National Institute for Health and Care Excellence

Draft for consultation

Type 2 diabetes in adults: management

[F7] 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

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Draft for Consultation

This evidence review was developed by NICE

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Appendices

Appendix L GRADE tables – Model 5: Type 2 diabetes and higher cardiovascular risk

L.1 Adding

L.1.1 Metformin

L.1.1.1 Adding metformin compared to adding placebo

Table 1: Clinical evidence profile: Adding metformin 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: 35 month(s)											
2	RCT	serious[1]	not serious	serious[2]	very serious[3]	NA	11/402	6/400	PETO OR 1.82 (0.69, 4.78)	12 more per 1000 (8 fewer to 32 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 52 month(s)											
1 (kooy 2009)	RCT	serious[1]	not serious	NA[4]	very serious[3]	NA	3/196	1/194	RR 2.97 (0.31, 28.30)	10 more per 1000 (4 fewer to 141 more)	very low
hospitalisation for heart failure at end of follow up Mean follow-up: 52 month(s)											

1 (kooy 2009)	RCT	serious[1]	not serious	NA[4]	very serious[3]	NA	3/196	4/194	RR 0.74 (0.17, 3.27)	5 fewer per 1000 (17 fewer to 47 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 14.9 month(s)											
4	RCT	not serious	not serious	not serious	not serious	NA	291/394	285/395	RR 1.03 (0.90, 1.17)	21 more per 1000 (70 fewer to 125 more)	high
severe hypoglycaemic episodes at end of follow up Mean follow-up: 15 month(s)											
2	RCT	not serious	not serious	very serious[5]	very serious[3]	NA	17/283	8/279	RR 2.62 (0.27, 25.56)	46 more per 1000 (21 fewer to 704 more)	very low
hba1c change (%, lower values are better, mean difference) at end of follow up Mean follow-up: 19.6 month(s)											
6	RCT	serious[1]	not serious	very serious[5]	serious[6]	NA	611	610	MD -0.47 (-0.80, -0.13)	MD 0.47 lower (0.80 lower to 0.13 lower)	very low
weight change (kg, lower values are better, mean difference) at end of follow up Mean follow-up: 14.9 month(s)											
4	RCT	serious[1]	not serious	very serious[5]	serious[7]	NA	388	393	MD -1.19 (-3.92, 1.54)	MD 1.19 lower (3.92 lower to 1.54 higher)	very low
bmi change (kg/m2, lower values are better, mean difference) at end of follow up Mean follow-up: 35 month(s)											

2	RCT	not serious	not serious	not serious	not serious	NA	402	400	MD -0.99 (-1.18, -0.80)	MD 0.99 lower (1.18 lower to 0.80 lower)	high

1. >33.3% of the studies in the meta-analysis were at moderate 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 both ends of the defined MIDs (0.80, 1.25)

4. Only one study so no inconsistency

5. I2 > 75%

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 (-2.40, 2.40)

L.1.1.2 Adding metformin compared to adding insulin

Table 2: Clinical evidence profile: Adding metformin 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 Mean follow-up: 6 month(s)											
1 (civera 2008)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	0/12	1/13	PETO OR 0.15 (0.00, 7.39)	77 fewer per 1000 (222 fewer to 68 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 6 month(s)											
1 (civera 2008)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	0/12	1/13	PETO OR 0.15 (0.00, 7.39)	77 fewer per 1000	very low

										(222 fewer to 68 more)	
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
1 (civera 2008)	RCT	serious[1]	not serious	NA[2]	serious[4]	NA	12	13	MD 0.70 (-0.40, 1.80)	MD 0.70 higher (0.40 lower to 1.80 higher)	low
weight change (kg, lower values are better, change score) at end of follow up Mean follow-up: 5.5 month(s)											
1 (civera 2008)	RCT	serious[1]	not serious	NA[2]	serious[5]	NA	12	13	MD -1.30 (-3.42, 0.82)	MD 1.30 lower (3.42 lower to 0.82 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 (-0.50, 0.50)

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

L.1.2 DPP-4 inhibitors

L.1.2.1 Adding alogliptin compared to adding placebo

Table 3: 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 Mean follow-up: 6 month(s)											
4	RCT	very serious[1]	not serious	serious[2]	very serious[3]	NA	3/1481	0/430	RD 0.00 (-0.01, 0.01)	2 more per 1000 (5 fewer to 10 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 6 month(s)											
3	RCT	very serious[1]	not serious	serious[2]	very serious[4]	NA	2/1084	0/333	RD 0.00 (-0.01, 0.01)	2 more per 1000 (6 fewer to 10 more)	very low
non-fatal myocardial infarction at end of follow up Mean follow-up: 6 month(s)											
1 (pratley 2009a)	RCT	not serious	not serious	NA[5]	very serious[6]	NA	3/397	0/97	PETO OR 3.49 (0.20, 60.57)	8 more per 1000 (1 fewer to 16 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 6 month(s)											
4	RCT	very serious[1]	not serious	not serious	serious[7]	NA	148/1481	50/429	RR 1.07 (0.80, 1.44)	9 more per 1000 (23 fewer to 51 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)											
3	RCT	very serious[1]	not serious	serious[2]	very serious[8]	NA	3/1084	3/333	RD -0.01 (-0.02, 0.01)	6 fewer per 1000 (17 fewer to 6 more)	very low
hba1c change (%, lower values are better, mean difference) at end of follow up Mean follow-up: 6 month(s)											
3	RCT	very serious[1]	not serious	not serious	serious[9]	NA	1084	333	MD -0.53 (-0.63, -0.42)	MD 0.53 lower (0.63 lower to 0.42 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)											
4	RCT	not serious	not serious	not serious	not serious	NA	1480	430	MD 0.17 (-0.09, 0.43)	MD 0.17 higher (0.09 lower to 0.43 higher)	high

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. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.5 (0.8-0.9 = serious, <0.8 = very serious).

4. 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).

5. Only one study so no inconsistency

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

7. 95% confidence intervals cross one end 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 = 0.58 (0.8-0.9 = serious, <0.8 = very serious).

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

L.1.2.2 Adding linagliptin compared to adding placebo

Table 4: 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 Mean follow-up: 8.5 month(s)											
10	RCT	not serious	not serious	serious[1]	very serious[2]	NA	373/5274	380/4996	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (12 fewer to 8 more)	very low
all-cause mortality at end of follow up Mean follow-up: 26.4 month(s)											

1 (rosenstock 2019a)	RCT	not serious	not serious	NA[3]	not serious	NA	3494	3485	HR 0.98 (0.84, 1.14)	Not estimable	high
cardiovascular mortality at end of follow up Mean follow-up: 8.5 month(s)											
10	RCT	not serious	not serious	serious[1]	very serious[4]	NA	261/5274	266/4996	RD 0.00 (-0.00, 0.01)	2 more per 1000 (3 fewer to 6 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 26.4 month(s)											
1 (rosenstock 2019a)	RCT	not serious	not serious	NA[3]	not serious	NA	3494	3485	HR 0.96 (0.81, 1.14)	Not estimable	high
4-point mace at end of follow up Mean follow-up: 15.9 month(s)											
2	RCT	not serious	not serious	not serious	not serious	NA	466/3645	460/3637	RR 1.01 (0.90, 1.14)	1 more per 1000 (13 fewer to 18 more)	high
4-point mace at end of follow up Mean follow-up: 26.4 month(s)											
1 (rosenstock 2019a)	RCT	not serious	not serious	NA[3]	not serious	NA	3494	3486	HR 1.00 (0.88, 1.14)	Not estimable	high
5-point mace at end of follow up Mean follow-up: 9.9 month(s)											
2	RCT	very serious[5]	not serious	serious[1]	very serious[6]	NA	18/836	11/730	RD 0.01 (-0.00, 0.02)	9 more per 1000 (5 fewer to 23 more)	very low
non-fatal stroke at end of follow up Mean follow-up: 10.7 month(s)											
4	RCT	not serious	not serious	serious[1]	very serious[7]	NA	67/3990	74/3804	RD -0.00 (-0.01, 0.00)	2 fewer per 1000 (8 fewer to 4 more)	very low
non-fatal stroke at end of follow up Mean follow-up: 26.4 month(s)											

1 (rosenstock 2019a)	RCT	not serious	not serious	NA[3]	serious[8]	NA	3494	3485	HR 0.88 (0.63, 1.23)	Not estimable	moderate
non-fatal myocardial infarction at end of follow up Mean follow-up: 10.7 month(s)											
4	RCT	not serious	not serious	serious[1]	very serious[9]	NA	158/3956	135/3856	RD 0.01 (-0.00, 0.01)	6 more per 1000 (3 fewer to 14 more)	very low
non-fatal myocardial infarction at end of follow up Mean follow-up: 26.4 month(s)											
1 (rosenstock 2019a)	RCT	not serious	not serious	NA[3]	serious[8]	NA	3494	3485	HR 1.15 (0.91, 1.45)	Not estimable	moderate
unstable angina at end of follow up Mean follow-up: 12.5 month(s)											
3	RCT	not serious	not serious	serious[1]	very serious[10]	NA	43/3839	47/3652	RD -0.00 (-0.01, 0.00)	1 fewer per 1000 (6 fewer to 4 more)	very low
unstable angina at end of follow up Mean follow-up: 26.4 month(s)											
1 (rosenstock 2019a)	RCT	not serious	not serious	NA[3]	very serious[11]	NA	3494	3484	HR 0.87 (0.57, 1.33)	Not estimable	low
hospitalisation for heart failure at end of follow up Mean follow-up: 10.7 month(s)											
4	RCT	not serious	not serious	serious[1]	very serious[12]	NA	210/4033	228/3825	RD -0.00 (-0.01, 0.01)	5 fewer per 1000 (15 fewer to 5 more)	very low
hospitalisation for heart failure at end of follow up Mean follow-up: 26.4 month(s)											
1 (rosenstock 2019a)	RCT	not serious	not serious	NA[3]	serious[8]	NA	3494	3484	HR 0.90 (0.74, 1.09)	Not estimable	moderate
acute kidney injury at end of follow up Mean follow-up: 26.4 month(s)											

1 (rosenstock 2019a)	RCT	not serious	not serious	NA[3]	serious[8]	NA	96/3494	102/3485	RR 0.94 (0.71, 1.24)	2 fewer per 1000 (8 fewer to 7 more)	moderate
persistent signs of worsening kidney disease at end of follow up Mean follow-up: 26.4 month(s)											
1 (rosenstock 2019a)	RCT	not serious	not serious	NA[3]	not serious	NA	763/3494	819/3485	RR 0.93 (0.85, 1.01)	17 fewer per 1000 (35 fewer to 3 more)	high
persistent signs of worsening kidney disease at end of follow up Mean follow-up: 26.4 month(s)											
1 (rosenstock 2019a)	RCT	not serious	not serious	NA[3]	serious[8]	NA	3494	3485	HR 0.86 (0.78, 0.95)	Not estimable	moderate
development of end stage kidney disease at end of follow up Mean follow-up: 15.9 month(s)											
2	RCT	not serious	not serious	serious[1]	very serious[13]	NA	63/3699	64/3585	RD -0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	very low
death from renal causes at end of follow up Mean follow-up: 26.4 month(s)											
1 (rosenstock 2019a)	RCT	not serious	not serious	NA[3]	very serious[11]	NA	1/3494	1/3485	PETO OR 1.00 (0.06, 15.95)	0 fewer per 1000 (1 fewer to 1 more)	low
cardiac arrhythmia at end of follow up Mean follow-up: 5.5 month(s)											
1 (barnett 2013)	RCT	not serious	not serious	NA[3]	very serious[11]	NA	1/162	0/79	PETO OR 4.43 (0.07, 288.02)	6 more per 1000 (6 fewer to 18 more)	low
diabetic ketoacidosis at end of follow up Mean follow-up: 5.5 month(s)											
2	RCT	not serious	not serious	not serious	not serious	NA	0/238	0/240	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	high

hypoglycaemia episodes at end of follow up Mean follow-up: 7.2 month(s)											
12	RCT	not serious	not serious	serious[1]	very serious[14]	NA	1450/6589	1261/5436	RD 0.00 (-0.01, 0.02)	4 more per 1000 (11 fewer to 20 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 7.2 month(s)											
12	RCT	not serious	not serious	serious[1]	very serious[15]	NA	116/6589	116/5436	RD -0.00 (-0.01, 0.00)	1 fewer per 1000 (6 fewer to 4 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 7.2 month(s)											
12	RCT	not serious	not serious	serious[16]	serious[17]	NA	6495	5195	MD -0.53 (-0.62, -0.44)	MD 0.53 lower (0.62 lower to 0.44 lower)	low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
10	RCT	serious[18]	not serious	not serious	not serious	NA	2783	1680	MD 0.10 (-0.08, 0.28)	MD 0.10 higher (0.08 lower to 0.28 higher)	moderate

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

2. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.31 (0.8-0.9 = serious, <0.8 = very serious).

3. Only one study so no inconsistency

4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.23 (0.8-0.9 = serious, <0.8 = very serious).

5. >33.3% of the studies in the meta-analysis were at high risk of bias

6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.27 (0.8-0.9 = serious, <0.8 = very serious).

7. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.24 (0.8-0.9 = serious, <0.8 = very serious).

8. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

9. 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).

10. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.15 (0.8-0.9 = serious, <0.8 = very serious).

11. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

12. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.54 (0.8-0.9 = serious, <0.8 = very serious).

13. 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).

14. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.6 (0.8-0.9 = serious, <0.8 = very serious).

15. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.55 (0.8-0.9 = serious, <0.8 = very serious).

16. I2 between 50% and 75%

17. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

18. >33.3% of the studies in the meta-analysis were at moderate risk of bias

L.1.2.3 Adding linagliptin compared to adding metformin

Table 5: Adding linagliptin compared to adding metformin

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: 12 month(s)											
1 (komorizono 2020)	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
cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)											
1 (komorizono 2020)	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
hypoglycaemia episodes at end of follow up Mean follow-up: 12 month(s)											
1 (inagaki 2013)	RCT	serious[3]	not serious	NA[1]	very serious[4]	NA	1/185	0/124	PETO OR 5.31 (0.10, 289.71)	5 more per 1000 (5 fewer to 16 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											
1 (inagaki 2013)	RCT	serious[3]	not serious	NA[1]	serious[2]	NA	0/185	0/124	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (13 fewer to 13 more)	low
hba1c change (%, lower values are better, change scores and final values) at end of follow up Mean follow-up: 12 month(s)											
2	RCT	serious[3]	not serious	not serious	not serious	NA	208	165	MD 0.10 (0.08, 0.12)	MD 0.10 higher (0.08 higher to 0.12 higher)	moderate

weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (komorizono 2020)	RCT	not serious	not serious	NA[1]	serious[5]	NA	23	25	MD 2.60 (1.21, 3.99)	MD 2.60 higher (1.21 higher to 3.99 higher)	moderate

1. Only one study so no inconsistency

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

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

L.1.2.4 Adding saxagliptin compared to adding placebo

Table 6: 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 Mean follow-up: 12 month(s)											
7	RCT	very serious[1]	not serious	serious[2]	very serious[3]	NA	425/10043	381/9246	RD 0.00 (-0.00, 0.01)	4 more per 1000 (2 fewer to 10 more)	very low
all-cause mortality at end of follow up Mean follow-up: 25.2 month(s)											
1 (scirica 2013)	RCT	very serious[1]	not serious	NA[4]	serious[5]	NA	8280	8212	HR 1.11 (0.96, 1.28)	Not estimable	very low
cardiovascular mortality at end of follow up Mean follow-up: 11.9 month(s)											

5	RCT	very serious[1]	not serious	serious[2]	very serious[3]	NA	271/9586	261/8933	RD 0.00 (-0.00, 0.01)	1 more per 1000 (4 fewer to 6 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 25.2 month(s)											
1 (scirica 2013)	RCT	very serious[1]	not serious	NA[4]	not serious	NA	8280	8212	HR 1.03 (0.87, 1.22)	Not estimable	low
3-point mace at end of follow up Mean follow-up: 25.2 month(s)											
1 (scirica 2013)	RCT	very serious[1]	not serious	NA[4]	not serious	NA	613/8280	609/8212	RR 1.00 (0.90, 1.11)	0 fewer per 1000 (8 fewer to 8 more)	low
3-point mace at end of follow up Mean follow-up: 25.2 month(s)											
1 (scirica 2013)	RCT	very serious[1]	not serious	NA[4]	not serious	NA	8280	8212	HR 1.00 (0.89, 1.12)	Not estimable	low
non-fatal stroke at end of follow up Mean follow-up: 15.3 month(s)											
2	RCT	very serious[1]	not serious	not serious	serious[5]	NA	158/8523	142/8460	RR 1.10 (0.88, 1.38)	2 more per 1000 (2 fewer to 6 more)	very low
non-fatal stroke at end of follow up Mean follow-up: 25.2 month(s)											
1 (scirica 2013)	RCT	very serious[1]	not serious	NA[4]	serious[5]	NA	8240	8173	HR 1.11 (0.88, 1.40)	Not estimable	very low
non-fatal myocardial infarction at end of follow up Mean follow-up: 15.6 month(s)											
2	RCT	very serious[1]	not serious	serious[2]	not serious	NA	266/8474	278/8404	RR 0.95 (0.80, 1.12)	2 fewer per 1000 (6 fewer to 4 more)	Very low
non-fatal myocardial infarction at end of follow up Mean follow-up: 25.2 month(s)											

1 (scirica 2013)	RCT	very serious[1]	not serious	NA[4]	serious[5]	NA	8240	8173	HR 0.95 (0.80, 1.13)	Not estimable	very low
unstable angina at end of follow up Mean follow-up: 25.2 month(s)											
1 (scirica 2013)	RCT	very serious[1]	not serious	NA[4]	serious[5]	NA	97/8280	81/8212	RR 1.19 (0.89, 1.59)	2 more per 1000 (1 fewer to 6 more)	very low
unstable angina at end of follow up Mean follow-up: 25.2 month(s)											
1 (scirica 2013)	RCT	very serious[1]	not serious	NA[4]	serious[5]	NA	8280	8212	HR 1.19 (0.89, 1.59)	Not estimable	very low
hospitalisation for heart failure at end of follow up Mean follow-up: 25.2 month(s)											
1 (scirica 2013)	RCT	very serious[1]	not serious	NA[4]	serious[5]	NA	289/8240	228/8173	RR 1.26 (1.06, 1.49)	7 more per 1000 (2 more to 14 more)	very low
hospitalisation for heart failure at end of follow up Mean follow-up: 25.2 month(s)											
1 (scirica 2013)	RCT	very serious[1]	not serious	NA[4]	serious[5]	NA	8240	8173	HR 1.27 (1.07, 1.51)	Not estimable	very low
persistent signs of worsening kidney disease at end of follow up Mean follow-up: 25.2 month(s)											
1 (scirica 2013)	RCT	very serious[1]	not serious	NA[4]	serious[5]	NA	183/8280	166/8212	RR 1.09 (0.89, 1.35)	2 more per 1000 (2 fewer to 7 more)	very low
persistent signs of worsening kidney disease at end of follow up Mean follow-up: 25.2 month(s)											
1 (scirica 2013)	RCT	very serious[1]	not serious	NA[4]	serious[5]	NA	8280	8212	HR 1.10 (0.89, 1.36)	Not estimable	very low
development of end stage kidney disease at end of follow up Mean follow-up: 25.2 month(s)											

