### Appendix D: GRADE tables and metaanalysis results

D.1 GRADE TABLES

## D.1.1 Review question 1: Which pharmacological blood glucose lowering therapies should be used to control blood glucose levels in people with type 2 diabetes?

D.1.1.1 Table 1: Modified GRADE profile: Network meta-analyses for initial therapy

Assessment time points/ Measure	Number of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality			
Change in HbA1c									
3 months	68	serious <sup>1</sup>	not serious <sup>2</sup>	not serious <sup>3</sup>	not serious	Moderate			
6 months	62	serious <sup>1</sup>	not serious <sup>2</sup>	not serious <sup>3</sup>	not serious	Moderate			
12 months	21	serious <sup>1</sup>	not serious <sup>2</sup>	not serious <sup>3</sup>	serious <sup>4</sup>	Low			
24 months	6	serious <sup>1</sup>	not serious <sup>2</sup>	not serious <sup>3</sup>	not serious	Moderate			
Hypoglycaemia at study endpoint									
Study endpoint	44	serious <sup>1</sup>	not serious <sup>2</sup>	not serious <sup>3</sup>	serious <sup>4</sup>	Low			
Adverse events at s	tudy endpoint								
Dropouts due to adverse events	73	serious <sup>1</sup>	not serious <sup>2</sup>	not serious <sup>3</sup>	serious <sup>4</sup>	Low			
Total dropouts	73	serious <sup>1</sup>	not serious <sup>2</sup>	not serious <sup>3</sup>	serious <sup>4</sup>	Low			
Nausea	29	serious <sup>1</sup>	not serious <sup>2</sup>	not serious <sup>3</sup>	serious <sup>4</sup>	Low			
Change in body wei	ght								
12 months	12	serious <sup>1</sup>	serious <sup>5</sup>	not serious <sup>3</sup>	serious <sup>4</sup>	Low <sup>6</sup>			
24 months	6	serious <sup>1</sup>	serious <sup>5</sup>	not serious <sup>3</sup>	serious <sup>4</sup>	Low <sup>6</sup>			
10		10 70/							

<sup>1</sup>Downgrade 1 level: baseline HbA1c ranged from 5.3 to 12.7%

<sup>2</sup>Assessed based on residual deviance, deviance information criterion and  $tau^2$  ( $tau^2 < 0.5$ )

<sup>3</sup>Considered not serious as population, interventions, comparator and outcomes are as defined in protocol

<sup>4</sup>Downgrade 1 level: no interventions had probability of being best and worse  $\geq 0.5$ 

<sup>5</sup>Downgrade 1 level:  $tau^2 \ge 0.5$ 

<sup>6</sup>Maximum downgrade by 2 levels

#### D.1.1.2 Table 2: Modified GRADE profile: Network meta-analyses for first intensification

Assessment time points/ Measure	Number of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Change in HbA1c						

Assessment time points/ Measure	Number of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality				
3 months	20	not serious <sup>1</sup>	not serious <sup>2</sup>	not serious <sup>3</sup>	serious <sup>4</sup>	Moderate				
6 months	22	not serious <sup>1</sup>	not serious <sup>2</sup>	not serious <sup>3</sup>	serious <sup>4</sup>	Moderate				
12 months	16	not serious <sup>1</sup>	not serious <sup>2</sup>	not serious <sup>3</sup>	serious <sup>4</sup>	Moderate				
24 months	6	not serious <sup>1</sup>	not serious <sup>2</sup>	not serious <sup>3</sup>	serious <sup>4</sup>	Moderate				
Hypoglycaemia at s	tudy endpoint									
Study endpoint	21	not serious <sup>1</sup>	serious <sup>5</sup>	not serious <sup>3</sup>	serious <sup>4</sup>	Low				
Adverse events at s	Adverse events at study endpoint									
Dropouts due to adverse events	27	not serious <sup>1</sup>	serious <sup>5</sup>	not serious <sup>3</sup>	serious <sup>4</sup>	Low				
Total dropouts	29	not serious <sup>1</sup>	not serious <sup>2</sup>	not serious <sup>3</sup>	serious <sup>4</sup>	Moderate				
Nausea	11	not serious <sup>1</sup>	serious⁵	not serious <sup>3</sup>	serious <sup>4</sup>	Low				
Change in body wei	ight									
12 months	8	not serious <sup>1</sup>	serious⁵	not serious <sup>3</sup>	serious <sup>4</sup>	Low				
24 months	8	not serious <sup>1</sup>	serious⁵	not serious <sup>3</sup>	serious <sup>4</sup>	Low				
<sup>1</sup> Baseline HbA1c ranged from 7.1 to 9.9% <sup>2</sup> Assessed based on residual deviance, deviance information criterion and tau <sup>2</sup> (tau <sup>2</sup> < 0.5) <sup>3</sup> Considered not serious as population, interventions, comparator and outcomes are as defined in protocol <sup>4</sup> Deviation of the protocol tau and the protocol tau and ta										

<sup>4</sup>Downgrade 1 level: no interventions had probability of being best and worse  $\geq 0$ 

<sup>5</sup>Downgrade 1 level: tau<sup>2</sup>≥0.5

### D.1.1.3 Table 3: Modified GRADE profile: Network meta-analyses for second intensification

Assessment time points/ Measure	Number of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality		
Change in HbA1c								
Up to 12 months	37	serious <sup>1</sup>	not serious <sup>2</sup>	not serious <sup>3</sup>	not serious	Moderate		
Hypoglycaemia at study endpoint								
Study endpoint	34	serious <sup>1</sup>	not serious <sup>2</sup>	not serious <sup>3</sup>	serious <sup>4</sup>	Low		
Adverse events at s	tudy endpoint							
Dropouts due to adverse events	25	serious <sup>1</sup>	serious⁵	not serious <sup>3</sup>	serious <sup>4</sup>	Low <sup>6</sup>		

Assessment time points/ Measure	Number of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality					
Total dropouts	25	serious <sup>1</sup>	not serious <sup>2</sup>	not serious <sup>3</sup>	serious <sup>4</sup>	Low					
Nausea	4	serious <sup>1</sup>	serious <sup>5</sup>	not serious <sup>3</sup>	serious <sup>4</sup>	Low <sup>6</sup>					
Change in body wei	Change in body weight										
Up to 12 months 27 serious <sup>1</sup> not serious <sup>2</sup> not serious <sup>3</sup> serious <sup>4</sup> Low											
<sup>1</sup> Downgrade 1 level: baseline HbA1c ranged from 7.8 to 11%											
<sup>2</sup> Assessed based on residual deviance, deviance information criterion and tau <sup>2</sup> (tau <sup>2</sup> < 0.5)											

<sup>3</sup>Considered not serious as population, interventions, comparator and outcomes are as defined in protocol

<sup>4</sup>Downgrade 1 level: no interventions had probability of being best and worse  $\ge 0.5$ 

<sup>5</sup>Downgrade 1 level:  $tau^2 \ge 0.5$ 

<sup>6</sup>Maximum downgrade by 2 levels

# D.1.2 Review question 2: What are the serious adverse effects of long-term use of pharmacological interventions to control blood glucose in people with type 2 diabetes?

#### D.1.2.1 Table 4: GRADE profile for acarbose

Number of studies	Design		Qualit	y assessment			Effect (§	95% CI)	Quality	
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Outcome	Estimate		
Acarbose plus existing therapy (n=973) compared to placebo plus existing therapy (n=973); mean 3 years follow-up; subgroup of the UKPDS study										
1 (Holman 1999)	RCT	not serious	not serious	serious <sup>1</sup>	not serious	NA	Any diabetes related end point Microvascular disease	RR 1.00 (0.81 to 1.23) RR 0.91 (0.61 to 1.35)	Moderate	
RR, rate ratio; NA, not applicable										

<sup>1</sup> The range of existing therapies varied among participants in the trial. Existing therapy could be adjusted if required according to the UKPDS protocol

#### D.1.2.2 Table 5: GRADE profile for DPP-4 inhibitors (linagliptin)

Number of studies	Design		Qı	ality assessn	nent		Effect	: (95% CI)	Quality
studies		Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Outcome	Estimate	
DPP-4 inhibitor (linagliptin) plus metformin (n=776) compared to sulfonylurea (glimepiride) plus metformin (n=775); mean 2 year follow-up; people with type 2 diabetes on a stable dos of metformin									a stable dose
1 (Gallwitz 2012)	RCT	not serious	not serious	serious <sup>1</sup>	not serious	NA	All cause mortality Any cardiovascular event <sup>∓</sup> Cardiovascular death Myocardial infarction Stroke Admission due to unstable angina	RR not significant RR 0.46 (0.23 to 0.91) RR 1.00 (0.14 to 7.07) RR 0.60 (0.22 to 1.64) RR 0.27 (0.08 to 0.97) RR 1.00 (0.20 to 4.93)	Moderate
RR, rate ratio	R, rate ratio; NA, not applicable								

<sup>1</sup> Pioglitazone could be used as rescue treatment if participants had a FPG over 13.3mmol/l at any time or HbA1c higher than 8.5 during weeks 28 to 104 of the trial <sup>‡</sup> Any cardiovascular event defined as cardiovascular death, myocardial infarction, stroke and admission due to unstable angina

#### D.1.2.3 Table 6: GRADE profile for insulin

	Number of	Quality assessment	Ef	Effect (95% CI)						
studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Outcome	Estimate		
	Insulin compare	ed to diet ald	one (overall n:	=1941); mean 7 ye	ar follow-up; p	eople with type	e 2 diabetes			
	1 (Bruno 1999, 2003)	cohort	serious <sup>1,2</sup>	not serious	serious <sup>3</sup>	not serious	NA	All cause mortality Cardiovascular mortality	Adj RR 1.71 (1.18 to 2.48) Adj RR 1.35 (0.79 to 2.32)	Very low

Number of			Qu	ality assessme	nt		Effe	ect (95% CI)	Quality Quality Very low Cople with Very low		
studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Outcome	Estimate	Quality		
							Ischaemic heart mortality Cerebrovascular mortality Chronic renal failure	Adj RR 2.95 (1.07 to 8.10) Adj RR 1.00 (0.41 to 2.45) Adj RR 2.26 (0.82 to 6.19)			
Insulin (n=333)	compared t	o oral antidiab	etic medication (	n=unclear, up t	o 1045); media	n 3.1 year foll	ow-up; people with type 2 diabet	es attending retinopathy screening			
1 (Henriccson 1997)	cohort	serious <sup>1</sup>	not serious	not serious	not serious	NA	People who changed from oral medication to insulin compared to those remaining on oral medicatio - Blindness/visual impairment - Progression of retinopathy 3 or more levels	n Adj RR 2.7 (1.8 to 4.0) Adj RR 1.6 (1.3 to 1.9)	Very low		
Diet alone (n=9 type 2 diabetes	9) compare and suspe	d to oral antidi cted myocardia	abetic drugs (n=2 al infarction who	250) compared took part in the	to new insulin DIGAMI RCT (	users (n=245) 24 hour insul	compared to existing insulin use in infusion compared to conventi	ers (n=271); mean 3 year follow-up; peo onal management)	ple with		
1 (Aas (2009)	cohort	serious <sup>1,2</sup>	not serious	not serious	not serious	NA	Existing insulin users compared to other groups - cardiovascular death New insulin users compared to oth groups - Reinfarction	HR 2.38 (1.34 to 4.22) her HR 2.49 (1.23 to 5.03)	Very low		
RR, rate ratio; N Adj RR, adjuste HR. hazard ratio	R, rate ratio; NA, not applicable dj RR, adjusted rate ratio – see evidence tables for details of individual adjustments that were applied R bazard ratio										

<sup>1</sup> Unclear if researchers were blinded to group allocation when assessing outcomes
 <sup>2</sup> Allocation to groups was based on baseline therapy which is likely to be confounded with the outcomes under investigation, although adjustments for covariates were made in the analysis
 <sup>3</sup> Analysis was performed according to baseline therapy. Unclear if patients changed therapy during follow-up, and if so how this was accounted for in the final analysis

#### D.1.2.4 Table 7: **GRADE** profile for metformin

Number of studies	Design		Qu	ality assessme	nt		Effe	Quality			
studies	Ŭ	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Outcome	Estimate			
Metformin (n=79) compared to diet alone (n=990); mean 7.7 year follow-up; people with type 2 diabetes and coronary artery disease											
1 (Fisman 2001)	cohort	serious <sup>1,2</sup>	not serious	serious <sup>3</sup>	not serious	NA	All cause mortality	Adj HR 1.19 (0.76 to 1.84)	Very low		
Metformin pl	us existing d	iabetes thera	py (n=289) com	pared to existin	g diabetes the	rapy alone (	n=1064); mean 10 year follow-up; ur	clear population, part of ZODIAC study			
1 (Landman 2010)	cohort	serious <sup>1,2</sup>	not serious	serious <sup>3</sup>	not serious	NA	All cause mortality Cancer mortality Cardiovascular mortality	Adj HR 0.94 (0.73 to 1.22) Adj HR 0.43 (0.23 to 0.80) Adj HR 2.27 (1.36 to 3.78)	Very low		

Metformin p	Metformin plus sulfonylurea (glyburide) (n=253) compared to diet alone (n=990); mean 7.7 year follow-up mean; people with type 2 diabetes and coronary artery disease											
1 (Fisman 2001)	cohort	serious <sup>1,2</sup>	not serious	serious <sup>3</sup>	not serious	NA	All cause mortality	Adj HR 1.53 (1.20 to 1.96)	Very low			
PD roto roti	o: NA not onn	liaahla										

RR, rate ratio; NA, not applicable

Adj HR, adjusted hazard ratio - see evidence tables for details of adjustments that were made

<sup>1</sup> Allocation to groups was based on baseline therapy which is likely to be confounded with the outcomes under investigation, although adjustments for covariates were made in the analysis

<sup>2</sup> Unclear if researchers were blinded to group allocation when assessing outcomes

<sup>3</sup> Analysis was performed according to baseline therapy. Unclear if patients changed therapy during follow-up, and if so how this was accounted for in the final analysis

#### D.1.2.5 Table 8: GRADE profile for sulfonylurea

Number of Estudies	Design	Design		ity assessme	nt		Effect (95% CI)		
studies	Ŭ	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Outcome	Estimate	
Sulfonylurea com	pared to die	t alone (overa	all n=1941); me	an 7 year foll	ow-up; peop	le with type	2 diabetes		
1 (Bruno 1999)	cohort	serious <sup>1,2</sup>	not serious	serious <sup>3</sup>	not serious	NA	All cause mortality Cardiovascular mortality Ischaemic heart mortality Cerebrovascular mortality	Adj RR 1.14 (0.82 to 1.58) Adj RR 1.02 (0.64 to 1.63) Adj RR 1.63 (0.64 to 1.14) Adj RR 1.09 (0.52 to 2.32)	Very low
Glyburide (n=953)	compared t	to diet alone (	n=990); mean	7.7 year follow	w up; people	with type 2	diabetes and coronary artery disease		
1 (Fisman 2001)	cohort	serious <sup>1,2</sup>	not serious	serious <sup>3</sup>	not serious	NA	All cause mortality	Adj HR 1.21 (1.02 to 1.44)	Very low
Sulfonylurea plus	biguanides	compared to	diet alone (ove	erall n=1941);	mean 7 yea	r follow-up;	people with type 2 diabetes		
1 (Bruno 1999)	cohort	serious <sup>1,2</sup>	not serious	serious <sup>3</sup>	not serious	none	All cause mortality Cardiovascular mortality Ischaemic heart mortality Cerebrovascular mortality	Adj RR 1.13 (0.79 to 1.62) Adj RR 1.04 (0.62 to 1.75) Adj RR 2.49 (0.96 to 6.50) Adj RR 0.91 (0.39 to 2.12)	Very low

RR= Rate ratio; NA, not applicable

<sup>1</sup> Allocation to groups was based on baseline therapy which is likely to be confounded with the outcomes under investigation, although adjustments for covariates was made in the analysis <sup>2</sup> Unclear if researchers were blinded to group allocation when assessing outcomes

<sup>3</sup> Analysis was performed according to baseline therapy. Unclear if patients changed therapy during follow-up, and if so how this was accounted for in the final analysis

D.1.3 Review question 3: What are the optimal target values for HbA1c, fasting blood glucose and post prandial blood glucose in people with type 2 diabetes?

	Quality a	assessmen	it					
Number of cohort studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Number of people	Effect (95% CI)	Quality
All-cause mortality	1	_	_	_	1			
1 (Landman 2010) – ZODIAC 5 to 10 year follow-up <u>Subgroup</u> : (Van Hateren 2011, ZODIAC-20) 10 year follow-up	N	NA	Ν	Ν	NA	1145	Categorical with 6.5-7.0% as a reference: <6.5% HR 1.11 (0.71, 1.74) 7 to 8% HR 1.40 (0.99, 1.97) 8 to 9% HR 1.43 (0.97, 2.10) $\geq$ 9% HR 2.26 (1.39, 3.67) Per 1% HbA1c decrease: updated mean baseline HbA1c: HR 1.21 (1.07, 1.36) <u>Subgroup</u> : age >75 years (n=374) Per 1% HbA1c increase: <5yrs diabetes duration: HR 1.51 (1.17, 1.95) 5 to 11yrs diabetes duration: HR 1.04 (0.84, 1.28) $\geq$ 11yrs diabetes duration: HR 1.05 (0.85, 1.30)	High
1 (Adler 1999) – UKPDS Median 10.4 year follow- up	Ν	NA	Ν	N	NA	3642	Per 1% HbA1c decrease: Risk reduction baseline HbA1c: 6% (2, 10)	High

D.1.3.1 Table 9: Full GRADE profile for optimal target values for HbA1c in relation to mortality

	Quality a	assessmer	nt					
Number of cohort studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Number of people	Effect (95% CI)	Quality
1 (Zoungas 2012) – ADVANCE Mean 4.5 year follow-up	S1	NA	Ν	Ν	NA	11,086	<7%: HR 1.01 (0.85, 1.21) >7%: HR 1.38 (1.29, 1.48) Per 1% HbA1c increase: 6.0%: HR 1.35 (1.27, 1.43) 6.5%: HR 1.38 (1.29, 1.46) 7.0%: HR 1.38 (1.29, 1.48) 7.5%: HR 1.38 (1.27, 1.49) Per 1% HbA1c decrease: 6.0%: HR 0.36 (0.21, 0.62) 6.5%: HR 0.73 (0.55, 0.96) 7.0%: HR 1.01 (0.85, 1.21) 7.5%: HR 1.16 (1.02, 1.32) Subgroup: age <65 years ( <i>n</i> not reported) Per 1% HbA1c increase: >7%: HR 1.33 (1.16, 1.53) Subgroup: age ≥65 years ( <i>n</i> not reported) Per 1% HbA1c increase: >7%: HR 1.40 (1.30, 1.52) Subgroup: male (n=6383) Per 1% HbA1c increase: >7%: HR 1.32 (1.20, 1.44)	Moderate

	Quality a	issessmen	t					
Number of cohort studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Number of people	Effect (95% CI)	Quality
							Subgroup: female (n=4703) Per 1% HbA1c increase: >7%: HR 1.45 (1.31, 1.61)Subgroup: duration of diabetes <7 years (n not reported) Per 1% HbA1c increase: >7%: HR 1.51 (1.33, 1.71)Subgroup: duration of diabetes ≥7 years (n not reported) Per 1% HbA1c increase: >7%: HR 1.33 (1.22, 1.45)Subgroup: no macrovascular disease (n~7514) 	

	Quality a	assessmen	it					
Number of cohort studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Number of people	Effect (95% CI)	Quality
							<ul> <li>&gt;7%: HR 1.37 (1.26, 1.49)</li> <li><u>Subgroup</u>: microvascular disease (n=1153)</li> <li>Per 1% HbA1c increase:</li> <li>&gt;7%: HR 1.42 (1.25, 1.62)</li> </ul>	
1 (Eeg-Olofsson 2010) 5 to 6 year follow-up	S <sup>2</sup>	NA	Ν	Ν	NA	18,334	Categorical with 6.0-6.9% as a reference: 7.0 to 7.9% HR 1.08 (0.95 to 1.23) 8.0 to 8.9% HR 1.19 (1.03 to 1.38), p=0.02 Per 1% HbA1c increase: Baseline HbA1c: HR 1.09 (1.05, 1.14), p<0.001 Subgroup: duration of diabetes $\leq$ 7 years (n=10,016) Per 1% HbA1c increase: Baseline HbA1c: HR 1.13 (1.05, 1.21) Subgroup: duration of diabetes >7 years (n=8318) Per 1% HbA1c increase: Baseline HbA1c: HR 1.07 (1.01, 1.13) Subgroup: previous CVD (n=3276) Per 1% HbA1c increase: Baseline HbA1c: HR 1.08 (1.01, 1.15)	Moderate

	Quality a	assessmen	ıt	_	-			
Number of cohort studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Number of people	Effect (95% CI)	Quality
							<u>Subgroup</u> : no previous CVD (n=15,058) Per 1% HbA1c increase: Baseline HbA1c: HR 1.10 (1.04, 1.16)	
1 (Drechsler 2009) - 4D study Median 4 year follow-up	Ν	NA	S <sup>3</sup>	Ν	NA	1255	Categorical with ≤6% as a reference: >6 to ≤8% HR 1.34 (1.10, 1.63) >8% HR 1.34 (1.02, 1.76) Per unit increase in HbA1c: HR 1.09 (1.02 to 1.17)	Moderate
1 (Hunt 2013) Mean 4.4 year follow-up	Ν	NA	S <sup>4</sup>	Ν	NA	892,223	Non-Hispanic White (n=548,808) Categorical with 7.0-8.0% as a reference: <7.0% HR 0.99 (0.97, 1.00) 8.0-9.0% HR 1.10 (1.08, 1.13) ≥9.0% HR 1.17 (1.14, 1.20) Non-Hispanic Black (n=108,356) Categorical with 7.0-8.0% as a reference: <7.0% HR 1.07 (1.02, 1.12) 8.0-9.0% HR 1.00 (0.94, 1.06) ≥9.0% HR 1.09 (1.03, 1.15) Hispanic (n=123,670) Categorical with 7.0-8.0% as a reference: <7.0% HR 1.02 (0.95, 1.09) 8.0-9.0% HR 1.09 (1.00, 1.19)	Moderate

