Appendix D: GRADE tables and meta-analysis 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[1]	not serious[2]	not serious[3]	not serious	Moderate
6 months	62	serious[1]	not serious[2]	not serious[3]	not serious	Moderate
12 months	21	serious[1]	not serious[2]	not serious[3]	serious[4]	Low
24 months	6	serious[1]	not serious[2]	not serious[3]	not serious	Moderate
Hypoglycaemia at study endpoint						
Study endpoint	44	serious[1]	not serious[2]	not serious[3]	serious[4]	Low
Adverse events at study endpoint						
Dropouts due to adverse events	73	serious[1]	not serious[2]	not serious[3]	serious[4]	Low
Total dropouts	73	serious[1]	not serious[2]	not serious[3]	serious[4]	Low
Nausea	29	serious[1]	not serious[2]	not serious[3]	serious[4]	Low
Change in body weight						
12 months	12	serious[1]	serious[5]	not serious[3]	serious[4]	Low[6]
24 months	6	serious[1]	serious[5]	not serious[3]	serious[4]	Low[6]

[1]Downgrade 1 level: baseline HbA1c ranged from 5.3 to 12.7%
[2]Assessed based on residual deviance, deviance information criterion and tau^2 (tau^2<0.5)
[3]Considered not serious as population, interventions, comparator and outcomes are as defined in protocol
[4]Downgrade 1 level: no interventions had probability of being best and worse ≥0.5
[5]Downgrade 1 level: tau^2≥0.5
[6]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[1]	not serious[2]	not serious[3]	serious[4]	Moderate
6 months	22	not serious[1]	not serious[2]	not serious[3]	serious[4]	Moderate
12 months	16	not serious[1]	not serious[2]	not serious[3]	serious[4]	Moderate
24 months	6	not serious[1]	not serious[2]	not serious[3]	serious[4]	Moderate
Hypoglycaemia at study endpoint						
Study endpoint	21	not serious[1]	serious[5]	not serious[3]	serious[4]	Low
Adverse events at study endpoint						
Dropouts due to adverse events	27	not serious[1]	serious[5]	not serious[3]	serious[4]	Low
Total dropouts	29	not serious[1]	not serious[2]	not serious[3]	serious[4]	Moderate
Nausea	11	not serious[1]	serious[5]	not serious[3]	serious[4]	Low
Change in body weight						
12 months	8	not serious[1]	serious[5]	not serious[3]	serious[4]	Low
24 months	8	not serious[1]	serious[5]	not serious[3]	serious[4]	Low

[1]Baseline HbA1c ranged from 7.1 to 9.9%
[2]Assessed based on residual deviance, deviance information criterion and tau^2 (tau^2<0.5)
[3]Considered not serious as population, interventions, comparator and outcomes are as defined in protocol
[4]Downgrade 1 level: no interventions had probability of being best and worse ≥0.5
[5]Downgrade 1 level: tau^2≥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[1]	not serious[2]	not serious[3]	not serious	Moderate
Hypoglycaemia at study endpoint						
Study endpoint	34	serious[1]	not serious[2]	not serious[3]	serious[4]	Low
Adverse events at study endpoint						
Dropouts due to adverse events	25	serious[1]	serious[5]	not serious[3]	serious[4]	Low[6]

Assessment time points/ Measure	Number of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Total dropouts	25	serious[1]	not serious[2]	not serious[3]	serious[4]	Low
Nausea	4	serious[1]	serious[5]	not serious[3]	serious[4]	Low[6]
Change in body weight						
Up to 12 months	27	serious[1]	not serious[2]	not serious[3]	serious[4]	Low

[1]Downgrade 1 level: baseline HbA1c ranged from 7.8 to 11%
[2]Assessed based on residual deviance, deviance information criterion and tau^2 (tau^2<0.5)
[3]Considered not serious as population, interventions, comparator and outcomes are as defined in protocol
[4]Downgrade 1 level: no interventions had probability of being best and worse ≥0.5
[5]Downgrade 1 level: tau^2≥0.5
[6]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	Quality 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[1]	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
[1] 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	Quality assessment					Effect (95% CI)		Quality
		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 dose of metformin									
1 (Gallwitz 2012)	RCT	not serious	not serious	serious[1]	not serious	NA	All cause mortality Any cardiovascular event[ŦŦ] 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; NA, not applicable
[1] 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
[ŦŦ] 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 studies	Design	Quality assessment					Effect (95% CI)		Quality
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Outcome	Estimate	
Insulin compared to diet alone (overall n=1941); mean 7 year follow-up; people with type 2 diabetes									
1 (Bruno 1999, 2003)	cohort	serious[1,2]	not serious	serious[3]	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 studies	Design	Quality assessment					Effect (95% CI)		Quality
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Outcome	Estimate	
							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 to oral antidiabetic medication (n=unclear, up to 1045); median 3.1 year follow-up; people with type 2 diabetes attending retinopathy screening									
1 (Henriccson 1997)	cohort	serious[1]	not serious	not serious	not serious	NA	People who changed from oral medication to insulin compared to those remaining on oral medication - Blindness/visual impairment - Progression of retinopathy 3 or more levels	 Adj RR 2.7 (1.8 to 4.0) Adj RR 1.6 (1.3 to 1.9)	Very low
Diet alone (n=99) compared to oral antidiabetic drugs (n=250) compared to new insulin users (n=245) compared to existing insulin users (n=271); mean 3 year follow-up; people with type 2 diabetes and suspected myocardial infarction who took part in the DIGAMI RCT (24 hour insulin infusion compared to conventional management)									
1 (Aas (2009)	cohort	serious[1,2]	not serious	not serious	not serious	NA	Existing insulin users compared to other groups - cardiovascular death New insulin users compared to other groups - Reinfarction	 HR 2.38 (1.34 to 4.22) HR 2.49 (1.23 to 5.03)	Very low

RR, rate ratio; NA, not applicable
Adj RR, adjusted rate ratio – see evidence tables for details of individual adjustments that were applied
HR, hazard ratio

[1] *Unclear if researchers were blinded to group allocation when assessing outcomes*
[2] *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*
[3] *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	Quality assessment					Effect (95% CI)		Quality
		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[1,2]	not serious	serious[3]	not serious	NA	All cause mortality	Adj HR 1.19 (0.76 to 1.84)	Very low
Metformin plus existing diabetes therapy (n=289) compared to existing diabetes therapy alone (n=1064); mean 10 year follow-up; unclear population, part of ZODIAC study									
1 (Landman 2010)	cohort	serious[1,2]	not serious	serious[3]	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 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[1,2]	not serious	serious[3]	not serious	NA	All cause mortality	Adj HR 1.53 (1.20 to 1.96)	Very low

RR, rate ratio; NA, not applicable
Adj HR, adjusted hazard ratio – see evidence tables for details of adjustments that were made
[1] *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*
[2] *Unclear if researchers were blinded to group allocation when assessing outcomes*
[3] *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 studies	Design	Quality assessment					Effect (95% CI)		Quality
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Outcome	Estimate	
Sulfonylurea compared to diet alone (overall n=1941); mean 7 year follow-up; people with type 2 diabetes									
1 (Bruno 1999)	cohort	serious[1,2]	not serious	serious[3]	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 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[1,2]	not serious	serious[3]	not serious	NA	All cause mortality	Adj HR 1.21 (1.02 to 1.44)	Very low
Sulfonylurea plus biguanides compared to diet alone (overall n=1941); mean 7 year follow-up; people with type 2 diabetes									
1 (Bruno 1999)	cohort	serious[1,2]	not serious	serious[3]	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
[1] *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*
[2] *Unclear if researchers were blinded to group allocation when assessing outcomes*
[3] *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?

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

Number of cohort studies	Quality assessment					Number of people	Effect (95% CI)	Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other			
All-cause mortality								
1 (Landman 2010) – ZODIAC 5 to 10 year follow-up Subgroup: (Van Hateren 2011, ZODIAC-20) 10 year follow-up	N	NA	N	N	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) ≥9% HR 2.26 (1.39, 3.67) Per 1% HbA1c decrease: updated mean baseline HbA1c: HR 1.21 (1.07, 1.36) Subgroup: 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) ≥11yrs diabetes duration: HR 1.05 (0.85, 1.30)	High
1 (Adler 1999) – UKPDS Median 10.4 year follow-up	N	NA	N	N	NA	3642	Per 1% HbA1c decrease: Risk reduction baseline HbA1c: 6% (2, 10)	High

Number of cohort studies	Quality assessment					Number of people	Effect (95% CI)	Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other			
1 (Zoungas 2012) – ADVANCE Mean 4.5 year follow-up	S[1]	NA	N	N	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 (*n* not reported) Per 1% HbA1c increase: >7%: HR 1.33 (1.16, 1.53) Subgroup: age ≥65 years (*n* 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

Number of cohort studies	Quality assessment					Number of people	Effect (95% CI)	Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other			
							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) Per 1% HbA1c increase: >7%: HR 1.35 (1.24, 1.47) Subgroup: macrovascular disease (n=3572) Per 1% HbA1c increase: >7%: HR 1.42 (1.27, 1.59) Subgroup: no microvascular disease (n~9933) Per 1% HbA1c increase:	

Number of cohort studies	Quality assessment					Number of people	Effect (95% CI)	Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other			
							>7%: HR 1.37 (1.26, 1.49) Subgroup: microvascular disease (n=1153) Per 1% HbA1c increase: >7%: HR 1.42 (1.25, 1.62)	
1 (Eeg-Olofsson 2010) 5 to 6 year follow-up	S[2]	NA	N	N	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 ≤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

Number of cohort studies	Quality assessment					Number of people	Effect (95% CI)	Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other			
							Subgroup: 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	N	NA	S[3]	N	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	N	NA	S[4]	N	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

Number of cohort studies	Quality assessment					Number of people	Effect (95% CI)	Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other			
							≥9.0% HR 1.15 (1.06, 1.25)	
Mortality related to diabetes								
1 (Adler 1999) – UKPDS Median 10.4 year follow-up	N	NA	N	N	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	N	NA	S[3]	N	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 sudden death								
1 (Drechsler 2009) - 4D study Median 4 year follow-up	N	NA	S[3]	N	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	N	NA	N	S[5]	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

Number of cohort studies	Quality assessment					Number of people	Effect (95% CI)	Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other			
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[2]	NA	N	N	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 ≤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

Number of cohort studies	Quality assessment					Number of people	Effect (95% CI)	Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other			
							Per 1% HbA1c increase: Baseline HbA1c: HR 1.09 (1.01, 1.17) Subgroup: 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	N	NA	S[3]	S[5]	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

[1] *Downgrade by 1 level: post-hoc analysis*
[2] *Downgrade by 1 level: participants from non-mandatory diabetes register*
[3] *Downgrade by 1 level: participants receiving dialysis*
[4] *Downgrade by 1 level: >97% sample were male*
[5] *Downgrade by 1 level: wide confidence interval and/or small sample size <400*

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

studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	people		
Composite of combined cardiovascular events								
1 (Drechsler 2009) - 4D study Median 4 year follow-up	N	NA	S[1]	N	NA	1255	Categorical with ≤6% as a reference: >6 to ≤8% HR 1.31 (1.05, 1.65) >8% HR 1.37 (1.00, 1.87) Per unit increase in HbA1c: HR 1.09 (1.01 to 1.18)	Moderate
Macrovascular events								
1 (Zoungas 2012) – ADVANCE Mean 4.5 year follow-up	S[2]	NA	N	N	NA	11,086 (event rate NR)	<7%: HR 1.02 (0.86, 1.21) >7%: HR 1.38 (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) Per 1% HbA1c decrease: 6.0%: HR 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) Subgroup: age <65 years (*n* not reported) Per 1% HbA1c increase: >7%: HR 1.34 (1.19, 1.50) Subgroup: age ≥65 years (*n* not reported)	Moderate

Number of cohort studies	Quality assessment					Number of people	Effect (95% CI)	Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other			
							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) Per 1% HbA1c increase: >7%: HR 1.54 (1.38, 1.72) Subgroup: duration of diabetes ≥7 years (*n* not reported) Per 1% HbA1c increase: >7%: HR 1.30 (1.21, 1.41) Subgroup: no macrovascular disease (n~7514) Per 1% HbA1c increase: >7%: HR 1.37 (1.26, 1.49) Subgroup: macrovascular disease (n=3572)	

Number of cohort studies	Quality assessment					Number of people	Effect (95% CI)	Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other			
							Per 1% HbA1c increase: >7%: HR 1.38 (1.25, 1.52) Subgroup: no microvascular disease (n~9933) Per 1% HbA1c increase: >7%: HR 1.37 (1.27, 1.48) Subgroup: microvascular disease (n=1153) Per 1% HbA1c increase: >7%: HR 1.44 (1.27, 1.62)	
Cardiovascular disease (fatal/non-fatal)								
1 (Eeg-Olofsson 2010) 5 to 6 year follow-up	S[3]	NA	N	N	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 ≤7 years (n=10,016) Per 1% HbA1c increase: Baseline HbA1c: HR 1.08 (1.03, 1.13) Subgroup: duration of diabetes >7 years (n=8318)	Moderate

Number of cohort studies	Quality assessment					Number of people	Effect (95% CI)	Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other			
							Per 1% HbA1c increase: Baseline HbA1c: HR 1.10 (1.06, 1.14) Subgroup: previous CVD (n=3276) Per 1% HbA1c increase: Baseline HbA1c: HR 1.10 (1.05, 1.16) Subgroup: no previous CVD (n=15,058) Per 1% HbA1c increase: Baseline HbA1c: HR 1.09 (1.06, 1.13)	
Myocardial infarction (fatal and non-fatal)								
1 (Drechsler 2009) - 4D study Median 4 year follow-up	N	NA	S[1]	N	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	N	NA	N	N	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-fatal)								
1 (Eeg-Olofsson 2010)	S[3]	NA	N	N	NA	18,334	Categorical with 6.0-6.9% as a reference:	Moderate

Number of cohort studies	Quality assessment					Number of people	Effect (95% CI)	Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other			
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) Subgroup: duration of diabetes ≤7 years (n=10,016) Per 1% HbA1c increase: Baseline HbA1c: HR 1.09 (1.03, 1.15) Subgroup: duration of diabetes >7 years (n=8318) Per 1% HbA1c increase: Baseline HbA1c: HR 1.11 (1.06, 1.16) Subgroup: previous CVD (n=3276) Per 1% HbA1c increase: Baseline HbA1c: HR 1.08 (1.02, 1.15) Subgroup: no previous CVD (n=15,058) Per 1% HbA1c increase: Baseline HbA1c: HR 1.12 (1.07, 1.16)	
1 (Schulze 2004) Mean 7.4 year follow-up	N	NA	N	S[4-6]	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

Number of cohort studies	Quality assessment					Number of people	Effect (95% CI)	Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other			
							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 (Stratton 2000, UKPDS)	N	NA	N	N	NA	3642	Per 1% HbA1c decrease: Risk reduction baseline HbA1c: 0% (-12, 11)	High
Newly diagnosed angina								
1 (Adler 1999) – UKPDS Median 10 to 10.3 years (Stratton 2000, UKPDS)	N	NA	N	N	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-fatal)								
1 (Drechsler 2009) - 4D study Median 4 year follow-up	N	NA	S[1]	S[4]	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[3]	NA	N	N	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

Number of cohort studies	Quality assessment					Number of people	Effect (95% CI)	Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other			
							Baseline HbA1c: HR 1.06 (0.98, 1.14) 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) Per 1% HbA1c increase: Baseline HbA1c: HR 1.11 (1.03, 1.20) Subgroup: 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)	N	NA	N	N	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 disease								
1 (Adler 1999) – UKPDS Median 10.4 years (Stratton 2000, UKPDS)	N	NA	N	S[4]	NA	2398	Per 1% HbA1c increase: OR 1.28 (1.12, 1.46) Amputation or PVD death (n=3642) : Per 1% HbA1c decrease:	High

Number of cohort studies	Quality assessment					Number of people	Effect (95% CI)	Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other			
							Risk reduction baseline HbA1c: 28% (18, 37)	
1 (Zhao 2013) – LSUHLS study Lower-extremity amputation Mean 6.83 year follow-up	N	NA	N[7]	N	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

Number of cohort studies	Quality assessment					Number of people	Effect (95% CI)	Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other			
							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 (*n* not reported) Categorical with <6% as a reference and baseline HbA1c: 6.0 to 6.9% HR 2.02 (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)	

