National Institute for Health and Care Excellence

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Draft for consultation

Type 2 diabetes in adults: management

[F5] 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

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Appendices

Appendix I Forest plots – Model 3: Type 2 diabetes and chronic kidney disease

I.1 DPP-4 inhibitors

I.1.1 Adding linagliptin compared to adding placebo

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

Study or Subgroup	Linagliptin Events	Linagliptin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
McGill 2013	3	68	3	65	75.2%	0.96 [0.20, 4.57]
Groop 2017	2	182	1	178	24.8%	1.96 [0.18, 21.38]
Total (95% CI)		**250**		**243**	**100.0%**	**1.20 [0.33, 4.38]**
Total events	5		4			

Heterogeneity: Chi² = 0.24, df = 1 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.28 (P = 0.78)

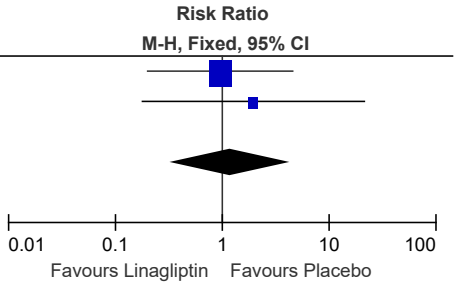


Figure 2: Non-fatal stroke at end of follow up

Study or Subgroup	Linagliptin Events	Linagliptin Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Groop 2017	0	182	0	178	73.0%	0.00 [-0.01, 0.01]
McGill 2013	1	68	1	65	27.0%	-0.00 [-0.04, 0.04]
Total (95% CI)		**250**		**243**	**100.0%**	**-0.00 [-0.01, 0.01]**
Total events	1		1			

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.03 (P = 0.98)

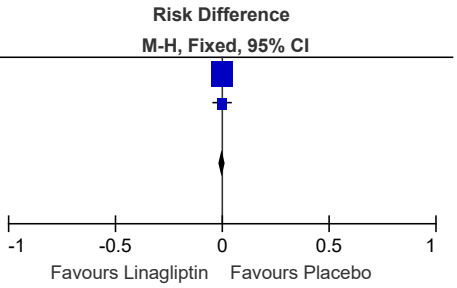


Figure 3: Non-fatal myocardial infarction at end of follow up

Study or Subgroup	Linagliptin Events	Linagliptin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Groop 2017	1	182	0	178	19.8%	2.93 [0.12, 71.56]
McGill 2013	4	68	2	65	80.2%	1.91 [0.36, 10.08]
Total (95% CI)		**250**		**243**	**100.0%**	**2.11 [0.49, 9.20]**
Total events	5		2			

Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² = 0%
Test for overall effect: Z = 1.00 (P = 0.32)

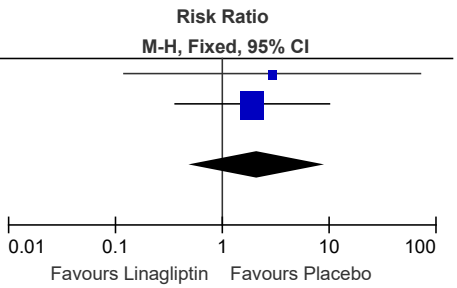


Figure 4: Hospitalisation for heart failure at end of follow up

Study or Subgroup	Linagliptin Events	Linagliptin Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Groop 2017	0	182	0	178	7.9%	0.00 [-0.01, 0.01]
Rosenstock 2019A	162	2109	188	2074	92.1%	-0.01 [-0.03, 0.00]
Total (95% CI)		**2291**		**2252**	**100.0%**	**-0.01 [-0.03, 0.00]**
Total events	162		188			

Heterogeneity: Chi² = 5.34, df = 1 (P = 0.02); I² = 81%
Test for overall effect: Z = 1.61 (P = 0.11)

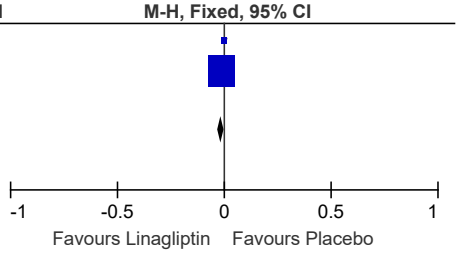


Figure 5: Hypoglycaemia episodes at end of follow up

Study or Subgroup	Linagliptin Events	Linagliptin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Groop 2017	24	182	10	178	23.6%	2.35 [1.16, 4.77]
McGill 2013	43	68	32	65	76.4%	1.28 [0.95, 1.74]
Total (95% CI)		**250**		**243**	**100.0%**	**1.54 [1.14, 2.07]**
Total events	67		42			

Heterogeneity: Chi² = 2.68, df = 1 (P = 0.10); I² = 63%
Test for overall effect: Z = 2.82 (P = 0.005)

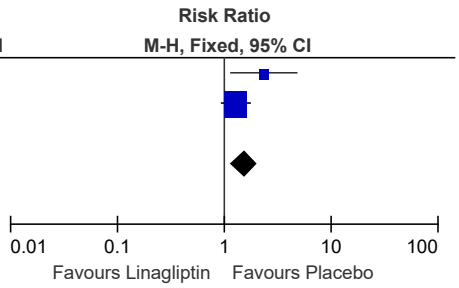


Figure 6: Severe hypoglycaemic episodes at end of follow up

Study or Subgroup	Linagliptin Events	Linagliptin Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Groop 2017	0	182	0	178	73.0%	0.00 [-0.01, 0.01]
McGill 2013	3	68	3	65	27.0%	-0.00 [-0.07, 0.07]
Total (95% CI)		**250**		**243**	**100.0%**	**-0.00 [-0.02, 0.02]**
Total events	3		3			

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.91); I² = 0%
Test for overall effect: Z = 0.05 (P = 0.96)

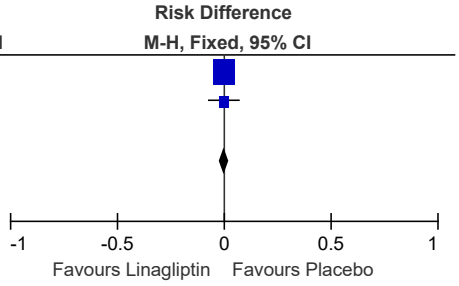


Figure 7: HbA1c change (%, lower scores are better, change and final scores) at end of follow-up

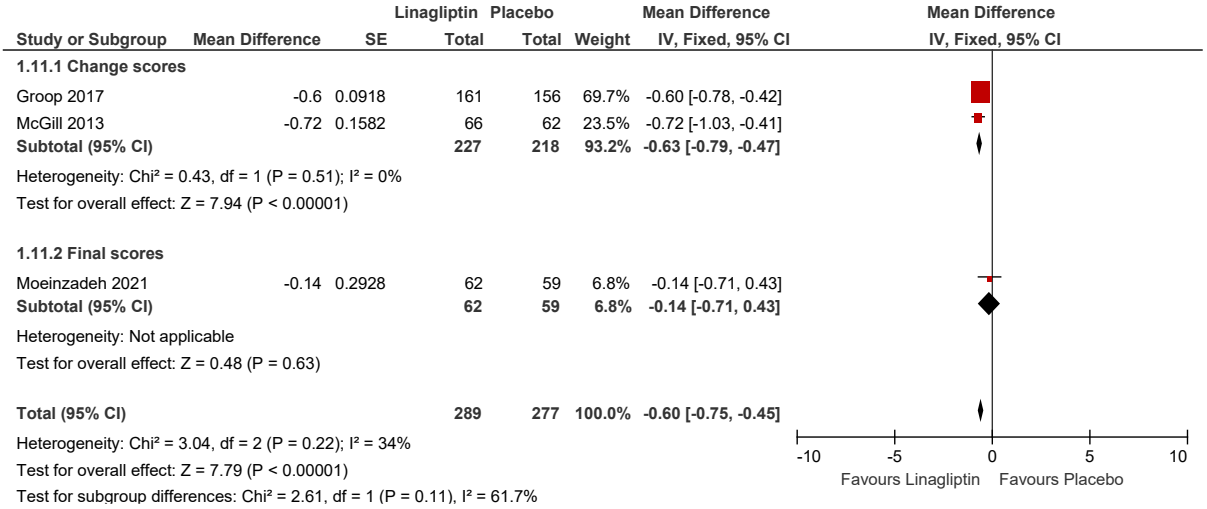
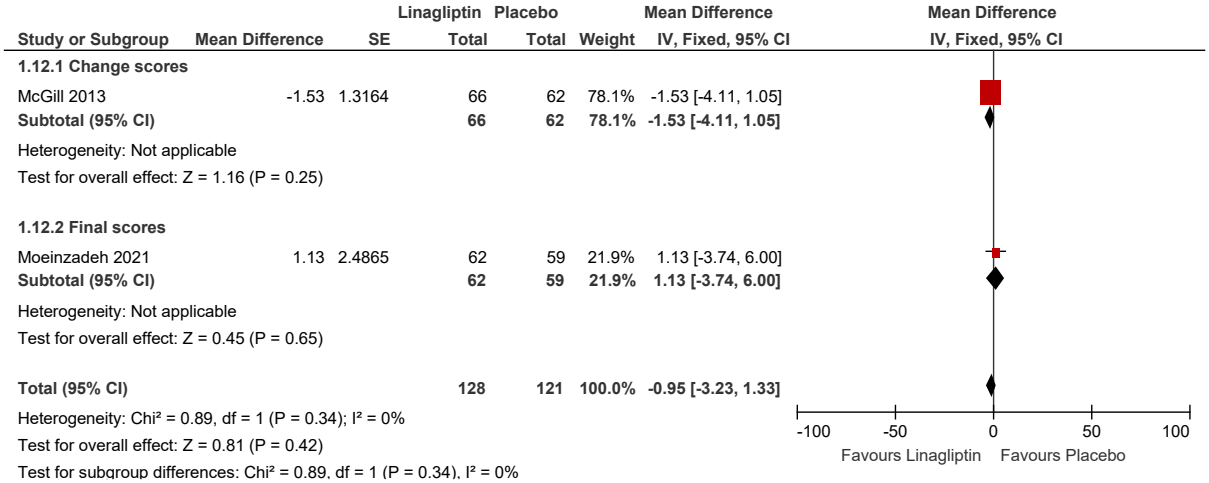


Figure 8: Weight change (kg, lower scores are better, change and final scores) at end of follow-up



I.1.2 Adding linagliptin compared to adding liraglutide

There are no forest plots reported for this comparison (all outcomes include a single study).

I.1.3 Adding saxagliptin compared to adding placebo

There are no forest plots reported for this comparison (all outcomes include a single study).

I.1.4 Adding sitagliptin compared to adding linagliptin

There are no forest plots reported for this comparison (all outcomes include a single study).

I.1.5 Adding sitagliptin compared to adding liraglutide

There are no forest plots reported for this comparison (all outcomes include a single study).

I.1.6 Adding vildagliptin compared to adding sitagliptin

There are no forest plots reported for this comparison (all outcomes include a single study).

I.2 GLP-1 receptor agonist

I.2.1 Adding dulaglutide compared to adding insulin

There are no forest plots reported for this comparison (all outcomes include a single study).

I.2.2 Adding exenatide compared to adding insulin

There are no forest plots reported for this comparison (all outcomes include a single study).

I.2.3 Adding liraglutide compared to adding placebo

There are no forest plots reported for this comparison (all outcomes include a single study).