1 (scirica 2013)	RCT	very serious[1]	not serious	NA[4]	very serious[6]	NA	51/8280	55/8212	PETO OR 0.92 (0.63, 1.35)	1 fewer per 1000 (3 fewer to 2 more)	very low
development of end stage kidney disease at end of follow up Mean follow-up: 25.2 month(s)											
1 (scirica 2013)	RCT	very serious[1]	not serious	NA[4]	very serious[6]	NA	8280	8212	HR 0.90 (0.61, 1.33)	Not estimable	very low
death from renal causes at end of follow up Mean follow-up: 25.2 month(s)											
1 (scirica 2013)	RCT	very serious[1]	not serious	NA[4]	very serious[6]	NA	10/8280	5/8212	PETO OR 1.93 (0.70, 5.32)	1 more per 1000 (0 more to 2 more)	very low
cardiac arrhythmia at end of follow up Mean follow-up: 12 month(s)											
1 (matthaei 2015a)	RCT	serious[7]	not serious	NA[4]	very serious[6]	NA	0/153	1/162	PETO OR 0.14 (0.00, 7.22)	6 fewer per 1000 (18 fewer to 6 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 11.2 month(s)											
8	RCT	very serious[1]	not serious	serious[2]	very serious[8]	NA	1310/10328	1134/9534	RD 0.00 (-0.01, 0.01)	2 more per 1000 (10 fewer to 15 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 11 month(s)											
6	RCT	very serious[1]	not serious	serious[2]	very serious[9]	NA	180/9818	143/9222	RD 0.00 (-0.00, 0.01)	4 more per 1000 (0 more to 7 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 25.2 month(s)											
1 (scirica 2013)	RCT	very serious[1]	not serious	NA[4]	serious[5]	NA	8280	8212	HR 1.22 (0.82, 1.82)	Not estimable	very low
hba1c change (%, lower values are better, change scores and final values) at end of follow up Mean follow-up: 11.2 month(s)											

8	RCT	very serious[1]	not serious	very serious[10]	serious[11]	NA	10234	9487	MD -0.50 (-0.67, -0.33)	MD 0.50 lower (0.67 lower to 0.33 lower)	very low
weight change (kg, lower values are better, change scores and final values) at end of follow up Mean follow-up: 11.9 month(s)											
6	RCT	very serious[1]	not serious	serious[12]	not serious	NA	9545	9160	MD 0.21 (-0.15, 0.57)	MD 0.21 higher (0.15 lower to 0.57 higher)	very low
bmi change (kg/m2, lower values are better, change scores and final values) at end of follow up Mean follow-up: 12.2 month(s)											
4	RCT	very serious[1]	not serious	not serious	not serious	NA	9035	8847	MD 0.02 (-0.06, 0.10)	MD 0.02 higher (0.06 lower to 0.10 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. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.08 (0.8-0.9 = serious, <0.8 = very serious).

4. Only one study so no inconsistency

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

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

7. >33.3% of the studies in the meta-analysis were at moderate risk of bias

8. 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).

9. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.57 (0.8-0.9 = serious, <0.8 = very serious).

10. I2 > 75%

11. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

12. I2 between 50% and 75%

L.1.2.5 Adding sitagliptin compared to adding placebo

Table 7: 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
health-related quality of life - overall (iwqol lite scores, higher values are better, change scores) at end of follow up											
1 (gadde 2017)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	122	61	MD 0.30 (-3.83, 4.43)	MD 0.30 higher (3.83 lower to 4.43 higher)	low
health-related quality of life - subscale well being (dmsat well being scores, higher values are better, change scores) at end of follow up											
1 (gadde 2017)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	122	61	MD -1.10 (-9.37, 7.17)	MD 1.10 lower (9.37 lower to 7.17 higher)	low
all-cause mortality at end of follow up											
16	RCT	not serious	not serious	serious[3]	very serious[4]	NA	3/3483	6/3080	RD -0.00 (-0.00, 0.00)	1 fewer per 1000 (3 fewer to 2 more)	very low
cardiovascular mortality at end of follow up											

11	RCT	not serious	not serious	serious[3]	very serious[5]	NA	0/2305	3/2087	RD -0.00 (-0.00, 0.00)	1 fewer per 1000 (5 fewer to 2 more)	very low
non-fatal stroke at end of follow up											
1 (ba 2017)	RCT	not serious	not serious	NA[2]	very serious[6]	NA	0/248	1/249	PETO OR 0.14 (0.00, 6.85)	4 fewer per 1000 (12 fewer to 4 more)	low
non-fatal myocardial infarction at end of follow up											
3	RCT	serious[7]	not serious	serious[3]	very serious[6]	NA	1/678	2/713	PETO OR 0.56 (0.06, 5.41)	1 fewer per 1000 (6 fewer to 4 more)	very low
unstable angina at end of follow up											
2	RCT	not serious	not serious	serious[3]	very serious[6]	NA	1/570	1/568	PETO OR 1.00 (0.06, 15.95)	0 fewer per 1000 (5 fewer to 5 more)	very low
diabetic ketoacidosis at end of follow up											
1 (shankar 2017a)	RCT	serious[7]	not serious	NA[2]	very serious[6]	NA	0/234	1/233	RR 0.33 (0.01, 8.11)	3 fewer per 1000 (4 fewer to 30 more)	very low
hypoglycaemia episodes at the end of follow up											
20	RCT	not serious	not serious	serious[3]	very serious[8]	NA	608/4022	535/3445	RD 0.02 (0.00, 0.04)	18 more per 1000 (1 more to 35 more)	very low
severe hypoglycaemic episodes at the end of follow up											
16	RCT	not serious	not serious	serious[3]	very serious[9]	NA	38/3252	36/3001	RD 0.00 (-0.01, 0.01)	1 more per 1000 (5 fewer to 6 more)	very low
hba1c change (%, lower values are better, mean difference) at end of follow up											

23	RCT	very serious[1]	not serious	very serious[10]	not serious	NA	4055	3568	MD -0.71 (-0.80, -0.61)	MD 0.71 lower (0.80 lower to 0.61 lower)	very low
weight change (kg, lower values are better, mean difference) at end of follow up											
20	RCT	not serious	not serious	very serious[10]	not serious	NA	3221	2951	MD 0.13 (-0.13, 0.39)	MD 0.13 higher (0.13 lower to 0.39 higher)	low
bmi change (kg/m2, lower values are better, final values) at end of follow up											
3	RCT	very serious[1]	not serious	very serious[10]	serious[11]	NA	237	229	MD -1.50 (-2.35, -0.66)	MD 1.50 lower (2.35 lower to 0.66 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. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.38 (0.8-0.9 = serious, <0.8 = very serious).

5. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.71 (0.8-0.9 = serious, <0.8 = very serious).

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

7. >33.3% of the studies in the meta-analysis were at moderate risk of bias

8. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.1 (0.8-0.9 = serious, <0.8 = very serious).

9. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.04 (0.8-0.9 = serious, <0.8 = very serious).

10. I2 > 75%

11. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

L.1.2.6 Adding sitagliptin compared to adding metformin

Table 8: Clinical evidence profile: Adding sitagliptin compared to adding metformin

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: 12 month(s)											
1 (derosa 2010b)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	2/75	0/76	PETO OR 7.59 (0.47, 122.49)	27 more per 1000 (10 fewer to 63 more)	very low
hba1c change (%, lower values are better, final and change scores) at end of follow-up Mean follow-up: 9 month(s)											
2	RCT	very serious[1]	not serious	very serious[4]	very serious[5]	NA	104	103	MD -0.33 (-1.25, 0.60)	MD 0.33 lower (1.25 lower to 0.60 higher)	very low
weight change (kg, lower values are better, final and change values) at end of follow-up Mean follow-up: 9 month(s)											
2	RCT	very serious[1]	not serious	very serious[4]	serious[6]	NA	104	103	MD 1.47 (-0.53, 3.47)	MD 1.47 higher (0.53 lower to 3.47 higher)	very low
bmi change (kg/m2, lower values are better, final and change values) at end of follow-up Mean follow-up: 9 month(s)											

2	RCT	very serious[1]	not serious	serious[7]	serious[8]	NA	104	103	MD 0.41 (0.02, 0.80)	MD 0.41 higher (0.02 higher to 0.80 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. I2 > 75%

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. I2 between 50% and 75%

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

L.1.2.7 Adding sitagliptin compared to adding insulin

Table 9: 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
health-related quality of life - subscale mental component (sf36, higher values are better, change scores) at end of follow up Mean follow-up: 24 month(s)											
1 (group 2022)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	1236	1209	MD 0.12 (-0.48, 0.72)	MD 0.12 higher (0.48 lower to 0.72 higher)	low
health-related quality of life - subscale physical component (sf36, higher values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (group 2022)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	1236	1209	MD 0.23 (-0.32, 0.78)	MD 0.23 higher (0.32 lower to 0.78 higher)	low
all-cause mortality at end of follow-up Mean follow-up: 33 month(s)											
2	RCT	serious[3]	not serious	serious[4]	very serious[5]	NA	41/1495	43/1489	PETO OR 0.95 (0.61, 1.47)	1 fewer per 1000 (13 fewer to 10 more)	very low
all-cause mortality at end of follow up Mean follow-up: 60 month(s)											

1 (group 2022)	RCT	serious[3]	not serious	NA[2]	very serious[5]	NA	1267	1263	HR 0.98 (0.68, 1.41)	Not estimable	very low
cardiovascular mortality at end of follow-up Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	serious[3]	not serious	NA[2]	very serious[5]	NA	21/1264	21/1257	RR 0.99 (0.55, 1.81)	0 fewer per 1000 (8 fewer to 14 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	serious[3]	not serious	NA[2]	very serious[5]	NA	1264	1257	HR 1.00 (0.55, 1.82)	Not estimable	very low
3-point mace at end of follow-up Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	serious[3]	not serious	NA[2]	very serious[5]	NA	69/1264	65/1257	RR 1.06 (0.76, 1.47)	3 more per 1000 (12 fewer to 24 more)	very low
3-point mace at end of follow up Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	serious[3]	not serious	NA[2]	very serious[5]	NA	1264	1257	HR 1.06 (0.76, 1.48)	Not estimable	very low
4-point mace at end of follow up Mean follow-up: 60 month(s)											

1 (group 2022)	RCT	very serious[1]	not serious	NA[2]	serious[6]	NA	78/1268	71/1263	RR 1.09 (0.80, 1.49)	5 more per 1000 (11 fewer to 28 more)	very low
non-fatal myocardial infarction Mean follow-up: 5.5 month(s)											
1 (aschner 2012)	RCT	very serious[1]	not serious	NA[2]	very serious[5]	NA	1/264	0/237	PETO OR 6.67 (0.13, 338.11)	4 more per 1000 (4 fewer to 11 more)	very low
unstable angina at the end of follow-up Mean follow-up: 32.8 month(s)											
2	RCT	very serious[1]	not serious	serious[4]	very serious[5]	NA	15/1532	11/1500	PETO OR 1.35 (0.62, 2.92)	2 more per 1000 (4 fewer to 9 more)	very low
hospitalisation for heart failure at end of follow up Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	serious[3]	not serious	NA[2]	very serious[5]	NA	1264	1257	HR 1.15 (0.67, 1.96)	Not estimable	very low
hospitalisation for heart failure at end of follow-up Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	serious[3]	not serious	NA[2]	very serious[5]	NA	30/1264	26/1257	RR 1.15 (0.68, 1.93)	3 more per 1000 (7 fewer to 19 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 16.6 month(s)											

5	RCT	very serious[1]	not serious	very serious[7]	not serious	NA	398/1833	691/1795	RR 0.41 (0.23, 0.72)	227 fewer per 1000 (295 fewer to 107 fewer)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	1253	1245	HR 0.63 (0.59, 0.67)	Not estimable	low
at night hypoglycaemic episodes Mean follow-up: 5.8 month(s)											
2	RCT	serious[3]	not serious	serious[8]	not serious	NA	21/492	70/463	RR 0.28 (0.11, 0.71)	108 fewer per 1000 (134 fewer to 43 fewer)	low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 19.2 month(s)											
4	RCT	very serious[1]	not serious	serious[4]	serious[6]	NA	11/1821	24/1789	PETO OR 0.47 (0.24, 0.91)	7 fewer per 1000 (14 fewer to 1 fewer)	very low
hba1c change (%, lower values are better, mean difference) at end of follow-up Mean follow-up: 14.4 month(s)											
7	RCT	very serious[1]	not serious	serious[8]	not serious	NA	880	998	MD 0.18 (-0.09, 0.46)	MD 0.18 higher (0.09 lower to 0.46 higher)	very low
bmi change (kg/m2, lower values are better, change scores and final values) at end of follow-up Mean follow-up: 7.8 month(s)											
3	RCT	not serious	not serious	not serious	serious[9]	NA	60	57	MD -0.39 (-1.00, 0.23)	MD 0.39 lower (1.00 lower to 0.23 higher)	moderate

weight change (kg, lower values are better, mean difference) at end of follow-up Mean follow-up: 6.8 month(s)											
6	RCT	very serious[1]	not serious	serious[8]	serious[10]	NA	603	576	MD -1.89 (-2.62, -1.16)	MD 1.89 lower (2.62 lower to 1.16 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. >33.3% of the studies in the meta-analysis were at moderate risk of bias

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

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

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

7. I2 > 75%

8. I2 between 50% and 75%

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

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

L.1.2.8 Adding vildagliptin compared to adding placebo

Table 10: Clinical evidence profile: Adding vildagliptin 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: 6.1 month(s)											
12	RCT	Very serious[1]	not serious	serious[2]	very serious[3]	NA	3/2191	5/1659	RD -0.00 (-0.01, 0.00)	1 fewer per 1000 (6 fewer to 3 more)	very low

cardiovascular mortality at end of follow-up Mean follow-up: 6.4 month(s)											
8	RCT	serious[4]	not serious	serious[2]	very serious[5]	NA	1/1304	1/971	RD 0.00 (-0.01, 0.01)	0 more per 1000 (6 fewer to 6 more)	very low
non-fatal stroke at end of follow-up Mean follow-up: 5.5 month(s)											
3	RCT	serious[4]	not serious	serious[2]	very serious[6]	NA	1/797	3/461	PETO OR 0.19 (0.02, 1.48)	5 fewer per 1000 (13 fewer to 2 more)	very low
progression of liver disease at end of follow-up Mean follow-up: 5.5 month(s)											
1 (strain 2013)	RCT	not serious	serious[7]	NA[8]	serious[9]	NA	0/139	0/139	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	low
hypoglycaemia episodes at end of follow-up Mean follow-up: 6.4 month(s)											
15	RCT	very serious[1]	not serious	serious[2]	very serious[10]	NA	116/3031	93/2229	RD 0.01 (-0.01, 0.01)	4 more per 1000 (6 fewer to 15 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 6.0 month(s)											
13	RCT	serious[4]	not serious	serious[2]	very serious[11]	NA	6/2642	11/1840	RD -0.00 (-0.01, 0.00)	3 fewer per 1000 (8 fewer to 2 more)	very low
hba1c change (%, lower values are better, mean difference) at end of follow-up Mean follow-up: 6.0 month(s)											
14	RCT	very serious[1]	not serious	very serious[12]	not serious	NA	2601	1894	MD -0.69 (-0.77, -0.62)	MD 0.69 lower (0.77 lower to 0.62 lower)	very low
weight change (kg, lower values are better, change and final scores) at end of follow-up Mean follow-up: 5.8 month(s)											
7	RCT	very serious[1]	not serious	very serious[12]	not serious	NA	1108	835	MD 0.07 (-0.89, 1.04)	MD 0.7 higher (0.89 lower to 1.04 higher)	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. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.3 (0.8-0.9 = serious, <0.8 = very serious).

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

5. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.05 (0.8-0.9 = serious, <0.8 = very serious).

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

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

8. Only one study so no inconsistency

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

10. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.07 (0.8-0.9 = serious, <0.8 = very serious).

11. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.59 (0.8-0.9 = serious, <0.8 = very serious).