Number of cohort studies	Quality assessment					Number of people	Effect (95% CI)	Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other			
							Subgroup: age 50-59yrs (*n* not reported) Categorical with <6% as a reference and baseline HbA1c: 6.0 to 6.9% HR 1.13 (0.66, 1.94) 7.0 to 7.9% HR 1.50 (0.86, 2.63) 8.0 to 8.9% HR 2.26 (1.22, 4.18) 9.0 to 9.9% HR 3.69 (2.10, 6.47) ≥10% HR 2.89 (1.73, 4.82) Subgroup: age <50yrs (*n* not reported) Categorical with <6% as a reference and baseline HbA1c: 6.0 to 6.9% HR 1.80 (0.95, 3.43) 7.0 to 7.9% HR 2.41 (1.27, 4.57) 8.0 to 8.9% HR 2.34 (1.25, 4.38) 9.0 to 9.9% HR 3.01 (1.63, 5.57) ≥10% HR 3.93 (2.26, 6.84)	

[1] *Downgrade by 1 level: participants receiving dialysis*
[2] *Downgrade by 1 level: post-hoc analysis*
[3] *Downgrade by 1 level: participants from non-mandatory diabetes register*
[4] *Downgrade by 1 level: wide confidence interval and/or small sample size <400*
[5] *Downgrade by 1 level: all participants female*
[6] *Downgrade by 1 level: participants self-reported (questionnaire) some inclusion criteria*
[7] *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

Number of cohort studies	Quality assessment					Number of people	Effect (95% CI)	Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other			
Microvascular end points								
1 (Adler 1999) – UKPDS Median 10.4 years (Stratton 2000, UKPDS)	N	NA	N	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[1]	NA	N	N	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) Subgroup: age <65 years (*n* not reported) Per 1% HbA1c increase: >6.5%: HR 1.40 (1.30, 1.50) Subgroup: age ≥65 years (*n* not reported)	Moderate

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

Number of cohort studies	Quality assessment					Number of people	Effect (95% CI)	Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other			
							Per 1% HbA1c increase: >6.5%: HR 1.30 (1.17, 1.43) Subgroup: no microvascular disease (n~9933) Per 1% HbA1c increase: >6.5%: HR 1.40 (1.32, 1.49) Subgroup: microvascular disease (n=1153) Per 1% HbA1c increase: >6.5%: HR 1.36 (1.23, 1.50)	
Retinopathy								
1 (Molyneaux 1998) Median 28 month follow-up	S[2]	NA	N	N	NA	963	Per 10% HbA1c decrease: Relative risk reduction: 24% (16, 32)	Moderate
1 (Morisaki 1994) 5 year follow-up	S[2]	NA	S[3,4]	S[5]	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

Number of cohort studies	Quality assessment					Number of people	Effect (95% CI)	Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other			
							Without retinopathy HbA1c 7.1±1.2	
1 (Nakagami 1997) 10 year follow-up	S[2]	NA	S[4]	S[5]	NA	137	Retinopathy prevalence at HbA1c: <6%: 0% 6 to 6.9%: 17.2% 7 to 7.9%: 14.3% 8 to 8.9%: 41.9% ≥9%: 54.8% Multivariate logistic regression analysis showed that mean HbA1c over 10 year follow-up period was the only significant predictor of retinopathy	Very low
1 (Salinero-Fort 2013) – MADIABETES 4 year follow-up	N	NA	N[6]	N	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)	N	NA	N	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[2]	NA	N	S[5]	NA	399	Per 10% HbA1c decrease: Relative risk reduction: 9% (-2, 19)	Very low
1 (Torffvit and Agardh	S[2]	NA	S[7]	S[5]	NA	385	Cox regression analysis showed that HbA1c	Very low

Number of cohort studies	Quality assessment					Number of people	Effect (95% CI)	Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other			
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[2]	NA	N	N	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

[1] *Downgrade by 1 level: post-hoc analysis*
[2] *Downgrade by 1 level: single centre study*
[3] *Downgrade by 1 level: participants all >60yrs*
[4] *Downgrade by 1 level: sample all Japanese*
[5] *Downgrade by 1 level: wide confidence interval and/or small sample size <400*
[6] *Downgrade by 1 level: attrition of 12.5% and housebound individuals excluded*
[7] *Downgrade by 1 level: blood pressure and albuminuria outcomes reported*

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

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

Number of cohort studies	Quality assessment					Number of people	Effect (95% CI)	Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other			
1 (Adler 1999, UKPDS) Median 10 to 10.3 year follow-up up	N	NA	N	N	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	N	NA	N	N	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-fatal)								
1 (Adler 1999, UKPDS) Median 10 to 10.3 year follow-up	N	NA	N	N	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 profile: intensive vs. conventional target values

Nunber of studies	Design	Quality assessment					Number of people		Effect (95% CI)	Quality
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Intensive	Conventional		
All-cause mortality										
16	RCT	not serious[1]	not serious[2]	not serious[3]	not serious[4]	NA	762/4296	381/2208	RR 0.98 (0.88 to 1.09)	High
Cardiovascular mortality										
14	RCT	not serious[1]	not serious[2]	not serious[3]	serious[4]	NA	445/4225	195/2131	RR 1.15 (0.98 to 1.35)	Moderate
Macrovascular complications										
8	RCT	not serious[1]	serious[6]	not serious[3]	very serious[7]	NA	394/3543	235/1791	RR 0.98 (0.74 to 1.3)	Low
Non-fatal myocardial infarction										
9	RCT	not serious[1]	not serious[2]	not serious[3]	not serious[4]	NA	342/3995	187/1907	RR 0.92 (0.78 to 1.09)	High
Congestive heart failure										
8	RCT	not serious[1]	not serious[2]	not serious[3]	serious[5]	NA	120/3777	75/1683	RR 0.82 (0.62 to 1.08)	Moderate
Non-fatal stroke										
8	RCT	not serious[1]	not serious[2]	not serious[3]	serious[5]	NA	156/3791	65/1697	RR 1.06 (0.8 to 1.41)	Moderate
Amputation of lower extremity										
7	RCT	not serious[1]	not serious[2]	not serious[3]	serious[5]	NA	36/3500	20/1579	RR 0.73 (0.42 to 1.25)	Moderate
Microvascular complications										
3	RCT	not serious[1]	not serious[2]	not serious[3]	serious[5]	NA	253/3154	130/1222	RR 0.75 (0.61 to 0.92)	Moderate
Nephropathy										

Nunber of studies	Design	Quality assessment					Number of people		Effect (95% CI)	Quality
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Intensive	Conventional		
7	RCT	not serious[1]	very serious[8]	not serious[3]	very serious[7]	NA	45/3167	66/1587	RR 0.64 (0.32 to 1.29)	Low
Retinopathy										
5	RCT	not serious[1]	very serious[8]	not serious[3]	serious[5]	NA	441/3098	273/1516	RR 0.79 (0.56 to 1.11)	Low
End stage renal disease										
4	RCT	not serious[1]	not serious[9]	not serious[3]	very serious[7]	NA	28/3365	11/1438	RR 0.94 (0.47 to 1.89)	Low
Mild hypoglycaemia										
12	RCT	not serious[1]	serious[6]	not serious[3]	not serious[4]	NA	791/4200	263/2120	RR 1.85 (1.53 to 2.25)	Moderate
Severe hypoglycaemia										
13	RCT	not serious[1]	not serious[2]	not serious[3]	serious[5]	NA	53/3688	11/1764	RR 2.23 (1.22 to 4.08)	Moderate

NA, not applicable
[1] No apparent risk of bias in the included studies
[2] Low inconsistency (I^2 < 30%)
[3] Population, intervention and outcome as specified in the review protocol
[4] Confidence intervals around the point estimate in a single zone
[5] Confidence intervals around the point estimate cross into 2 zones
[6] Serious inconsistency (I^2 = 46%)
[7] Confidence intervals around the point estimate cross into 3 zones
[8] Very serious inconsistency (I^2 > 60%)
[9] 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)

Number of studies	Design	Quality assessment					Number of people		Effect (95% CI)	Quality
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other	SMBG	No SMBG		
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[1]	not serious	serious[2,3,4]	not serious	NA	2217	2084	MD -0.22 (-0.31 to -0.13) Subgroup analysis based on current medication: 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% Subgroup analysis based on type of SMBG: Standard SMBG: MD -0.21 (-0.31 to -0.11) Enhanced SMBG: MD -0.29 (-0.49 to -0.09) Subgroup analysis based on frequency of SMBG: <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 prespecified subgroups at 1 year follow-up										
1	RCT	not serious	not serious	serious[3]	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 blood glucose (mmol/L) from 26 to 52 weeks (subgroup based on current therapy) (follow-up 24 to 52 weeks; Better indicated by lower values)										
6	RCT	serious[1]	not serious	serious[4,5]	not serious	NA	835	810	MD -0.38 (-0.68 to -0.07) Subgroup analysis based on current medication: Diet ± OADs: MD -0.26 (-0.59 to 0.07) Diet, OADs ± insulin: MD -1.33 (-2.27 to -0.38) Subgroup analysis based on type of SMBG: Standard SMBG: MD -0.31 (-0.63 to 0.00) Enhanced SMBG: MD -1.57 (-2.94 to -0.20) Subgroup analysis based on frequency of SMBG: <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
Postprandial blood glucose (mg/dL) at 26 weeks for adults with type 2 diabetes on diet, antidiabetic and/or insulin medicines (follow-up 6 months; Better indicated by lower values)										
1	RCT	serious[1]	not serious	serious[4]	not serious	NA	96	48	MD -71.78 (-96.62 to -46.94) Subgroup analysis based on type of SMBG: Standard SMBG: MD -61.30 (-97.61 to -24.99) Enhanced SMBG: MD -81.00 (-111.05 to -46.95)	Low

Any hypoglycaemia from 26 to 52 weeks (subgroup based on frequency of SMBG) (follow-up 6 to 12 months)											
6	RCT	serious[1]	not serious	serious[3,4]	serious[6]	NA	203/1354 (15%)	88/1138 (7.7%)	RR 1.62 (1.19 to 2.22) <u>Subgroup analysis based on current medication:</u> Diet alone: RR 1.27 (0.66 to 2.44) Diet ± OADs: RR 1.80 (1.16 to 2.79), I2=47% Diet, OADs ± insulin: RR 1.30 (0.70 to 2.39) <u>Subgroup analysis based on frequency of SMBG:</u> <1 per day: RR 2.28 (1.61 to 3.23) 1-2 times per day: RR 1.26 (0.89 to 1.79) >2 per day: RR 0.51 (0.06 to 4.37)		Low
Severe hypoglycaemia from 26 to 52 weeks (subgroup based on current therapy) (follow-up 6 to 12 months)											
3	RCT	not serious	not serious	serious[3]	serious[6]	NA	1/853 (0.1%)	4/727 (0.6%)	RR 0.35 (0.07 to 1.77) <u>Subgroup analysis based on current medication:</u> Diet ± OADs: RR 0.17 (0.01 to 4.12) Diet, OADs ± insulin: RR 0.45 (0.07 to 2.99) <u>Subgroup analysis based on frequency of SMBG:</u> <1 per day: RR 0.17 (0.01 to 4.12) 1-2 times per day: RR 0.45 (0.07 to 2.99)		Low
Adverse events at 6 months for adults with type 2 diabetes on oral antidiabetes medicines (follow-up 6 months)											
1	RCT	not serious	not serious	not serious	serious[6]	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	

[1] 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
[2] Studies conducted before 1995 when the management of diabetes and other related conditions may have differed compared with current practice
[3] 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. Two studies (Lim 2011 and Lu 2011) had baseline BMI of approximately 25kg/m^2 which is close to the normal range and may not be representative of patients with type 2 diabetes
[4] 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
[5] Some trials used indirect comparators for example weight control program, provision of financial rewards for weight loss and changes in habits
[6] 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
Ŧ intervention group relates to more intensive SMBG (this has not been combined with less intensive monitoring)

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 from 12 to 52 weeks in adults with type 2 diabetes not on insulin (follow-up 3 to 12 months; Better indicated by lower values)										
3	RCT	serious[1]	not serious	serious[2]	serious[3]	NA	439	408	MD 0.31 lower (0.67 lower to 0.05 higher)	Low
Any hypoglycaemia at 52 weeks in adults with type 2 diabetes not on insulin (follow-up 12 months)										
2	RCT	serious[1]	not serious	serious[4]	serious[3]	NA	48/407	37/377	RR 1.28 (0.88 to 1.86)	Low
Any hypoglycaemia at 3 month follow-up in people treated with oral antidiabetes and/or insulin medicines										
1	RCT	serious[1]	not serious	serious[2]	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

[1] Unclear randomisation and allocation concealment. One trial had some risk of attrition bias as dropouts were slightly younger, more likely to be African-American, have a higher Hba1c and fewer comorbid conditions, however both ITT and per protocol analyses were carried out
[2] 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
[3] 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
[4] 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

Number of studies	Design	Quality assessment					Number of people		Effect (95% CI)	Quality
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other	SMBG plus telecare	SMBG		
HbA1c from 12 to 52 weeks in adults with type 2 diabetes on diet, oral antidiabetes and insulin medicines (follow-up 12 to 52 weeks; Better indicated by lower values)										
5	RCT	serious[1]	not serious	serious[2]	serious[3]	NA	260	295	MD -0.57 (-1.06 to -0.08)	Low
Fasting plasma glucose (mmol/L) from 26 to 44 weeks in adults with type 2 diabetes on diet, oral antidiabetes and insulin medicines (follow-up 26 to 44 weeks; Better indicated by lower values)										
2	RCT	serious[1]	not serious	serious[2]	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 diabetes on diet, oral antidiabetes and insulin medicines (follow-up 26 weeks; Better indicated by lower values)										

Number of studies	Design	Quality assessment					Number of people		Effect (95% CI)	Quality
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other	SMBG plus telecare	SMBG		
1	RCT	serious[1]	not serious	serious[2]	serious[3]	NA	49	47	MD -19.7 (-42.84 to 3.44)	Low
Any hypoglycaemia at 52 weeks in adults with type 2 diabetes on diet, oral antidiabetes and insulin medicines (follow-up 26 weeks)										
1	RCT	serious[1]	not serious	serious[2]	serious[3]	NA	16/51	12/51	RR 1.33 (0.7 to 2.53)	Low
Total symptomatic hypoglycaemia at 44 week follow-up in people treated with insulin therapy										
1	RCT	serious[1]	not serious	not serious	serious[3]	NA	1.89 events per patient year	1.76 events per patient year	Rate ratio[¥] 1.07 (0.89 to 1.29)	Very low
Severe nocturnal hypoglycaemia at 44 week follow-up in people treated with insulin therapy										
1	RCT	serious[1]	not serious	not serious	serious[3]	NA	0.04 events per patient year	0.02 events per patient year	Rate ratio 2.00 (0.44 to 9.06)	Very low

[1] 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
[2] 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
[3] 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.1.5.4 Table 17: Mobile phone (automated) glucometer vs. standard glucometer

Number of studies	Design	Quality assessment					Number of people		Effect (95% CI)	Quality
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Mobile phone glucometer	Glucometer		
HbA1c at 12 weeks (Better indicated by lower values)										
1	RCT	serious[1]	no serious inconsistency	serious[2]	serious[3]	NA	35	34	MD 0.29 (-0.25 to 0.83)	Low
Fasting plasma glucose (mmol/L) at 12 weeks (follow-up 12 weeks; Better indicated by lower values)										
1	RCT	serious[1]	no serious	serious[2]	no serious	NA	35	34	MD -0.33 (-1.64 to 0.99)	Low

Number of studies	Design	Quality assessment					Number of people		Effect (95% CI)	Quality
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Mobile phone glucometer	Glucometer		
			inconsistency		imprecision					
Postprandial blood glucose (mg/dL) at 12 weeks (follow-up 12 weeks; Better indicated by lower values)										
1	RCT	serious[1]	no serious inconsistency	serious[2]	serious[3]	NA	35	34	MD -11.57 (-46.55 to 23.41)	Low

[1] *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*
[2] *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*
[3] *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 studies	Design	Quality assessment					Number of people		Effect (95% CI)	Quality
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other	CGM	SMBG		
Hba1c from 12 to 52 weeks (follow-up 12 to 52 weeks; Better indicated by lower values)										
2	RCT	serious[1]	no serious inconsistency	serious[2]	serious[3]	NA	79	78	MD -0.46 (-0.87 to -0.06)	Low
Fasting plasma glucose (mmol/L) at 12 weeks (follow-up 12 weeks; Better indicated by lower values)										
1	RCT	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	NA	29	28	MD -0.7 (-1.62 to 0.22)	Low
Postprandial blood glucose (mmol/L) at 12 weeks (follow-up 12 weeks; Better indicated by lower values)										
1	RCT	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	NA	29	28	MD -0.9 (-2.67 to 0.87)	Low

