortality at 30 days. TAVI was associated with an increased risk of heart failure symptoms but shorter length of hospital stay. TAVI was associated with a reduced risk of major bleeding for both the transfemoral route and the transapical route, a reduced risk of acute kidney injury for the transfemoral route, a reduced risk of new AF, but had an increased risk of aortic regurgitation, permanent pacemaker implantation and of aortic valve reinsertion. There were no differences in the risk of stroke and the risk of myocardial infarction between the treatment groups. The quality of some safety evidence was graded as moderate with reduced certainty.

No analyses based on TAVI valve size or delivery sheath type/size were reported.

10.2 Implications for service provision

If the numbers of TAVI procedures carried out in the NHS continues to rise, this may have implications for the organisation of specialised interventional cardiology services. No factors outside the remit of this systematic review were evaluated.

10.3 Suggested further research or data collection

Good quality evidence in the form of RCTs and systematic reviews is available with long-term follow-ups. The main uncertainties refer to the efficacy and safety of TAVI according to different risk stratification groups. This is mostly due to variations in the study criteria but also due to a lack of precision with current risk stratification tools for patients with symptomatic aortic valve disease. An individual patient data meta-analysis with sufficiently wide inclusion criteria could provide more definitive indications on the safety and efficacy of TAVI for different surgical risk groups and assist in an improved patient stratification for this patient population, although it is unclear whether the trial and registry datasets can reliable allow this.

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12 APPENDICES

12.1 Appendix 1. Literature search strategies and resources

Electronic databases including: The Cochrane Library (Wiley) (CDSR, DARE, HTA and CENTRAL), CRD Centre for Reviews and Dissemination Databases (DARE, NHS EED and HTA), MEDLINE (Ovid), MEDLINE in Process (Ovid), EMBASE (Ovid), ZETOC (British Library) and PubMed (US NLH) were searched from March 2011 (April 19th 2011 being the date on which the electronic searches for the NICE rapid overview were conducted) to 8th August 2016. An information specialist conducted the searches using the search strategy devised for the NICE rapid overview (see below the MEDLINE search strategy). This strategy was then adapted to be run across each of the different databases.

Relevant websites were searched and experts contacted. Conference abstracts in published conference proceedings were searched to capture any unique safety events not reported in published full-text literature. Hand searching of reference lists of relevant studies was carried out. Clinical trials registers, including ClinicalTrials.gov and WHO ICTRP, were searched to locate any key trials which are emerging. Language filter were not used for the searches, although non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base. Literature search results were uploaded to and managed using EndNote X7.0.1 software.

Database: MEDLINE (Ovid) 1946 to July Week 3 2016
Search Strategy:

1 Aortic valve/ab
2 heart valve diseases/ or exp aortic valve stenosis/
3 (aortic* adj stenosis).tw.
4 (valv* adj3 disease).tw.
5 or/1-4
6 ((percutan* or transcath*) adj3 (heart* or aortic*) adj3 valve*).tw.
7 ((percutan* or transcath*) adj3 valve*).tw.
8 PAVR.tw.
9 TAVR.tw.
10 TAVI.tw.
11 ((transap* or transventric* or percutan* or transcath*) adj3 (deliver* or access* or approach* or minimal*)).tw.

12 or/6-11

13 5 and 12

14 animals/ not humans/

15 13 not 14

16 limit 15 to yr="2011 - current"

17 (201101$ or 201102$).ed.

18 16 not 17

Database: Ovid MEDLINE In-Process & Other Non-Indexed Citations August 01, 2016

Search Strategy:

1 (Aortic valve* adj3 abnormal*).tw.

2 (aortic* adj stenosis).tw.

3 (valv* adj3 disease).tw.

4 or/1-3

5 ((percutan* or transcath*) adj3 (heart* or aortic*) adj3 valve*).tw.

6 ((percutan* or transcath*) adj3 valve*).tw.

7 PAVR.tw.

8 TAVR.tw.

9 TAVI.tw)

10 ((transap* or transventric* or percutan* or transcath*) adj3 (deliver* or access* or approach* or minimal*)).tw.

11 or/5-10

12 4 and 11

13 limit 12 to yr="2011 - current"

Database: Embase (Ovid) 1974 to 2016 August 01

Search Strategy:

1 aorta valve/

2 exp valvular heart disease/

3 aorta valve stenosis/

4 (aortic* adj stenosis).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

5 (aortic adj stenosis).tw.

6 (valv* adj3 disease).tw.

7 or/1-5

8 ((percutan* or transcath*) adj3 (heart* or aortic*) adj3 valve*).tw.

9 ((percutan* or transcath*) adj3 valve*).tw.

10 PAVR.tw.

11 TAVR.tw.

12 TAVI.tw.

13 ((transap* or transventric* or percutan* or transcath*) adj3 (deliver* or access* or approach* or minimal*)).tw.

14 or/8-13

15 7 and 14

16 animals/ not humans/

17 15 not 16

18 limit 17 to yr="2011 - 2016"

Database: Cochrane Library (Wiley): CENTRAL Issue 7 of 12 July 2016, CDSR Issue 8 of 12 August 2016, HTA Issue 3 of 4 July 2016, DARE Issue 2 of 4 (April 2015), EED Issue 2 of 4 April 2015

Search Name: TAVI NICE strategy update 2011-2016

Searched 8 August 2016

Search strategy:

#1 MeSH descriptor: [Aortic Valve] explode all trees and with qualifier(s): [Abnormalities - AB]

#2 MeSH descriptor: [Heart Valve Diseases] this term only

#3 MeSH descriptor: [Aortic Valve Stenosis] explode all trees

#4 aortic* near/3 stenosis

#5 valv* near/3 disease

#6 #1 or #2 or #3 or #4 or #5

#7 (percutan* or transcath*) near/3 (heart* or aortic*) near/3 (valve*)

#8 (percutan* or transcath*) near/3 (valve*)

#9 PAVR or TAVI or TAVR

#10 (transap* or transventric* or percutan* or transcath*) near/3 (deliver* or access* or approach* or minimal*)

#11 #7 or #8 or #9 or #10

#12 #6 and #11

#13 #6 and #11 Publication Year from 2011 to 2016

Database: PubMed (US NLM)

Searched 8 August 2016

Search strategy:

((aortic valve stenosis[MeSH Terms]) OR "aortic valve/abnormalities"[MeSH Terms]) OR heart valve diseases[MeSH Terms] and publisher[SB]
(((valv* disease* OR aortic stenosis) and publisher [SB]))
TAVI or TAVR or PAVR) and publisher[SB]
(percutaneous or transcath*) AND (valve* OR heart OR aortic) *) and publisher[SB]
(transap* OR transcentric OR percutan* OR transcath*) and publisher[SB] AND (deliver* OR access* OR approach* OR minimal*) and publisher[SB]

Database: PubMed (US NLM)
Searched 9 August 2016
Search strategy:

#1	Search ((aortic valve stenosis[MeSH Terms]) OR "aortic valve/abnormalities"[MeSH Terms]) OR heart valve diseases[MeSH Terms]
#2	Search (((valv* disease* OR aortic stenosis) and publisher [SB]))
#3	Search (#1 or #2)
#4	Search ((percutaneous or transcath*) AND (valve* OR heart OR aortic) *) and publisher[SB])
#5	Search TAVI or TAVR or PAVR) and publisher[SB]
#6	Search (transap* OR transcentric OR percutan* OR transcath*) and publisher[SB] AND (deliver* OR access* OR approach* OR minimal*) and publisher[SB]
#7	Search (#4 or #5 or #6)
#8	Search (#7 and #3)
#9	Search (#7 and #3) Sort by: Author Filters: Publication date from 2011/01/01 to 2016/08/31

Database: ZETOC British Library
Searched : 8 Aug 2016
Search strategy:

Terms used: "aortic valve*" or "aortic stenosis" or "heart valve*" date: 2011-2016 TAVI or TAVR or PAVR date: 2011-2016

12.2 Appendix 2. Data extraction form template

Reviewer:

Table of study characteristics

Study ID	*(1st author & year of publication)*
Study design	
Setting	
Funding source/conflict interest	
Inclusion/exclusion criteria	
Recruitment methods	
Patients' risk level for SAVR	
Number of patients recruited or randomised	
Number of patient withdrawals	
Age (mean; SD)	
Gender (number and % of males)	
Trade name of TAVI device (valve), manufacturer	
Key/unique features of the valve	*Type (e.g. balloon expandable valve, or using self-expanding nitinol stent), size/diameter, whether retrievable, etc.*
Trade name of delivery system	*Introducer sheath trade name and diameter*
Key/unique features of delivery system	*(e.g. motorized introducer sheath, or sheath-less delivery system)*
Delivery route	
Positioning feature	
Procedural duration	
Comparator	*Characteristics of standard therapy*
Follow-up period	
Primary outcome	
Secondary outcome	
Statistical analysis	
Conclusion drawn by study author(s)	

Note: where appropriate please extract data separately for comparison groups.

Table of results (This table will be adapted for safety data extraction from non-comparative studies)

(Insert 1st author & year publication)	**TAVI**	**Comparator**	**Data analysis**
No. randomised	N=	N=	
Primary outcome*			e.g. RR (95% CI), p value
Secondary outcome*			

*Wherever necessary please specify time to the outcome measurement, definition/measurement of the outcome, number of patients included in the analysis for the outcome measure.

12.3 Appendix 3. Observational studies reporting long-term or rare safety outcomes

Table I below presents the key findings of long-term safety events of TAVI for severe aortic stenosis from a number of non-comparative observational studies identified. Long-term in this case refers to studies with follow-up: i) > 5 years for patients unsuitable for SAVR and patients for whom SAVR was considered suitable but would pose a high risk; ii) > 2 years for patients with an intermediate or low risk; iii) > 1 year for studies reporting valve function/durability.

Table I. Long-term safety outcomes from non-comparative observational studies

Study	Population risk level	TAVI valve	Follow-up period	Key long-term outcomes	Key finding
Barbanti et al. 2015	353 high risk patients; unclear whether suitable for SAVR or not (transfemoral: 89.8%, subclavian: 10.2%). Age: mean 81.5 (SD 6.3) years. Risk score: median LogEuroSCORE 21.5% (15-31); Mean STS 9.5% (SD 10)	Medtronic CoreValve 100%	Only consecutive patients with 5-year follow-up were included in analysis	• Prosthetic valve failure • Neurological event rate	• Late prosthesis failure occurred in 5 cases(1.4%); late mild stenosis observed in 10 cases (2.8%). No other cases of structural or non-structural deterioration were observed. Transaortic gradient slightly increased at 5 years 12.8 (SD 10.9) mm Hg • Overall neurological event rate was 7.5% of which more than two-thirds occurred early after the procedure
Bouleti et al. 2015	123 patients considered to be unsuitable or at high risk for surgery (transfemoral: 68.3%, transapical: 30.1%). Age: mean 81.5 (SD 8.4) years. Risk score: EuroSCORE II 7.8% (SD 5.6); STS 7.1% (SD 4.7)	• Edwards SAPIEN 90.3% • Medtronic CoreValve 9.7%	Up to 6 years (median 3.6 years IQR: 2.6-4.7)	• Survival rate • Major stroke • Prosthetic valve dysfunction	Time-to-event data: • All-cause survival at 6 years was 31% (SD 5%); Cardiovascular survival rate at 6 years was 66% ± 5% • Cumulative rates of major stroke at 6 years after TAVI were 16.0% (SD 4.0%). There was no difference in the rates of stroke according to the presence or absence of atrial fibrillation (16.2% (SD 7.0%) and 17.0% (SD 5.0%) respectively, p=0.42). • 5 patients had prosthetic dysfunction: 3/5 had stenosis at 1.3, 3.2 and 5 years; 1/5 had aortic regurgitation grade 3 at 4.8 years and 1/5 had aortic regurgitation grade 4 at 2.o years
Ludman et al. 2015 UK TAVI Registry	3980 patients high risk patients; unclear whether suitable for SAVR or not (transfemoral: 71.2%, transapical: 19.2%, subclavian: 4.8%, direct aortic 4.8%). Age: mean 81.3 (SD 7.6) years. Risk score: LogEuroSCORE 21.9% (SD 13.7)	• Edwards SAPIEN (n=2036, 51.8%) • Medtronic CoreValve (n=1897, 48.2%) • Other valve (n=41, 1%)	6-8 years	Overall survival (n=3671)	Mortality / Survival / Upper 95%CI / Lower 95%CI 6 years: 0.6271 / 0.3729 / 0.3306 / 0.4153 7 years: 0.707 / 0.2930 / 0.2096 / 0.3813 8 years: no data / 0.2930 / 0.2096 / 0.3813
Papadopoulos et al. 2016	312 patients considered to be unsuitable or at high risk for surgery (transapical: 100%).	• Cribier Edwards • Edwards	At the time of discharge, at 6 months, at 12	Prosthetic valve function	• Late follow-up at 4.1 (SD 2.3) years, n=174 patients: Improvement of effective aortic orifice area: 1.52 (SD 0.2) cm^2

