National Institute for Health and Care Excellence

1

Draft for consultation

Type 2 diabetes in adults: management

[F4] Evidence reviews for subsequent pharmacological management of type 2 diabetes

NICE guideline GID-NG10336

Evidence reviews underpinning recommendations 1.8.6-1.8.32, 1.8.34,1.8.38-1.8.60 and recommendations for research in the NICE guideline

August 2025

Draft for Consultation

This evidence review was developed by NICE

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

ISBN:

Contents

Appendices

Appendix G Forest plots – Model 2: Type 2 diabetes and cardiovascular disease

G.1 DPP-4 inhibitors

G.1.1 Adding alogliptin compared to adding placebo

There are no forest plots for this comparison (all outcomes in a single study)

G.1.2 Adding linagliptin compared to adding glimepiride

There are no forest plots for this comparison (all outcomes in a single study)

G.1.3 Adding saxagliptin compared to adding placebo

There are no forest plots for this comparison (all outcomes in a single study)

G.1.4 Adding sitagliptin compared to adding placebo

There are no forest plots for this comparison (all outcomes in a single study)

G.1.5 Adding sitagliptin compared to adding insulin

There are no forest plots for this comparison (all outcomes in a single study)

G.2 GLP-1 receptor agonist

G.2.1 Adding dulaglutide compared to adding placebo

There are no forest plots for this comparison (all outcomes in a single study)

G.2.2 Adding exenatide compared to adding insulin

There are no forest plots for this comparison (all outcomes included in a single study)

G.2.3 Adding liraglutide compared to adding sitagliptin

There are no forest plots for this comparison (all outcomes included in a single study)

G.2.4 Adding liraglutide compared to adding insulin

There are no forest plots for this comparison (all outcomes included in a single study)

G.2.5 Adding exenatide compared to adding placebo

There are no forest plots for this comparison (all outcomes in a single study)

G.2.6 Adding lixisenatide compared to adding placebo

There are no forest plots for this comparison (all outcomes in a single study)

G.3 Dual GIP/GLP-1 receptor co-agonists

G.3.1 Adding tirzepatide compared to adding insulin

There are no forest plots for this comparison (all outcomes included in a single study)

G.4 SGLT2 inhibitors

G.4.1 Adding canagliflozin compared to adding placebo

There are no forest plots for this comparison (all outcomes in a single study)

G.4.2 Adding dapagliflozin compared to adding placebo

Figure 1: All-cause mortality at end of follow-up

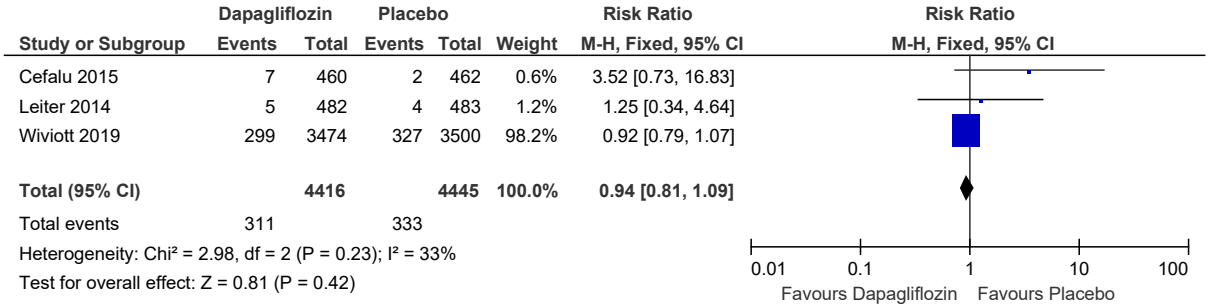


Figure 2: Cardiovascular mortality at end of follow-up

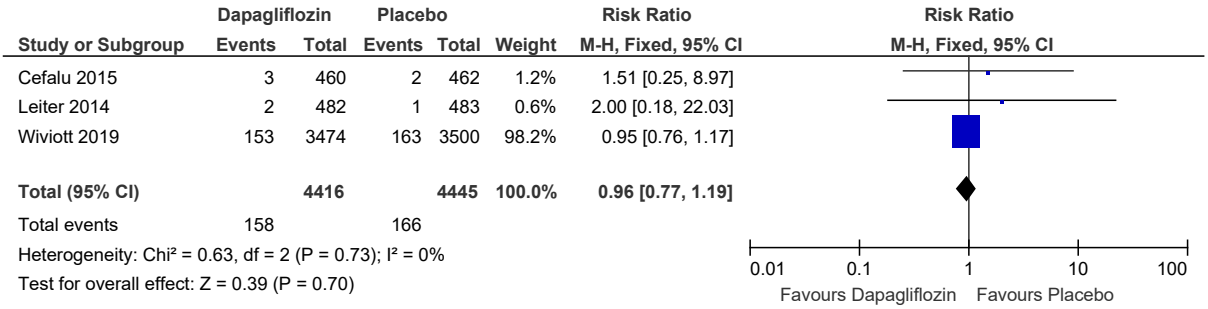
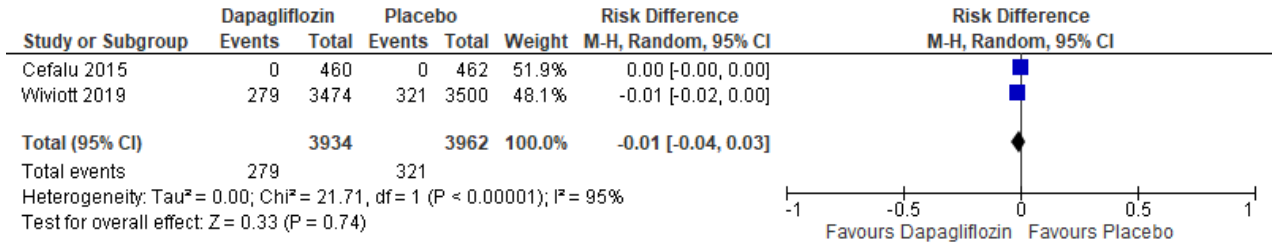


Figure 3: Non-fatal myocardial infarction at end of follow-up



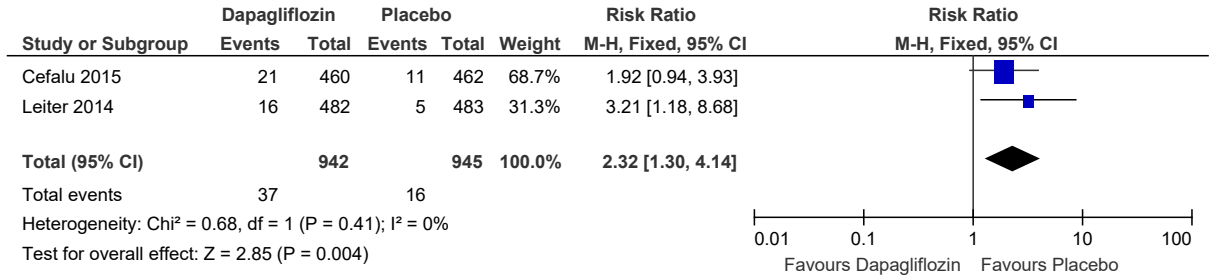
1

2

Figure 4: Hospitalisation for heart failure at end of follow-up

3

Figure 5: Persistent signs of worsening kidney disease at end of follow-up



4

5

Figure 6: Hypoglycaemia episodes at end of follow-up

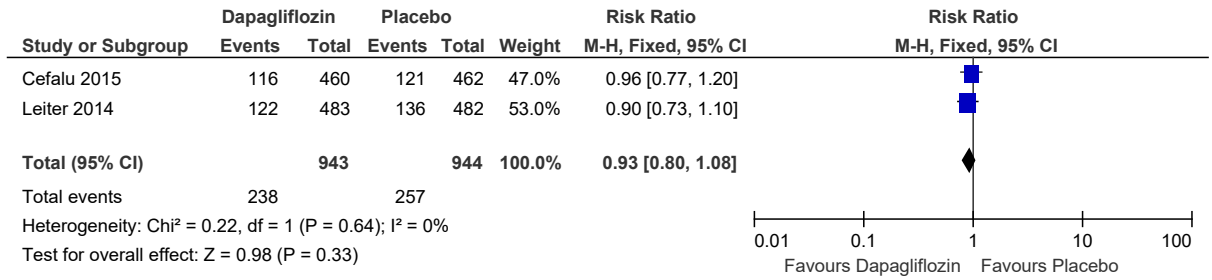


Figure 7: HbA1c change (%, lower values are better, change scores) at end of follow-up

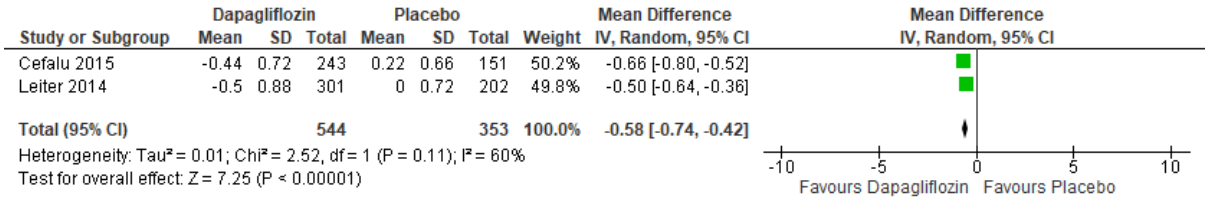
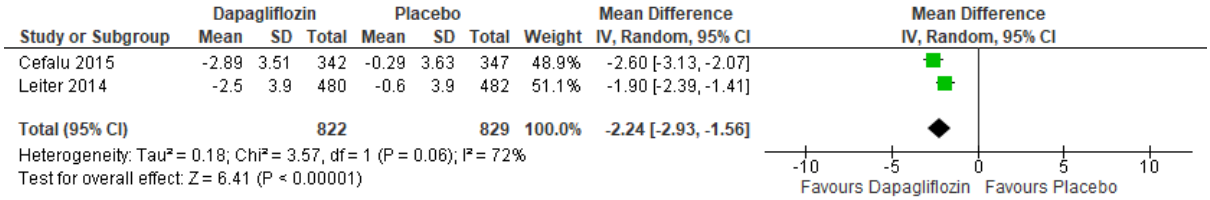