[1] *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*
[2] *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 of studies	Design	Quality assessment					Number of people		Effect (95% CI)	Quality
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other	CGM	SMBG		

[3] *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)

Number of studies	Design	Quality assessment					Number of people		Effect (95% CI)	Quality
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Fortnightly	Monthly		
Hba1c in patients not on insulin at study end (%; follow up approx. 6 months; Better indicated by lower values)										
1 (Bonomo 2010)	RCT	S1	NA	N	N	NA	177	96	MD 0.04 (-0.20 to 0.28) <u>Subgroup: people compliant with SMBG</u> MD -0.31 (-0.59 to -0.03)	Moderate
Hypoglycaemia in compliant patients not on insulin (defined as BG <3.3 mmol/L)										
1 (Bonomo 2010)	RCT	S1	NA	N	S2	NA	177	96	RR 0.30 (0.03 to 2.86)	Low

[1] *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*

[2] *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	Inconsistency	Indirectness	Imprecision	Other considerations	4 times weekly	Once weekly		
Hba1c at study end in patients not on insulin (%; Better indicated by lower values)										
1 (Scherbaum 2008)	RCT	N	NA	S2	N	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 of SMBG<3.2mmol/L or several events;										
1 (Scherbaum 2008)	RCT	N	NA	S2	S3	NA	18/102 (18%)	5/100 (5%)	RR 3.53 (1.36 to 9.14)	Moderate
Adverse events (hyperglycaemia, deteriorating neuropathy, retinopathy or nephropathy, multiple events or other events)										
1 (Scherbaum 2008)	RCT	N	NA	S2	S1	NA	8/102 (7.8%)	14/100 (14%)	RR 0.56 (0.25 to 1.28)	Low
Serious adverse events (hypoglycaemic shock, hyperosmolar coma, inpatient stay or death)										
1 (Scherbaum 2008)	RCT	N	NA	S2	S1	NA	15/102 (14.7%)	20/100 (20%)	RR 0.74 (0.40 to 1.35)	Low

[1] *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*
[2] *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*
[3] *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 assessment							No of patients			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Forearm	fingertip	Effect (95% CI)	Quality
Change in Hba1c in patients on insulin (follow up approx. 6 months; Better indicated by lower values)										
1 (Knapp 2009)	RCT	N	NA	N	N	none	89	85	MD 0.10 higher (0.29 lower to 0.49 higher)	High

Quality assessment							No of patients			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	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 episode per month)										
1 (Knapp 2009)	RCT	N	NA	N	S1	none	3/89 (3.4%)	3/85 (3.5%)	RR 0.96 (0.20 to 4.60)	Moderate
Severe hypoglycaemia (requiring urgent medical attention)										
1 (Knapp 2009)	RCT	N	NA	N	S1	none	3/89	1/85	RR 2.87 (0.30 to 27.01)	Moderate

[1] *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

Number of RCTs	Quality assessment					Number of people		Relative effect (95% CI)	Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Aspirin	Control		
All-cause mortality; follow-up for up to 5 years									
1 (ETDRS)†	N	NA	S[7]	N	NA	587	565	HR 0.99 (0.83 to 1.17)	Moderate
1 (Sacco 2003)-PPP	VS[1,2]	NA	N	S[4]	NA	25/519	20/512	RR 1.23 (0.69 to 2.19)	Very low
Cardiovascular mortality; follow-up for up to 5 years									
1 (ETDRS)†	N	NA	S[7]	N	NA	587	565	CV death: HR 0.97 (0.79 to 1.19)	Moderate
1 (Sacco 2003)-PPP	VS[1,2]	NA	N	S[4]	NA	10/519	8/512	CV mortality: RR 1.23 (0.49 to 3.10)	Very low
1 (Ogawa 2008)-JPAD	S[1]	NA	N	S[3]	NA	0/1262	5/1277	Fatal MI: HR not estimable due to no events in aspirin group	Low
Cerebrovascular mortality; follow-up for median 4.4 years									
1 (Ogawa 2008)-JPAD	S[1]	NA	N	S[3]	NA	1/1262	5/1277	Fatal stroke: HR 0.20 (0.024 to 1.74)	Low
Coronary and cerebrovascular mortality; follow-up for median 4.4 years									
1 (Ogawa 2008)-JPAD	S[1]	NA	N	S[3]	NA	1/1262	10/1277	HR 0.10 (0.01 to 0.79)	Low
Non-cardiovascular mortality; follow-up to median 3.7 years									
1 (Sacco 2003)-PPP	VS[1,2]	NA	N	S[4]	NA	15/519	12/512	RR 1.23 (0.58 to 2.61)	Very low
Any atherosclerotic event[a]; follow-up from median 3.7 to 4.4 years									
1 (Sacco 2003)-PPP	VS[1,2]	NA	N	S[4]	NA	20/519	22/512	RR 0.90 (0.50 to 1.62)	Very low

Number of RCTs	Quality assessment					Number of people		Relative effect (95% CI)	Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Aspirin	Control		
1 (Ogawa 2008)-JPAD	S[1]	NA	N	S[3]	NA	68/1262	86/1277	HR 0.80 (0.58 to 1.10) Subgroup: age ≥ 65 years: HR 0.68 (0.46 to 0.99 < 65 years: HR 1.00 (0.57 to 1.70) Subgroup: sex Male: HR 0.74 (0.49 to 1.12) Female: HR 0.88 (0.53 to 1.44) Subgroup: cardiovascular risk factors Hypertensive: HR 0.88 (0.60 to 1.30) Normotensive: HR 0.64 (0.36 to 1.13) Dyslipidaemia: HR 0.88 (0.57 to 1.37) Normolipidaemia: HR 0.71 (0.45 to 1.14) Current/past smoking: HR 0.73 (0.47 to 1.14) Non-smoker: HR 0.83 (0.53 to 1.31) Subgroup: renal function eGFR ≥ 90: HR 0.87 (0.36 to 2.12)[d] eGFR 60-89: HR 0.53 (0.34 to 0.83)[d] eGFR < 60: HR 1.24 (0.69 to 2.23)[d] Subgroup: existing therapies Insulin: HR 1.00 (0.50 to 2.00)[d] OHA: HR 0.77 (0.52 to 1.14)[d] Diet alone: HR 0.20 (0.06 to 0.68)[d]	Low
Coronary heart disease events; follow-up from median 3.7 to 5 years									

Number of RCTs	Quality assessment					Number of people		Relative effect (95% CI)	Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Aspirin	Control		
1 (ETDRS)†	N	NA	S[7]	N	NA	587	565	MI: HR 0.85 (0.70 to 1.05)	Moderate
								CV event[b]: HR 0.97 (0.82 to 1.15)	
1 (Sacco 2003)-PPP	VS[1,2]	NA	N	S[4]	NA	53/519	59/512	Total CV events: RR 0.89 (0.62 to 1.26)	Very low
						5/519	10/512	All MI: RR 0.49 (0.17 to 1.40)	
						13/519	16/512	Angina: RR 0.80 (0.39 to 1.64)	
1 (Ogawa 2008)-JPAD	S[1]	NA	N	S[3]	NA	28/1262	35/1277	Any fatal or nonfatal event: HR 0.81 (0.49 to 1.33)	Low
						12/1262	9/1277	Nonfatal MI: HR 1.34 (0.57 to 3.19)	
						12/1262	11/1277	Stable angina: HR 1.10 (0.49 to 2.50)	
						4/1262	10/1277	Unstable angina: HR 0.40 (0.13 to 1.29)	
								Cardiovascular events subgrouped by cardiovascular risk: In low risk group: HR 0.53 (0.23 to 1.21) In high risk group: HR 0.78 (0.55 to 1.11)	
Cerebrovascular events; follow-up from median 3.7 to 5 years									
1 (ETDRS)†	N	NA	S[7]	S	NA	587	565	Stroke: HR 1.09 (0.78 to 1.53)	Low
1 (Sacco 2003)-PPP	VS[1,2]	NA	N	S[4]	NA	9/519	10/512	All stroke: RR 0.89 (0.36 to 2.17)	Very low
						7/519	10/512	Transient ischaemic attack: RR 0.69 (0.27 to 1.79)	
1 (Ogawa 2008)-JPAD	S[1]	NA	N	S[3]	NA	28/1262	32/1277	Any fatal or nonfatal event: HR 0.84 (0.53 to 1.32)	Low
						22/1262	24/1277	Nonfatal ischaemic stroke: HR 0.93 (0.52 to 1.66)	
						5/1262	3/1277	Nonfatal haemorrhagic stroke: HR 1.68 (0.40 to 7.04)	
						5/1262	8/1277	Transient ischaemic attack: HR 0.63 (0.21 to 1.93)	

Number of RCTs	Quality assessment					Number of people		Relative effect (95% CI)	Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Aspirin	Control		
								Cerebrovascular events subgrouped by blood pressure control[c]: In non-aspirin group: HR 2.84 (1.52 to 5.52) indicating higher incidence in unattained group In aspirin group: HR 1.64 (0.83 to 3.29) indicating no difference in incidence in unattained vs. attained No HR reported for aspirin vs. non-aspirin but reported as not significant	
Peripheral artery disease; follow-up from median 3.7 to 4.4 years									
1 (Sacco 2003)-PPP	VS[1,2]	NA	N	S[4]	NA	11/519	13/512	RR 0.83 (0.38 to 1.84)	Very low
1 (Ogawa 2008)-JPAD	S[1]	NA	N	S[3]	NA	7/1262	11/1277	HR 0.64 (0.25 to 1.65)	Low
Revascularisation; follow-up to median 3.7 years									
1 (Sacco 2003)-PPP	VS[1,2]	NA	N	S[4]	NA	8/519	10/512	RR 0.79 (0.31 to 1.97)	Very low
								Creatinine clearance: MD -2.30 (-5.42 to 0.82)	
								Urine protein:creatinine ratio: MD -0.30 (-0.53 to -0.07)	
								% proteinuria change: MD -17.80 (-22.95 to -12.65)	
Adverse events: Any bleeding; follow-up for median 4.4 years									
1 (ETDRS 1992)	N	NA	S[7,8]	NA	NA	587	565	Only a few patients (2%) in both groups had some indication of bleeding[‡]	Low

Number of RCTs	Quality assessment					Number of people		Relative effect (95% CI)	Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Aspirin	Control		
1 (Ogawa 2008)-JPAD	S[1]	NA	N	S[3]	NA	1251	1272	Haemorrhagic events subgrouped by renal function: eGFR ≥ 90: HR not estimable eGFR 60-89: HR 1.03 (0.24 to 4.35) eGFR < 60: HR: 0.87 (0.10 to 7.27)	Low
	S[1]	NA	N	N	NA	21/1262	6/1277	Other bleeding: RR 3.54 (1.43 to 8.75)	Moderate
	S[1]	NA	N	S[3]	NA	12/1262	4/1277	Gastrointestinal bleeding: RR 3.04 (0.98 to 9.39)	Low
Non-bleeding gastrointestinal event; follow-up for median 4.4 years									
1 (Ogawa 2008)-JPAD	S[1]	NA	N	N	NA	47/1262	4/1277	RR 11.89 (4.30 to 32.90)	Moderate
Other adverse event[e]; follow-up for median 4.4 years									
1 (Ogawa 2008)-JPAD	S[1]	NA	N	S[3]	NA	5/1262	0/1277	RR 11.13 (0.62 to 201.08)	Low

Number of RCTs	Quality assessment					Number of people		Relative effect (95% CI)	Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Aspirin	Control		

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

[1] *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.*

[2] *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*

[3] *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*

[4] *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)*

[7] *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*

[8] *Downgrade by 1 level: for all patients (including those with type 1 or mixed diabetes)*

[a] *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*

[b] *CV event was defined as CV death, myocardial infarction or stroke*

[c] *unattained group had systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg and the attained group had systolic BP < 140mmHg and/or diastolic BP < 90mmHg*

[d] *adjusted for age, hypertension, dyslipidaemia and history of smoking*

[e] *Anaemia and asthma*

[†] *Unpublished subgroup analysis for people with type 2 diabetes without a history of cardiovascular disease from the ETDRS trial was provided by the authors*

[‡] *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

Number of RCTs	Quality assessment					Number of people		Effect (95% CI)	Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	PDE-5 inhibitor	Placebo		
Erectile function IIEF- EF domain (follow-up 12 to 16 weeks)									
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[1]	not serious	serious[2,3]	serious[4]	NA	2142	1174	MD 5.58 (4.48 to 6.68)	Low
Erectile function (SEP Q2 positive response) (follow-up 12 weeks)									
5 (Goldstein 2003, 2012; Hatzichristou 2008; Ishii 2006; Ziegler 2006)	serious[1]	not serious	serious[2,3]	not serious	NA	1059/1559	274/616	RR 1.47 (1.33 to 1.61)	Low
Erectile function (SEP Q3- positive response) (follow-up 12 weeks)									
5 (Goldstein 2003, 2012; Hatzichristou 2008; Ishii 2006; Ziegler 2006)	serious[1]	not serious	serious[2,3]	not serious	NA	800/1551	160/618	RR 1.87 (1.61 to 2.16)	Low
Erectile function GEQ (Improvement) (follow-up 12 to 16 weeks)									
8 (Boulton 2001; Escobar-Jimenez 2002; Goldstein 2003; Hatzichristou 2008; Rendell 1999; Saenz de	not serious	not serious	serious[2,3]	not serious	NA	623/1064	116/743	RR 3.62 (2.57 to 5.09)	Moderate

Number of RCTs	Quality assessment					Number of people		Effect (95% CI)	Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	PDE-5 inhibitor	Placebo		
Tejada 2002; Safarinejad 2004; Stuckey 2003)									
Adverse events (follow-up 12 to 16 weeks)									
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[1]	serious[5]	serious[2,3]	not serious	NA	610/9064	115/5249	RR 2.69 (1.87 to 3.86)	Low
Adverse events - Headache (follow-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[1]	serious[5]	serious[3]	not serious	NA	185/2065	43/1126	RR 3.08 (1.46 to 6.48)	Low
Adverse events - Flushing (follow-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[1]	not serious	serious[3]	not serious	NA	191/2065	6/1126	RR 8.65 (4.5 to 16.66)	Low
Adverse events - Bronchitis									

Number of RCTs	Quality assessment					Number of people		Effect (95% CI)	Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	PDE-5 inhibitor	Placebo		
1 (Ziegler 2006)	not serious	not serious	serious[3]	not serious	NA	3/163	4/155	RR 0.71 (0.16 to 3.14)	Moderate
Adverse events - Upper respiratory tract infections (follow-up 12 to 16 weeks)									
7 (Goldstein 2003, 2012; Ishii 2006; Rendell 1999; Saenz de Tejada 2002; Safarinejad 2004; Ziegler 2006)	serious[1]	serious[4]	serious[3]	not serious	NA	147/1814	43/875	RR 1.12 (0.57 to 2.2)	Low
Adverse events - Discontinuation due to AE (follow-up 12 to 16 weeks)									
9 (Goldstein 2003, 2012; Hatzichristou 2008; Ishii 2006; Rendell 1999; Saenz de Tejada 2002; Safarinejad 2004; Stuckey 2003; Ziegler 2006)	serious[1]	not serious	serious[2,3]	not serious	NA	46/2013	14/1167	RR 1.67 (0.89 to 3.13)	Low
Adverse events - Dyspepsia (follow-up 12 weeks)									
4 (Boulton 2001; Goldstein 2012; Rendell 1999; Stuckey 2003)	not serious	not serious	serious[3]	not serious	NA	26/601	2/465	RR 6.09 (1.77 to 20.94)	Moderate
Adverse events - Abnormal vision (follow-up 12 weeks)									
3 (Boulton 2001; Rendell 1999; Stuckey 2003)	not serious	not serious	serious[3]	not serious	NA	12/343	3/335	RR 2.92 (0.71 to 11.99)	Moderate

[1] 2 studies (Saenz de Tejada 2002, Ishii 2006) do not report allocation concealment to determine if performance bias was present
[2] 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.