Study	Population risk level	TAVI valve	Follow-up period	Key long-term outcomes	Key finding
	Age: mean 79.8 (SD 5.8) years. Risk score: LogEuroSCORE II 23.9% (SD17.2); STS 9.8% (SD 8.6)	SAPIEN • Edwards SAPIEN XT • Edwards SAPIEN 3	months and yearly thereafter. 11 patients with mean follow-up time beyond 8 years		Paravalvular leaks (grade I to II): 59 (34%) Paravalvular leaks (>grade II): 19 (11%) Mean ejection fraction: 0.53 (SD 0.09) Decrease in mean transvalvular aortic gradient • Overall survival data at 8-10 years from graph ~40% Improvement of effective aortic orifice area 1. (SD 0.5) cm^2 and mean transvalvular aortic gradient Paravalvular leaks (grade I to II): 4/11 (36%) Paravalvular leaks (>grade II): 1/11 (9%) Mean ejection fraction: 0.49 (SD 0.11) Stent reconstruction showed stable structural behaviour of the stent beyond 8 years.
Rodés-Cabau et al. 2012	339 patients unsuitable or at very high risk for surgery (transfemoral: 48%, transapical: 52%). Age: mean 81 (SD 8) years Risk score: STS 9.8% (SD 6.4)	• Cribier-Edwards valve (n=57) • Edwards SAPIEN valve (n=275) • Edwards SAPIEN XT valve (n=7)	Most patients were followed at 1 year after the procedure and annually thereafter	Prosthetic valve durability	A mild non-clinically significant decrease in valve area occurred at 2-year follow-up ($p<0.01$), but no further reduction in valve area was observed up to 4-year follow-up. No changes in residual aortic regurgitation and no cases of structural valve failure were observed during the follow-up period.
Salinas et al. 2016	79 patients considered to be unsuitable or at high risk for surgery (transfemoral: 81%, transapical: 19%). Age: mean 82.3 (SD 6.1) years. Risk score: LogEuroSCORE 16.9% (SD9.1); STS 5.9% (SD2.9)	• Edwards SAPIEN (n=14, 17.7%) • Edwards SAPIEN XT (n=65, 82.3%)	2.5 to max 6.5 years	Prosthetic valve dysfunction	Follow-up >2.5 years: a 15.3% prosthetic valve dysfunction rate according to VARC-2 (moderate aortic regurgitation and/or mean gradient of 20 mmHg to 25 mmHg) without need for repeat valve replacement. There were no documented cases of aortic complication, mitral valve lesions, endocarditis, or prosthetic valve thrombosis.
Tan et et al. 2015	47 patients at risk of annular injury who underwent TAVI Age: 82 (SD 7.6) years. Risk score: STS 7.8% (SD 3.5)	Excessive oversizing of a balloon expandable Edwards SAPIEN XT valve	1 year	Prosthetic valve function and frame durability	There was no evidence of stent frame recoil, deformation, or fracture at 1 year.

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Salinas P, Moreno R, Calvo L, Sánchez-Recalde Á, Jiménez-Valero S, Galeote G, et al. Long-term Follow-up After Transcatheter Aortic Valve Implantation for Severe Aortic Stenosis. Rev Esp Cardiol (Engl Ed). 2016;**69**:37-44.

Study	Population risk level	TAVI valve	Follow-up period	Key long-term outcomes	Key finding
Tan JS, Leipsic J, Perlman G, Stub D, Dvir D, Hansson NC, et al. A Strategy of Underexpansion and Ad Hoc Post-Dilation of Balloon-Expandable Transcatheter Aortic Valves in Patients at Risk of Annular Injury: Favorable Mid-Term Outcomes. JACC Cardiovasc Interv. 2015;**8**:1727-32					

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Table II below lists a number of potentially relevant observational studies identified that described safety events of TAVI for severe aortic stenosis, which were considered as rare.

Table II. Observational studies reporting rare safety events

Safety event	Study
Acute myocardial infarction	Wendler O, et al. The JUPITER registry: Thirty-day primary endpoint Results of a second generation transapical TAVI system. EuroIntervention. Conference: EuroPCR 2014. Zhao QM, et al. Procedural Results and 30-day clinical events analysis following Edwards transcatheter aortic valve implantation in 48 consecutive patients: initial experience. Chinese Medical Journal 2012;**125**:2807-2810.
Acute myocardial injury from damage to apical epicardial collateral circulation	Khan ZA, et al. When we should say no to TAVR-Defining the line between utility and futility. Cardiovasc Revasc Med 2016;**17**:424-7.
Acute occlusion of right coronary artery	Wolf A, et al. Successful repositioning of a direct flow medical 25-mm valve due to acute occlusion of right coronary artery during transcatheter aortic valve replacement procedure. JACC: Cardiovascular Interventions 2015;**8**:e33-34.
Acute severe occlusion of the left main coronary artery	Gul M, et al. Acute severe occlusion of the left main coronary artery following transcatheter aortic valve implantation. Anadolu Kardiyoloji Dergisi 2012;**12**:282-283. Koyama Y, et al. Left Anterior Descending Coronary Artery Obstruction Associated with an Apical Suture after Transcatheter Aortic Valve Replacement. JACC: Cardiovascular Interventions 2016;**9**:499-500.
Aortic arch rupture	Dahdouh Z, et al. Aortic arch rupture: an uncommon but fatal complication during transcatheter aortic valve implantation. Jacc: Cardiovascular Interventions 2013;**6**:416-417.
Aortic dissection	Sugrue R, et al. Trans-catheter aortic valve implantation: Adverse outcomes of 120 cases in two centres. Irish Journal of Medical Science 2012;**181**:S321. Walther T, et al. Incidence of procedural complications in 9271 consecutive tav I patients: Analysis from the German aortic valve registry." Journal of the American College of Cardiology 2014;**1**:A1942. Babin-Ebell J, et al. Life-threatening complications during transcatheter aortic valve replacement requiring surgical rescue therapy. Thoracic and Cardiovascular Surgeon. Conference: 42nd Annual Meeting of the German Society for Cardiovascular and Thoracic Surgery Freiburg Germany. 2013;**61**:(no pagination).
Aorta perforation	Abugameh A, et al. Ascending aorta perforation following dislocation of percutaneous transcatheter aortic valve implantation (TAVI). Thoracic and Cardiovascular Surgeon. Conference: 41st Annual Meeting of the German Society for Cardiovascular and Thoracic Surgery: One Heart One Team Freiburg Germany. Conference Start 2012;**60**:(no pagination).
Aortic rupture (abdominal)	Lange R, et al. Incidence and treatment of procedural cardiovascular complications associated with trans-arterial and trans-apical interventional aortic valve implantation in 412 consecutive patients. European Journal of Cardio-thoracic Surgery 2011;**40**:1105-1113.
Aorto-Right Ventricular Defect (lethal)	Leroux L, et al. Lethal Aorto-Right Ventricular Defect After Transcatheter Aortic Valve Implantation in a Patient With Radiation-Induced Porcelain Aorta: Notes of Caution. Canadian Journal of Cardiology 2016;**32**:135.
Apical left ventricular thrombus	Singh V, et al. Transseptal antegrade transcatheter aortic valve replacement for no-access option patients: A contemporary experience. Journal of the American College of Cardiology 2013;**1**:E1900.
Apical tear	Hassan W, et al. First middle east transcatheter aortic valve implantation (TAVI) experience: Immediate and 20 months follow-up. Catheterization and Cardiovascular Interventions 2011;**77**:S139.
Baloon rupture	Gul M, et al. Rupture of the Novaflex balloon during TAVI procedure and subsequent dissection of the right iliac arteries with ruptured balloon. Turk Kardiyoloji Dernegi Arsivi 2012;**40**:325.
Catheter induced ventricular septum defect	Babin-Ebell J, et al. Life-threatening complications during transcatheter aortic valve replacement requiring surgical rescue therapy." Thoracic and Cardiovascular Surgeon. Conference: 42nd Annual Meeting of the German Society for Cardiovascular and Thoracic Surgery Freiburg Germany 2013;**61**:(no pagination).
Circumflex artery occlusion	Mukherjee C, et al. Rare complication of circumflex artery occlusion during transfemoral aortic valve replacement (TAVR). The international journal of cardiovascular imaging 2014;**30**:1463-1464.
Cutaneo-pericardial fistula	Scheid M, et al. Cutaneo-pericardial fistula after transapical aortic valve implantation. Interactive Cardiovascular & Thoracic Surgery 2013;**16**:558-559.
Delayed ventricular apical bleed	Soon J L, et al. The contemporary outcome of fifty two consecutive surgical transcatheter valve implantation performed in one year. EuroIntervention 2012;**8**:N212.
Distal coronary embolisation	Tsujimura A, et al. Distal coronary embolisation during transcatheter aortic valve implantation. BMJ Case Reports 2016; in press.
Early valve degeneration	Harbaoui B, et al. Early Edwards SAPIEN Valve Degeneration after Transcatheter Aortic Valve Replacement. JACC: Cardiovascular Interventions 2016;**9**:198-199.