I.2.4 Adding semaglutide compared to adding placebo

Figure 9: All-cause mortality at follow-up, risk ratio

Figure 10: Cardiovascular mortality at end of follow-up, risk ratio

Figure 11: Acute kidney injury at end of follow-up, risk ratio

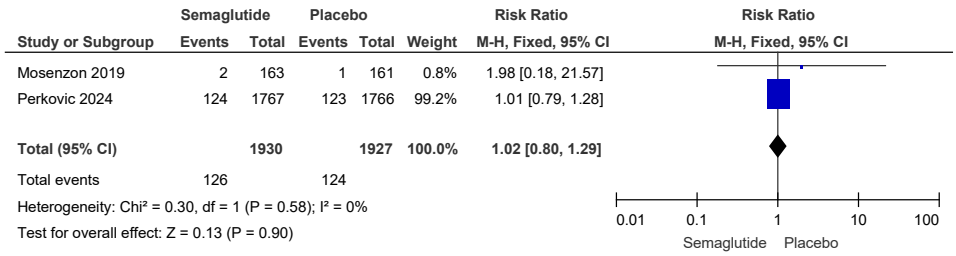


Figure 12: Severe hypoglycaemic episodes at end of follow-up, risk difference

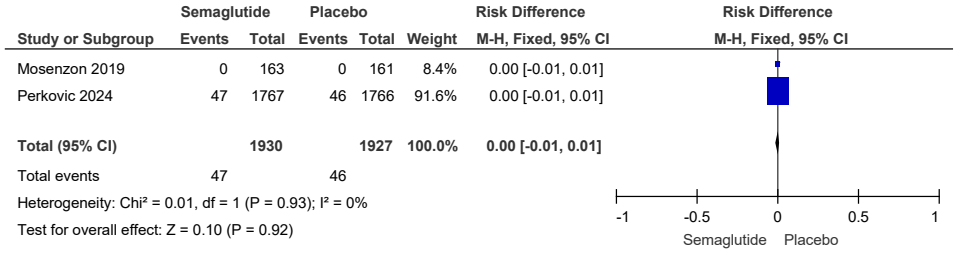


Figure 13: HbA1c change (%, lower values are better, change scores) at end of follow-up

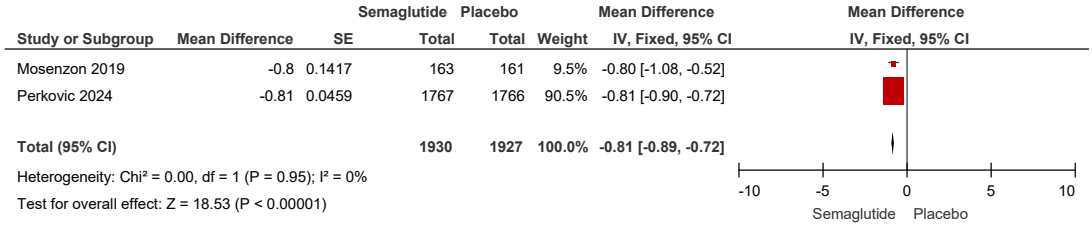
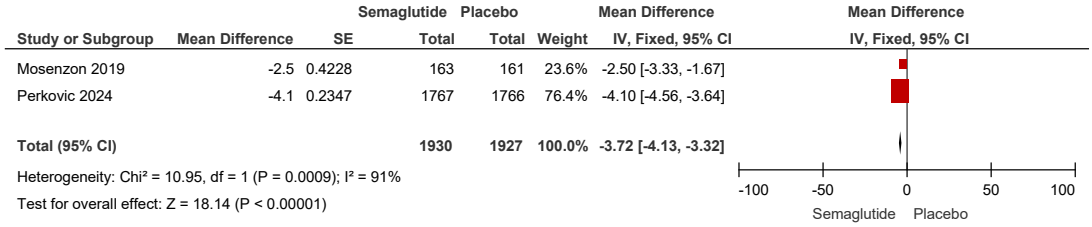


Figure 14: Weight change (kg, lower values are better, change scores) at end of follow-up



I.2.5 Adding semaglutide compared to adding dulaglutide

There are no forest plots reported for this comparison (all outcomes include a single study).

I.2.6 Switching to semaglutide compared to dulaglutide (switching from dulaglutide)

There are no forest plots reported for this comparison (all outcomes include a single study).

I.2.7 Switching to semaglutide compared to liraglutide (switching from liraglutide)

There are no forest plots reported for this comparison (all outcomes include a single study).