Number of RCTs	Quality assessment					Number of people		Effect (95% CI)	Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	PDE-5 inhibitor	Placebo		
[3] 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.									
[4] Standard deviations were not reported in the paper and were calculated using p-values									
[5] pairwise comparisons of the included studies (direct comparisons) showed an I^2 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									

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

No of studies	Quality assessment						Number of patients			
	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Placebo	Effect/ outcome	Quality
Erectile Function (measured with International Index of Erectile Function [IIEF] mean score on EF domain, sum of questions 1-5 and 15; range of scores 1-30; better efficacy is indicated by higher values)										
Sildenafil vs. placebo										
1 (Boulton et al 2001)	RCTs	N	N	N	S[2]	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. placebo										

	Quality assessment						Number of patients			
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[1]	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. placebo										
2 (Hatzichristou 2008, Saenz 2002)	RCT (3 arms)	S[4]	N	S[3]	S[5]	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	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Placebo	Effect/ outcome	Quality

[1] *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.*
[2] *Downgrade by 1 level: small sample used which may have increased risk of a type 2 error*
[3] *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.*
[4] *Downgrade by 1 level: 1 study (Saenz 2002) does not report allocation concealment to determine if performance bias was present*
[5] *Downgrade by 1 level: subgroup analyses were exploratory post-hoc analyses in one study*
[*] *P<0.0001 vs. placebo*

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

Quality assessment							Number of patients			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Placebo	Effect/ outcome	Quality
EF (IIEF EF domain)										
Tadalafil on demand vs. Tadalafil three times per week										
Buvat 2006	RCT*	S[1]	NA	S[2]	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. Mean change from baseline 8.9 (SE 0.3) on demand and 9.1 (SE 0.3) for 3 times per week	Low
Erectile function (mean scores of SEP Q2 successful insertion)										
Tadalafil on demand vs. Tadalafil three times per week										

Quality assessment							Number of patients			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Placebo	Effect/ outcome	Quality
Buvat 2006	RCT*	S[1]	NA	S[2]	N	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
Erectile function (mean scores of SEP Q3 successful intercourse)										
Tadalafil on demand vs. Tadalafil three times per week										
Buvat 2006	RCT*	S[1]	NA	S[2]	N	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 (any)										
Tadalafil on demand vs. Tadalafil three times per week										
Buvat 2006	RCT*	S[1]	NA	S[2]	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 versus tadalafil										
Kamenov 2004	RCT	N	NA	S[3, 4]	N	none	7/24 (tadalafil)	6/25 (vardenafil)	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 assessment							Number of patients			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Placebo	Effect/ outcome	Quality

[1] Downgrade by 1 level: open label study with one week washout period, which may not be sufficient to avoid carry-over effects
[2] 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.
[3] Downgrade by 1 level: this trial was restricted to first intake of the intervention rather than continued treatment
[4] 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?

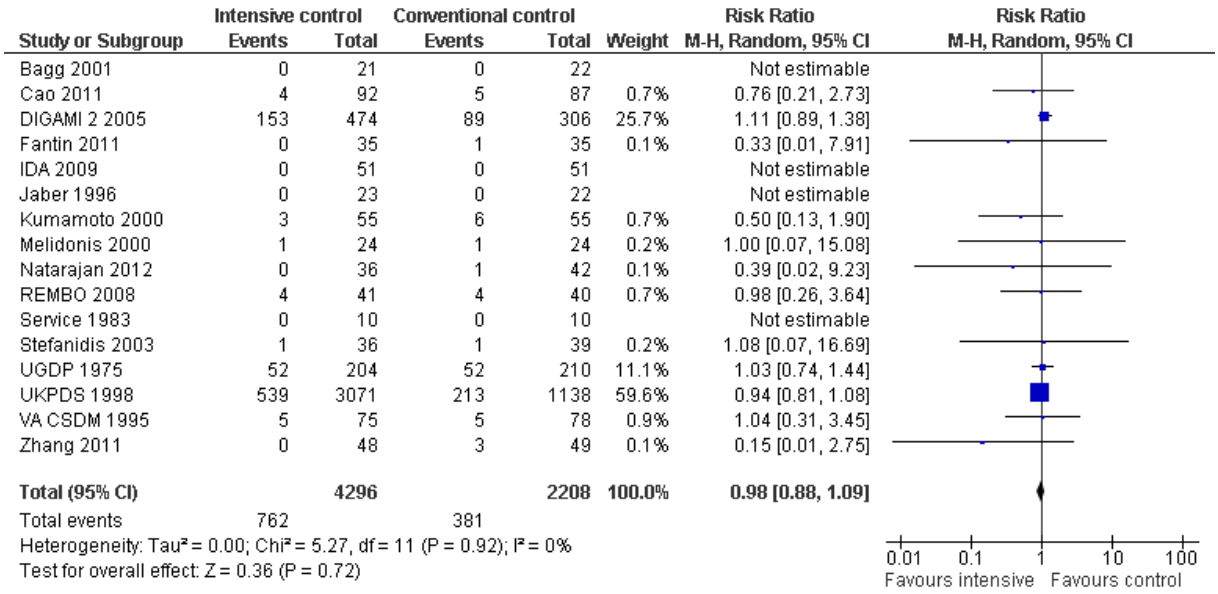

Figure 1: Forest plot for all-cause mortality

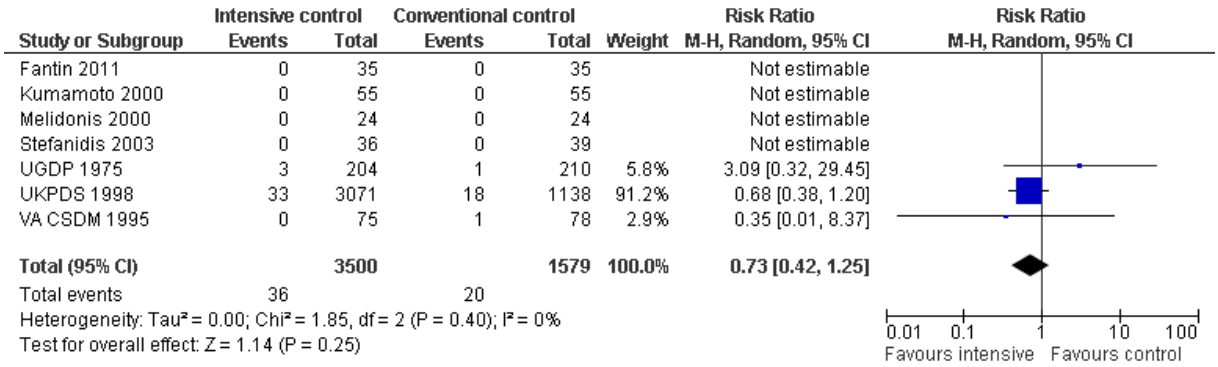

Figure 2: Forest plot for amputation

Study or Subgroup	Intensive control Events	Total	Conventional control Events	Total	Weight	Risk Ratio 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]
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: Tau² = 0.00; Chi² = 2.08, df = 5 (P = 0.84); I² = 0%
Test for overall effect: Z = 1.42 (P = 0.15)

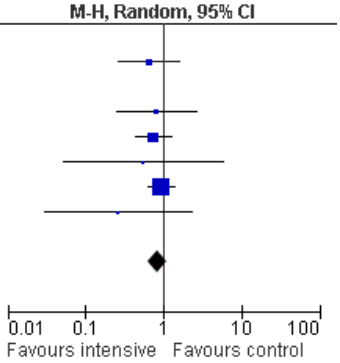

Figure 3: Forest plot for coronary heart failure

Study or Subgroup	Intensive control Events	Total	Conventional control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
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% CI)		**201**		**207**	**100.0%**	**1.14 [0.42, 3.15]**
Total events	8		7			

Heterogeneity: Tau² = 0.00; Chi² = 1.58, df = 3 (P = 0.66); I² = 0%
Test for overall effect: Z = 0.26 (P = 0.79)

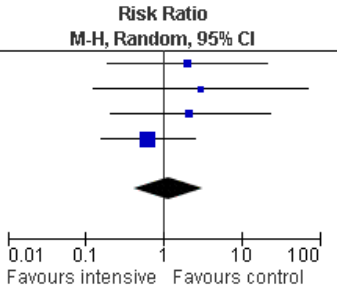

Figure 4: Forest plot for cardiovascular revascularisation

Study or Subgroup	Intensive control Events	Total	Conventional control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
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]
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 = 0.00; Chi² = 3.18, df = 9 (P = 0.96); I² = 0%
Test for overall effect: Z = 1.67 (P = 0.09)

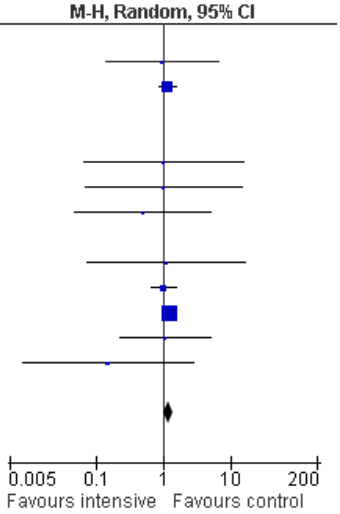

Figure 5: Forest plot for cardiovascular mortality

Study or Subgroup	Intensive control Events	Total	Conventional control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
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 applicable
Test for overall effect: Z = 0.16 (P = 0.87)

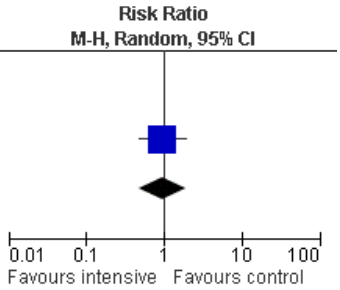

Figure 6: Forest plot for end stage renal disease

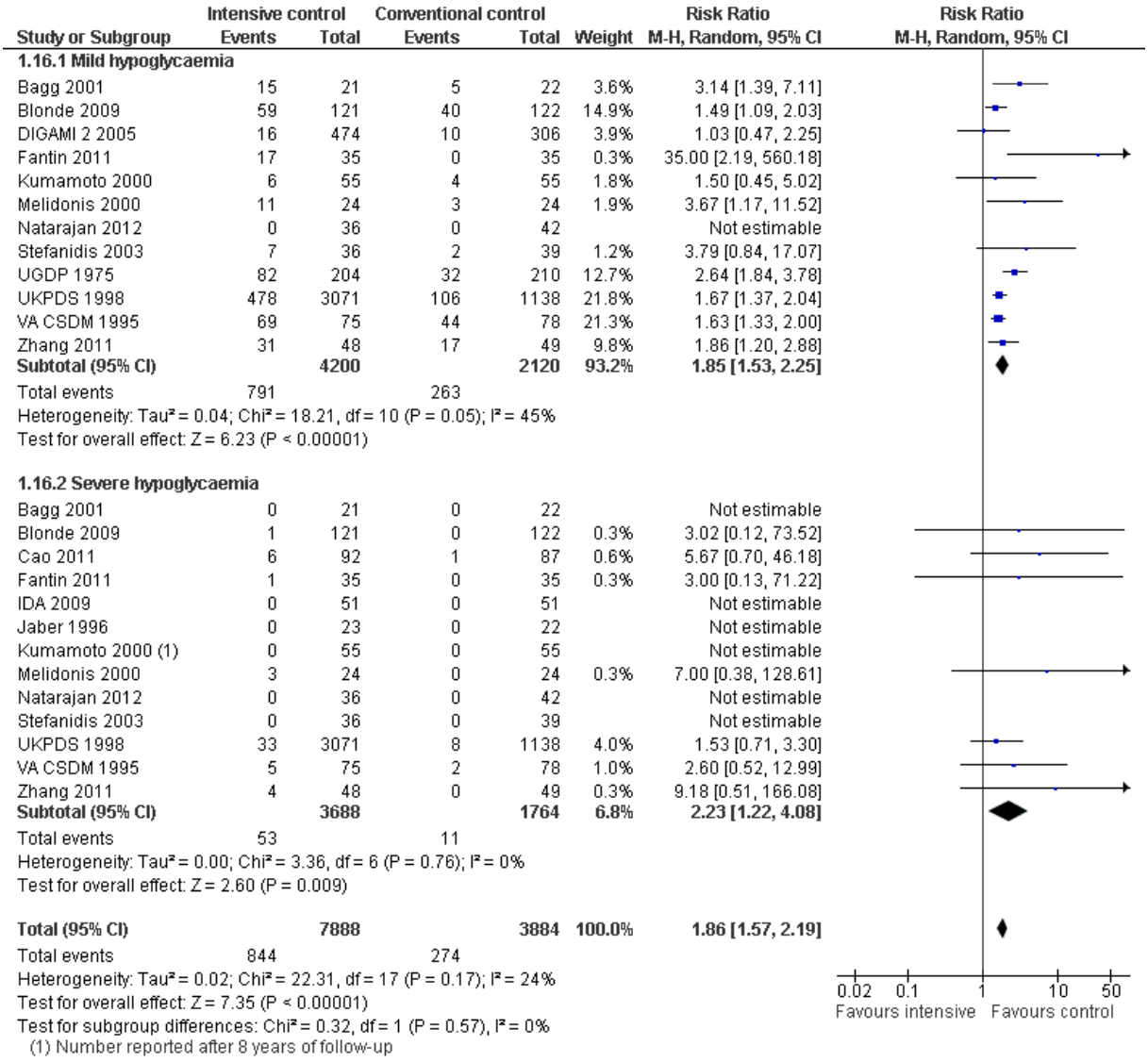

Figure 7: Forest plot for hypoglycaemia

Study or Subgroup	Intensive control Events	Total	Conventional control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
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]
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]
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: Tau² = 0.05; Chi² = 12.86, df = 7 (P = 0.08); I² = 46%
Test for overall effect: Z = 0.14 (P = 0.89)

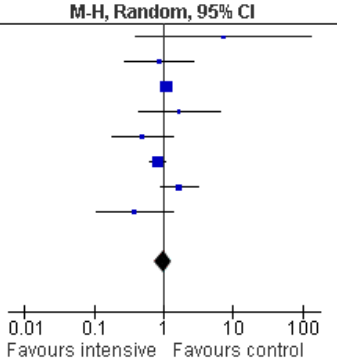

Figure 8: Forest plot for macrovascular complications

Study or Subgroup	Intensive control Events	Total	Conventional control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
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 = 0.00; Chi² = 0.82, df = 1 (P = 0.37); I² = 0%
Test for overall effect: Z = 2.79 (P = 0.005)

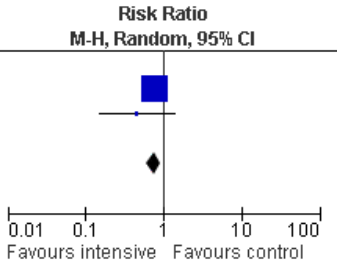

Figure 9: Forest plot for microvascular complications

Study or Subgroup	Intensive control Events	Total	Conventional control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
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: Tau² = 0.46; Chi² = 14.59, df = 5 (P = 0.01); I² = 66%
Test for overall effect: Z = 1.24 (P = 0.22)

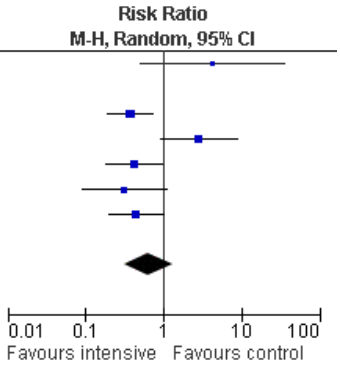

Figure 10: Forest plot for nephropathy

Study or Subgroup	Intensive control Events	Total	Conventional control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
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: Tau² = 0.00; Chi² = 3.61, df = 5 (P = 0.61); I² = 0%
Test for overall effect: Z = 0.96 (P = 0.34)

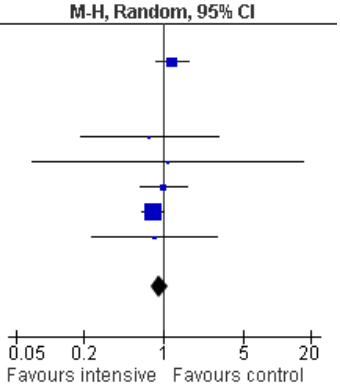

Figure 11: Forest plot for non-fatal myocardial infarction

Study or Subgroup	Intensive control Events	Total	Conventional control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
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]
VA CSDM 1995	2	75	5	78	3.2%	0.42 [0.08, 2.08]
Total (95% CI)		**3791**		**1697**	**100.0%**	**1.06 [0.80, 1.41]**
Total events	156		65			

Heterogeneity: Tau² = 0.00; Chi² = 2.68, df = 4 (P = 0.61); I² = 0%
Test for overall effect: Z = 0.41 (P = 0.68)