	Quality as	ssessmen	it	_	-			
Number of cohort studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Number of people	Effect (95% CI)	Quality
Mortality related to diabe	tes						23.070 HIV 1.13 (1.00, 1.23)	
1 (Adler 1999) – UKPDS Median 10.4 year follow- up	N	NA	Ν	Ν	NA	3642	Per 1% HbA1c decrease: Risk reduction baseline HbA1c: 9% (3, 14)	High
Sudden death								
1 (Drechsler 2009) - 4D study Median 4 year follow-up	Ν	NA	S <sup>3</sup>	Ν	NA	1255	Categorical with ≤6% as a reference: >6 to ≤8% HR 1.85 (1.22, 2.81) >8% HR 2.26 (1.33, 3.85) Per unit increase in HbA1c: HR 1.21 (1.06 to 1.38)	Moderate
Mortality except for sudd	len death							
1 (Drechsler 2009) - 4D study Median 4 year follow-up	Ν	NA	S <sup>3</sup>	Ν	NA	1255	Categorical with ≤6% as a reference: >6 to ≤8% HR 1.19 (0.96, 1.50) >8% HR 1.10 (0.80, 1.52) Per unit increase in HbA1c: HR 1.04 (0.96 to 1.13)	Moderate
Cardiovascular mortality								
1 (Landman 2010) – ZODIAC 5 to 10 year follow-up Subgroup: (Van Hateren 2011, ZODIAC-20	Ν	NA	Ν	S <sup>5</sup>	NA	1145	Categorical with 6.5-7.0% as a reference: <6.5% HR 0.94 (0.47, 1.91) 7 to 8% HR 1.40 (0.84, 2.31) 8 to 9% HR 1.71 (0.99, 2.96) ≥9% HR 3.13 (1.62, 6.05)	Moderate

	Quality as	sessmen	ıt					
Number of cohort studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Number of people	Effect (95% CI)	Quality
10 year follow-up							Subgroup: age >75 years (n=374) Per 1% HbA1c increase: <5yrs diabetes duration: HR 1.72 (1.19, 2.48) 5 to 11yrs diabetes duration: HR 1.18 (0.87, 1.60) ≥11yrs diabetes duration: HR 1.16 (0.86, 1.58)	
1 (Eeg-Olofsson 2010) 5 to 6 year follow-up	S <sup>2</sup>	NA	Ν	Ν	NA	18,334	Categorical with 6.0-6.9% as a reference: 7.0 to 7.9% HR 1.11 (0.96 to 1.29) 8.0 to 8.9% HR 1.27 (1.07 to 1.50) Per 1% HbA1c increase: HR baseline HbA1c: 1.10 (1.05, 1.16) Subgroup: duration of diabetes $\leq$ 7 years (n=10,016) Per 1% HbA1c increase: Baseline HbA1c: HR 1.14 (1.05, 1.24) Subgroup: duration of diabetes >7 years (n=8318) Per 1% HbA1c increase: Baseline HbA1c: HR 1.07 (1.01, 1.14) Subgroup: previous CVD (n=3276)	Moderate

	Quality as	ssessmer	nt								
Number of cohort studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Number of people	Effect (95% CI)	Quality			
							Per 1% HbA1c increase: Baseline HbA1c: HR 1.09 (1.01, 1.17) <u>Subgroup</u> : no previous CVD (n=15,058) Per 1% HbA1c increase: Baseline HbA1c: HR 1.11 (1.04, 1.19)				
1 (Drechsler 2009) - 4D study (Heart failure death) Median 4 year follow-up	Ν	NA	S <sup>3</sup>	S⁵	NA	1255	Categorical with ≤6% as a reference: >6 to ≤8% HR 1.53 (0.70, 3.33) >8% HR 2.12 (0.75, 5.98) Per unit increase in HbA1c: HR 1.30 (1.00 to 1.68)	Low			
<ul> <li><sup>1</sup> Downgrade by 1 level: post-hoc analysis</li> <li><sup>2</sup> Downgrade by 1 level: participants from non-mandatory diabetes register</li> <li><sup>3</sup> Downgrade by 1 level: participants receiving dialysis</li> <li><sup>4</sup> Downgrade by 1 level: &gt;97% sample were male</li> <li><sup>5</sup> Downgrade by 1 level; wide confidence interval and/or small sample size &lt;400</li> </ul>											

(a) <Insert Note here>

### D.1.3.2 Table 10: Full GRADE profile for optimal target values for HbA1c in relation to macrovascular complications

		Number		
Number of cohort	Quality assessment	of	Effect (95% CI)	Quality

studies						neonle		
	3S	ncy	SS	E		PP		
	f bia	iste	tne	isio				
	k of	suc	irec	rec	er			
	Ris	lnce	Indi	lmp	Oth			
Composite of combined	cardiovas	cular events	5	<u> </u>				
1 (Drechsler 2009) - 4D	Ν	NA	S <sup>1</sup>	Ν	NA	1255	Categorical with ≤6% as a reference:	Moderate
study							>6 to ≤8% HR 1.31 (1.05, 1.65)	
Median 4 year follow-up							>8% HR 1.37 (1.00, 1.87)	
							Per unit increase in HbA1c	
							HR 1.09 (1.01 to 1.18)	
Macrovascular events								
	<b>c</b> <sup>2</sup>	ΝΑ	NI	N	ΝΔ	11.096	-7% · HP 1 02 (0 96, 1 21)	Modorato
ADVANCE	5	NA	IN	IN		(event	<7%: HR 1 38 (1 30, 1 47)	wouerate
Mean 4.5 year follow-up						rate NR)	2776. TIX 1.30 (1.30, 1.47)	
							Per 1% HbA1c increase:	
							6.0%: HR 1.35 (1.27, 1.42)	
							6.5%: HR 1.37 (1.29, 1.45)	
							7.0%: HR 1.38 (1.30, 1.47)	
							7.5%: HR 1.39 (1.29, 1.50)	
							Dor 19/ Hb 110 degrages	
							6.0% HP 0.41 (0.25.0.68)	
							6.5%: HR 0.77 (0.59, 1.00)	
							7.0%: HR 1.02 (0.86, 1.21)	
							7.5% HR 1.13 (1.00, 1.28)	
							1.070.1110 (1.00, 1.20)	
							Subgroup: age <65 years (n not reported)	
							Per 1% HbA1c increase:	
							>7%: HR 1.34 (1.19, 1.50)	
							Subgroup: ago SEE vooro (p pot reported)	
							<u>Subgroup</u> . age <os (millior="" reported)<="" td="" years=""><td></td></os>	

	Quality a	assessment						
Number of cohort studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Number of people	Effect (95% CI)	Quality
							Per 1% HbA1c increase:	,,
							>7%: HR 1.40 (1.30, 1.51)	
							Subgroup: male (n=6383)         Per 1% HbA1c increase:         >7%: HR 1.38 (1.27, 1.50)         Subgroup: female (n=4703)         Per 1% HbA1c increase:         >7%: HR 1.35 (1.23, 1.48)         Subgroup: duration of diabetes <7 years (n not reported)	
							Subgroup: duration of diabetes $>7$ years (n	
							not reported)	
							Per 1% HbA1c increase:	
							>7%: HR 1.30 (1.21, 1.41)	
							<u>Subgroup</u> : no macrovascular disease (n~7514) Per 1% HbA1c increase: >7%: HR 1.37 (1.26, 1.49)	
							Subgroup: macrovascular disease (n=3572)	

	Quality a	assessment			-			
Number of cohort studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Number of people	Effect (95% CI)	Quality
							Per 1% HbA1c increase: >7%: HR 1.38 (1.25, 1.52) <u>Subgroup</u> : no microvascular disease (n~9933) Per 1% HbA1c increase: >7%: HR 1.37 (1.27, 1.48) <u>Subgroup</u> : microvascular disease (n=1153) Per 1% HbA1c increase: >7%: HR 1.44 (1.27, 1.62)	
Cardiovascular disease ( 1 (Eeg-Olofsson 2010) 5 to 6 year follow-up	fatal/non- S <sup>3</sup>	fatal) NA	Ν	Ν	NA	18,334	Categorical with 6.0-6.9% as a reference: 7.0 to 7.9% HR 1.18 (1.08 to 1.29) 8.0 to 8.9% HR 1.31 (1.18 to 1.45) Per 1% HbA1c increase: Baseline HbA1c: HR 1.10 (1.07, 1.13) Subgroup: duration of diabetes $\leq$ 7 years (n=10,016) Per 1% HbA1c increase: Baseline HbA1c: HR 1.08 (1.03, 1.13) Subgroup: duration of diabetes >7 years	Moderate

	Quality a	assessment						
Number of cohort studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Number of people	Effect (95% CI)	Quality
							Per 1% HbA1c increase: Baseline HbA1c: HR 1.10 (1.06, 1.14) <u>Subgroup</u> : previous CVD (n=3276) Per 1% HbA1c increase: Baseline HbA1c: HR 1.10 (1.05, 1.16) <u>Subgroup</u> : no previous CVD (n=15,058) Per 1% HbA1c increase: Baseline HbA1c: HR 1.09 (1.06, 1.13)	
Myocardial infarction (fat	tal and no	n-fatal)						
1 (Drechsler 2009) - 4D study Median 4 year follow-up	Ν	NA	S <sup>1</sup>	Ν	NA	1255	Categorical with ≤6% as a reference: >6 to ≤8% HR 0.94 (0.68, 1.30) >8% HR 0.77 (0.47, 1.26) Per unit increase in HbA1c: HR 0.94 (0.83 to 1.07)	Moderate
1 (Adler 1999) – UKPDS Median 10 to 10.4 year follow-up (Stratton 2000, UKPDS) Median 10.4 year follow- up	Ν	NA	Ν	Ν	NA	3845	Categorical with ≤6.3% as a reference: >6.3 to ≤7.6 HR 1.2 (0.9, 1.5) >7.6 HR 1.5 (1.2, 1.8) Per 1% HbA1c decrease (n=3642): Risk reduction baseline HbA1c: 5% (0, 9)	High
Coronary heart disease (	fatal/non-f	fatal)						
1 (Eeg-Olofsson 2010)	S	NA	Ν	Ν	NA	18,334	Categorical with 6.0-6.9% as a reference:	Moderate

	Quality a	ssessment			_			
Number of cohort studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Number of people	Effect (95% CI)	Quality
5 to 6 year follow-up							7.0 to 7.9% HR 1.25 (1.11 to 1.39) 8.0 to 8.9% HR 1.36 (1.20 to 1.55) Per 1% HbA1c increase: HR baseline HbA1c: 1.11 (1.07, 1.15) $\underline{Subgroup}$ : duration of diabetes $\leq$ 7 years (n=10,016) Per 1% HbA1c increase: Baseline HbA1c: HR 1.09 (1.03, 1.15) $\underline{Subgroup}$ : duration of diabetes >7 years (n=8318) Per 1% HbA1c increase: Baseline HbA1c: HR 1.11 (1.06, 1.16) $\underline{Subgroup}$ : previous CVD (n=3276) Per 1% HbA1c increase: Baseline HbA1c: HR 1.08 (1.02, 1.15) $\underline{Subgroup}$ : no previous CVD (n=15,058) Per 1% HbA1c increase:	
1 (Schulze 2004) Mean 7.4 year follow-up	N	NA	N	S <sup>4-6</sup>	NA	921	Categorical into quartiles of median HbA1c with 5.21% as a reference: 5.80% RR 2.49 (1.19, 5.23)	Very low

	Quality a	issessment						
Number of cohort studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Number of people	Effect (95% CI)	Quality
							6.90% RR 3.19 (1.56, 6.53) 8.97% RR 4.92 (2.46, 9.85)	
Heart failure								
1 (Adler 1999) – UKPDS Median 10.4 years	Ν	NA	N	Ν	NA	3642	Per 1% HbA1c decrease: Risk reduction baseline HbA1c: 0% (-12, 11)	High
(Stratton 2000, UKPDS)								
Newly diagnosed angina								
1 (Adler 1999) – UKPDS Median 10 to 10.3 years (Stratton 2000, UKPDS)	Ν	NA	Ν	Ν	NA	3836	Categorical with ≤6.3% as a reference: >6.3 to ≤7.6 HR 1.5 (1.1, 2.0) >7.6 HR 1.6 (1.1, 2.1)	High
Stroke (fatal and non-fata	al)							
1 (Drechsler 2009) - 4D study Median 4 year follow-up	N	NA	S <sup>1</sup>	S <sup>4</sup>	NA	1255	Categorical with ≤6% as a reference: >6 to ≤8% HR 1.56 (0.93, 2.62) >8% HR 1.67 (0.84, 3.30) Per unit increase in HbA1c: HR 1.11 (0.93 to 1.32)	Low
1 (Eeg-Olofsson 2010) 5 to 6 year follow-up	S <sup>3</sup>	NA	Ν	Ν	NA	18,334	Per 1% HbA1c increase: HR baseline HbA1c: 1.08 (1.03, 1.13) <u>Subgroup</u> : duration of diabetes ≤7 years (n=10,016) Per 1% HbA1c increase:	Moderate

	Quality a	assessment						
Number of cohort studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Number of people	Effect (95% CI)	Quality
							Baseline HbA1c: HR 1.06 (0.98, 1.14) <u>Subgroup</u> : duration of diabetes >7 years (n=8318) Per 1% HbA1c increase: Baseline HbA1c: HR 1.07 (1.01, 1.14) <u>Subgroup</u> : previous CVD (n=3276) Per 1% HbA1c increase: Baseline HbA1c: HR 1.11 (1.03, 1.20) <u>Subgroup</u> : no previous CVD (n=15,058) Per 1% HbA1c increase: Baseline HbA1c: HR 1.06 (1.00, 1.12)	
1 (Adler 1999) – UKPDS Median 10 to 10.3 years (Stratton 2000, UKPDS)	Ν	NA	Ν	Ν	NA	3670	Categorical with ≤6.3% as a reference: >6.3 to ≤7.6 HR 1.2 (0.8, 1.7) >7.6 HR 1.1 (0.7, 1.6) Per 1% HbA1c decrease (n=3642): Risk reduction baseline HbA1c: -4% (-14, 6)	High
Peripheral vascular disea	ase							
1 (Adler 1999) – UKPDS Median 10.4 years	N	NA	Ν	S <sup>4</sup>	NA	2398	Per 1% HbA1c increase: OR 1.28 (1.12, 1.46)	High
(Stratton 2000, UKPDS)							Amputation or PVD death (n=3642) : Per 1% HbA1c decrease:	

	Quality a	assessment						
Number of cohort studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Number of people	Effect (95% CI)	Quality
							Risk reduction baseline HbA1c: 28% (18, 37)	
1 (Zhao 2013) – LSUHLS study Lower-extremity amputation Mean 6.83 year follow-up	Ν	NA	N <sup>7</sup>	Ν	NA	35,368	African Americans (n=19,808) Categorical with <6% as a reference and baseline HbA1c: 6.0 to 6.9% HR 1.73 (1.07, 2.80) 7.0 to 7.9% HR 1.65 (0.99, 2.77) 8.0 to 8.9% HR 1.96 (1.14, 3.36) 9.0 to 9.9% HR 3.02 (1.81, 5.04) ≥10% HR 3.30 (2.10, 5.20) Per 1% HbA1c increase: Baseline HbA1c: HR 1.12 (1.08, 1.17) Whites (n=15,560) Categorical with <6% as a reference and baseline HbA1c: 6.0 to 6.9% HR 1.16 (0.66, 2.02) 7.0 to 7.9% HR 2.28 (1.35, 3.85) 8.0 to 8.9% HR 2.38 (1.36, 4.18) 9.0 to 9.9% HR 2.99 (1.71, 5.22) ≥10% HR 3.25 (1.98, 5.33) Per 1% HbA1c increase: Baseline HbA1c: HR 1.15 (1.09, 1.21)	Moderate

	Quality a	ssessment						
Number of cohort studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Number of people	Effect (95% CI)	Quality
							Subgroup: male (n=13,363 at baseline)Categorical with <6% as a reference and baseline HbA1c:6.0 to 6.9% HR 1.48 (0.95, 2.26)7.0 to 7.9% HR 1.85 (1.20, 2.85)8.0 to 8.9% HR 2.19 (1.40, 3.42)9.0 to 9.9% HR 3.15 (2.04, 4.85)≥10% HR 2.84 (1.93, 4.17)Subgroup: female (n=22,005 at baseline)Categorical with <6% as a reference and baseline HbA1c:6.0 to 6.9% HR 1.63 (0.80, 3.32)7.0 to 7.9% HR 2.37 (1.17, 4.80)8.0 to 8.9% HR 2.26 (1.04, 4.91)9.0 to 9.9% HR 3.43 (1.63, 7.24)≥10% HR 4.96 (2.50, 9.71)Subgroup: age 60-94yrs ( <i>n</i> not reported) Categorical with <6% as a reference and baseline HbA1c:6.0 to 6.9% HR 3.43 (1.63, 7.24)≥10% HR 4.96 (2.50, 9.71)Subgroup: age 60-94yrs ( <i>n</i> not reported) Categorical with <6% as a reference and baseline HbA1c:6.0 to 6.9% HR 3.02 (0.94, 4.35)7.0 to 7.9% HR 3.19 (1.42, 7.18) 8.0 to 8.9% HR 3.06 (1.18, 7.95) 9.0 to 9.9% HR 2.37 (0.80, 7.01)≥10% HR 3.19 (1.27, 8.00)	

	Quality a	assessment						
Number of cohort studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Number of people	Effect (95% CI)	Quality
							Subgroup: age 50-59yrs ( <i>n</i> not reported)         Categorical with <6% as a reference and	
<sup>1</sup> Downgrade by 1 level: pa <sup>2</sup> Downgrade by 1 level: po <sup>3</sup> Downgrade by 1 level: pa <sup>4</sup> Downgrade by 1 level: wn <sup>5</sup> Downgrade by 1 level: wn	articipants ost-hoc ana articipants ide confide	receiving dial alysis from non-mai ence interval a	lysis ndatory dia and/or sma	abetes regi all sample s	ster size <400			

<sup>5</sup> Downgrade by 1 level: all participants female
 <sup>6</sup> Downgrade by 1 level: participants self-reported (questionnaire) some inclusion criteria
 <sup>7</sup> Downgrade by 1 level: >60% were female and ~98% from low income background

D.1.3.3	Table 11:	Full GRADE profile for optimal target values for HbA1c in relation to microvascular	complications
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	Quality a	assessment						
Number of cohort studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Number of people	Effect (95% CI)	Quality
Microvascular end points	S							
1 (Adler 1999) – UKPDS Median 10.4 years (Stratton 2000, UKPDS)	Ν	NA	Ν	NA	NA	3642	Per 1% HbA1c decrease: Risk reduction baseline HbA1c: 23% (20, 27)	High
1 (Zoungas 2012) – ADVANCE Mean 4.5 year follow-up	S <sup>1</sup>	NA	Ν	Ν	NA	11,086 (event rate NR)	HR <6.5%: 1.02 (0.76, 1.39) HR >6.5%: 1.40 (1.33, 1.47) Per 1% HbA1c increase: 6.0%: HR 1.39 (1.32, 1.46) 6.5%: HR 1.40 (1.33, 1.47) 7.0%: HR 1.38 (1.30, 1.46) 7.5%: HR 1.33 (1.24, 1.42) Per 1% HbA1c decrease: 6.0%: HR 0.67 (0.36, 1.23) 6.5%: HR 1.02 (0.76, 1.02) 7.0%: HR 1.33 (1.10, 1.60) 7.5%: HR 1.51 (1.32, 1.72) <u>Subgroup</u> : age <65 years ( <i>n</i> not reported) Per 1% HbA1c increase: >6.5%: HR 1.40 (1.30, 1.50) <u>Subgroup</u> : age ≥65 years ( <i>n</i> not reported)	Moderate

	Quality a	assessment						
Number of cohort studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Number of people	Effect (95% CI)	Quality
							Per 1% HbA1c increase:	
							>6.5%: HR 1.39 (1.29, 1.50)	
							<u>Subgroup</u> : male (n=6383) Per 1% HbA1c increase: >6.5%: HR 1.42 (1.33, 1.52) <u>Subgroup</u> : female (n=4703)	
							Per 1% HbA1c increase:	
							>6.5%: HR 1.39 (1.29, 1.50)	
							<u>Subgroup</u> : duration of diabetes <7 years ( <i>n</i> not reported) Per 1% HbA1c increase: >6.5%: HR 1.27 (1.14, 1.40)	
							<u>Subgroup</u> : duration of diabetes ≥7 years ( <i>n</i> not reported)	
							Per 1% HbA1c increase:	
							>0.5%: HK 1.45 (1.36, 1.54)	
							<u>Subgroup</u> : no macrovascular disease (n~7514) Per 1% HbA1c increase: >6.5%: HR 1.44 (1.35, 1.53)	
							Subgroup: macrovascular disease (n=3572)	