Safety event	Study
Elliptic distortion of the aortic prosthesis	Kosek M, et al. Transcatheter aortic valve implantation in patients with bicuspid aortic valve: A series of cases. Kardiologia Polska 2015;**73**:627-636.
False left ventricular apical aneurysm	Kammler J, et al. False left ventricular apical aneurysm--a rare complication after transapical aortic valve replacement. Journal of Invasive Cardiology 2011;**23**:534-535.
Guide wire thrombus formation	Wiper A, et al. Guide wire thrombus formation during trans-femoral TAVI. Cardiovascular Revascularization Medicine 2014;**15**:360-361.
Iatrogenic chordal rupture	Cincin A, et al. A Case of Iatrogenic Chordal Rupture after Transcatheter Aortic Valve Implantation Procedure Requiring a Second Valve. Journal of Heart Valve Disease 2015;**24**:133-138. D'Ancona G, et al. Iatrogenic mitral valve chordal rupture during placement of an inflatable and repositionable percutaneous aortic valve prosthesis. The Journal of heart valve disease 2015;**24**:169-172.
Iliac artery rupture	Dahdouh Z, et al. Life-threatening iliac artery rupture during transcatheter aortic valve implantation (TAVI): diagnosis and management. Heart 2013;**99**:1217-1218
Intercostal artery pseudoaneurysm	Lenders G, et al. Intercostal artery pseudoaneurysm: a rare complication of transaortic transcatheter aortic valve implantation. Interactive Cardiovascular & Thoracic Surgery 2012;**15**:550-552.
Interventricular septum rupture	Martinez MI, et al. Interventricular septum rupture after transcatheter aortic valve implantation. European Heart Journal 2012;**33**:190. Garrido JM, et al. Interventricular septal rupture after transcatheter aortic valve implantation: surgical and perioperative management. Journal of Cardiac Surgery 2014;**29**:478-481.
Late prosthesis migration and rotation	Pang PY, et al. A survivor of late prosthesis migration and rotation following percutaneous transcatheter aortic valve implantation. European Journal of Cardio-thoracic Surgery 2012;**41**:1195-1196.
Left ventricular pseudoaneurysm	Matsumoto T, et al. Transseptal closure of left ventricular pseudoaneurysm post-transapical transcatheter aortic valve replacement. JACC: Cardiovascular Interventions 2014;**7**:e177-178. Morjan M, et al. Left ventricular pseudoaneurysm following transfemoral aortic valve implantation. Journal of Cardiac Surgery 2013;**28**:510-511.
Major bleeding from the apex	Wilbring M, et al. Transapical transcatheter aortic valve implantation using a repositionable second-generation device: Initial clinical Results and further follow-up of patients treated with the JenaValveTM. Thoracic and Cardiovascular Surgeon. Conference 2014;**62**:(no pagination).
Mitral valve destruction by wire entrapment	Babin-Ebell J, et al. Life-threatening complications during transcatheter aortic valve replacement requiring surgical rescue therapy. Thoracic and Cardiovascular Surgeon. Conference: 42nd Annual Meeting of the German Society for Cardiovascular and Thoracic Surgery Freiburg Germany. 2013;**61**:(no pagination)
Multivessel coronary artery spasm	Kaneko H, et al. Multivessel Coronary Artery Spasm After Transcatheter Aortic Valve Replacement. JACC: Cardiovascular Interventions 2016;**9**:621-622.
Papillary muscle rupture	de la Torre Hernandez JM, et al. Papillary muscle rupture: first report of this complication in a retrograde transfemoral aortic valve implantation. Catheterization & Cardiovascular Interventions 2011;**78**:647-649.
Perforation of the medial circumflex branch of the common femoral artery	Shannon J, et al. Iatrogenic perforation of the medial circumflex artery following femoral venous cannulation for transcatheter aortic valve replacement, presenting with retroperitoneal hematoma and successfully managed by percutaneous embolization and coiling. Catheterization and Cardiovascular Interventions 2012;**80**:1002-1006.
Pseudoaneurysm at the left ventricular apical access site	Karimi A, et al. Percutaneous transfemoral closure of a pseudoaneurysm at the left ventricular apical access site for transcatheter aortic valve implantation. Journal of Invasive Cardiology 2015;**27**:E27-E29. Ramlawi B, et al. Minimally Invasive Repair of Left Ventricular Pseudoaneurysm after Transapical Transcatheter Aortic Valve Replacement. Texas Heart Institute Journal 2016;**43**:75-77.
Pseudoaneurysm of the apex	Dahle G, Rein KA. Surgical treatment of pseudoaneurysm of the apex after transapical transcatheter aortic valve implantation. Innovations: Technology and Techniques in Cardiothoracic and Vascular Surgery 2015;**10**:S92-S93.
Ruptured pseudoaneurysm of a renal artery	Roman AJ, et al. Dissection and ruptured pseudoaneurysm of a renal artery: a non-described complication during transcatheter aortic-valve implantation. European Heart Journal 2013;34:941.
Takotsubo syndrome	Kustrzycka-Kratochwil D, et al. CoreValve transcatheter aortic valve implantation complicated by stress cardiomyopathy (tako-tsubo) and septic shock. Postepy w Kardiologii Interwencyjnej 2012;**8**:335-337.
Valve embolisation	Higgins J, et al. Transapical aortic valve implantation: The Vancouver experience. Annals of Cardiothoracic Surgery 2012;**1**:138-144. Rezq A, et al. Effectiveness and possible complications of post dilatation in patients with residual significant aortic regurgitation following valve implantation using both edwards and corevalve systems: A single center study. Journal of the American College of Cardiology 2012;**60**:B243.

12.4 Appendix 4. Table of excluded studies with rationale for exclusion

Three systematic reviews and one meta-analysis comparing TAVI with SAVR included either a mix of studies in both patients for whom SAVR was considered suitable but would pose a high risk and patients with low risk (Nagaraja et al. 2014; Cao et al. 2013), or a mix of studies in both patients for whom SAVR was considered suitable but would pose a high risk and patients with an intermediate risk (Siontis et al. 2016), but the reviews did not conduct analyses separately for the different risk groups. The findings of the reviews are not directly relevant to our individual review questions by population risk level. See table I below.

Table I. Systematic reviews on TAVI vs SAVR excluded from our analyses

Study	Population risk level	Key outcomes and follow-up	Searches	Studies included	Note
Cao et al. 2016	Not stated, but likely to be all comers	Mortality, stroke, myocardial infarction, acute renal failure	MEDLINE, EMBASE, Cochrane Library, ACP journal Club, NHS Economic Evaluation Database, etc (Jan 2000 to My 2014)	3 RCTs (PARTNER 1A, US CoreValve, STACCATO) in 3 papers, 10 matched observational studies and 11 unmatched comparative studies.	No separate analyses for different risk levels.
Nagaraja et al. 2014	Suitable for SAVR but with a high risk; low risk	30-day and 1-yr mortality, AKI, myocardial infraction, and stroke	MEDLINE (from 1950), PubMed (from 1946), EMBASE (from 1949), Current Contents Connect (from 1998), the Cochrane library, Google scholar, Science Direct and Web of Science until May 2014.	3 RCTs (**PARTNER 1A, US CoreValve, STACCATO**) in 3 papers,10 propensity score matched studies, 5 case matched studies and 2 studies that provided adjusted analysis.	No separate analyses for different risk levels.
Cao et al. 2013	Suitable for SAVR but with a high risk; low risk	Mortality, stroke, MI, vascular complications, PPI, AR, major bleeding, acute renal failure. Follow-up: up to 2 years	Ovid Medline, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, ACP Journal Club, and Database of Abstracts of Review of Effectiveness from 1 January, 2000 to 15 July, 2012.	2 RCTs (**PARTNER 1A, STACCATO**) in 3 papers; 11 observational studies.	No separate analyses for different risk levels.
Siontis et al. 2016	Suitable for SAVR but with a high risk; Intermediate risk	All-cause mortality, stroke, MI, AKI, new-onset AF, major bleeding, major vascular complications, valve endocarditis, PPI, PR. Follow-up: 2 years	Medline, Embase, and Cochrane databases. Date unclear.	4 RCTs (**PARTNER 1A**, **PARTNER 2A**, **US CoreValve**, **NOTION**) in 8 papers	No separate analyses for different risk levels. Subgroup: TF vs SAVR; TA vs SAVR

Abbreviation: AF, atrial fibrillation; AKI, acute kidney injury; AR, aortic regurgitation; MI, myocardial infarction; PPI, permanent pacemaker implantation; PR, paravalvular regurgitation; RCT, randomised controlled trial; TF, transfemoral; TA, transapical

One systematic review (Takagi et al. 2016) compared TAVI with sutureless aortic valve replacement (SU-AVR). Population risk levels were not specified but it seemed to be patients of any risk level. See table II below.

Table II. Systematic review on TAVI vs sutureless aortic valve replacement excluded from our analyses

Systematic review	Population risk level	Comparison	Key outcomes and follow-up length	Searches	Studies included
Takagi et al. 2016	Non-specific, seemed to have included any risk level	TAVI vs SU-AVR	In-hospital or 30-day all-cause mortality, bleeding complications, acute kidney injury, conduction disturbance, paravalvular aortic regurgitation (30-day)	MEDLINE and EMBASE were searched through June 2015	No RCTs; 7 observational comparative studies (enrolling a total of 945 patients) were included

Table III below shows the comparative studies in which population risk level was unclear and that were excluded from our analyses.

Table III. Comparative studies excluded from our analyses and reason for exclusion

Study	Risk level assessment and/or indications for TAVI	Reason for exclusion
Amonn K, Stortecky S, Brinks H, Gahl B, Windecker S, Wenaweser P, et al. Quality of life in high-risk patients: comparison of transcatheter aortic valve implantation with surgical aortic valve replacement. Eur J Cardiothorac Surg 2013;**43**:34-41.	High risk patients • Interdisciplinary heart team on the basis of EuroSCORE, STS score and technical feasibility of either therapy	Unclear if it is suitable or unsuitable for SAVR, or a mixed high risk population
Appel CF, Hultkvist H, Nylander E, Ahn H, Nielsen NE, Freter W, et al. Transcatheter versus surgical treatment for aortic stenosis: Patient selection and early outcome. Scand Cardiovasc J 2012;**46**:301-7.	Patients for whom SAVR infers an unacceptable high risk • LogEuroSCORE >15% • Patients with LogEuroSCORE <15% were not excluded	Unclear if it is suitable or unsuitable for SAVR, or a mixed high risk population
Bagur R, Rodés-Cabau J, Gurvitch R, Dumont É, Velianou JL, Manazzoni J, et al. Need for permanent pacemaker as a complication of transcatheter aortic valve implantation and surgical aortic valve replacement in elderly patients with severe aortic stenosis and similar baseline electrocardiographic findings. JACC Cardiovasc Interv 2012;**5**:540-51.	Mean LogEuroSCORE and STS score presented in population characteristics were significantly higher in TAVI group (26±17%; 9.2±5.7%) compared with SAVR group (12±9%; 3.6±1.5%)	Risk level unclear; possibly high risk
Bauer F, Coutant V, Bernard M, Stepowski D, Tron C, Cribier A, et al. Patients With Severe Aortic Stenosis and Reduced Ejection Fraction: Earlier Recovery of Left Ventricular Systolic Function After Transcatheter Aortic Valve Implantation Compared With Surgical Valve Replacement. Echocardiography 2013;**30**:865-70.	High risk or contra-indicated patients for SAVR based on the inclusion criteria of the REVIVE and PARTNER European trials and the SOURCE European Registry	Unclear if it is suitable or unsuitable for SAVR, or a mixed high risk population
Conradi L, Seiffert M, Treede H, Silaschi M, Baldus S, Schirmer J, et al. Transcatheter aortic valve implantation versus surgical aortic valve replacement: A propensity score analysis in patients at high surgical risk. J Thorac Cardiovasc Surg 2012;**143**:64-71.	All patients were considered to be at high surgical risk owing to comorbidities with a LogEuroSCORE ≥20%.	Unclear if it is suitable or unsuitable for SAVR, or a mixed high risk population
Davies JE Jr, McAlexander WW, Sasse MF, Leesar MA, Melby SJ, Singh SP, et al. Impact of Transcatheter Aortic Valve Replacement on Surgical Volumes and Outcomes in a Tertiary Academic Cardiac Surgical Practice. J Am Coll Surg 2016;**222**:645-55.	High risk or non-operable risk patients. Study indications for TAVR mimicked the FDA guidelines and those of the PARTNER trial.	A mixed high risk population
D'Onofrio A, Rizzoli G, Messina A, Alfieri O, Lorusso R, Salizzoni S, et al. Conventional surgery, sutureless valves, and transapical aortic valve replacement: What is the best option for patients with aortic valve stenosis? A multicenter, propensity-matched analysis. J Thorac Cardiovasc Surg 2013;**146**:1065-70.	The main indication for TAVI was associated with 1 or more of the following: (1) porcelain aorta; (2) high surgical risk (LogEuroSCORE I >20%; STS score >10%); and (3) other serious comorbidities	Unclear if it is suitable or unsuitable for SAVR, or a mixed high risk population
Falcone M, Russo A, Mancone M, Carriero G, Mazzesi G, Miraldi F, et al. Early, intermediate and late infectious complications after transcatheter or surgical aortic-valve replacement: a prospective cohort study. Clin Microbiol Infect 2014;**20**:758–63.	Patients were qualified for a TAVI if they fulfilled the following criteria: (i) age ≥75 years and a LogEuroSCORE ≥20% or (ii) LogEuroSCORE <20% and at least one of the following: cirrhosis of liver, pulmonary	Risk level unclear; possibly high risk or unsuitable for SAVR