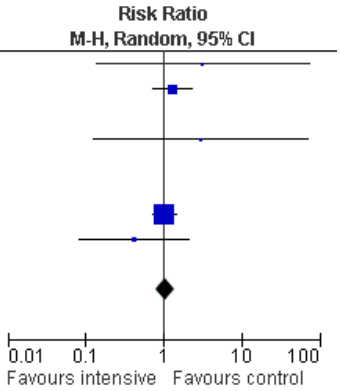

Figure 12: Forest plot for non-fatal stroke

Study or Subgroup	Intensive control Events	Total	Conventional control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
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
Test for overall effect: Not applicable

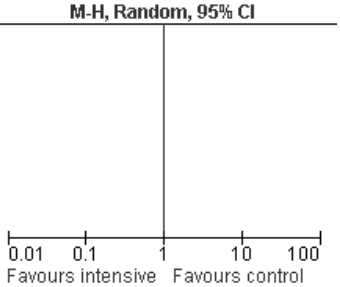

Figure 13: Forest plot for peripheral vascularisation

Study or Subgroup	Intensive control Events	Total	Conventional control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
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; Chi² = 3.05, df = 2 (P = 0.22); I² = 34%
Test for overall effect: Z = 1.53 (P = 0.13)

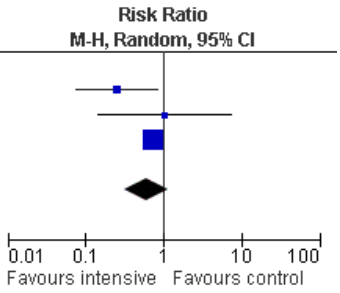

Figure 14: Forest plot for retinal photocoagulation

Study or Subgroup	Intensive control Events	Total	Conventional control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
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; Chi² = 10.46, df = 3 (P = 0.02); I² = 71%
Test for overall effect: Z = 1.35 (P = 0.18)

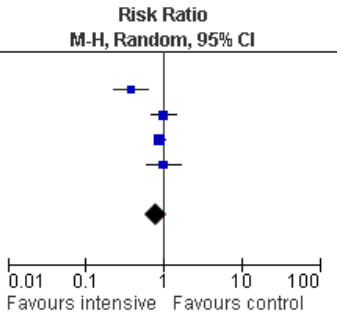

Figure 15: Forest plot for retinopathy

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

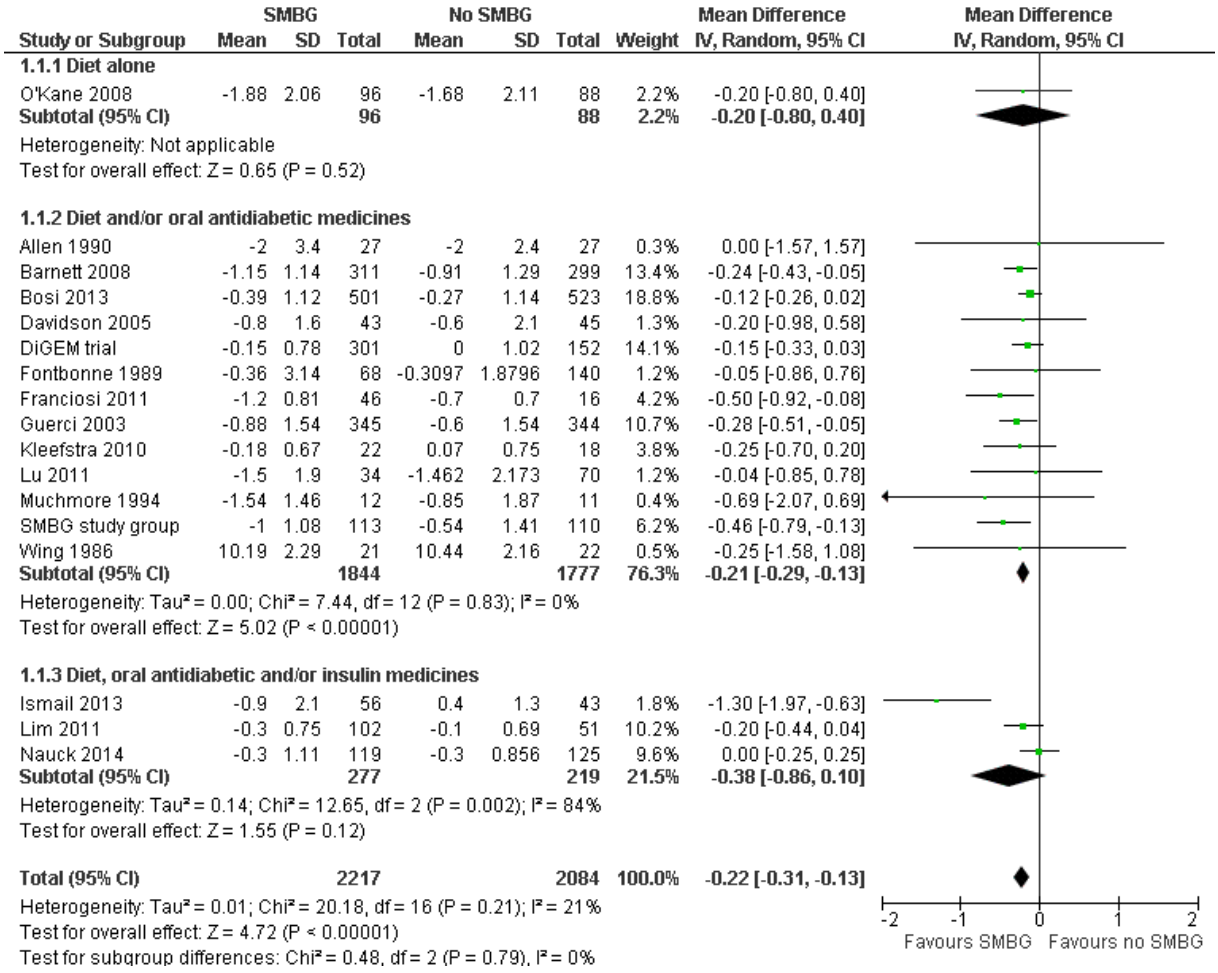

Figure 16: Forest plot for HbA1c (subgroup for current therapies)

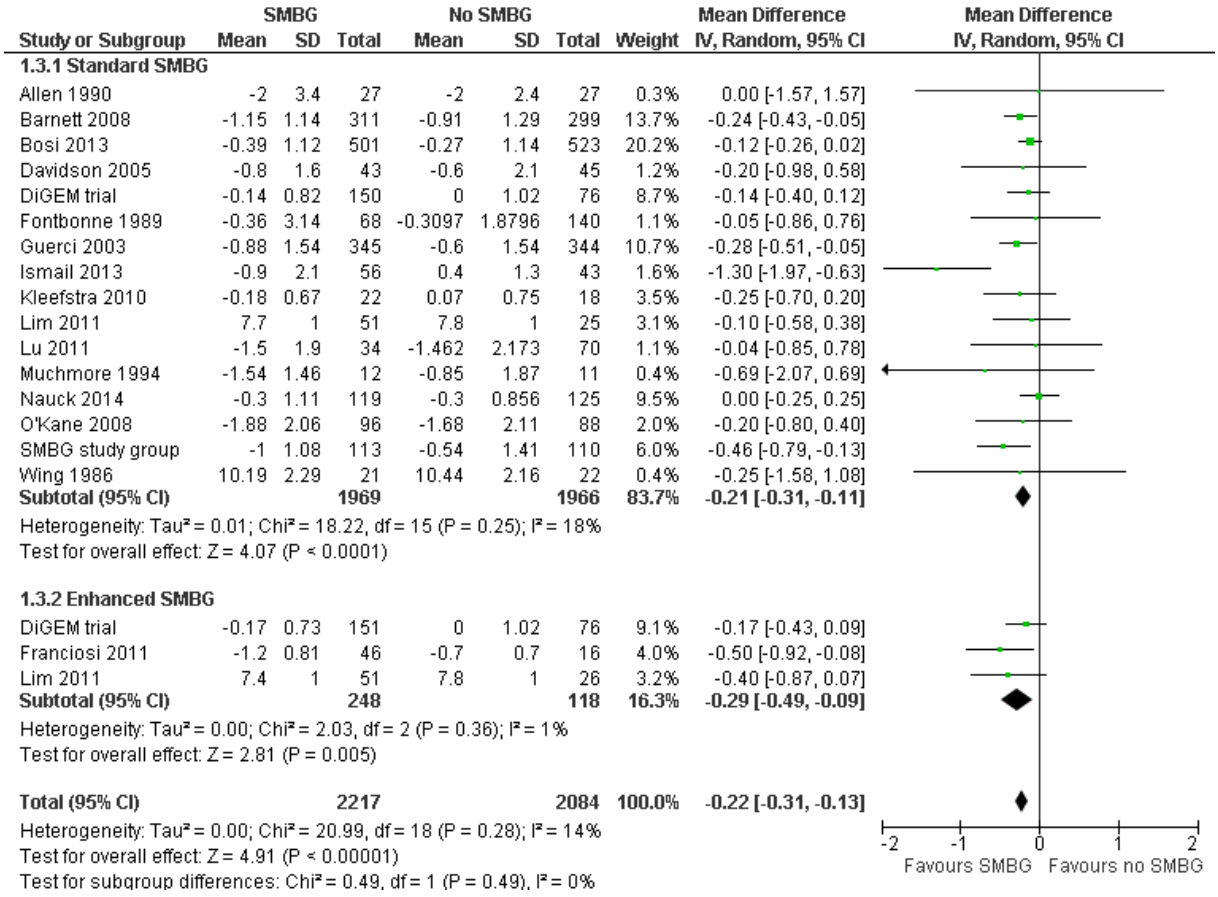

Figure 17: Forest plot for HbA1c (subgroup for SMBG type)

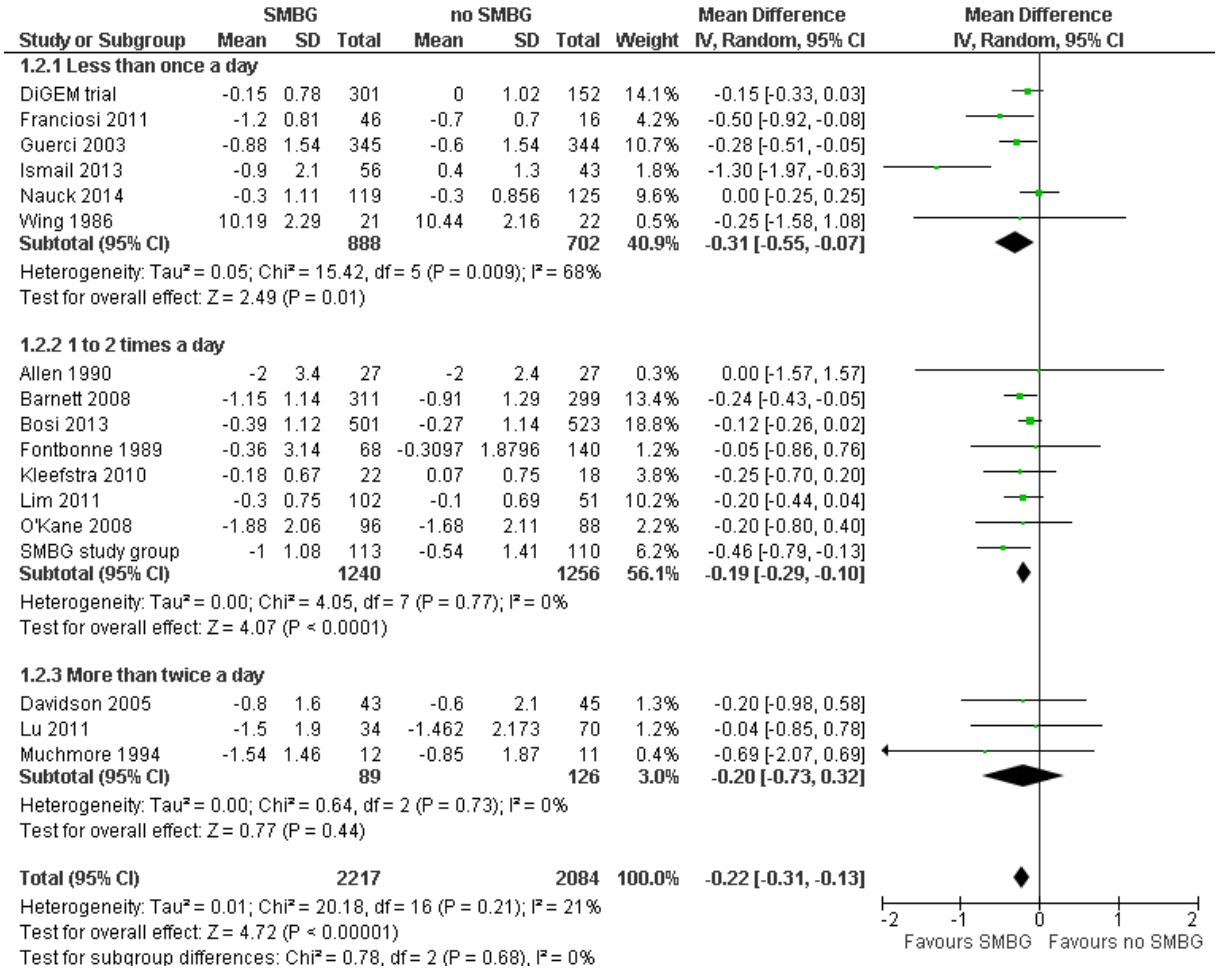

Figure 18: Forest plot for HbA1c (subgroup for SMBG frequency)

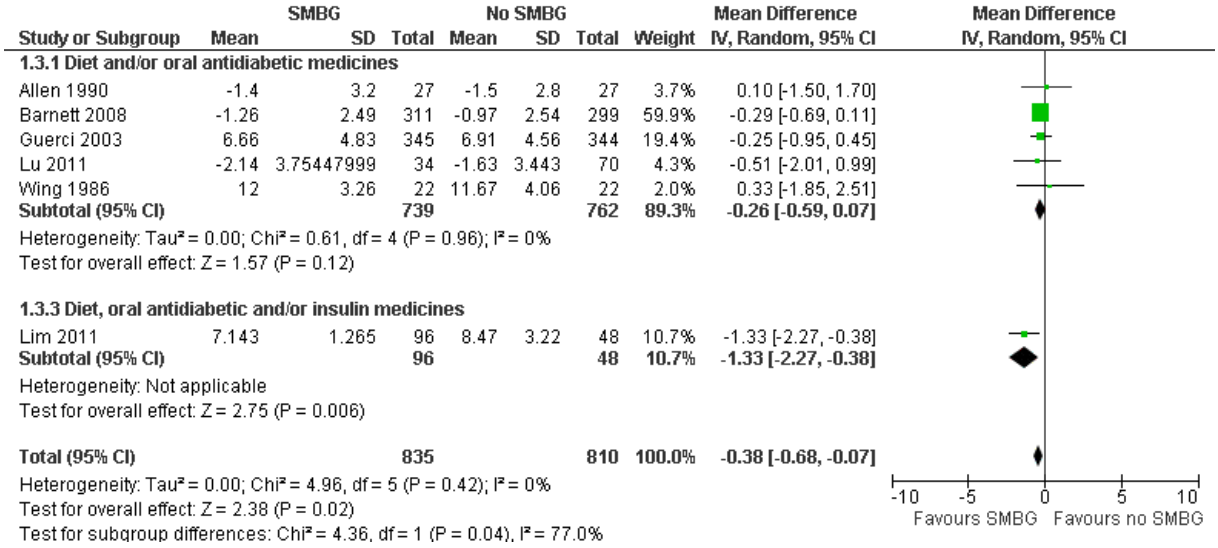

Figure 19: Forest plot for fasting blood glucose (subgroup for current therapies)