	Quality a	issessment						
Number of cohort studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Number of people	Effect (95% CI)	Quality
							Per 1% HbA1c increase: >6.5%: HR 1.30 (1.17, 1.43) <u>Subgroup</u> : no microvascular disease (n~9933) Per 1% HbA1c increase: >6.5%: HR 1.40 (1.32, 1.49) <u>Subgroup</u> : microvascular disease (n=1153) Per 1% HbA1c increase:	
Patheorettas							>6.5%: HR 1.36 (1.23, 1.50)	
1 (Molyneaux 1998) Median 28 month follow- up	S <sup>2</sup>	NA	N	N	NA	963	Per 10% HbA1c decrease: Relative risk reduction: 24% (16, 32)	Moderate
1 (Morisaki 1994) 5 year follow-up	S <sup>2</sup>	NA	S <sup>3,4</sup>	S⁵	NA	114	Multivariate logistic regression analysis showed that HbA1c was the only significant predictor of retinopathy Retinopathy prevalence at HbA1c: <7%: 2% ≧7 to <8%: 20% ≧8 to <9%: 40% ≥9%: 61% With retinopathy HbA1c 8.8±1.1	Very low

	Quality a	assessment			_			
Number of cohort studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Number of people	Effect (95% CI)	Quality
1 (Nakagami 1997) 10 year follow-up	S <sup>2</sup>	NA	S <sup>4</sup>	S <sup>5</sup>	NA	137	Without retinopathy HbA1c 7.1±1.2         Retinopathy prevalence at HbA1c:         <6%: 0%	Very low
1 (Salinero-Fort 2013) – MADIABETES 4 year follow-up	N	NA	N <sup>6</sup>	Ν	NA	2405	Categorical with <7% as a reference: 7 to 8% HR 1.39 (1.01, 1.92) >8% HR 1.90 (1.30, 2.77)	Moderate
Cataract extraction								
1 (Adler 1999) – UKPDS Median 10.4 years (Stratton 2000, UKPDS)	Ν	NA	Ν	NA	NA	3642	Per 1% HbA1c decrease: Risk reduction baseline HbA1c: 9% (2, 16)	High
Nephropathy								
1 (Molyneaux 1998) Microalbuminuria Median 28 month follow- up	S <sup>2</sup>	NA	Ν	S⁵	NA	399	Per 10% HbA1c decrease: Relative risk reduction: 9% (-2, 19)	Very low
1 (Torffvit and Agardh	S <sup>2</sup>	NA	S <sup>7</sup>	S⁵	NA	385	Cox regression analysis showed that HbA1c	Very low

	Quality a	assessment						
Number of cohort studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Number of people	Effect (95% CI)	Quality
2001) Albuminuria Median 9 year follow-up							significantly predicted greater fractional albumin clearance (p<0.01) and development of renal failure (p<0.05) Normoalbuminuria mean HbA1c 7.8±1.5 Micro/macro-albuminuria HbA1c 8.5±1.6	
1 (Hsu 2012) Microalbuminuria 5 to 7 year follow-up	S <sup>2</sup>	NA	Ν	Ν	NA	821	Per 1% HbA1c decrease: Baseline HbA1c ≤8%: HR 1.13 (0.91, 1.39) Baseline HbA1c >8%: HR 1.18 (1.04, 1.34)	Moderate
<ol> <li><sup>1</sup> Downgrade by 1 level: po</li> <li><sup>2</sup> Downgrade by 1 level: si</li> <li><sup>3</sup> Downgrade by 1 level: pa</li> <li><sup>4</sup> Downgrade by 1 level: sa</li> <li><sup>5</sup> Downgrade by 1 level: with</li> <li><sup>6</sup> Downgrade by 1 level: at</li> <li><sup>7</sup> Downgrade by 1 level: blood</li> </ol>	ost-hoc and ngle centre articipants ample all J ide confide trition of 12 d pressure a	alysis e study all >60yrs apanese ence interval 2.5% and ho and albuminum	and/or sm usebound ia outcome:	all sample : individuals s reported	size <400 excluded			

### D.1.3.4 Table 12: Full GRADE profile for optimal target values for fasting blood glucose in relation to macrovascular complications

	Quality a	assessment							
Number of cohort studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Number of people	Effect (95% CI)	Quality	
Myocardial infarction (fatal and non-fatal)									

	Quality a	assessment		-				
Number of cohort studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Number of people	Effect (95% CI)	Quality
1 (Adler 1999, UKPDS) Median 10 to 10.3 year follow-up up	Ν	NA	Ν	Ν	NA	5045	Categorical with ≤9.7 mmol/L as a reference: >9.7 to ≤13.4 HR 1.1 (0.9, 1.4) >13.4 HR 1.3 (1.1, 1.6) Baseline data extracted at diagnosis only, not after dietary run-in Model controlled for age at diabetes diagnosis, sex and ethnicity	High
Newly diagnosed angina								
1 (Adler 1999, UKPDS) Median 10 to 10.3 year follow-up	Ν	NA	Ν	Ν	NA	5036	Categorical with ≤9.7 mmol/L as a reference: >9.7 to ≤13.4 HR 1.3 (1.0, 1.7) >13.4 HR 1.2 (0.9, 1.5) Baseline data extracted at diagnosis only, not after dietary run-in Model controlled for age at diabetes diagnosis, sex and ethnicity	High
Stroke (fatal and non-fata	al)							
1 (Adler 1999, UKPDS) Median 10 to 10.3 year follow-up	Ν	NA	Ν	Ν	NA	5040	Categorical with ≤9.7 mmol/L as a reference: >9.7 to ≤13.4 HR 1.3 (0.9, 1.7) >13.4 HR 1.3 (1.0, 1.8) Baseline data extracted at diagnosis only, not after dietary run-in Model controlled for age at diabetes diagnosis, sex and ethnicity	High

# D.1.4 Review question 4: Should intensive or conventional target values be used to control blood glucose levels in people with type 2 diabetes?

D.1.4.1	Table 13:	Full GRADE p	profile: intensive vs.	conventional	target values
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Nunber		Quality as	ssessment				Number o	f people					
of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Intensive	Conventional	Effect (95% CI)	Quality			
All-caus	e mortality												
16	RCT	not serious <sup>1</sup>	not serious <sup>2</sup>	not serious <sup>3</sup>	not serious <sup>4</sup>	NA	762/4296	381/2208	RR 0.98 (0.88 to 1.09)	High			
Cardiov	Cardiovascular mortality												
14	RCT	not serious <sup>1</sup>	not serious <sup>2</sup>	not serious <sup>3</sup>	serious <sup>4</sup>	NA	445/4225	195/2131	RR 1.15 (0.98 to 1.35)	Moderate			
Macrova	iscular com	plications											
8	RCT	not serious <sup>1</sup>	serious <sup>6</sup>	not serious <sup>3</sup>	very serious <sup>7</sup>	NA	394/3543	235/1791	RR 0.98 (0.74 to 1.3)	Low			
Non-fata	I myocardia	al infarction											
9	RCT	not serious <sup>1</sup>	not serious <sup>2</sup>	not serious <sup>3</sup>	not serious <sup>4</sup>	NA	342/3995	187/1907	RR 0.92 (0.78 to 1.09)	High			
Conges	tive heart fa	ilure											
8	RCT	not serious <sup>1</sup>	not serious <sup>2</sup>	not serious <sup>3</sup>	serious⁵	NA	120/3777	75/1683	RR 0.82 (0.62 to 1.08)	Moderate			
Non-fata	I stroke												
8	RCT	not serious <sup>1</sup>	not serious <sup>2</sup>	not serious <sup>3</sup>	serious⁵	NA	156/3791	65/1697	RR 1.06 (0.8 to 1.41)	Moderate			
Amputa	tion of lowe	r extremity											
7	RCT	not serious <sup>1</sup>	not serious <sup>2</sup>	not serious <sup>3</sup>	serious⁵	NA	36/3500	20/1579	RR 0.73 (0.42 to 1.25)	Moderate			
Microva	scular com	plications											
3	RCT	not serious <sup>1</sup>	not serious <sup>2</sup>	not serious <sup>3</sup>	serious⁵	NA	253/3154	130/1222	RR 0.75 (0.61 to 0.92)	Moderate			
Nephrop	bathy												

Nunber		Quality as	sessment				Number o	f people			
of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Intensive	Conventional	Effect (95% CI)	Quality	
7	RCT	not serious <sup>1</sup>	very serious <sup>8</sup>	not serious <sup>3</sup>	very serious <sup>7</sup>	NA	45/3167	66/1587	RR 0.64 (0.32 to 1.29)	Low	
Retinopa	athy										
5	RCT	not serious <sup>1</sup>	very serious <sup>8</sup>	not serious <sup>3</sup>	serious <sup>5</sup>	NA	441/3098	273/1516	RR 0.79 (0.56 to 1.11)	Low	
End stag	je renal dise	ase									
4	RCT	not serious <sup>1</sup>	not serious <sup>9</sup>	not serious <sup>3</sup>	very serious <sup>7</sup>	NA	28/3365	11/1438	RR 0.94 (0.47 to 1.89)	Low	
Mild hyp	oglycaemia										
12	RCT	not serious <sup>1</sup>	serious <sup>6</sup>	not serious <sup>3</sup>	not serious <sup>4</sup>	NA	791/4200	263/2120	RR 1.85 (1.53 to 2.25)	Moderate	
Severe h	ypoglycaen	nia									
13	RCT	not serious <sup>1</sup>	not serious <sup>2</sup>	not serious <sup>3</sup>	serious⁵	NA	53/3688	11/1764	RR 2.23 (1.22 to 4.08)	Moderate	
NA, not a <sup>1</sup> No app <sup>2</sup> Low inc <sup>3</sup> Popula <sup>4</sup> Confide <sup>5</sup> Confide <sup>6</sup> Serious <sup>7</sup> Confide	3       RCT       not serious'       not serious'       serious'       NA $53/3688$ $11/1764$ RR 2.23 (1.22 to 4.08)       Moderate         IA, not applicable       No apparent risk of bias in the included studies       No apparent risk of bias in the included studies       No       No       Population, intervention and outcome as specified in the review protocol       No       Confidence intervals around the point estimate in a single zone       No       Serious inconsistency ( $l^2 = 46\%$ )       Confidence intervals around the point estimate cross into 3 zones       Serious and the point estimate cross into 3 zones       No       No <td< td=""></td<>										

<sup>8</sup> Very serious inconsistency (l<sup>2</sup> > 60%)
 <sup>9</sup> Data only provided by a single study

- D.1.5 Review question 5: Should self-monitoring be used to manage blood glucose levels in people with type 2 diabetes?
- D.1.5.1 Table 14: SMBG vs. no SMBG (up to 1 year follow-up)

							Numbe	er of						
Number		Qualit	ty assessment				people							
of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	SMBG	No SMBG	Effect (95% CI)	Quality				
HbA1c fro	HbA1c from 24 to 52 weeks (subgroup based on current therapy) (follow-up 24 to 52 weeks; Better indicated by lower values)													
17	RCT	serious <sup>1</sup>	not serious	serious <sup>2,3,4</sup>	not serious	NA	2217	2084	MD -0.22 (-0.31 to -0.13) <u>Subgroup analysis based on current medication:</u> Diet alone: MD -0.2 (-0.8 to 0.4) Diet ± OADs: MD -0.21 (-0.29 to -0.13) Diet, OADs ± insulin: MD -0.38 (-0.86 to 0.10), I2=84% <u>Subgroup analysis based on type of SMBG:</u> Standard SMBG: MD -0.21 (-0.31 to -0.11) Enhanced SMBG: MD -0.29 (-0.49 to -0.09) <u>Subgroup analysis based on frequency of SMBG:</u> <1 per day: MD -0.31 (-0.55 to -0.07), I2=68% 1-2 times per day: MD -0.19 (-0.29 to -0.10) >2 per day: MD -0.20 (-0.73 to 0.32)	Low				
Change in	) Hba1c (%)	by presp	ecified subaroups	at 1 vear follow	/-up									
1	RCT	not serious	not serious	serious <sup>3</sup>	not serious	NA	151∓	152	Diet alone: MD 0.12 lower (0.29 lower to 0.05 higher) Oral therapy: MD 0.19 lower (0.40 lower to 0.02 higher) Diabetes duration <36 months: MD 0.17 lower (0.37 lower to 0.03 higher) >36 months: MD 0.17 lower (0.37 lower to 0.03 higher) No diabetic complications: MD 0.23 lower (0.43 to 0.03 lower) With complications: MD 0.36 lower (0.55 to 0.17 lower)	Moderate				
Fasting bl	ood alucos	e (mmol/l	L) from 26 to 52 we	eeks (subaroup	based on curre	nt thera	v) (follo	w-up 24	to 52 weeks: Better indicated by lower values)					
6	RCT	serious <sup>1</sup>	not serious	serious <sup>4,5</sup>	not serious	NA	835	810	MD -0.38 (-0.68 to -0.07) <u>Subgroup analysis based on current medication:</u> Diet ± OADs: MD -0.26 (-0.59 to 0.07) Diet, OADs ± insulin: MD -1.33 (-2.27 to -0.38) <u>Subgroup analysis based on type of SMBG:</u> Standard SMBG: MD -0.31 (-0.63 to 0.00) Enhanced SMBG: MD -1.57 (-2.94 to -0.20) <u>Subgroup analysis based on frequency of SMBG:</u> <1 per day: MD -0.20 (-0.86 to 0.47) 1-2 times per day: MD -0.55 (-1.30 to 0.20), I2=54% >2 per day: MD -0.51 (-2.01 to 0.99)	Low				
Postprano	lial blood gl	lucose (m	ng/dL) at 26 weeks	for adults with	type 2 diabetes	on diet,	, antidiab	etic and/	or insulin medicines (follow-up 6 months; Better indicated by lowe	r values)				
1	RCT	serious <sup>1</sup>	not serious	serious <sup>4</sup>	not serious	NA	96	48	MD -71.78 (-96.62 to -46.94) <u>Subgroup analysis based on type of SMBG:</u> Standard SMBG: MD -61.30 (-97.61 to -24.99) Enhanced SMBG: MD -81.00 (-111.05 to -46.95)	Low				

				0				RR 1.62 (1.19 t	o 2.22)		
RCT	serious <sup>1</sup>	not serious	serious <sup>3,4</sup>	serious⁵	NA	203/1354 (15%)	88/1138 (7.7%)	Subgroup analy Diet alone: RR Diet ± OADs: R Diet, OADs ± ir	<u>vsis based on current medication:</u> 1.27 (0.66 to 2.44) R 1.80 (1.16 to 2.79), I2=47% Isulin: RR 1.30 (0.70 to 2.39)		Low
								Subgroup analy <1 per day: RR 1-2 times per d >2 per day: RR	<u>vsis based on frequency of SMBG:</u> 2.28 (1.61 to 3.23) ay: RR 1.26 (0.89 to 1.79) 0.51 (0.06 to 4.37)		
e hvpoalvc	aemia from 26 t	o 52 weeks (su	baroup based	on current ther	apv) (follo	w-up 6 to	12 mont	hs)			
RCT	not serious	not serious	serious <sup>3</sup>	serious <sup>6</sup>	NA	1/853 (0.1%)	4/727 (0.6%)	RR 0.35 (0.07 f <u>Subgroup anal</u> Diet ± OADs: R Diet, OADs ± ir	o 1.77) / <u>sis based on current medication:</u> R 0.17 (0.01 to 4.12) /sulin: RR 0.45 (0.07 to 2.99)		Low
								<u>Subgroup anal</u> <1 per day: RR 1-2 times per d	<u>/sis based on frequency of SMBG:</u> 0.17 (0.01 to 4.12) ay: RR 0.45 (0.07 to 2.99)		
se events a	t 6 months for a	adults with typ	e 2 diabetes on	oral antidiabe	tes medici	nes (follo	w-up 6 m	ionths)			
RCT	not serious	not serious	not serious	serious <sup>6</sup>	none	41/311 (13.2%)	45/299 (15.1%)	RR 0.88 (0.59 to 1.3)	18 fewer per 1000 (from 62 fewer to 45 more)	⊕⊕⊕O MODERATE	
clear randon l outcome as erally not rep udies conduc seline charad ating good b t/m <sup>2</sup> which is als conducte me trials use e 95% confic d glucose an	nisation and alloc isessors but this orted ted before 1995 cteristics varied a blood glucose con close to the non- d in non-western d indirect compa- lence interval pa- d 3 kg for body to	cation concealm was not reported when the mana across studies. Introl. These par mal range and r countries when rators for exam sses through th weight. For all o	ent in several tri d in the majority gement of diabe Overall baseline ticipants may no nay not be repre e care may have ple weight contr e minimal import ther outcomes a	ais. Although bli of trials. Particip tes and other re Hba1c levels ra to be representation sentative of pat e differed and in ol program, provi tant difference (I relative risk reoch	Inding of pa pants in the lated condi inged from ' tive of peop ients with ty cluded part vision of fina MID) which luction or in	rticipants of two treating tions may 7.5% to 10 le with typ pe 2 diabour icipants wi ancial rewa is 0.5% fo crease of	and resea ment grou have diffi 0.4%. Spe e 2 diabe etes ho may n ards for w r change 25% or n	archers may no ups may have re ecifically, the Die etes. Two studie ot be represent reight loss and in Hba1c levels nore for binary c	t be possible due to the nature of self-more aceived different care and the characterist with current practice GEM trial had baseline Hba1c levels of ap s (Lim 2011 and Lu 2011) had baseline B ative of people with type 2 diabetes in the changes in habits by 1 mmol/L for fasting blood glucose, 1 m outcomes were considered clinically impor	ntoring, it is po ics of drop out proximately 7. MI of approxin UK mol/L for postp tant	ossible ts wer .5% nately orandi

### D.1.5.2 Table 15: SMBG plus education vs. conventional SMBG (up to 1 year)

No of	Design	Quality assessment	Number of people	Effect (95% CI)	Quality					
studies		Risk of bias	Inconsistency	Indirectness	Imprecision	Other	SMBG plus education	SMBG		
---	------------------------------	-----------------------	---	--	--------------------------------------	-------------	---------------------------	--------------	---	--------------
Hba1c fro	om 12 to 52	weeks in	adults with type	2 diabetes not or	n insulin (follow	-up 3 to	12 months: Be	etter indica	ated by lower values)	
3	RCT	serious <sup>1</sup>	not serious	serious <sup>2</sup>	serious <sup>3</sup>	NA	439	408	MD 0.31 lower (0.67 lower to 0.05 higher)	Low
Any hypo	oglycaemia	at 52 wee	eks in adults with	type 2 diabetes i	not on insulin (f	ollow-uj	o 12 months)			
2	RCT	serious <sup>1</sup>	not serious	serious <sup>4</sup>	serious <sup>3</sup>	NA	48/407	37/377	RR 1.28 (0.88 to 1.86)	Low
Any hypo	oglycaemia	at 3 mon	th follow-up in pe	ople treated with	oral antidiabet	es and/c	or insulin medi	cines		
1	RCT	serious <sup>1</sup>	not serious	serious <sup>2</sup>	not serious	NA	32	31	Frequency of events was not significantly higher in intervention (4.11± 0.96%) vs. control (2.24 ± 0.64%, p>0.05)	Moderate
<sup>1</sup> Unclea comorbi <sup>2</sup> One tr	r randomisa d conditions,	tion and a however	allocation concealm both ITT and per p	ent. One trial had rotocol analyses	some risk of att were carried out	rition bia:	s as dropouts w	ere slightly	younger, more likely to be African-American, have a higher Hbar	ic and fewer

<sup>2</sup> One trial was conducted in Brazil where care may have differed and included participants who may not be representative of people with type 2 diabetes in the UK <sup>3</sup> The 95% confidence interval passes through the minimal important difference (MID) which is 0.5% for change in Hba1c levels, 1 mmol/L for fasting blood glucose, 1 mmol/L for postprandial blood glucose and 3 kg for body weight. For all other outcomes a relative risk reduction or increase of 25% or more for binary outcomes were considered clinically important

<sup>4</sup> Baseline characteristics varied across studies. Overall baseline Hba1c levels ranged from 7.5% to 10.4%. Specifically, the DiGEM trial had baseline Hba1c levels of approximately 7.5% indicating good blood glucose control. These participants may not be representative of people with type 2 diabetes

### D.1.5.3 Table 16: SMBG plus telecare vs. conventional SMBG

Numbe r of		Qualit	y assessme	nt			Number of p	people		
studie	Desi	Risk of	Inconsiste	Indirectne	Imprecisi		SMBG plus			
S	gn	bias	ncy	SS	on	Other	telecare	SMBG	Effect (95% CI)	Quality
HbA1c fr	om 12 to	52 weeks	in adults with t	ype 2 diabete	s on diet, ora	I antidiabet	es and insulin	medicines (follow-up	o 12 to 52 weeks; Better indicated by lower values)	)
5	RCT	serious <sup>1</sup>	not serious	serious <sup>2</sup>	serious <sup>3</sup>	NA	260	295	MD -0.57 (-1.06 to -0.08)	Low
Fasting p values)	olasma gli	ucose (mi	nol/L) from 26 t	to 44 weeks ir	adults with	type 2 diabe	etes on diet, ora	al antidiabetes and ir	nsulin medicines (follow-up 26 to 44 weeks; Better	indicated by lower
2	RCT	serious <sup>1</sup>	not serious	serious <sup>2</sup>	not serious	NA	164	171	MD -0.19 (-0.61 to 0.24)	Low
Postprandial blood glucose (mg/dL) at 26 weeks in older adults with type 2 dia values)							etes on diet, ora	al antidiabetes and ir	nsulin medicines (follow-up 26 weeks; Better indic	ated by lower