I.3 SGLT2 inhibitors

I.3.1 Adding canagliflozin compared to adding placebo

Figure 15: All-cause mortality at end of follow-up, risk ratio

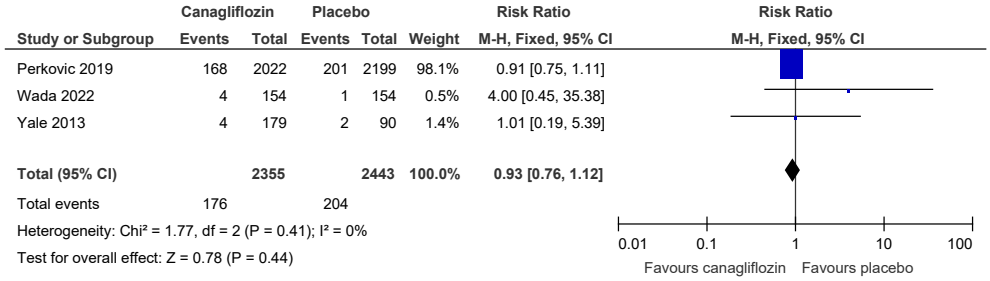


Figure 16: All-cause mortality at end of follow-up, hazard ratio

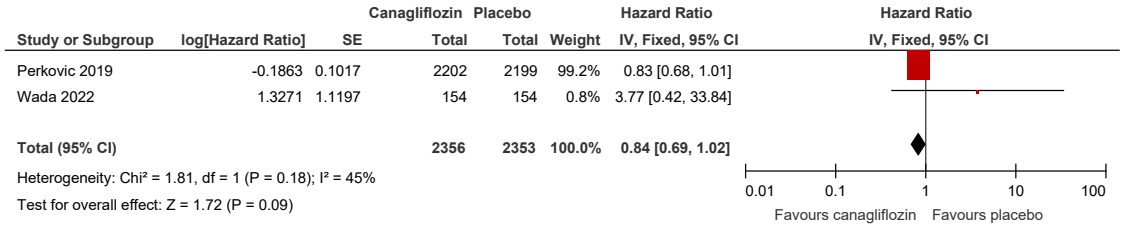


Figure 17: Cardiovascular mortality at end of follow-up, risk ratio

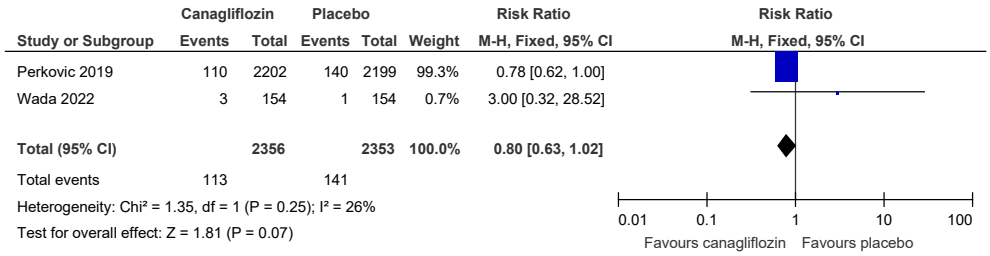


Figure 18: Cardiovascular mortality at end of follow-up, hazard ratio

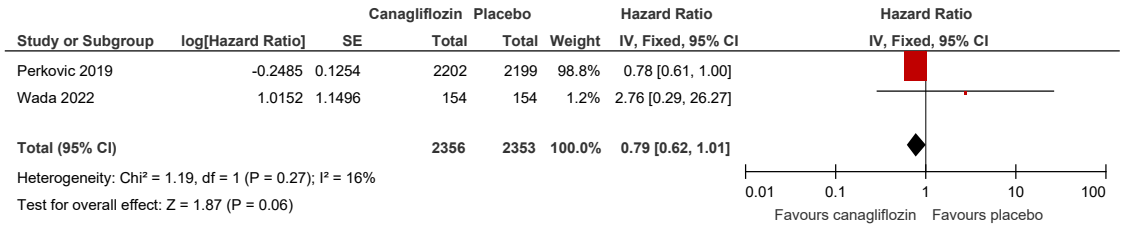


Figure 19: 5-point MACE at end of follow-up, risk ratio

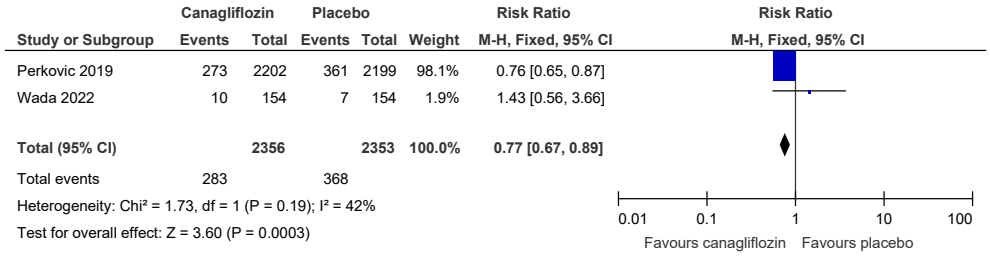


Figure 20: 5-point MACE at end of follow-up, hazard ratio

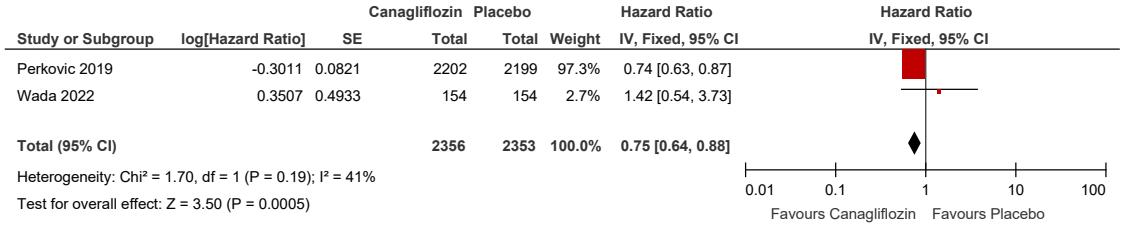


Figure 21: Hospitalisation for heart failure at end of follow-up, risk ratio

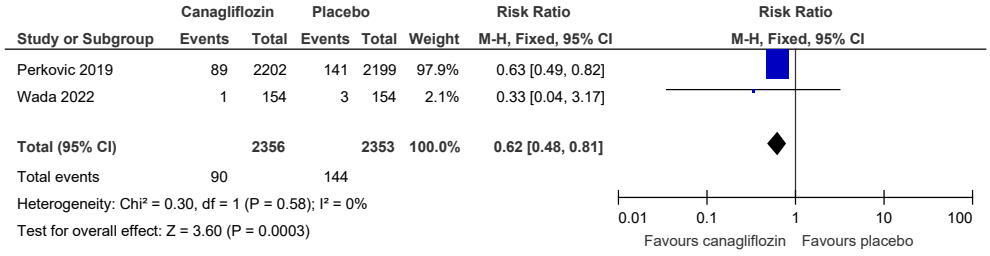


Figure 22: Hospitalisation for heart failure at end of follow-up, hazard ratio

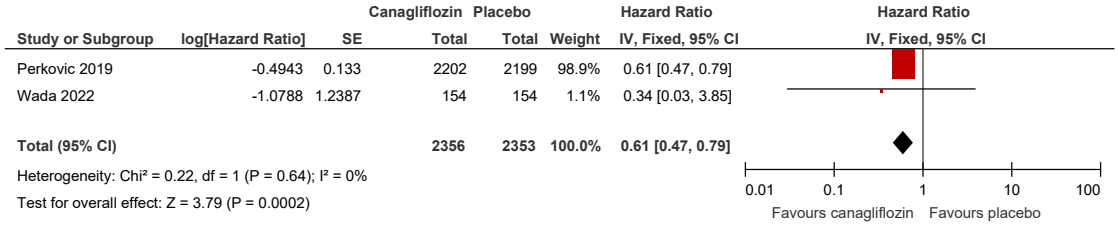


Figure 23: Diabetic ketoacidosis at end of follow-up

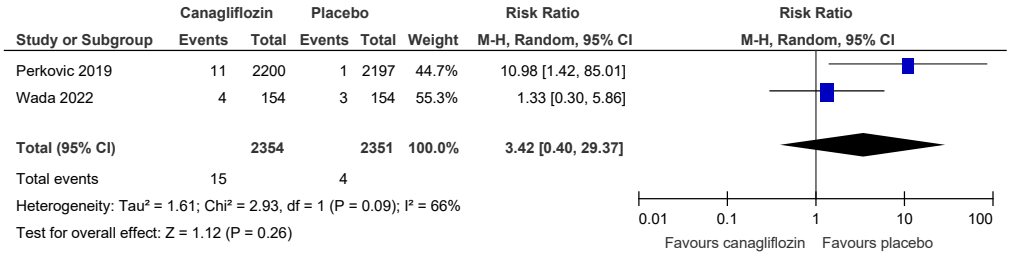


Figure 24: Hypoglycaemia episodes at end of follow-up

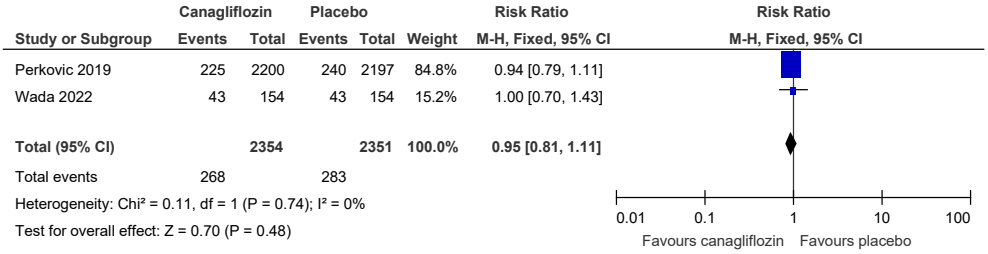


Figure 25: HbA1c change (%, lower values are better, change scores) at end of follow-up

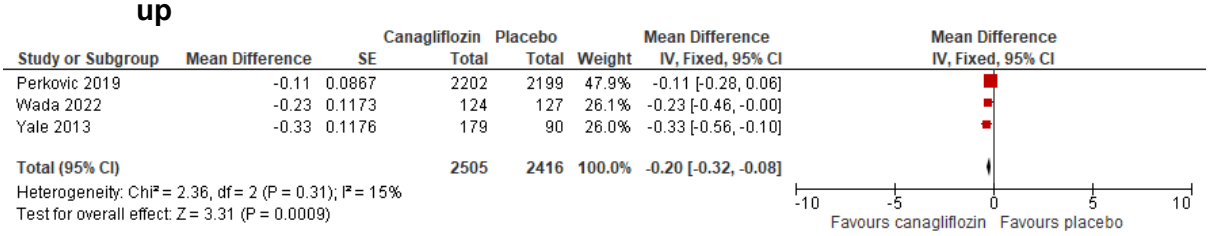
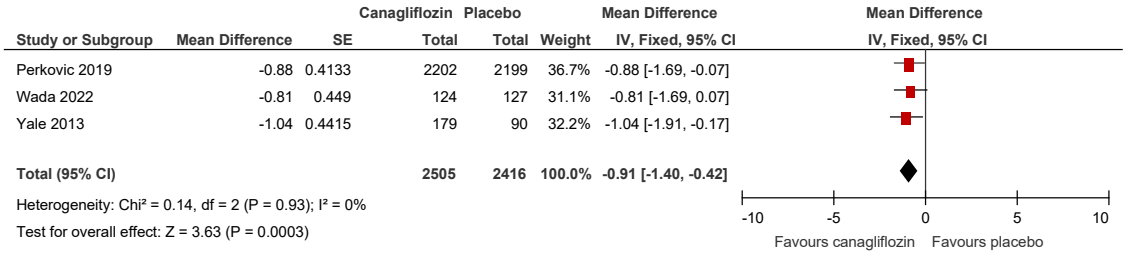


Figure 26: Weight change (kg, lower values are better, change scores) at end of follow-up



I.3.2 Adding dapagliflozin compared to adding placebo

Figure 27: All-cause mortality at end of follow up

Study or Subgroup	Dapagliflozin Events	Dapagliflozin Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
Fioretto 2018	0	160	0	161	31.3%	0.00 [-0.01, 0.01]
Kohan 2014	5	168	5	84	11.0%	-0.03 [-0.09, 0.03]
Pollock 2019	1	145	0	148	27.8%	0.01 [-0.01, 0.03]
Wiviott 2019 CKD	254	2944	315	2940	29.9%	-0.02 [-0.04, -0.01]
Total (95% CI)		**3417**		**3333**	**100.0%**	**-0.01 [-0.03, 0.02]**
Total events	260		320			

Heterogeneity: Tau² = 0.00; Chi² = 16.86, df = 3 (P = 0.0008); I² = 82%
Test for overall effect: Z = 0.65 (P = 0.51)

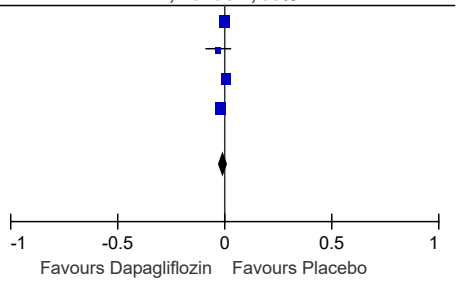


Figure 28: Cardiovascular mortality at end of follow up

Study or Subgroup	Dapagliflozin Events	Dapagliflozin Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Fioretto 2018	0	160	0	161	5.0%	0.00 [-0.01, 0.01]
Kohan 2014	4	168	3	84	3.5%	-0.01 [-0.06, 0.03]
Wiviott 2019 CKD	126	2944	138	2940	91.5%	-0.00 [-0.01, 0.01]
Total (95% CI)		**3272**		**3185**	**100.0%**	**-0.00 [-0.01, 0.01]**
Total events	130		141			

Heterogeneity: Chi² = 0.57, df = 2 (P = 0.75); I² = 0%
Test for overall effect: Z = 0.84 (P = 0.40)

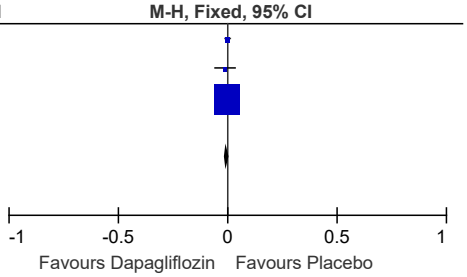


Figure 29: Persistent signs of worsening kidney disease at end of follow up

Study or Subgroup	Dapagliflozin Events	Dapagliflozin Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Kohan 2014	5	168	3	84	87.4%	0.82 [0.19, 3.66]
Pollock 2019	0	145	1	148	12.6%	0.14 [0.00, 6.96]
Total (95% CI)		**313**		**232**	**100.0%**	**0.66 [0.16, 2.65]**
Total events	5		4			

Heterogeneity: Chi² = 0.70, df = 1 (P = 0.40); I² = 0%
Test for overall effect: Z = 0.59 (P = 0.56)

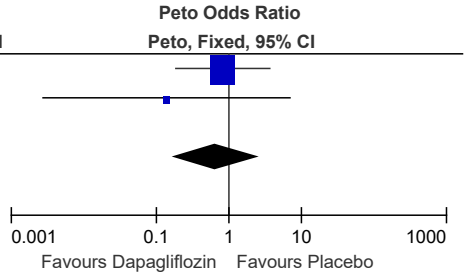


Figure 30: Diabetic ketoacidosis at end of follow up

Study or Subgroup	Dapagliflozin Events	Dapagliflozin Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Fioretto 2018	0	160	0	161	4.9%	0.00 [-0.01, 0.01]
Pollock 2019	1	145	0	148	4.5%	0.01 [-0.01, 0.03]
Wiviott 2019 CKD	6	2944	6	2940	90.6%	-0.00 [-0.00, 0.00]
Total (95% CI)		**3249**		**3249**	**100.0%**	**0.00 [-0.00, 0.00]**
Total events	7		6			

Heterogeneity: Chi² = 0.54, df = 2 (P = 0.76); I² = 0%
Test for overall effect: Z = 0.26 (P = 0.80)

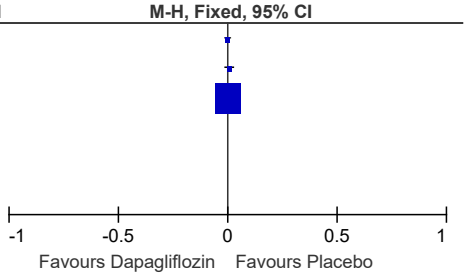


Figure 31: Hypoglycaemia episodes at end of follow up

Study or Subgroup	Dapagliflozin Events	Dapagliflozin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fioretto 2018	17	160	18	161	17.3%	0.95 [0.51, 1.78]
Kohan 2014	71	168	43	84	55.1%	0.83 [0.63, 1.09]
Pollock 2019	35	145	29	148	27.6%	1.23 [0.80, 1.90]
Total (95% CI)		**473**		**393**	**100.0%**	**0.96 [0.77, 1.20]**
Total events	123		90			

Heterogeneity: Chi² = 2.42, df = 2 (P = 0.30); I² = 17%
Test for overall effect: Z = 0.37 (P = 0.71)

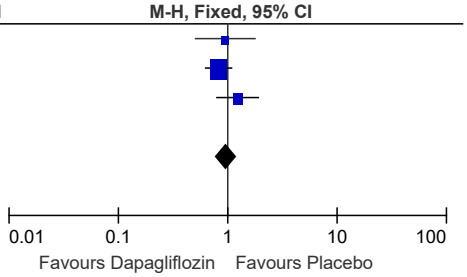


Figure 32: Severe hypoglycaemic episodes at end of follow up

Study or Subgroup	Dapagliflozin Events	Dapagliflozin Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Fioretto 2018	0	160	0	161	4.8%	0.00 [-0.01, 0.01]
Kohan 2014	2	168	4	84	3.3%	-0.04 [-0.08, 0.01]
Pollock 2019	0	145	1	148	4.4%	-0.01 [-0.03, 0.01]
Wiviott 2019 CKD	25	2944	43	2940	87.5%	-0.01 [-0.01, -0.00]
Total (95% CI)		**3417**		**3333**	**100.0%**	**-0.01 [-0.01, -0.00]**
Total events	27		48			

Heterogeneity: Chi² = 2.66, df = 3 (P = 0.45); I² = 0%
Test for overall effect: Z = 2.61 (P = 0.009)

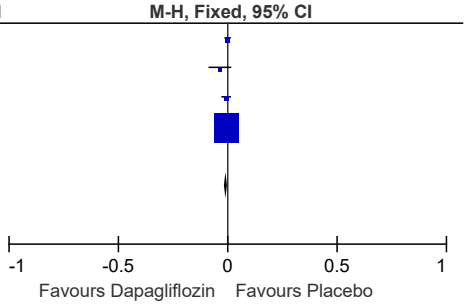


Figure 33: HbA1c change (%, lower values are better, change scores) at end of follow up

Study or Subgroup	Mean Difference	SE	Dapagliflozin Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Fioretto 2018	-0.34	0.1361	159	161	39.1%	-0.34 [-0.61, -0.07]
Kohan 2014	-0.28	0.4632	18	4	3.4%	-0.28 [-1.19, 0.63]
Pollock 2019	-0.16	0.1122	140	145	57.5%	-0.16 [-0.38, 0.06]
Total (95% CI)			**317**	**310**	**100.0%**	**-0.23 [-0.40, -0.07]**