12. I2 > 75%

L.1.2.9 Adding vildagliptin compared to adding metformin

Table 11: Clinical evidence profile: Adding vildagliptin compared to adding metformin

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: 5.5 month(s)											
1 (ji 2016b)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/2562	0/500	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (3 fewer to 3 more)	low
cardiovascular mortality at end of follow-up Mean follow-up: 5.5 month(s)											
1 (ji 2016b)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/2562	0/500	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (3 fewer to 3 more)	low
acute kidney injury at end of follow-up Mean follow-up: 5.5 month(s)											
1 (filozof 2010b)	RCT	not serious	serious[3]	NA[2]	very serious[4]	NA	1/456	0/458	PETO OR 7.42 (0.15, 374.03)	2 more per 1000 (2 fewer to 6 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	very serious[1]	not serious	not serious	very serious[4]	NA	27/3018	9/958	RR 0.66 (0.31, 1.41)	3 fewer per 1000 (6 fewer to 4 more)	very low
hba1c change (%, lower values are better, change and final scores) at end of follow-up Mean follow-up: 5.5 month(s)											

2	RCT	very serious[1]	not serious	not serious	not serious	NA	2957	942	MD -0.14 (-0.20, -0.08)	MD 0.14 lower (0.20 lower to 0.08 lower)	low
weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (ji 2016b)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	2501	484	MD -0.51 (-0.77, -0.25)	MD 0.51 lower (0.77 lower to 0.25 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. Largest proportion of studies in the meta-analysis came from partially direct studies

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

L.1.2.10 Adding vildagliptin compared to adding insulin

Table 12: Clinical evidence profile: Adding vildagliptin 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 Mean follow-up: 5.5 month(s)											
1 (forst 2015)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/82	1/79	PETO OR 0.13 (0.00, 6.57)	13 fewer per 1000 (37 fewer to 12 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)											

1 (forst 2015)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	12/82	23/79	RR 0.50 (0.27, 0.94)	145 fewer per 1000 (213 fewer to 18 fewer)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)											
1 (forst 2015)	RCT	very serious[1]	not serious	NA[2]	serious[5]	NA	0/82	0/79	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (24 fewer to 24 more)	very low
hba1c change (%, lower values are better, mean difference) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (forst 2015)	RCT	very serious[1]	not serious	NA[2]	serious[6]	NA	82	79	MD 0.30 (0.05, 0.55)	MD 0.30 higher (0.05 higher to 0.55 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 (0.80, 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)

L.1.2.11 Adding vildagliptin compared to adding saxagliptin

Table 13: Clinical evidence profile: Adding vildagliptin compared to adding saxagliptin

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: 5.5 month(s)											

2	RCT	very serious[1]	not serious	not serious	serious[2]	NA	0/100	0/102	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (27 fewer to 27 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	very serious[1]	not serious	not serious	serious[2]	NA	0/100	0/102	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (27 fewer to 27 more)	very low
hospitalisation for heart failure at end of follow-up Mean follow-up: 5.5 month(s)											
1 (chen 2016)	RCT	very serious[1]	not serious	NA[3]	serious[2]	NA	0/37	0/36	RD 0.00 (-0.05, 0.05)	0 fewer per 1000 (52 fewer to 52 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)											
3	RCT	very serious[1]	not serious	not serious	very serious[4]	NA	7/157	9/162	RR 0.81 (0.25, 2.65)	11 fewer per 1000 (42 fewer to 92 more)	very low
at night hypoglycaemic episodes Mean follow-up: 5.5 month(s)											
1 (chen 2016)	RCT	very serious[1]	not serious	NA[3]	serious[2]	NA	0/37	0/36	RD 0.00 (-0.05, 0.05)	0 fewer per 1000 (52 fewer to 52 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	very serious[1]	not serious	not serious	serious[2]	NA	0/94	0/96	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (29 fewer to 29 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow-up Mean follow-up: 5.5 month(s)											
3	RCT	very serious[1]	not serious	not serious	not serious	NA	157	162	MD -0.08 (-0.20, 0.04)	MD 0.08 lower (0.20 lower to 0.04 higher)	low
weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 5.5 month(s)											

1 (li 2014a)	RCT	very serious[1]	not serious	NA[3]	not serious	NA	57	60	MD 0.10 (-0.63, 0.83)	MD 0.10 higher (0.63 lower to 0.83 higher)	low
bmi change (kg/m2, lower values are better, change scores) at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	very serious[1]	not serious	not serious	not serious	NA	94	96	MD -0.01 (-0.25, 0.24)	MD 0.01 lower (0.25 lower to 0.24 higher)	low

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

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

3. Only one study so no inconsistency

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

L.1.3 GLP-1 receptor agonist

L.1.3.1 Adding dulaglutide compared to adding placebo

Table 14: 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
health-related quality of life - overall (eq-5d-5l uk index, -0.59-1, higher values are better, changes scores) at end of follow up Mean follow-up: 6.5 month(s)											
1 (pozzilli 2017)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	150	150	MD -0.01 (-0.07, 0.05)	MD 0.01 lower (0.07 lower to 0.05 higher)	very low

all-cause mortality at end of follow up Mean follow-up: 13.3 month(s)											
8	RCT	not serious	not serious	serious[4]	not serious	NA	320/6428	349/5696	RD -0.01 (-0.01, 0.00)	5 fewer per 1000 (14 fewer to 3 more)	moderate
all-cause mortality at end of follow up Mean follow-up: 64.8 month(s)											
1 (gerstein 2019a)	RCT	not serious	not serious	NA[2]	serious[5]	NA	4949	4952	HR 0.90 (0.80, 1.01)	Not estimable	moderate
cardiovascular mortality at end of follow up Mean follow-up: 17.8 month(s)											
8	RCT	not serious	not serious	serious[4]	not serious	NA	541/6428	595/5696	RD -0.01 (-0.02, 0.00)	10 fewer per 1000 (20 fewer to 1 more)	moderate
cardiovascular mortality at end of follow up Mean follow-up: 64.8 month(s)											
1 (gerstein 2019a)	RCT	not serious	not serious	NA[2]	serious[5]	NA	4949	4952	HR 0.91 (0.78, 1.06)	Not estimable	moderate
3-point mace at end of follow up Mean follow-up: 64.8 month(s)											
1 (gerstein 2019a)	RCT	not serious	not serious	NA[2]	not serious	NA	594/4949	663/4952	RR 0.90 (0.81, 0.99)	14 fewer per 1000 (26 fewer to 1 fewer)	high
3-point mace at end of follow up Mean follow-up: 64.8 month(s)											
1 (gerstein 2019a)	RCT	not serious	not serious	NA[2]	serious[5]	NA	4949	4952	HR 0.88 (0.79, 0.99)	Not estimable	moderate
non-fatal stroke at end of follow up Mean follow-up: 25.6 month(s)											

3	RCT	not serious	not serious	serious[4]	serious[5]	NA	138/5338	175/5162	RR 0.78 (0.63, 0.98)	7 fewer per 1000 (13 fewer to 1 fewer)	low
non-fatal stroke at end of follow up Mean follow-up: 64.8 month(s)											
1 (gerstein 2019a)	RCT	not serious	not serious	NA[2]	serious[5]	NA	4949	4952	HR 0.76 (0.61, 0.95)	Not estimable	moderate
non-fatal myocardial infarction at end of follow up Mean follow-up: 25.6 month(s)											
3	RCT	not serious	not serious	serious[4]	serious5	NA	206/5382	214/5242	RR 0.96 (0.80, 1.16)	2 fewer per 1000 (8 fewer to 6 more)	low
non-fatal myocardial infarction at end of follow up Mean follow-up: 64.8 month(s)											
1 (gerstein 2019a)	RCT	not serious	not serious	NA[2]	serious[5]	NA	4949	4952	HR 0.96 (0.79, 1.16)	Not estimable	moderate
unstable angina at end of follow up Mean follow-up: 25.6 month(s)											
3	RCT	not serious	not serious	serious[4]	serious[5]	NA	89/5382	79/5242	RR 1.12 (0.83, 1.51)	2 more per 1000 (3 fewer to 8 more)	low
unstable angina at end of follow up Mean follow-up: 64.8 month(s)											
1 (gerstein 2019a)	RCT	not serious	not serious	NA[2]	serious[5]	NA	4949	4952	HR 1.14 (0.84, 1.54)	Not estimable	moderate
hospitalisation for heart failure at end of follow up Mean follow-up: 64.8 month(s)											
1 (gerstein 2019a)	RCT	not serious	not serious	NA[2]	serious[5]	NA	213/4949	226/4952	RR 0.94 (0.79, 1.13)	3 fewer per 1000 (10 fewer to 6 more)	moderate

hospitalisation for heart failure at end of follow up Mean follow-up: 64.8 month(s)											
1 (gerstein 2019a)	RCT	not serious	not serious	NA[2]	serious[5]	NA	4949	4952	HR 0.93 (0.77, 1.12)	Not estimable	moderate
acute kidney injury at end of follow up Mean follow-up: 35.6 month(s)											
2	RCT	not serious	not serious	serious[4]	very serious[6]	NA	6150/6193	6750/6799	RR 0.91 (0.65, 1.29)	1 fewer per 1000 (5 fewer to 4 more)	Very low
persistent signs of worsening kidney disease at end of follow up Mean follow-up: 64.8 month(s)											
1 (gerstein 2019a)	RCT	not serious	not serious	NA[2]	not serious	NA	453/4949	500/4952	RR 0.91 (0.80, 1.02)	9 fewer per 1000 (20 fewer to 2 more)	high
persistent signs of worsening kidney disease at end of follow up Mean follow-up: 64.8 month(s)											
1 (gerstein 2019a)	RCT	not serious	not serious	NA[2]	serious[5]	NA	4949	4952	HR 0.89 (0.78, 1.01)	Not estimable	moderate
development of end stage kidney disease at end of follow up Mean follow-up: 64.8 month(s)											
1 (gerstein 2019a)	RCT	not serious	not serious	NA[2]	very serious[6]	NA	3/4949	6/4952	PETO OR 0.51 (0.14, 1.90)	1 fewer per 1000 (2 fewer to 1 more)	low
cardiac arrhythmia at end of follow up Mean follow-up: 35.4 month(s)											
2	RCT	not serious	not serious	serious[4]	very serious[7]	NA	216/4999	192/5007	RD 0.00 (-0.00, 0.01)	5 more per 1000 (3 fewer to 13 more)	very low
diabetic ketoacidosis at end of follow up Mean follow-up: 5.8 month(s)											

2	RCT	not serious	not serious	not serious	not serious	NA	0/333	0/195	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	high
progression of liver disease at end of follow up Mean follow-up: 64.8 month(s)											
1 (gerstein 2019a)	RCT	not serious	not serious	NA[2]	serious[5]	NA	25/4949	40/4952	PETO OR 0.63 (0.39, 1.02)	3 fewer per 1000 (6 fewer to 0 more)	moderate
hypoglycaemia episodes at end of follow up Mean follow-up: 6 month(s)											
6	RCT	not serious	not serious	not serious	serious[5]	NA	159/920	101/603	RR 1.22 (0.97, 1.54)	38 more per 1000 (5 fewer to 91 more)	moderate
at night hypoglycaemic episodes at end of follow up Mean follow-up: 6.1 month(s)											
3	RCT	not serious	not serious	not serious	very serious[6]	NA	69/533	63/357	RR 0.94 (0.68, 1.29)	11 fewer per 1000 (56 fewer to 51 more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 14.4 month(s)											
7	RCT	not serious	not serious	serious[4]	very serious[8]	NA	66/5869	74/5555	RD -0.00 (-0.01, 0.00)	1 fewer per 1000 (6 fewer to 3 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 12.5 month(s)											
9	RCT	not serious	not serious	very serious[9]	not serious	NA	7034	5873	MD -0.90 (-1.08, -0.73)	MD 0.90 lower (1.08 lower to 0.73 lower)	low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12.5 month(s)											
9	RCT	not serious	not serious	not serious	not serious	NA	6559	5729	MD -1.44 (-1.60, -1.27)	MD 1.44 lower (1.60 lower to 1.27 lower)	high

bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 25.6 month(s)											
3	RCT	not serious	not serious	not serious	not serious	NA	5053	5058	MD -0.53 (-0.61, -0.46)	MD 0.53 lower (0.61 lower to 0.46 lower)	high

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 (-0.03, 0.03)

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

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

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

7. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.41 (0.8-0.9 = serious, <0.8 = very serious).

8. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.3 (0.8-0.9 = serious, <0.8 = very serious).

9. I2 > 75%

L.1.3.2 Adding dulaglutide compared to adding insulin

Table 15: Clinical evidence profile: Adding dulaglutide 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 Mean follow-up: 13.9 month(s)											

3	RCT	very serious[1]	not serious	serious[2]	very serious[3]	NA	4/1648	5/811	PETO OR 0.36 (0.09, 1.45)	4 fewer per 1000 (10 fewer to 2 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 17.7 month(s)											
1 (giorgino 2015)	RCT	not serious	not serious	NA[4]	very serious[3]	NA	1/545	0/262	PETO OR 4.40 (0.07, 289.01)	2 more per 1000 (2 fewer to 5 more)	low
non-fatal stroke at end of follow up Mean follow-up: 6 month(s)											
1 (araki 2015b)	RCT	not serious	not serious	NA[4]	very serious[3]	NA	2/181	0/180	PETO OR 7.39 (0.46, 118.59)	11 more per 1000 (4 fewer to 26 more)	low
non-fatal myocardial infarction at end of follow up Mean follow-up: 6 month(s)											
1 (araki 2015b)	RCT	not serious	not serious	NA[4]	very serious[3]	NA	1/181	0/180	PETO OR 7.35 (0.15, 370.34)	6 more per 1000 (5 fewer to 16 more)	low
falls requiring hospitalisation at end of follow up Mean follow-up: 6 month(s)											
1 (araki 2015b)	RCT	not serious	not serious	NA[4]	very serious[3]	NA	1/181	0/180	PETO OR 7.35 (0.15, 370.34)	6 more per 1000 (5 fewer to 16 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 11.9 month(s)											
3	RCT	not serious	not serious	serious[5]	serious[6]	NA	361/1241	297/695	RR 0.66 (0.51, 0.84)	147 fewer per 1000 (208 fewer to 70 fewer)	low
at night hypoglycaemic episodes at end of follow up Mean follow-up: 11.9 month(s)											
3	RCT	not serious	not serious	not serious	not serious	NA	156/1241	181/695	RR 0.47 (0.39, 0.57)	138 fewer per 1000 (159 fewer to 112 fewer)	high
severe hypoglycaemic episodes at end of follow up Mean follow-up: 11.9 month(s)											

4	RCT	not serious	not serious	serious[2]	very serious[7]	NA	18/1829	17/991	RD -0.00 (-0.01, 0.01)	4 fewer per 1000 (15 fewer to 7 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 11.9 month(s)											
4	RCT	not serious	not serious	very serious[8]	serious[9]	NA	1819	988	MD -0.33 (-0.51, -0.15)	MD 0.33 lower (0.51 lower to 0.15 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 8 month(s)											
3	RCT	not serious	not serious	serious[5]	serious[10]	NA	1638	808	MD -2.60 (-3.15, -2.05)	MD 2.60 lower (3.15 lower to 2.05 lower)	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 both ends of the defined MIDs (0.80, 1.25)

4. Only one study so no inconsistency

5. I2 between 50% and 75%

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

7. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.66 (0.8-0.9 = serious, <0.8 = very serious).

8. I2 > 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)

L.1.3.3 Adding dulaglutide compared to adding exenatide

Table 16: Clinical evidence profile: Adding dulaglutide compared to adding exenatide

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: 12 month(s)											
1 (wysham 2014 52 weeks)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	2/559	0/276	RR 2.47 (0.12, 51.34)	0 fewer per 1000 (0 more to 0 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)											
1 (wysham 2014 52 weeks)	RCT	serious[1]	not serious	NA[2]	Very serious[3]	NA	2/559	0/276	PETO OR 4.46 (0.23, 85.07)	4 more per 1000 (1 fewer to 9 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 6 month(s)											
1 (wysham 2014 26 weeks)	RCT	serious[1]	not serious	NA[2]	serious[4]	NA	59/559	44/276	RR 0.66 (0.46, 0.95)	54 fewer per 1000 (86 fewer to 8 fewer)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											
1 (wysham 2014 52 weeks)	RCT	serious[1]	not serious	NA[2]	serious[4]	NA	0/559	2/276	PETO OR 0.05 (0.00, 0.92)	7 fewer per 1000 (17 fewer to 3 more)	low

hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (wysham 2014 52 weeks)	RCT	serious[1]	not serious	NA[2]	not serious	NA	559	276	MD -0.13 (-0.32, 0.06)	MD 0.13 lower (0.32 lower to 0.06 higher)	moderate
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
1 (wysham 2014 26 weeks)	RCT	serious[1]	not serious	NA[2]	not serious	NA	559	276	MD 0.52 (-0.18, 1.22)	MD 0.52 higher (0.18 lower to 1.22 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. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

L.1.3.4 Adding dulaglutide compared to adding sitagliptin

Table 17: Clinical evidence profile: Adding dulaglutide 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
all-cause mortality at end of follow up Mean follow-up: 12 month(s)											
1 (nauck 2014 dulaglutide v sitagliptin)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	1/606	2/315	RR 0.26 (0.02, 2.86)	5 fewer per 1000 (6 fewer to 12 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)											
1 (nauck 2014 dulaglutide v sitagliptin)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/606	1/315	PETO OR 0.05 (0.00, 3.35)	3 fewer per 1000 (9 fewer to 3 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											
1 (nauck 2014 dulaglutide v sitagliptin)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/606	0/315	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (5 fewer to 5 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (nauck 2014 dulaglutide v sitagliptin)	RCT	serious[4]	not serious	NA[2]	serious[5]	NA	606	315	MD -0.53 (-0.68, -0.38)	MD 0.53 lower (0.68 lower to 0.38 lower)	low

weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (nauck 2014 dulaglutide v sitagliptin)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	606	315	MD -0.89 (-1.49, -0.29)	MD 0.89 lower (1.49 lower to 0.29 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. >33.3% of the studies in the meta-analysis were at moderate risk of bias

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

L.1.3.5 Adding exenatide compared to adding placebo

Table 18: 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
health-related quality of life - overall (iqwol-lite, 0-100, higher values are better, changes scores) at end of follow up Mean follow-up: 6.5 month(s)											
1 (gadde 2017)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	181	61	MD -1.00 (-5.13, 3.13)	MD 1.00 lower (5.13 lower to 3.13 higher)	low
health-related quality of life - subscale barriers to activity (diabetes health profile, 0-100, lower values are better, changes scores) at end of follow up Mean follow-up: 6 month(s)											
1 (joubert 2021)	RCT	serious[3]	not serious	NA[2]	serious[4]	NA	28	18	MD -4.30 (-9.75, 1.15)	MD 4.30 lower (9.75 lower to 1.15 higher)	low
health-related quality of life - subscale disinhibited eating (diabetes health profile, 0-100, lower values are better, changes scores) at end of follow up Mean follow-up: 6 month(s)											
1 (joubert 2021)	RCT	serious[3]	not serious	NA[2]	serious[5]	NA	28	18	MD -8.09 (-19.75, 3.57)	MD 8.09 lower (19.75 lower to	low

										3.57 higher)	
health-related quality of life - subscale well being (dmsat, 0-100, higher values are better, changes scores) at end of follow up Mean follow-up: 6.5 month(s)											
1 (gadde 2017)	RCT	very serious[1]	not serious	NA[2]	serious[6]	NA	181	61	MD 7.10 (-0.95, 15.15)	MD 7.10 higher (0.95 lower to 15.15 higher)	very low
health-related quality of life - subscale psychological distress (diabetes health profile, 0-100, lower values are better, changes scores) at end of follow up Mean follow-up: 6 month(s)											
1 (joubert 2021)	RCT	serious[3]	not serious	NA[2]	serious[7]	NA	28	18	MD 2.73 (-3.04, 8.50)	MD 2.73 higher (3.04 lower to 8.50 higher)	low
all-cause mortality at end of follow up Mean follow-up: 10.6 month(s)											
8	RCT	not serious	not serious	serious[8]	not serious	NA	508/8590	587/8151	RD -0.01 (-0.02, -0.00)	9 fewer per 1000 (17 fewer to 2 fewer)	moderate
all-cause mortality at end of follow up Mean follow-up: 38.4 month(s)											
1 (holman 2017)	RCT	not serious	not serious	NA[2]	serious[9]	NA	7356	7396	HR 0.86 (0.77, 0.97)	Not estimable	moderate
cardiovascular mortality at end of follow up Mean follow-up: 10.6 month(s)											