Numbe r of		Qualit	y assessme	nt			Number of p	people		
studie s	Desi gn	Risk of bias	Inconsiste ncy	Indirectne ss	Imprecisi on	Other	SMBG plus telecare	SMBG	Effect (95% CI)	Quality
1	RCT	serious <sup>1</sup>	not serious	serious <sup>2</sup>	serious <sup>3</sup>	NA	49	47	MD -19.7 (-42.84 to 3.44)	Low
Any hypo	glycaem	ia at 52 w	eeks in adults v	with type 2 dia	abetes on die	t, oral antid	iabetes and ins	ulin medicines (follo	w-up 26 weeks)	
1	RCT	serious <sup>1</sup>	not serious	serious <sup>2</sup>	serious <sup>3</sup>	NA	16/51	12/51	RR 1.33 (0.7 to 2.53)	Low
Total sym	ptomatio	: hypogly	caemia at 44 we	eek follow-up	in people tre	ated with in	sulin therapy			
1	RCT	serious <sup>1</sup>	not serious	not serious	serious <sup>3</sup>	NA	1.89 events per patient year	1.76 events per patient year	Rate ratio <sup>*</sup> 1.07 (0.89 to 1.29)	Very low
Severe no	octurnal I	hypoglyca	emia at 44 wee	ek follow-up ir	n people treat	ed with ins	ulin therapy			
1	RCT	serious <sup>1</sup>	not serious	not serious	serious <sup>3</sup>	NA	0.04 events per patient year	0.02 events per patient year	Rate ratio 2.00 (0.44 to 9.06)	Very low

blind outcome assessors but this was not reported in the majority of trials. Participants in the two treatment groups may have received different care and the characteristics of drop outs were generally not reported <sup>2</sup> Trials conducted in non-western countries where care may have differed and included participants who may not be representative of people with type 2 diabetes in the UK

<sup>3</sup> The 95% confidence interval passes through the minimal important difference (MID) which is 0.5% for change in Hba1c levels, 1 mmol/L for fasting blood glucose, 1 mmol/L for postprandial blood glucose and 3 kg for body weight. For all other outcomes a relative risk reduction or increase of 25% or more for binary outcomes were considered clinically important

#### Table 17: Mobile phone (automated) glucometer vs. standard glucometer D.1.5.4

Numbe		Quality a	ssessment			Number of people				
of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Mobile phone glucometer	Glucometer	Effect (95% CI)	Quality
HbA1c at	12 weeks (B	etter indicate	d by lower values)							
1	RCT	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	serious <sup>3</sup>	NA	35	34	MD 0.29 (-0.25 to 0.83)	Low
Fasting p	lasma gluco	se (mmol/L) a	t 12 weeks (follow-up 12	weeks; Better in	dicated by lower val	ues)				
1	RCT	serious <sup>1</sup>	no serious	serious <sup>2</sup>	no serious	NA	35	34	MD -0.33 (-1.64 to 0.99)	Low

Number		Quality as	sessment				Number of people				
of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Mobile phone glucometer	Glucometer	Effect (95% CI)	Quality	
			inconsistency		imprecision						
Postprand	ial blood glu	ucose (mg/dL)	at 12 weeks (follow-up 1	2 weeks; Better	indicated by lower va	alues)					
1	RCT	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	serious <sup>3</sup>	NA	35	34	MD -11.57 (-46.55 to 23.41)	Low	

<sup>1</sup> Unclear randomisation and allocation concealment in several trials. Although blinding of participants and researchers may not be possible due to the nature of self-monitoring, it is possible to blind outcome assessors but this was not reported in the majority of trials. Participants in the two treatment groups may have received different care and the characteristics of drop outs were generally not reported

<sup>2</sup> Trials conducted in non-western countries where care may have differed and included participants who may not be representative of people with type 2 diabetes in the UK

<sup>3</sup> The 95% confidence interval passes through the minimal important difference (MID) which is 0.5% for change in Hba1c levels, 1 mmol/L for fasting blood glucose, 1 mmol/L for postprandial blood glucose and 3 kg for body weight. For all other outcomes a relative risk reduction or increase of 25% or more for binary outcomes were considered clinically important

# D.1.5.5 Table 18: SMBG plus continuous glucose monitoring (CGM) vs. conventional SMBG

Number of		Quality assess	nent	f people						
studies	Design	Risk of bias	Inconsistency	SMBG	Effect (95% CI)	Quality				
Hba1c from 12	2 to 52 week	s (follow-up 12 to 52 v	weeks; Better indicated by	y lower values)						
2	RCT	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	serious <sup>3</sup>	NA	79	78	MD -0.46 (-0.87 to -0.06)	Low
Fasting plasm	a glucose (r	nmol/L) at 12 weeks (f	follow-up 12 weeks; Bette	er indicated by lov	ver values)					
1	RCT	no serious risk of bias	no serious inconsistency	serious <sup>2</sup>	serious <sup>3</sup>	NA	29	28	MD -0.7 (-1.62 to 0.22)	Low
Postprandial k	blood glucos	se (mmol/L) at 12 wee	ks (follow-up 12 weeks; B	Better indicated by	v lower values)					
1	RCT	no serious risk of bias	no serious inconsistency	serious <sup>2</sup>	serious <sup>3</sup>	NA	29	28	MD -0.9 (-2.67 to 0.87)	Low
<sup>1</sup> Unclear rando outcome asses reported <sup>2</sup> Trials associated	omisation and sors but this	d allocation concealmen was not reported in the	nt in several trials. Although majority of trials. Participa	h blinding of particip nts in the two treat	pants and research ment groups may	hers may have rec	not be possib eived different	le due to the natur care and the char	re of self-monitoring, it is po- racteristics of drop outs were	ssible to blind e generally not

<sup>2</sup> Trials conducted in non-western countries where care may have differed and included participants who may not be representative of people with type 2 diabetes in the UK

						Number	incente			
Number of		Quality assessi	nent		1		Number of	people		
studies	Design	Risk of bias	Inconsistency	Indirectness	Other	CGM	SMBG	Effect (95% CI)	Quality	

<sup>3</sup> The 95% confidence interval passes through the minimal important difference (MID) which is 0.5% for change in Hba1c levels, 1 mmol/L for fasting blood glucose, 1 mmol/L for postprandial blood glucose and 3 kg for body weight. For all other outcomes a relative risk reduction or increase of 25% or more for binary outcomes were considered clinically important

#### D.1.5.6 Table 19: Frequency of SMBG testing (monthly vs. fortnightly)

		Quality assessment					Number	of people		
Number of studies	Desig n	Risk of bias	Inconsiste ncy	Indirectnes s	Imprecisio n	Other	Fortnig htly	Monthly	Effect (95% CI)	Quality
Hba1c in pat	tients not	on insi	ulin at s	tudy en	d (%; fo	llow up a	approx. 6 n	nonths; Bett	er indicated by lower values)	
1 (Bonomo 2010)	RCT	S1	NA	Ν	Ν	NA	177	96	MD 0.04 (-0.20 to 0.28)	Moderate
									Subgroup: people compliant with SMBG	
									MD -0.31 (-0.59 to -0.03)	
Hypoglycae	mia in co	mpliant	patient	s not or	n insulir	n (defined	l as BG <3.	.3 mmol/L)		
1 (Bonomo 2010)	RCT	S1	NA	Ν	S2	NA	177	96	RR 0.30 (0.03 to 2.86)	Low
<sup>1</sup> Downgrade k	by 1 level:	Unclear r	andomisa	ation and	allocatio	n concealn	nent in sever	al trials. Althou	igh blinding of participants and researchers may not be pos	ssible due to the

<sup>1</sup> Downgrade by 1 level: Unclear randomisation and allocation concealment in several trials. Although blinding of participants and researchers may not be possible due to the nature of self-monitoring, it is possible to blind outcome assessors but this was not reported in the majority of trials. Participants in the two treatment groups may have received different care and the characteristics of drop outs were generally not reported

<sup>2</sup> Downgrade by 1 level: The 95% confidence interval passes through the minimal important difference (MID) which is 0.5% for change in Hba1c levels, 1 mmol/L for fasting blood glucose, 1 mmol/L for postprandial blood glucose, 3kg for body weight, 3 BMI point and 3 cm for waist circumference. For all other outcomes a relative risk reduction or increase of 25% or more for binary outcomes were considered clinically important

#### D.1.5.7 Table 20: Frequency of SMBG testing (four times weekly vs. once weekly)

Quality assessment	No of patients	Effect (95% CI)	Quality

No of studies	Design	Risk of bias	Inconsiste ncy	Indirectne ss	Imprecisi on	Other conside rations	4 times weekly	Once weekly		
Hba1c at study e	nd in pati	ents n	ot on i	insulin	(%; B	etter indi	cated by lo	ower value	s)	
1 (Scherbaum 2008)	RCT	Ν	NA	S2	Ν	NA	95	93	3 months: MD 0.00 (-0.28 to 0.28) 6 months: MD 0.10 (-0.20 to 0.40) 12 months: MD 0.20 (-0.10 to 0.50)	Moderate
Hypoglycaemia (	one event	t of SN	/IBG<3	.2mmo	ol/L or	several e	events;			
1 (Scherbaum 2008)	RCT	Ν	NA	S2	S3	NA	18/102 (18%)	5/100 (5%)	RR 3.53 (1.36 to 9.14)	Moderate
Adverse events (	hyperglyo	caemia	a, dete	riorati	n <mark>g ne</mark> t	iropathy,	retinopath	y or nephr	opathy, multiple events or other events)	
1 (Scherbaum 2008)	RCT	Ν	NA	S2	S1	NA	8/102 (7.8%)	14/100 (14%)	RR 0.56 (0.25 to 1.28)	Low
Serious adverse	events (h	ypogly	ycaem	ic sho	ck, hy	perosmol	lar coma, i	npatient st	ay or death)	
1 (Scherbaum 2008)	RCT	Ν	NA	S2	S1	NA	15/102 (14.7%)	20/100 (20%)	RR 0.74 (0.40 to 1.35)	Low
<sup>1</sup> Downgrade by 1 le blood glucose, 1 mm increase of 25% or 1 <sup>2</sup> Downgrado by 1 le	evel: The 95 nol/L for po- more for bir	5% con stprand hary out	fidence lial bloo tcomes	interval d gluco were co	passes se, 3kg onsidere	s through th for body w ed clinically	he minimal in veight, 3 BMI v important	portant diffe point and 3	erence (MID) which is 0.5% for change in Hba1c levels, 1 mmol/L cm for waist circumference. For all other outcomes a relative risk	for fasting reduction or

<sup>2</sup> Downgrade by 1 level: participants may not be representative of people with type 2 diabetes in the UK as baseline Hba1c <7.5% indicating good blood glucose control <sup>3</sup> Downgrade by 1 level: Few events so estimates of effect may be fragile

# D.1.5.8 Table 21: Location of SMBG testing (forearm vs. fingertip)

Quality assessm	ent						No of patie	ents			
		k of bias	onsisten	irectnes	orecision	าer าsiderati s				Quality	
No of studies	Design	Ris	cy C	lnd s	Ē		Forearm	fingertip	Effect (95% CI)	Quality	
No of studies Change in Hba1c	Design : in patient	s on	<mark>은 </mark>	ာ (follo	<u>Ē</u> ow up	approx. 6	Forearm months; Be	fingertip etter indicate	Effect (95% CI) ed by lower values)	Quality	

Quality assessm	ent						No of patie	ents		
No of studies	Design	Risk of bias	Inconsisten cy	Indirectnes s	Imprecision	Other considerati ons	Forearm	fingertip	Effect (95% CI)	Quality
									Subgroup analysis based on baseline HbA1c levels: ≤7%: MD 0.00 (-0.41 to 0.41) 7.0-8.5%: MD 0.00 (-0.52 to 0.52) >8.5%: MD 0.20 (-0.45 to 0.85)	
Hypoglycaemia (	more than	one	episo	de per	month	n)				
1 (Knapp 2009)	RCT	Ν	NA	Ν	S1	none	3/89 (3.4%)	3/85 (3.5%)	RR 0.96 (0.20 to 4.60)	Moderate
Severe hypoglyc	aemia (req	luirir	ng urg	ent me	dical a	attention)				
1 (Knapp 2009)	RCT	N	NA	N	S1	none	3/89	1/85	RR 2.87 (0.30 to 27.01)	Moderate

<sup>1</sup> Downgrade by 1 level: The 95% confidence interval passes through the minimal important difference (MID) which is 0.5% for change in Hba1c levels, 1 mmol/L for fasting blood glucose, 1 mmol/L for postprandial blood glucose, 3kg for body weight, 3 BMI point and 3 cm for waist circumference. For all other outcomes a relative risk reduction or increase of 25% or more for binary outcomes were considered clinically important

# D.1.6 Review question 6: Should aspirin and/or clopidogrel be used for primary prevention of cardiovascular disease in people with type 2 diabetes?

D.1.6.1 Full GRADE Table 22: Aspirin therapy for primary prevention of cardiovascular disease

		Quali	ty assess	sment		Νι	umber of people			
Number of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Aspirin	Contro	bl	Relative effect (95% CI)	Quality
All-cause mor	tality; fo	llow-up f	or up to {	5 years						
1 (ETDRS)†	Ν	NA	S <sup>7</sup>	Ν	NA	587	565	HR 0.99 (	0.83 to 1.17)	Moderate
1 (Sacco 2003)-PPP	VS <sup>1,2</sup>	NA	Ν	S <sup>4</sup>	NA	25/519	20/512	RR 1.23 (	0.69 to 2.19)	Very low
Cardiovascula	ar mortal	ity; follo	w-up for	up to 5 y	ears					
1 (ETDRS)†	Ν	NA	S <sup>7</sup>	Ν	NA	587	565	CV death:	HR 0.97 (0.79 to 1.19)	Moderate
1 (Sacco 2003)-PPP	VS <sup>1,2</sup>	NA	Ν	$S^4$	NA	10/519	8/512	CV mortal	ity: RR 1.23 (0.49 to 3.10)	Very low
1 (Ogawa 2008)-JPAD	S <sup>1</sup>	NA	Ν	S <sup>3</sup>	NA	0/1262	5/1277	Fatal MI: I	HR not estimable due to no events group	Low
Cerebrovascu	ılar morta	ality; foll	ow-up fo	r median	4.4 years	S				
1 (Ogawa 2008)-JPAD	S <sup>1</sup>	NA	Ν	S <sup>3</sup>	NA	1/1262	5/1277	Fatal strok	ke: HR 0.20 (0.024 to 1.74)	Low
Coronary and	cerebro	vascular	mortality	; follow-	up for me	edian 4.4 year	S			
1 (Ogawa 2008)-JPAD	S <sup>1</sup>	NA	Ν	S <sup>3</sup>	NA	1/1262	10/1277	HR 0.10 (	0.01 to 0.79)	Low
Non-cardiovas	scular m	ortality; f	ollow-up	to media	an 3.7 yea	ars				
1 (Sacco 2003)-PPP	VS <sup>1,2</sup>	NA	Ν	$S^4$	NA	15/519	12/512	RR 1.23 (	0.58 to 2.61)	Very low
Any atheroscl	erotic ev	ent <sup>a</sup> ; foll	ow-up fro	om media	an 3.7 to	4.4 years				
1 (Sacco 2003)-PPP	VS <sup>1,2</sup>	NA	Ν	$S^4$	NA	20/519	22/512	RR 0.90 (	0.50 to 1.62)	Very low

		Quali	ty ass	essme	ent		N	umber of people			
Number of RCTs	Risk of bias	Inconsistency		Indirectness	Imprecision	Other	Aspirin	Contro	bl	Relative effect (95% CI)	Quality
1 (Ogawa 2008)-JPAD	S <sup>1</sup>	NA	Ν	S	3	NA	68/1262	86/1277	HR 0.80 (f Subgroup ≥ 65 years < 65 years Subgroup Male: HR Female: H Subgroup Hypertens Normoten Dyslipidae Normolipid Current/pa Non-smok Subgroup eGFR ≥ 9 eGFR 60- eGFR < 6 Subgroup Insulin: HF OHA: HR Diet alone	0.58 to 1.10) arrow and arrow and	Low

#### Coronary heart disease events; follow-up from median 3.7 to 5 years

		Quali	ty assess	sment		N	umber of people			
Number of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Aspirin	Contro	bl	Relative effect (95% CI)	Quality
1 (ETDRS)†	N _	NA _	S <sup>7</sup>	N	NA	587	565	MI: HR 0.8	85 (0.70 to 1.05)	Moderate
								CV event <sup>b</sup>	2: HR 0.97 (0.82 to 1.15)	
1 (Sacco	VS <sup>1,2</sup>	NA	Ν	S <sup>4</sup>	NA	53/519	59/512	Total CV e	events: RR 0.89 (0.62 to 1.26)	Very low
2003)-PPP						5/519	10/512	All MI: RR	0.49 (0.17 to 1.40)	
						13/519	16/512	Angina: R	R 0.80 (0.39 to 1.64)	
1 (Ogawa 2008)-JPAD	S <sup>1</sup>	NA	Ν	S <sup>3</sup>	NA	28/1262	35/1277	Any fatal o 1.33)	or nonfatal event: HR 0.81 (0.49 to	Low
						12/1262	9/1277	Nonfatal M	/II: HR 1.34 (0.57 to 3.19)	
						12/1262	11/1277	Stable and	gina: HR 1.10 (0.49 to 2.50)	
						4/1262	10/1277	Unstable a	angina: HR 0.40 (0.13 to 1.29)	
								Cardiovas	cular events subgrouped by	
								cardiovas	cular risk:	
								In low risk	group: HR 0.53 (0.23 to 1.21)	
Carabravacau	lor ovor		up from	modion	276051	0070		in nigh ris	k group: HR 0.78 (0.55 to 1.11)	
			-up from	median	5.7 to 5 y		565	Chrokes LI	$24.00(0.70 \pm 0.452)$	Low
1 (ETDRS)T	IN VO <sup>1,2</sup>		5	5 0 <sup>4</sup>		587	202	Stroke: Hr		LOW
1 (Sacco 2003)-PPP	VS /	NA	N	5	NA	9/519	10/512	All stroke:	RR 0.89 (0.36 to 2.17)	very low
2000/111						7/519	10/512	Transient 1.79)	ischaemic attack: RR 0.69 (0.27 to	
1 (Ogawa 2008)-JPAD	S <sup>1</sup>	NA	N	S <sup>3</sup>	NA	28/1262	32/1277	Any fatal o 1.32)	or nonfatal event: HR 0.84 (0.53 to	Low
						22/1262	24/1277	Nonfatal is 1.66)	schaemic stroke: HR 0.93 (0.52 to	
						5/1262	3/1277	Nonfatal h to 7.04)	naemorrhagic stroke: HR 1.68 (0.40	
						5/1262	8/1277	Transient 1.93)	ischaemic attack: HR 0.63 (0.21 to	

	Quality assessment					N	umber of people			
Number of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Aspirin	Contro	bl	Relative effect (95% CI)	Quality
								Cerebrova pressure of In non-asp indicating group In aspirin indicating unattained No HR rep reported a	ascular events subgrouped by blood control <sup>c</sup> : pirin group: HR 2.84 (1.52 to 5.52) higher incidence in unattained group: HR 1.64 (0.83 to 3.29) no difference in incidence in d vs. attained ported for aspirin vs. non-aspirin but as not significant	
Peripheral art	ery disea	ase; follo	w-up fro	m mediar	າ 3.7 to 4	.4 years				
1 (Sacco 2003)-PPP	VS <sup>1,2</sup>	NA	Ν	S <sup>4</sup>	NA	11/519	13/512	RR 0.83 (	0.38 to 1.84)	Very low
1 (Ogawa 2008)-JPAD	S <sup>1</sup>	NA	Ν	S <sup>3</sup>	NA	7/1262	11/1277	HR 0.64 (	0.25 to 1.65)	Low
Revascularisa	ation; fol	low-up to	o median	3.7 years	5					
1 (Sacco	VS <sup>1,2</sup>	NA	Ν	$S^4$	NA	8/519	10/512	RR 0.79 (	0.31 to 1.97)	Very low
2003)-PPP								Creatinine 0.82)	e clearance: MD -2.30 (-5.42 to	
								Urine prot to -0.07)	ein:creatinine ratio: MD -0.30 (-0.53	
								% protein 12.65)	uria change: MD -17.80 (-22.95 to -	
Adverse even	ts: Any b	leeding;	follow-u	p for mee	dian 4.4 y	/ears				
1 (ETDRS 1992)	Ν	NA	S <sup>7,8</sup>	NA	NA	587	565	Only a few some indi	v patients (2%) in both groups had cation of bleeding <sup>‡</sup>	Low

		Quali	ty asses	sment		Νι	umber of people	per of people				
Number of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Aspirin	Contro	51	Relative effect (95% CI)	Quality		
1 (Ogawa 2008)-JPAD	S <sup>1</sup>	NA	N	S <sup>3</sup>	NA	1251	1272	<u>Haemorrh</u> <u>function:</u> eGFR ≥ 90 eGFR 60-4 eGFR < 60	agic events subgrouped by renal D: HR not estimable 89: HR 1.03 (0.24 to 4.35) D: HR: 0.87 (0.10 to 7.27)	Low		
	S <sup>1</sup>	NA	Ν	Ν	NA	21/1262	6/1277	Other blee	eding: RR 3.54 (1.43 to 8.75)	Moderate		
	S <sup>1</sup>	NA	Ν	S <sup>3</sup>	NA	12/1262	4/1277	Gastrointe 9.39)	stinal bleeding: RR 3.04 (0.98 to	Low		
Non-bleeding	gastroin	testinal e	event; fo	low-up fo	or media	n 4.4 years						
1 (Ogawa 2008)-JPAD	S <sup>1</sup>	NA	Ν	Ν	NA	47/1262	4/1277	RR 11.89	(4.30 to 32.90)	Moderate		
Other adverse	event <sup>e</sup> ;	follow-uj	p f <mark>or</mark> med	lian 4.4 y	ears							
1 (Ogawa 2008)-JPAD	S <sup>1</sup>	NA	Ν	S <sup>3</sup>	NA	5/1262	0/1277	RR 11.13	(0.62 to 201.08)	Low		

		Qualit	ty assess	sment		Nu	umber of people		
Number of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Aspirin	Control	Relative effect (95% CI)	Quality

Abbreviations: BP blood pressure; CV cardiovascular; eGFR estimated glomerular filtration rate; HR hazard ratio; MD mean difference; MI myocardial infarction; OHA Oral hypoglycaemic agents; RCT randomised controlled trial; RR relative risk, RRI relative risk increase; RRR relative risk reduction

NB: data from ETDRS (unpublished 2013) are from multivariate analysis; data from the JPAD trial (Ogawa et al. 2008) are from Cox proportional hazards model (not specified as multivariate) in multiple publications; data from the PPP trial (Sacco et al. 2003) are relative risks as multivariate analyses using Cox regression are not reported for people with diabetes

<sup>1</sup> Downgrade by 1 level: not placebo controlled trial (control group not given aspirin) and in Ogawa et al. (2008) only outcome assessor was blinded to treatment status.