Study	Risk level assessment and/or indications for TAVI	Reason for exclusion
	insufficiency (FEV1 ≤ 1 L) or porcelain aorta	
Forsberg LM, Tamás E, Vánky F, Nielsen NE, Engvall J, Nylander E. Left and right ventricular function in aortic stenosis patients 8 weeks post-transcatheter aortic valve implantation or surgical aortic valve replacement. Eur J Echocardiogr 2011;**12**:603-11.	High risk or contra-indicated patients for SAVR ass assessed by a team of surgeons and cardiologists	Unclear if it is suitable or unsuitable for SAVR, or a mixed high risk population
Giannini C, Petronio AS, Nardi C, De Carlo M, Guarracino F, Delle Donne MG, et al. Left ventricular reverse remodelling in percutaneous and surgical aortic bioprostheses: an echocardiographic study. J Am Soc Echocardiogr 2011;**24**:28-36.	High risk or inoperable	A mixed high risk population
Hannan EL, Samadashvili Z, Stamato NJ, Lahey SJ, Wechsler A, Jordan D, et al. Utilization and 1-Year Mortality for Transcatheter Aortic Valve Replacement and Surgical Aortic Valve Replacement in New York Patients With Aortic Stenosis. JACC Cardiovasc Interv 2016;**9**:578-85.	Low-medium (<3%) and high risk (≥3%) patients based on NYS in-hospital/30-day mortality risk model for isolated valve surgery	A mixed population. Unclear whether patients with a high risk are suitable for SAVR
Hoffmann R, Almutairi B, Herpertz R, Lotfipour S, Stöhr R, Aktug O, et al. Two-year mortality after transcatheter aortic valve implantation versus medical therapy for high-surgical risk or inoperable aortic stenosis patients. J Heart Valve Dis 2013;**22**:71-8.	High operative risk (LogEuroSCORE>20%) or other conditions related to a high operative risk such as significant frailty	Unclear if it is suitable or unsuitable for SAVR, or a mixed high risk population
Holzhey DM, Shi W, Rastan A, Borger MA, Hänsig M, Mohr FW. Transapical versus conventional aortic valve replacement--a propensity-matched comparison. Heart Surg Forum 2012;**15**:E4-8.	All patients >75 years and with a EuroSCORE >9%	Risk level unclear
Idrees J, Roselli EE, Raza S, Krishnaswamy A, Mick S, Kapadia S, et al. Aborted sternotomy due to unexpected porcelain aorta: does transcatheter aortic valve replacement offer an alternative choice? J Thorac Cardiovasc Surg 2015;**149**:131-4.	The choice of procedure type was based on a thorough preoperative assessment to determine the operative risk, anatomic feasibility, and need for additional procedures for cardiac comorbidities	Risk level unclear
Im E, Hong MK, Ko YG, Shin DH, Kim JS, Kim BK, et al. Comparison of Early Clinical Outcomes Following Transcatheter Aortic Valve Implantation versus Surgical Aortic Valve Replacement versus Optimal Medical Therapy in Patients Older than 80 Years with Symptomatic Severe Aortic Stenosis. Yonsei Med J 2013;**54**:596–602.	High risk or inoperable	A mixed high risk population
Johansson M, Nozohoor S, Kimblad PO, Harnek J, Olivecrona GK, Sjögren J. Transapical Versus Transfemoral Aortic Valve Implantation: A Comparison of Survival and Safety. Ann Thorac Surg 2011;**91**:57-63.	All patients were at high surgical risk or presented technical challenges to conventional AVR (risk estimated using the LogEuroSCORE and STS score, together with clinical judgment)	Unclear if it is suitable or unsuitable for SAVR, or a mixed high risk population
Kala P, Tretina M, Poloczek M, Ondrasek J, Malik P, Pokorny P, et al. Quality of life after transcatheter aortic valve implantation and surgical replacement in high-risk elderly patients. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2013;**157**:75-80.	High risk patients >75 years with a LogEuroSCORE > 15%	Unclear if it is suitable or unsuitable for SAVR, or a mixed high risk population
Keyl C, Schneider J, Beyersdorf F, Ruile P, Siepe M, Pioch K, et al. Right ventricular function after aortic valve replacement: a pilot study comparing surgical and transcatheter procedures using 3D echocardiography. Eur J Cardiothorac Surg 2016;**49**:966-71.	Mean LogEuroSCORE presented in population characteristics were significantly higher in TAVI group (11.9±5.8%) compared with SAVR group (7.0±3.3%)	Risk level unclear
Kobrin DM, McCarthy FH, Herrmann HC, Anwaruddin S, Kobrin S, Szeto WY, et al. Transcatheter and Surgical Aortic Valve Replacement in Dialysis Patients: A Propensity-Matched Comparison. Ann Thorac Surg 2015;**100**:1230-6.	High risk or inoperable risk dialysis patients	A mixed high risk population
Kocaaslan C, Ketenci B, Yılmaz M, Kehlibar T, Memetoğlu ME, Ertaş G, et al. Comparison of Transcatheter Aortic Valve Implantation versus Surgical Aortic Valve Replacement to Improve Quality of Life in Patients >70 Years of Age with Severe Aortic Stenosis. Braz J Cardiovasc Surg 2016;**31**:1-6.	A hospital council decided on the type of procedure to be performed. Mean LogEuroSCORE presented in population characteristics for the TAVI group was 9.75±1.27%	Risk level unclear
Latib A, Maisano F, Bertoldi L, Giacomini A, Shannon J, Cioni M, et al. Transcatheter vs surgical aortic valve replacement in intermediate-surgical-risk patients with aortic stenosis: A propensity score–matched case-control study. Am Heart J 2012;**164**:910-7.	Included moderate-to-high risk patients. High risk was defined as Logistic Euro-SCORE ≥20%, or STS≥10%, or conditions not captured by the 2 scores that the cardiac surgeon considered to increase the risk for standard SAVR. TAVR vs SAVR risk scores	A mixed moderate (or low)- to high-risk population

Study	Risk level assessment and/or indications for TAVI	Reason for exclusion
	(mean±SD): Logistic Euro-SCORE scores 23.2±15.1 vs 24.4±13.4 and STS score 4.6±2.3 vs 4.6±2.6.	
McCabe JM, Huang PH, Riedl LA, Devireddy SR, Grondell J, Connors AC, et al. Incidence and Implications of Idiopathic Thrombocytopenia Following Transcatheter Aortic Valve Replacement With the Edwards Sapien Valves: A Single Center Experience. Catheter Cardiovasc Interv 2014;**83**:633-41.	High surgical risk	Unclear if it is suitable or unsuitable for SAVR, or a mixed high risk population
Möllmann H, Bestehorn K, Bestehorn M, Papoutsis K, Fleck E, Ertl G, et al. In-hospital outcome of transcatheter vs. surgical aortic valve replacement in patients with aortic valve stenosis: complete dataset of patients treated in 2013 in Germany. Clin Res Cardiol 2016;**105**:553-9.	Patients were categorized into four risk groups using the LogEuroSCORE I: <10, 10–20, 20–30, and >30%	A mixed population of all risk levels
Motloch LJ, Reda S, Rottlaender D, Khatib R, Müller-Ehmsen J, Seck C, et al. Postprocedural Atrial Fibrillation After Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement. Ann Thorac Surg 2012;**93**:124-31.	Patients who were denied SAVR due to high perioperative risk.	A mixed high risk population
Nemec P, Ondrasek J, Malik P, Tretina M, Pokorny P, Poloczek M, et al. Comparison of the surgical and transcatheter aortic valve replacement in high-risk patients. Cor et Vasa 2012;**54**:e76-83.	High risk patients >75 years with a LogEuroSCORE > 15%	Unclear if it is suitable or unsuitable for SAVR, or a mixed high risk population
Olsson K, Nilsson J, Hörnsten Å, Näslund U. Patients' self-reported function, symptoms and health-related quality of life before and 6 months after transcatheter aortic valve implantation and surgical aortic valve replacement. Eur J Cardiovasc Nurs 2016; Epub ahead of print.	Patients were not accepted for surgery due to high risk	A mixed high risk population; possibly unsuitable for SAVR
Onorati F, D'Errigo P, Grossi C, Barbanti M, Ranucci M, Covello DRet al. Effect of severe left ventricular systolic dysfunction on hospital outcome after transcatheter aortic valve implantation or surgical aortic valve replacement: Results from a propensity-matched population of the Italian OBSERVANT multicenter study. J Thorac Cardiovasc Surg 2014;**147**:568-75.	High risk	Unclear if it is suitable or unsuitable for SAVR, or a mixed high risk population
Pilgrim T, Wenaweser P, Meuli F, Huber C, Stortecky S, Seiler C, et al. Clinical Outcome of High-Risk Patients with Severe Aortic Stenosis and Reduced Left Ventricular Ejection Fraction Undergoing Medical Treatment or TAVI. PLoS One 2011;**6**:e27556.	High risk or inoperable	A mixed high risk population
Retzlaff B, Wessel N, Riedl M, Gapelyuk A, Malberg H, Bauernschmitt N, et al. Preserved autonomic regulation in patients undergoing transcatheter aortic valve implantation (TAVI) – a prospective, comparative study. Biomed Tech (Berl) 2011;**56**:185-93.	High risk; no further details	Unclear if it is suitable or unsuitable for SAVR, or a mixed high risk population
Stöhr R, Dohmen G, Herpertz R, Brehmer K, Aktug O, Koos R, et al. Thirty-day outcome after transcatheter aortic valve implantation compared with surgical valve replacement in patients with high-risk aortic stenosis: a matched comparison. Coron Artery Dis 2011;**22**:595-600.	High operative risk (LogEuroSCORE>20%) or other conditions related to a high operative risk such as significant frailty	Unclear if it is suitable or unsuitable for SAVR, or a mixed high risk population
Stortecky S, Brinks H, Wenaweser P, Huber C, Pilgrim T, Windecker S, et al. Transcatheter Aortic Valve Implantation or Surgical Aortic Valve Replacement as Redo Procedure After Prior Coronary Artery Bypass Grafting. Ann Thorac Surg 2011;**92**:1324-30.	LogEuroSCORE was significantly higher for the TAVI cohort (35.5±17), whereas the STS score revealed no differences between the two groups (TAVI vs SAVR)	Risk level unclear
Sulženko J, Toušek P, Kočka V, Bednář F, Línková H, Petr R, et al. Degenerative changes and immune response after transcatheter aortic valve implantation. Comparison with surgical aortic valve replacement. J Cardiol 2016; Epub ahead of print.	TAVI patients had more comorbidities evaluated in LogEuroSCORE I [TAVI: 21.0 (5.0;46.0) vs. SAVR: 6.15 (2.54; 11.17)]	Risk level unclear
Tamburino C, Barbanti M, Capodanno D, Mignosa C, Gentile M, Aruta P, et al. Comparison of Complications and Outcomes to One Year of Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement in Patients With Severe Aortic Stenosis. Am J Cardiol 2012;**109**:1487-93.	High risk or contra-indicated patients for SAVR	Unclear if it is suitable or unsuitable for SAVR, or a mixed high risk population
Thongprayoon C, Cheungpasitporn W, Srivali N, Harrison AM, Gunderson TM, Kittanamongkolchai W, et al. AKI after Transcatheter or Surgical Aortic Valve Replacement. J Am Soc Nephrol 2016;**27**:1854-60.	High risk patients	Unclear if it is suitable or unsuitable for SAVR, or a mixed high risk population
Tokarek T, Siudak Z, Dziewierz A, Sobczyński R, Zasada W, Sorysz D, et al. Assessment of Quality of Life in Patients After Surgical and Transcatheter Aortic Valve Replacement. Catheter Cardiovasc Interv 2016;**88**:E80-8.	High risk patients although reported mean LogEuroSCORE 9.5 (7-14)%	Unclear if it is suitable or unsuitable for SAVR, or a mixed

Study	Risk level assessment and/or indications for TAVI	Reason for exclusion
		high risk population
Uddin A, Fairbairn TA, Djoukhader IK, Igra M, Kidambi A, Motwani M, et al. Consequence of cerebral embolism after transcatheter aortic valve implantation compared with contemporary surgical aortic valve replacement: effect on health-related quality of life. Circ Cardiovasc Interv 2015;**8**:e001913.	TAVI patients were selected by a multidisciplinary heart team in accordance with contemporary UK guidance	Risk level unclear
Wenaweser P, Pilgrim T, Kadner A, Huber C, Stortecky S, Buellesfeld L, et al. Clinical Outcomes of Patients With Severe Aortic Stenosis at Increased Surgical Risk According to Treatment Modality. J Am Coll Cardiol 2011;**58**:2151-62.	At increased surgical risk (EuroSCORE >15% and/or with comorbid conditions)	Risk level unclear; possibly high risk
Wendt D, Al-Rashid F, Kahlert P, El-Chilali K, Demircioglu E, Neuhäuser M, et al. Conventional aortic valve replacement or transcatheter aortic valve implantation in patients with previous cardiac surgery. J Cardiol 2015;**66**:292-7.	High-risk patients with a LogEuroSCORE-I > 20%, or at high risk due to the presence of other coexisting illnesses not reflected by the EuroSCORE	Unclear if it is suitable or unsuitable for SAVR, or a mixed high risk population

Table IV below shows the non-comparative observational studies excluded from our analyses.