8	RCT	not serious	not serious	serious[8]	not serious	NA	340/8590	384/8151	RD -0.01 (-0.01, 0.00)	5 fewer per 1000 (11 fewer to 1 more)	moderate
cardiovascular mortality at end of follow up Mean follow-up: 38.4 month(s)											
1 (holman 2017)	RCT	not serious	not serious	NA[2]	serious[9]	NA	7356	7396	HR 0.88 (0.76, 1.02)	Not estimable	moderate
3-point mace at end of follow up Mean follow-up: 38.4 month(s)											
1 (holman 2017)	RCT	not serious	not serious	NA[2]	not serious	NA	839/7356	905/7396	RR 0.93 (0.85, 1.02)	8 fewer per 1000 (18 fewer to 2 more)	high
3-point mace at end of follow up Mean follow-up: 38.4 month(s)											
1 (holman 2017)	RCT	not serious	not serious	NA[2]	not serious	NA	7356	7396	HR 0.91 (0.83, 1.00)	Not estimable	high
non-fatal myocardial infarction at end of follow up Mean follow-up: 6.8 month(s)											
2	RCT	very serious[1]	not serious	serious[8]	very serious[10]	NA	1/435	1/184	PETO OR 0.36 (0.02, 7.65)	3 fewer per 1000 (15 fewer to 8 more)	very low
unstable angina at end of follow up Mean follow-up: 38.4 month(s)											
1 (holman 2017)	RCT	not serious	serious[11]	NA[2]	serious[9]	NA	171/7356	151/7396	RR 1.14 (0.92, 1.41)	3 more per 1000 (2 fewer to 8 more)	low
hospitalisation for heart failure at end of follow up Mean follow-up: 22.2 month(s)											
2	RCT	not serious	not serious	serious[8]	serious[9]	NA	220/7384	231/7414	RR 0.96 (0.80, 1.15)	1 fewer per 1000	low

										(6 fewer to 5 more)	
hospitalisation for heart failure at end of follow up Mean follow-up: 38.4 month(s)											
1 (holman 2017)	RCT	not serious	not serious	NA[2]	serious[9]	NA	7356	739 6	HR 0.94 (0.78, 1.13)	Not estimable	moderate
acute kidney injury at end of follow up Mean follow-up: 6.4 month(s)											
1 (guja 2017)	RCT	not serious	not serious	NA[2]	very serious[10]	NA	1/232	0/2 31	PETO OR 7.36 (0.15, 370.79)	4 more per 1000 (4 fewer to 13 more)	low
development of end stage kidney disease at end of follow up Mean follow-up: 38.4 month(s)											
1 (holman 2017)	RCT	not serious	not serious	NA[2]	serious[9]	NA	55/73 56	65/ 739 6	PETO OR 0.85 (0.59, 1.22)	1 fewer per 1000 (4 fewer to 2 more)	moderate
death from renal causes at end of follow up Mean follow-up: 38.4 month(s)											
1 (holman 2017)	RCT	not serious	not serious	NA[2]	very serious[10]	NA	5/735 6	5/7 396	PETO OR 1.01 (0.29, 3.47)	0 more per 1000 (1 fewer to 1 more)	low
cardiac arrhythmia at end of follow up Mean follow-up: 38.4 month(s)											
1 (holman 2017)	RCT	not serious	not serious	NA[2]	serious[9]	NA	322/7 356	350 /73 96	RR 0.93 (0.80, 1.07)	4 fewer per 1000 (10 fewer to 3 more)	moderate
diabetic ketoacidosis at end of follow up Mean follow-up: 5.5 month(s)											
2	RCT	very serious[1]	not serious	serious[8]	very serious[12]	NA	1/160	0/4 9	RD 0.01 (-0.04, 0.05)	5 more per 1000	very low

										(38 fewer to 49 more)	
hypoglycaemia episodes at end of follow up Mean follow-up: 6.9 month(s)											
13	RCT	serious[3]	not serious	serious[8]	not serious	NA	455/2480	171/1398	RD 0.06 (0.01, 0.10)	56 more per 1000 (10 more to 102 more)	low
at night hypoglycaemic episodes at end of follow up Mean follow-up: 7 month(s)											
1 (buse 2011)	RCT	serious[3]	not serious	NA[2]	serious[9]	NA	23/137	32/122	RR 0.64 (0.40, 1.03)	94 fewer per 1000 (158 fewer to 8 more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 9.5 month(s)											
11	RCT	not serious	not serious	serious[8]	very serious[13]	NA	248/9363	220/8514	RD 0.00 (-0.00, 0.01)	3 more per 1000 (2 fewer to 8 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 10.9 month(s)											
13	RCT	very serious[1]	not serious	serious[14]	not serious	NA	9820	8682	MD -0.72 (-0.82, -0.63)	MD 0.72 lower (0.82 lower to 0.63 lower)	very low
hba1c change (mmol/l, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
1 (harreiter 2021)	RCT	serious[3]	not serious	NA[2]	not serious	NA	16	14	MD -0.52 (-0.86, -0.17)	MD 0.52 lower	moderate

										(0.86 lower to 0.17 lower)	
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 10.6 month(s)											
14	RCT	very serious[1]	not serious	serious[14]	not serious	NA	9846	8719	MD -1.58 (-2.00, -1.17)	MD 1.58 lower (2.00 lower to 1.17 lower)	very low
bmi change (kg/m2, lower values are better, change and final scores) at end of follow up Mean follow-up: 7.8 month(s)											
3	RCT	very serious[1]	serious[11]	not serious	not serious	NA	125	114	MD -1.28 (-1.51, -1.06)	MD 1.28 lower (1.51 lower to 1.06 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. >33.3% of the studies in the meta-analysis were at moderate risk of bias

4. 95% confidence intervals cross one end of the defined MIDs (-8.33, 8.33)

5. 95% confidence intervals cross one end of the defined MIDs (-11.68, 11.68)

6. 95% confidence intervals cross one end of the defined MIDs (-11.43, 11.43)

7. 95% confidence intervals cross one end of the defined MIDs (-7.78, 7.78)

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

9. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

10. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

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

12. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.21 (0.8-0.9 = serious, <0.8 = very serious).

13. 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).

14. I2 between 50% and 75%

L.1.3.6 Adding exenatide compared to adding insulin

Table 19: 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
health-related quality of life - overall (eq-5d, -0.59-1.0, higher values are better, change scores) at end of follow up Mean follow-up: 20.8 month(s)											
2	RCT	very serious[1]	not serious	not serious	not serious	NA	450	438	MD -0.00 (-0.03, 0.02)	MD 0.00 lower (0.03 lower to 0.02 higher)	low
health-related quality of life - overall (iwqol, 0-100, higher values are better, change scores) at end of follow up Mean follow-up: 6.5 month(s)											
2	RCT	serious[2]	not serious	not serious	not serious	NA	358	368	MD 3.71 (1.95, 5.46)	MD 3.71 higher (1.95 higher to 5.46 higher)	moderate

all-cause mortality at end of follow up Mean follow-up: 12.2 month(s)											
6	RCT	very serious[1]	not serious	serious[3]	very serious[4]	NA	5/1251	2/1224	RD 0.00 (-0.00, 0.01)	2 more per 1000 (3 fewer to 8 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 6.2 month(s)											
4	RCT	serious[2]	not serious	serious[3]	very serious[5]	NA	2/765	0/753	RD 0.00 (-0.00, 0.01)	3 more per 1000 (4 fewer to 9 more)	very low
non-fatal stroke at end of follow up Mean follow-up: 6 month(s)											
1 (inagaki 2012)	RCT	not serious	not serious	NA[6]	very serious[7]	NA	1/215	0/212	PETO OR 7.29 (0.14, 367.26)	5 more per 1000 (4 fewer to 14 more)	low
non-fatal myocardial infarction at end of follow up Mean follow-up: 7 month(s)											
1 (diamant 2014)	RCT	serious[2]	not serious	NA[6]	very serious[7]	NA	0/315	2/312	PETO OR 0.13 (0.01, 2.14)	6 fewer per 1000 (15 fewer to 2 more)	very low
acute kidney injury at end of follow up Mean follow-up: 7 month(s)											
1 (diamant 2014)	RCT	serious[2]	not serious	NA[6]	very serious[7]	NA	1/315	0/312	PETO OR 7.32 (0.15, 368.87)	3 more per 1000 (3 fewer to 9 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 7.6 month(s)											
8	RCT	serious[2]	not serious	not serious	not serious	NA	178/1081	269/1071	RR 0.66 (0.56, 0.77)	86 fewer per 1000 (111 fewer to 58 fewer)	moderate
at night hypoglycaemic episodes at end of follow up Mean follow-up: 7.2 month(s)											
6	RCT	serious[2]	not serious	serious[8]	not serious	NA	150/1147	257/1130	RR 0.54 (0.38, 0.76)	105 fewer per 1000 (141 fewer to 55 fewer)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 10.9 month(s)											

10	RCT	very serious[1]	not serious	serious[3]	very serious[9]	NA	11/1738	21/1704	RD -0.01 (-0.01, 0.00)	6 fewer per 1000 (13 fewer to 1 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 9.2 month(s)											
15	RCT	serious[2]	not serious	very serious[10]	not serious	NA	2059	2010	MD -0.09 (-0.24, 0.06)	MD 0.09 lower (0.24 lower to 0.06 higher)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 9.2 month(s)											
15	RCT	very serious[1]	not serious	very serious[10]	not serious	NA	2015	1976	MD -4.26 (-5.05, -3.48)	MD 4.26 lower (5.05 lower to 3.48 lower)	very low
bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 7.1 month(s)											
6	RCT	serious[2]	not serious	very serious[10]	serious[11]	NA	604	594	MD -1.34 (-1.88, -0.79)	MD 1.34 lower (1.88 lower to 0.79 lower)	very low

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

2. >33.3% of the studies in the meta-analysis were at moderate risk of bias

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

4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.35 (0.8-0.9 = serious, <0.8 = very serious).

5. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.51 (0.8-0.9 = serious, <0.8 = very serious).

6. Only one study so no inconsistency

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

8. I2 between 50% and 75%

9. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.73 (0.8-0.9 = serious, <0.8 = very serious).

10. I2 > 75%

11. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

L.1.3.7 Adding exenatide compared to adding liraglutide

Table 20: Clinical evidence profile: Adding exenatide compared to adding liraglutide

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: 6 month(s)											
1 (buse 2013)	RCT	serious[1]	not serious	NA 2	very serious[3]	NA	2/461	2/450	PETO OR 0.98 (0.14, 6.95)	0 fewer per 1000 (9 fewer to 8 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 6 month(s)											
2	RCT	not serious	not serious	not serious	serious[4]	NA	129/693	100/685	RR 1.29 (1.02, 1.62)	42 more per 1000 (3 more to 91 more)	moderate
severe hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)											
2	RCT	serious[1]	not serious	serious[5]	very serious[6]	NA	1/693	0/685	RD 0.00 (-0.00, 0.01)	1 more per 1000 (3 fewer to 6 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)											
2	RCT	serious[1]	not serious	not serious	not serious	NA	621	621	MD 0.26 (0.16, 0.35)	MD 0.26 higher (0.16 higher to 0.35 higher)	moderate

weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)											
2	RCT	serious[1]	not serious	not serious	not serious	NA	635	633	MD 0.69 (0.30, 1.07)	MD 0.69 higher (0.30 higher to 1.07 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. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

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

6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.29 (0.8-0.9 = serious, <0.8 = very serious).

L.1.3.8 Adding exenatide compared to adding sitagliptin

Table 21: Clinical evidence profile: Adding exenatide 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
health-related quality of life - overall (ed-5d index, -0.59-1, higher values are better, changes scores) Mean follow-up: 6 month(s)											
1 (bergenstal 2010)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	129	139	MD -0.01 (-0.07, 0.05)	MD 0.01 lower (0.07 lower to 0.05 higher)	very low
health-related quality of life - overall (iqwol, 0-100, higher values are better, changes scores) Mean follow-up: 6.5 month(s)											

1 (gadde 2017)	RCT	serious[4]	not serious	NA[2]	not serious	NA	181	122	MD -1.30 (-4.35, 1.75)	MD 1.30 lower (4.35 lower to 1.75 higher)	moderate
health-related quality of life - subscale well being (dmsat, 0-100, higher values are better, changes scores) Mean follow-up: 6.5 month(s)											
1 (gadde 2017)	RCT	serious[4]	not serious	NA[2]	not serious	NA	181	122	MD 8.20 (1.54, 14.86)	MD 8.20 higher (1.54 higher to 14.86 higher)	moderate
all-cause mortality at end of follow up Mean follow-up: 6 month(s)											
1 (bergenstal 2010)	RCT	serious[4]	not serious	NA[2]	very serious[5]	NA	0/160	1/166	PETO OR 0.14 (0.00, 7.08)	6 fewer per 1000 (18 fewer to 6 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 6 month(s)											
1 (bergenstal 2010)	RCT	serious[4]	not serious	NA[2]	very serious[5]	NA	0/160	1/166	PETO OR 0.14 (0.00, 7.08)	6 fewer per 1000 (18 fewer to 6 more)	very low
non-fatal myocardial infaRCTion at end of follow up Mean follow-up: 6.5 month(s)											
1 (gadde 2017)	RCT	not serious	not serious	NA[2]	serious[6]	NA	0/181	0/122	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	moderate
unstable angina at end of follow up Mean follow-up: 6 month(s)											
1 (bergenstal 2010)	RCT	serious[4]	not serious	NA[2]	serious[6]	NA	0/160	0/166	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	low
acute kidney injury at end of follow up Mean follow-up: 6 month(s)											
1 (bergenstal 2010)	RCT	serious[4]	not serious	NA[2]	serious[6]	NA	0/160	0/166	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 6.2 month(s)											

2	RCT	serious[4]	not serious	serious[7]	very serious[5]	NA	2/341	6/288	PETO OR 0.35 (0.09, 1.44)	15 fewer per 1000 (33 fewer to 3 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 6.2 month(s)											
2	RCT	serious[4]	not serious	not serious	not serious	NA	0/341	0/288	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	moderate
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 6.2 month(s)											
2	RCT	not serious	not serious	not serious	serious[8]	NA	341	288	MD -0.44 (-0.74, -0.14)	MD 0.44 lower (0.74 lower to 0.14 lower)	moderate
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6.2 month(s)											
2	RCT	not serious	not serious	very serious[9]	not serious	NA	341	288	MD -0.69 (-2.26, 0.88)	MD 0.69 lower (2.26 lower to 0.88 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 (-0.03, 0.03)

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 (0.80, 1.25)

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

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

8. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

9. I2 > 75%

L.1.3.9 Adding liraglutide compared to adding placebo

Table 22: 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
health-related quality of life - overall (iwqol, higher values are better, change score) at end of follow-up Mean follow-up: 12.8 month(s)											
1 (davies 2015)	RCT	very serious [1]	not serious	NA[2]	not serious	NA	615	211	MD 3.23 (1.18, 5.28)	MD 3.23 higher (1.18 higher to 5.28 higher)	low
health-related quality of life - subscale barriers to activity (sf-36 physical role subscale, higher values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (miras 2019)	RCT	serious [3]	not serious	NA[2]	very serious [4]	NA	53	27	MD 14.20 (-5.77, 34.17)	MD 14.20 higher (5.77 lower to 34.17 higher)	very low
health-related quality of life - subscale barriers to activity (modified diabetes quality of life clinical trial questionnaire - lifestyle flexibility subscale, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)											
1 (vanderheiden 2016a)	RCT	serious [3]	not serious	NA[2]	serious [5]	NA	32	34	MD -0.10 (-0.51, 0.31)	MD 0.10 lower (0.51 lower to 0.31 higher)	low
health-related quality of life - subscale blood glucose control (modified diabetes quality of life clinical trial questionnaire - glycaemia control											

perception subscale, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)											
1 (vanderheiden 2016a)	RCT	serious [3]	not serious	NA[2]	serious [6]	NA	32	34	MD -1.10 (-1.78, -0.42)	MD 1.10 lower (1.78 lower to 0.42 lower)	low
health-related quality of life - subscale current health perception (modified diabetes quality of life clinical trial questionnaire - current health perception subscale, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)											
1 (vanderheiden 2016a)	RCT	serious [3]	not serious	NA[2]	serious [7]	NA	32	34	MD -0.30 (-0.88, 0.28)	MD 0.30 lower (0.88 lower to 0.28 higher)	low
health-related quality of life - subscale emotional effects (sf-36 emotional role functioning subscale, higher values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (miras 2019)	RCT	serious [3]	not serious	NA[2]	very serious [8]	NA	53	27	MD 6.30 (-9.49, 22.09)	MD 6.30 higher (9.49 lower to 22.09 higher)	very low
health-related quality of life - subscale fatigue (sf-36 vitality subscale, higher values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (miras 2019)	RCT	serious [3]	not serious	NA[2]	very serious [4]	NA	53	27	MD 0.20 (-8.77, 9.17)	MD 0.20 higher (8.77 lower to 9.17 higher)	very low
health-related quality of life - subscale general health (sf-36 general health perception, higher values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (miras 2019)	RCT	serious [3]	not serious	NA[2]	serious [9]	NA	53	27	MD 6.20 (-1.66, 14.06)	MD 6.20 higher (1.66 lower to 14.06 higher)	low

health related-quality of life - subscale general health (modified diabetes quality of life clinical trial questionnaire - general health perception subscale, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)											
1 (vanderheiden 2016a)	RCT	serious [3]	not serious	NA[2]	serious [10]	NA	32	34	MD -0.30 (-0.68, 0.08)	MD 0.30 lower (0.68 lower to 0.08 higher)	low
health-related quality of life - subscale hypoglycaemia fear (modified diabetes quality of life clinical trial questionnaire - hypoglycaemia subscale, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)											
1 (vanderheiden 2016a)	RCT	serious [3]	not serious	NA[2]	not serious	NA	32	34	MD 0.00 (-0.27, 0.27)	MD 0.00 lower (0.27 lower to 0.27 higher)	moderate
health-related quality of life - lifestyle impact (modified diabetes quality of life clinical trial questionnaire - treatment impact subscale, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)											
1 (vanderheiden 2016a)	RCT	serious [3]	not serious	NA[2]	serious [11]	NA	32	34	MD -0.20 (-0.41, 0.01)	MD 0.20 lower (0.41 lower to 0.01 higher)	low
health-related quality of life - subscale pain (sf-36 bodily pain subscale, higher values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (miras 2019)	RCT	serious [3]	not serious	NA[2]	very serious [12]	NA	53	27	MD -3.40 (-17.95, 11.15)	MD 3.40 lower (17.95 lower to 11.15 higher)	very low
health-related quality of life - subscale physical functioning (sf-36 physical function subscale, higher values are better, change scores) at end of follow-up Mean follow-up: 9.2 month(s)											