<sup>2</sup> Downgrade by 1 level: Open label trial which was stopped prematurely due to ethical grounds when newly available evidence from other trials on the benefit of aspirin in primary prevention was strictly consistent with the results of the second planned interim analysis. The baseline characteristics showed that patients in the aspirin group were more likely to be hypertensive, take antihypertensive medications and have hypercholesterolemia compared with the non-aspirin group. In addition, at the end of the trial approximately 12% in the control group were taking aspirin and 28% in the aspirin group had discontinued aspirin therapy

<sup>3</sup> Downgrade by 1 level: The JPAD trial did not achieve the planned statistical power due to the lower than expected incidence of atherosclerotic events. Any sub-group analyses based on this trial will also be underpowered (which may have increased the risk of a type two error) and/or the 95% confidence interval crosses the minimal important difference (this is the GRADE default of a RRR or RRI of >25%). %). In addition, many of the outcomes relating to macrovascular complications show very low event rates and indicate that the results are fragile

<sup>4</sup> Downgrade by 1 level: the 95% confidence interval crosses the minimal important difference (this is the GRADE default of a RRR or RRI of >25% or 0.5 in either direction for a continuous outcome )

<sup>7</sup> Downgrade by 1 level: patients included in this trial had one of the following categories of diabetic retinopathy: mild non-proliferative with macular oedema, moderate to severe non-proliferative or early proliferative with or without macular oedema

<sup>8</sup> Downgrade by 1 level: for all patients (including those with type 1 or mixed diabetes)

<sup>a</sup> any atherosclerotic event was defined as a composite of sudden death, death from coronary, cerebrovascular and aortic causes, nonfatal acute MI, unstable angina, newly developed exertional angina, nonfatal ischaemic and haemorrhagic stroke, transient ischaemic attack or nonfatal aortic and peripheral vascular disease <sup>b</sup> CV event was defined as CV death, myocardial infarction or stroke

<sup>c</sup> unattained group had systolic BP  $\geq$  140 mmHg and/or diastolic BP  $\geq$  90 mmHg and the attained group had systolic BP < 140mmHg and/or diastolic BP < 90mmHg

<sup>d</sup> adjusted for age, hypertension, dyslipidaemia and history of smoking

<sup>e</sup> Anaemia and asthma

<sup>†</sup> Unpublished subgroup analysis for people with type 2 diabetes without a history of cardiovascular disease from the ETDRS trial was provided by the authors

<sup>*t*</sup> haemoglobin < 100 g/L or haematocrit < 0.30, haematuria, or blood in the stool

# D.1.7 Review question 7: What pharmacological treatment should be used to manage erectile dysfunction in men with type 2 diabetes?

# D.1.7.1 Full GRADE QTable 23: Pairwise comparisons of any PDE-5 inhibitor vs. placebo

	Quality ass	essment				Number o	of people		
Number of RCTs	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other	PDE-5 inhibitor	Placebo	Effect (95% CI)	Quality
Erectile function IIEF- EF do	omain (follow	-up 12 to 16 w	veeks)						
11 (Boulton 2001; Escobar- Jimenez 2002; Goldstein 2003, 2012; Hatzichristou 2008; Ishii 2006; Rendell 1999; Saenz de Tejada 2002; Safarinejad 2004; Stuckey 2003; Ziegler 2006)	serious <sup>1</sup>	not serious	serious <sup>2,3</sup>	serious <sup>4</sup>	NA	2142	1174	MD 5.58 (4.48 to 6.68)	Low
Erectile function (SEP Q2 po	ositive respo	nse) (follow-u	ıp 12 weeks)						
5 (Goldstein 2003, 2012; Hatzichristou 2008; Ishii 2006; Ziegler 2006)	serious <sup>1</sup>	not serious	serious <sup>2,3</sup>	not serious	NA	1059/155 9	274/616	RR 1.47 (1.33 to 1.61)	Low
Erectile function (SEP Q3- p	ositive respo	onse) (follow-	up 12 weeks)	)					
5 (Goldstein 2003, 2012; Hatzichristou 2008; Ishii 2006; Ziegler 2006)	serious <sup>1</sup>	not serious	serious <sup>2,3</sup>	not serious	NA	800/1551	160/618	RR 1.87 (1.61 to 2.16)	Low
Erectile function GEQ (Impre	ovement) (fo	llow-up 12 to	16 weeks)						
8 (Boulton 2001; Escobar- Jimenez 2002; Goldstein 2003; Hatzichristou 2008; Rendell 1999; Saenz de	not serious	not serious	serious <sup>2,3</sup>	not serious	NA	623/1064	116/743	RR 3.62 (2.57 to 5.09)	Moderate

	Quality ass	essment				Number o	f people		
Number of RCTs	Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other	PDE-5 inhibitor	Placebo	Effect (95% CI)	Quality
Tejada 2002; Safarinejad 2004; Stuckey 2003)									
Adverse events (follow-up 1	2 to 16 week	s)							
11 (Boulton 2001; Escobar- Jimenez 2002; Goldstein 2003, 2012; Hatzichristou 2008; Ishii 2006; Rendell 1999; Saenz de Tejada 2002; Safarinejad 2004; Stuckey 2003; Ziegler 2006)	serious <sup>1</sup>	serious <sup>5</sup>	serious <sup>2,3</sup>	not serious	NA	610/9064	115/5249	RR 2.69 (1.87 to 3.86)	Low
Adverse events - Headache	(follow-up 1	2 to 16 weeks)	)						
10 (Boulton 2001; Escobar- Jimenez 2002; Goldstein 2003, 2012; Ishii 2006; Rendell 1999; Saenz de Tejada 2002; Safarinejad 2004; Stuckey 2003; Ziegler 2006)	serious <sup>1</sup>	serious <sup>5</sup>	serious <sup>3</sup>	not serious	NA	185/2065	43/1126	RR 3.08 (1.46 to 6.48)	Low
Adverse events - Flushing (f	ollow-up 12	to 16 weeks)							
10 (Boulton 2001; Escobar- Jimenez 2002; Goldstein 2003, 2012; Ishii 2006; Rendell 1999; Saenz de Tejada 2002; Safarinejad 2004; Stuckey 2003; Ziegler 2006)	serious <sup>1</sup>	not serious	serious <sup>3</sup>	not serious	NA	191/2065	6/1126	RR 8.65 (4.5 to 16.66)	Low
Adverse events - Bronchitis									

		Quality ass	essment				Number o	of people		
Number of RCTs		Risk of bias	Inconsistenc y	Indirectnes s	Imprecision	Other	PDE-5 inhibitor	Placebo	Effect (95% CI)	Quality
1 (Ziegler 2006)	not serious	not seriou	s serious <sup>3</sup>		not serious	NA	3/163	4/155	RR 0.71 (0.16 to 3.14)	Moderate
Adverse events - Upp	oer resp	oiratory tract	infections (fo	ollow-up 12 to	o 16 weeks)					
7 (Goldstein 2003, 201 2006; Rendell 1999; S de Tejada 2002; Safar 2004; Ziegler 2006)	2; Ishii aenz inejad	serious <sup>1</sup>	serious <sup>4</sup>	serious <sup>3</sup>	not serious	NA	147/1814	43/875	RR 1.12 (0.57 to 2.2)	Low
Adverse events - Dis	continu	ation due to	AE (follow-u	p 12 to 16 we	eks)					
9 (Goldstein 2003, 201 Hatzichristou 2008; Ish 2006; Rendell 1999; S de Tejada 2002; Safar 2004; Stuckey 2003; Z 2006)	2; aenz inejad ïegler	serious <sup>1</sup>	not serious	serious <sup>2,3</sup>	not serious	NA	46/2013	14/1167	RR 1.67 (0.89 to 3.13)	Low
Adverse events - Dy	yspepsi	ia (follow-up	12 weeks)							
4 (Boulton 2001; Golds 2012; Rendell 1999; S 2003)	stein tuckey	not serious	not serious	serious <sup>3</sup>	not serious	NA	26/601	2/465	RR 6.09 (1.77 to 20.94)	Moderate
Adverse events - Al	bnorma	l vision (foll	ow-up 12 wee	ks)						
3 (Boulton 2001; Rend 1999; Stuckey 2003)	lell	not serious	not serious	serious <sup>3</sup>	not serious	NA	12/343	3/335	RR 2.92 (0.71 to 11.99)	Moderate

<sup>1</sup> 2 studies (Saenz de Tejada 2002, Ishii 2006) do not report allocation concealment to determine if performance bias was present <sup>2</sup> 1 study (Hatzichristou 2008) used low doses (2.5mg and 5mg) of tadalafil, which are licensed for use but are recommended in people who anticipate frequent use of the drug. 10mg is generally recommended (but not for continuous daily use). The other study examining tadalafil (Saenz de Tejada 2002) used 10mg and 20mg, therefore these arms combined represent a wide range of different doses.

	Quality ass	essment				Number o	of people		
		Inconsistenc	Indirectnes			PDE-5			
Number of RCTs	Risk of bias	У	s	Imprecision	Other	inhibitor	Placebo	Effect (95% CI)	Quality

<sup>3</sup> 2 studies (Stuckey 2003, Zieglar 2006) were conducted solely in men with type 1 diabetes and the mean age in these studies were generally lower in comparison to the other included studies. One study (Ishii 2006) did not report the proportion of men with type 2 diabetes.

<sup>4</sup> Standard deviations were not reported in the paper and were calculated using p-values
<sup>5</sup> pairwise comparisons of the included studies (direct comparisons) showed an l<sup>2</sup> of 68% headaches, 59% for upper respiratory tract infection and 53% for any adverse event. These values indicate substantial heterogeneity which cannot be fully accounted for

#### Full GRADE Table 24: Sub-group analyses by baseline HbA1c level D.1.7.2

	Quality a	ssess	ment				Number of patients			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Placebo	Effect/ outcome	Quality
Erectile Function scores 1-30; be	on (measu tter efficad	red wit cy is ir	th Intendicate	ernatic ed by	onal In highe	dex of E r values	Erectile Function	n [IIEF] me	an score on EF domain, sum of questions 1-5 and 1	5; range of
Sildenafil vs. pl	acebo									
1 (Boulton et al 2001)	RCTs	Ν	Ν	Ν	S <sup>2</sup>	none	47	47	Mean change from baseline in sildenafil group stratified by baseline Hba1c level: <8.3%: 8.9* ≥8.3%: 8.2* Mean change from baseline in placebo group stratified by baseline Hba1c level*: <8.3%: 0.6 ≥8.3%: -0.5	Moderate
Vardenafil vs. p	lacebo									

	Quality assessment									
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Placebo	Effect/ outcome	Quality
1 (Zieglar et al 2006)	RCTs	N	NA	S <sup>1</sup>	N	none	154	149	Mean endpoint in vardenafil group stratified by baseline Hba1c level: Good (<7%): 21* moderate (7-8%): 21* Poor (>8%): 18* Mean endpoint in placebo group stratified by baseline Hba1c level: Good (<7%): 15 moderate (7-8%): 14 Poor (>8%): 16 Interaction term between treatment and level of glycaemic control was not statistically significant	Moderate
Tadalafil vs. pla	acebo									
2 (Hatzichristou 2008, Saenz 2002)	RCT (3 arms)	S <sup>4</sup>	Ν	S <sup>3</sup>	S⁵	none	339	169	Mean change from baseline in tadalafil group stratified by baseline Hba1c level (comparison with placebo): Good (<7%): 3.8 (2.5 mg), 6.6 (5 mg) 9.7 (10 mg), 8.3 (20 mg), Fair (7-9.5%): 7.3 (2.5 mg), 3.2 (5 mg), 6.0 (10 mg), 6.7 (20 mg) Poor (>9.5%): 1.4 (2.5 mg), 4.7 (5 mg), 3.8 (10 mg), 8.3 (20 mg) Mean change from baseline in placebo group: Good (<7%): -1.0, 1.4 Fair (7-9.5%): -0.9, 1.4 Poor (>9.5%): 3.9, 0.5	Very low

	Quality assessment						Number of patients			
No of studies	Design	Risk of bias	nconsistency	ndirectness	mprecision	Other considerations	Intervention	Placebo	Effect/ outcome	Quality

<sup>1</sup> Downgrade by 1 level: 2 studies (Stuckey 2003, Zieglar 2006) were conducted solely in men with type 1 diabetes and the mean age in these studies were generally lower in comparison to the other included studies.

<sup>2</sup> Downgrade by 1 level: small sample used which may have increased risk of a type 2 error

<sup>3</sup> Downgrade by 1 level: 1 study (Hatzichristou 2008) used low doses (2.5mg and 5mg) of tadalafil, which are licensed for use but are recommended in people who anticipate frequent use of the drug. 10mg is generally recommended (but not for continuous daily use). The other study examining Tadalafil (Saenz 2002) used 10mg and 20mg, therefore these arms combined represent a wide range of different doses.

<sup>4</sup> Downgrade by 1 level: 1 study (Saenz 2002) does not report allocation concealment to determine if performance bias was present

<sup>5</sup> Downgrade by 1 level: subgroup analyses were exploratory post-hoc analyses in one study

<sup>\*</sup>P<0.0001 vs. placebo

# D.1.7.3 Full GRADE Table 25: PDE-5 inhibitor vs. PDE-5 inhibitor

Quality assessm	nent						Number of pa	itients		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Placebo	Effect/ outcome	Quality
EF (IIEF EF domain)										
Tadalafil on den	nand vs. T	adalafil t	hree tin	nes per v	week					
Buvat 2006   RCT*   S <sup>1</sup> NA   S <sup>2</sup> N   none   762   762   Mean score at endpoint was 21.7 (SE 0.3) for tadalafil on demand and 22.0 (SE 0.3) for 3 times per week.   Low     Mean change from baseline 8.9 (SE 0.3) on demand and 9.1 (SE 0.3) for 3 times per week   Mean change from baseline 8.9 (SE 0.3) on demand and 9.1 (SE 0.3) for 3 times per week										
Erectile function (mean scores of SEP Q2 successful insertion)										
Tadalafil on demand vs. Tadalafil three times per week										

Quality assessm	nent						Number of pa	itients		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Placebo	Effect/ outcome	Quality
Buvat 2006	RCT*	S <sup>1</sup>	NA	S <sup>2</sup>	Ν	none	762	762	Percentage of people answering 'yes' at endpoint was 73.0% on demand and 74.9% for 3 times per week (p<0.05)	Low
<b>Erectile function</b>	(mean so	cores of	SEP Q3	success	ful inter	course)				
Tadalafil on dem	hand vs. T	adalafil t	three tin	n <mark>es per</mark> v	week					
Buvat 2006	RCT*	S <sup>1</sup>	NA	S <sup>2</sup>	Ν	none	762	762	Percentage of people answering 'yes' at endpoint was 58.0% on demand and 60.5% for 3 times per week (p<0.05).	Low
Adverse event (a	any)									
Tadalafil on dem	and vs. T	adalafil (	three tin	nes per	week					
Buvat 2006	RCT*	S <sup>1</sup>	NA	S <sup>2</sup>	N	none	762	762	Treatment emergent adverse events (3 times per week, on demand): Dyspepsia: (5.8, 5.9%) Headache: (5.6, 4.7%) Back pain: (2.1, 2.5%) Flushing: (2.1, 1.6%) Myalgia: (2.0, 1.4%)	Low
Vardenafil versu	is tadalafi	I								
Kamenov 2004	RCT	Ν	NA	S <sup>3, 4</sup>	N	none	7/24 (tadalafil)	6/25 (vardenaf il)	Side effects (Tadalafil, Vardenafil): Headache: (8.3, 8.0%) Flush: (4.2, 8.0%) Nasal congestion: (0, 8.0%) Myalgia: (8.4, 0%) Dyspepsia: (8.4, 4.0%) Total: (29.2, 24.0%)	Low

Quality assessm	Quality assessment							tients		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Placebo	Effect/ outcome	Quality
<sup>1</sup> Downgrade by 1 level: open label study with one week washout period, which may not be sufficient to avoid carry-over effects <sup>2</sup> Downgrade by 1 level: patients received 20mg tadalafil which is usually recommended for those patients in whom tadalafil 10mg does not produce an adequate effect. <sup>3</sup> Downgrade by 1 level: this trial was restricted to first intake of the intervention rather than continued treatment <sup>4</sup> Downgrade by 1 level: conducted in men with diabetic neuropathy * Post hoc of open label crossover RCT										

# D.2 RESULTS FROM META-ANALYSES

D.2.1 Review question 1: Which pharmacological blood glucose lowering therapies should be used to control blood glucose levels in people with type 2 diabetes?

For network meta-analyses results, see Appendix J

D.2.2 Review question 2: What are the serious adverse effects of long-term use of pharmacological interventions to control blood glucose in people with type 2 diabetes?

No meta-analyses were undertaken for this question.

D.2.3 Review question 3: What are the optimal target values for HbA1c, fasting blood glucose and post prandial blood glucose in people with type 2 diabetes?

No meta-analyses were undertaken for this question.

# D.2.4 Review question 4: Should intensive or conventional target values be used to control blood glucose levels in people with type 2 diabetes?

	Intensive c	ontrol	Conventional	Conventional control		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Bagg 2001	0	21	0	22		Not estimable	
Cao 2011	4	92	5	87	0.7%	0.76 [0.21, 2.73]	
DIGAMI 2 2005	153	474	89	306	25.7%	1.11 [0.89, 1.38]	+
Fantin 2011	0	35	1	35	0.1%	0.33 [0.01, 7.91]	
IDA 2009	0	51	0	51		Not estimable	
Jaber 1996	0	23	0	22		Not estimable	
Kumamoto 2000	3	55	6	55	0.7%	0.50 [0.13, 1.90]	
Melidonis 2000	1	24	1	24	0.2%	1.00 [0.07, 15.08]	
Natarajan 2012	0	36	1	42	0.1%	0.39 [0.02, 9.23]	
REMBO 2008	4	41	4	40	0.7%	0.98 [0.26, 3.64]	
Service 1983	0	10	0	10		Not estimable	
Stefanidis 2003	1	36	1	39	0.2%	1.08 [0.07, 16.69]	
UGDP 1975	52	204	52	210	11.1%	1.03 [0.74, 1.44]	+
UKPDS 1998	539	3071	213	1138	59.6%	0.94 [0.81, 1.08]	•
VA CSDM 1995	5	75	5	78	0.9%	1.04 [0.31, 3.45]	
Zhang 2011	0	48	3	49	0.1%	0.15 [0.01, 2.75]	
Total (95% CI)		4296		2208	100.0%	0.98 [0.88, 1.09]	
Total events	762		381				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup> =	5.27, df=	= 11 (P = 0.92);	I²=0%			
Test for overall effect:	Z = 0.36 (P =	0.72)	. //				U.U1 U.1 1 1U 1UU Equation internatival Equation control
		· ·					Favours intensive Favours control

# Figure 1: Forest plot for all-cause mortality

	Intensive control		Conventional control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Fantin 2011	0	35	0	35		Not estimable	
Kumamoto 2000	0	55	0	55		Not estimable	
Melidonis 2000	0	24	0	24		Not estimable	
Stefanidis 2003	0	36	0	39		Not estimable	
UGDP 1975	3	204	1	210	5.8%	3.09 [0.32, 29.45]	
UKPDS 1998	33	3071	18	1138	91.2%	0.68 [0.38, 1.20]	
VA CSDM 1995	0	75	1	78	2.9%	0.35 [0.01, 8.37]	
Total (95% Cl)		3500		1579	100.0%	0.73 [0.42, 1.25]	•
Total events	36		20				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup> =						
Test for overall effect:	Z=1.14 (P=	Favours intensive Favours control					

# Figure 2: Forest plot for amputation

Church and Carlo and an	Intensive c	ontrol	Conventional c	ontrol	187-1-1-1-4	Risk Ratio	Risk Ratio
Study of Subgroup	Events	Total	Events	Total	weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Bagg 2001	0	21	0	22		Not estimable	
DIGAMI 2 2005	9	474	9	306	9.5%	0.65 [0.26, 1.61]	
Fantin 2011	0	35	0	35		Not estimable	
Melidonis 2000	4	24	5	24	5.6%	0.80 [0.24, 2.62]	
REMBO 2008	14	41	19	41	27.2%	0.74 [0.43, 1.26]	
Stefanidis 2003	1	36	2	39	1.4%	0.54 [0.05, 5.72]	
UKPDS 1998	91	3071	36	1138	54.6%	0.94 [0.64, 1.37]	<b>+</b>
VA CSDM 1995	1	75	4	78	1.7%	0.26 [0.03, 2.27]	
Total (95% CI)		3777		1683	100.0%	0.82 [0.62, 1.08]	•
Total events	120		75				
Heterogeneity: Tau <sup>2</sup> =	: 0.00; Chi <sup>2</sup> =	2.08, df=	= 5 (P = 0.84); I <sup>2</sup> =	= 0%			
Test for overall effect:	Z=1.42 (P=	0.15)					Favours intensive Favours control