Heterogeneity: Chi² = 1.05, df = 2 (P = 0.59); I² = 0%
Test for overall effect: Z = 2.75 (P = 0.006)

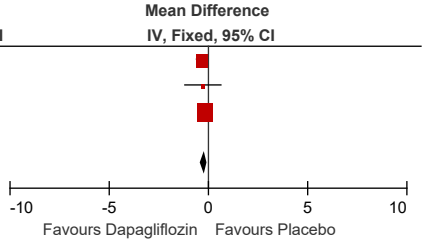
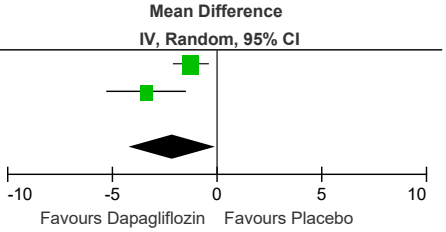


Figure 34: Weight change (kg, lower values are better, change scores) at end of follow up

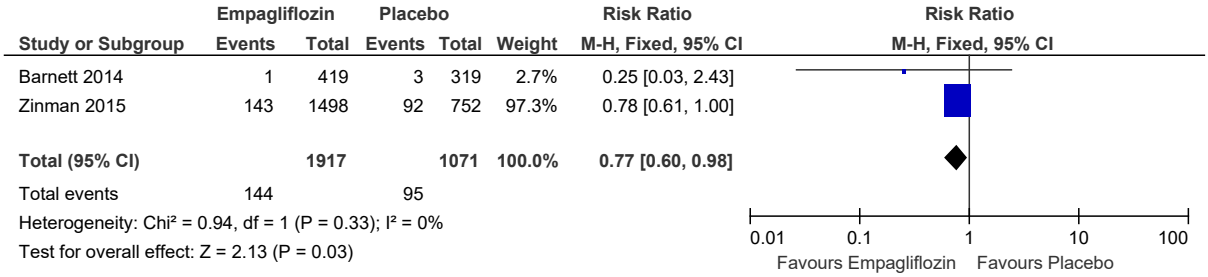
Study or Subgroup	Dapagliflozin Mean	Dapagliflozin SD	Dapagliflozin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Fioretto 2018	-3.17	3.78	159	-1.92	3.75	161	58.0%	-1.25 [-2.08, -0.42]
Kohan 2014	-0.76	5.09	92	2.63	5.12	42	42.0%	-3.39 [-5.26, -1.52]
Total (95% CI)			**251**			**203**	**100.0%**	**-2.15 [-4.22, -0.08]**

Heterogeneity: Tau² = 1.75; Chi² = 4.23, df = 1 (P = 0.04); I² = 76%
Test for overall effect: Z = 2.04 (P = 0.04)



I.3.3 Adding empagliflozin compared to adding placebo

Figure 35: All-cause mortality at end of follow up



I.3.4 Adding empagliflozin compared to adding linagliptin

There are no forest plots reported for this comparison (all outcomes include a single study).

I.3.5 Adding ertugliflozin compared to adding placebo

Figure 36: HbA1c change (%, lower values are better, change scores) at end of follow-up

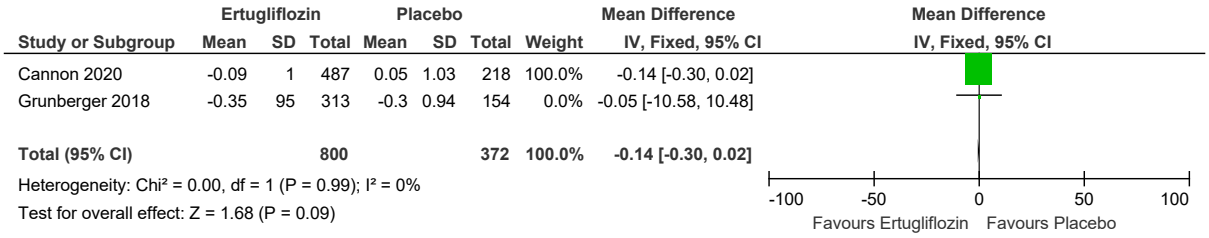
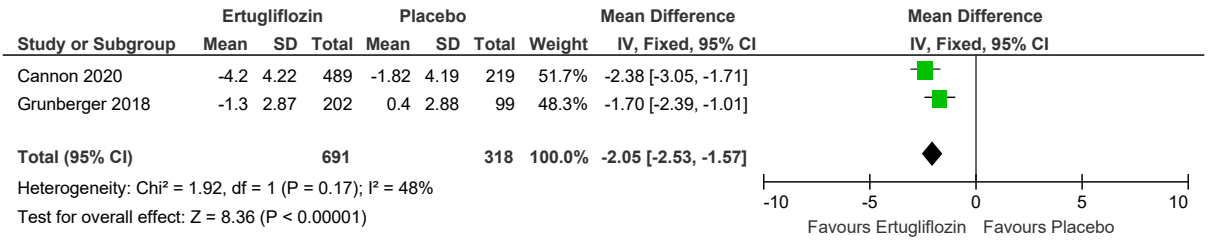


Figure 37: Weight change (kg, lower values are better, change scores) at end of follow-up



I.4 Sulphonylureas

I.4.1 Adding glimepiride compared to adding insulin

There are no forest plots reported for this comparison (all outcomes include a single study).

I.5 Thiazolidinediones

I.5.1 Adding pioglitazone compared to adding placebo

There are no forest plots reported for this comparison (all outcomes include a single study).

I.6 Combinations

I.6.1 Adding dapagliflozin + saxagliptin compared to adding placebo

There are no forest plots reported for this comparison (all outcomes include a single study).

I.6.2 Adding dapagliflozin + saxagliptin compared to adding dapagliflozin

There are no forest plots reported for this comparison (all outcomes include a single study).

Appendix J GRADE tables – Model 3: Type 2 diabetes and chronic kidney disease

J.1 DPP-4 inhibitors

J.1.1 Adding linagliptin compared to adding placebo

Table 1: Clinical evidence profile: Adding linagliptin 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 – 8.8 months											
2	RCT	very serious[1]	not serious	not serious	very serious[2]	NA	5/250	4/243	RR 1.20 (0.33, 4.38)	3 more per 1000 (11 fewer to 56 more)	very low
cardiovascular mortality at end of follow up – 5.5 months											
1 (groop 2017)	RCT	not serious	not serious	NA[3]	very serious[2]	NA	2/182	0/178	PETO OR 7.27 (0.45, 116.68)	11 more per 1000 (4 fewer to 26 more)	low
non-fatal stroke at end of follow up – 8.8 months											
2	RCT	not serious	not serious	serious[4]	very serious[5]	NA	1/250	1/243	RD -0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	very low

non-fatal myocardial infarction at end of follow up – 8.8 months											
2	RCT	very serious[1]	not serious	serious[4]	very serious[2]	NA	5/250	2/243	RR 2.11 (0.49, 9.20)	9 more per 1000 (4 fewer to 68 more)	very low
hospitalisation for heart failure at end of follow up – 16 months											
2	RCT	not serious	not serious	serious[4]	very serious[6]	NA	162/2291	188/2252	RD -0.01 (-0.03, 0.00)	13 fewer per 1000 (28 fewer to 3 more)	very low
hospitalisation for heart failure at end of follow up – 26.4 months											
1 (rosenstock 2019a)	RCT	not serious	not serious	NA[3]	serious[7]	NA	2109	2074	HR 0.84 (0.68, 1.04)	Not estimable	moderate
acute kidney injury at end of follow up – 12 months											
1 (mcgill 2013)	RCT	very serious[1]	not serious	NA[3]	very serious[2]	NA	5/68	4/65	RR 1.19 (0.34, 4.25)	12 more per 1000 (41 fewer to 200 more)	very low
development of end stage kidney disease at end of follow up – 5.5 months											
1 (groop 2017)	RCT	not serious	not serious	NA[3]	not serious	NA	0/182	0/178	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (11 fewer to 11 more)	high
hypoglycaemia episodes at end of follow up – 8.8 months											

2	RCT	very serious[1]	not serious	serious[8]	serious[7]	NA	67/250	42/243	RR 1.54 (1.14, 2.07)	93 more per 1000 (24 more to 184 more)	very low
severe hypoglycaemic episodes at end of follow up – 8.8 months											
2	RCT	not serious	not serious	serious[4]	very serious[5]	NA	3/250	3/243	RD -0.00 (-0.02, 0.02)	0 fewer per 1000 (21 fewer to 20 more)	very low
hba1c change (%, lower scores are better, change and final scores) at end of follow up – 7.8 months											
3	RCT	not serious	not serious	not serious	serious[9]	NA	289	277	MD -0.60 (-0.75, -0.45)	MD 0.60 lower (0.75 lower to 0.45 lower)	moderate
weight change (kg, lower scores are better, change and final scores) at end of follow up – 9 months											
2	RCT	very serious[1]	not serious	not serious	serious[10]	NA	128	121	MD -0.95 (-3.23, 1.33)	MD 0.95 lower (3.23 lower to 1.33 higher)	very low

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

2. 95% confidence intervals cross both ends 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 = 0.03 (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 = 0.63 (0.8-0.9 = serious, <0.8 = very serious).

7. 95% confidence intervals cross one end 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)

J.1.2 Switching from or adding to linagliptin compared to switching from or adding to liraglutide

Table 2: Clinical evidence profile: Linagliptin compared to liraglutide (switching from, or adding to, other glucose-lowering drugs)

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 - 48 months											
1 (hiramatsu 2018)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	2/45	2/45	RR 1.00 (0.15, 6.79)	0 fewer per 1000 (38 fewer to 257 more)	very low
non-fatal myocardial infarction at end of follow up - 48 months											
1 (hiramatsu 2018)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	2/45	1/45	RR 2.00 (0.19, 21.28)	22 more per 1000	very low

										(18 fewer to 451 more)	
hospitalisation for heart failure at end of follow up - 48 months											
1 (hiramatsu 2018)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	3/45	3/45	RR 1.00 (0.21, 4.69)	0 fewer per 1000 (52 fewer to 246 more)	very low
development of end stage kidney disease at end of follow up - 48 months											
1 (hiramatsu 2018)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	3/45	3/45	RR 1.00 (0.21, 4.69)	0 fewer per 1000 (52 fewer to 246 more)	very low
cardiac arrhythmia at end of follow up - 48 months											
1 (hiramatsu 2018)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	2/45	1/45	RR 2.00 (0.19, 21.28)	22 more per 1000 (18 fewer to 451 more)	very low
hba1c change (%, lower values are better, final scores) at end of follow up - 48 months											
1 (hiramatsu 2018)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	32	32	MD -0.05 (-0.34, 0.24)	MD 0.05 lower (0.34 lower to 0.24 higher)	low

bmi change (kg/m2, lower values are better, final scores) at end of follow up - 48 months											
1 (hiramatsu 2018)	RCT	very serious[1]	not serious	NA[2]	very serious[4]	NA	32	32	MD 0.10 (-1.84, 2.04)	MD 0.10 higher (1.84 lower to 2.04 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 (-0.80, 0.80)

J.1.3 Adding saxagliptin compared to adding placebo

Table 3: 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
all-cause mortality at end of follow up – 12 months											
1 (nowicki 2011a)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	3/85	4/85	RR 0.75 (0.17, 3.25)	12 fewer per 1000 (39 fewer to 106 more)	very low
hypoglycaemia episodes at end of follow up – 12 months											

1 (nowicki 2011a)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	8/85	4/85	RR 2.00 (0.63, 6.39)	47 more per 1000 (18 fewer to 254 more)	very low
development of end stage kidney disease at end of follow up – 12 months											
1 (nowicki 2011a)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/85	2/85	PETO OR 0.13 (0.01, 2.16)	24 fewer per 1000 (56 fewer to 9 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up – 12 months											
1 (nowicki 2011a)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	26	34	MD -0.63 (-1.24, -0.02)	MD 0.63 lower (1.24 lower to 0.02 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. 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 (-0.50, 0.50)