2	RCT	not serious	not serious	not serious	not serious	NA	251	225	MD 0.36 (-1.00, 1.71)	MD 0.36 higher (1.00 lower to 1.71 higher)	high
health-related quality of life - subscale satisfaction (modified diabetes quality of life clinical trial questionnaire - treatment satisfaction subscale, lower values are better, chnage score) at end of follow-up Mean follow-up: 6 month(s)											
1 (vanderheiden 2016a)	RCT	serious [3]	not serious	NA[2]	serious [13]	NA	32	34	MD -0.30 (-0.57, -0.03)	MD 0.30 lower (0.57 lower to 0.03 lower)	low
health-related quality of life - subscale social (sf-36 social role functioning subscale, higher values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (miras 2019)	RCT	serious [3]	not serious	NA[2]	very serious [12]	NA	53	27	MD -5.60 (-17.15, 5.95)	MD 5.60 lower (17.15 lower to 5.95 higher)	very low
health-related quality of life - subscale social or vocational worry (modified diabetes quality of life clinical questionnaire - social or vocational worry subscale, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)											
1 (vanderheiden 2016a)	RCT	serious [3]	not serious	NA[2]	serious [14]	NA	32	34	MD -0.30 (-0.64, 0.04)	MD 0.30 lower (0.64 lower to 0.04 higher)	low
health-related quality of life - subscale social stigma (modified diabetes quality of life clinical questionnaire - social stigma subscale, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)											
1 (vanderheiden 2016a)	RCT	serious [3]	not serious	NA[2]	serious [15]	NA	32	34	MD 0.30 (-0.14, 0.74)	MD 0.30 higher (0.14 lower to 0.74 higher)	low

health-related quality of life - subscale wellbeing (sf-36 mental health subscale, higher values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (miras 2019)	RCT	serious [3]	not serious	NA[2]	very serious [12]	NA	53	27	MD 0.60 (-7.31, 8.51)	MD 0.60 higher (7.31 lower to 8.51 higher)	very low
all-cause mortality at end of follow up Mean follow-up: 12.1 month(s)											
11	RCT	very serious [1]	not serious	serious [16]	not serious	NA	387/7214	450/5882	RD -0.00 (-0.01, 0.01)	1 fewer per 1000 (9 fewer to 6 more)	very low
all-cause mortality at end of follow up (hazard ratio) Mean follow-up: 45.6 month(s)											
1 (marso 2016a)	RCT	not serious	not serious	NA[2]	serious [17]	NA	4688	4672	HR 0.85 (0.74, 0.98)	Not estimable	moderate
cardiovascular mortality at end of follow up Mean follow-up: 13.5 month(s)											
9	RCT	not serious	not serious	serious [16]	not serious	NA	222/6936	278/5630	RD -0.00 (-0.01, 0.01)	1 fewer per 1000 (9 fewer to 7 more)	moderate
cardiovascular mortality at end of follow up (hazard ratio) Mean follow-up: 45.6 month(s)											
1 (marso 2016a)	RCT	not serious	not serious	NA[2]	serious [17]	NA	4688	4672	HR 0.78 (0.66, 0.92)	Not estimable	moderate
3-point mace at end of follow up Mean follow-up: 45.6 month(s)											

1 (marso 2016a)	RCT	not serious	not serious	NA[2]	serious [17]	NA	608/4668	694/4672	RR 0.88 (0.79, 0.97)	18 fewer per 1000 (31 fewer to 4 fewer)	moderate
3-point mace at end of follow up (hazard ratio) Mean follow-up: 45.6 month(s)											
1 (marso 2016a)	RCT	not serious	not serious	NA[2]	serious [17]	NA	4668	4672	HR 0.87 (0.78, 0.97)	Not estimable	moderate
non-fatal stroke at end of follow up Mean follow-up: 28.8 month(s)											
2	RCT	not serious	not serious	serious [16]	serious [17]	NA	159/4952	178/4814	RR 0.89 (0.72, 1.10)	4 fewer per 1000 (10 fewer to 4 more)	low
non-fatal stroke at end of follow up (hazard ratio) Mean follow-up: 45.6 month(s)											
1 (marso 2016a)	RCT	not serious	not serious	NA[2]	serious [17]	NA	4668	4672	HR 0.89 (0.72, 1.10)	Not estimable	moderate
non-fatal myocardial infarction at end of follow up Mean follow-up: 28.8 month(s)											
2	RCT	not serious	not serious	serious [16]	serious [17]	NA	282/4952	317/4814	RR 0.89 (0.76, 1.04)	7 fewer per 1000 (16 fewer to 2 more)	low
non-fatal myocardial infarction at end of follow up (hazard ratio) Mean follow-up: 45.6 month(s)											
1 (marso 2016a)	RCT	not serious	not serious	NA[2]	serious [17]	NA	4668	4672	HR 0.88 (0.75, 1.03)	Not estimable	moderate

unstable angina at end of follow up Mean follow-up: 28.8 month(s)											
2	RCT	not serious	not serious	serious [16]	very serious [18]	NA	122/4952	124/4814	RD -0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 6 more)	very low
unstable angina at end of follow up (hazard ratio) Mean follow-up: 45.6 month(s)											
1 (marso 2016a)	RCT	not serious	not serious	NA[2]	very serious [19]	NA	4668	4672	HR 0.98 (0.76, 1.26)	Not estimable	low
hospitalisation for heart failure at end of follow up Mean follow-up: 45.6 month(s)											
1 (marso 2016a)	RCT	not serious	not serious	NA[2]	serious [17]	NA	218/4668	248/4672	RR 0.88 (0.74, 1.05)	6 fewer per 1000 (14 fewer to 3 more)	moderate
hospitalisation for heart failure at end of follow up (hazard ratio) Mean follow-up: 45.6 month(s)											
1 (marso 2016a)	RCT	not serious	not serious	NA[2]	serious [17]	NA	4668	4672	HR 0.87 (0.73, 1.04)	Not estimable	moderate
acute kidney injury at end of follow up Mean follow-up: 21.2 month(s)											
3	RCT	not serious	not serious	serious [16]	serious [17]	NA	112/5154	100/4914	RR 1.11 (0.85, 1.44)	2 more per 1000 (3 fewer to 9 more)	low
persistent signs of worsening kidney disease at end of follow up Mean follow-up: 25.6 month(s)											
2	RCT	not serious	not ser	serious [16]	serious [17]	NA	269/4721	337/	RR 0.80	15 fewer per 1000 (23	low

			ious					4699	(0.68, 0.93)	fewer to 5 fewer)	
persistent signs of worsening kidney disease at end of follow up (hazard ratio) Mean follow-up: 45.6 month(s)											
1 (marso 2016a)	RCT	not serious	not serious	NA[2]	serious [17]	NA	4668	4672	HR 0.78 (0.67, 0.91)	Not estimable	moderate
development of end stage kidney disease at end of follow up Mean follow-up: 29.2 month(s)											
2	RCT	not serious	not serious	serious [16]	very serious [19]	NA	57/5300	64/4884	RR 0.88 (0.62, 1.25)	2 fewer per 1000 (5 fewer to 3 more)	very low
development of end stage kidney disease at end of follow up (hazard ratio) Mean follow-up: 45.6 month(s)											
1 (marso 2016a)	RCT	not serious	not serious	NA[2]	serious [17]	NA	4668	4672	HR 0.87 (0.61, 1.24)	Not estimable	moderate
death from renal causes at end of follow up Mean follow-up: 34.8 month(s)											
2	RCT	very serious [1]	not serious	serious [16]	very serious [19]	NA	9/5392	5/4793	PETO OR 1.63 (0.56, 4.74)	1 more per 1000 (1 fewer to 2 more)	very low
death from renal causes at end of follow up (hazard ratio) Mean follow-up: 45.6 month(s)											
1 (marso 2016a)	RCT	very serious [1]	not serious	NA[2]	very serious [19]	NA	4668	4672	HR 1.59 (0.52, 4.86)	Not estimable	very low

hypoglycaemia episodes at end of follow up Mean follow-up: 12.1 month(s)											
13	RCT	not serious	not serious	serious [20]	serious [17]	NA	2527/7762	2417/6183	RR 1.18 (1.02, 1.36)	69 more per 1000 (6 more to 142 more)	low
at night hypoglycaemic episodes at end of follow up Mean follow-up: 7.2 month(s)											
2	RCT	not serious	not serious	serious [16]	serious [21]	NA	6/357	11/244	RD -0.02 (-0.10, 0.06)	16 fewer per 1000 (95 fewer to 63 more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12.1 month(s)											
13	RCT	not serious	not serious	serious [16]	not serious	NA	129/8133	157/6051	RD -0.01 (-0.01, -0.00)	5 fewer per 1000 (10 fewer to 0 more)	moderate
hba1c change (mmol/mol, lower values are better, change score) at end of follow up Mean follow-up: 6 month(s)											
1 (bizino 2019)	RCT	very serious [1]	not serious	NA[2]	serious [22]	NA	23	26	MD -2.90 (-8.09, 2.29)	MD 2.90 lower (8.09 lower to 2.29 higher)	very low
hba1c change (%, lower values are better, change scores and final values) at end of follow up Mean follow-up: 9.9 month(s)											
19	RCT	very serious [1]	not serious	very serious [23]	not serious	NA	7950	5870	MD -0.88 (-1.03, -0.72)	MD 0.88 lower (1.03 lower to 0.72 lower)	very low
weight change (kg, lower values are better, change scores and final values) at end of follow up Mean follow-up: 8.8 month(s)											

19	RCT	serious [3]	not serious	very serious [23]	serious [24]	NA	7276	5496	MD -2.02 (-2.85, -1.20)	MD 2.02 lower (2.85 lower to 1.20 lower)	very low
bmi change (kg/m2, lower values are better, change scores and final values) at end of follow up Mean follow-up: 7.4 month(s)											
9	RCT	not serious	not serious	serious [20]	serious [25]	NA	1471	2829	MD -1.08 (-1.37, -0.79)	MD 1.08 lower (1.37 lower to 0.79 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. >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 (-2.00, 2.00)

5. 95% confidence intervals cross one end of the defined MIDs (-0.38, 0.38)

6. 95% confidence intervals cross one end of the defined MIDs (-0.55, 0.55)

7. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

8. 95% confidence intervals cross both ends of the defined MIDs (-4.00, 4.00)

9. 95% confidence intervals cross one end of the defined MIDs (-2.00, 2.00)

10. 95% confidence intervals cross one end of the defined MIDs (-0.40, 0.40)

11. 95% confidence intervals cross one end of the defined MIDs (-0.33, 0.33)

12. 95% confidence intervals cross both ends of the defined MIDs (-3.00, 3.00)

13. 95% confidence intervals cross one end of the defined MIDs (-0.35, 0.35)

14. 95% confidence intervals cross one end of the defined MIDs (-0.42, 0.42)

15. 95% confidence intervals cross one end of the defined MIDs (-0.53, 0.53)

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

17. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

18. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.07 (0.8-0.9 = serious, <0.8 = very serious).

19. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

20. I2 between 50% and 75%

21. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.81 (0.8-0.9 = serious, <0.8 = very serious).

22. 95% confidence intervals cross one end of the defined MIDs (-5.50, 5.50)

23. I2 > 75%

24. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

25. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

L.1.3.10 Adding liraglutide compared to adding insulin

Table 23: 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
health-related quality of life - subscale mental component (SF-36, higher values are better, change score) at end of follow-up Mean follow-up: 15 month(s)											
2	RCT	very serious[1]	not serious	not serious	not serious	NA	1277	1270	MD 0.04 (-0.10, 0.18)	MD 0.04 higher	low

										(0.10 lower to 0.18 higher)	
health-related quality of life -subscale physical component (SF-36, higher values are better, change score) at end of follow-up Mean follow-up: 9 month(s)											
2	RCT	very serious[1]	not serious	very serious[2]	not serious	NA	1277	1270	MD 0.48 (-0.29, 1.24)	MD 0.48 higher (0.29 lower to 1.24 higher)	very low
all-cause mortality at end of follow up Mean follow-up: 18 month(s)											
5	RCT	serious[3]	not serious	serious[4]	very serious[5]	NA	29/2023	43/2022	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (12 fewer to 8 more)	very low
all-cause mortality at end of follow-up (hazard ratio) Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	serious[3]	not serious	NA[6]	serious[7]	NA	1262	1263	HR 0.65 (0.40, 1.05)	Not estimable	low
cardiovascular mortality at end of follow up Mean follow-up: 21 month(s)											
4	RCT	serious[3]	not serious	serious[4]	serious[8]	NA	9/1876	21/1879	RD -0.00 (-0.01, 0.01)	3 fewer per 1000 (12 fewer to 6 more)	very low
cardiovascular mortality at end of follow-up (hazard ratio) Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	serious[3]	not serious	NA[6]	serious[7]	NA	1251	1257	HR 0.43 (0.20, 0.95)	Not estimable	low
3-point mace at end of follow up Mean follow-up: 36 month(s)											

2	RCT	serious[3]	not serious	not serious	serious[7]	NA	49/1665	66/1670	RR 0.75 (0.52, 1.07)	10 fewer per 1000 (19 fewer to 3 more)	low
3-point mace at end of follow up (hazard ratio) Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	serious[3]	not serious	NA[6]	serious[7]	NA	1251	1257	HR 0.74 (0.51, 1.07)	Not estimable	low
4-point mace at end of follow up Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	very serious[1]	not serious	NA[6]	serious[7]	NA	54/1262	71/1263	RR 0.76 (0.54, 1.07)	13 fewer per 1000 (26 fewer to 4 more)	very low
non-fatal myocardial infarction at end of follow up Mean follow-up: 12 month(s)											
1 (gough 2014)	RCT	not serious	not serious	NA[6]	very serious[9]	NA	1/414	1/413	PETO OR 1.00 (0.06, 15.98)	0 fewer per 1000 (7 fewer to 7 more)	low
unstable angina at end of follow up Mean follow-up: 33 month(s)											
2	RCT	very serious[1]	not serious	serious[4]	very serious[9]	NA	7/1442	10/1442	PETO OR 0.70 (0.27, 1.82)	2 fewer per 1000 (8 fewer to 4 more)	very low
non-fatal stroke at end of follow up Mean follow-up: 5.8 month(s)											
2	RCT	serious[3]	not serious	serious[4]	very serious[9]	NA	4/661	1/663	PETO OR 3.34 (0.57, 19.37)	5 more per 1000 (2 fewer to 11 more)	very low
hospitalisation for heart failure at end of follow up Mean follow-up: 60 month(s)											

1 (group 2022)	RCT	serious[3]	not serious	NA[6]	serious[7]	NA	14/1251	26/1257	RR 0.54 (0.28, 1.03)	9 fewer per 1000 (15 fewer to 1 more)	low
hospitalisation for heart failure at end of follow-up (hazard ratio) Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	serious[3]	not serious	NA[6]	serious[7]	NA	1251	1257	HR 0.54 (0.28, 1.04)	Not estimable	low
acute kidney injury at end of follow up Mean follow-up: 6 month(s)											
1 (pasquel 2021)	RCT	very serious[1]	serious[10]	NA[6]	very serious[9]	NA	1/136	3/137	RR 0.34 (0.04, 3.19)	15 fewer per 1000 (21 fewer to 48 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 11.9 month(s)											
9	RCT	not serious	not serious	very serious[2]	not serious	NA	527/2781	100 0/2799	RR 0.46 (0.31, 0.68)	193 fewer per 1000 (246 fewer to 115 fewer)	low
hypoglycaemia episodes at end of follow-up (hazard ratio) Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	very serious[1]	not serious	NA[6]	not serious	NA	1233	1245	HR 0.61 (0.53, 0.70)	Not estimable	low
at night hypoglycaemic episodes at end of follow up Mean follow-up: 5.8 month(s)											
3	RCT	not serious	not serious	serious[4]	not serious	NA	15/891	93/895	RD -0.06 (-0.23, 0.12)	57 fewer per 1000 (234 fewer to 121 more)	moderate

severe hypoglycaemic episodes at end of follow up Mean follow-up: 13.6 month(s)											
7	RCT	very serious[1]	not serious	serious[4]	very serious[11]	NA	22/2608	23/2615	RD -0.00 (-0.01, 0.00)	0 fewer per 1000 (6 fewer to 5 more)	very low
hba1c change (%, lower values are better, change scores and final values) at end of follow up Mean follow-up: 12.6 month(s)											
9	RCT	not serious	not serious	serious[12]	not serious	NA	1697	1804	MD -0.10 (-0.29, 0.09)	MD 0.10 lower (0.29 lower to 0.09 higher)	moderate
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6.7 month(s)											
8	RCT	not serious	not serious	serious[12]	not serious	NA	1352	1376	MD -4.13 (-4.81, -3.45)	MD 4.13 lower (4.81 lower to 3.45 lower)	moderate
bmi change (kg/m2, lower values are better, change scores and final values) at end of follow up Mean follow-up: 8 month(s)											
3	RCT	serious[3]	not serious	not serious	serious[13]	NA	95	94	MD -1.18 (-1.73, -0.63)	MD 1.18 lower (1.73 lower to 0.63 lower)	low

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

2. I2 > 75%

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

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 = 0.65 (0.8-0.9 = serious, <0.8 = very serious).

6. Only one study so no inconsistency

7. 95% confidence intervals cross one end 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 = 0.87 (0.8-0.9 = serious, <0.8 = very serious).

9. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

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

11. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.04 (0.8-0.9 = serious, <0.8 = very serious).