# Figure 3: Forest plot for coronary heart failure

	Intensive co	ntrol	Conventional co	ontrol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Fantin 2011	2	35	1	35	18.6%	2.00 [0.19, 21.06]	
Kumamoto 2000	1	55	0	55	10.2%	3.00 [0.12, 72.08]	
Stefanidis 2003	2	36	1	39	18.5%	2.17 [0.21, 22.89]	
VA CSDM 1995	3	75	5	78	52.8%	0.62 [0.15, 2.52]	
Total (95% Cl)		201		207	100.0%	1.14 [0.42, 3.15]	-
Total events	8		7				
Heterogeneity: Tau² =	= 0.00; Chi <sup>2</sup> = 1	.58, df=	= 3 (P = 0.66); I <sup>2</sup> =	0%			
Test for overall effect:	Z = 0.26 (P = 1	0.79)					Favours intensive Favours control

# Figure 4: Forest plot for cardiovascular revascularisation

	Intensive c	ontrol	Conventional o	control		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Bagg 2001	0	21	0	22		Not estimable	
Cao 2011	2	92	2	87	0.7%	0.95 [0.14, 6.57]	
DIGAMI 2 2005	104	474	59	306	32.0%	1.14 [0.86, 1.51]	+
IDA 2009	0	51	0	51		Not estimable	
Jaber 1996	0	23	0	22		Not estimable	
Kumamoto 2000	1	55	1	55	0.3%	1.00 [0.06, 15.59]	
Melidonis 2000	1	24	1	24	0.4%	1.00 [0.07, 15.08]	
REMBO 2008	1	41	2	40	0.5%	0.49 [0.05, 5.17]	
Service 1983	0	10	0	10		Not estimable	
Stefanidis 2003	1	36	1	39	0.3%	1.08 [0.07, 16.69]	
UGDP 1975	31	204	32	210	12.6%	1.00 [0.63, 1.57]	+
UKPDS 1998	301	3071	91	1138	51.8%	1.23 [0.98, 1.53]	<b>—</b>
VA CSDM 1995	3	75	3	78	1.1%	1.04 [0.22, 4.99]	
Zhang 2011	0	48	3	49	0.3%	0.15 [0.01, 2.75]	
Total (95% CI)		4225		2131	100.0%	1.15 [0.98, 1.35]	•
Total events	445		195				
Heterogeneity: Tau² =							
Test for overall effect:	: Z=1.67 (P=	0.09)					Favours intensive Favours control

# Figure 5: Forest plot for cardiovascular mortality

	Intensive c	ontrol	Conventional	control		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Fantin 2011	0	35	0	35		Not estimable	
Kumamoto 2000	0	55	0	55		Not estimable	
UGDP 1975	0	204	0	210		Not estimable	
UKPDS 1998	28	3071	11	1138	100.0%	0.94 [0.47, 1.89]	
Total (95% CI)		3365		1438	100.0%	0.94 [0.47, 1.89]	+
Total events	28		11				
Heterogeneity: Not ap	oplicable						
Test for overall effect: Z = 0.16 (P = 0.87)							Favours intensive Favours control

# Figure 6: Forest plot for end stage renal disease

	Intensive c	ontrol	Conventiona	l control		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.16.1 Mild hypoglyca	aemia						
Bagg 2001	15	21	5	22	3.6%	3.14 [1.39, 7.11]	<b></b>
Blonde 2009	59	121	40	122	14.9%	1.49 [1.09, 2.03]	-
DIGAMI 2 2005	16	474	10	306	3.9%	1.03 [0.47, 2.25]	_ <b>_</b>
Fantin 2011	17	35	0	35	0.3%	35.00 [2.19, 560.18]	
Kumamoto 2000	6	55	4	55	1.8%	1.50 [0.45, 5.02]	
Melidonis 2000	11	24	3	24	1.9%	3.67 [1.17, 11.52]	
Natarajan 2012	0	36	0	42		Not estimable	
Stefanidis 2003	7	36	2	39	1.2%	3.79 [0.84, 17.07]	+
UGDP 1975	82	204	32	210	12.7%	2.64 [1.84, 3.78]	-
UKPDS 1998	478	3071	106	1138	21.8%	1.67 [1.37, 2.04]	+
VA CSDM 1995	69	75	44	78	21.3%	1.63 [1.33, 2.00]	-
Zhang 2011	31	48	17	49	9.8%	1.86 [1.20, 2.88]	
Subtotal (95% CI)		4200		2120	93.2%	1.85 [1.53, 2.25]	♦
Total events	791		263				
Heterogeneity: Tau <sup>2</sup> =	: 0.04; Chi <sup>2</sup> = 1	18.21, df:	= 10 (P = 0.05	); I² = 45%			
Test for overall effect:	Z = 6.23 (P <	0.00001)	)				
1.16.2 Severe hypogi	lycaemia						
Bagg 2001	0	21	0	22		Not estimable	
Blonde 2009	1	121	0	122	0.3%	3.02 [0.12, 73.52]	
Cao 2011	6	92	1	87	0.6%	5.67 [0.70, 46.18]	
Fantin 2011	1	35	0	35	0.3%	3.00 [0.13, 71.22]	
IDA 2009	0	51	0	51		Not estimable	
Jaber 1996	0	23	0	22		Not estimable	
Kumamoto 2000 (1)	0	55	0	55		Not estimable	
Melidonis 2000	3	24	0	24	0.3%	7.00 [0.38, 128.61]	
Natarajan 2012	0	36	0	42		Not estimable	
Stefanidis 2003	0	36	0	39		Not estimable	
UKPDS 1998	33	3071	8	1138	4.0%	1.53 [0.71, 3.30]	- <b>+</b>
VA CSDM 1995	5	75	2	78	1.0%	2.60 [0.52, 12.99]	
Zhang 2011	4	48	0	49	0.3%	9.18 [0.51, 166.08]	
Subtotal (95% CI)		3688		1764	6.8%	2.23 [1.22, 4.08]	◆
Total events	53		11				
Heterogeneity: Tau² =	: 0.00; Chi <sup>z</sup> = 3	3.36, df =	6 (P = 0.76); f	²=0%			
Test for overall effect:	Z = 2.60 (P =	0.009)					
Total (95% Cl)		7888		3884	100.0%	1.86 [1.57, 2.19]	•
Total events	844		274				
Heterogeneity: Tau <sup>2</sup> =	: 0.02; Chi <sup>2</sup> = 2	22.31, df:	= 17 (P = 0.17	); <b>I</b> ² = 24%			
Test for overall effect:	Z=7.35 (P <	0.00001)	)				U.UZ U.1 1 10 50
Test for subgroup diff	, ferences: Chi <b>r</b>	<sup>e</sup> = 0.32, d	if = 1 (P = 0.57	′), I² = 0%			ravours intensive ravours control

(1) Number reported after 8 years of follow-up

Figure 7: Forest plot for hypoglycaemia

	Intensive c	ontrol	Conventional o	control		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Bagg 2001	3	21	0	22	0.9%	7.32 [0.40, 133.66]	
Becker 2003	5	106	6	108	5.3%	0.85 [0.27, 2.70]	
DIGAMI 2 2005	183	474	108	306	33.9%	1.09 [0.91, 1.32]	•
Fantin 2011	5	35	3	35	4.0%	1.67 [0.43, 6.45]	<b>-</b>
Kumamoto 2000	5	55	10	55	6.7%	0.50 [0.18, 1.37]	
UKPDS 1998	169	2729	87	1138	30.6%	0.81 [0.63, 1.04]	
VA CSDM 1995	21	75	13	78	14.0%	1.68 [0.91, 3.11]	<b>+-</b> -
Zhang 2011	3	48	8	49	4.5%	0.38 [0.11, 1.36]	
Total (95% CI)		3543		1791	100.0%	0.98 [0.74, 1.30]	•
Total events	394		235				
Heterogeneity: Tau <sup>2</sup> =	= 0.05; Chi <sup>2</sup> =	12.86, dt	f = 7 (P = 0.08); f	²= 46%			
Test for overall effect	: Z = 0.14 (P =		Favours intensive Favours control				

# Figure 8: Forest plot for macrovascular complications

	Intensive c	Conventional	control		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Fantin 2011	0	35	0	35		Not estimable	
UKPDS 1998	249	3071	121	1138	96.7%	0.76 [0.62, 0.94]	
Zhang 2011	4	48	9	49	3.3%	0.45 [0.15, 1.37]	
Total (95% CI)		3154		1222	100.0%	0.75 [0.61, 0.92]	•
Total events	253		130				
Heterogeneity: Tau² =							
Test for overall effect:	Favours intensive Favours control						

# Figure 9: Forest plot for microvascular complications

	Intensive c	ontrol	Conventional o	ontrol		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl		
Bagg 2001	4	21	1	22	7.8%	4.19 [0.51, 34.50]			
Fantin 2011	0	35	0	35		Not estimable			
Kumamoto 2000	9	55	24	55	21.8%	0.38 [0.19, 0.73]			
UGDP 1975	11	204	4	210	15.9%	2.83 [0.92, 8.75]			
UKPDS 1998	11	2729	11	1138	19.7%	0.42 [0.18, 0.96]			
VA CSDM 1995	3	75	10	78	14.6%	0.31 [0.09, 1.09]			
Zhang 2011	7	48	16	49	20.2%	0.45 [0.20, 0.99]			
Total (95% CI)		3167		1587	100.0%	0.64 [0.32, 1.29]	•		
Total events	45		66						
Heterogeneity: Tau <sup>2</sup> =	= 0.46; Chi <sup>2</sup> =	14.59, di	f = 5 (P = 0.01); P	²= 66%					
Test for overall effect		Eavours intensive Eavours control							
		Favours intensive Favours control							

# Figure 10: Forest plot for nephropathy

	Intensive c	nsive control Conventional control				Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl		
Bagg 2001	0	21	0	22		Not estimable			
DIGAMI 2 2005	84	474	46	306	26.6%	1.18 [0.85, 1.64]			
Fantin 2011	0	35	0	35		Not estimable			
Kumamoto 2000	0	55	0	55		Not estimable			
Melidonis 2000	3	24	4	24	1.5%	0.75 [0.19, 3.00]			
Stefanidis 2003	1	36	1	39	0.4%	1.08 [0.07, 16.69]			
UGDP 1975	29	204	30	210	12.9%	1.00 [0.62, 1.60]	-+		
UKPDS 1998	221	3071	101	1138	56.8%	0.81 [0.65, 1.02]			
VA CSDM 1995	4	75	5	78	1.8%	0.83 [0.23, 2.98]			
Total (95% CI)		3995		1907	100.0%	0.92 [0.78, 1.09]	•		
Total events	342		187						
Heterogeneity: Tau <sup>2</sup> =									
Test for overall effect:	Favours intensive Favours control								

# Figure 11: Forest plot for non-fatal myocardial infarction

	Intensive control Conventional control					Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events Total		Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl		
Bagg 2001	1	21	0	22	0.8%	3.14 [0.13, 72.96]			
DIGAMI 2 2005	32	474	16	306	24.0%	1.29 [0.72, 2.31]			
Fantin 2011	0	35	0	35		Not estimable			
Kumamoto 2000	1	55	0	55	0.8%	3.00 [0.12, 72.08]			
Melidonis 2000	0	24	0	24		Not estimable			
Stefanidis 2003	0	36	0	39		Not estimable			
UKPDS 1998	120	3071	44	1138	71.2%	1.01 [0.72, 1.42]	<b>—</b>		
VA CSDM 1995	2	75	5	78	3.2%	0.42 [0.08, 2.08]			
Total (95% Cl)		3791		1697	100.0%	1.06 [0.80, 1.41]			
Total events	156		65						
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup> = 3								
Test for overall effect:	Z=0.41 (P=	Favours intensive Favours control							

# Figure 12: Forest plot for non-fatal stroke

	Intensive co	ontrol	Conventional o	:ontrol		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Rand	om, 95% Cl	
Fantin 2011	0	35	0	35		Not estimable			
Kumamoto 2000	0	55	0	55		Not estimable			
Melidonis 2000	0	24	0	24		Not estimable			
Stefanidis 2003	0	36	0	39		Not estimable			
VA CSDM 1995	0	75	0	78		Not estimable			
Total (95% CI)		225		231		Not estimable			
Total events	0		0						
Heterogeneity: Not applicable									100
Test for overall effect: Not applicable							Favours intensive	Favours co	ntrol

# Figure 13: Forest plot for peripheral vascularisation

	Intensive c	ontrol	Conventional of	control		Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl			
Fantin 2011	0	35	0	35		Not estimable				
Kumamoto 2000	3	55	12	55	21.0%	0.25 [0.07, 0.84]				
UGDP 1975	2	204	2	210	9.8%	1.03 [0.15, 7.24]				
UKPDS 1998	229	3071	117	1138	69.2%	0.73 [0.59, 0.90]	•			
Total (95% CI)		3365		1438	100.0%	0.60 [0.31, 1.15]	•			
Total events	234		131							
Heterogeneity: Tau² =	= 0.15; Chi <sup>2</sup> =									
Test for overall effect	: Z = 1.53 (P =	Favours intensive Favours control								

# Figure 14: Forest plot for retinal photocoagulation

	Intensive c	ontrol	Conventional c	ontrol		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Events Total		Events Total		M-H, Random, 95% Cl	M-H, Random, 95% Cl		
Fantin 2011	0	35	0	35		Not estimable			
Kumamoto 2000	13	55	34	55	19.9%	0.38 [0.23, 0.64]			
UGDP 1975	44	204	45	210	25.8%	1.01 [0.70, 1.45]	+		
UKPDS 1998	363	2729	172	1138	34.0%	0.88 [0.74, 1.04]	•		
VA CSDM 1995	21	75	22	78	20.3%	0.99 [0.60, 1.65]	+		
Total (95% CI)		3098		1516	100.0%	0.79 [0.56, 1.11]	•		
Total events	441		273						
Heterogeneity: Tau² =	= 0.08; Chi <sup>2</sup> =	10.46, dt	<sup>r</sup> = 3 (P = 0.02); P	²= 71%				1	
Test for overall effect:	: Z = 1.35 (P =	0.18)					Favours intensive Favours control	U	

# Figure 15: Forest plot for retinopathy

# D.2.5 Review question 5: Should self-monitoring be used to manage blood glucose levels in people with type 2 diabetes?

# D.2.5.1 SMBG vs no SMBG

	SMBG No SMBG						Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
1.1.1 Diet alone									
O'Kane 2008 Subtotal (95% CI)	-1.88	2.06	96 <b>96</b>	-1.68	2.11	88 <b>88</b>	2.2% <b>2.2</b> %	-0.20 [-0.80, 0.40] - <b>0.20 [-0.80, 0.40]</b>	-
Heterogeneity: Not a	oplicable	1							
Test for overall effect	Z= 0.65	5 (P = 0	).52)						
1.1.2 Diet and/or ora	l antidial	oetic n	nedicin	es					
Allen 1990	-2	3.4	27	-2	2.4	27	0.3%	0.00 F-1.57, 1.571	
Barnett 2008	-1.15	1.14	311	-0.91	1.29	299	13.4%	-0.24 [-0.43, -0.05]	
Bosi 2013	-0.39	1.12	501	-0.27	1.14	523	18.8%	-0.12 I-0.26, 0.021	-=-
Davidson 2005	-0.8	1.6	43	-0.6	2.1	45	1.3%	-0.20 [-0.98, 0.58]	
DiGEM trial	-0.15	0.78	301	0	1.02	152	14.1%	-0.15 [-0.33, 0.03]	
Fontbonne 1989	-0.36	3.14	68	-0.3097	1.8796	140	1.2%	-0.05 [-0.86, 0.76]	
Franciosi 2011	-1.2	0.81	46	-0.7	0.7	16	4.2%	-0.50 [-0.92, -0.08]	<b>_</b>
Guerci 2003	-0.88	1.54	345	-0.6	1.54	344	10.7%	-0.28 [-0.51, -0.05]	
Kleefstra 2010	-0.18	0.67	22	0.07	0.75	18	3.8%	-0.25 [-0.70, 0.20]	<del></del>
Lu 2011	-1.5	1.9	34	-1.462	2.173	70	1.2%	-0.04 [-0.85, 0.78]	
Muchmore 1994	-1.54	1.46	12	-0.85	1.87	11	0.4%	-0.69 [-2.07, 0.69]	←
SMBG study group	-1	1.08	113	-0.54	1.41	110	6.2%	-0.46 [-0.79, -0.13]	
Wing 1986	10.19	2.29	21	10.44	2.16	22	0.5%	-0.25 [-1.58, 1.08]	
Subtotal (95% CI)			1844			1777	76.3%	-0.21 [-0.29, -0.13]	•
Heterogeneity: Tau <sup>2</sup> =	= 0.00; C	hi <b>²</b> = 7	.44, df=	= 12 (P = 1	0.83); <b>I<sup>z</sup> =</b>	0%			
Test for overall effect	Z = 5.02	? (P < (	0.00001	)					
1.1.3 Diet, oral antidi	abetic a	nd/or i	nsulin I	medicine	s				
Ismail 2013	-0.9	2.1	56	0.4	1.3	43	1.8%	-1.30 [-1.97, -0.63]	
Lim 2011	-0.3	0.75	102	-0.1	0.69	51	10.2%	-0.20 [-0.44, 0.04]	
Nauck 2014	-0.3	1.11	119	-0.3	0.856	125	9.6%	0.00 [-0.25, 0.25]	-+-
Subtotal (95% CI)			277			219	21.5%	-0.38 [-0.86, 0.10]	
Heterogeneity: Tau <sup>2</sup> =	= 0.14; C	hi² = 1	2.65, df	'= 2 (P = )	0.002); I <sup>z</sup>	= 84%			
Test for overall effect	Z=1.55	5 (P = 0	0.12)						
Total (95% CI)			2217			2084	100.0%	-0.22 [-0.31, -0.13]	•
Heterogeneity: Tau <sup>2</sup> =	= 0.01; C	hi <b>=</b> 2	0.18, df	= 16 (P =	0.21); I <sup>2</sup>	= 21%			
Test for overall effect	Z= 4.72	? (P < (	).00001	)					-Z -1 U 1 Z
Test for subgroup dif	ferences	: Chi²	= 0.48,	df = 2 (P =	= 0.79), l <sup>a</sup>	= 0%			ravours SNIBO ravours no SNIBO

# Figure 16: Forest plot for HbA1c (subgroup for current therapies)

	SMBG No SMBG						Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl	
1.3.1 Standard SMBC	3									
Allen 1990	-2	3.4	27	-2	2.4	27	0.3%	0.00 [-1.57, 1.57]		
Barnett 2008	-1.15	1.14	311	-0.91	1.29	299	13.7%	-0.24 [-0.43, -0.05]		
Bosi 2013	-0.39	1.12	501	-0.27	1.14	523	20.2%	-0.12 [-0.26, 0.02]		
Davidson 2005	-0.8	1.6	43	-0.6	2.1	45	1.2%	-0.20 [-0.98, 0.58]		
DiGEM trial	-0.14	0.82	150	0	1.02	76	8.7%	-0.14 [-0.40, 0.12]	-+-	
Fontbonne 1989	-0.36	3.14	68	-0.3097	1.8796	140	1.1%	-0.05 [-0.86, 0.76]		
Guerci 2003	-0.88	1.54	345	-0.6	1.54	344	10.7%	-0.28 [-0.51, -0.05]		
Ismail 2013	-0.9	2.1	56	0.4	1.3	43	1.6%	-1.30 [-1.97, -0.63]		
Kleefstra 2010	-0.18	0.67	22	0.07	0.75	18	3.5%	-0.25 [-0.70, 0.20]	<b>-</b> _ <del>_</del> _	
Lim 2011	7.7	1	51	7.8	1	25	3.1%	-0.10 [-0.58, 0.38]		
Lu 2011	-1.5	1.9	34	-1.462	2.173	70	1.1%	-0.04 [-0.85, 0.78]		
Muchmore 1994	-1.54	1.46	12	-0.85	1.87	11	0.4%	-0.69 [-2.07, 0.69]	←	
Nauck 2014	-0.3	1.11	119	-0.3	0.856	125	9.5%	0.00 [-0.25, 0.25]	-+-	
O'Kane 2008	-1.88	2.06	96	-1.68	2.11	88	2.0%	-0.20 [-0.80, 0.40]		
SMBG study group	-1	1.08	113	-0.54	1.41	110	6.0%	-0.46 [-0.79, -0.13]		
Wing 1986	10.19	2.29	21	10.44	2.16	22	0.4%	-0.25 [-1.58, 1.08]		
Subtotal (95% CI)			1969			1966	83.7%	-0.21 [-0.31, -0.11]	•	
Heterogeneity: Tau² =	= 0.01; C	hi² = 1	8.22, dt	í= 15 (P =	0.25); I <sup>z</sup>	= 18%				
Test for overall effect:	Z=4.07	? (P < (	0.0001)							
1.3.2 Enhanced SMB	G									
DiGEM trial	-017	073	151	n	1.02	76	9.1%	-0176043009		
Franciosi 2011	-1.2	0.10	46	-07	0.7	16	4.0%	-0.50 (-0.92 -0.08)		
Lim 2011	74	1	51	7.8	1	26	3.7%	-0.40[-0.87_0.07]	<b>_</b>	
Subtotal (95% CI)	1.4		248	1.0		118	16.3%	-0.29 [-0.49, -0.09]	•	
Heterogeneity: Tau <sup>2</sup> =	: 0.00: C	hi <b>²</b> = 2	.03. df=	= 2 (P = 0.	36): <b> ²</b> = 1	1%			-	
Test for overall effect: $Z = 2.81$ (P = 0.005)										
Total (95% Cl)			2217			2084	100.0%	-0.22 [-0.31, -0.13]	•	
Heterogeneity: Tau <sup>2</sup> =	= 0.00; C	hi <b>²</b> = 2	0.99. dt	(= 18 (P =	0.28); <b> </b> ²	= 14%				
Test for overall effect:	Z = 4,91		0.00001	)					-2 -1 0 1 2	
Test for subgroup dif	ferences	: Chi²	= 0.49,	, df = 1 (P =	= 0.49), l <sup>a</sup>	²= 0%			Favours SMBG Favours no SMBG	