Table IV. Excluded non-comparative observational studies reporting long-term safety outcomes and reason for exclusion

Study	N	TAVI		Population risk level	Follow-up period	Key long-term outcomes	Reason for exclusion
		Valve	Route				
Barbanti et al. 2016	995	Medtronic CoreValve	Mainly transfemoral (subclavian or direct aortic in some cases)	2 groups: STS≤7% (n=697) vs. STS>7% (n=298)	3 years	All-cause and cardiovascular mortality, neurologic events (stroke and TIA), MI, bleeding, vascular complications and AKI	Varying levels of surgical risk. Data not informative
Collas et al. 2015	861	Edwards SAPIEN or Medtronic CoreValve	Mainly transfemoral but also transapical, subclavian or direct aortic	Not candidates for SAVR (low, intermediate and high risk EuroSCORE cohorts)	3 years	Overall survival	Varying levels of surgical risk. Data not informative
D'Onofrio et al. 2016	338	Medtronic CoreValve or Edwards SAPIEN, Edwards SAPIEN XT, Edwards SAPIEN 3	Transfemoral for CoreValve; transfemoral or transapical for SAPIEN	Unsuitable or at high risk for SAVR	5 years	Overall survival	Mixed high risk population; follow-up period covered by comparative studies
Holzhey et al. 2012	439	Cribier Edwards, Edwards SAPIEN THV, Edwards SAPIEN XT	Transapical	Mixed risk level; possibly high risk	~5.6 years	Overall survival and haemodynamic performance	Varying levels of surgical risk. Data not informative
Unbehaun 2015	730	Edwards SAPIEN THV, Edwards SAPIEN XT	Transapical	Unsuitable or at high risk for SAVR	Up to 5 years (median 1.56years)	Overall survival	Mixed high risk population; follow-up period covered by comparative studies
Wang 2014	599	No details	No details	Consecutive patients. Mixed risk level	Up to 5 years (mean ~2.5 years)	Overall survival	Varying levels of surgical risk. Data not informative

References:

Barbanti M, Schiltgen M, Verdoliva S, Bosmans J, Bleiziffer S, Gerckens U, et al. Three-Year Outcomes of Transcatheter Aortic Valve Implantation in Patients With Varying Levels of Surgical Risk (from the CoreValve ADVANCE Study). Am J Cardiol. 2016;**117**:820-7.

Collas VM1, Dubois C, Legrand V, Kefer J, De Bruyne B, Dens J, et al. Midterm clinical outcome following Edwards SAPIEN or Medtronic Corevalve transcatheter aortic valve implantation (TAVI): Results of the Belgian TAVI registry. Catheter Cardiovasc Interv. 2015;**86**:528-35.

D'Onofrio A, Facchin M, Besola L, Manzan E, Tessari C, Bizzotto E, et al. Intermediate Clinical and Haemodynamic Outcomes After Transcatheter Aortic Valve Implantation. Ann Thorac Surg. 2016;**101**:881-8.

Holzhey DM, Hänsig M, Walther T, Seeburger J, Misfeld M, Linke A, et al. Transapical aortic valve implantation - The Leipzig experience. Ann Cardiothorac Surg. 2012;**1**:129-37.

Unbehaun A, Pasic M, Drews T, Penkalla A, Dreysse S, Klein C et al. Transapical aortic valve implantation: predictors of survival up to 5 years in730 patients. An update. Eur J Cardiothorac Surg 2015;4**7**:281–90.

Wang TK, Sathananthan J, Chieng N, Gamble GD, Haydock DA, Ruygrok PN Aortic valve replacement in over 70- and over 80-year olds: 5-year cohort study. Asian Cardiovasc Thorac Ann. 2014;**22**:526-33

12.5 Appendix 5. Risk of bias of the RCTs

Trial	Risk item	Authors' judgement	Support for judgement
PARTNER 1B	Random sequence generation (selection bias)	Low risk	Computer-generated randomized blocks at each site and for each subgroup
	Allocation concealment (selection bias)	Unclear risk	Not specified
	Blinding of participants and personnel (performance bias)	High risk	Not blinded
	Blinding of outcome assessment (detection bias)	Low risk	Independent Data Safety Monitoring Board reviewed all safety data
	Incomplete outcome data (attrition bias)	Low risk	
	Selective reporting (reporting bias)	Unclear risk	QoL not reported
	Other bias	High risk	Supported by Edwards Lifesciences
PARTNER 1A	Random sequence generation (selection bias)	Low risk	Computer-generated randomized blocks at each site and for each subgroup
	Allocation concealment (selection bias)	Unclear risk	Not specified
	Blinding of participants and personnel (performance bias)	High risk	Not blinded
	Blinding of outcome assessment (detection bias)	Low risk	Independent Data Safety Monitoring Board reviewed all safety data
	Incomplete outcome data (attrition bias)	Low risk	
	Selective reporting (reporting bias)	Low risk	QoL reported in Reynolds 2012
	Other bias	High risk	Supported by Edwards Lifesciences
US CoreValve	Random sequence generation (selection bias)	Low risk	Assigned a patient identification number in the interactive voice/web randomization service (IXRS)
	Allocation concealment (selection bias)	Unclear risk	Not specified
	Blinding of participants and personnel (performance bias)	High risk	Not blinded
	Blinding of outcome assessment (detection bias)	Low risk	Independent Data Safety Monitoring Board performed comprehensive data reviews

Trial	Risk item	Authors' judgement	Support for judgement
	Incomplete outcome data (attrition bias)	Low risk	
	Selective reporting (reporting bias)	Low risk	
	Other bias	High risk	Medtronic funded the trial and developed the protocol in collaboration with the study steering committee. Medtronic was responsible for the selection of the clinical sites, monitoring of the data, and management of all source data and statistical analyses
PARTNER 2A	Random sequence generation (selection bias)	Low risk	Subjects randomised according to a computer generated randomisation scheme
	Allocation concealment (selection bias)	Unclear risk	Not specified
	Blinding of participants and personnel (performance bias)	High risk	Not blinded
	Blinding of outcome assessment (detection bias)	Low risk	Data were analysed by an independent biostatistical consultant
	Incomplete outcome data (attrition bias)	Low risk	
	Selective reporting (reporting bias)	Unclear risk	Health-related quality of life not reported although pre-specified
	Other bias	High risk	Supported by Edwards Lifesciences. The trial was designed and monitored by the sponsor (Edwards Lifesciences) and the executive committee. The sponsor funded the trial and participated in the selection of the trial sites, the collection of the data, and data monitoring
STACCATO	Random sequence generation (selection bias)	Low risk	Randomisation implemented using a web-based clinical trials support system
	Allocation concealment (selection bias)	Unclear risk	Not specified
	Blinding of participants and personnel (performance bias)	High risk	Not blinded
	Blinding of outcome assessment (detection bias)	Low risk	
	Incomplete outcome data (attrition bias)	High risk	Study terminated early after advice from the DSBM (70 patients recruited from 200 planned)
	Selective reporting (reporting bias)	High risk	Not all secondary endpoints results were reported
	Other bias	Low risk	No industry involvement.
NOTION	Random sequence generation (selection bias)	Unclear risk	Randomisation method not specified
	Allocation concealment (selection bias)	Low risk	Allocation sequence in permuted blocks with unknown block size for the investigators
	Blinding of participants and personnel (performance bias)	High risk	Not blinded
	Blinding of outcome assessment (detection bias)	Low risk	An independent clinical events committee adjudicated all clinical events. An independent statistician confirmed the statistical analysis.
	Incomplete outcome data (attrition bias)	Low risk	
	Selective reporting (reporting bias)	High risk	Quality of Life (SF-36) not reported
	Other bias	Low risk	Not industry funded.

12.6 Appendix 6. Evidence grading using the GRADE framework

TAVI compared with medical therapy for severe aortic stenosis in patients unsuitable for SAVR

Quality assessment							Impact	Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
All-cause mortality (follow up: 5 years)									
1	randomised trials	serious [a,b,c]	not serious	not serious	not serious	none	TAVI (71.8%) versus medical therapy (93.6%); HR 0·50, 95% CI 0·39 to 0·65; p<0·0001	⊕⊕⊕◯ MODERATE	CRITICAL
Quality of life (not reported)									
1	randomised trials	serious [a,b,c]	not serious	not serious	not serious	none	KCCQ summary score was 26 points higher, SF-12 physical score 5.7 points higher and SF-12 mental health 6.4 points higher with than with the control at 1 year (p<0.001 for all the three comparisons).	⊕⊕⊕◯ MODERATE	IMPORTANT
30-day mortality (follow up: 30 days)									
1	randomised trials	serious [a,b,c]	not serious	not serious	not serious	none	TAVI versus medical therapy: 2.6% versus 5.9%, p=0.09	⊕⊕⊕◯ MODERATE	CRITICAL
Major bleeding (follow up: 3 years)									
1	randomised trials	serious [a,b,c]	not serious	not serious	not serious	none	TAVI (32.0%) versus medical therapy (32.9%); HR, 1.69; 95% CI 1.06 to 2.70; p=0.03	⊕⊕⊕◯ MODERATE	IMPORTANT
Stroke (follow up: 5 years)									
1	randomised trials	serious [a,b,c]	not serious	not serious	not serious	none	The hazard of stroke higher was higher with TAVI than medical therapy up to 3 years (HR 2.81, 95% CI 1.26 to 6.26, p=0.012), then the significance did not maintain at 5 years.	⊕⊕⊕◯ MODERATE	IMPORTANT
New PPI (follow up: 3 years)									

Quality assessment							Impact	Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
1	randomised trials	serious [a,b,c]	not serious	not serious	not serious	none	No statistically significant differences between TAVI and SAVR in the proportion of patients requiring PPI at 1 year (4.7% vs 8.6%), 2 years (6.4% vs 8.6%) and 3 years (7.6% vs 8.6%)	⊕⊕⊕◯ MODERATE	IMPORTANT
Repeat hospital admission (follow up: 5 years)									
1	randomised trials	serious [a,b,c]	not serious	not serious	not serious	none	TAVI (47.6%) versus medical therapy (87.3%); HR, 0.40; 95% CI, 0.29 to 0.55; p<0.0001	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: confidence interval; HR: hazard ratio; PPI, permanent pacemaker implantation; TAVI: transcatheter aortic valve implantation
a. Unblinded
b. Not free from industry funding
c. Allocation concealment process not specified

TAVI compared with SAVR for severe aortic stenosis in patients for whom SAVR is considered suitable but poses a high risk

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TAVI	SAVR	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow up: range 3 years to 5 years)												
2	randomised trials	serious [a,b,c]	not serious	not serious	serious [d]	none	356/742 (48.0%)	335/752 (44.5%)	**HR 0.97** (0.83 to 1.12)	**10 fewer per 1,000** (from 38 more to 58 fewer)	⊕⊕◯◯ LOW	CRITICAL
Quality of life: EQ-5D (follow-up: 1 year)												
2	randomised trials	serious [a,b,c]	not serious	not serious	not serious	none	359	284	-	**MD 0.03 more** (0 to 0.06 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
30-day mortality (follow up: 30 days)												
2	randomised trials	serious [a,b,c]	not serious	not serious	not serious	none	27/742 (3.6%)	43/752 (5.7%)	**RR 0.64** (0.40 to 1.02)	**21 fewer per 1,000** (from 1 more to 34 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
All stroke (follow up: 2 years)												
2	randomised trials	serious [a,b,c]	serious [e]	not serious	very serious [d]	none	64/742 (8.6%)	66/752 (8.8%)	**RR 1.11** (0.51 to 2.41)	**10 more per 1,000** (from 43 fewer to 124 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Major bleeding (follow up: 2 years)												
2	randomised trials	serious [a,b,c]	not serious	not serious	not serious	none	183/742 (24.7%)	230/752 (30.6%)	**RR 0.78** (0.54 to 1.13)	**67 fewer per 1,000** (from 40 more to 141 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
Myocardial infarction (follow up: 2 years)												
2	randomised trials	serious [a,b,c]	not serious	not serious	very serious [d]	none	7/742 (0.9%)	11/752 (1.5%)	**RR 0.51** (0.06 to 4.05)	**7 fewer per 1,000** (from 14 fewer to 45 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Acute kidney injury (follow up: 2 years)												
2	randomised trials	serious [a,b,c]	not serious	not serious	serious [d]	none	44/742 (5.9%)	75/752 (10.0%)	**RR 0.64** (0.31 to 1.34)	**36 fewer per 1,000** (from 34 more to 69 fewer)	⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval; **HR:** Hazard Ratio; **RR:** Risk ratio; **MD:** Mean difference

a. Unblinded

b. Not free from industry funding

c. Allocation concealment process not specified
d. A 25% relative risk reduction or increase (RR 0.75 and 1.25)
e. Statistical heterogeneity between RCTs

12.7 Appendix 7. Ongoing trials and matched comparisons

WHO ICTRP and ClinicalTrials.gov were searched August 2016 for trials from 2011 onwards. Four duplicates were removed. A total of 241 references were hand searched. We found eight RCTs comparing TAVI to SAVR or other non-TAVI controls (and 6 TAVI vs other TAVI comparisons) and three TAVI cohorts. We have not included "ancillary" ongoing trials such as comparisons of TAVI with or without valvuloplasty.)