12. I2 between 50% and 75%

13. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

L.1.3.11 Adding liraglutide compared to adding dulaglutide

Table 24: Adding liraglutide 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
all-cause mortality at end of follow up Mean follow-up: 6 month(s)											
1 (dungan 2014)	RCT	not serious	not serious	NA[1]	not serious	NA	0/299	0/300	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	high
cardiovascular mortality at end of follow up Mean follow-up: 6 month(s)											

1 (dungan 2014)	RCT	not serious	not serious	NA[1]	not serious	NA	0/299	0/300	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	high
falls requiring hospitalisation at end of follow up Mean follow-up: 6 month(s)											
1 (dungan 2014)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	1/299	0/300	PETO OR 7.41 (0.15, 373.63)	3 more per 1000 (3 fewer to 10 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 6 month(s)											
1 (dungan 2014)	RCT	not serious	not serious	NA[1]	serious[3]	NA	26/299	17/300	RR 1.53 (0.85, 2.77)	30 more per 1000 (8 fewer to 100 more)	moderate
at night hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)											
1 (dungan 2014)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	4/299	6/300	RR 0.67 (0.19, 2.35)	7 fewer per 1000 (16 fewer to 27 more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)											
1 (dungan 2014)	RCT	not serious	not serious	NA[1]	not serious	NA	0/299	0/300	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	high
hba1c change (%, lower values are better, change score) at end of follow up Mean follow-up: 6 month(s)											
1 (dungan 2014)	RCT	not serious	not serious	NA[1]	not serious	NA	299	300	MD -0.06 (-0.20, 0.08)	MD 0.06 lower (0.20 lower to 0.08 higher)	high
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)											
1 (dungan 2014)	RCT	not serious	not serious	NA[1]	not serious	NA	299	300	MD 0.71 (0.16, 1.26)	MD 0.71 higher (0.16 higher to 1.26 higher)	high

1. Only one study so no inconsistency

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

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

L.1.3.12 Adding liraglutide compared to adding saxagliptin

Table 25: Clinical evidence profile: Adding liraglutide compared to adding saxagliptin

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 the end of follow-up Mean follow-up: 5.5 month(s)											
1 (li 2014a)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	4/61	3/60	RR 1.31 (0.31, 5.61)	16 more per 1000 (35 fewer to 231 more)	very low
severe hypoglycaemic episodes at the end of follow-up Mean follow-up: 5.5 month(s)											
1 (li 2014a)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	0/61	0/60	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (32 fewer to 32 more)	very low
hba1c change (%, lower values are better, final values) at the end of follow-up Mean follow-up: 5.5 month(s)											
1 (li 2014a)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	61	60	MD -0.27 (-0.47, -0.07)	MD 0.27 lower (0.47 lower to 0.07 lower)	low

weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (li 2014a)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	61	60	MD -5.10 (-6.01, -4.19)	MD 5.10 lower (6.01 lower to 4.19 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 (li 2014a)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	61	60	MD -1.80 (-2.11, -1.49)	MD 1.80 lower (2.11 lower to 1.49 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. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.

L.1.3.13 Adding liraglutide compared to adding sitagliptin

Table 22: Clinical evidence profile: Adding liraglutide compared to adding sitagliptin (adding therapy)

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 mental component (SF-36, higher values are better, change scores) at end of follow up **Mean follow-up: 24 month(s)**											
1 (group 2022)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	1218	1236	MD -0.27 (-0.85, 0.31)	MD 0.27 lower (0.85 lower to 0.31 higher)	low
health-related quality of life - subscale physical component (SF-36, higher values are better, change scores) at end of follow up **Mean follow-up: 12 month(s)**											
1 (group 2022)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	1218	1236	MD 0.66 (0.11, 1.21)	MD 0.66 higher (0.11 higher to 1.21 higher)	low
all-cause mortality at the end of follow-up **Mean follow-up: 21 month(s)**											
4	RCT	serious[3]	not serious	serious[4]	not serious	NA	28/2208	44/1996	RD -0.01	8 fewer per 1000	low

									(-0.02, -0.00)	(16 fewer to 0 more)	
all-cause mortality at the end of follow-up **Mean follow-up: 60 month(s)**												
1 (group 2022)	RCT	serious[3]	not serious	NA[2]	serious[5]	NA	1262	1267	HR 0.66 (0.41, 1.07)	Not estimable	low
cardiovascular mortality at the end of follow-up **Mean follow-up: 26 month(s)**												
3	RCT	serious[3]	not serious	serious[4]	not serious	NA	9/1873	23/1667	RD -0.01 (-0.01, 0.00)	6 fewer per 1000 (13 fewer to 1 more)	low
cardiovascular mortality at the end of follow-up **Mean follow-up: 60 month(s)**												
1 (group 2022)	RCT	serious[3]	not serious	NA[2]	serious[5]	NA	1251	1264	HR 0.44 (0.20, 0.95)	Not estimable	low
3-point mace at end of follow-up **Mean follow-up: 60 month(s)**												
1 (group 2022)	RCT	serious[3]	not serious	NA[2]	serious[5]	NA	48/1251	69/1264	RR 0.70 (0.49, 1.01)	16 fewer per 1000 (28 fewer to 0 more)	low

3-point mace at the end of follow-up **Mean follow-up: 60 month(s)**											
1 (group 2022)	RCT	serious[3]	not serious	NA[2]	serious[5]	NA	1251	1264	HR 0.70 (0.48, 1.02)	Not estimable	low
4-point mace at end of follow-up **Mean follow-up: 60 month(s)**											
1 (group 2022)	RCT	very serious[1]	not serious	NA[2]	serious[5]	NA	54/1262	78/1268	RR 0.70 (0.50, 0.98)	19 fewer per 1000 (31 fewer to 2 fewer)	very low
non-fatal stroke at the end of follow-up **Mean follow-up: 6 month(s)**											
1 (zang 2016)	RCT	not serious	not serious	NA[2]	very serious[6]	NA	0/183	1/184	PETO OR 0.14 (0.00, 6.86)	5 fewer per 1000 (16 fewer to 5 more)	low
non-fatal myocardial infarction at the end of follow-up **Mean follow-up: 6 month(s)**											
1 (webb 2020)	RCT	not serious	not serious	NA[2]	very serious[6]	NA	0/38	1/38	PETO OR 0.14 (0.00, 6.82)	26 fewer per 1000 (77 fewer to 25 more)	low
unstable angina at end of follow-up											

Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	very serious[1]	not serious	NA[2]	serious[5]	NA	7/1262	15/1268	RR 0.47 (0.19, 1.15)	6 fewer per 1000 (10 fewer to 2 more)	very low
hospitalisation for heart failure at the end of follow-up Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	serious[3]	not serious	NA[2]	serious[5]	NA	14/1251	30/1264	RR 0.47 (0.25, 0.88)	13 fewer per 1000 (18 fewer to 3 fewer)	low
hospitalisation for heart failure at the end of follow-up Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	serious[3]	not serious	NA[2]	serious[5]	NA	1262	1267	HR 0.47 (0.25, 0.88)	Not estimable	low
cardiac arrhythmia at the end of follow-up Mean follow-up: 6 month(s)											
1 (zang 2016)	RCT	not serious	not serious	NA[2]	very serious[6]	NA	0/183	1/184	PETO OR 0.14 (0.00, 6.86)	5 fewer per 1000 (16 fewer to 5 more)	low
diabetic ketoacidosis at the end of follow-up Mean follow-up: 6 month(s)											

1 (zang 2016)	RCT	not serious	not serious	NA[2]	very serious[6]	NA	1/183	0/184	PETO OR 7.43 (0.15, 374.43)	5 more per 1000 (5 fewer to 16 more)	low
hypoglycaemia episodes at the end of follow-up Mean follow-up: 14.5 month(s)											
7	RCT	very serious[1]	not serious	serious[7]	very serious[6]	NA	361/2291	387/2096	RR 0.84 (0.50, 1.39)	30 fewer per 1000 (92 fewer to 72 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	1233	1253	HR 0.97 (0.84, 1.12)	Not estimable	low
at night hypoglycaemic episodes at the end of follow-up Mean follow-up: 6 month(s)											
1 (zang 2016)	RCT	not serious	not serious	NA[2]	not serious	NA	0/183	0/184	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (11 fewer to 11 more)	high
severe hypoglycaemic episodes at the end of follow-up Mean follow-up: 15.9 month(s)											

6	RCT	very serious[1]	not serious	serious[4]	very serious[8]	NA	14/2296	10/2084	RD 0.00 (-0.00, 0.01)	2 more per 1000 (3 fewer to 6 more)	very low
hba1c change (%, lower values are better, final values) at the end of follow-up Mean follow-up: 13.4 month(s)											
8	RCT	serious[3]	not serious	very serious[9]	serious[10]	NA	1335	1084	MD -0.33 (-0.56, -0.10)	MD 0.33 lower (0.56 lower to 0.10 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 6.8 month(s)											
6	RCT	serious[3]	not serious	serious[7]	serious[11]	NA	975	786	MD -2.10 (-2.65, -1.55)	MD 2.10 lower (2.65 lower to 1.55 lower)	very low
bmi change (kg/m2, lower values are better, change scores) at end of follow-up Mean follow-up: 5.8 month(s)											
4	RCT	serious[3]	not serious	serious[7]	serious[12]	NA	274	282	MD -0.68 (-1.01, -0.35)	MD 0.68 lower (1.01 lower to 0.35 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. >33.3% of the studies in the meta-analysis were at moderate risk of bias

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

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

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

7. I2 between 50% and 75%

8. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.13 (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. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

12. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

L.1.3.14 Adding liraglutide compared to adding vildagliptin

Table 23: Clinical evidence profile: Adding liraglutide 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
hypoglycaemia episodes at the end of follow-up Mean follow-up: 5.5 month(s)											
1 (li 2014a)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	4/61	5/57	RR 0.75 (0.21, 2.65)	22 fewer per 1000	very low

										(69 fewer to 144 more)	
severe hypoglycaemic episodes at the end of follow-up Mean follow-up: 5.5 month(s)											
1 (li 2014a)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	0/61	0/57	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (33 fewer to 33 more)	very low
hba1c change (%, lower values are better, final values) at the end of follow-up Mean follow-up: 5.5 month(s)											
1 (li 2014a)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	61	57	MD -0.25 (-0.45, -0.05)	MD 0.25 lower (0.45 lower to 0.05 lower)	low
weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (li 2014a)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	61	57	MD -5.20 (-6.08, -4.32)	MD 5.20 lower (6.08 lower to 4.32 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 (li 2014a)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	61	57	MD -1.80 (-2.09, -1.51)	MD 1.80 lower (2.09 lower to 1.51 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. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.

L.1.3.15 Adding lixisenatide compared to adding placebo

Table 26: 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
health-related quality of life - subscale physical component (sf-12 scores, higher values are better, mean difference) at end of follow-up Mean follow-up: 5.3 month(s)											
1 (meneilly 2017)	RCT	not serious	not serious	NA[1]	serious[2]	NA	175	173	MD 1.73 (0.01, 3.45)	MD 1.73 higher (0.01 higher to 3.45 higher)	moderate
health-related quality of life - subscale mental component (sf-12 scores, higher values are better, mean difference) at end of follow-up Mean follow-up: 5.3 month(s)											
1 (meneilly 2017)	RCT	not serious	not serious	NA[1]	not serious	NA	175	173	MD 0.33 (-1.57, 2.23)	MD 0.33 higher (1.57 lower to 2.23 higher)	high
all-cause mortality at end of follow-up											

Mean follow-up: 6.7 month(s)											
10	RCT	not serious	not serious	serious[3]	very serious[4]	NA	5/3030	8/1914	RD -0.00 (-0.01, 0.00)	3 fewer per 1000 (7 fewer to 1 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 5.5 month(s)											
9	RCT	not serious	not serious	serious[3]	very serious[5]	NA	2/2708	2/1754	RD -0.00 (-0.00, 0.00)	0 fewer per 1000 (4 fewer to 3 more)	very low
non-fatal stroke at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	not serious	not serious	not serious	very serious[6]	NA	3/350	0/351	PETO OR 7.49 (0.78, 72.21)	9 more per 1000 (1 fewer to 18 more)	low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 5.5 month(s)											
1 (pan 2014)	RCT	not serious	not serious	NA[1]	very serious[6]	NA	1/196	0/194	PETO OR 7.31 (0.15, 368.62)	5 more per 1000 (5 fewer to 15 more)	low
hypoglycaemia episodes at end of follow-up Mean follow-up: 6.7 month(s)											
10	RCT	not serious	not serious	not serious	serious[7]	NA	396/3030	191/1914	RR 1.44 (1.18, 1.76)	44 more per 1000 (18 more to 76 more)	moderate
severe hypoglycaemic episodes at end of outcome Mean follow-up: 6.7 month(s)											
10	RCT	not serious	not serious	serious[3]	not serious	NA	7/3030	0/1914	RD 0.00 (-0.00, 0.01)	2 more per 1000 (1 fewer to 6 more)	moderate
hba1c change (%, lower values are better, mean difference) at end of follow-up											

Mean follow-up: 6.7 month(s)											
10	RCT	not serious	not serious	serious[8]	serious[9]	NA	2977	1889	MD -0.51 (-0.63, -0.40)	MD 0.51 lower (0.63 lower to 0.40 lower)	low
weight change (kg, lower values are better, mean difference) at end of follow-up Mean follow-up: 6.7 month(s)											
10	RCT	not serious	not serious	not serious	not serious	NA	3012	1898	MD -0.74 (-1.02, -0.46)	MD 0.74 lower (1.02 lower to 0.46 lower)	high

1. Only one study so no inconsistency

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

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

4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.65 (0.8-0.9 = serious, <0.8 = very serious).

5. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.09 (0.8-0.9 = serious, <0.8 = very serious).

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

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)

L.1.3.16 Adding lixisenatide compared to adding insulin

Table 27: Clinical evidence profile: Adding lixisenatide 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 Mean follow-up: 6.2 month(s)											
3	RCT	serious[1]	not serious	serious[2]	very serious[3]	NA	2/707	5/1411	RD -0.00 (-0.01, 0.00)	1 fewer per 1000 (6 fewer to 5 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 6.2 month(s)											
3	RCT	serious[1]	not serious	serious[2]	very serious[4]	NA	1/707	3/1411	RD -0.00 (-0.01, 0.00)	1 fewer per 1000 (6 fewer to 4 more)	very low
non-fatal stroke at end of follow up Mean follow-up: 7 month(s)											
1 (rosenstock 2016b)	RCT	serious[1]	not serious	NA[5]	very serious[6]	NA	1/233	1/467	RR 2.00 (0.13, 31.90)	2 more per 1000 (2 fewer to 66 more)	very low
unstable angina at end of follow up Mean follow-up: 7 month(s)											
1 (rosenstock 2016b)	RCT	serious[1]	not serious	NA[5]	very serious[6]	NA	0/233	1/467	PETO OR 0.22 (0.00, 14.30)	2 fewer per 1000 (6 fewer to 2 more)	very low
hospitalisation for heart failure at end of follow up Mean follow-up: 7 month(s)											

1 (rosenstock 2016b)	RCT	serious[1]	not serious	NA[5]	very serious[6]	NA	0/233	2/467	PETO OR 0.22 (0.01, 4.23)	4 fewer per 1000 (10 fewer to 2 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 6.2 month(s)											
3	RCT	serious[1]	not serious	very serious[7]	not serious	NA	125/707	618/1411	RR 0.29 (0.12, 0.71)	310 fewer per 1000 (386 fewer to 126 fewer)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 6.2 month(s)											
3	RCT	serious[1]	not serious	serious[2]	very serious[6]	NA	1/707	4/1411	PETO OR 0.55 (0.09, 3.51)	1 fewer per 1000 (5 fewer to 2 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 6.2 month(s)											
3	RCT	not serious	not serious	serious[8]	serious[9]	NA	700	1402	MD 0.36 (0.17, 0.54)	MD 0.36 higher (0.17 higher to 0.54 higher)	low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6.2 month(s)											
3	RCT	not serious	not serious	very serious[7]	serious[10]	NA	703	1402	MD -2.73 (-3.59, -1.87)	MD 2.73 lower (3.59 lower to 1.87 lower)	very low

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

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

3. 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).

4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.08 (0.8-0.9 = serious, <0.8 = very serious).