# Figure 17:Forest plot for HbA1c (subgroup for SMBG type)

	5	SMBG no SMBG						Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl	
1.2.1 Less than once	e a day									
DIGEM trial	-0.15	0.78	301	0	1.02	152	14.1%	-0.15 [-0.33, 0.03]		
Franciosi 2011	-1.2	0.81	46	-0.7	0.7	16	4.2%	-0.50 [-0.92, -0.08]	<b>_</b> _	
Guerci 2003	-0.88	1.54	345	-0.6	1.54	344	10.7%	-0.28 [-0.51, -0.05]		
Ismail 2013	-0.9	2.1	56	0.4	1.3	43	1.8%	-1.30 [-1.97, -0.63]		
Nauck 2014	-0.3	1.11	119	-0.3	0.856	125	9.6%	0.00 [-0.25, 0.25]	-+-	
Wing 1986	10.19	2.29	21	10.44	2.16	22	0.5%	-0.25 [-1.58, 1.08]		
Subtotal (95% CI)			888			702	40.9%	-0.31 [-0.55, -0.07]	•	
Heterogeneity: Tau <sup>2</sup> = 0.05; Chi <sup>2</sup> = 15.42, df = 5 (P = 0.009); l <sup>2</sup> = 68%										
Test for overall effect: Z = 2.49 (P = 0.01)										
1.2.2 1 to 2 times a d	lav									
Allen 1990	-2	3.4	27	-2	24	27	0.3%	0.00 [-1.57, 1.57]		
Barnett 2008	-1.15	1.14	311	-0.91	1.29	299	13.4%	-0.24 [-0.43, -0.05]		
Bosi 2013	-0.39	1.12	501	-0.27	114	523	18.8%	-0.12[-0.26_0.02]		
Fontbonne 1989	-0.36	3.14	68	-0.3097	1.8796	140	1.2%	-0.05 [-0.86, 0.76]		
Kleefstra 2010	-0.18	0.67	22	0.07	0.75	18	3.8%	-0.25 [-0.70, 0.20]		
Lim 2011	-0.3	0.75	102	-0.1	0.69	51	10.2%	-0.20 [-0.44, 0.04]		
O'Kane 2008	-1.88	2.06	96	-1.68	2.11	88	2.2%	-0.20 [-0.80, 0.40]		
SMBG study group	-1	1.08	113	-0.54	1.41	110	6.2%	-0.46 [-0.79, -0.13]		
Subtotal (95% CI)			1240			1256	56.1%	-0.19 [-0.29, -0.10]	◆	
Heterogeneity: Tau <sup>2</sup> =	= 0.00; C	hi² = 4	.05, df=	= 7 (P = 0.	77); I <sup>z</sup> = 0	0%				
Test for overall effect:	Z= 4.07	7 (P < (	0.0001)							
1.2.3 More than twic	veheo									
Davideon 2005	.00	16	40	-06	2.1	45	1 204	0.201.000.0501		
Daviuson 2005	-0.0	1.0	24	-0.0	2.1	40	1.3%	-0.20 [-0.36, 0.36]		
Muchmore 1994	-1.54	1.0	12	-0.95	1.97	11	0.4%	-0.04 [-0.03, 0.70]	←─────	
Subtotal (95% CI)	-1.54	1.40	89	-0.05	1.07	126	3.0%	-0.20 [-0.73, 0.32]	-	
Heterogeneity: Tau <sup>2</sup> =	= 0.00; C	hi² = 0	.64. df=	= 2 (P = 0.	73); l² = (	0%				
Test for overall effect:	Z=0.77	7 (P = (	0.44)							
Total (95% CI)			2217			2084	100.0%	-0.22 [-0.31, -0.13]	•	
Heterogeneity: Tau <sup>2</sup> =	= 0.01: C	hi <b>²</b> = 2	0.18. di	í = 16 (P =	0.21): F	= 21%				
Test for overall effect:	Z = 4.70	 2.(P<1	0.000001	)		2.0			-2 -1 0 1 2	
Test for subgroup dif	ferences	: Chi²	= 0.78,	, df=2 (P=	= 0.68), l <sup>2</sup>	'= 0%			Favours SMBG Favours no SMBG	

# Figure 18: Forest plot for HbA1c (subgroup for SMBG frequency)

		SMBG	No	SMBG			Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl		
1.3.1 Diet and/or oral	l antidial	betic medicine	es								
Allen 1990	-1.4	3.2	27	-1.5	2.8	27	3.7%	0.10 [-1.50, 1.70]	_ <b>+</b> _		
Barnett 2008	-1.26	2.49	311	-0.97	2.54	299	59.9%	-0.29 [-0.69, 0.11]	•		
Guerci 2003	6.66	4.83	345	6.91	4.56	344	19.4%	-0.25 [-0.95, 0.45]	-		
Lu 2011	-2.14	3.75447999	34	-1.63	3.443	70	4.3%	-0.51 [-2.01, 0.99]			
Wing 1986	12	3.26	22	11.67	4.06	_22	2.0%	0.33 [-1.85, 2.51]			
Subtotal (95% CI)			739			762	89.3%	-0.26 [-0.59, 0.07]	•		
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.61, df = 4 (P = 0.96); l <sup>2</sup> = 0%											
Test for overall effect: Z = 1.57 (P = 0.12)											
1.3.3 Diet, oral antidi	abetic a	nd/or insulin r	nedicir	ies							
Lim 2011	7.143	1.265	96	8.47	3.22	48	10.7%	-1.33 [-2.27, -0.38]	-		
Subtotal (95% CI)			96			48	10.7%	-1.33 [-2.27, -0.38]	•		
Heterogeneity: Not ap	oplicable	1									
Test for overall effect: Z = 2.75 (P = 0.006)											
Total (95% CI)			835			810	100.0%	-0.38 [-0.68, -0.07]	•		
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 4.96, df = 5 (P = 0.42); l <sup>2</sup> = 0%											
Test for overall effect:		-10 -5 0 5 10 Eavours SMPG Eavours no SMPG									
Test for subgroup differences: Chi <sup>2</sup> = 4,36, df = 1 (P = 0.04), I <sup>2</sup> = 77.0%											

# Figure 19: Forest plot for fasting blood glucose (subgroup for current therapies)

		SMBG No SMBG						Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl		
1.6.1 Standard SMBC	ì										
Allen 1990	-1.4	3.2	27	-1.5	2.8	27	3.7%	0.10 [-1.50, 1.70]	_ <b>_</b>		
Barnett 2008	-1.26	2.49	311	-0.97	2.54	299	59.9%	-0.29 [-0.69, 0.11]	•		
Guerci 2003	6.66	4.83	345	6.91	4.56	344	19.4%	-0.25 [-0.95, 0.45]	+		
Lim 2011	7.337	0.866	47	8.47	3.22	24	5.6%	-1.13 [-2.44, 0.18]			
Lu 2011	-2.14	3.75447999	34	-1.63	3.443	70	4.3%	-0.51 [-2.01, 0.99]			
Wing 1986	12	3.26	22	11.67	4.06	22	2.0%	0.33 [-1.85, 2.51]			
Subtotal (95% CI)			786			786	94.9%	-0.31 [-0.63, 0.00]	•		
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.20, df = 5 (P = 0.82); l <sup>2</sup> = 0% Test for overall effect: Z = 1.93 (P = 0.05)											
1.6.3 Enhanced SMB	G										
Lim 2011	6.899	1.648	49	8.47	3.22	24	5.1%	-1.57 [-2.94, -0.20]			
Subtotal (95% CI)			49			24	5.1%	-1.57 [-2.94, -0.20]	•		
Heterogeneity: Not ap	plicable										
Test for overall effect: Z = 2.25 (P = 0.02)											
Total (95% Cl)			835			810	100.0%	-0.38 [-0.69, -0.07]	•		
Heterogeneity: Tau <sup>2</sup> =											
Test for overall effect:	Z = 2.39	) (P = 0.02)							Favoure SMBG Favoure no SMBG		
Test for subgroup diff											

# Figure 20: Forest plot for fasting blood glucose (subgroup for SMBG types)

		SMBG		No	SMBG			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
1.4.1 Less than once	a day								
Guerci 2003	6.66	4.83	345	6.91	4.56	344	19.4%	-0.25 [-0.95, 0.45]	-
Wing 1986	12	3.26	22	11.67	4.06	22	2.0%	0.33 [-1.85, 2.51]	_ <u>_</u>
Subtotal (95% CI)			367			366	21.4%	-0.20 [-0.86, 0.47]	•
Heterogeneity: Tau <sup>2</sup> =	0.00; Cł	ni² = 0.25, df =	1 (P =	0.62); I <sup>z</sup>	= 0%				
Test for overall effect:	Z = 0.57	(P = 0.57)							
1.4.2 1 to 2 times a d	ay								
Allen 1990	-1.4	3.2	27	-1.5	2.8	27	3.7%	0.10 [-1.50, 1.70]	<u> </u>
Barnett 2008	-1.26	2.49	311	-0.97	2.54	299	59.9%	-0.29 [-0.69, 0.11]	•
Lim 2011	7.143	1.265	96	8.47	3.22	48	10.7%	-1.33 [-2.27, -0.38]	
Subtotal (95% CI)			434			374	74.3%	-0.55 [-1.30, 0.20]	•
Heterogeneity: Tau <sup>2</sup> =	0.24; Cł	ni² = 4.35, df =	2 (P =	0.11); P	= 54%				
Test for overall effect:	Z=1.43	(P = 0.15)							
1.4.3 More than twic	e a day								
Lu 2011	-2.14	3.75447999	34	-1.63	3.443	70	4.3%	-0.51 [-2.01, 0.99]	
Subtotal (95% CI)			34			70	4.3%	-0.51 [-2.01, 0.99]	-
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.67	(P = 0.50)							
T-4-1 (05%) ON			005			0.40	400.00	0.001.0.00 0.071	
10tal (95% CI)			835			810	100.0%	-0.38 [-0.68, -0.07]	•
Heterogeneity: Tau <sup>2</sup> =	0.00; Cł	ni² = 4.96, df =	5 (P =	0.42); I <sup>z</sup>	= 0%				-10 -5 0 5 10
Test for overall effect:	Z = 2.38	(P = 0.02)							Favours SMBG Favours no SMBG
Test for subgroup diff	erences:	: Chi <sup>z</sup> = 0.52, (	#f = 2 (F	P = 0.77	), I <b>z</b> = 09	Ж			

# Figure 21: Forest plot for fasting blood glucose (subgroup for SMBG frequency)



#### Figure 22: Forest plot for postprandial blood glucose

	SMBG no SMBG		BG		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.6.1 Diet alone							
O'Kane 2008	18	96	13	88	15.9%	1.27 [0.66, 2.44]	
Subtotal (95% CI)		96		88	15.9%	1.27 [0.66, 2.44]	<b>•</b>
Total events	18		13				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.72 (	(P = 0.4)	17)				
		4.					
1.6.2 Diet and/or oral	antidiape	anc me	alcines				
Barnett 2008	27	311	21	299	19.9%	1.24 [0.71, 2.14]	- <b>1</b>
DiGEM trial	76	301	14	152	20.5%	2.74 [1.60, 4.68]	
Guerci 2003	53	510	25	478	24.4%	1.99 [1.26, 3.14]	
Lu 2011 Cubtotol (05%, CD	1	34	4	69	2.0%	0.51 [0.06, 4.37]	
Subtotal (95% CI)		1120	~ ~ ~	998	00.8%	1.80 [1.10, 2.79]	-
lotal events	157		64 5 - 16 - 27		0.17 47		
Heterogeneity: Tau-=	0.09; Ch	r = 5.6	5,01=3( 	P = 0.1	3); 1*= 47	%	
l est for overall effect:	Z = 2.64 i	(P = 0.0	108)				
1.6.3 Diet, oral antidia	abetic an	d/or ins	sulin med	licines			
Lim 2011	28	102	11	52	17.3%	1.30 [0.70, 2.39]	
Subtotal (95% CI)		102		52	17.3%	1.30 [0.70, 2.39]	+
Total events	28		11				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.83 (	(P = 0.4)	10)				
Total (95% CI)		1354		1138	100.0%	1.62 [1.19, 2.22]	◆
Total events	203		88				
Heterogeneity: Tau <sup>2</sup> =	0.05; Ch	i <sup>2</sup> = 7.5	7, df = 5 (	P = 0.1	8); I <sup>2</sup> = 34	%	
Test for overall effect:	Z = 3.03 (	(P = 0.0	)02)				0.01 0.1 1 10 100 Eavoure SMPG Eavoure to SMPC
Test for subgroup diff	erences:	Chi <sup>z</sup> =	1.14. df=	2 (P =	0.57), I <sup>z</sup> =	0%	

### Figure 23: Forest plot for any hypoglycaemia (subgroup for current therapies)

	SMBG no SMBG		BG		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.7.1 Less than once	a day						
DiGEM trial	76	301	14	152	20.5%	2.74 [1.60, 4.68]	
Guerci 2003	53	510	25	478	24.4%	1.99 [1.26, 3.14]	
Subtotal (95% CI)		811		630	44.8%	2.28 [1.61, 3.23]	●
Total events	129		39				
Heterogeneity: Tau <sup>2</sup> =	0.00; Ch	i <b>z</b> = 0.81	0, df = 1 (	P = 0.3	7); I <sup>z</sup> = 09	6	
Test for overall effect:	Z = 4.63 (	(P < 0.0	10001)				
1.7.2 1 to 2 times a d	ay						
Barnett 2008	27	311	21	299	19.9%	1.24 [0.71, 2.14]	
Lim 2011	28	102	11	52	17.3%	1.30 [0.70, 2.39]	
O'Kane 2008	18	96	13	88	15.9%	1.27 [0.66, 2.44]	
Subtotal (95% CI)		509		439	53.1%	1.26 [0.89, 1.79]	•
Total events	73		45				
Heterogeneity: Tau <sup>2</sup> =	0.00; Ch	i <sup>z</sup> = 0.01	1, df = 2 (	P = 0.9	9); I <sup>z</sup> = 09	6	
Test for overall effect:	Z=1.33)	(P = 0.1	8)				
1.7.3 More than 2 tim	es a dav						
Lu 2011	1	34	4	60	2.0%	0.51.00.06.4.371	
Subtotal (95% CI)		34	4	69	2.0%	0.51 [0.06, 4.37]	
Total events	1		4				
Heterogeneity: Not an	nlicable						
Test for overall effect:	Z = 0.62	P = 0.5	54)				
			.,				
Total (95% CI)		1354		1138	100.0%	1.62 [1.19, 2.22]	◆
Total events	203		88				
Heterogeneity: Tau <sup>2</sup> =	0.05; Ch	i <sup>2</sup> = 7.5	7, df = 5 (	P = 0.1	8); I <b>²</b> = 34	%	
Test for overall effect:	Z = 3.03 (	(P = 0.0	02)				Favours SMBG Favours no SMBG
Test for subgroup diff	erences:	Chi <sup>2</sup> = I	6.69, df=	2 (P =	0.04), I <sup>z</sup> =	: 70.1%	

#### Figure 24: Forest plot for any hypoglycaemia (subgroup for SMBG frequency)



#### Figure 25: Forest plot for severe hypoglycaemia (subgroup for current therapies)

	SMB	G	no SM	BG		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95%	CI	
10.9.1 Less than onc	e a day								
DiGEM trial	0	301	1	152	26.2%	0.17 [0.01, 4.12]			
Subtotal (95% CI)		301		152	26.2%	0.17 [0.01, 4.12]			
Total events	0		1						
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 1.09 (	P = 0.2	28)						
	_								
10.9.2 1 to 2 times a	day								
Bosi 2013	0	501	1	523	26.1%	0.35 [0.01, 8.52]		-	
Lim 2011	1	51	2	52	47.6%	0.51 [0.05, 5.45]			
Subtotal (95% Cl)		552		575	73.8%	0.45 [0.07, 2.99]			
Total events	1		3						
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi	<b>z</b> = 0.0	4, df = 1 (	P = 0.8	5); I <sup>z</sup> = 0%				
Test for overall effect:	Z = 0.83 (	P = 0.4	0)						
Total (95% Cl)		853		727	100.0%	0.35 [0.07, 1.77]			
Total events	1		4						
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi	<b>z</b> = 0.3	0, df = 2 (	P = 0.8	6); I <sup>z</sup> = 0%				
Test for overall effect:	Z=1.27 (	P = 0.2	20)				Eavours SMBG Eavour	s no SMBG	
Test for subgroup diff	erences:	Chi²=I	0.26, df=	1 (P =	0.61), I <b>²</b> =	0%			

#### Figure 26: Forest plot for severe hypoglycaemia (subgroup for SMBG frequency)

	SMB	G	no SM	BG		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Barnett 2008	41	311	45	299	100.0%	0.88 [0.59, 1.30]	
Total (95% CI)		311		299	100.0%	0.88 [0.59, 1.30]	+
Total events	41		45				
Heterogeneity: Not ap Test for overall effect:	plicable Z = 0.66 (	(P = 0.6	51)				0.01 0.1 1 10 100 Favours SMBG Favours no SMBG

#### Figure 27: Forest plot for fasting adverse events

#### D.2.5.2 SMBG plus education vs. conventional SMBG



#### Figure 28: Forest plot for HbA1c



#### Figure 29: Forest plot for any hypoglycaemia

#### D.2.5.3 SMBG plus telecare vs. conventional SMBG

	SM	3G plus teleca	re		SMBG			Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl		
6.1.1 Insulin											
Del Prato 2012	-0.7	0.64342832	115	-0.7	0.67349833	124	24.5%	0.00 [-0.17, 0.17]	+		
Lim 2011	7.4	1	49	7.7	1	47	21.6%	-0.30 [-0.70, 0.10]	-=-		
Tildesley 2010 Subtotal (95% Cl)	7.6	0.74	24 188	8.4	1.4	23 <b>194</b>	17.5% <b>63.6</b> %	-0.80 [-1.44, -0.16] - <b>0.27 [-0.68, 0.13]</b>	_ <b>_</b>		
Heterogeneity: Tau² =	0.09; Ch	i <sup>2</sup> = 6.84, df = 2	(P = 0.0	03); I <b>2</b> = 1	71%						
Test for overall effect:	Z = 1.33	(P = 0.18)									
6.1.2 Current treatme	ent not sj	ecified									
Kwon 2004	-0.65	1.2055704	51	0.43	1.05211691	50	20.9%	-1.08 [-1.52, -0.64]			
Quinn 2011	-1.6	1.5555	21	-0.7	1.4434	51	15.4%	-0.90 [-1.67, -0.13]			
Subtotal (95% CI)			72			101	36.4%	-1.04 [-1.42, -0.65]	•		
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.16, df = 1 (P = 0.69); l <sup>2</sup> = 0% Test for overall effect: Z = 5.30 (P < 0.00001)											
Total (95% CI)			260			295	100.0%	-0.57 [-1.06, -0.08]	•		
Heterogeneity: Tau² =	0.25; Ch	i <sup>2</sup> = 27.49, df =	4 (P < 0	.0001);	I² = 85%						
Test for overall effect:	Z = 2.29	(P = 0.02)						Fov	-4 -Z U Z 4		
Test for subgroup diff	erences:	ray									

#### Figure 30: Forest plot for HbA1c

	SMBG plus telecare			SMBG			Mean Difference		Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl	
Del Prato 2012	6.36	1.727	115	6.36	1.455	124	57.4%	0.00 [-0.41, 0.41]		
Lim 2011	6.899	1.648	49	7.337	0.866	47	42.6%	-0.44 [-0.96, 0.09]	-	
Total (95% CI)			164			171	100.0%	-0.19 [-0.61, 0.24]	•	
Heterogeneity: Tau <sup>2</sup> = 1 Test for overall effect: 2	0.04; Chi Z = 0.86 (	² = 1.68, P = 0.39)	df = 1 (F	9 = 0.20)	Fa	-10 -5 0 5 vours SMBG+telecare Favours SMBG	10			

# Figure 31: Forest plot for fasting blood glucose



#### Figure 32: Forest plot for postprandial blood glucose
	SMBG plus tele	SMB	G		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Lim 2011	16	51	12	51	100.0%	1.33 [0.70, 2.53]	-
Total (95% CI)		51		51	100.0%	1.33 [0.70, 2.53]	•
Total events	16		12				
Heterogeneity: Not ap Test for overall effect:	oplicable : Z = 0.88 (P = 0.3	18)				F	0.01 0.1 1 10 100 avours SMBG+telecare Favours SMBG

### Figure 33: Forest plot for any hypoglycaemia

### D.2.5.4 Automated mobile phone glucometer vs. standard glucometer

	Mobile pho	one glucometer Glucometer						Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% C	I IV, Fixed, 95% Cl
Cho 2009	7.29	1.14	35	7	1.14	34	100.0%	0.29 [-0.25, 0.83]	] -
Total (95% Cl)			35			34	100.0%	0.29 [-0.25, 0.83]	ı , <b>,                                 </b>
Heterogeneity: Not ap Test for overall effect:	plicable Z = 1.06 (P =	0.29)						I	-4 -2 0 2 4 Favours Mobile glucometer Favours Glucometer

### Figure 34: Forest plot for HbA1c

	Mobile pho	ohone glucometer Glucometer				er.		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% C	IV, Fixed, 95% Cl
Cho 2009	7.998	2.64	35	8.324	2.935	34	100.0%	-0.33 [-1.64, 0.99	
Total (95% Cl)	nliachla		35			34	100.0%	-0.33 [-1.64, 0.99	
Test for overall effect:	pricable Z = 0.48 (P =	0.63)							-'10 -'5 Ó 5 10' Favours Mobile glucometer Favours Glucometer

### Figure 35: Forest plot for fasting blood glucose

	Mobile pho	one glucon	Glucometer				Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Cho 2009	211.5	61.5	35	223.07	84.6	34	100.0%	-11.57 [-46.55, 23.41]	
Total (95% Cl)			35			34	100.0%	-11.57 [-46.55, 23.41]	
Test for overall effect:	plicable Z = 0.65 (P =	0.52)						1	-100 -50 Ó 50 100 avours Mobile glucometer Favours Glucometer

## Figure 36: Forest plot for postprandial blood glucose

### D.2.5.5 SMBG plus continuous glucose monitoring vs conventional SMBG

	0	GM:		S	MBG		Mean Difference Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl		IV, Random, 95% Cl	
Ehrhardt 2011	-0.8	1.5	50	-0.2	1.3	50	54.1%	-0.60 [-1.15, -0.05]			
Yoo 2008	8	1.2	29	8.3	1.1	28	45.9%	-0.30 [-0.90, 0.30]			
Total (95% CI)			79			78	100.0%	-0.46 [-0.87, -0.06]		-	
Heterogeneity: Tau <sup>2</sup> =	0.00; C	F									
Test for overall effect:	Z = 2.24	(P =	0.03)						-2		
										Favours CGM Favours SMBG	

### Figure 37: Forest plot for HbA1c

	CGM SMBG							Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% Cl
Yoo 2008	6.5	1.2	29	7.2	2.2	28	100.0%	-0.70 [-1.62, 0.22]	
Total (95% CI)			29			28	100.0%	-0.70 [-1.62, 0.22]	•
Heterogeneity: Not ap Test for overall effect:	plicable Z = 1.48	: 3 (P =	0.14)						-10 -5 0 5 10 Favours CGM Favours SMBG



	CGM SMBG							Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% Cl
Yoo 2008	10	2.5	29	10.9	4.1	28	100.0%	-0.90 [-2.67, 0.87]	
<b>Total (95% CI)</b> Heterogeneity: Not ap Test for overall effect:	plicable Z = 1.00	) (P =	<b>29</b> 0.32)			28	<b>100.0</b> %	-0.90 [-2.67, 0.87]	-10 -5 0 5 10 Favours CGM Favours SMBG

Figure 39: Forest plot for postprandial blood glucose

# D.2.6 Review question 6: Should aspirin and/or clopidogrel be used for primary prevention of cardiovascular disease in people with type 2 diabetes?