J.1.4 Sitagliptin compared to linagliptin

Table 4: Clinical evidence profile: Sitagliptin compared to linagliptin (switching from, or adding to, other glucose-lowering drugs)

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 - 48 months											
1 (hiramatsu 2018)	RCT	very serious [1]	not serious	NA[2]	very serious[3]	NA	2/49	2/45	RR 0.92 (0.13, 6.25)	4 fewer per 1000 (38 fewer to 233 more)	very low
non-fatal myocardial infarction at end of follow up - 48 months											
1 (hiramatsu 2018)	RCT	very serious [1]	not serious	NA[2]	very serious[3]	NA	3/49	2/45	RR 1.38 (0.24, 7.87)	17 more per 1000 (34 fewer to 305 more)	very low
hospitalisation for heart failure at end of follow up - 48 months											
1 (hiramatsu 2018)	RCT	very serious [1]	not serious	NA[2]	very serious[3]	NA	3/49	3/45	RR 0.92 (0.20, 4.32)	5 fewer per 1000 (54 fewer to 221 more)	very low
development of end stage kidney disease at end of follow up - 48 months											
1 (hiramatsu 2018)	RCT	very serious [1]	not serious	NA[2]	very serious[3]	NA	5/49	3/45	RR 1.53 (0.39, 6.04)	35 more per 1000 (41 fewer to 336 more)	very low
cardiac arrhythmia at end of follow up - 48 months											

1 (hiramatsu 2018)	RCT	very serious [1]	not serious	NA[2]	very serious[3]	NA	2/49	2/45	RR 0.92 (0.13, 6.25)	4 fewer per 1000 (38 fewer to 233 more)	very low
hba1c change (%, lower values are better, final scores) at end of follow up - 48 months											
1 (hiramatsu 2018)	RCT	very serious [1]	not serious	NA[2]	serious[4]	NA	34	32	MD 0.34 (-0.02, 0.70)	MD 0.34 higher (0.02 lower to 0.70 higher)	very low
bmi change (kg/m2, lower values are better, final scores) at end of follow up - 48 months											
1 (hiramatsu 2018)	RCT	very serious [1]	not serious	NA[2]	very serious[5]	NA	34	32	MD 1.10 (-1.05, 3.25)	MD 1.10 higher (1.05 lower to 3.25 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 one end of the defined MIDs (-0.50, 0.50)

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

J.1.5 Sitagliptin compared to liraglutide

Table 5: Clinical evidence profile: Sitagliptin compared to liraglutide (switching from, or adding to, other glucose-lowering drugs)

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 - 48 months											
1 (hiramatsu 2018)	RCT	very serious [1]	not serious	NA[2]	very serious[3]	NA	2/49	2/45	RR 0.92 (0.13, 6.25)	4 fewer per 1000 (38 fewer to 233 more)	very low
non-fatal myocardial infarction at end of follow up - 48 months											
1 (hiramatsu 2018)	RCT	very serious [1]	not serious	NA[2]	very serious[3]	NA	3/49	1/45	RR 2.76 (0.30, 25.54)	39 more per 1000 (16 fewer to 545 more)	very low
hospitalisation for heart failure at end of follow up - 48 months											
1 (hiramatsu 2018)	RCT	very serious [1]	not serious	NA[2]	very serious[3]	NA	3/49	3/45	RR 0.92 (0.20, 4.32)	5 fewer per 1000 (54 fewer to 221 more)	very low
development of end stage kidney											

disease at end of follow up - 48 months											
1 (hiramatsu 2018)	RCT	very serious [1]	not serious	NA[2]	very serious[3]	NA	5/49	3/45	RR 1.53 (0.39, 6.04)	35 more per 1000 (41 fewer to 336 more)	very low
cardiac arrhythmia at end of follow up - 48 months											
1 (hiramatsu 2018)	RCT	very serious [1]	not serious	NA[2]	very serious[3]	NA	2/49	1/45	RR 1.84 (0.17, 19.57)	19 more per 1000 (18 fewer to 413 more)	very low
hba1c change (%, lower values are better, final scores) at end of follow up - 48 months											
1 (hiramatsu 2018)	RCT	very serious [1]	not serious	NA[2]	serious[4]	NA	34	32	MD 0.29 (-0.11, 0.69)	MD 0.29 higher (0.11 lower to 0.69 higher)	very low
bmi change (kg/m2, lower values are better, final scores) at end of follow up – 48 months											
1 (hiramatsu 2018)	RCT	very serious [1]	not serious	NA[2]	serious[5]	NA	34	32	MD 1.20~(-0.62, 3.02)	MD 1.20 higher~(0.62 lower to	very low

										3.02 higher)	

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 one end of the defined MIDs (-0.50, 0.50)

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

J.1.6 Adding vildagliptin compared to adding sitagliptin

Table 6: Clinical evidence profile: Adding vildagliptin compared to adding sitagliptin

all-cause mortality at end of follow up – 5.5 months	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
1 (kothny 2015)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	2/83	2/65	RR 0.78 (0.11, 5.41)	7 fewer per 1000 (27 fewer to 136 more)	low
cardiovascular mortality at end of follow up – 5.5 months											
1 (kothny 2015)	RCT	very serious[3]	not serious	NA[1]	very serious[2]	NA	1/83	0/65	PETO OR 5.95 (0.11, 308.70)	12 more per 1000 (11 fewer to 36 more)	very low

hypoglyaemia episodes at end of follow up – 5.5 months											
1 (kothny 2015)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	13/83	10/65	RR 1.02 (0.48, 2.17)	3 more per 1000 (80 fewer to 180 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up – 5.5 months											
1 (kothny 2015)	RCT	serious[4]	not serious	NA[1]	not serious	NA	78	62	MD 0.02 (-0.33, 0.37)	MD 0.02 higher (0.33 lower to 0.37 higher)	moderate

1. Only one study so no inconsistency

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

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

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

J.2 GLP-1 receptor agonists

J.2.1 Switching to dulaglutide compared to insulin

Table 7: Clinical evidence profile: Switching to dulaglutide compared to switching to insulin

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect	Absolute effect	Certainty

									(95% CI)		
all-cause mortality at end of follow up - 12 months											
1 (tuttle 2018)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	8/382	4/194	RR 1.02 (0.31, 3.33)	0 more per 1000 (14 fewer to 48 more)	very low
cardiovascular mortality at end of follow up - 12 months											
1 (tuttle 2018)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	8/382	4/194	RR 1.02 (0.31, 3.33)	0 more per 1000 (14 fewer to 48 more)	very low
persistent signs of worsening kidney disease at end of follow up - 12 months											
1 (tuttle 2018)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	152/382	91/194	RR 0.85 (0.70, 1.03)	71 fewer per 1000 (141 fewer to 14 more)	very low
development of end stage kidney disease at end of follow up - 12 months											
1 (tuttle 2018)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	22/382	16/194	RR 0.70	25 fewer	very low

									(0.38, 1.30)	per 1000 (52 fewer to 25 more)	
death from renal causes at end of follow up - 12 months											
1 (tuttle 2018)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/382	0/194	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	low
hypoglycaemia episodes at end of follow up - 12 months											
1 (tuttle 2018)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	12/382	16/194	RR 0.38 (0.18, 0.79)	51 fewer per 1000 (67 fewer to 17 fewer)	low
at night hypoglycaemic episodes at end of follow up - 12 months											
1 (tuttle 2018)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	84/382	93/194	RR 0.46 (0.36, 0.58)	259 fewer per 1000 (306 fewer to 200 fewer)	low

severe hypoglycaemic episodes at end of follow up - 12 months											
1 (tuttle 2018)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	5/382	13/194	RR 0.20 (0.07, 0.54)	54 fewer per 1000 (62 fewer to 31 fewer)	low
hba1c change (%, lower values are better, change scores) at end of follow-up - 12 months											
1 (tuttle 2018)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	363	186	MD -0.10 (-0.34, 0.14)	MD 0.10 lower (0.34 lower to 0.14 higher)	low
weight change (kg, lower values are better, change scores) at end of follow-up - 12 months											
1 (tuttle 2018)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	382	194	MD -3.80 (-4.81, -2.79)	MD 3.80 lower (4.81 lower to 2.79 lower)	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 one end of the defined MIDs (0.80, 1.25)

J.2.2 Switching to exenatide compared to switching to insulin

Table 8: Clinical evidence profile: Switching to exenatide compared to switching to 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 (wang 2020b)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	10/46	20/46	RR 0.50 (0.26, 0.95)	217 fewer per 1000 (320 fewer to 23 fewer)	very low
severe hypoglycaemic episodes at end of follow-up - 5.5 months											
1 (wang 2020b)	RCT	very serious[1]	not serious	NA[2]	very serious[4]	NA	0/46	2/46	Peto OR 0.13 (0.01, 2.15)	44 fewer per 1000 (102 fewer to 15 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow-up - 5.5 months											
1 (wang 2020b)	RCT	very serious[1]	not serious	NA[2]	serious[5]	NA	43	38	MD 0.22 (-0.43, 0.87)	MD 0.22 higher (0.43 lower to 0.87 higher)	very low

weight change (kg, lower values are better, change scores) at end of follow-up - 5.5 months											
1 (wang 2020b)	RCT	very serious[1]	not serious	NA[2]	serious[6]	NA	43	38	MD -2.68 (-4.47, -0.89)	MD 2.68 lower (4.47 lower to 0.89 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. 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. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

6. 95% confidence intervals cross one end of the defined MIDs (-3.00, 3.00)

J.2.3 Adding Liraglutide compared to adding placebo

Table 9: Clinical evidence profile: Adding liraglutide 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 – 6 months											

1 (davies 2016)	RCT	serious [1]	not serious	NA[2]	very serious[3]	NA	4/140	1/137	PETO OR 3.31 (0.57, 19.33)	21 more per 1000 (10 fewer to 52 more)	very low
cardiovascular mortality at end of follow up – 6 months											
1 (davies 2016)	RCT	serious [1]	not serious	NA[2]	very serious[3]	NA	2/140	1/137	PETO OR 1.92 (0.20, 18.57)	7 more per 1000 (17 fewer to 31 more)	very low
diabetic ketoacidosis at end of follow up – 6 months											
1 (davies 2016)	RCT	serious [1]	not serious	NA[2]	very serious[3]	NA	1/140	0/137	PETO OR 7.23 (0.14, 364.57)	7 more per 1000 (7 fewer to 21 more)	very low
hypoglycaemia episodes at end of follow up – 6 months											
1 (davies 2016)	RCT	serious [1]	not serious	NA[2]	serious[4]	NA	29/140	36/137	RR 0.79 (0.51, 1.21)	56 fewer per 1000 (128 fewer to 55 more)	low
severe hypoglycaemic episodes at end of follow up – 6 months											

1 (davies 2016)	RCT	serious [1]	not serious	NA[2]	very serious[3]	NA	1/140	0/137	PETO OR 7.23 (0.14, 364.57)	7 more per 1000 (7 fewer to 21 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up – 6 months											
1 (davies 2016)	RCT	serious [1]	not serious	NA[2]	serious[5]	NA	140	137	MD -0.66 (-0.90, -0.42)	MD 0.66 lower (0.90 lower to 0.42 lower)	low
weight change (kg, lower values are better, change scores) at end of follow up – 6 months											
1 (davies 2016)	RCT	serious [1]	not serious	NA[2]	not serious	NA	140	137	MD -1.32 (-2.24, -0.40)	MD 1.32 lower (2.24 lower to 0.40 lower)	moderate
bmi change (kg/m2, lower values are better, change scores) at end of follow up – 6 months											
1 (davies 2016)	RCT	serious [1]	not serious	NA[2]	serious[6]	NA	140	137	MD -0.50	MD 0.50 lower	low