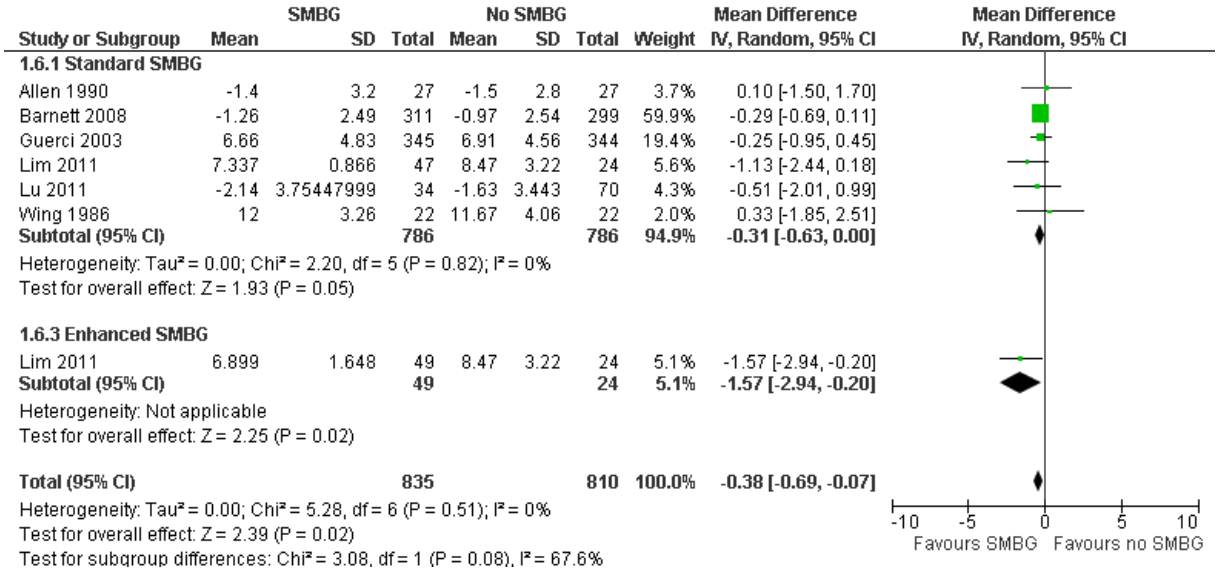

Figure 20: Forest plot for fasting blood glucose (subgroup for SMBG types)

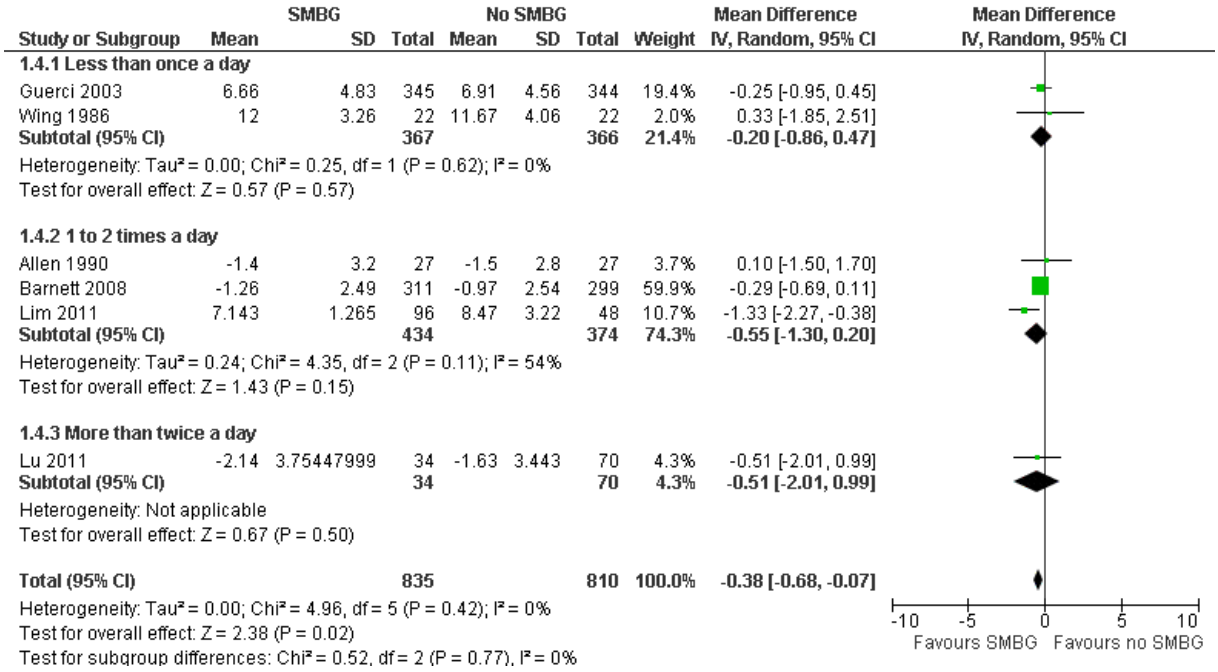

Figure 21: Forest plot for fasting blood glucose (subgroup for SMBG frequency)

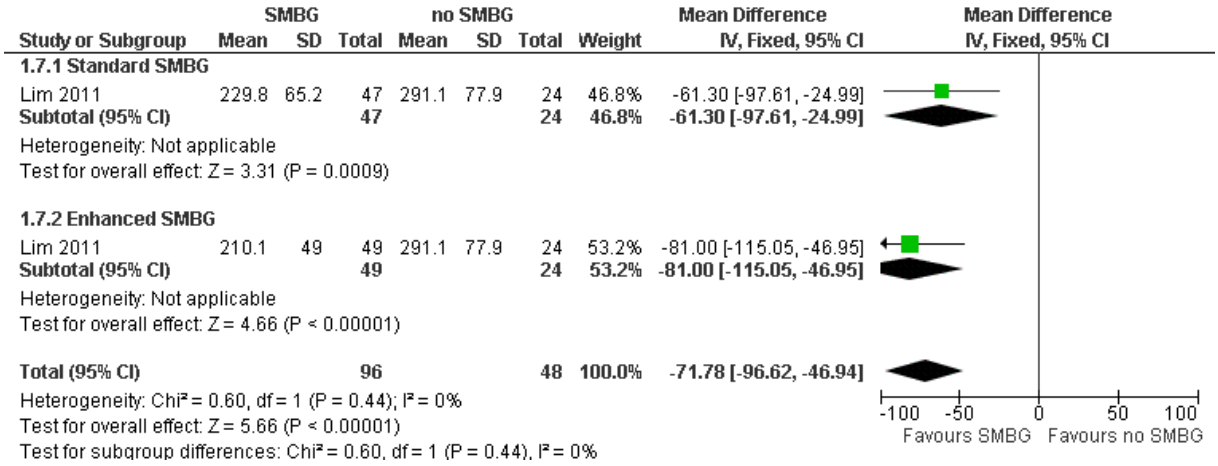

Figure 22: Forest plot for postprandial blood glucose

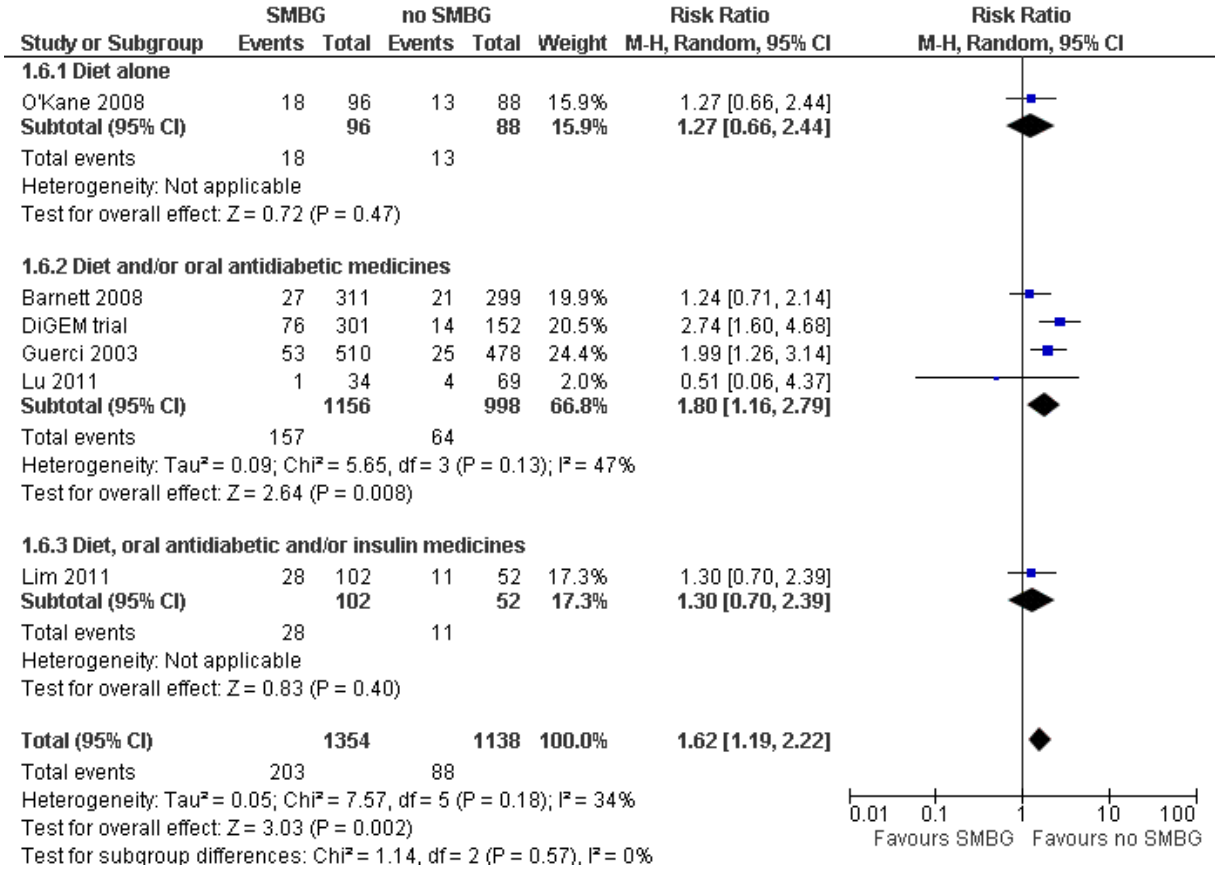

Figure 23: Forest plot for any hypoglycaemia (subgroup for current therapies)

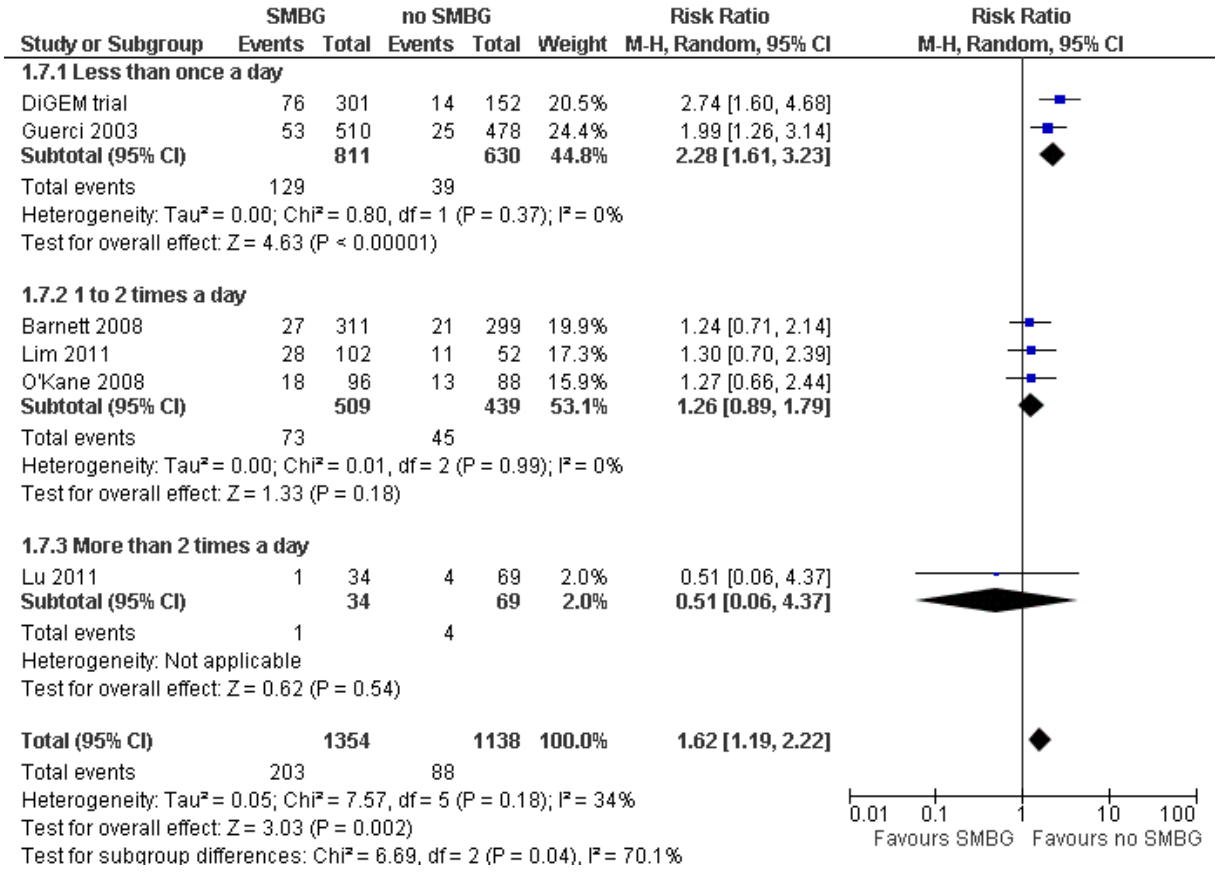

Figure 24: Forest plot for any hypoglycaemia (subgroup for SMBG frequency)

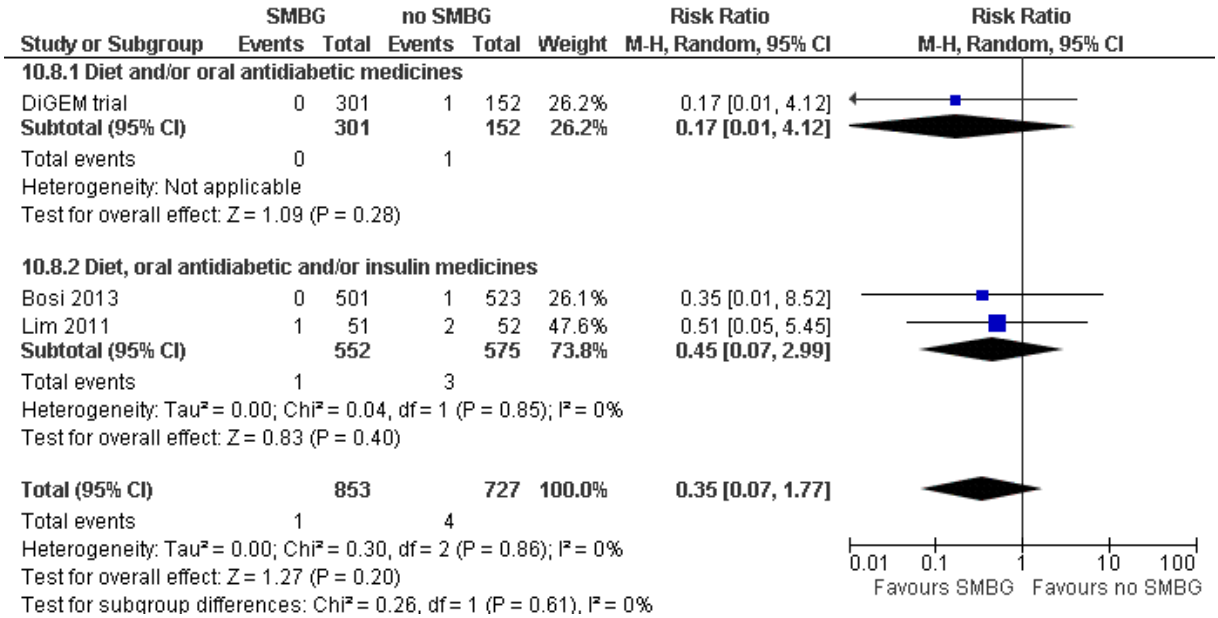

Figure 25: Forest plot for severe hypoglycaemia (subgroup for current therapies)