Figure 8: Weight change (kg, lower values are better, change scores) at end of follow-up



G.4.3 Adding dapagliflozin compared to adding vildagliptin

There are no forest plots for this comparison (all outcomes included in a single study)

G.4.4 Adding empagliflozin compared to adding sitagliptin

There are no forest plots for this comparison (all outcomes in a single study)

G.4.5 Adding empagliflozin compared to adding placebo

Figure 9: All-cause mortality at end of follow-up

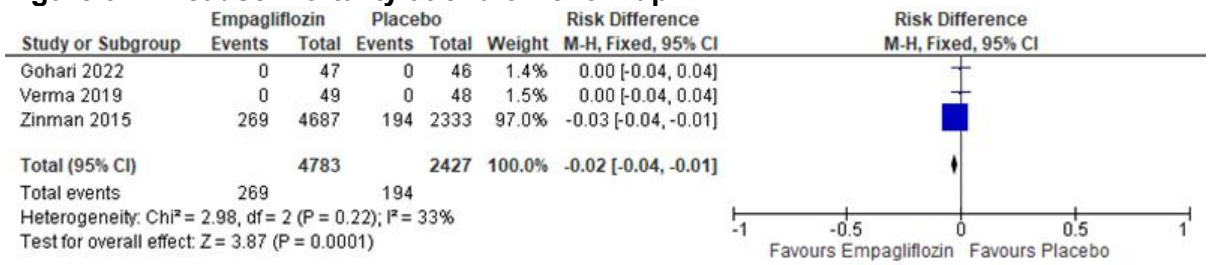


Figure 10: Cardiovascular mortality at end of follow

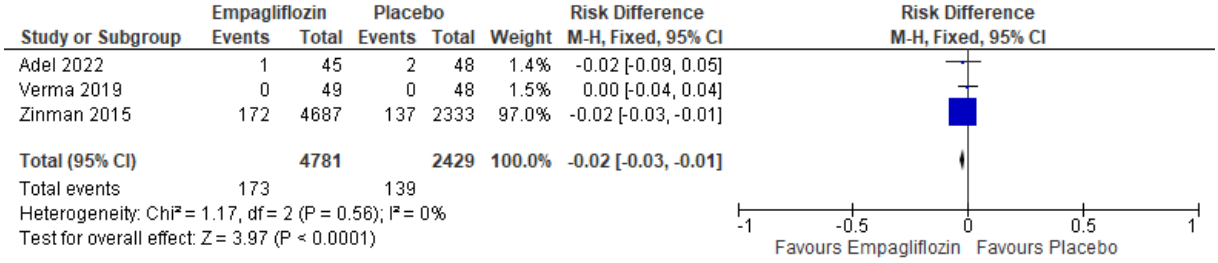


Figure 11: Non-fatal stroke at end of follow-up

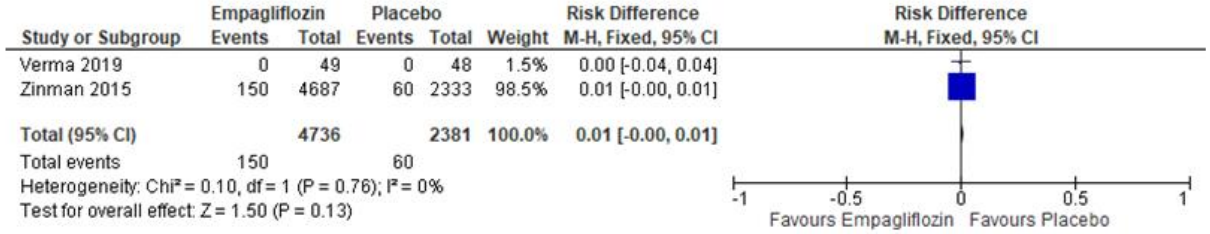


Figure 12: Non-fatal myocardial infarction at end of follow-up

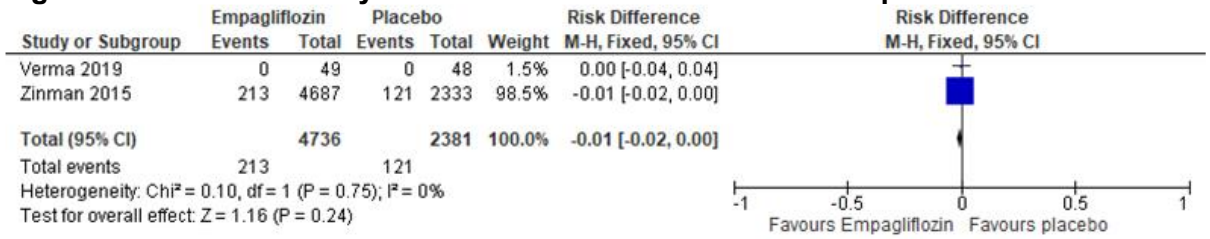


Figure 13: Unstable angina at end of follow-up

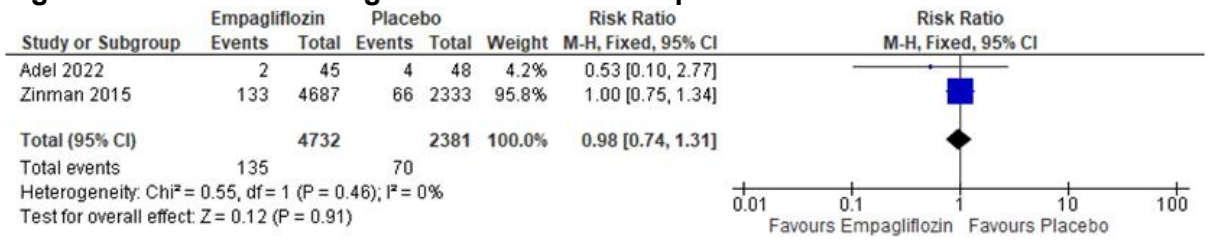
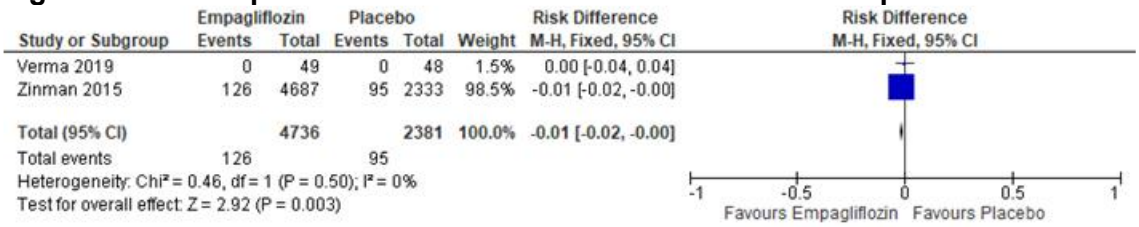


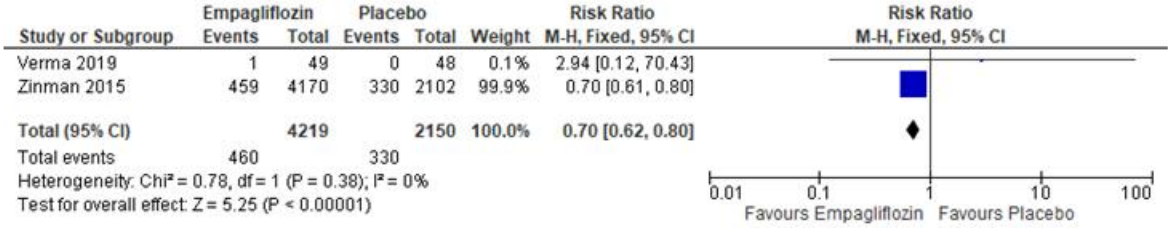
Figure 14: Hospitalisation for heart failure at end of follow-up



1

2

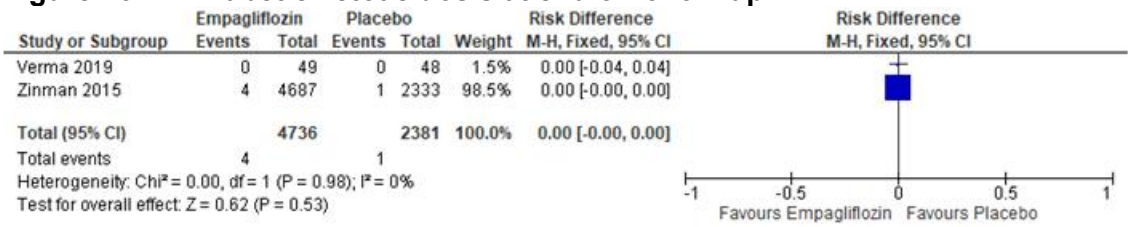
Figure 15: Persistent signs of worsening kidney disease at end of follow-up



3

4

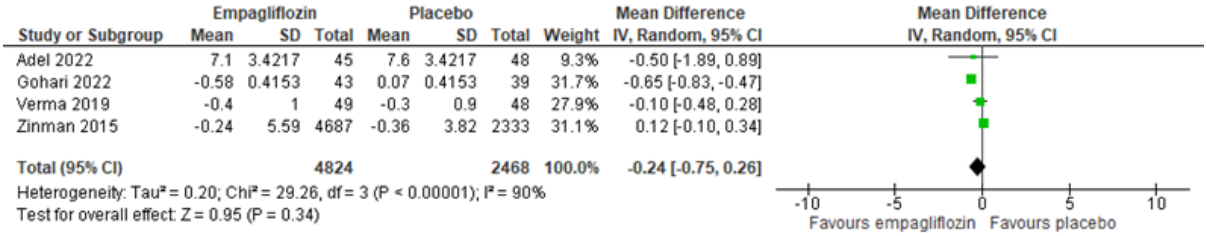
Figure 16: Diabetic ketoacidosis at end of follow-up