Comparisons of TAVI compared to SAVR or standard practice

Trial ID	Official title	Expected completion date	Status	Valve and route	Brief description
ISRCTN57819173	The United Kingdom Transcatheter Aortic Valve Implantation (UK TAVI) Trial. A multi-centre randomised controlled trial to assess the clinical effectiveness and cost utility of TAVI, compared with conventional surgical aortic valve replacement (AVR), in patients with severe symptomatic aortic stenosis at intermediate or high operative risk	Expected to run until July 2016	Completed	Any commercially available device	RCT Non-inferiority of TAVI versus SAVR in patients at intermediate or high operative risk over a 5-year period.
NCT01586910	Safety and Efficacy Study of the Medtronic CoreValve® System in the Treatment of Severe, Symptomatic Aortic Stenosis in Intermediate Risk Subjects Who Need Aortic Valve Replacement (SURTAVI). (SURTAVI)	October 2016 (final collection date for primary outcome)	Recruiting	Self-Expanding Medtronic CoreValve	RCT TAVI vs SAVR in patients with severe AS at intermediate surgical risk
NCT02675114	A Prospective, Randomized, Controlled, Multi-Center Study to Establish the Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low Risk Patients Requiring Aortic Valve Replacement Who Have Severe, Calcific, Symptomatic Aortic Stenosis (PARTNER 3)	March 2027	Recruiting	Sapien 3 Transcatheter Heart Valve and Edwards Commander Delivery System	RCT TAVI vs SAVR Low risk patients (<2% operative mortality risk)
NCT02701283	Transcatheter Aortic Valve Replacement With the Medtronic Transcatheter Aortic Valve Replacement System In Patients at Low Risk for Surgical Aortic Valve Replacement	March 2023	Recruiting	Medtronic CoreValve System TAVI device or the Medtronic Corevalve Evolut R System Transcatheter Aortic Valve Implantation (TAVI)	RCT TAVI vs SAVR in subjects who have a low predicted risk of operative mortality for SAVR with a commercially approved surgical bioprothesis
NCT02825134	Nordic Aortic Valve Intervention Trial 2 - A Randomized Multicenter Comparison of Transcatheter Versus Surgical Aortic Valve	June 2024	Not yet recruiting	Retrograde transfemoral transcatheter aortic valve replacement with any CE mark	TAVI vs SAVR Low risk for conventional surgery (STS Score <4%) aged 18-75 years

Trial ID	Official title	Expected completion date	Status	Valve and route	Brief description
	Replacement in Younger Low Surgical Risk Patients With Severe Aortic Stenosis (Notion-2)			approved aortic bioprosthesis with or without concomitant percutaneous coronary intervention.	
NCT02661451	Transcatheter Aortic Valve Replacement to UNload the Left Ventricle in Patients With ADvanced Heart Failure: A Randomized Trial (TAVR UNLOAD)	March 2018 (final data collection date for primary outcome measure)	recruiting	SAPIEN 3 THV via a transfemoral approach	RCT: TAVR in heart failure patients with moderate aortic valve stenosis as compared with optimum heart failure treatment
TAVI cohorts					
NCT01675596	The SOLACE-AU Clinical Trial. A Multicentre, Non-Randomised Controlled Study of the Safety, Performance, Quality of Life and Cost Effectiveness Outcomes of the Edwards SAPIEN XT™ Transcatheter Heart Valve in an Australian Population	2018	Recruiting	Edwards SAPIEN XT™ valve with the NovaFlex delivery system	Cohort TAVI outcomes. Outcomes to be compared to SAVR patients in cohort A of the PARTNER II trial
NCT02838199	TRANscatheter or SurgIcal Aortic Valve ReplacemenT in All-Comers With Severe Not yet open Aortic Valve Stenosis (TRANSIT)	December 2020	Not yet recruiting	Edwards Sapien3	RCT To determine superiority of TAVI to SAVR with bio-prosthesis
NCT02711540	Retrospective Analysis of Procedural Aspects of Transcatheter Aortic Valve Implantation (TAVI) on periprocedural stroke rates in the United Kingdom	July 2016 (final date for primary outcome measure)	Active, not recruiting	All patients who had TAVI in the UK	Retrospective cohort analysis of all TAVI patients in the UK for stroke predictors
NCT02404467	Feasibility And Safety of Early Discharge After Transfemoral Transcatheter Aortic Valve Implantation The FAST-TAVI Study	March 2017	Recruiting	Valve type unspecified TF-TAVI	Prospective observational. Evaluation of whether patients considered high or intermediate risk for surgery, but relatively low risk for TAVI, can be discharged early after the procedure (within the first 2-3 days) without additional risks.
NCT02695147	Direct Aortic vs Subclavian Access for TAVI: a Review of the Outcomes in the UK	June 2016 (Final data collection date for primary outcome measure)	Ongoing but not recruiting patients	Any TAVI procedure using any valve type performed via the subclavian approach Vs Any TAVI procedure using any valve type performed via the direct aortic approach	Retrospective cohort study
Comparisons of different types of TAVI					
NCT02737150	SecOnd-generation seLf-expandable Versus Balloon-expandable Valves and gEneral Versus Local Anesthesia in TAVI (SOLVE-TAV)	April 2021	Recruiting	CoreValve Evolut R self-expandable valve Edwards Sapien 3 balloon valve	RCT to demonstrate equivalence of second-generation self-expandable valves (CoreValve Evolut R) in comparison to second-generation balloon-expandable valves (Edwards Sapien 3) and of local anesthesia with conscious sedation in comparison to general anesthesia with respect to safety

Trial ID	Official title	Expected completion date	Status	Valve and route	Brief description
					and efficacy in high-risk patients with severe aortic stenosis undergoing transcatheter aortic valve implantation. RCT with 4 arms: Core Valve and Balloon valve each 1. under local anesthesia with conscious sedation 2. under general anesthesia STS risk score ≥10% and/or high risk/contraindication to conventional surgical aortic valve replacement
NCT02163850	SALUS Trial TranScatheter Aortic Valve RepLacement System Pivotal Trial The Safety and Effectiveness of the Direct Flow Medical Tanscatheter Aortic Valve System	December 2021	Recruiting	Direct Flow Medical	RCT of TAVI with Direct Flow vs Medtronic CoreValve or Edwards Sapien In in high and extreme risk patients were severe AS
NCT02000115	Portico Re-sheathable Transcatheter Aortic Valve System US IDE Trial	June 2018 (final data collection date for primary outcome measure)	Recruiting	St Judes Medical Portico via transfemoral and alternative delivery methods	RCT of St Judes Portico system vs "Commercially available transcatheter aortic valve" A high risk cohort and extreme risk cohorts.
NCT02202434	REPRISE III: Repositionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of Lotus™ Valve System - Randomized Clinical Evaluation	January 2017 (final data collection date for primary outcome measure)	recruiting	Lotus™ Valve System	RCT TAVI with Lotus system vs TAVI with CoreValve system in subjects with calcific AS, who are considered at extreme or high risk for surgical valve replacement.

12.8 Appendix 8. Haemodynamic performance

1. In patients who are considered unsuitable for SAVR

Haemodynamic performance data were reported in patients who were considered unsuitable for SAVR in the PARTNER 1B trial (Makkar et al. 2012; Kapadia et al. 2014; Kapadia et al. 2015), for patients undergoing TAVI only.

Mean aortic-valve area and aortic-valve gradients

There was a statistically significant improvement in aortic-valve area among patients undergoing TAVI 30 days after the procedure. The valve area remained stable over the course of follow-up at the follow-up points up to 5 years (table I). Similar to the pattern for aortic-valve area, there was a sustained reduction in the mean transvalvular gradient across the aortic valve over follow-up (table II).

Table I. Aortic-valve area: the TAVI group (unsuitable for SAVR)

Follow-up	Reference for PARTNER 1B trial	Number of patients*	**Median area (IQR)**, cm^2	Analysis
Baseline	Makkar et al. 2012	158	0.62 (0.52 to 0.76)	Between baseline and 30-day: p<0.001; between 30-day and 2-year: p=0.89
30-day	Makkar et al. 2012	137	1.5 (1.19 to 1.80)	
2-year	Makkar et al. 2012	65	1.53 (1.28 to 1.85)	
Follow-up	Reference	Number of patients§	**Mean area (SD)**, cm^2	Analysis
Baseline	Kapadia et al. 2014	NR	0.64 (0.18)	Between baseline and 30-day: p<0.001; it remained stable over the course of follow-up at 1, 2, 3 and 5 years.
30-day	Kapadia et al. 2014	145	1.55 (0.43)	
1-year	Kapadia et al. 2014	91	1.62 (0.47)	
2-year	Kapadia et al. 2014	73	1.56 (0.47)	
3-year	Kapadia et al. 2014	44	1.52 (0.48)	
4-year	Kapadia et al. 2015	31	1.46 (NR)	
5-year	Kapadia et al. 2015	15	1·52 (0·28)	

Abbreviation: IQR, interquartile range; NR, not reported; SD, standard deviation. * The numbers of patients for whom data on ejection fraction were available at each of those time points. § Based on number of patients with echocardiographic follow-up at each of the time points.

Table II. Aortic-valve gradient: the TAVI group (unsuitable for SAVR)

Follow-up	Reference for PARTNER 1B trial	Number of patients*	**Median gradient (IQR)**, mm Hg	Analysis
Baseline	Makkar et al. 2012	162	42.7 (32.5 to 52.4)	Between baseline and 30-day: p<0.001; between 30-day and 2-year: p=0.59
30-day	Makkar et al. 2012	143	9.3 (7.1 to 12.3)	
2-year	Makkar et al. 2012	65	9.7 (7.7 to 13.3)	
Follow-up	Reference	Number of patients§	**Mean gradient (SD)**, cm^2	Analysis
Baseline	Kapadia et al. 2014	NR	44.2 (14.9)	Similar to the aortic-valve area, there was a sustained reduction in the mean transvalvular gradient across the aortic valve over follow-up.
30-day	Kapadia et al. 2014	145	10.2 (4.5)	
1-year	Kapadia et al. 2014	91	10.8 (5.5)	
2-year	Kapadia et al. 2014	73	10.8 (4.5)	
3-year	Kapadia et al. 2014	44	11.3 (6.1)	
4-year	Kapadia et al. 2015	31	10.9 (NR)	
5-year	Kapadia et al. 2015	15	10·6 (3·9)	

Abbreviation: IQR, interquartile range; NR, not reported; SD, standard deviation. * The numbers of patients for whom data on ejection fraction were available at each of those time points. § Based on number of patients with echocardiographic follow-up at each of the time points.

Ejection fraction

Ejection fraction in patients undergoing TAVI in the PARTNER 1B trial showed no statistically significant changes between 30 days to 2 (table III).