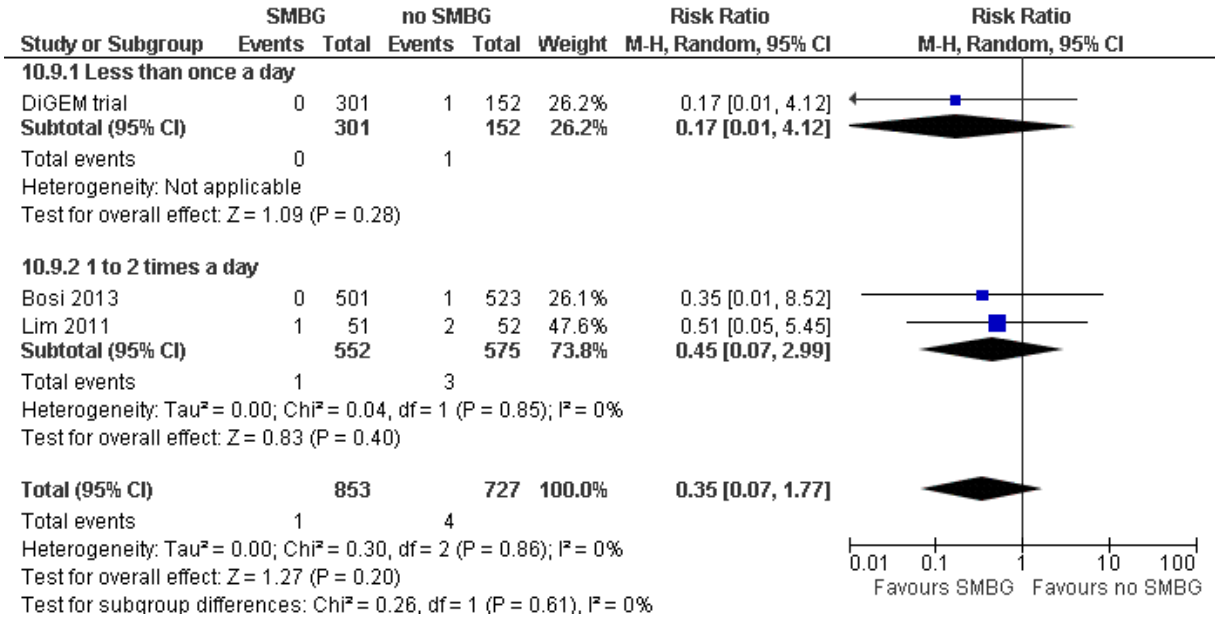

Figure 26: Forest plot for severe hypoglycaemia (subgroup for SMBG frequency)