									(-0.83, -0.17)	(0.83 lower to 0.17 lower)	

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 (0.80, 1.25)

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

6. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

J.2.4 Adding semaglutide compared to adding placebo

Table 10: Clinical evidence profile: Adding semaglutide 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
health-related quality of life - subscale physical component (sf-36 version 2 [acute version], 0-100, higher values are better, change score) at end of follow up ~ Mean follow-up: 6 month(s)											
1 (mosenzon 2019)	RCT	not serious	not serious	NA[1]	serious[2]	NA	163	161	MD 1.98~(0.57, 3.39)	MD 1.98 higher~(0.57 higher to 3.39 higher)	moderate

health-related quality of life - subscale mental component (sf-36 version 2 [acute version], 0-100, higher values are better, change score) at end of follow up ~ Mean follow-up: 6 month(s)											
1 (mosenzon 2019)	RCT	not serious	not serious	NA[1]	not serious	NA	163	161	MD 0.68~(-1.23, 2.59)	MD 0.68 higher (1.23 lower to 2.59 higher)	high
all-cause mortality at end of follow up ~ Mean follow-up: 40.8 month(s)											
1 (perkovic 2024)	RCT	not serious	not serious	NA[1]	serious[3]	NA	1767	1766	HR 0.80~(0.67, 0.96)	Not estimable	moderate
all-cause mortality at end of follow up ~ Mean follow-up: 23.4 month(s)											
2	RCT	not serious	not serious	not serious	serious[3]	NA	228/1930	281/1927	RR 0.81~(0.69, 0.95)	28 fewer per 1000~(45 fewer to 7 fewer)	moderate
cardiovascular mortality at end of follow up ~ Mean follow-up: 40.8 month(s)											
1 (perkovic 2024)	RCT	not serious	not serious	NA[1]	serious[3]	NA	1767	1766	HR 0.71~(0.56, 0.90)	Not estimable	moderate
cardiovascular mortality at end of follow up ~											

Mean follow-up: 23.4 month(s)											
2	RCT	not serious	not serious	not serious	serious[3]	NA	124/1930	170/1927	RR 0.73~(0.58, 0.91)	24 fewer per 1000~(37 fewer to 8 fewer)	moderate
3-point mace at end of follow-up ~ Mean follow-up: 40.8 month(s)											
1 (perkovic 2024)	RCT	not serious	not serious	NA[1]	serious[3]	NA	1767	1766	HR 0.82~(0.58, 0.99)	Not estimable	moderate
3-point mace at end of follow-up ~ Mean follow-up: 40.8 month(s)											
1 (perkovic 2024)	RCT	not serious	not serious	NA[1]	serious[3]	NA	212/1767	254/1766	RR 0.83~(0.70, 0.99)	24 fewer per 1000~(43 fewer to 2 fewer)	moderate
non-fatal stroke at end of follow-up ~ Mean follow-up: 40.8 month(s)											
1 (perkovic 2024)	RCT	not serious	not serious	NA[1]	serious[3]	NA	1767	1766	HR 1.22~(0.84, 1.77)	Not estimable	moderate
non-fatal stroke at end of follow-up ~ Mean follow-up: 40.8 month(s)											
1 (perkovic 2024)	RCT	not serious	not serious	NA[1]	serious[3]	NA	63/1767	51/1766	RR 1.23~(0.86, 1.78)	7 more per 1000~(4 fewer to 22 more)	moderate
non-fatal myocardial infarction at end of											

follow-up ~ Mean follow-up: 40.8 month(s)											
1 (perkovic 2024)	RCT	not serious	not serious	NA[1]	serious[3]	NA	1767	1766	HR 0.80~(0.55, 1.16)	Not estimable	moderate
non-fatal myocardial infarction at end of follow-up ~ Mean follow-up: 40.8 month(s)											
1 (perkovic 2024)	RCT	not serious	not serious	NA[1]	serious[3]	NA	52/1767	64/1766	RR 0.81~(0.57, 1.16)	7 fewer per 1000~(16 fewer to 6 more)	moderate
unstable angina at end of follow-up ~ Mean follow-up: 40.8 month(s)											
1 (perkovic 2024)	RCT	not serious	not serious	NA[1]	serious[3]	NA	12/1767	22/1766	PETO OR 0.55~(0.28, 1.08)	6 fewer per 1000~(12 fewer to 1 more)	moderate
hospitalisation for heart failure at end of follow up ~ Mean follow-up: 6 month(s)											
1 (mosenzon 2019)	RCT	not serious	not serious	NA[1]	very serious[4]	NA	0/163	1/161	PETO OR 0.13~(0.00, 6.74)	6 fewer per 1000~(18 fewer to 6 more)	low
acute kidney injury at end of follow up ~ Mean follow-up: 23.4 month(s)											
2	RCT	not serious	not serious	not serious	very serious[4]	NA	126/1930	124/1927	RR 1.02~(0.80, 1.29)	1 more per 1000~(13	low

										fewer to 19 more)	
persistent signs of worsening kidney disease at end of follow-up ~ Mean follow-up: 40.8 month(s)											
1 (perkovic 2024)	RCT	not serious	not serious	NA[1]	serious[3]	NA	1767	1766	HR 0.73~(0.59, 0.89)	Not estimable	moderate
persistent signs of worsening kidney disease at end of follow-up ~ Mean follow-up: 40.8 month(s)											
1 (perkovic 2024)	RCT	not serious	not serious	NA[1]	serious[3]	NA	165/1767	213/1766	RR 0.77~(0.64, 0.94)	27 fewer per 1000~(44 fewer to 7 fewer)	moderate
development of end stage kidney disease at end of follow-up ~ Mean follow-up: 40.8 month(s)											
1 (perkovic 2024)	RCT	not serious	not serious	NA[1]	serious[3]	NA	1767	1766	HR 0.84~(0.63, 1.12)	Not estimable	moderate
development of end stage kidney disease at end of follow-up ~ Mean follow-up: 40.8 month(s)											
1 (perkovic 2024)	RCT	not serious	not serious	NA[1]	serious[3]	NA	87/1767	100/1766	RR 0.87~(0.66, 1.15)	7 fewer per 1000~(19 fewer to 8 more)	moderate

death from renal causes at end of follow-up ~ Mean follow-up: 40.8 month(s)											
1 (perkovic 2024)	RCT	not serious	not serious	NA[1]	very serious[4]	NA	1767	1766	HR 0.97~(0.27, 3.48)	Not estimable	low
death from renal causes at end of follow-up ~ Mean follow-up: 40.8 month(s)											
1 (perkovic 2024)	RCT	not serious	not serious	NA[1]	very serious[4]	NA	5/1767	5/1766	PETO OR 1.00~(0.29, 3.46)	0 fewer per 1000~(4 fewer to 4 more)	low
hypoglycaemia episodes at end of follow up ~ Mean follow-up: 6 month(s)											
1 (mosenzon 2019)	RCT	not serious	not serious	NA[1]	serious[3]	NA	9/163	3/161	RR 2.96~(0.82, 10.75)	37 more per 1000~(3 fewer to 182 more)	moderate
cardiac arrhythmia at end of follow-up ~ Mean follow-up: 40.8 month(s)											
1 (perkovic 2024)	RCT	not serious	not serious	NA[1]	serious[3]	NA	31/1767	22/1766	RR 1.41~(0.82, 2.42)	5 more per 1000~(2 fewer to 18 more)	moderate
diabetic ketoacidosis at end of follow-up ~ Mean follow-up: 40.8 month(s)											

1 (perkovic 2024)	RCT	very serious[5]	not serious	NA[1]	very serious[4]	NA	10/1767	7/1766	PETO OR 1.42~(0.55, 3.69)	2 more per 1000~(3 fewer to 6 more)	very low
severe hypoglycaemic episodes at end of follow up ~ Mean follow-up: 40.8 month(s)											
1 (perkovic 2024)	RCT	not serious	not serious	NA[1]	very serious[4]	NA	1767	1766	HR 1.02~(0.62, 1.68)	Not estimable	low
severe hypoglycaemic episodes at end of follow up ~ Mean follow-up: 23.4 month(s)											
2	RCT	not serious	not serious	serious[6]	very serious[7]	NA	47/1930	46/1927	RD 0.00~(-0.01, 0.01)	1 more per 1000~(9 fewer to 10 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up ~ Mean follow-up: 23.4 month(s)											
2	RCT	not serious	not serious	not serious	not serious	NA	1930	1927	MD -0.81~(-0.89, -0.72)	MD 0.81 lower~(0.89 lower to 0.72 lower)	high
weight change (kg, lower values are better, change scores) at end of follow up ~ Mean follow-up: 14.9 month(s)											

2	RCT	very serious[5]	not serious	very serious[8]	not serious	NA	1930	1927	MD -3.72~(-4.13, -3.32)	MD 3.72 lower~(4.13 lower to 3.32 lower)	very low
bmi change (kg/m2, lower values are better, change scores) at end of follow up ~ Mean follow-up: 6 month(s)											
1 (mosenzon 2019)	RCT	not serious	not serious	NA[1]	serious[9]	NA	163	161	MD -0.90~(-1.20, -0.60)	MD 0.90 lower~(1.20 lower to 0.60 lower)	moderate

1. Only one study so no inconsistency

2. 95% confidence intervals cross one end of the defined MIDs (-2.00, 2.00)

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

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

7. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.03 (0.8-0.9 = serious, <0.8 = very serious).

8. I2 > 75%

9. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

J.2.5 Adding semaglutide compared to adding dulaglutide

Table 11: **Clinical evidence profile: Adding semaglutide compared to adding dulaglutide**

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
health-related quality of life - overall (dtr-qol, 0-100, higher values are better, final score) at end of follow up – Mean follow-up: 5.5 month(s)											
1 (kimura 2023)	RCT	very serious [1]	not serious	NA[2]	not serious	NA	54	53	MD 0.90 (-4.35, 6.15)	MD 0.90 higher (4.35 lower to 6.15 higher)	low
hospitalisation for heart failure at end of follow up – Mean follow-up: 5.5 month(s)											
1 (kimura 2023)	RCT	serious [3]	not serious	NA[2]	very serious[4]	NA	1/54	0/53	PETO OR 7.25 (0.14, 365.61)	19 more per 1000 (17 fewer to 54 more)	very low
diabetic ketoacidosis at end of follow up –											

Mean follow-up: 5.5 month(s)											
1 (kimura 2023)	RCT	serious [3]	not serious	NA[2]	serious[5]	NA	0/54	0/53	RD 0.00 (-0.04, 0.04)	0 fewer per 1000 (36 fewer to 36 more)	low
progression of liver disease at end of follow up – Mean follow-up: 5.5 month(s)											
1 (kimura 2023)	RCT	serious [3]	not serious	NA[2]	very serious[4]	NA	18/54	13/53	RR 1.36 (0.74, 2.49)	88 more per 1000 (63 fewer to 365 more)	very low
severe hypoglycaemic episodes at end of follow up – Mean follow-up: 5.5 month(s)											
1 (kimura 2023)	RCT	serious [3]	not serious	NA[2]	serious[5]	NA	0/54	0/53	RD 0.00 (-0.04, 0.04)	0 fewer per 1000 (36 fewer to 36 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up – Mean follow-up: 5.5 month(s)											