5

6

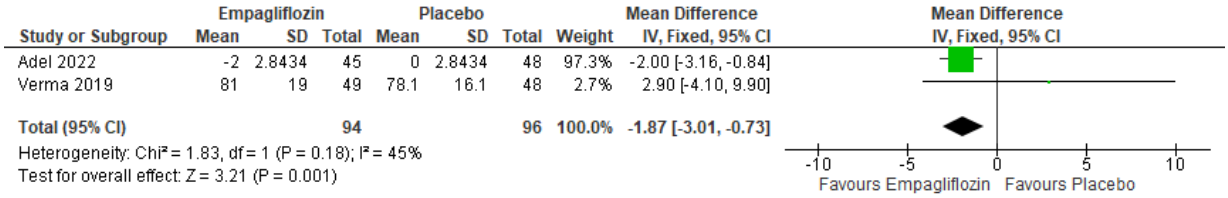
Figure 17: HbA1c change (%, lower values are better, change scores and final values) at end of follow-up



7

8

Figure 18: Weight change (kg, lower values are better, change scores and final values) at end of follow-up



G.4.6 Adding ertugliflozin compared to adding placebo

There are no forest plots for this comparison (all outcomes in a single study)

G.5 Sulfonylureas

G.5.1 Adding glimepiride compared to adding pioglitazone

There are no forest plots for this comparison (all outcomes in a single study)

G.6 Thiazolidinediones

G.6.1 Adding pioglitazone compared to adding placebo

Figure 19: All-cause mortality at end of follow-up

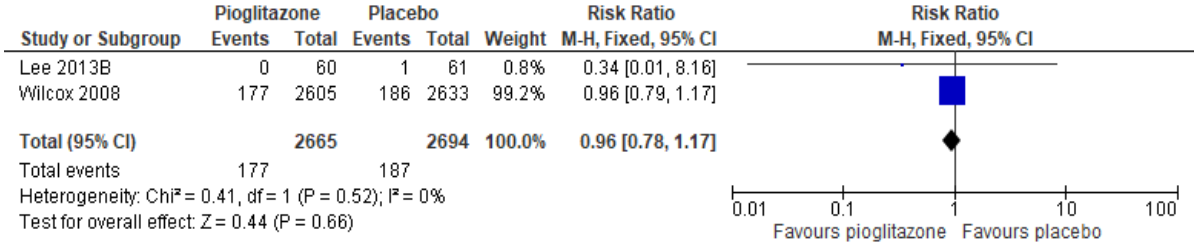
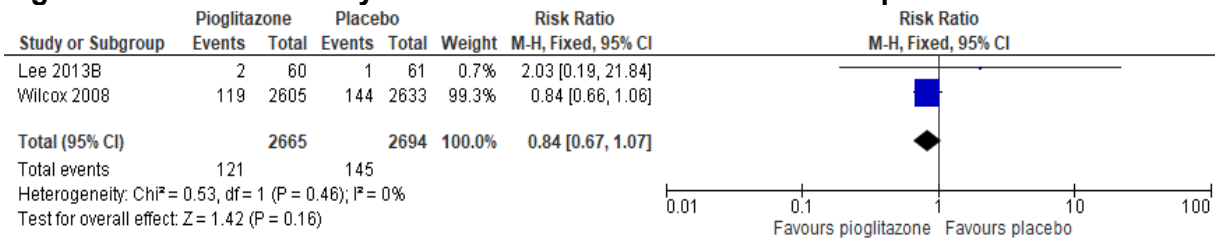


Figure 20: Non-fatal myocardial infarction at end of follow-up



Appendix H GRADE tables – Model 2: Type 2 diabetes and cardiovascular disease

H.1 DPP-4 inhibitors

H.1.1 Adding alogliptin compared to adding placebo

Table 1: clinical evidence profile: Adding alogliptin compared to adding placebo

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
all-cause mortality at end of follow-up – 18.0 months											
1 (white 2013)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	153/2701	173/2679	RR 0.88 (0.71, 1.08)	8 fewer per 1000 (19 fewer to 5 more)	very low
all-cause mortality at end of follow-up – 18.0 months											
1 (white 2013)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	2701	2679	HR 0.88 (0.71, 1.09)	Not estimable	very low
cardiovascular mortality at end of follow-up – 18.0 months											

1 (white 2013)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	112/2701	130/2679	RR 0.85 (0.67, 1.09)	7 fewer per 1000 (16 fewer to 5 more)	very low
cardiovascular mortality at end of follow-up – 18.0 months											
1 (white 2013)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	2701	2679	HR 0.85 (0.66, 1.10)	Not estimable	very low
4-point mace at end of follow-up – 18.0 months											
1 (white 2013)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	344/2701	359/2679	RR 0.95 (0.83, 1.09)	7 fewer per 1000 (23 fewer to 12 more)	low
non-fatal stroke at end of follow-up – 18.0 months											
1 (white 2013)	RCT	very serious[1]	not serious	NA[2]	very serious[4]	NA	29/2701	32/2679	RR 0.90 (0.55, 1.48)	1 fewer per 1000 (5 fewer to 6 more)	very low
non-fatal stroke at end of follow-up – 18.0 months											
1 (white 2013)	RCT	very serious[1]	not serious	NA[2]	very serious[4]	NA	2701	2679	HR 0.91 (0.55, 1.51)	Not estimable	very low

non-fatal myocardial infarction at end of follow-up – 18.0 months											
1 (white 2013)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	187/2701	173/2679	RR 1.07 (0.88, 1.31)	5 more per 1000 (8 fewer to 20 more)	very low
non-fatal myocardial infarction at end of follow-up – 18.0 months											
1 (white 2013)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	2701	2679	HR 1.08 (0.88, 1.33)	Not estimable	very low
unstable angina at end of follow-up – 18.0 months											
1 (white 2013)	RCT	very serious[1]	serious[5]	NA[2]	very serious[4]	NA	43/2701	47/2679	RR 0.91 (0.60, 1.37)	2 fewer per 1000 (7 fewer to 6 more)	very low
hospitalisation for heart failure at end of follow-up – 18.0 months											
1 (white 2013)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	106/2701	89/2679	RR 1.18 (0.90, 1.56)	6 more per 1000 (3 fewer to 19 more)	very low
hospitalisation for heart failure at end of follow-up – 18.0 months											

1 (white 2013)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	2701	2679	HR 1.19 (0.90, 1.57)	Not estimable	very low
development of end stage kidney disease at end of follow-up – 18.0 months											
1 (white 2013)	RCT	very serious[1]	not serious	NA[2]	very serious[4]	NA	24/2701	22/2679	PETO OR 1.08 (0.61, 1.93)	1 more per 1000 (4 fewer to 6 more)	very low
hypoglycaemia episodes at end of follow-up – 18.0 months											
1 (white 2013)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	181/2701	173/2679	RR 1.04 (0.85, 1.27)	2 more per 1000 (10 fewer to 17 more)	very low
severe hypoglycaemic episodes at end of follow-up – 18.0 months											
1 (white 2013)	RCT	very serious[1]	not serious	NA[2]	very serious[4]	NA	18/2701	16/2679	PETO OR 1.12 (0.57, 2.19)	1 more per 1000 (4 fewer to 5 more)	very low
hba1c change (%, lower values are better, mean difference) at end of follow-up – 18.0 months											
1 (white 2013)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	2701	2679	MD -0.36 (-0.43, -0.29)	MD 0.36 lower	low

										(0.43 lower to 0.29 lower)	
weight change (kg, lower values are better, mean difference) at end of follow-up – 18.0 months											
1 (white 2013)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	2701	2679	MD 0.06 (-0.25, 0.37)	MD 0.06 higher (0.25 lower to 0.37 higher)	low

1. >33.3% of the studies in the meta-analysis were at high risk of bias

2. Only one study so no inconsistency

3. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

4. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

5. Largest proportion of studies in the meta-analysis came from partially direct studies

H.1.2 Adding saxagliptin compared to adding placebo

Table 2: clinical evidence profile: Adding saxagliptin compared to adding placebo

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty

3-point mace at end of follow-up – 25.2 months											
1 (scirica 2013)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	546/6494	550/6465	RR 0.99 (0.88, 1.11)	1 fewer per 1000 (10 fewer to 9 more)	low
3-point mace at end of follow-up – 25.2 months											
1 (scirica 2013)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	6494	6465	HR 0.97 (0.86, 1.09)	Not estimable	low

1. >33.3% of the studies in the meta-analysis were at high risk of bias

2. Only one study so no inconsistency

H.1.3 Adding sitagliptin compared to adding placebo

Table 2: clinical evidence profile: Adding sitagliptin compared to adding placebo

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
all-cause mortality at end of follow-up											
1 (green 2015)	RCT	not serious	not serious	NA[1]	not serious	NA	547/7332	537/7339	RR 1.02 (0.91, 1.14)	1 more per 1000 (7 fewer to 10 more)	high
all-cause mortality at end of follow-up											

1 (green 2015)	RCT	not serious	not serious	NA[1]	not serious	NA	7332	7339	HR 1.01 (0.90, 1.13)	Not estimable	high
cardiovascular mortality at end of follow-up											
1 (green 2015)	RCT	not serious	not serious	NA[1]	not serious	NA	380/7332	366/7339	RR 1.04 (0.90, 1.20)	2 more per 1000 (5 fewer to 10 more)	high
cardiovascular mortality at end of follow-up											
1 (green 2015)	RCT	not serious	not serious	NA[1]	not serious	NA	7332	7339	HR 1.03 (0.89, 1.19)	Not estimable	high
4-point mace at end of follow-up											
1 (green 2015)	RCT	not serious	not serious	NA[1]	not serious	NA	839/7332	851/7339	RR 0.99 (0.90, 1.08)	2 fewer per 1000 (11 fewer to 9 more)	high
4-point mace at end of follow-up											
1 (green 2015)	RCT	not serious	not serious	NA[1]	not serious	NA	7332	7339	HR 0.98 (0.89, 1.08)	Not estimable	high
non-fatal myocardial infarction at end of follow-up											