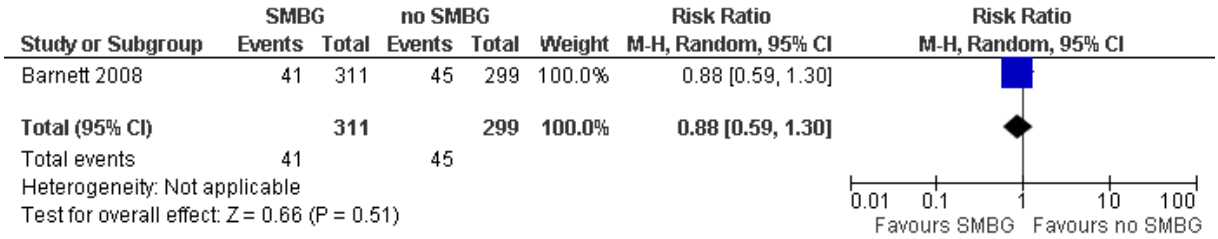

Figure 27: Forest plot for fasting adverse events

D.2.5.2 SMBG plus education vs. conventional SMBG

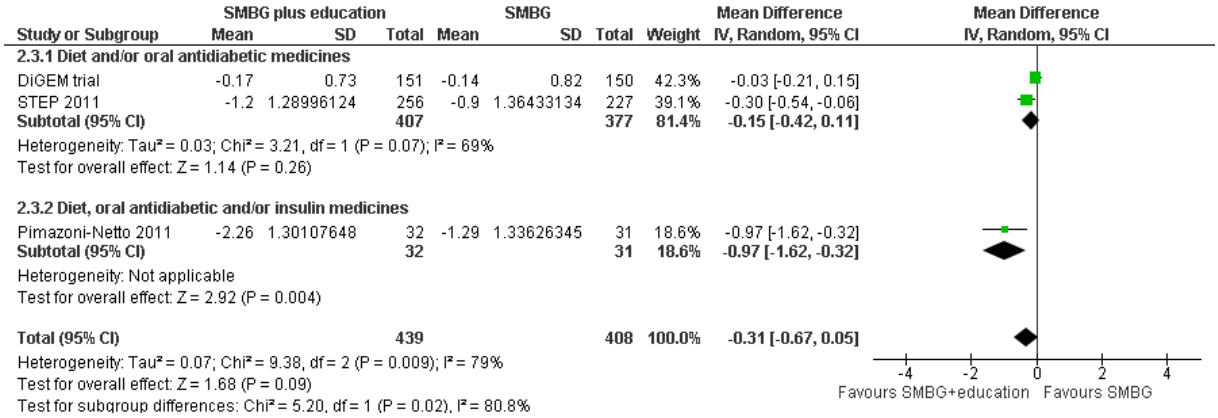

Figure 28: Forest plot for HbA1c

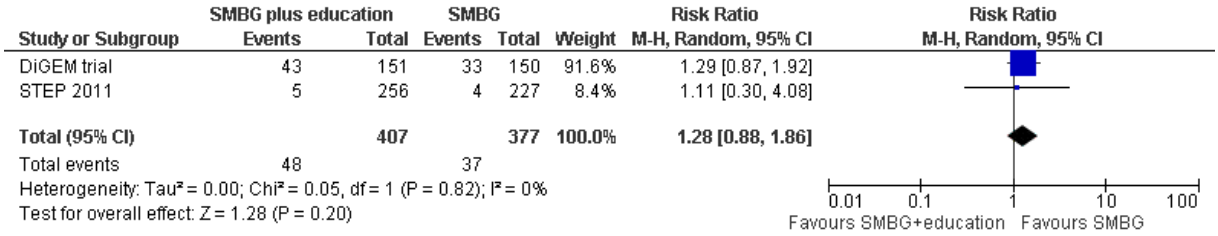

Figure 29: Forest plot for any hypoglycaemia

D.2.5.3 SMBG plus telecare vs. conventional SMBG

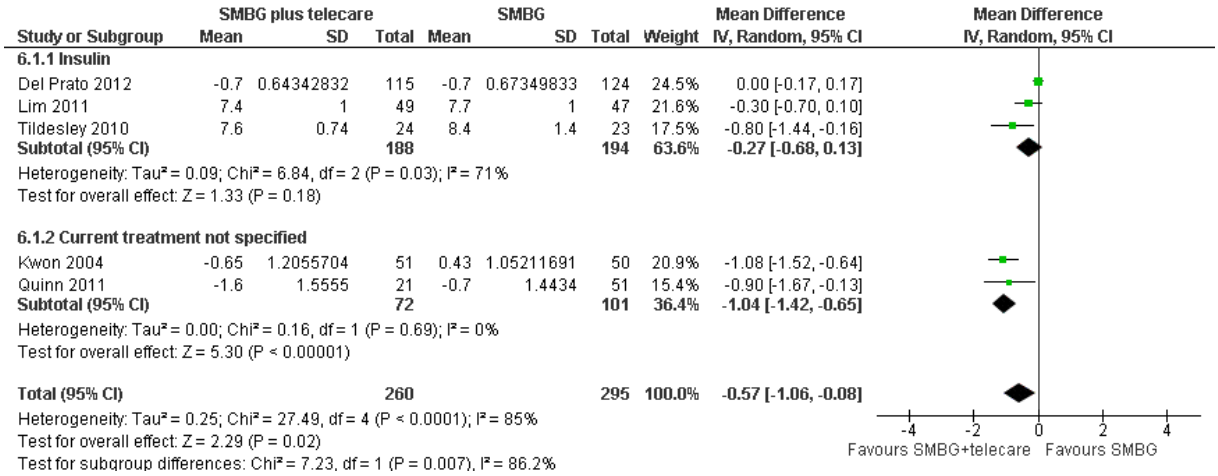

Figure 30: Forest plot for HbA1c

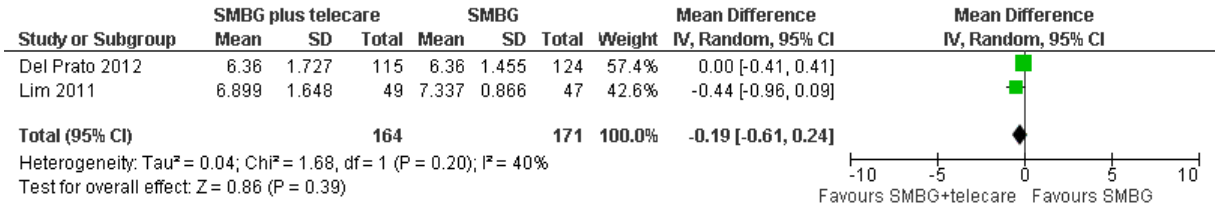

Figure 31: Forest plot for fasting blood glucose

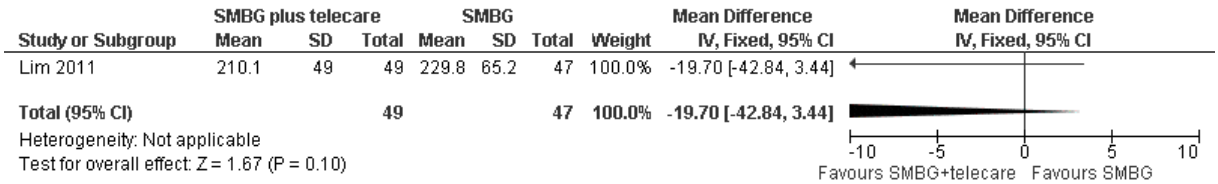

Figure 32: Forest plot for postprandial blood glucose

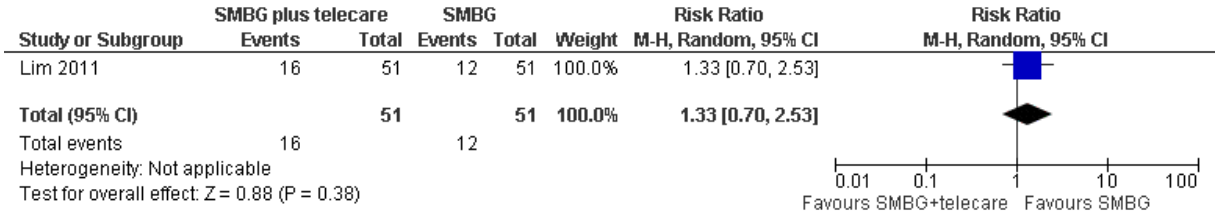

Figure 33: Forest plot for any hypoglycaemia

D.2.5.4 Automated mobile phone glucometer vs. standard glucometer

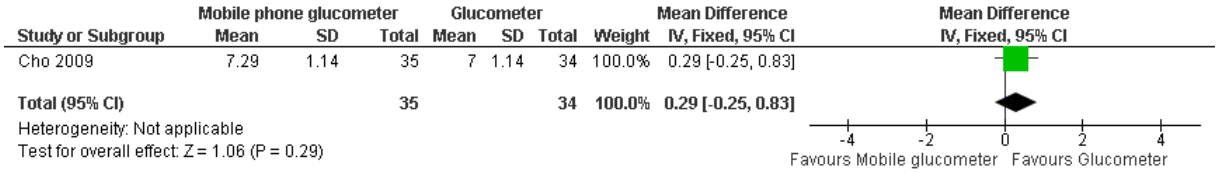

Figure 34: Forest plot for HbA1c

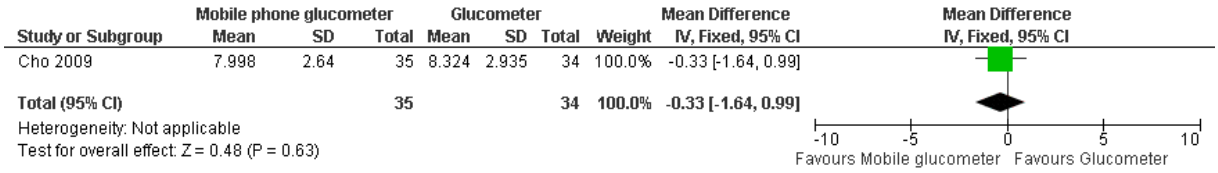

Figure 35: Forest plot for fasting blood glucose

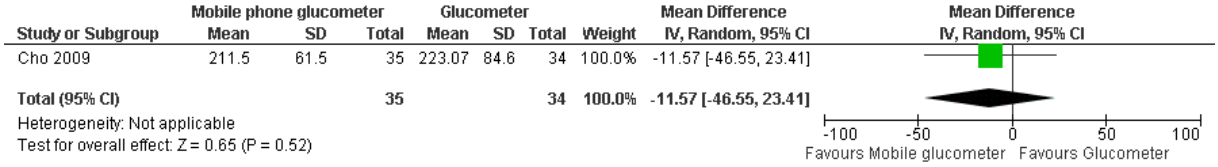

Figure 36: Forest plot for postprandial blood glucose

D.2.5.5 SMBG plus continuous glucose monitoring vs conventional SMBG

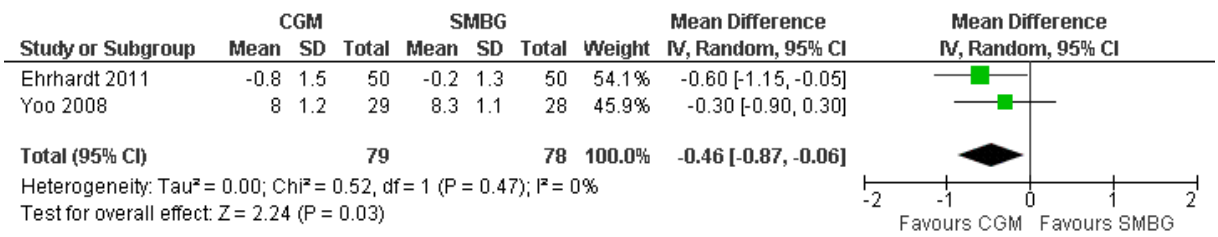

Figure 37: Forest plot for HbA1c

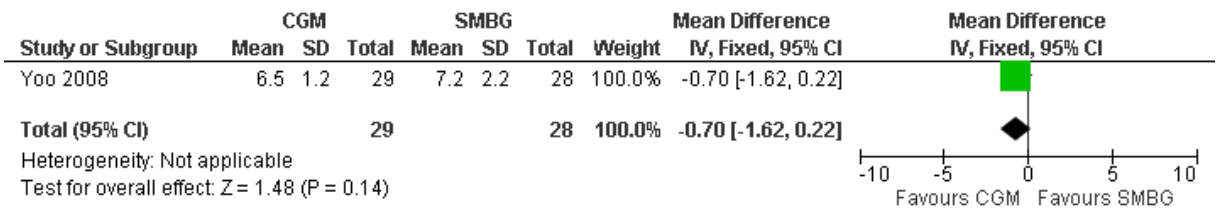

Figure 38: Forest plot for fasting blood glucose

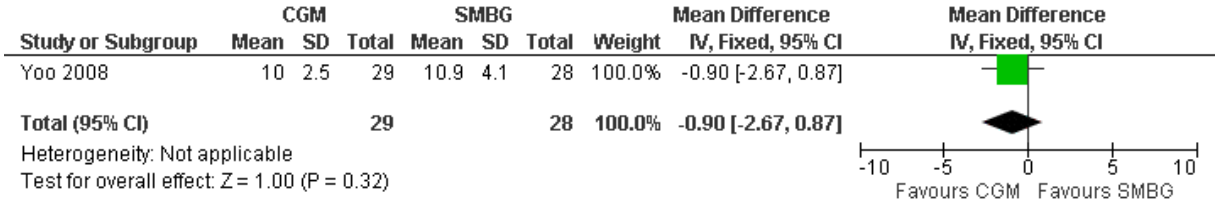

Figure 39: Forest plot for postprandial blood glucose

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

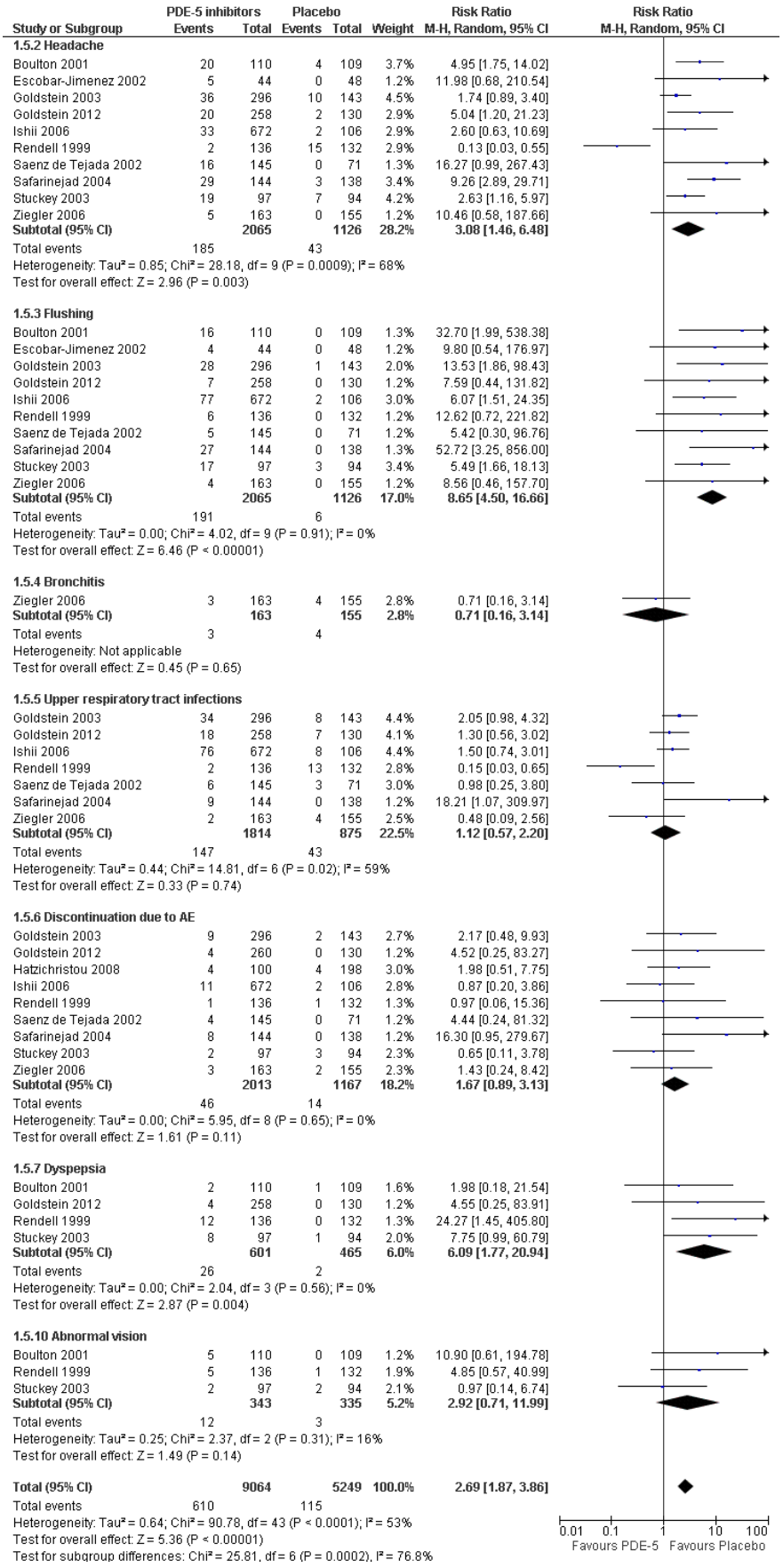

Figure 40: Forest plot for adverse events

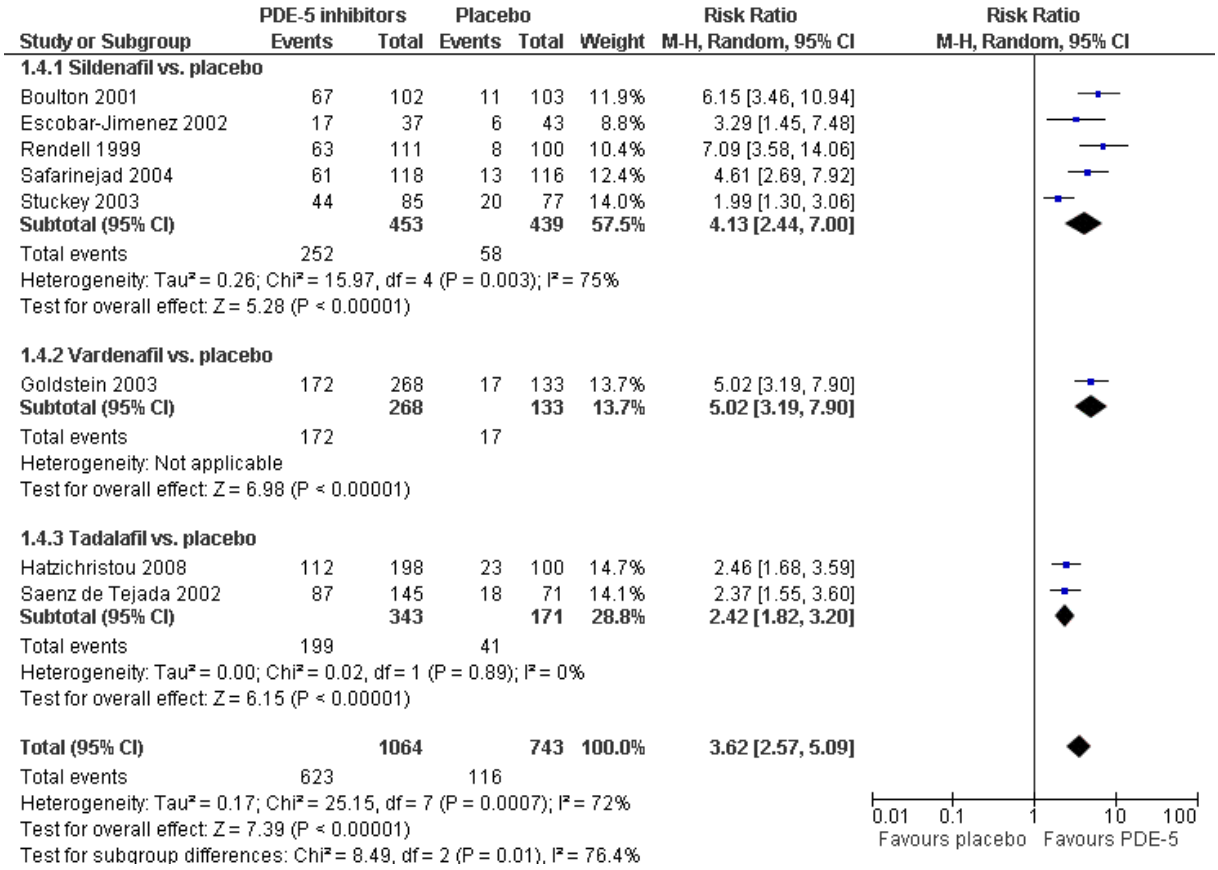

Figure 41: Forest plot for global efficacy question

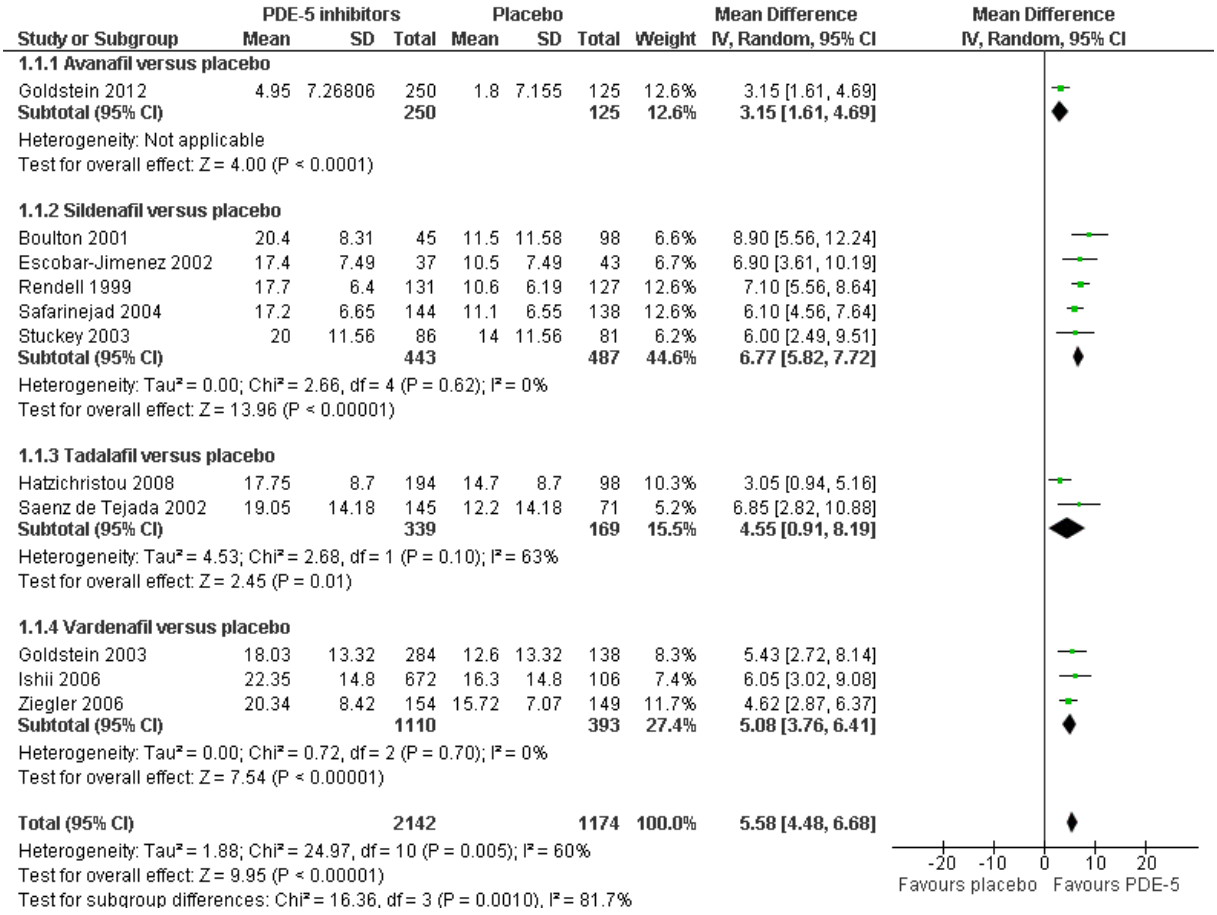

Figure 42: Forest plot for IIEF – erectile function domain

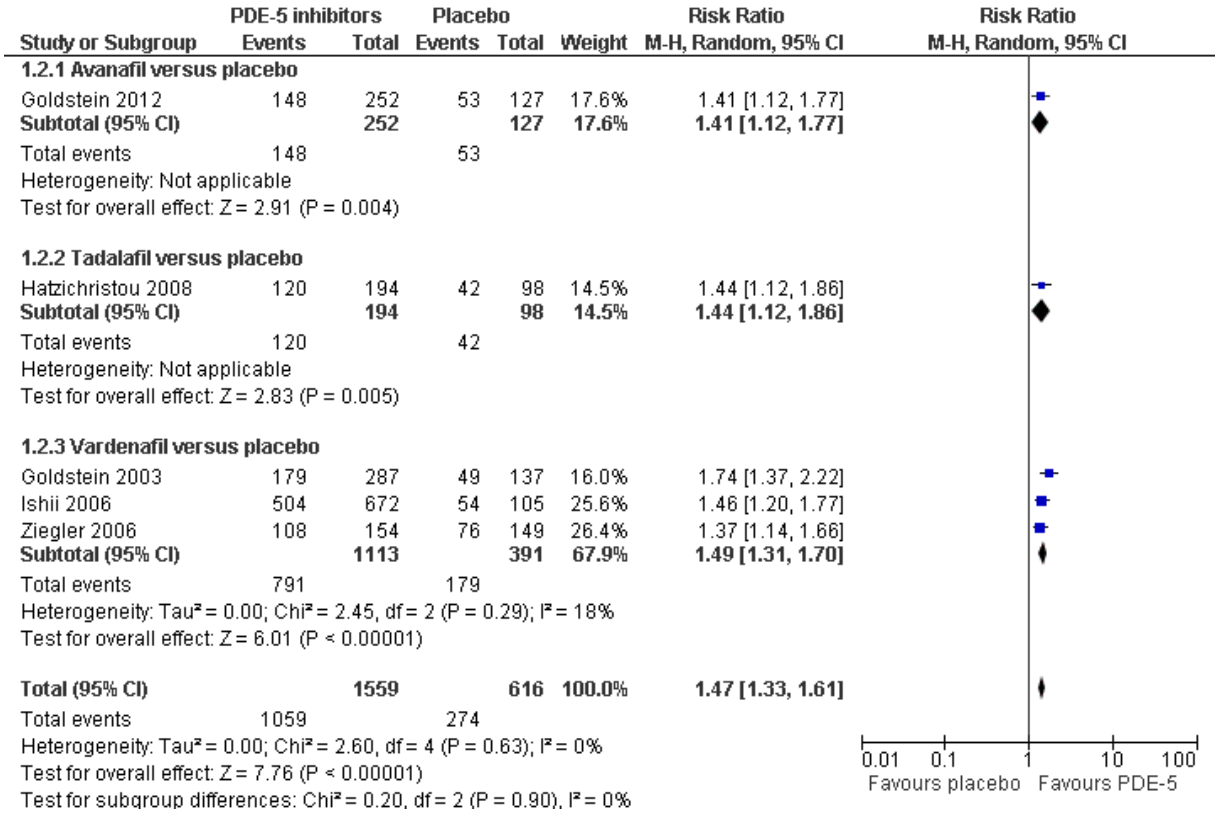

Figure 43: Forest plot for SEP – Q2

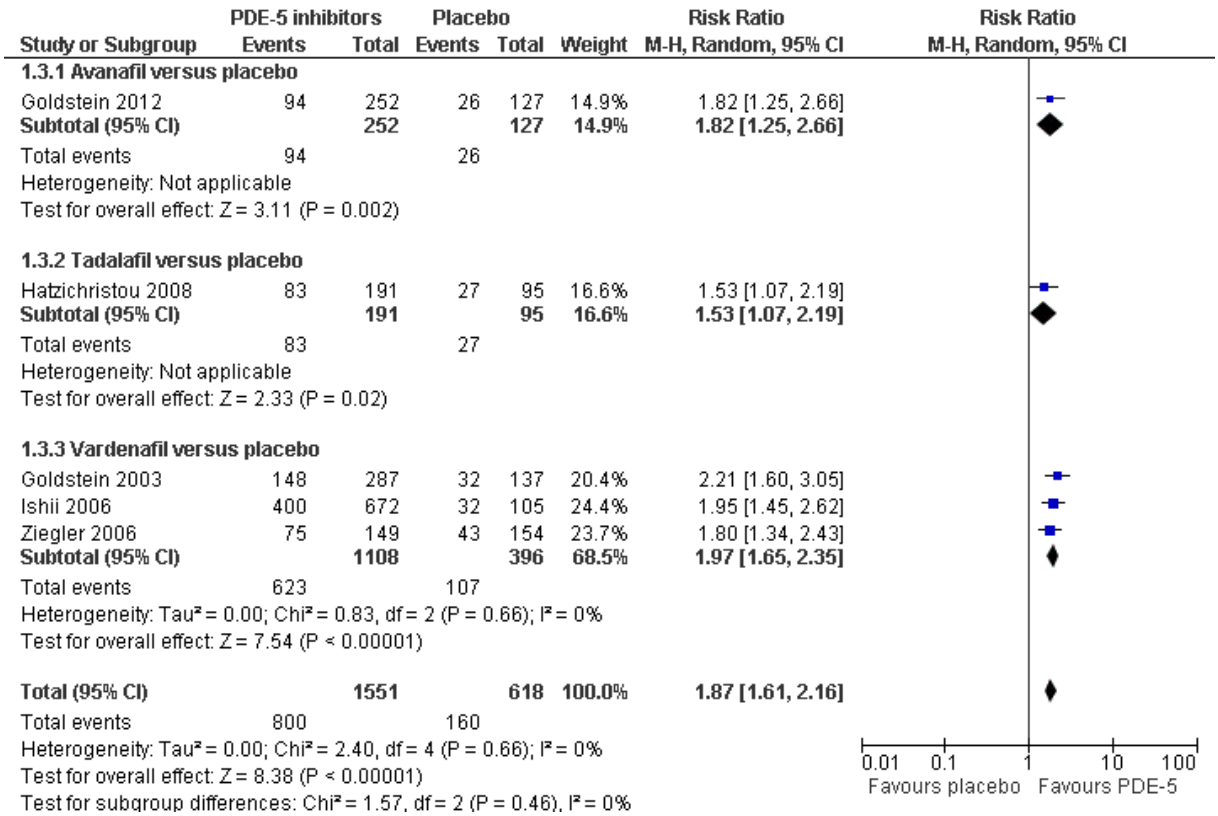

Figure 44: Forest plot for SEP – Q3