1 (kimura 2023)	RCT	serious [3]	not serious	NA[2]	serious[6]	NA	54	53	MD -0.40 (-0.63, -0.17)	MD 0.40 lower (0.63 lower to 0.17 lower)	low
weight change (kg, lower values are better, change scores) at end of follow up – Mean follow-up: 5.5 month(s)											
1 (kimura 2023)	RCT	serious [3]	not serious	NA[2]	serious[7]	NA	54	53	MD -2.50 (-3.36, -1.64)	MD 2.50 lower (3.36 lower to 1.64 lower)	low
bmi change (kg/m2, lower values are better, change scores) at end of follow up – Mean follow-up: 5.5 month(s)											
1 (kimura 2023)	RCT	serious [3]	not serious	NA[2]	serious[8]	NA	54	53	MD -1.00 (-1.33, -0.67)	MD 1.00 lower (1.33 lower to 0.67 lower)	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. >33.3% of the studies in the meta-analysis were at moderate risk of bias

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

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

6. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

7. 95% confidence intervals cross one end of the defined MIDs (-3.00, 3.00)

8. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

Table 12: Clinical evidence profile: Switching to semaglutide compared to dulaglutide (switching from dulaglutide)

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 – Mean follow-up: 5.5 month(s)											
1 (takahashi 2023)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	2/35	1/35	RR 2.00 (0.19, 21.06)	29 more per 1000 (23 fewer to 573 more)	very low
severe hypoglycaemic episodes at end of follow up – Mean follow-up: 5.5 month(s)											
1 (takahashi 2023)	RCT	serious[1]	not serious	NA[2]	very serious[4]	NA	0/35	0/35	RD 0.00 (-0.05, 0.05)	0 fewer per 1000 (54 fewer to 54 more)	very low
hba1c change (%, lower values are better, change scores) at end											

of follow up – Mean follow-up: 5.5 month(s)											
1 (takahashi 2023)	RCT	serious[1]	not serious	NA[2]	serious[5]	NA	31	32	MD -0.60 (-0.91, -0.29)	MD 0.60 lower (0.91 lower to 0.29 lower)	low
weight change (kg, lower values are better, change scores) at end of follow up – Mean follow-up: 5.5 month(s)											
1 (takahashi 2023)	RCT	serious[1]	not serious	NA[2]	serious[6]	NA	31	32	MD -2.70 (-3.55, -1.85)	MD 2.70 lower (3.55 lower to 1.85 lower)	low
bmi change (kg/m2, lower values are better, change scores) at end of follow up – Mean follow-up: 5.5 month(s)											
1 (takahashi 2023)	RCT	serious[1]	not serious	NA[2]	serious[7]	NA	31	32	MD -1.00 (-1.34, -0.66)	MD 1.00 lower (1.34 lower to 0.66 lower)	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. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.

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

6. 95% confidence intervals cross one end of the defined MIDs (-3.00, 3.00)

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

J.2.6 Switching to semaglutide compared to liraglutide

Table 13: Clinical evidence profile: Switching to semaglutide compared to liraglutide (switching from liraglutide)

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 – Mean follow-up: 5.5 month(s)											
1 (takahashi 2023)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	1/20	3/20	RR 0.33 (0.04, 2.94)	100 fewer per 1000 (144 fewer to 291 more)	very low
severe hypoglycaemic episodes at end of follow up – Mean follow-up: 5.5 month(s)											
1 (takahashi 2023)	RCT	serious[1]	not serious	NA[2]	very serious[4]	NA	0/20	0/20	RD 0.00 (-0.09, 0.09)	0 fewer per 1000 (92 fewer to 92 more)	very low

hba1c change (%, lower scores are better, change scores) at end of follow up – Mean follow-up: 5.5 month(s)											
1 (takahashi 2023)	RCT	serious[1]	not serious	NA[2]	serious[5]	NA	19	18	MD -0.50 (-0.86, -0.14)	MD 0.50 lower (0.86 lower to 0.14 lower)	low
weight change (kg, lower scores are better, change scores) at end of follow up – Mean follow-up: 5.5 month(s)											
1 (takahashi 2023)	RCT	serious[1]	not serious	NA[2]	not serious	NA	19	18	MD -0.20 (-1.87, 1.47)	MD 0.20 lower (1.87 lower to 1.47 higher)	moderate
bmi change (kg/m2, lower scores are better, change scores) at end of follow up – Mean follow-up: 5.5 month(s)											
1 (takahashi 2023)	RCT	serious[1]	not serious	NA[2]	not serious	NA	19	18	MD 0.00 (-0.65, 0.65)	MD 0.00 lower (0.65 lower to 0.65 higher)	moderate

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

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

J.3 SGLT2 inhibitors

J.3.1 Adding canagliflozin compared to adding placebo

Table 14: 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 - 22.8 months											
3	RCT	not serious	not serious	not serious	serious[1]	NA	176/2355	204/2443	RR 0.93 (0.76, 1.12)	6 fewer per 1000 (20 fewer to 10 more)	moderate
all-cause mortality at end of follow-up – 28.2 months											
2	RCT	not serious	not serious	not serious	serious[1]	NA	2356	2353	HR 0.84 (0.69, 1.02)	Not estimable	moderate
cardiovascular mortality at end of follow-up – 28.2 months											

2	RCT	not serious	not serious	not serious	serious[1]	NA	113/2356	141/2353	RR 0.80 (0.63, 1.02)	12 fewer per 1000 (22 fewer to 1 more)	moderate
cardiovascular mortality at end of follow-up – 28.2 months											
2	RCT	not serious	not serious	not serious	serious[1]	NA	2356	2353	HR 0.79 (0.62, 1.01)	Not estimable	moderate
5-point mace at end of follow-up – 28.2 months											
2	RCT	not serious	not serious	not serious	serious[1]	NA	283/2356	368/2353	RR 0.77 (0.67, 0.89)	36 fewer per 1000 (52 fewer to 18 fewer)	moderate
5-point mace at end of follow-up – 28.2 months											
2	RCT	not serious	not serious	not serious	serious[1]	NA	2356	2353	HR 0.75 (0.64, 0.88)	Not estimable	moderate
hospitalisation for heart failure at end of follow-up – 28.2 months											
2	RCT	not serious	not serious	not serious	serious[1]	NA	90/2356	144/2353	RR 0.62	23 fewer per 1000	moderate

									(0.48, 0.81)	(32 fewer to 12 fewer)	
hospitalisation for heart failure at end of follow-up – 28.2 months											
2	RCT	not serious	not serious	not serious	not serious	NA	2356	2353	HR 0.61 (0.47, 0.79)	Not estimable	high
acute kidney injury at end of follow-up – 31.4 months											
1 (perkovic 2019)	RCT	not serious	not serious	NA[2]	serious[1]	NA	86/2200	98/2197	RR 0.88 (0.66, 1.16)	6 fewer per 1000 (15 fewer to 7 more)	moderate
acute kidney injury at end of follow-up – 31.4 months											
1 (perkovic 2019)	RCT	not serious	not serious	NA[2]	serious[1]	NA	2200	2197	HR 0.85 (0.64, 1.13)	Not estimable	moderate
persistent signs of kidney disease at end of follow-up – 31.4 months											
1 (perkovic 2019)	RCT	NA	NA	NA[2]	not serious	NA	118/2202	188/2199	RR 0.63 (0.50, 0.78)	32 fewer per 1000 (43 fewer to 19 fewer)	

persistent signs of worsening kidney disease at end of follow-up – 31.4 months											
1 (perkovic 2019)	RCT	not serious	not serious	NA[2]	not serious	NA	2202	2199	HR 0.60 (0.48, 0.75)	Not estimable	high
development of end stage kidney disease at end of follow-up – 31.4 months											
1 (perkovic 2019)	RCT	not serious	not serious	NA[2]	serious[1]	NA	116/2202	165/2199	RR 0.70 (0.56, 0.88)	22 fewer per 1000 (33 fewer to 9 fewer)	moderate
development of end stage kidney disease at end of follow-up – 31.4 months											
1 (perkovic 2019)	RCT	not serious	not serious	NA[2]	serious[1]	NA	2202	2199	HR 0.68 (0.54, 0.86)	Not estimable	moderate
death from renal cause at end of follow-up – 31.4 months											
1 (perkovic 2019)	RCT	NA	NA	NA[2]	very serious[3]	NA	2/2202	5/2199	PETO OR 0.42 (0.10, 1.86)	1 fewer per 1000 (4 fewer to 1 more)	

diabetic ketoacidosis at end of follow-up – 28.2 months											
2	RCT	not serious	not serious	serious[4]	very serious[3]	NA	15/2354	4/2351	RR 3.42 (0.40, 29.37)	4 more per 1000 (1 fewer to 48 more)	very low
diabetic ketoacidosis at end of follow-up – 31.4 months											
1 (perkovic 2019)	RCT	not serious	not serious	NA[2]	not serious	NA	2200	2197	HR 10.80 (1.39, 83.92)	Not estimable	high
hypoglycaemia episodes at end of follow-up – 28.2 months											
2	RCT	not serious	not serious	not serious	not serious	NA	268/2354	283/2351	RR 0.95 (0.81, 1.11)	7 fewer per 1000 (23 fewer to 13 more)	high
hypoglycaemia episodes at end of follow-up – 31.4 months											
1 (perkovic 2019)	RCT	not serious	not serious	NA[2]	serious[1]	NA	2200	2197	HR 0.92 (0.77, 1.10)	Not estimable	moderate
hba1c change (%, lower values are better, change											

scores) at end of follow-up – 22.8 months											
3	RCT	not serious	not serious	not serious	not serious	NA	2505	2416	MD -0.20 (-0.32, -0.08)	MD 0.20 lower (0.32 lower to 0.08 lower)	high
weight change (kg, lower values are better, change scores) at end of follow-up – 22.8 months											
3	RCT	not serious	not serious	not serious	not serious	NA	2505	2416	MD -0.90 (-1.38, -0.43)	MD 0.90 lower (1.38 lower to 0.43 lower)	high

1. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

2. Only one study so no inconsistency

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

4. I^2 between 50% and 75%

J.3.2 Adding dapagliflozin compared to adding placebo

Table 15: 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 – Mean follow-up: 21.4 month(s)											
4	RCT	very serious[1]	not serious	serious[2]	not serious	NA	260/3417	320/3333	RD -0.01 (-0.03, 0.02)	8 fewer per 1000 (30 fewer to 15 more)	very low
cardiovascular mortality at end of follow up – Mean follow-up: 26.6 month(s)											
3	RCT	serious[3]	not serious	serious[2]	very serious[4]	NA	130/3272	141/3185	RD -0.00 (-0.01, 0.01)	4 fewer per 1000 (14 fewer to 6 more)	very low
3-point mace at end of follow up – Mean follow-up: 50.4 month(s)											
1 (wiviott 2019)	RCT	serious[3]	not serious	NA[5]	not serious	NA	347/2944	372/2940	RR 0.93 (0.81, 1.07)	9 fewer per 1000 (24 fewer to 9 more)	moderate
hospitalisation for heart failure at end of follow up – Mean follow-up: 50.4 month(s)											
1 (wiviott 2019)	RCT	serious[3]	not serious	NA[5]	serious[6]	NA	122/2944	166/2940	RR 0.73 (0.58, 0.92)	15 fewer per 1000 (23 fewer to 4 fewer)	low
acute kidney injury at end of follow up – Mean follow-up: 24 month(s)											
1 (kohan 2014)	RCT	very serious[1]	not serious	NA[5]	very serious[7]	NA	0/168	1/84	PETO OR 0.05 (0.00, 3.18)	12 fewer per 1000 (35 fewer to 11 more)	very low

persistent signs of worsening kidney disease at end of follow up – Mean follow-up: 14.8 month(s)											
2	RCT	very serious[1]	not serious	serious[2]	very serious[7]	NA	5/313	4/232	PETO OR 0.66 (0.16, 2.65)	1 fewer per 1000 (23 fewer to 20 more)	very low
development of end stage kidney disease at end of follow up – Mean follow-up: 24 month(s)											
1 (kohan 2014)	RCT	very serious[1]	not serious	NA[5]	very serious[7]	NA	2/168	2/84	RR 0.50 (0.07, 3.49)	12 fewer per 1000 (22 fewer to 59 more)	very low
diabetic ketoacidosis at end of follow up – Mean follow-up: 20.5 month(s)											
3	RCT	serious[3]	not serious	serious[2]	very serious[8]	NA	7/3249	6/3249	RD 0.00 (-0.00, 0.00)	0 more per 1000 (2 fewer to 3 more)	very low
hypoglycaemia episodes at end of follow up – Mean follow-up: 11.7 month(s)											
3	RCT	very serious[1]	not serious	not serious	serious[6]	NA	123/473	90/393	RR 0.96 (0.77, 1.20)	9 fewer per 1000 (53 fewer to 46 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 21.4 month(s)											