1 (green 2015)	RCT	not serious	not serious	NA[1]	not serious	NA	289/7332	302/7339	RR 0.96 (0.82, 1.12)	2 fewer per 1000 (7 fewer to 5 more)	high
unstable angina at end of follow-up											
1 (green 2015)	RCT	not serious	not serious	NA[1]	serious[2]	NA	116/7332	129/7339	RR 0.90 (0.70, 1.15)	2 fewer per 1000 (5 fewer to 3 more)	moderate
unstable angina at end of follow-up											
1 (green 2015)	RCT	not serious	not serious	NA[1]	serious[2]	NA	7332	7339	HR 0.90 (0.70, 1.16)	Not estimable	moderate
hospitalisation for heart failure at end of follow-up											
1 (green 2015)	RCT	not serious	not serious	NA[1]	not serious	NA	228/7332	229/7339	RR 1.00 (0.83, 1.19)	0 fewer per 1000 (5 fewer to 6 more)	high
hospitalisation for heart failure at end of follow-up											
1 (green 2015)	RCT	not serious	not serious	NA[1]	not serious	NA	7332	7339	HR 1.00 (0.83, 1.20)	Not estimable	high
persistent signs of worsening kidney disease at end of follow-up											

1 (green 2015)	RCT	not serious	not serious	NA[1]	not serious	NA	552/7332	553/7339	RR 1.00 (0.89, 1.12)	0 fewer per 1000 (8 fewer to 9 more)	high
development of end stage kidney disease at end of follow-up											
1 (green 2015)	RCT	not serious	not serious	NA[1]	serious[2]	NA	100/7332	111/7339	RR 0.90 (0.69, 1.18)	1 fewer per 1000 (5 fewer to 3 more)	moderate
severe hypoglycaemic episodes at end of follow-up											
1 (green 2015)	RCT	not serious	not serious	NA[1]	serious[2]	NA	160/7332	143/7339	RR 1.12 (0.90, 1.40)	2 more per 1000 (2 fewer to 8 more)	moderate
severe hypoglycaemic episodes at end of follow-up											
1 (green 2015)	RCT	not serious	not serious	NA[1]	serious[2]	NA	7332	7339	HR 1.12 (0.89, 1.41)	Not estimable	moderate
hba1c change (%, lower value is better, mean difference) at end of follow-up											
1 (green 2015)	RCT	very serious[3]	not serious	NA[1]	not serious	NA	1434	1386	MD -0.32 (-0.35, -0.29)	MD 0.32 lower (0.35 lower to 0.29 lower)	low

1. Only one study so no inconsistency

2. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

3. >33.3% of the studies in the meta-analysis were at high risk of bias

H.1.4 Adding linagliptin compared to adding glimepiride

Table 3: clinical evidence profile: – Adding linagliptin compared to adding glimepiride

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
3-point mace at end of follow-up – 75.6 months											
1 (rosenstock 2019b)	RCT	not serious	not serious	NA[1]	serious[2]	NA	190/1051	199/1038	RR 0.94 (0.79, 1.13)	11 fewer per 1000 (41 fewer to 25 more)	moderate
3-point mace at end of follow-up – 75.6 months											
1 (rosenstock 2019b)	RCT	not serious	not serious	NA[1]	serious[2]	NA	1962	1963	HR 0.94 (0.77, 1.15)	Not estimable	moderate

1. Only one study so no inconsistency

2. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

H.1.5 Adding sitagliptin compared to adding insulin

Table 4: clinical evidence profile: Adding sitagliptin compared to adding insulin

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
hospitalisation for heart failure at the end of follow-up – 12 months											
1 (arturi 2017)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/10	0/12	RD 0.00 (-0.16, 0.16)	0 fewer per 1000 (161 fewer to 161 more)	very low
severe hypoglycaemic episodes at the end of follow-up – 12 months											
1 (arturi 2017)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/10	0/12	RD 0.00 (-0.16, 0.16)	0 fewer per 1000 (161 fewer to 161 more)	very low
hba1c change (%, lower values are better, final values) at the end of follow-up – 12 months											
1 (arturi 2017)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	10	12	MD 1.30 (0.11, 2.49)	MD 1.30 higher (0.11 higher to 2.49 higher)	very low

1. >33.3% of the studies in the meta-analysis were at high risk of bias

2. Only one study so no inconsistency

3. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.

4. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

H.2 GLP-1 receptor agonist

H.2.1 Adding dulaglutide compared to adding placebo

Table 3: clinical evidence profile: Adding dulaglutide compared to adding placebo

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
3-point mace at the end of follow-up – 64.8 months											
1 (gerstein 2019a)	RCT	serious[1]	not serious	NA[2]	serious[3]	NA	280/1560	315/1554	RR 0.89 (0.77, 1.02)	23 fewer per 1000 (47 fewer to 5 more)	low
3-point mace at end of follow-up – 64.8 months											
1 (gerstein 2019a)	RCT	serious[1]	not serious	NA[2]	serious[3]	NA	1560	1554	HR 0.87 (0.74, 1.02)	Not estimable	low

1. >33.3% of the studies in the meta-analysis were at moderate risk of bias

2. Only one study so no inconsistency

3. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

H.2.2 Adding exenatide compared to adding insulin

Table 4: clinical evidence profile: Adding exenatide compared to adding insulin

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
all-cause mortality at end of follow-up											
1 (chen 2017)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	1/14	0/12	PETO OR 6.41 (0.13, 326.59)	72 more per 1000 (63 fewer to 206 more)	very low
hba1c change (%, lower values are better, final values) at end of follow-up											
1 (chen 2017)	RCT	very serious[1]	not serious	NA[2]	very serious[4]	NA	11	12	MD 0.30 (-0.89, 1.49)	MD 0.30 higher (0.89 lower to 1.49 higher)	very low
bmi change (kg/m2, lower values are better, final values) at end of follow-up											
1 (chen 2017)	RCT	very serious[1]	not serious	NA[2]	serious[5]	NA	11	12	MD -2.40 (-5.14, 0.34)	MD 2.40 lower (5.14 lower to 0.34 higher)	very low

1. >33.3% of the studies in the meta-analysis were at high risk of bias

2. Only one study so no inconsistency

3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

4. 95% confidence intervals cross both ends of the defined MIDs (-0.50, 0.50)

5. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

H.2.3 Adding exenatide compared to adding placebo

Table 5: clinical evidence profile: –Adding exenatide compared to adding placebo

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
3-point mace at the end of follow-up – 38.4 months											
1 (holman 2017)	RCT	not serious	not serious	NA[1]	not serious	NA	722/5394	786/5388	RR 0.92 (0.84, 1.01)	12 fewer per 1000 (24 fewer to 1 more)	high
3-point mace at end of follow-up – 38.4 months											
1 (holman 2017)	RCT	not serious	not serious	NA[1]	not serious	NA	5394	5388	HR 0.90 (0.82, 0.99)	Not estimable	high

1. Only one study so no inconsistency

H.2.4 Adding liraglutide compared to adding sitagliptin

Table 6: Clinical evidence profile:

Adding liraglutide compared to adding sitagliptin

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
hospitalisation for heart failure at the end of follow-up – 12 months											
1 (arturi 2017)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/10	0/10	RD 0.00 (-0.17, 0.17)	0 fewer per 1000 (174 fewer to 174 more)	very low
severe hypoglycaemic episodes at the end of follow-up – 12 months											
1 (arturi 2017)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/10	0/10	RD 0.00 (-0.17, 0.17)	0 fewer per 1000 (174 fewer to 174 more)	very low
hba1c change (%, lower values are better, final values) at the end of follow-up – 12 months											
1 (arturi 2017)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	10	10	MD -1.10 (-1.98, -0.22)	MD 1.10 lower (1.98 lower to 0.22 lower)	very low

1. >33.3% of the studies in the meta-analysis were at high risk of bias

2. Only one study so no inconsistency

3. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.

4. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

H.2.5 Adding liraglutide compared to adding insulin

Table 7: Clinical evidence profile: Adding liraglutide compared to adding insulin

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
hospitalisation for heart failure at the end of follow-up – 12 months											
1 (arturi 2017)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/10	0/12	RD 0.00 (-0.16, 0.16)	0 fewer per 1000 (161 fewer to 161 more)	very low
severe hypoglycaemic episodes at the end of follow-up – 12 months											
1 (arturi 2017)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/10	0/12	RD 0.00 (-0.16, 0.16)	0 fewer per 1000 (161 fewer to 161 more)	very low
hba1c change (%, lower values are better, final values) at the end of follow-up – 12 months											
1 (arturi 2017)	RCT	very serious[1]	not serious	NA[2]	very serious[4]	NA	10	12	MD 0.20 (-0.99, 1.39)	MD 0.20 higher (0.99 lower to 1.39 higher)	very low

1. >33.3% of the studies in the meta-analysis were at high risk of bias

2. Only one study so no inconsistency

3. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.

4. 95% confidence intervals cross both ends of the defined MIDs (-0.50, 0.50)

H.2.6 Adding lixisenatide compared to adding placebo

Table 8: Clinical evidence profile: Adding lixisenatide compared to adding placebo

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
all-cause mortality at end of follow-up - 25 months											
1 (pfeffer 2015)	RCT	not serious	not serious	NA[1]	serious[2]	NA	211/3034	223/3034	RR 0.95 (0.79, 1.13)	4 fewer per 1000 (15 fewer to 10 more)	moderate
all-cause mortality at end of follow-up - 25 months											
1 (pfeffer 2015)	RCT	not serious	not serious	NA[1]	serious[2]	NA	3034	3034	HR 0.94 (0.78, 1.13)	Not estimable	moderate
cardiovascular mortality at end of follow-up - 25 months											

1 (pfeffer 2015)	RCT	not serious	not serious	NA[1]	serious[2]	NA	156/3034	158/3034	RR 0.99 (0.80, 1.22)	1 fewer per 1000 (11 fewer to 12 more)	moderate
cardiovascular mortality at end of follow-up - 25 months											
1 (pfeffer 2015)	RCT	not serious	not serious	NA[1]	serious[2]	NA	3034	3034	HR 0.98 (0.78, 1.22)	Not estimable	moderate
5-point mace at end of follow-up - 25 months											
1 (pfeffer 2015)	RCT	not serious	not serious	NA[1]	not serious	NA	456/3034	469/3034	RR 0.97 (0.86, 1.09)	4 fewer per 1000 (21 fewer to 15 more)	high
5-point mace at end of follow-up - 25 months											
1 (pfeffer 2015)	RCT	not serious	not serious	NA[1]	not serious	NA	3034	3034	HR 0.97 (0.85, 1.10)	Not estimable	high
unstable angina at end of follow-up - 25 months											
1 (pfeffer 2015)	RCT	not serious	not serious	NA[1]	very serious[3]	NA	11/3034	10/3034	PETO OR 1.10 (0.47, 2.59)	0 more per 1000 (3 fewer to 3 more)	low
unstable angina at end of follow-up - 25 months											