Table III. Ejection fraction: the TAVI group (unsuitable for SAVR)

Makkar et al. 2012	n*	Ejection fraction (%), median (IQR)	Analysis
• Before TAVI	164	56.1 (46.8 to 61.6)	p=0.69 for the difference between 30 days and 2 years.
• 30-day	145	60.0 (55.0 to 65.0)	
• 2-year	67	59.4 (54.6 to 60.8)	

Abbreviation: n, number of patients; IQR, interquartile range. * Based on as-treated population.

Aortic regurgitation

Paravalvular aortic regurgitation and transaravalvular aortic regurgitation were reported for patients in the TAVI group in the PARTNER 1B trial (Makkar et al. 2012; Kapadia et al. 2014).

In patients who underwent TAVI, over the time period from 30 days up to 3 years the proportion of patients with trace or mild paravalvular regurgitation increased, while the proportion of patients with mild, moderate or severe paravalvular aortic regurgitation decreased. Overall, there was a statistically significant improvement in paravalvular aortic regurgitation from 30 days to 2 years (table IV). The proportion of patients with mild, moderate or severe transvalvular aortic regurgitation also decreased from 30 days to 2 years (table V). The authors stated that, when both transvalvular and paravalvular regurgitation were considered in an evaluation of the total volume load, the TAVI group and the

control group had similar degrees of total aortic regurgitation at both 1 year and 2 years, owing to the higher prevalence and severity of valvular regurgitation among patients in the control group (data were not presented). None of the patients in the TAVI group had aortic regurgitation that worsened to a moderate-to-severe level during the follow-up period.

Table IV. Paravalvular aortic regurgitation: the TAVI group (unsuitable for SAVR)

Patients at follow-up (%)	Reference for PARTNER 1B	Number of patients*	None	Trace	Mild	Moderate	Severe	Analysis
30-day	Kapadia et al. 2014	145	15.2	20.0	52.4	11.7	0.7	p=0.001 for the difference between 30 days and 2 years (Makkar et al. 2012).
6-month	Kapadia et al. 2014;	106	26.4	12.3	52.8	8.5	0.0	
1-year	Kapadia et al. 2014	91	25.3	20.9	45.1	8.8	0.0	
2-year	Kapadia et al. 2014	73	32.9	28.8	34.2	4.1	0.0	
3-year	Kapadia et al. 2014	44	36.4	27.3	31.8	4.5	0.0	

* As-treated and with echocardiographic data.

Table V. Transvalvular aortic regurgitation: the TAVI group (unsuitable for SAVR)

Patients at follow-up (%)	Reference for PARTNER 1B	Number of patients*	None	Trace	Mild	Moderate	Severe	Analysis
30-day	Makkar et al. 2012	144	32.6	38.9	27.8	0.7	0.0	p=0.75 for the difference between 30 days and 2 years.
2-year	Makkar et al. 2012	67	28.4	49.3	17.9	4.5	0.0	

* As-treated and with data on ejection fraction.

Other statement

The authors stated that, in patients who underwent TAVI, echocardiographic analyses revealed excellent valve haemodynamic outcomes that remained durable over the course of 2 years, with no evidence of valve migration, leaflet thickening, or calcification (Makkar et al. 2012); there was no echocardiographic or clinical evidence of structural valve deterioration with maintained valve areas and gradients at 3 years of follow-up (Kapadia et al. 2014), and no structural valve deterioration or migration, and improvements in valve area and gradient were maintained at 5 years (Kapadia 2015).

2. In patients for whom SAVR is considered suitable but poses a high risk

Mean aortic-valve area and aortic-valve gradients

Data on mean aortic-valve area and mean aortic-valve gradients in patients for whom SAVR is considered suitable but poses a high risk were reported in the PARTNER 1A trial (Hahn et al. 2013; Kodali et al. 2012) and the US CoreValve trial (Reardon et al. 2015). In both trials there were no significant differences in baseline aortic-valve area or aortic-valve gradients between the treatment groups, and the authors mentioned that both treatment groups showed a statistically significant increase in aortic-valve area and decrease in aortic valve gradients from baseline to discharge or 30 days of follow-up, which remained stable over 2 years.

Compared with SAVR, TAVI had a statistically significantly larger aortic-valve area up to 1 year of follow-up; the differences became insignificant at 2 years and 5 years in the PARTNER 1A trial whilst still significant at 3 years in the US CoreValve trial. TAVI also had a statistically significantly smaller aortic-valve gradient at the follow-up points, except at 6 months, 2 years and 5 years in the PARTNER 1A trial where the differences were insignificant, and that test for significance at 2 years was not reported in the US CoreValve trial. See table VI, figure I, table VII and figure II below for details.

Subgroup analyses of aortic-valve area and aortic-valve gradient in female patients in the US CoreValve trial (Skelding et al. 2016) showed a similar pattern to the analyses that included both sex groups in this trial (table VI and table VII).

Table VI. Aortic-valve area (SAVR is suitable but poses a high risk)

Follow-up	Reference	TAVI		SAVR		Analysis
		n	Mean (SD), cm^2	n	Mean (SD), cm^2	
Baseline	PARTNER 1A (Smith et al. 2012)*	319	0.7 (0.2)	297	0.6 (0.2)	p=0.32
	US CoreValve (Adams et al. 2014)§	349	0.72 (0.23)	306	0.73 (0.24)	NS
	US CoreValve (Skelding et al. 2016)‡	166	0.68 (0.20)	143	0.68 (0.24)	p=0.77
30-day	PARTNER 1A (Smith et al. 2012)*	279	1.7 (0.5)	228	1.5 (0.4)	p=0.001
	US CoreValve (Adams et al. 2014)§	344	1.95 (0.56)	280	1.60 (0.51)	p<0.001
	US CoreValve (Skelding et al. 2016)‡	159	1.80 (0.53)	133	1.44 (0.47)	p<0.001
6-month	PARTNER 1A (Smith et al. 2012)*	235	1.7 (0.5)	165	1.5 (0.5)	p=0.01
	US CoreValve (Skelding et al. 2016)‡	136	1.81 (0.49)	106	1.46 (0.42)	p<0.001
1-year	PARTNER 1A (Smith et al. 2012)*	219	1.6 (0.5)	155	1.4 (0.5)	p=0.002
	US CoreValve (Adams et al. 2014)§	274	1.91 (0.51)	206	1.57 (0.49)	p<0.001
	US CoreValve (Skelding et al. 2016)‡	130	1.81 (0.45)	94	1.45 (0.45)	p<0.001

2-year	PARTNER 1A (Hahn et al. 2013)§	110	1.5 (0.46)	139	1.57 (0.42)	p=0.160
	US CoreValve (Reardon et al. 2015)§	NR	1.87 (NR)	NR	1.51 (NR)	NR
3-year	US CoreValve (Deeb et al. 2016)§	179	1.79 (0.48)	133	1.53 (0.52)	p<0.0001
5-year	PARTNER 1A (Mack et al. 2015)*	53	1.6 (NR)	46	1.5 (NR)	p=0.29

Abbreviation: n, number of patients; NR, not reported; NS, non-significant; SD, standard deviation. * Based on as-treated population. § Based on number of patients implanted. ‡ In female patients with echocardiogram results.

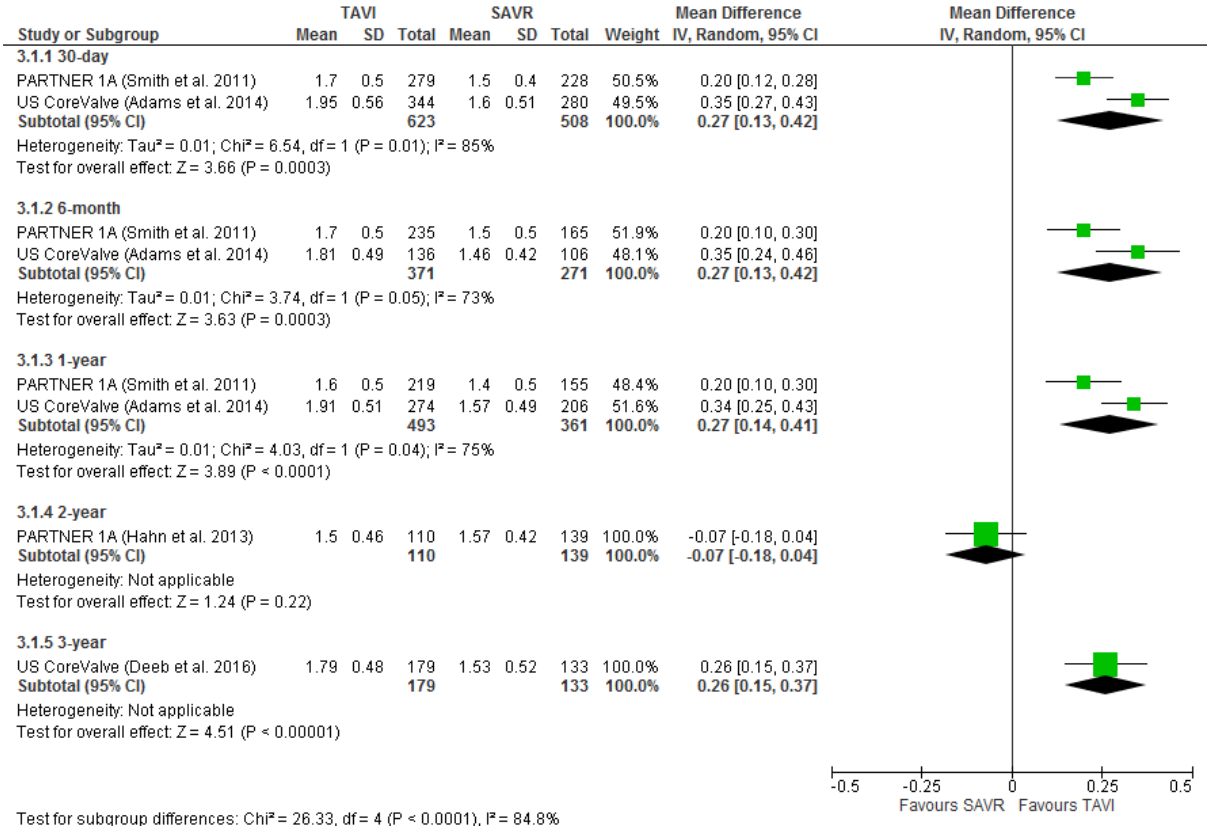

Figure I. Aortic-valve area (SAVR is suitable but poses a high risk)

Table VII. Aortic-valve gradient (SAVR is suitable but poses a high risk)

Follow-up	Reference	TAVI		SAVR		Analysis
		n	Mean (SD), mm Hg	n	Mean (SD), mm Hg	
Baseline	PARTNER 1A (Smith et al. 2012)*	327	42.7 (14.5)	301	43.5 (14.3)	p=0.51
	US CoreValve (Adams et al. 2014)§	387	48.27 (15.31)	350	47.65 (13.85)	NS
	US CoreValve (Skelding et al. 2016)‡	183	51.16 (16.15)	168	50.82 (14.85)	p=0.84
30-day	PARTNER 1A (Smith et al. 2012)*	287	9.9 (4.8)	231	10.8 (5.0)	p=0.04
	US CoreValve (Adams et al. 2014)§	356	8.88 (3.87)	311	11.71 (5.71)	p<0.001
	US CoreValve (Skelding et al. 2016)‡	165	8.92 (4.17)	147	12.24 (5.39)	p<0.001
6-month	PARTNER 1A (Smith et al. 2012)*	246	10.2 (4.3)	170	10.8 (4.8)	p=0.16
	US CoreValve (Skelding et al. 2016)‡	145	9.11 (4.65)	121	12.70 (5.49)	p<0.001
1-year	PARTNER 1A (Smith et al. 2012)*	227	10.2 (4.3)	159	11.5 (5.4)	p=0.008
	US CoreValve (Adams et al. 2014)§	291	9.07 (3.49)	224	12.40 (7.38)	p<0.001
	US CoreValve (Skelding et al. 2016)‡	136	9.23 (3.62)	104	12.97 (6.23)	p<0.001
2-year	PARTNER 1A (Hahn et al. 2013)§	112	11.1 (5.2)	144	10.2 (4.7)	p=0.161
	US CoreValve (Reardon et al. 2015)§	NR	8.5 (NR)	NR	12.1 (NR)	NR
3-year	US CoreValve (Deeb et al. 2016)§	190	7.62 (3.57)	140	11.40 (6.81)	p<0.0001
5-year	PARTNER 1A (Mack et al. 2015)*	56	10·7 (NR)	48	10·6 (NR)	p=0.92

Abbreviation: n, number of patients; NR, not reported; NS, non-significant; SD, standard deviation. * Based on as-treated population. § Based on number of patients implanted. ‡ In female patients with echocardiogram results.