4	RCT	serious[3]	not serious	serious[2]	not serious	NA	27/3417	48/3333	RD -0.01 (-0.01, -0.00)	7 fewer per 1000 (12 fewer to 2 fewer)	low
hba1c change (%, lower values are better, change scores) at end of follow up – Mean follow-up: 11.7 month(s)											
3	RCT	very serious[1]	not serious	not serious	not serious	NA	317	310	MD -0.23 (-0.40, -0.07)	MD 0.23 lower (0.40 lower to 0.07 lower)	low
weight change (kg, lower values are better, change scores) at end of follow up – Mean follow-up: 14.8 month(s)											
2	RCT	serious[3]	not serious	very serious[9]	serious[10]	NA	251	203	MD -2.15 (-4.22, -0.08)	MD 2.15 lower (4.22 lower to 0.08 lower)	very low
weight change (%, lower values are better, change scores) at end of follow up – Mean follow-up: 5.5 month(s)											
1 (pollock 2019)	RCT	very serious[1]	not serious	NA[5]	not serious	NA	144	148	MD -0.87 (-2.17, 0.43)	MD 0.87 lower (2.17 lower to 0.43 higher)	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. >33.3% of the studies in the meta-analysis were at moderate risk of bias

4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.25 (0.8-0.9 = serious, <0.8 = very serious).

5. Only one study so no inconsistency

6. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

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 = 0.06 (0.8-0.9 = serious, <0.8 = very serious).

9. I2 > 75%

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

J.3.3 Adding empagliflozin compared to adding placebo

Table 16: 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 – 24.6 months											
2	RCT	not serious	not serious	not serious	serious[1]	NA	144/1917	95/1071	RR 0.77 (0.60, 0.98)	21 fewer per 1000 (36 fewer to 2 fewer)	moderate

all-cause mortality at end of follow-up – 37.2 months											
1 (zinman 2015)	RCT	not serious	not serious	NA[2]	serious[1]	NA	1498	752	HR 0.76 (0.59, 0.98)	Not estimable	moderate
cardiovascular mortality at end of follow-up – 37.2 months											
1 (zinman 2015)	RCT	not serious	not serious	NA[2]	serious[1]	NA	94/1498	65/752	RR 0.73 (0.54, 0.98)	24 fewer per 1000 (40 fewer to 1 fewer)	moderate
cardiovascular mortality at end of follow up – 37.2 months											
1 (zinman 2015)	RCT	not serious	not serious	NA[2]	serious[1]	NA	1498	752	HR 0.71 (0.52, 0.97)	Not estimable	moderate
hospitalisation for heart failure at end of follow-up – 37.2 months											
1 (zinman 2015)	RCT	not serious	not serious	NA[2]	serious[1]	NA	66/1498	53/752	RR 0.63 (0.44, 0.89)	26 fewer per 1000 (39 fewer to 8 fewer)	moderate
hospitalisation for heart failure at end of follow up – 37.2 months											

1 (zinman 2015)	RCT	not serious	not serious	NA[2]	serious[1]	NA	1498	752	HR 0.61 (0.42, 0.89)	Not estimable	moderate
cardiac arrhythmia at end of follow-up – 12 months											
1 (barnett 2014)	RCT	not serious	not serious	NA[2]	very serious[3]	NA	3/419	5/319	PETO OR 0.45 (0.11, 1.85)	9 fewer per 1000 (24 fewer to 7 more)	low
hypoglycaemia episodes at end of follow-up – 12 months											
1 (barnett 2014)	RCT	not serious	not serious	NA[2]	serious[1]	NA	114/419	88/319	RR 0.99 (0.78, 1.25)	4 fewer per 1000 (61 fewer to 69 more)	moderate
severe hypoglycaemia episodes at end of follow-up – 12 months											
1 (barnett 2014)	RCT	not serious	not serious	NA[2]	very serious[3]	NA	6/419	6/319	RR 0.76 (0.25, 2.34)	4 fewer per 1000 (14 fewer to 25 more)	low
hba1c change (%, lower values are better, change scores) at end of follow-up – 12 months											

1 (barnett 2014)	RCT	not serious	not serious	NA[2]	serious[4]	NA	419	319	MD -0.46 (-0.59, -0.33)	MD 0.46 lower (0.59 lower to 0.33 lower)	moderate
weight change (kg, lower values are better, change scores) at end of follow-up – 12 months											
1 (barnett 2014)	RCT	not serious	not serious	NA[2]	not serious	NA	419	319	MD -1.55 (-2.00, -1.10)	MD 1.55 lower (2.00 lower to 1.10 lower)	high

1. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

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 (-0.50, 0.50)

J.3.4 Adding empagliflozin compared to adding linagliptin

Table 17: Clinical evidence profile: Adding empagliflozin compared to adding linagliptin

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 – 12 months											

1 (Raman 2022)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	23/52	16/55	RR 1.52 (0.91, 2.54)	151 more per 1000 (26 fewer to 448 more)	very low
hba1c change (%, lower values are better, final scores) at end of follow up – 12 months											
1 (Raman 2022)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	52	55	MD -0.34 (-0.67, -0.01)	MD 0.34 lower (-0.67 lower to -0.01 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. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
4. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

J.3.5 Adding ertugliflozin compared to adding placebo

Table 18: 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 – 12 months											

1 (grunberger 2018)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	7/313	3/154	RR 1.15 (0.30, 4.38)	3 more per 1000 (14 fewer to 66 more)	very low
hypoglycaemia episodes at end of follow up – 12 months											
1 (grunberger 2018)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	67/313	35/154	RR 0.94 (0.66, 1.35)	13 fewer per 1000 (78 fewer to 80 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up – 29 months											
2	RCT	very serious[1]	not serious	not serious	not serious	NA	800	372	MD -0.14 (-0.30, 0.02)	MD 0.14 lower (0.30 lower to 0.02 higher)	low
weight change (kg, lower values are better, change scores) at end of follow up – 29 months											
2	RCT	very serious[1]	not serious	not serious	serious[4]	NA	691	318	MD -2.05 (-2.53, -1.57)	MD 2.05 lower (2.53 lower to 1.57 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. 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)

J.4 Sulphonylureas

J.4.1 Adding glimepiride compared to adding insulin

Table 19: 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	very serious[1]	not serious	NA[2]	not serious	NA	7/29	19/26	RR 0.33 (0.17, 0.66)	489 fewer per 1000 (609 fewer to 251 fewer)	low
hba1c change (%, lower values are better, final scores) at end of follow up - 5.5 months											
1 (li 2014c)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	29	26	MD -0.60 (-1.29, 0.09)	MD 0.60 lower (1.29 lower to 0.09 higher)	very low
weight change (kg, lower values are better, final											

scores) at end of follow up - 5.5 months											
1 (li 2014c)	RCT	very serious[1]	not serious	NA[2]	very serious[4]	NA	29	26	MD -2.90 (-11.66, 5.86)	MD 2.90 lower (11.66 lower to 5.86 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 one end of the defined MIDs (-0.50, 0.50)

4. 95% confidence intervals cross both ends of the defined MIDs (-3.00, 3.00)

J.5 Thiazolidinediones

J.5.1 Adding pioglitazone compared to adding placebo

Table 20: 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
hypoglycaemia episodes at end of follow up - 6 months											
1 (galle 2012)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	2/20	2/19	RR 0.95 (0.15, 6.08)	5 fewer per 1000 (90 fewer to 535 more)	very low
severe hypoglycaemic											

episodes at end of follow up - 6 months											
1 (galle 2012)	RCT	very serious[1]	not serious	NA[2]	very serious[4]	NA	0/20	0/19	RD 0.00 (-0.09, 0.09)	0 fewer per 1000 (95 fewer to 95 more)	
hba1c change (%, lower is better, scores) at end of follow up - 6 months											
1 (galle 2012)	RCT	very serious[1]	not serious	NA[2]	serious[5]	NA	19	17	MD -0.81 (-1.46, -0.16)	MD 0.81 lower (1.46 lower to 0.16 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. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

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

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

J.6 Combinations

J.6.1 Adding dapagliflozin + saxagliptin compared to adding placebo

Table 21 Clinical evidence profile: **Adding dapagliflozin + 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

all-cause mortality at end of follow up – 34 months											
1 (pollock 2019)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	1/152	0/148	PETO OR 7.20 (0.14, 362.84)	7 more per 1000 (6 fewer to 19 more)	very low
persistent signs of worsening kidney disease at end of follow up – 34 months											
1 (pollock 2019)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	3/152	1/148	PETO OR 2.67 (0.37, 19.17)	13 more per 1000 (13 fewer to 39 more)	very low
diabetic ketoacidosis at end of follow up – 34 months											
1 (pollock 2019)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	0/152	0/148	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (13 fewer to 13 more)	very low
hypoglycaemia episodes at end of follow up – 34 months											
1 (pollock 2019)	RCT	very serious[1]	not serious	NA[2]	serious[5]	NA	50/152	29/148	RR 1.68 (1.13, 2.50)	133 more per 1000 (25 more to 294 more)	very low
severe hypoglycaemic episodes at end of follow up – 34 months											
1 (pollock 2019)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	2/152	1/148	PETO OR 1.90 (0.20, 18.46)	6 more per 1000 (16 fewer to 29 more)	very low

hba1c change (%, lower values are better, change scores) at end of follow up – 34 months											
1 (pollock 2019)	RCT	very serious[1]	not serious	NA[2]	serious[6]	NA	151	145	MD -0.58 (-0.80, -0.36)	MD 0.58 lower (0.80 lower to 0.36 lower)	very low
weight change (%, lower values are better, change scores) at end of follow up – 34 months											
1 (pollock 2019)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	152	148	MD -0.04 (-1.32, 1.24)	MD 0.04 lower (1.32 lower to 1.24 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 both ends of the defined MIDs (0.80, 1.25)

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

5. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

6. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

J.6.2 Adding dapagliflozin + saxagliptin compared to adding dapagliflozin

Table 22: Clinical evidence profile: **Adding dapagliflozin + saxagliptin compared to adding dapagliflozin**

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 (pollock 2019)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	1/152	1/145	PETO OR 0.95 (0.06, 15.33)	0 fewer per 1000 (19 fewer to 18 more)	very low
persistent signs of worsening kidney disease at end of follow up – 34 months											
1 (pollock 2019)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	3/152	0/145	PETO OR 7.15 (0.74, 69.32)	20 more per 1000 (2 fewer to 42 more)	very low
diabetic ketoacidosis at end of follow up – 34 months											
1 (pollock 2019)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/152	1/145	PETO OR 0.13 (0.00, 6.51)	7 fewer per 1000 (20 fewer to 7 more)	very low
hypoglycaemia episodes at end of follow up – 34 months											
1 (pollock 2019)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	50/152	35/145	RR 1.36 (0.94, 1.97)	88 more per 1000 (14 fewer to 234 more)	very low
severe hypoglycaemic episodes at end of follow up – 34 months											

1 (pollock 2019)	RCT	very seriou s[1]	not serious	NA[2]	very serious[3]	NA	2/152	0/145	PETO OR 7.10 (0.44, 114.19)	13 more per 1000 (5 fewer to 31 more)	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 one end of the defined MIDs (0.80, 1.25)