1 (pfeffer 2015)	RCT	not serious	not serious	NA[1]	very serious[3]	NA	3034	3034	HR 1.11 (0.47, 2.62)	Not estimable	low
hospitalisation for heart failure at end of follow-up - 25 months											
1 (pfeffer 2015)	RCT	not serious	not serious	NA[1]	serious[2]	NA	122/3034	127/3034	RR 0.96 (0.75, 1.23)	2 fewer per 1000 (10 fewer to 9 more)	moderate
hospitalisation for heart failure at end of follow-up - 25 months											
1 (pfeffer 2015)	RCT	not serious	not serious	NA[1]	serious[2]	NA	3034	3034	HR 0.96 (0.75, 1.23)	Not estimable	moderate
hypoglycaemia episodes at end of follow-up - 25 months											
1 (pfeffer 2015)	RCT	not serious	not serious	NA[1]	not serious	NA	504/3034	462/3034	RR 1.09 (0.97, 1.22)	14 more per 1000 (4 fewer to 34 more)	high
severe hypoglycaemic episodes at end of follow-up- 25 months											
1 (pfeffer 2015)	RCT	not serious	not serious	NA[1]	serious[2]	NA	14/3034	24/3034	PETO OR 0.59 (0.31, 1.11)	3 fewer per 1000 (7 fewer to 1 more)	moderate
hba1c change (%, lower values are better, change scores) at the end of follow-up - 25 months											

1 (pfeffer 2015)	RCT	not serious	not serious	NA[1]	not serious	NA	3034	3034	MD -0.27 (-0.31, -0.23)	MD 0.27 lower (0.31 lower to 0.23 lower)	high
weight change (kg, lower values are better, change scores) at the end of follow-up - 25 months											
1 (pfeffer 2015)	RCT	not serious	not serious	NA[1]	not serious	NA	3034	3034	MD -0.70 (-0.90, -0.50)	MD 0.70 lower (0.90 lower to 0.50 lower)	high

1. Only one study so no inconsistency

2. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

H.3 Dual GIP/GLP-1 receptor co-agonists

H.3.1 Adding tirzepatide compared to adding insulin

Table 9: Clinical evidence profile: Adding tirzepatide compared to adding insulin

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
all-cause mortality at end of follow-up – 24 months											

1 (del prato 2021)	RCT	not serious	not serious	NA[1]	serious[2]	NA	25/991	35/1000	RR 0.72 (0.43, 1.20)	10 fewer per 1000 (20 fewer to 7 more)	moderate
all-cause mortality at end of follow-up – 24 months											
1 (del prato 2021)	RCT	not serious	not serious	NA[1]	serious[2]	NA	991	1000	HR 0.70 (0.42, 1.17)	Not estimable	moderate
cardiovascular mortality at end of follow-up – 24 months											
1 (del prato 2021)	RCT	not serious	not serious	NA[1]	very serious[3]	NA	16/995	21/1000	RR 0.77 (0.40, 1.46)	5 fewer per 1000 (13 fewer to 10 more)	low
4-point mace at end of follow-up – 24 months											
1 (del prato 2021)	RCT	not serious	not serious	NA[1]	serious[2]	NA	47/995	62/1000	RR 0.76 (0.53, 1.10)	15 fewer per 1000 (29 fewer to 6 more)	moderate
4-point mace at end of follow-up – 24 months											
1 (del prato 2021)	RCT	not serious	not serious	NA[1]	serious[2]	NA	995	1000	HR 0.74 (0.51, 1.07)	Not estimable	moderate
non-fatal stroke at end of follow-up – 24 months											

1 (del prato 2021)	RCT	not serious	not serious	NA[1]	very serious[3]	NA	11/995	13/1000	RR 0.85 (0.38, 1.89)	2 fewer per 1000 (8 fewer to 12 more)	low
non-fatal myocardial infarction at end of follow-up – 24 months											
1 (del prato 2021)	RCT	not serious	not serious	NA[1]	very serious[3]	NA	19/995	26/1000	RR 0.73 (0.41, 1.32)	7 fewer per 1000 (15 fewer to 8 more)	low
unstable angina at end of follow-up – 24 months											
1 (del prato 2021)	RCT	not serious	not serious	NA[1]	very serious[3]	NA	4/995	8/1000	RR 0.50 (0.15, 1.66)	4 fewer per 1000 (7 fewer to 5 more)	low
hospitalisation for heart failure at end of follow-up – 24 months											
1 (del prato 2021)	RCT	not serious	not serious	NA[1]	very serious[3]	NA	4/995	6/1000	RR 0.67 (0.19, 2.37)	2 fewer per 1000 (5 fewer to 8 more)	low
hypoglycaemia episodes at end of follow-up – 24 months											
1 (del prato 2021)	RCT	not serious	not serious	NA[1]	not serious	NA	346/995	641/1000	RR 0.54 (0.49, 0.60)	293 fewer per 1000	high

										(325 fewer to 258 fewer)	
severe hypoglycaemia episodes at end of follow-up – 24 months											
1 (del prato 2021)	RCT	not serious	not serious	NA[1]	serious[2]	NA	4/995	11/1000	RR 0.37 (0.12, 1.14)	7 fewer per 1000 (10 fewer to 2 more)	moderate
hba1c change (%, lower values are better, change scores) at end of follow-up – 24 months											
1 (del prato 2021)	RCT	not serious	not serious	NA[1]	not serious	NA	981	978	MD -0.98 (-1.06, -0.90)	MD 0.98 lower (1.06 lower to 0.90 lower)	high
weight change (kg, change scores, lower values are better) at end of follow-up – 24 months											
1 (del prato 2021)	RCT	not serious	not serious	NA[1]	not serious	NA	981	978	MD -11.35 (-11.90, -10.80)	MD 11.35 lower (11.90 lower to 10.80 lower)	high

1. Only one study so no inconsistency

2. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

H.4 SGLT2 inhibitors

H.4.1 Adding canagliflozin compared to adding placebo

Table 8: Clinical evidence profile: Adding canagliflozin compared to adding placebo

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
all-cause mortality at end of follow-up - 43 months											
1 (mahaffey 2018)	RCT	not serious	not serious	NA[1]	serious[2]	NA	2900	3756	HR 0.90 (0.75, 1.07)	Not estimable	moderate
cardiovascular mortality at the end of follow-up - 43 months											
1 (mahaffey 2018)	RCT	not serious	not serious	NA[1]	serious[2]	NA	2900	3756	HR 0.86 (0.70, 1.06)	Not estimable	moderate
3-point mace at the end of follow-up - 43 months											
1 (mahaffey 2018)	RCT	not serious	not serious	NA[1]	serious[2]	NA	2900	3756	HR 0.83 (0.72, 0.95)	Not estimable	moderate
non-fatal stroke at the end of - 43 months											
1 (mahaffey 2018)	RCT	not serious	not serious	NA[1]	serious[2]	NA	2900	3756	HR 0.88 (0.67, 1.16)	Not estimable	moderate

non-fatal myocardial infarction at the end of follow-up - 43 months											
1 (mahaffey 2018)	RCT	not serious	not serious	NA[1]	serious[2]	NA	2900	3756	HR 0.79 (0.63, 0.99)	Not estimable	moderate
hospitalisation for heart failure at the end of follow-up - 43 months											
1 (mahaffey 2018)	RCT	not serious	not serious	NA[1]	serious[2]	NA	2900	3756	HR 0.68 (0.51, 0.90)	Not estimable	moderate
persistent signs of worsening kidney disease at the end of follow-up - 43 months											
1 (mahaffey 2018)	RCT	not serious	not serious	NA[1]	serious[2]	NA	2900	3756	HR 0.74 (0.67, 0.82)	Not estimable	moderate
development of end stage kidney disease at the end of follow-up - 43 months											
1 (mahaffey 2018)	RCT	not serious	not serious	NA[1]	very serious[3]	NA	2900	3756	HR 0.69 (0.18, 2.64)	Not estimable	low
diabetic ketoacidosis at the end of follow-up - 43 months											
1 (mahaffey 2018)	RCT	not serious	not serious	NA[1]	very serious[3]	NA	2900	3756	HR 4.62 (0.56, 38.04)	Not estimable	low

hypoglycaemia episodes at the end of follow-up - 43 months											
1 (mahaffey 2018)	RCT	not serious	not serious	NA[1]	serious [2]	NA	2900	3756	HR 1.19 (0.94, 1.50)	Not estimable	moderate

1. Only one study so no inconsistency

2. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

H.4.2 Adding dapagliflozin compared to adding placebo

Table 9: clinical evidence profile: Adding dapagliflozin compared to adding placebo

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
all-cause mortality at end of follow-up – 24.7 months											
3	RCT	serious[1]	not serious	not serious	not serious	NA	311/4416	333/4445	RR 0.94 (0.81, 1.09)	4 fewer per 1000 (14 fewer to 7 more)	moderate
all-cause mortality at end of follow-up – 50.4 months											

1 (wiviott 2019)	RCT	serious[1]	not serious	NA[3]	serious[2]	NA	3474	3500	HR 0.92 (0.79, 1.07)	Not estimable	low
cardiovascular mortality at end of follow-up – 24.7 months											
3	RCT	serious[1]	not serious	not serious	serious[2]	NA	158/4416	166/4445	RR 0.96 (0.77, 1.19)	2 fewer per 1000 (8 fewer to 7 more)	low
cardiovascular mortality at end of follow-up – 50.4 months											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[3]	serious[2]	NA	3474	3500	HR 0.94 (0.76, 1.16)	Not estimable	low
3-point mace at end of follow-up – 50.4 months											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[3]	not serious	NA	483/3474	537/3500	RR 0.91 (0.81, 1.02)	14 fewer per 1000 (29 fewer to 2 more)	moderate
3-point mace at end of follow-up – 50.4 months											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[3]	serious[2]	NA	3474	3500	HR 0.90 (0.79, 1.03)	Not estimable	low
non-fatal stroke at end of follow-up – 50.4 months											