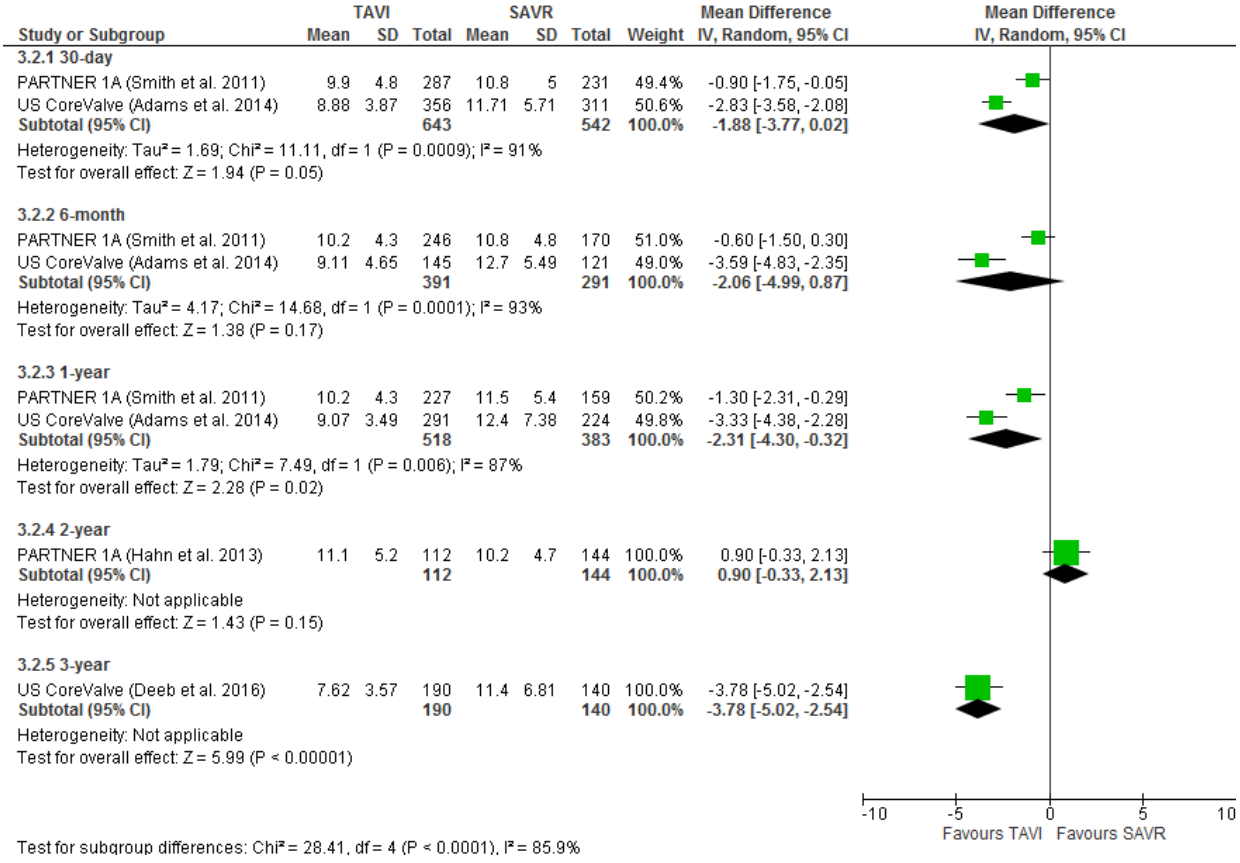

Figure II. Aortic-valve gradient (SAVR is suitable but poses a high risk)

Ejection fraction

Both the PARTNER 1A trial and the CoreValve trial found no statistically significant differences between the treatments on ejection fraction up to 2 years and 3 years respectively (table VIII).

Table VIII. Ejection fraction (SAVR is suitable but poses a high risk)

Follow-up	Reference	TAVI		SAVR		Analysis
		n	% (SD)	n	% (SD)	
Baseline	PARTNER 1A (Hahn et al. 2013)	313	52.6 (13.4)	295	53.4 (12.6)	p=0.4602
	CoreValve (Deeb et al. 2016)	390	56.9 (12.5)	354	56.0 (12.2)	NS
Discharge	PARTNER 1A (Hahn et al. 2013)	305	55.4 (11.0)	257	53.8 (12.1)	p=0.1064
30-day	PARTNER 1A (Hahn et al. 2013)	275	56.0 (11.2)	227	56.2 (11.3)	p=0.8290
6-month	PARTNER 1A (Hahn et al. 2013)	231	56.7 (10.2)	171	57.0 (9.8)	p=0.7596
1-year	PARTNER 1A (Hahn et al. 2013)	215	56.6 (10.4)	155	57.1 (10.4)	p=0.7018
	CoreValve (Deeb et al. 2016)	303	57.8 (11.0)	230	58.2 (8.9)	NS
2-year	PARTNER 1A (Hahn et al. 2013)	145	56.0 (10.0)	114	57.4 (10.4)	p=0.2902
3-year	CoreValve (Deeb et al. 2016)	190	56.8 (11.0)	140	58.0 (9.2)	NS

Abbreviation: NS, non-significant; n, number of patients; SD, standard deviation. Note: p<0.0001 in the TAVI group and p=0.487 in the SAVR group for change from baseline to first post-implant value; p=0.970 in the TAVI group and p<0.0001 in the SAVR group for change from fist post-implant to 2 years.

Other statement

In the PARTNER 1A study in which an Edwards SAPIEN heart-valve balloon-expanding valve was used, the authors stated that, no patients had structural valve deterioration requiring surgical replacement (Kodali et al. 2012), and no evidence of stent recoil in the TAVI group during follow-up to 2 years in either arm of this study (Hahn et al. 2013). No structural valve deterioration requiring surgical valve replacement occurred in either group even with few patients remaining at risk at 4 and 5 years (Mack et al. 2015).

In the US Core Valve trial in which a Medtronic CoreValve self-expanding valve was used, the authors stated that, there was no evidence of clinical valve thrombosis or structural valve deterioration in either group; no differences were found in the occurrence of structural valve deterioration over time up to 3 years (Deeb et al. 2016).

3. In patients for whom SAVR is considered suitable and not to pose a high risk

Mean aortic-valve area and aortic-valve gradients

None of the 4 systematic reviews we included for evidence in patients for whom SAVR is considered suitable and not to pose a high risk (Gargiulo et al. 2016; Siemieniuk et al. 2016; Khan et al. 2016; Arora et al. 2016) reported on mean aortic-valve area or mean aortic-valve gradients. However, all the 3 RCTs identified in patients with an intermediate or low risk (PARTNER 2A; NOTION; STACCATO) reported on theses outcomes. More information about the RCTs is presented in section 5.7.2.

Compared with SAVR, TAVI had statistically significant larger mean aortic-valve area and smaller aortic-valve gradient at 30 days, 1 year and 2 years of time points (table IX and table X).

Table IX. Aortic-valve area (SAVR is suitable and not to pose a high risk)

Follow-up	Reference	TAVI		SAVR		Analysis
		n	Mean (SD), cm^2	n	Mean (SD), cm^2	
30-day	PARTNER 2A (Leon et al. 2016)*	890	1.7 (0.5)	788	1.5 (0.4)	p<0.001
	STACCATO (Nielsen et al. 2012)‡	28	1.39 (0.28)	36	1.29 (0.27)	¥
	NOTION (Thyregod et al. 2015; Søndergaard et al. 2016)§	NR	1.7	NR	1.4	p<0.001
1-year	PARTNER 2A (Leon et al. 2016)*	751	1.6 (0.4)	633	1.4 (0.4)	p<0.001
	NOTION (Thyregod et al. 2015; Søndergaard et al. 2016)§	NR	1.7	NR	1.3	p<0.001
2-year	PARTNER 2A (Leon et al. 2016)*	626	1.5 (0.4)	536	1.4 (0.4)	p<0.001
	NOTION (Søndergaard et al. 2016)§	NR	1.6 (NR)	NR	1.3 (NR)	p<0.001
Baseline to 1-year	NOTION (Thyregod et al. 2015)§	NR	1.0 (0.5)	NR	0.6 (0.5)	p<0.001

Abbreviation: a-TAVI, thoracotomy through the apex of the heart; n, number of patients; NR, not reported; SD, standard deviation. * In the valve implanted population. ǂ In patients with echocardiogram results; the TAVI was transapical. ¥ The authors stated 'increased significantly after the procedure in both groups, but slightly more in the a-TAVI than in SAVR treated patients" § Based on as-treated population.

Table X. Aortic-valve gradient (SAVR is suitable and not to pose a high risk)

Follow-up	Reference	TAVI		SAVR		Analysis
		n	Mean (SD), mm Hg	n	Mean (SD), mm Hg	
30-day	PARTNER 2A (Leon et al. 2016)*	890	9.7 (3.5)	788	10.9 (4.3)	p<0.001
	STACCATO (Nielsen et al. 2012)ǂ	28	20 (6)	36	24 (11)	¥
	NOTION (Thyregod et al. 2015; Thyregod et al. 2016; Søndergaard et al. 2016)§	NR	8.3 (NR)	NR	12.2 (NR)	p<0.001
1-year	PARTNER 2A (Leon et al. 2016)*	751	10.7 (4.5)	633	11.5 (4.4)	p<0.001
	NOTION (Thyregod et al. 2015; Søndergaard et al. 2016)§	NR	8.6 (NR)	NR	12.5 (NR)	p<0.001
2-year	PARTNER 2A (Leon et al. 2016)*	626	10.8 (4.6)	536	11.7 (4.8)	p<0.001
	NOTION (Søndergaard et al. 2016)§	NR	9.0 (NR)	NR	13.0 (NR)	p<0.001
Baseline to 1-year	NOTION (Thyregod et al. 2015)§	NR	-34.8 (18.0)	NR	-32.0 (18.3)	p=0.23

Abbreviation: a-TAVI, thoracotomy through the apex of the heart; n, number of patients; NR, not reported; SD, standard deviation. * In the valve implanted population. ǂ In patients with echocardiogram results; the TAVI was transapical. ¥ The authors stated "Decreased significantly after the procedure in both groups, but slightly more in the a-TAVI than in SAVR treated patients". § Based on as-treated population.

Ejection fraction

No data on ejection fraction were reported comparing TAVI with SAVR in patients for whom SAVR is considered suitable and not to pose a high risk reported.

4. Summary of haemodynamic performance data

***In patients unsuitable for SAVR*:**

Echocardiography showed a sustained increase in aortic valve area and decrease in transvalvular gradient after TAVI, with no evidence of valve migration, leaflet thickening, or calcification structural valve deterioration.

In patients for whom SAVR is considered suitable but poses a high risk:

In both the PARTNER 1A trial and the US CoreValve trial, aortic-valve areas and gradients improved significantly after the procedures in both groups. At 1 year, TAVI had a statistically significantly better improvement than SAVR with respect to the mean aortic-valve area and mean aortic-valve gradient up to 1 year of follow-up, and the superiority of TAVI remained to 3 years of follow-up in the US

CoreValve trial. No structural valve deterioration requiring surgical valve replacement occurred in either group up to 5 years.

In patients for whom SAVR is considered suitable and not to pose a high risk:

Mean aortic-valve area and aortic-valve gradients improved in both treatment groups after the procedures. TAVI with an Edwards SAPIEN XT balloon-expanding valve in the PARTNER 2A trial and with a Medtronic CoreValve self-expanding valve in the NOTION trial both showed statistically better improvement than SAVR at 30 days, 1 year and 2 years.