No meta-analyses were undertaken for this question.

## D.2.7 Review question 7: What pharmacological treatment should be used to manage erectile dysfunction in men with type 2 diabetes?

D.2.7.1 PDE-5 inhibitor vs. placebo

Study or Subaroup	PDE-5 inhibi Events	tors Total	Placel Events	bo Total	Weight	Risk Ratio M-H. Random, 95% Cl	Risk Ratio M-H. Random, 95% Cl
1.5.2 Headache							
Boulton 2001	20	110	4	109	3.7%	4.95 [1.75, 14.02]	———
Escobar-Jimenez 2002	5	44	0	48	1.2%	11.98 [0.68, 210.54]	
Goldstein 2003	36	296	10	143	4.5%	1.74 [0.89, 3.40]	
Goldstein 2012	20	258	2	130	2.9%	5.04 [1.20, 21.23]	
Ishii 2006	33	672	2	106	2.9%	2.60 [0.63, 10.69]	
Rendell 1999	2	136	15	132	2.9%	0.13 [0.03, 0.55]	
Saenz de Tejada 2002	16	145	0	71	1.3%	16.27 [0.99, 267.43]	
Safarinejad 2004	29	144	3	138	3.4%	9.26 [2.89, 29.71]	
Stuckey 2003	19	97	7	94	4.2%	2.63 [1.16, 5.97]	<b>_</b> _
Ziegler 2006	5	163	0	155	1.2%	10.46 [0.58, 187.66]	<b>→</b>
Subtotal (95% CI)		2065		1126	28.2%	3.08 [1.46, 6.48]	◆
Total events	185		43				
Heterogeneity: Tau <sup>2</sup> = 0.8 Test for overall effect: Z =	5; Chi <sup>2</sup> = 28.18 2.96 (P = 0.00	3, df = 9 3)	(P = 0.0)	009); I <sup>z</sup>	= 68%		
1.5.3 Flushing							
Boulton 2001	16	110	0	109	1.3%	32.70 [1.99. 538.38]	
Escobar-Jimenez 2002	4	44	0	48	1.2%	9.80 [0.54, 176.97]	
Goldstein 2003	28	296	1	143	2.0%	13.53 [1.86, 98.43]	
Goldstein 2012	7	258	0	130	1.2%	7.59 [0.44, 131.82]	
Ishii 2006	77	672	2	106	3.0%	6.07 [1.51, 24.35]	——
Rendell 1999	6	136	0	132	1.2%	12.62 [0.72, 221.82]	+
Saenz de Tejada 2002	5	145	0	71	1.2%	5.42 [0.30, 96.76]	
Safarinejad 2004	27	144	0	138	1.3%	52.72 [3.25, 856.00]	
Stuckey 2003	17	97	3	94	3.4%	5.49 [1.66, 18.13]	
Ziegler 2006	4	163	0	155	1.2%	8.56 [0.46, 157.70]	
Subtotal (95% CI)		2065		1126	17.0%	8.65 [4.50, 16.66]	
Total events	191		6				
Heterogeneity: Tau <sup>2</sup> = 0.0 Test for overall effect: Z =	I0; Chi² = 4.02, 6.46 (P ≤ 0.00	df = 9 001)	(P = 0.91)	; I² = 0	%		
1.5.4 Bronchitis							
Ziegler 2006	3	163	4	155	2.8%	0.71 [0.16, 3.14]	<del></del>
Subtotal (95% CI)		163		155	2.8%	0.71 [0.16, 3.14]	
Total events	3		4				
Heterogeneity: Not applic Test for overall effect: Z =	able 0.45 (P = 0.65	)					
155 Unner respiratory	ract infection	, s					
Goldstein 2003	24	- 706	p	142	1 100	2 05 10 0.2 1/ 221	L
Goldstein 2003	54 10	∠30 259	0 7	190	++.470 1/104	∠.00 [0.80, 4.32] 1.30 [0.66, 3.00]	_ <b>_</b>
Ishii 2006	76	672	é	106	4 4 94	1.50 [0.30, 3.02]	<b>+</b>
Rendell 1999	2	136	13	132	7.9%	0.15 [0.03, 0.65]	
Saenz de Teiada 2002	6	145	3	71	3.0%	0.98 [0.25, 3.80]	
Sachzide Tejada 2002 Soforineiod 2004	9	143	0	129	1 296	19 21 [1 07 209 07]	<b>,</b>
Ziegler 2006	2	163	4	155	2.5%	0.48 0 09 2 561	
Subtotal (95% CI)	2	1814	4	875	22.5%	1.12 [0.57, 2.20]	•
Total events	147		43				ſ
Heterogeneity: Tau <sup>2</sup> = 0.4 Test for overall effect: 7 =	4; Chi <sup>2</sup> = 14.81	l,df=6	(P = 0.0)	2); I <b>¤</b> =	59%		
156 Discontinuation du	eto ØF	,					
Coldetoin 2002	0.0 ME	200	~	140	2.70	2 1 7 10 40 0 021	
Coldstein 2003	9	296	2	143	2.1%	2.17 [0.48, 9.93]	
Goldstein 2012	4	260	U	130	1.2%	4.52 [0.25, 83.27]	
Hatzichristou 2008	4	100	4	198	3.0%	1.98 [0.51, 7.75]	
ISTIL 2006 Decidel 4969	11	072	2	106	2.8%	0.87 [0.20, 3.86]	
Rendell 1999 Reent de Triade 2000	1	136	1	132	1.3%	0.97 [0.06, 15.36]	
Saeriz de Tejada 2002	4	145	U	100	1.2%	4.44 [0.24, 81.32]	
Salarinejad 2004	8	144	0	138	1.2%	16.30 [0.95, 279.67]	
Biodlex 2003	2	97	3	94	∠.3%0 ວ.3%	0.00 [0.11, 3.78]	
Ziegier 2006 Subtotal (95% CN	ن	103	2	1167	∠.3% 19:204	1.43 [0.24, 8.42]	
Total overte	40	2013		1107	10.2%	1.07 [0.69, 3.13]	
Heterogeneity: Tau <sup>2</sup> = 0.0 Test for overall effect: 7 =	40 10; Chi <sup>2</sup> = 5.95, 1 61 (P = 0.11	df = 8 i	(P = 0.65)	; I² = 0	%		
157 Decembra		,					
Roulton 2004	2	110	4	100	1.00	1 00 0 10 01 54	
Coldition 2001	2	110	1	109	1.0%	1.88 [0.18, 21.54]	
Goldstein 2012 Bondoll 4999	4	∠58 400	U	130	1.2%	4.55 [U.25, 83.91]	
Renden 1999 Stuckov 2002	12	135	U 4	132	1.3%	Z4.Z7 [1.45, 405.80]	
Subtotal (95% Ch	8	604	1	94 465	∠.0% 6.0%	7.75 [0.99, 60.79] 6.09 [1 77 - 20 041	
Total evente	26	001	2	-103	0.0 /0	0.00 [1111, 20.04]	
Heterogeneity: Tau <sup>2</sup> = 0.0 Test for overall effect: 7 =	20 10; Chi² = 2.04, 2.87 (P = 0.00	df = 3 i 4)	(P = 0.56)	; <b> ²</b> = 0	%		
		•,					
1.5.10 Abnormal vision							
Boulton 2001	5	110	0	109	1.2%	10.90 [0.61, 194.78]	+
Rendell 1999	5	136	1	132	1.9%	4.85 [0.57, 40.99]	+
Stuckey 2003	2	97	2	94	2.1%	0.97 [0.14, 6.74]	
Subtotal (95% CI)		343		335	5.2%	2.92 [0.71, 11.99]	
Total events	12		3				
Heterogeneity: Tau <sup>2</sup> = 0.2 Test for overall effect: Z =	5; Chi² = 2.37, 1.49 (P = 0.14	df = 2 )	(P = 0.31)	; I² = 1	6%		
Total (95% CI)		9064		5249	100.0%	2.69 [1.87, 3.86]	•
Total events	610		115			[,]	•
Heterogeneity: Tau <sup>2</sup> = 0.6	i4; Chi <sup>2</sup> = 90.78	3. df = 4		0001)	I² = 53%		
Test for overall effect: 7 =	5.36 (P < 0.00	001)	- (. 0.)				
Test for subgroup differen	nces: Chi <sup>2</sup> = 25	5.81, df	= 6 (P = 1	0.0002	), l² = 76.8	8%	Favours PDE-5 Favours Placebo

## Figure 40: Forest plot for adverse events

	PDE-5 inhik	itors	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.4.1 Sildenafil vs. placel	bo						
Boulton 2001	67	102	11	103	11.9%	6.15 [3.46, 10.94]	
Escobar-Jimenez 2002	17	37	6	43	8.8%	3.29 [1.45, 7.48]	
Rendell 1999	63	111	8	100	10.4%	7.09 [3.58, 14.06]	
Safarinejad 2004	61	118	13	116	12.4%	4.61 [2.69, 7.92]	
Stuckey 2003	44	85	20	77	14.0%	1.99 [1.30, 3.06]	-
Subtotal (95% Cl)		453		439	57.5%	4.13 [2.44, 7.00]	•
Total events	252		58				
Heterogeneity: Tau <sup>2</sup> = 0.2	6; Chi <sup>2</sup> = 15.9	17, df = 4	l (P = 0.0	03); I <b>²</b> =	: 75%		
Test for overall effect: Z =	5.28 (P < 0.0	0001)					
1.4.2 Vardenafil vs. place	ebo						
Goldstein 2003	172	268	17	133	13.7%	5.02 [3.19, 7.90]	
Subtotal (95% Cl)		268		133	13.7%	5.02 [3.19, 7.90]	•
Total events	172		17				
Heterogeneity: Not applic	able						
Test for overall effect: Z =	6.98 (P < 0.0	0001)					
1.4.3 Tadalafil vs. placeb	in in						
Hatzichristou 2008	112	198	23	100	14.7%	24611683501	
Saenz de Tejada 2002	87	145	18	71	14.1%	2.40 [1.00, 3.00]	-
Subtotal (95% Cl)	01	343		171	28.8%	2.42 [1.82, 3.20]	•
Total events	199		41			. , .	
Heterogeneity: $Tau^2 = 0.0$		df = 1	(P = 0.89)	$1^{\circ}$ $\mathbf{I}^{2} = 0^{\circ}$	%		
Test for overall effect: Z =	6.15 (P < 0.0	0001)					
		,					
Total (95% CI)		1064		743	100.0%	3.62 [2.57, 5.09]	•
Total events	623		116				
Heterogeneity: Tau <sup>2</sup> = 0.1	7; Chi <sup>2</sup> = 25.1	5, df = 7	' (P = 0.0	007); <b>i</b> ²	= 72%		
Test for overall effect: Z =	7.39 (P < 0.0	0001)					U.UT U.1 1 1U 1UU Eavoure placebol Eavoure PDE 5
Test for subgroup differer	nces: Chi² = 8	.49, df=	2 (P = 0	.01), I <sup>z</sup> :	= 76.4%		Tavouis placebol Favouis FDE-3

## Figure 41: Forest plot for global efficacy question

	PDE	-5 inhibito	гs	Placebo				Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl			
1.1.1 Avanafil versus pla	ncebo											
Goldstein 2012 Subtotal (95% Cl)	4.95	7.26806	250 <b>250</b>	1.8	7.155	125 <b>125</b>	12.6% <b>12.6</b> %	3.15 [1.61, 4.69] <b>3.15 [1.61, 4.69]</b>				
Heterogeneity: Not applic	able											
Test for overall effect: Z = 4.00 (P < 0.0001)												
1.1.2 Sildenafil versus p	lacebo											
Boulton 2001	20.4	8.31	45	11.5	11.58	98	6.6%	8.90 [5.56, 12.24]				
Escobar-Jimenez 2002	17.4	7.49	37	10.5	7.49	43	6.7%	6.90 [3.61, 10.19]				
Rendell 1999	17.7	6.4	131	10.6	6.19	127	12.6%	7.10 [5.56, 8.64]	+			
Safarinejad 2004	17.2	6.65	144	11.1	6.55	138	12.6%	6.10 [4.56, 7.64]	+			
Stuckey 2003	20	11.56	86	14	11.56	81	6.2%	6.00 [2.49, 9.51]				
Subtotal (95% CI)			443			487	44.6%	6.77 [5.82, 7.72]	•			
Heterogeneity: Tau <sup>2</sup> = 0.0	00; Chi <b></b> =	2.66, df =	4 (P = 1	0.62); <b>I</b> ≊÷	= 0%							
Test for overall effect: Z =	13.96 (P	< 0.0000	1)									
1.1.3 Tadalafil versus pl	acebo											
Hatzichristou 2008	17.75	8.7	194	14.7	8.7	98	10.3%	3.05 [0.94, 5.16]	-			
Saenz de Tejada 2002	19.05	14.18	145	12.2	14.18	71	5.2%	6.85 [2.82, 10.88]				
Subtotal (95% CI)			339			169	15.5%	4.55 [0.91, 8.19]	◆			
Heterogeneity: Tau <sup>2</sup> = 4.5	53; Chi <b>=</b> =	2.68, df=	1 (P = 1	0.10); I <b>²</b> ÷	= 63%							
Test for overall effect: Z =	2.45 (P =	= 0.01)										
1.1.4 Vardenafil versus	placebo											
Goldstein 2003	18.03	13 32	284	12.6	13 32	138	8.3%	5 43 12 72 8 1 41				
Ishii 2006	22.35	14.8	672	16.3	14.8	106	74%	6 05 [3 02 9 08]				
Ziegler 2006	20.34	8 4 2	154	15.72	7 07	149	11.7%	4 62 [2.87 6 37]	+			
Subtotal (95% Cl)	20.04	0.42	1110	10.12	1.01	393	27.4%	5.08 [3.76, 6.41]	•			
Heterogeneity: $Tau^2 = 0.0$	)0: Chi₹=	072 df=	2 (P = 1	ר. זיין ירוק ר	= 0%							
Test for overall effect: Z =	7.54 (P	< 0.00001)	201-0	5.1 07,1 1	- 0,0							
Total (95% CI)			2142			1174	100.0%	5.58 [4.48, 6.68]	•			
Heterogeneity: Tau <sup>2</sup> = 1.8	38: Chi <sup>z</sup> =	24.97. df:	= 10 (P	= 0.005	): $ \mathbf{r}  = 60$	1%						
Test for overall effect: 7 =	9.95 (P -	< 0.000011		2.000	//· •·				-20 -10 0 10 20			
Test for subaroup differe	nces: Ch	i <sup>2</sup> = 16.36.	df = 3 (	P = 0.00	)10), I <b>²</b> =	= 81.7%	6		Favours placebo Favours PDE-5			

## Figure 42: Forest plot for IIEF – erectile function domain

	PDE-5 inhil	PDE-5 inhibitors Placebo			Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.2.1 Avanafil versus	placebo						
Goldstein 2012 Subtotal (95% CI)	148	252 <b>252</b>	53	127 <b>127</b>	17.6% <b>17.6</b> %	1.41 [1.12, 1.77] <b>1.41 [1.12, 1.77]</b>	<b>-</b> ♦
Total events	148		53				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 2.91 (P =	: 0.004)					
1.2.2 Tadalafil versus	s placebo						
Hatzichristou 2008 Subtotal (95% CI)	120	194 <b>19</b> 4	42	98 <b>98</b>	14.5% <b>14.5</b> %	1.44 [1.12, 1.86] <b>1.44 [1.12, 1.86]</b>	<b>-</b>
Total events	120		42				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 2.83 (P =	: 0.005)					
1.2.3 Vardenafil vers	us placebo						
Goldstein 2003	170	287	40	137	16.0%	1 74 [1 37 2 22]	+
Ishii 2006	504	672	54	105	25.6%	1 46 [1 20 1 77]	-
Ziegler 2006	108	154	76	149	26.4%	1.37 [1.14, 1.66]	-
Subtotal (95% CI)		1113		391	67.9%	1.49 [1.31, 1.70]	•
Total events	791		179				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup> =	2.45, df	= 2 (P = 0	).29); I <b>≃</b>	= 18%		
Test for overall effect:	Z=6.01 (P <	0.0000	1)				
Total (95% CI)		1559		616	100.0%	1.47 [1.33, 1.61]	•
Total events	1059		274				
Heterogeneity: Tau² =							
Test for overall effect:	Z = 7.76 (P <	0.0000	1)				Eavours placebol Eavours PDE-5
Test for subgroup diff							

## Figure 43: Forest plot for SEP – Q2

	PDE-5 inhil	pitors	Place	bo		Risk Ratio	Risk Ratio					
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl					
1.3.1 Avanafil versus	placebo											
Goldstein 2012 Subtotal (95% Cl)	94	252 <b>252</b>	26	127 <b>127</b>	14.9% 14.9%	1.82 [1.25, 2.66] <b>1.82 [1.25, 2.66]</b>						
Total events	94		26									
Heterogeneity: Not applicable												
Test for overall effect: Z = 3.11 (P = 0.002)												
1 3 2 Tadalafil voreue placobo												
Hatzichristou 2008	83	191 <b>101</b>	27	95 05	16.6%	1.53 [1.07, 2.19] 1.53 [1.07, 2.19]	<b>*</b>					
Total events	83	131	27	55	10.0 /4	1.55 [ 1.07, 2.15]	•					
Heterogeneity: Not applicable												
Test for overall effect: Z = 2.33 (P = 0.02)												
1.3.3 Vardenafil vers	us placebo											
Goldstein 2003	148	287	32	137	20.4%	2.21 [1.60, 3.05]	-					
Ishii 2006	400	672	32	105	24.4%	1.95 [1.45, 2.62]						
Ziegler 2006	75	149	43	154	23.7%	1.80 [1.34, 2.43]	1					
Subtotal (95% CI)		1108		396	68.5%	1.97 [1.65, 2.35]	•					
Total events	623		107									
Heterogeneity: Tau² =	0.00; Chi <sup>2</sup> =	0.83, df	= 2 (P = 0	).66); I <sup>z</sup>	= 0%							
Test for overall effect:	Z = 7.54 (P <	0.0000	1)									
Total (95% CI)		1551		618	100.0%	1.87 [1.61, 2.16]	•					
Total events	800		160									
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.40, df = 4 (P = 0.66); l <sup>2</sup> = 0%												
Test for overall effect:	Z = 8.38 (P <	0.0000	1)				U.UI U.1 1 10 100 Eavoure placebol Eavoure PDE-6					
Test for subgroup diff	erences: Ch	Tavours praceso Tavours I DE-3										

## Figure 44: Forest plot for SEP – Q3