1 (wiviott 2019)	RCT	serious[1]	not serious	NA[3]	serious[2]	NA	137/3474	142/3500	RR 0.97 (0.77, 1.22)	1 fewer per 1000 (9 fewer to 9 more)	low
non-fatal stroke at end of follow-up – 50.4 months											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[3]	serious[2]	NA	3474	3500	HR 0.97 (0.76, 1.24)	Not estimable	low
non-fatal myocardial infarction at end of follow-up – 31.2 months											
2	RCT	serious[1]	not serious	serious[4]	very serious[5]	NA	279/3934	321/3962	RD -0.01 (-0.02, 0.00)	10 fewer per 1000 (22 fewer to 2 more)	very low
non-fatal myocardial infarction at end of follow-up – 50.4 months											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[3]	serious[2]	NA	3474	3500	HR 0.87 (0.74, 1.02)	Not estimable	low
unstable angina at end of follow-up – 12 months											
1 (cefalu 2015)	RCT	very serious[6]	not serious	NA[3]	very serious[7]	NA	3/460	7/462	PETO OR 0.45 (0.13, 1.56)	9 fewer per 1000 (22 fewer to 5 more)	very low

hospitalisation for heart failure at end of follow-up – 31.2 months											
2	RCT	serious[1]	not serious	not serious	serious[2]	NA	154/3934	193/3962	RR 0.80 (0.65, 0.99)	10 fewer per 1000 (17 fewer to 1 fewer)	low
hospitalisation for heart failure at end of follow-up – 50.4 months											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[3]	serious[2]	NA	3474	3500	HR 0.78 (0.63, 0.97)	Not estimable	low
acute kidney injury at end of follow-up – 12 months											
1 (cefalu 2015)	RCT	very serious[6]	not serious	NA[3]	very serious[7]	NA	3/460	0/462	PETO OR 7.45 (0.77, 71.83)	7 more per 1000 (1 fewer to 14 more)	very low
persistent signs of worsening kidney disease at end of follow-up – 12 months											
2	RCT	very serious[6]	not serious	not serious	not serious	NA	37/942	16/945	RR 2.32 (1.30, 4.14)	22 more per 1000 (5 more to 53 more)	low
development of end stage kidney disease at end of follow-up – 12 months											

1 (cefalu 2015)	RCT	very serious[6]	not serious	NA[3]	very serious[7]	NA	6/460	3/462	PETO OR 1.97 (0.53, 7.31)	7 more per 1000 (6 fewer to 19 more)	very low
cardiac arrhythmia at end of follow-up – 50.4 months											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[3]	serious[2]	NA	141/3474	170/3500	RR 0.84 (0.67, 1.04)	8 fewer per 1000 (16 fewer to 2 more)	low
cardiac arrhythmia at end of follow-up – 50.4 months											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[3]	serious[2]	NA	3474	3500	HR 0.83 (0.66, 1.04)	Not estimable	low
progression of liver disease at end of follow-up – 12 months											
1 (cefalu 2015)	RCT	very serious[6]	not serious	NA[3]	very serious[7]	NA	9/460	9/462	RR 1.00 (0.40, 2.51)	0 more per 1000 (12 fewer to 29 more)	very low
hypoglycaemia episodes at end of follow-up – 12 months											
2	RCT	serious[1]	not serious	not serious	serious[2]	NA	238/943	257/944	RR 0.93 (0.80, 1.08)	20 fewer per 1000 (55 fewer to 21 more)	low

severe hypoglycaemic episodes at end of follow-up – 12 months											
1 (cefalu 2015)	RCT	very serious[6]	not serious	NA[3]	not serious	NA	0/460	0/462	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (4 fewer to 4 more)	low
hba1c change (%, lower values are better, change scores) at end of follow-up – 12 months											
2	RCT	very serious[6]	not serious	serious[8]	serious[9]	NA	544	353	MD -0.58 (-0.74, -0.42)	MD 0.58 lower (0.74 lower to 0.42 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow-up – 12 months											
2	RCT	not serious	not serious	serious[8]	serious[10]	NA	822	829	MD -2.24 (-2.93, -1.56)	MD 2.24 lower (2.93 lower to 1.56 lower)	low

1. >33.3% of the studies in the meta-analysis were at moderate risk of bias

2. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

3. Only one study so no inconsistency

4. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

5. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.67 (0.8-0.9 = serious, <0.8 = very serious).

6. >33.3% of the studies in the meta-analysis were at high risk of bias

7. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

8. I2 between 50% and 75%

9. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

10. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

H.4.3 Adding dapagliflozin compared to adding vildagliptin

Table 10: Clinical evidence profile: Adding dapagliflozin compared to adding vildagliptin

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
all-cause mortality at end of follow-up- 6 months											
1 (phrommintikul 2019)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	0/25	0/24	RD 0.00 (-0.08, 0.08)	0 fewer per 1000 (76 fewer to 76 more)	low
cardiovascular mortality at end of follow-up – 6 months											
1 (phrommintikul 2019)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	0/25	0/24	RD 0.00 (-0.08, 0.08)	0 fewer per 1000 (76 fewer to 76 more)	low

non-fatal stroke at end of follow-up – 6months											
1 (phrommintikul 2019)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	0/25	0/24	RD 0.00 (-0.08, 0.08)	0 fewer per 1000 (76 fewer to 76 more)	low
non-fatal myocardial infarction at end of follow-up – 6 months											
1 (phrommintikul 2019)	RCT	not serious	not serious	NA[1]	very serious[3]	NA	1/25	0/24	PETO OR 7.10 (0.14, 358.08)	40 more per 1000 (37 fewer to 117 more)	low
hospitalisation for heart failure – 6 months											
1 (phrommintikul 2019)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	0/25	0/25	RD 0.00 (-0.07, 0.07)	0 fewer per 1000 (75 fewer to 75 more)	low
hba1c change (%, lower values are better, change values) at end of follow-up – 6 months											
1 (phrommintikul 2019)	RCT	serious 4	not serious	NA[1]	very serious[5]	NA	21	22	MD 0.21 (-0.53, 0.95)	MD 0.21 higher (0.53 lower to 0.95 higher)	very low

weight change (kg, lower values are better, change scores) at end of follow-up – 6 months											
1 (phrommintikul 2019)	RCT	serious[4]	not serious	NA[1]	serious[6]	NA	21	22	MD -2.99 (-4.16, -1.82)	MD 2.99 lower (4.16 lower to 1.82 lower)	low
bmi change (kg/m2, lower scores are better, change scores) at end of follow-up – 6 months											
1 (phrommintikul 2019)	RCT	serious[4]	not serious	NA[1]	serious[7]	NA	21	22	MD -1.20 (-1.68, -0.72)	MD 1.20 lower (1.68 lower to 0.72 lower)	low

1. Only one study so no inconsistency

2. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.

3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

4. >33.3% of the studies in the meta-analysis were at moderate risk of bias

5. 95% confidence intervals cross both ends of the defined MIDs (-0.50, 0.50)

6. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

7. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

H.4.4 Adding empagliflozin compared to adding placebo

Table 10 Clinical evidence profile: Adding empagliflozin compared to adding placebo

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
all-cause mortality at end of follow-up **Mean follow-up: 16.4 month(s)**											
3	RCT	not serious	not serious	serious[1]	not serious	NA	269/4783	194/2427	RD -0.02 (-0.04, -0.01)	25 fewer per 1000 (38 fewer to 12 fewer)	moderate
all-cause mortality at end of follow-up **Mean follow-up: 37.2 month(s)**											
1 (zinman 2015)	RCT	not serious	not serious	NA[2]	serious[3]	NA	4687	2333	HR 0.68 (0.57, 0.81)	Not estimable	moderate
cardiovascular mortality at end of follow-up **Mean follow-up: 16.4 month(s)**											
3	RCT	not serious	not serious	serious[1]	not serious	NA	173/4781	139/2429	RD -0.02 (-0.03, -0.01)	20 fewer per 1000 (31 fewer to 10 fewer)	moderate
cardiovascular mortality at end of follow-up											

Mean follow-up: 37.2 month(s)											
1 (zinman 2015)	RCT	not serious	not serious	NA[2]	not serious	NA	4687	2333	HR 0.62 (0.49, 0.78)	Not estimable	high
3-point mace at end of follow-up **Mean follow-up: 6 month(s)**											
1 (verma 2019)	RCT	not serious	not serious	NA[2]	serious[4]	NA	0/49	0/48	RD 0.00 (-0.04, 0.04)	0 fewer per 1000 (39 fewer to 39 more)	moderate
4-point mace at end of follow-up **Mean follow-up: 37.2 month(s)**											
1 (zinman 2015)	RCT	not serious	not serious	NA[2]	serious[3]	NA	599/4687	333/2333	RR 0.90 (0.79, 1.01)	15 fewer per 1000 (30 fewer to 2 more)	moderate
4-point mace at end of follow-up **Mean follow-up: 37.2 month(s)**											
1 (zinman 2015)	RCT	not serious	not serious	NA[2]	serious[3]	NA	4687	2333	HR 0.89 (0.80, 0.99)	Not estimable	moderate
non-fatal stroke at end of follow-up **Mean follow-up: 21.6 month(s)**											

2	RCT	not serious	not serious	serious[1]	very serious[5]	NA	150/4736	60/2381	RD 0.01 (-0.00, 0.01)	6 more per 1000 (2 fewer to 14 more)	very low
non-fatal stroke at end of follow-up **Mean follow-up: 37.2 month(s)**											
1 (zinman 2015)	RCT	not serious	not serious	NA[2]	serious[3]	NA	4687	2333	HR 1.24 (0.92, 1.67)	Not estimable	moderate
non-fatal myocardial infarction at end of follow-up **Mean follow-up: 21.6 month(s)**											
2	RCT	not serious	not serious	serious[1]	very serious[6]	NA	213/4736	121/2381	RD -0.01 (-0.02, 0.00)	6 fewer per 1000 (17 fewer to 4 more)	very low
non-fatal myocardial infaRCTion at end of follow-up **Mean follow-up: 37.2 month(s)**											
1 (zinman 2015)	RCT	not serious	not serious	NA[2]	serious[3]	NA	4687	2333	HR 0.87 (0.70, 1.08)	Not estimable	moderate
unstable angina at end of follow-up **Mean follow-up: 21.6 month(s)**											

2	RCT	not serious	not serious	not serious	very serious[7]	NA	135/4732	70/2381	RR 0.98 (0.74, 1.31)	0 fewer per 1000 (8 fewer to 9 more)	low
unstable angina at end of follow-up **Mean follow-up: 37.2 month(s)**											
1 (zinman 2015)	RCT	not serious	not serious	NA[2]	very serious[7]	NA	4687	2333	HR 0.99 (0.74, 1.32)	Not estimable	low
hospitalisation for heart failure at end of follow-up **Mean follow-up: 21.6 month(s)**											
2	RCT	not serious	not serious	serious[1]	not serious	NA	126/4736	95/2381	RD -0.01 (-0.02, -0.00)	14 fewer per 1000 (23 fewer to 4 fewer)	moderate
hospitalisation for heart failure at end of follow-up **Mean follow-up: 37.2 month(s)**											
1 (zinman 2015)	RCT	not serious	not serious	NA[2]	serious[3]	NA	4687	2333	HR 0.65 (0.50, 0.85)	Not estimable	moderate
acute kidney injury at end of follow-up **Mean follow-up: 37.2 month(s)**											

1 (zinman 2015)	RCT	not serious	not serious	NA[2]	serious[3]	NA	45/4687	37/2333	RR 0.61 (0.39, 0.93)	6 fewer per 1000 (10 fewer to 1 fewer)	moderate
persistent signs of worsening kidney disease at end of follow-up **Mean follow-up: 21.6 month(s)**											
2	RCT	not serious	not serious	serious[1]	serious[3]	NA	460/4219	330/2150	RR 0.70 (0.62, 0.80)	45 fewer per 1000 (59 fewer to 30 fewer)	moderate
persistent signs of worsening kidney disease at end of follow-up **Mean follow-up: 37.2 month(s)**											
1 (zinman 2015)	RCT	not serious	not serious	NA[2]	not serious	NA	4170	2102	HR 0.62 (0.54, 0.71)	Not estimable	high
development of end stage kidney disease at end of follow-up **Mean follow-up: 37.2 month(s)**											
1 (zinman 2015)	RCT	not serious	not serious	NA[2]	very serious[7]	NA	6/4687	3/2333	PETO OR 1.00 (0.25, 3.99)	0 fewer per 1000 (2 fewer to 2 more)	low
cardiac arrhythmia at end of follow-up **Mean follow-up: 6 month(s)**											

1 (verma 2019)	RCT	not serious	not serious	NA[2]	very serious[7]	NA	1/49	0/48	PETO OR 7.24 (0.14, 364.94)	20 more per 1000 (19 fewer to 60 more)	low
diabetic ketoacidosis at end of follow-up Mean follow-up: 21.6 month(s)											
2	RCT	not serious	not serious	serious[1]	very serious[8]	NA	4/4736	1/2381	RD 0.00 (-0.00, 0.00)	0 more per 1000 (1 fewer to 2 more)	very low
progression of liver disease at end of follow-up Mean follow-up: 6 month(s)											
1 (verma 2019)	RCT	not serious	not serious	NA[2]	serious[4]	NA	0/49	0/48	RD 0.00 (-0.04, 0.04)	0 fewer per 1000 (39 fewer to 39 more)	moderate
hypoglycaemia episodes at end of follow-up Mean follow-up: 37.2 month(s)											
1 (zinman 2015)	RCT	not serious	not serious	NA[2]	not serious	NA	1303/4687	650/2333	RR 1.00 (0.92, 1.08)	1 fewer per 1000 (22 fewer to 23 more)	high
severe hypoglycaemia episodes at end of follow-up											

Mean follow-up: 37.2 month(s)											
1 (zinman 2015)	RCT	not serious	not serious	NA[2]	very serious[7]	NA	63/4687	36/2333	RR 0.87 (0.58, 1.31)	2 fewer per 1000 (6 fewer to 5 more)	low
hba1c change (%, lower values are better, change scores and final values) at end of follow-up **Mean follow-up: 16.4 month(s)**											
4	RCT	not serious	not serious	very serious[9]	serious[10]	NA	4824	2468	MD -0.24 (-0.75, 0.26)	MD 0.24 lower (0.75 lower to 0.26 higher)	very low
weight change (kg, lower values are better, change scores and final values) at end of follow-up **Mean follow-up: 6 month(s)**											
2	RCT	very serious[11]	serious[12]	not serious	serious[13]	NA	94	96	MD -1.87 (-3.01, -0.73)	MD 1.87 lower (3.01 lower to 0.73 lower)	very low
bmi change (kg/m2, lower values are better, final values) at end of follow-up **Mean follow-up: 6 month(s)**											

1 (verma 2019)	RCT	not serious	not serious	NA[2]	very serious[14]	NA	49	48	MD 0.90 (-1.28, 3.08)	MD 0.90 higher (1.28 lower to 3.08 higher)	low

1. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

2. Only one study so no inconsistency

3. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

4. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.

5. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.64 (0.8-0.9 = serious, <0.8 = very serious).

6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.37 (0.8-0.9 = serious, <0.8 = very serious).

7. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

8. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.17 (0.8-0.9 = serious, <0.8 = very serious).

9. I2 > 75%

10. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

11. >33.3% of the studies in the meta-analysis were at high risk of bias

12. Largest proportion of studies in the meta-analysis came from partially direct studies

13. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

14. 95% confidence intervals cross both ends of the defined MIDs (-0.80, 0.80)

H.4.5 Adding empagliflozin compared to adding sitagliptin

Table 12: Clinical evidence profile: Adding empagliflozin compared to adding sitagliptin

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
hba1c change (%, lower values are better, final values) at the end of follow-up - 6 months											
1 (oh 2021)	RCT	serious[1]	not serious	NA[2]	not serious	NA	48	49	MD 0.10 (-0.14, 0.34)	MD 0.10 higher (0.14 lower to 0.34 higher)	moderate
weight change (kg, lower values are better, final values) at the end of follow-up - 6 months											
1 (oh 2021)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	48	49	MD 0.20 (-4.16, 4.56)	MD 0.20 higher (4.16 lower to 4.56 higher)	very low

1. >33.3% of the studies in the meta-analysis were at moderate risk of bias

2. Only one study so no inconsistency

3. 95% confidence intervals cross both ends of the defined MIDs (-2.40, 2.40)

H.4.6 Adding ertugliflozin compared to adding placebo

Table 13: clinical evidence profile: Adding ertugliflozin compared to adding placebo

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
all-cause mortality at end of follow-up – 36 months											
1 (cannon 2020)	RCT	not serious	not serious	NA[1]	not serious	NA	473/5499	254/2747	RR 0.93 (0.80, 1.08)	6 fewer per 1000 (18 fewer to 7 more)	high
all-cause mortality at end of follow-up – 36 months											
1 (cannon 2020)	RCT	not serious	not serious	NA[1]	not serious	NA	5499	2747	HR 0.93 (0.80, 1.08)	Not estimable	high
cardiovascular mortality at end of follow-up – 36 months											
1 (cannon 2020)	RCT	not serious	not serious	NA[1]	serious[2]	NA	341/5499	184/2747	RR 0.93 (0.78, 1.10)	5 fewer per 1000 (15 fewer to 7 more)	moderate
cardiovascular mortality at end of follow-up – 36 months											

1 (cannon 2020)	RCT	not serious	not serious	NA[1]	serious[2]	NA	5499	2747	HR 0.92 (0.77, 1.10)	Not estimable	moderate
4-point mace at end of follow-up – 36 months											
1 (cannon 2020)	RCT	not serious	not serious	NA[1]	not serious	NA	823/5499	439/2747	RR 0.94 (0.84, 1.04)	10 fewer per 1000 (25 fewer to 7 more)	high
4-point mace at end of follow-up – 36 months											
1 (cannon 2020)	RCT	not serious	not serious	NA[1]	not serious	NA	5499	2747	HR 0.92 (0.82, 1.03)	Not estimable	high
non-fatal stroke at end of follow-up – 36 months											
1 (cannon 2020)	RCT	not serious	not serious	NA[1]	very serious[3]	NA	157/5499	78/2747	RR 1.01 (0.77, 1.31)	0 more per 1000 (7 fewer to 9 more)	low
non-fatal stroke at end of follow-up – 36 months											
1 (cannon 2020)	RCT	not serious	not serious	NA[1]	very serious[3]	NA	5499	2747	HR 1.00 (0.76, 1.32)	Not estimable	low

non-fatal myocardial infarction at end of follow-up – 36 months											
1 (cannon 2020)	RCT	not serious	not serious	NA[1]	serious[2]	NA	310/5499	148/2747	RR 1.05 (0.86, 1.27)	2 more per 1000 (7 fewer to 14 more)	moderate
non-fatal myocardial infarction at end of follow-up – 36 months											
1 (cannon 2020)	RCT	not serious	not serious	NA[1]	serious[2]	NA	5499	2747	HR 1.04 (0.86, 1.26)	Not estimable	moderate
unstable angina at the end of follow-up – 36 months											
1 (cannon 2020)	RCT	not serious	not serious	NA[1]	serious[2]	NA	145/5493	89/2745	RR 0.81 (0.63, 1.06)	6 fewer per 1000 (12 fewer to 2 more)	moderate
hospitalisation for heart failure at the end of follow-up – 36 months											
1 (cannon 2020)	RCT	not serious	not serious	NA[1]	serious[2]	NA	139/5499	99/2747	RR 0.70 (0.54, 0.90)	11 fewer per 1000 (16 fewer to 3 fewer)	moderate

hospitalisation for heart failure at the end of follow-up – 36 months											
1 (cannon 2020)	RCT	not serious	not serious	NA[1]	serious[2]	NA	5499	2747	HR 0.70 (0.54, 0.91)	Not estimable	moderate
acute kidney injury at the end of follow-up – 36 months											
1 (cannon 2020)	RCT	not serious	not serious	NA[1]	serious[2]	NA	101/5493	60/2745	RR 0.84 (0.61, 1.15)	3 fewer per 1000 (8 fewer to 3 more)	moderate
persistent signs of worsening kidney disease at the end of follow-up – 36 months											
1 (cannon 2020)	RCT	not serious	not serious	NA[1]	serious[2]	NA	168/5499	105/2747	RR 0.80 (0.63, 1.02)	8 fewer per 1000 (14 fewer to 1 more)	moderate
development of end stage kidney disease at end of follow-up – 36 months											
1 (cannon 2020)	RCT	very serious[4]	not serious	NA[1]	very serious[3]	NA	7/5499	3/2747	PETO OR 1.16 (0.31, 4.33)	0 more per 1000 (1 fewer to 2 more)	very low

death from renal causes at the end of follow-up – 36 months											
1 (cannon 2020)	RCT	very serious[4]	not serious	NA[1]	not serious	NA	0/5499	0/2747	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (1 fewer to 1 more)	low
cardiac arrhythmia at the end of follow-up – 36 months											
1 (cannon 2020)	RCT	not serious	not serious	NA[1]	serious[2]	NA	61/5493	37/2745	RR 0.82 (0.55, 1.24)	2 fewer per 1000 (6 fewer to 3 more)	moderate
diabetic ketoacidosis at the end of follow-up – 36 months											
1 (cannon 2020)	RCT	very serious[4]	not serious	NA[1]	serious[2]	NA	19/5493	2/2745	PETO OR 2.93 (1.18, 7.26)	3 more per 1000 (1 more to 5 more)	very low
hypoglycaemia episodes at the end of follow-up – 36 months											
1 (cannon 2020)	RCT	not serious	not serious	NA[1]	not serious	NA	1496/5493	790/2745	RR 0.95 (0.88, 1.02)	15 fewer per 1000 (35 fewer to 5 more)	high

severe hypoglycaemic episodes at the end of follow-up – 36 months											
1 (cannon 2020)	RCT	not serious	not serious	NA[1]	serious[2]	NA	284/5493	162/2745	RR 0.88 (0.73, 1.06)	7 fewer per 1000 (16 fewer to 3 more)	moderate
hba1c change (%, lower value is better, mead difference) end of follow-up – 36 months											
1 (cannon 2020)	RCT	very serious[4]	not serious	NA[1]	not serious	NA	5499	2747	MD -0.17 (-0.26, -0.08)	MD 0.17 lower (0.26 lower to 0.08 lower)	low
weight change (kg, lower value is better, change difference) at end of follow-up – 36 months											
1 (cannon 2020)	RCT	very serious[4]	not serious	NA[1]	serious[5]	NA	5499	2747	MD -2.60 (-3.05, -2.15)	MD 2.60 lower (3.05 lower to 2.15 lower)	very low

1. Only one study so no inconsistency

2. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

4. >33.3% of the studies in the meta-analysis were at high risk of bias

5. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

H.5 Sulfonylureas

H.5.1 Adding glimepiride compared to adding pioglitazone

Table 14: Clinical evidence profile: Adding glimepiride compared to adding pioglitazone

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
all-cause mortality at end of follow-up - 18 months											
1 (nissen 2008)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	2/273	3/270	PETO OR 0.66 (0.11, 3.84)	4 fewer per 1000 (20 fewer to 12 more)	very low
cardiovascular mortality at end of follow-up - 18 months											
1 (nissen 2008)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	1/273	3/270	PETO OR 0.36 (0.05, 2.58)	7 fewer per 1000 (22 fewer to 7 more)	very low
5-point mace at end of follow-up - 18 months											
1 (nissen 2008)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	13/273	11/270	RR 1.17 (0.53, 2.56)	7 more per 1000 (19 fewer to 64 more)	very low
non-fatal stroke at end of follow-up - 18 months											

1 (nissen 2008)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	1/273	0/270	PETO OR 7.31 (0.15, 368.34)	4 more per 1000 (3 fewer to 11 more)	very low
non-fatal myocardial infarction at end of follow-up - 18 months											
1 (nissen 2008)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	4/273	2/270	RR 1.98 (0.37, 10.71)	7 more per 1000 (5 fewer to 72 more)	very low
unstable angina at end of follow-up - 18 months											
1 (nissen 2008)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	2/273	4/270	RR 0.49 (0.09, 2.68)	7 fewer per 1000 (13 fewer to 25 more)	very low
hospitalisation for heart failure at end of follow-up - 18 months											
1 (nissen 2008)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	5/273	4/270	RR 1.24 (0.34, 4.55)	4 more per 1000 (10 fewer to 53 more)	very low
hypoglycaemia episodes at end of follow-up - 18 months											
1 (nissen 2008)	RCT	serious[1]	not serious	NA[2]	not serious	NA	101/273	41/270	RR 2.44 (1.77, 3.36)	218 more per 1000 (116 more to 358 more)	moderate
hba1c change (%, lower values are better, change scores) at end of follow-up - 18 months											

1 (nissen 2008)	RCT	serious[1]	not serious	NA[2]	not serious	NA	181	179	MD 0.19 (0.01, 0.37)	MD 0.19 higher (0.01 higher to 0.37 higher)	moderate
weight change (kg, lower values are better, final values) at end of follow-up - 18 months											
1 (nissen 2008)	RCT	serious[1]	not serious	NA[2]	serious[4]	NA	181	179	MD -2.90 (-7.06, 1.26)	MD 2.90 lower (7.06 lower to 1.26 higher)	low

1. >33.3% of the studies in the meta-analysis were at moderate risk of bias

2. Only one study so no inconsistency

3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

4. 95% confidence intervals cross one end of the defined MIDs (2.40, -2.40)

H.5.2 Adding glimepiride compared to adding insulin

Table 11: Clinical evidence profile: Adding glimepiride compared to adding insulin

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
hypoglycaemia episodes at end of follow-up – 5.5 months											
1 (li 2014c)	RCT	not serious	not serious	NA[1]	not serious	NA	7/29	19/29	RR 0.37 (0.18, 0.74)	414 fewer per 1000 (535 fewer to 170 fewer)	high

hba1c change (%, lower values are better) at end of follow-up – 5.5 months											
1 (li 2014c)	RCT	not serious	not serious	NA[1]	serious[2]	NA	29	26	MD -0.60 (-1.29, 0.09)	MD 0.60 lower (1.29 lower to 0.09 higher)	moderate
weight change (kg, lower values are better) at end of follow-up – 5.5. months											
1 (li 2014c)	RCT	not serious	not serious	NA[1]	very serious[3]	NA	29	26	MD -2.90 (-11.66, 5.86)	MD 2.90 lower (11.66 lower to 5.86 higher)	low

1. Only one study so no inconsistency

2. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

3. 95% confidence intervals cross both ends of the defined MIDs (-2.40, 2.40)

H.6 Thiazolidinedione

H.6.1 Adding pioglitazone compared to adding placebo

Table 12 Clinical evidence profile: Adding pioglitazone compared to adding placebo

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
all-cause mortality at end of follow-up											

2	RCT	very serious[1]	not serious	serious[2]	serious[3]	NA	177/2665	187/2694	RR 0.96 (0.78, 1.17)	3 fewer per 1000 (15 fewer to 12 more)	very low
all-cause mortality at end of follow-up											
1 (wilcox 2008)	RCT	very serious[1]	not serious	NA[4]	serious[3]	NA	2605	2633	HR 0.96 (0.78, 1.18)	Not estimable	very low
cardiovascular mortality at end of follow-up											
1 (wilcox 2008)	RCT	very serious[1]	not serious	NA[4]	serious[3]	NA	127/2605	136/2633	RR 0.94 (0.75, 1.19)	3 fewer per 1000 (13 fewer to 10 more)	very low
cardiovascular mortality at end of follow-up											
1 (wilcox 2008)	RCT	very serious[1]	not serious	NA[4]	serious[3]	NA	2605	2633	HR 0.94 (0.74, 1.19)	Not estimable	very low
3-point mace at end of follow-up											
1 (wilcox 2008)	RCT	very serious[1]	not serious	NA[4]	serious[3]	NA	257/2605	313/2633	RR 0.83 (0.71, 0.97)	20 fewer per 1000 (34 fewer to 4 fewer)	very low
3-point mace at end of follow-up											

1 (wilcox 2008)	RCT	very serious[1]	not serious	NA[4]	serious[3]	NA	2605	2633	HR 0.82 (0.70, 0.96)	Not estimable	very low
non-fatal stroke at end of follow-up											
1 (wilcox 2008)	RCT	very serious[1]	not serious	NA[4]	serious[3]	NA	86/2605	107/2633	RR 0.81 (0.61, 1.07)	8 fewer per 1000 (16 fewer to 3 more)	very low
non-fatal stroke at end of follow-up											
1 (wilcox 2008)	RCT	very serious[1]	not serious	NA[4]	serious[3]	NA	2605	2633	HR 0.81 (0.61, 1.08)	Not estimable	very low
non-fatal myocardial infarction at end of follow-up											
2	RCT	very serious[1]	not serious	not serious	serious[3]	NA	121/2665	145/2694	RR 0.84 (0.67, 1.07)	8 fewer per 1000 (18 fewer to 4 more)	very low
non-fatal myocardial infarction at end of follow-up											
1 (wilcox 2008)	RCT	very serious[1]	not serious	NA[4]	serious[3]	NA	2605	2633	HR 0.83 (0.65, 1.06)	Not estimable	very low
hospitalisation for heart failure at end of follow-up											

1 (wilcox 2008)	RCT	very serious[1]	not serious	NA[4]	serious[3]	NA	149/2605	108/2633	RR 1.39 (1.10, 1.78)	16 more per 1000 (4 more to 32 more)	very low
cardiac arrhythmia at end of follow-up											
1 (wilcox 2008)	RCT	very serious[1]	not serious	NA[4]	serious[3]	NA	42/2605	51/2633	RR 0.83 (0.56, 1.25)	3 fewer per 1000 (9 fewer to 5 more)	very low
hypoglycaemia episodes at end of follow-up											
1 (wilcox 2008)	RCT	very serious[1]	not serious	NA[4]	not serious	NA	726/2605	528/2633	RR 1.39 (1.26, 1.53)	78 more per 1000 (52 more to 107 more)	low
hba1c change (%, lower values are better, change scores) at end of follow-up											
1 (lee 2013b)	RCT	very serious[1]	not serious	NA[4]	serious[5]	NA	60	61	MD -0.84 (-1.55, -0.13)	MD 0.84 lower (1.55 lower to 0.13 lower)	very low

1. >33.3% of the studies in the meta-analysis were at high risk of bias

2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

3. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

4. Only one study so no inconsistency

5. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)