5. Only one study so no inconsistency

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

7. I2 > 75%

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)

L.1.3.17 Adding lixisenatide compared to adding liraglutide

Table 28: Clinical evidence profile: Adding lixisenatide compared to adding liraglutide

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
cardiac arrhythmia at end of follow-up Mean follow-up: 6 month(s)											
1 (nauck 2016b)	RCT	very serious[3]	not serious	NA[1]	very serious[2]	NA	1/202	0/202	PETO OR 7.39 (0.15, 372.38)	5 more per 1000 (5 fewer to 15 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 6 month(s)											

1 (nauck 2016b)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	5/202	3/202	RR 1.67 (0.40, 6.88)	10 more per 1000 (9 fewer to 87 more)	low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (nauck 2016b)	RCT	very serious[3]	not serious	NA[1]	not serious	NA	0/202	0/202	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (10 fewer to 10 more)	low
hba1c change (%, lower values are better, mean difference) at end of follow-up Mean follow-up: 6 month(s)											
1 (nauck 2016b)	RCT	not serious	not serious	NA[1]	serious[4]	NA	202	202	MD 0.60 (0.40, 0.80)	MD 0.60 higher (0.40 higher to 0.80 higher)	moderate
weight change (kg, lower values are better, mean difference) at end of follow-up Mean follow-up: 6 month(s)											
1 (nauck 2016b)	RCT	not serious	not serious	NA[1]	not serious	NA	0	0	MD 0.60 (-0.18, 1.38)	MD 0.60 higher (0.18 lower to 1.38 higher)	high

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

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

L.1.3.18 Adding lixisenatide compared to adding exenatide

Table 29: Clinical evidence profile: Adding lixisenatide compared to adding exenatide

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: 5.5 month(s)											
1 (rosenstock 2013)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	1/318	1/316	PETO OR 0.99 (0.06, 15.92)	0 fewer per 1000 (9 fewer to 9 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2013)	RCT	not serious	not serious	NA[1]	not serious	NA	8/318	25/316	RD -0.05 (-0.09, -0.02)	54 fewer per 1000 (88 fewer to 20 fewer)	high
severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2013)	RCT	not serious	not serious	NA[1]	not serious	NA	0/318	0/316	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	high
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2013)	RCT	not serious	not serious	NA[1]	not serious	NA	315	315	MD 0.17 (0.03, 0.31)	MD 0.17 higher (0.03 higher to 0.31 higher)	high

weight change (kg, lower vaues are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2013)	RCT	not serious	not serious	NA[1]	not serious	NA	315	315	MD 1.02 (0.46, 1.58)	MD 1.02 higher (0.46 higher to 1.58 higher)	high

1. Only one study so no inconsistency

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

L.1.3.19 Adding lixisenatide compared to adding sitagliptin

Table 30: Clinical evidence profile: Adding lixisenatide 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
all-cause mortality at end of follow-up Mean follow-up: 5.5 month(s)											
1 (van gaal 2014)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	0/158	0/161	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 5.5 month(s)											
1 (van gaal 2014)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	0/158	0/161	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	very low

hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)											
1 (van gaal 2014)	RCT	very serious[1]	not serious	NA[2]	very serious[4]	NA	1/158	3/161	RR 0.34 (0.04, 3.23)	12 fewer per 1000 (18 fewer to 42 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)											
1 (van gaal 2014)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	0/158	0/161	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	very low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (van gaal 2014)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	158	161	MD 0.00 (-0.28, 0.28)	MD 0.00 lower (0.28 lower to 0.28 higher)	low
weight change (kg, lower values are better, mean difference) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (van gaal 2014)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	152	160	MD -1.30 (-2.10, -0.50)	MD 1.30 lower (2.10 lower to 0.50 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. 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 (0.80, 1.25)

L.1.3.20 Adding semaglutide compared to adding placebo

Table 31: 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 mental component (sf-36, higher values are better, change scores) at end of follow-up Mean follow-up: 12.7 month(s)											
5	RCT	not serious	not serious	not serious	not serious	NA	3286	2429	MD 0.75 (0.28, 1.22)	MD 0.75 higher (0.28 higher to 1.22 higher)	high
health-related quality of life - subscale physical component (sf-36, higher values are better, change scores) at end of follow-up Mean follow-up: 12.7 month(s)											
5	RCT	not serious	not serious	not serious	not serious	NA	3286	2429	MD 0.55 (0.17, 0.93)	MD 0.55 higher (0.17 higher to 0.93 higher)	high
all-cause mortality at end of follow up Mean follow-up: 11.3 month(s)											
10	RCT	not serious	not serious	serious[1]	not serious	NA	94/5921	107/4382	RD -0.00 (-0.01, 0.00)	4 fewer per 1000 (9 fewer to 2 more)	moderate
all-cause mortality at end of follow up Mean follow-up: 20.4 month(s)											
2	RCT	not serious	not serious	very serious[2]	very serious[3]	NA	3239	3241	HR 0.75 (0.37, 1.52)	Not estimable	very low
cardiovascular mortality at end of follow up Mean follow-up: 11.3 month(s)											

7	RCT	not serious	not serious	serious[1]	not serious	NA	60/4540	76/3766	RD -0.00 (-0.01, 0.00)	4 fewer per 1000 (10 fewer to 2 more)	moderate
cardiovascular mortality at end of follow up Mean follow-up: 20.4 month(s)											
2	RCT	not serious	not serious	serious[4]	very serious[3]	NA	3239	3241	HR 0.72 (0.37, 1.41)	Not estimable	very low
3-point mace at end of follow up Mean follow-up: 20.4 month(s)											
2	RCT	not serious	not serious	not serious	serious[5]	NA	169/3239	222/3241	RR 0.76 (0.63, 0.92)	16 fewer per 1000 (26 fewer to 5 fewer)	moderate
3-point mace at end of follow up Mean follow-up: 20.4 month(s)											
2	RCT	not serious	not serious	not serious	serious[5]	NA	3239	3241	HR 0.76 (0.62, 0.92)	Not estimable	moderate
5-point mace at end of follow up Mean follow-up: 20.4 month(s)											
2	RCT	not serious	not serious	not serious	serious[5]	NA	282/3239	364/3241	RR 0.78 (0.67, 0.90)	25 fewer per 1000 (37 fewer to 12 fewer)	moderate
5-point mace at end of follow up Mean follow-up: 20.4 month(s)											
2	RCT	not serious	not serious	not serious	serious[5]	NA	3239	3241	HR 0.76 (0.65, 0.88)	Not estimable	moderate
non-fatal stroke at end of follow up Mean follow-up: 13 month(s)											
6	RCT	not serious	not serious	serious[1]	serious[5]	NA	47/4892	65/3771	PETO OR 0.64 (0.44, 0.93)	8 fewer per 1000 (13 fewer to 3 fewer)	low
non-fatal stroke at end of follow up Mean follow-up: 20.4 month(s)											

2	RCT	not serious	not serious	not serious	serious[5]	NA	3239	3241	HR 0.64 (0.43, 0.96)	Not estimable	moderate
non-fatal myocardial infarction at end of follow up Mean follow-up: 14.2 month(s)											
5	RCT	not serious	not serious	serious[1]	serious[6]	NA	91/4629	98/3638	RD -0.00 (-0.01, 0.00)	3 fewer per 1000 (10 fewer to 4 more)	low
non-fatal myocardial infarction at end of follow up Mean follow-up: 20.4 month(s)											
2	RCT	not serious	not serious	serious[4]	very serious[3]	NA	3239	3241	HR 0.91 (0.58, 1.43)	Not estimable	very low
unstable angina at end of follow up Mean follow-up: 17.6 month(s)											
3	RCT	not serious	not serious	serious[1]	very serious[3]	NA	34/3524	34/3383	PETO OR 0.99 (0.61, 1.60)	0 fewer per 1000 (5 fewer to 4 more)	very low
unstable angina at end of follow up Mean follow-up: 20.4 month(s)											
2	RCT	not serious	not serious	not serious	very serious[3]	NA	3239	3241	HR 0.97 (0.60, 1.56)	Not estimable	low
hospitalisation for heart failure at end of follow up Mean follow-up: 14.9 month(s)											
4	RCT	not serious	not serious	serious[1]	very serious[3]	NA	83/4048	79/3558	RR 1.02 (0.75, 1.38)	0 more per 1000 (6 fewer to 8 more)	very low
hospitalisation for heart failure at end of follow up Mean follow-up: 20.4 month(s)											
2	RCT	not serious	not serious	not serious	very serious[3]	NA	3239	3241	HR 1.03 (0.76, 1.41)	Not estimable	low
acute kidney injury at end of follow up Mean follow-up: 14.6 month(s)											

6	RCT	not serious	not serious	serious[1]	very serious[7]	NA	107/5024	108/4120	RD -0.00 (-0.01, 0.01)	1 fewer per 1000 (8 fewer to 5 more)	very low
persistent signs of worsening kidney disease at end of follow up Mean follow-up: 25.2 month(s)											
1 (marso 2016b)	RCT	not serious	not serious	NA[8]	serious[5]	NA	62/1648	100/1649	RR 0.62 (0.46, 0.85)	23 fewer per 1000 (33 fewer to 9 fewer)	moderate
persistent signs of worsening kidney disease at end of follow up Mean follow-up: 25.2 month(s)											
1 (marso 2016b)	RCT	not serious	not serious	NA[8]	serious[5]	NA	1648	1649	HR 0.64 (0.46, 0.89)	Not estimable	moderate
cardiac arrhythmia at end of follow up Mean follow-up: 25.2 month(s)											
1 (marso 2016b)	RCT	not serious	not serious	NA[8]	very serious[3]	NA	50/1648	58/1649	RR 0.86 (0.59, 1.25)	5 fewer per 1000 (14 fewer to 9 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 9.3 month(s)											
7	RCT	not serious	not serious	serious[4]	very serious[3]	NA	288/2418	82/1008	RR 1.31 (0.77, 2.25)	26 more per 1000 (19 fewer to 102 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 11.4 month(s)											
7	RCT	not serious	not serious	serious[1]	very serious[9]	NA	431/4801	371/3808	RD 0.01 (-0.00, 0.02)	11 more per 1000 (1 fewer to 23 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 12.6 month(s)											
7	RCT	not serious	not serious	very serious[2]	not serious	NA	4203	2696	MD -1.04 (-1.26, -0.82)	MD 1.04 lower (1.26 lower to 0.82 lower)	low

hba1c change (mmol/mol, lower values are better, change scores) at end of follow up Mean follow-up: 6.2 month(s)											
2	RCT	serious[10]	not serious	very serious[2]	serious[11]	NA	71	50	MD -14.67 (-27.41, -1.94)	MD 14.67 lower (27.41 lower to 1.94 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 11.2 month(s)											
9	RCT	not serious	not serious	very serious[2]	not serious	NA	4275	2747	MD -3.59 (-4.24, -2.94)	MD 3.59 lower (4.24 lower to 2.94 lower)	low
bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 11.8 month(s)											
4	RCT	not serious	not serious	very serious[2]	not serious	NA	1741	844	MD -1.26 (-1.60, -0.91)	MD 1.26 lower (1.60 lower to 0.91 lower)	low

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

2. I2 > 75%

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

4. I2 between 50% and 75%

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

6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.87 (0.8-0.9 = serious, <0.8 = very serious).

7. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.59 (0.8-0.9 = serious, <0.8 = very serious).

8. Only one study so no inconsistency

9. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.41 (0.8-0.9 = serious, <0.8 = very serious).

10. >33.3% of the studies in the meta-analysis were at moderate risk of bias

11. 95% confidence intervals cross one end of the defined MIDs (-5.50, 5.50)

L.1.3.21 Adding semaglutide compared to adding insulin

Table 32: Clinical evidence profile: Adding semagluitde 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
health-related quality of life - subscale mental component (sf-36 v2, higher values are better, change scores) at end of follow-up Mean follow-up: 12 month(s)											
1 (kellerer 2022)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	874	874	MD 0.59 (-0.14, 1.32)	MD 0.59 higher (0.14 lower to 1.32 higher)	low
health-related quality of life - subscale physical component (sf-36 v2, higher values are better, change scores) at end of follow-up Mean follow-up: 12 month(s)											
1 (kellerer 2022)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	874	874	MD 0.95 (0.37, 1.53)	MD 0.95 higher (0.37 higher to 1.53 higher)	low
all-cause mortality at end of follow up Mean follow-up: 9.5 month(s)											

2	RCT	serious[3]	not serious	serious[4]	not serious	NA	16/1596	3/1224	PETO OR 3.32 (1.32, 8.31)	8 more per 1000 (2 more to 13 more)	low
cardiovascular mortality at end of follow up Mean follow-up: 7 month(s)											
1 (aroda 2017)	RCT	very serious[1]	not serious	NA[2]	very serious[5]	NA	3/722	2/360	PETO OR 0.74 (0.11, 4.76)	1 fewer per 1000 (10 fewer to 8 more)	very low
unstable angina at end of follow up Mean follow-up: 12 month(s)											
1 (kellerer 2022)	RCT	serious[3]	not serious	NA[2]	very serious[5]	NA	1/874	1/864	PETO OR 0.99 (0.06, 15.82)	0 fewer per 1000 (3 fewer to 3 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 12 month(s)											
1 (kellerer 2022)	RCT	serious[3]	not serious	NA[2]	not serious	NA	328/874	527/864	RR 0.62 (0.56, 0.68)	235 fewer per 1000 (271 fewer to 195 fewer)	moderate
at night hypoglycaemic episodes at end of follow up Mean follow-up: 7 month(s)											
1 (aroda 2017)	RCT	very serious[1]	not serious	NA[2]	serious[6]	NA	7/722	8/360	RR 0.44 (0.16, 1.19)	13 fewer per 1000 (19 fewer to 4 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 9.5 month(s)											
2	RCT	very serious[1]	not serious	not serious	not serious	NA	40/1596	45/1224	RR 0.48 (0.32, 0.73)	19 fewer per 1000 (25 fewer to 10 fewer)	low

hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 8.7 month(s)											
2	RCT	very serious[1]	not serious	very serious[7]	serious[8]	NA	1596	1234	MD -0.49 (-0.79, -0.19)	MD 0.49 lower (0.79 lower to 0.19 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 8.7 month(s)											
2	RCT	very serious[1]	not serious	very serious[7]	not serious	NA	1596	1234	MD -6.69 (-8.73, -4.65)	MD 6.69 lower (8.73 lower to 4.65 lower)	very low
bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (kellerer 2022)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	874	874	MD -2.54 (-2.69, -2.39)	MD 2.54 lower (2.69 lower to 2.39 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. I2 between 50% and 75%

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

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

7. I2 > 75%

8. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

L.1.3.22 Adding semaglutide compared to adding dulaglutide

Table 33: 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 - subscale mental component (sf-36-v2, higher values are better, change scores) at end of follow-up Mean follow-up: 12 month(s)											
1 (yabe 2020)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	393	65	MD 0.26 (-0.86, 1.38)	MD 0.26 higher (0.86 lower to 1.38 higher)	low
health-related quality of life - subscale physical component (sf-36-v2, higher values are better, change scores) at end of follow-up Mean follow-up: 12 month(s)											
1 (yabe 2020)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	393	65	MD -0.12 (-0.88, 0.64)	MD 0.12 lower (0.88 lower to 0.64 higher)	low
all-cause mortality at end of follow up Mean follow-up: 11.2 month(s)											
2	RCT	not serious	not serious	serious[3]	very serious[4]	NA	2/994	4/663	RD -0.00 (-0.01, 0.00)	3 fewer per 1000 (10 fewer to 5 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 11.2 month(s)											

2	RCT	not serious	not serious	serious[3]	very serious[5]	NA	1/994	2/663	RD -0.00 (-0.01, 0.00)	1 fewer per 1000 (7 fewer to 4 more)	very low
acute kidney injury at end of follow up Mean follow-up: 12 month(s)											
1 (yabe 2020)	RCT	not serious	not serious	NA[2]	not serious	NA	0/393	0/65	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (21 fewer to 21 more)	high
death from renal causes at end of follow up Mean follow-up: 12 month(s)											
1 (yabe 2020)	RCT	not serious	not serious	NA[2]	not serious	NA	0/393	0/65	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (21 fewer to 21 more)	high
hypoglycaemia episodes at end of follow up Mean follow-up: 9 month(s)											
2	RCT	not serious	not serious	serious[3]	very serious[6]	NA	67/409	13/81	RD -0.03 (-0.12, 0.07)	26 fewer per 1000 (118 fewer to 67 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 11.2 month(s)											
2	RCT	not serious	not serious	serious[3]	very serious[7]	NA	7/994	8/663	PETO OR 0.87 (0.31, 2.41)	5 fewer per 1000 (15 fewer to 5 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 9.1 month(s)											
3	RCT	serious[8]	not serious	very serious[9]	serious[10]	NA	1010	679	MD -0.25 (-0.56, 0.06)	MD 0.25 lower	very low

										(0.56 lower to 0.06 higher)	
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 9.1 month(s)											
3	RCT	not serious	not serious	serious[11]	serious[12]	NA	1010	679	MD -2.45 (-3.26, -1.64)	MD 2.45 lower (3.26 lower to 1.64 lower)	low
bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 11.3 month(s)											
2	RCT	serious[8]	not serious	very serious[9]	serious[13]	NA	994	663	MD -0.74 (-1.05, -0.43)	MD 0.74 lower (1.05 lower to 0.43 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. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.45 (0.8-0.9 = serious, <0.8 = very serious).

5. 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).

6. 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).

7. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.32 (0.8-0.9 = serious, <0.8 = very serious).

8. >33.3% of the studies in the meta-analysis were at moderate risk of bias

9. I2 > 75%

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

11. I2 between 50% and 75%

12. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

13. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

L.1.3.23 Adding semaglutide compared to adding exenatide

Table 34: Clinical evidence profile: Adding semaglutide compared to adding exenatide

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 mental component (sf-36, higher values are better, change scores) at end of follow-up Mean follow-up: 12 month(s)											
1 (ahmann 2018)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	404	405	MD 0.16 (-1.14, 1.46)	MD 0.16 higher (1.14 lower to 1.46 higher)	low
health-related quality of life - subscale physical component (sf-36, higher values are better, change scores) at end of follow-up Mean follow-up: 12 month(s)											
1 (ahmann 2018)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	404	405	MD 0.46 (-0.64, 1.56)	MD 0.46 higher	low

										(0.64 lower to 1.56 higher)	
all-cause mortality at end of follow up Mean follow-up: 12 month(s)											
1 (ahmann 2018)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/405	2/404	PETO OR 0.13 (0.01, 2.16)	5 fewer per 1000 (12 fewer to 2 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											
1 (ahmann 2018)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	33/404	33/405	RR 1.00 (0.63, 1.59)	0 more per 1000 (30 fewer to 48 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (ahmann 2018)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	404	405	MD -0.60 (-0.77, -0.43)	MD 0.60 lower (0.77 lower to 0.43 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (ahmann 2018)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	404	405	MD -3.70 (-4.50, -2.90)	MD 3.70 lower (4.50 lower to 2.90 lower)	low
bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											

1 (ahmann 2018)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	404	405	MD -1.40 (-1.68, -1.12)	MD 1.40 lower (1.68 lower to 1.12 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 (-0.50, 0.50)

L.1.3.24 Adding semaglutide compared to adding liraglutide

Table 35: Clinical evidence profile: Adding semaglutide compared to adding liraglutide

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 mental component (sf-36 v2, higher values are better, change scores) at end of follow-up Mean follow-up: 7 month(s)											
1 (capehorn 2020)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	290	287	MD 1.00 (-0.11, 2.11)	MD 1.00 higher (0.11 lower to 2.11 higher)	low
health-related quality of life - subscale physical component (sf-36 v2, higher values are better, change scores) at end of follow-up Mean follow-up: 7 month(s)											

1 (capehorn 2020)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	290	287	MD 0.70 (-0.41, 1.81)	MD 0.70 higher (0.41 lower to 1.81 higher)	low
all-cause mortality at end of follow up Mean follow-up: 9.5 month(s)											
2	RCT	very serious[1]	not serious	serious[3]	very serious[4]	NA	3/575	4/571	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (11 fewer to 8 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 9.5 month(s)											
2	RCT	very serious[1]	not serious	serious[3]	very serious[5]	NA	1/575	2/571	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (9 fewer to 5 more)	very low
non-fatal stroke at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2019)	RCT	not serious	not serious	NA[2]	very serious[6]	NA	2/285	0/284	PETO OR 7.39 (0.46, 118.42)	7 more per 1000 (3 fewer to 17 more)	low
non-fatal myocardial infarction at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2019)	RCT	not serious	not serious	NA[2]	very serious[6]	NA	0/285	1/284	PETO OR 0.13 (0.00, 6.80)	4 fewer per 1000 (10 fewer to 3 more)	low
unstable angina at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2019)	RCT	not serious	not serious	NA[2]	very serious[6]	NA	1/285	0/284	PETO OR 7.36 (0.15, 371.08)	4 more per 1000 (3 fewer to 10 more)	low
acute kidney injury at end of follow up Mean follow-up: 12 month(s)											

1 (pratley 2019)	RCT	not serious	not serious	NA[2]	very serious[6]	NA	0/285	1/284	PETO OR 0.13 (0.00, 6.80)	4 fewer per 1000 (10 fewer to 3 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 9.5 month(s)											
2	RCT	very serious[1]	not serious	not serious	serious[7]	NA	7/575	14/571	RR 0.50 (0.20, 1.22)	12 fewer per 1000 (20 fewer to 5 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 7 month(s)											
1 (capehorn 2020)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/290	0/287	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 6.5 month(s)											
2	RCT	very serious[1]	not serious	very serious[8]	serious[9]	NA	568	559	MD -0.41 (-0.99, 0.17)	MD 0.41 lower (0.99 lower to 0.17 higher)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6.5 month(s)											
2	RCT	not serious	not serious	very serious[8]	serious[10]	NA	568	558	MD -2.55 (-5.03, -0.07)	MD 2.55 lower (5.03 lower to 0.07 lower)	very low
bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 9.5 month(s)											

2	RCT	very serious[1]	not serious	very serious[8]	serious[11]	NA	565	556	MD -0.90 (-1.68, -0.12)	MD 0.90 lower (1.68 lower to 0.12 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. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.08 (0.8-0.9 = serious, <0.8 = very serious).

5. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.13 (0.8-0.9 = serious, <0.8 = very serious).

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

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

8. I2 > 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)

11. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

L.1.3.25 Semaglutide compared to adding sitagliptin

Table 36: Clinical evidence profile - Semaglutide v sitagliptin

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 mental component (sf36 v2, higher values are better, change scores) at end of follow-up Mean follow-up: 16.5 month(s)											
2	RCT	not serious	not serious	not serious	not serious	NA	1649	718	MD 0.05 (-0.52, 0.63)	MD 0.05 higher (0.52 lower to 0.63 higher)	high
health-related quality of life - subscale physical component (sf36 v2, higher values are better, change scores) at end of follow-up Mean follow-up: 16.5 month(s)											
2	RCT	not serious	not serious	not serious	not serious	NA	1649	718	MD 0.09 (-0.33, 0.52)	MD 0.09 higher (0.33 lower to 0.52 higher)	high
all-cause mortality at end of follow up Mean follow-up: 12.5 month(s)											
4	RCT	not serious	not serious	serious[1]	very serious[2]	NA	14/3044	8/1413	PETO OR 0.74 (0.30, 1.87)	1 fewer per 1000 (6 fewer to 4 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 12.5 month(s)											
4	RCT	not serious	not serious	serious[1]	very serious[2]	NA	7/3044	4/1413	PETO OR 0.90 (0.25, 3.19)	1 fewer per 1000 (4 fewer to 3 more)	very low

non-fatal stroke at end of follow up Mean follow-up: 18 month(s)											
1 (rosenstock 2019c)	RCT	not serious	not serious	NA[3]	very serious[2]	NA	9/1395	1/466	PETO OR 2.24 (0.53, 9.39)	4 more per 1000 (2 fewer to 10 more)	low
non-fatal myocardial infarction at end of follow up Mean follow-up: 18 month(s)											
1 (rosenstock 2019c)	RCT	not serious	not serious	NA[3]	very serious[2]	NA	4/1395	2/466	PETO OR 0.64 (0.10, 4.08)	1 fewer per 1000 (8 fewer to 5 more)	low
unstable angina at end of follow up Mean follow-up: 18 month(s)											
1 (rosenstock 2019c)	RCT	not serious	not serious	NA[3]	very serious[2]	NA	6/1395	1/466	PETO OR 1.78 (0.32, 9.85)	2 more per 1000 (3 fewer to 8 more)	low
hospitalisation for heart failure at end of follow up Mean follow-up: 15 month(s)											
2	RCT	not serious	not serious	serious[1]	very serious[2]	NA	5/1648	4/716	PETO OR 0.42 (0.10, 1.87)	3 fewer per 1000 (9 fewer to 4 more)	very low
acute kidney injury at end of follow up Mean follow-up: 15 month(s)											
2	RCT	not serious	not serious	serious[1]	very serious[2]	NA	11/1648	3/716	PETO OR 1.32 (0.40, 4.39)	2 more per 1000 (4 fewer to 9 more)	very low
death from renal causes at end of follow up Mean follow-up: 18 month(s)											
1 (rosenstock 2019c)	RCT	not serious	not serious	NA[3]	very serious[2]	NA	1/1395	0/466	PETO OR 3.80 (0.04, 350.01)	1 more per 1000 (1 fewer to 2 more)	low
hypoglycaemia episodes at end of follow up											

Mean follow-up: 12.7 month(s)											
3	RCT	not serious	not serious	not serious	not serious	NA	358/2791	124/1163	RR 0.99 (0.83, 1.19)	1 fewer per 1000 (18 fewer to 20 more)	high
at night hypoglycaemic episodes at end of follow up Mean follow-up: 15 month(s)											
2	RCT	not serious	not serious	not serious	very serious[2]	NA	20/1648	7/716	RR 1.21 (0.51, 2.87)	2 more per 1000 (5 fewer to 18 more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 14 month(s)											
3	RCT	not serious	not serious	serious[1]	not serious	NA	1/2466	6/1123	RD -0.01 (-0.01, -0.00)	5 fewer per 1000 (11 fewer to 0 more)	moderate
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 13.1 month(s)											
4	RCT	not serious	not serious	very serious[4]	serious[5]	NA	3045	1415	MD -0.39 (-0.61, -0.17)	MD 0.39 lower (0.61 lower to 0.17 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 13.1 month(s)											
4	RCT	not serious	not serious	very serious[4]	serious[6]	NA	3045	1415	MD -2.03 (-2.77, -1.30)	MD 2.03 lower (2.77 lower to 1.30 lower)	very low
bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 13.1 month(s)											

4	RCT	not serious	not serious	very serious[4]	serious[7]	NA	3045	1415	MD -0.75 (-1.02, -0.49)	MD 0.75 lower (1.02 lower to 0.49 lower)	very low

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

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

3. Only one study so no inconsistency

4. I2 > 75%

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 (-2.40, 2.40)

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

L.1.3.26 Adding SC semaglutide compared to adding oral semaglutide

Table 37: Clinical evidence profile: Adding SC semaglutide compared to adding oral semaglutide

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 mental component (sf-36, higher values are better, change scores) at follow-up Mean follow-up: 6 month(s)											
1 (davies 2017)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	69	490	MD -0.43 (-2.63, 1.77)	MD 0.43 lower (2.63 lower to 1.77 higher)	low

health-related quality of life - subscale physical component (sf-36, higher values are better, change scores) at follow-up Mean follow-up: 6 month(s)											
1 (davies 2017)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	69	490	MD 0.22 (-1.30, 1.74)	MD 0.22 higher (1.30 lower to 1.74 higher)	low
all-cause mortality at end of follow up Mean follow-up: 6 month(s)											
1 (davies 2017)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/69	0/490	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	low
cardiovascular mortality at end of follow up Mean follow-up: 6 month(s)											
1 (davies 2017)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/69	0/490	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	low
non-fatal stroke at end of follow up Mean follow-up: 6 month(s)											
1 (davies 2017)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/69	0/490	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	low
non-fatal myocardial infaRCTion at end of follow up Mean follow-up: 6 month(s)											
1 (davies 2017)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/69	2/490	PETO OR 0.32 (0.00, 21.63)	4 fewer per 1000 (10 fewer to 2 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 6 month(s)											

1 (davies 2017)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	12/69	63/490	RR 1.35 (0.77, 2.38)	45 more per 1000 (30 fewer to 177 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)											
1 (davies 2017)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	1/69	1/490	PETO OR 32.67 (0.48, 2216.41)	12 more per 1000 (16 fewer to 41 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)											
1 (davies 2017)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	69	490	MD -0.41 (-0.62, -0.20)	MD 0.41 lower (0.62 lower to 0.20 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)											
1 (davies 2017)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	69	490	MD -1.12 (-2.29, 0.05)	MD 1.12 lower (2.29 lower to 0.05 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. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

L.1.4 Dual GIP/GLP-1 receptor co-agonists

L.1.4.1 Adding tirzepatide compared to adding placebo

Table 38: Clinical evidence profile: Adding tirzepatide 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 functioning (sf-36 physical function scores, higher values are better) at end of follow-up Mean follow-up: 18 month(s)											
1 (garvey 2023)	RCT	not serious	not serious	NA[1]	not serious	NA	623	315	MD 2.00 (1.04, 2.96)	MD 2.00 higher (1.04 higher to 2.96 higher)	high
all-cause mortality at end of follow-up Mean follow-up: 10.4 month(s)											
4	RCT	not serious	not serious	serious[2]	very serious[3]	NA	2/1234	1/510	RD -0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 7 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 8.8 month(s)											
2	RCT	not serious	not serious	not serious	not serious	NA	0/400	0/148	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	high
4-point mace at end of follow-up Mean follow-up: 11 month(s)											
1 (dahl 2022)	RCT	not serious	not serious	NA[1]	very serious[4]	NA	2/355	1/120	RR 0.68 (0.06, 7.39)	3 fewer per 1000 (8 fewer to 53 more)	low
cardiac arrhythmia at end of follow-up Mean follow-up: 18 month(s)											
1 (garvey 2023)	RCT	not serious	not serious	NA[1]	very serious[4]	NA	5/623	1/315	RR 2.53 (0.30, 21.55)	5 more per 1000 (2 fewer to 65 more)	low

persistent signs of worsening kidney disease at end of follow-up Mean follow-up: 18 month(s)											
1 (garvey 2023)	RCT	not serious	not serious	NA[1]	very serious[4]	NA	3/623	1/315	RR 1.52 (0.16, 14.52)	2 more per 1000 (3 fewer to 43 more)	low
progression of liver disease at end of follow-up Mean follow-up: 18 month(s)											
1 (garvey 2023)	RCT	not serious	not serious	NA[1]	very serious[4]	NA	2/623	0/315	PETO OR 4.51 (0.24, 85.06)	3 more per 1000 (1 fewer to 8 more)	low
hypoglycaemia episodes at end of follow-up Mean follow-up: 10.4 month(s)											
4	RCT	not serious	not serious	serious[5]	very serious[4]	NA	318/1234	94/514	RR 1.74 (0.75, 4.04)	136 more per 1000 (45 fewer to 556 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 10.4 month(s)											
4	RCT	not serious	not serious	serious[2]	very serious[6]	NA	3/1234	0/514	RD 0.00 (-0.00, 0.01)	2 more per 1000 (4 fewer to 9 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow-up Mean follow-up: 11.3 month(s)											
3	RCT	not serious	not serious	not serious	not serious	NA	1189	486	MD -1.53 (-1.65, -1.42)	MD 1.53 lower (1.65 lower to 1.42 lower)	high
hba1c change (mmol/mol, lower values are better, change scores) at end of follow-up Mean follow-up: 6.5 month(s)											
1 (heise 2022)	RCT	serious[7]	not serious	NA[1]	not serious	NA	41	24	MD -25.50 (-26.02, -24.98)	MD 25.50 lower (26.02 lower to 24.98 lower)	moderate
weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 10.1 month(s)											
4	RCT	not serious	not serious	very serious[8]	serious[9]	NA	1070	670	MD -6.55 (-12.94, -0.16)	MD 6.55 lower (12.94 lower to 0.16 lower)	very low

bmi change (kg/m2, lower values are better, change scores) at end of follow-up Mean follow-up: 12 month(s)											
2	RCT	not serious	not serious	very serious[8]	very serious[10]	NA	674	526	MD -0.83 (-6.76, 5.10)	MD 0.83 lower (6.76 lower to 5.10 higher)	very low

1. Only one study so no inconsistency

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

3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.04 (0.8-0.9 = serious, <0.8 = very serious).

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

5. I2 between 50% and 75%

6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.54 (0.8-0.9 = serious, <0.8 = very serious).

7. >33.3% of the studies in the meta-analysis were at moderate risk of bias

8. I2 > 75%

9. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

10. 95% confidence intervals cross both ends of the defined MIDs (-0.80, 0.80)

L.1.4.2 Adding tirzepatide compared to adding insulin

Table 39: 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 Mean follow-up: 11 month(s)											

3	RCT	serious[1]	not serious	not serious	serious[2]	NA	12/2481	15/1288	RR 0.55 (0.26, 1.18)	5 fewer per 1000 (9 fewer to 2 more)	low
cardiovascular mortality at end of follow-up Mean follow-up: 10.5 month(s)											
2	RCT	serious[1]	not serious	serious[3]	very serious[4]	NA	2/1764	2/580	PETO OR 0.25 (0.03, 2.45)	2 fewer per 1000 (7 fewer to 3 more)	very low
4-point mace at end of follow-up Mean follow-up: 10.5 month(s)											
2	RCT	not serious	not serious	not serious	very serious[4]	NA	15/1764	4/580	RR 1.11 (0.36, 3.44)	1 more per 1000 (4 fewer to 17 more)	low
non-fatal stroke at end of follow-up Mean follow-up: 9 month(s)											
1 (gao 2023)	RCT	serious[1]	not serious	NA[5]	very serious[4]	NA	10/687	2/220	RR 1.60 (0.35, 7.25)	5 more per 1000 (6 fewer to 57 more)	very low
non-fatal myocardial infaRCTion at end of follow-up Mean follow-up: 9 month(s)											
1 (gao 2023)	RCT	serious[1]	not serious	NA[5]	very serious[4]	NA	1/687	0/220	PETO OR 3.74 (0.04, 362.44)	1 more per 1000 (1 fewer to 4 more)	very low
cardiac arrhythmia at end of follow-up Mean follow-up: 9 month(s)											
1 (gao 2023)	RCT	serious[1]	not serious	NA[5]	very serious[4]	NA	0/687	1/220	PETO OR 0.02 (0.00, 1.57)	5 fewer per 1000 (13 fewer to 4 more)	very low

hospitalisation for heart failure at end of follow-up Mean follow-up: 9 month(s)											
1 (gao 2023)	RCT	serious[1]	not serious	NA[5]	very serious[4]	NA	1/687	0/220	PETO OR 3.74 (0.04, 362.44)	1 more per 1000 (1 fewer to 4 more)	very low
acute kidney injury Mean follow-up: 12 month(s)											
1 (rosenstock 2023)	RCT	serious[1]	not serious	NA[5]	very serious[4]	NA	1/717	0/708	PETO OR 7.30 (0.14, 367.77)	1 more per 1000 (1 fewer to 4 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 11 month(s)											
3	RCT	serious[1]	not serious	very serious[6]	not serious	NA	413/2481	607/1288	RR 0.34 (0.16, 0.70)	312 fewer per 1000 (394 fewer to 141 fewer)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 11 month(s)											
3	RCT	serious[1]	not serious	serious[3]	not serious	NA	4/2481	30/1288	RD -0.02 (-0.02, -0.01)	17 fewer per 1000 (24 fewer to 10 fewer)	low
hba1c change (%, lower values are better, change scores) at end of follow-up Mean follow-up: 11 month(s)											
3	RCT	serious[1]	not serious	very serious[6]	not serious	NA	2479	1287	MD -1.08 (-1.46, -0.70)	MD 1.08 lower (1.46 lower to 0.70 lower)	very low

weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 11 month(s)											
3	RCT	serious[1]	not serious	very serious[6]	not serious	NA	2479	1287	MD -10.90 (-14.29, -7.52)	MD 10.90 lower (14.29 lower to 7.52 lower)	very 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. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

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

5. Only one study so no inconsistency

6. I2 > 75%

L.1.4.3 Adding tirzepatide compared to adding dulaglutide

Table 40: Clinical evidence profile: Adding tirzepatide 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
all-cause mortality at end of follow up Mean follow-up: 6 month(s)											
1 (frias 2018)	RCT	not serious	not serious	NA[1]	serious[2]	NA	0/211	0/54	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (26 fewer to 26 more)	moderate
hypoglycaemia episodes at end of follow up Mean follow-up: 6 month(s)											

1 (frias 2018)	RCT	not serious	not serious	NA[1]	very serious[3]	NA	14/211	2/54	RR 1.79 (0.42, 7.65)	29 more per 1000 (21 fewer to 246 more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)											
1 (frias 2018)	RCT	not serious	not serious	NA[1]	serious[2]	NA	0/211	0/54	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (26 fewer to 26 more)	moderate
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)											
1 (frias 2018)	RCT	not serious	not serious	NA[1]	serious[4]	NA	211	54	MD -0.68 (-0.86, -0.50)	MD 0.68 lower (0.86 lower to 0.50 lower)	moderate
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)											
1 (frias 2018)	RCT	not serious	not serious	NA[1]	serious[5]	NA	211	54	MD -2.07 (-3.96, -0.18)	MD 2.07 lower (3.96 lower to 0.18 lower)	moderate
bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)											
1 (frias 2018)	RCT	not serious	not serious	NA[1]	serious[6]	NA	211	54	MD -1.30 (-1.93, -0.67)	MD 1.30 lower (1.93 lower to 0.67 lower)	moderate

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. 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 (-2.40, 2.40)

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

L.1.4.4 Adding tirzepatide compared to adding semaglutide

Table 41: Clinical evidence profile: Adding tirezepatide compared to adding semaglutide

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: 7.8 month(s)											
2	RCT	serious[1]	not serious	serious[2]	very serious[3]	NA	12/1454	1/513	RD 0.01 (-0.00, 0.01)	6 more per 1000 (1 fewer to 13 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 7.8 month(s)											
2	RCT	serious[1]	not serious	serious[2]	very serious[4]	NA	5/1455	0/513	RD 0.00 (-0.00, 0.01)	3 more per 1000 (2 fewer to 8 more)	very low
non-fatal myocardial infaRCTion at end of follow up Mean follow-up: 9 month(s)											
1 (frias 2021)	RCT	serious[1]	not serious	NA[5]	very serious[6]	NA	3/1409	0/469	PETO OR 3.80 (0.28, 51.93)	2 more per 1000 (0 more to 5 more)	very low
cardiac arrhythmia at end of follow up Mean follow-up: 9 month(s)											
1 (frias 2021)	RCT	serious[1]	not serious	not serious	very serious[6]	NA	2/1409	0/469	PETO OR 3.79 (0.15, 93.33)	1 more per 1000 (1 fewer to 3 more)	very low

hypoglycaemia episodes at end of follow up Mean follow-up: 6.5 month(s)											
2	RCT	serious[1]	not serious	not serious	very serious[6]	NA	15/1454	3/513	PETO OR 2.00 (0.71, 5.64)	4 more per 1000 (4 fewer to 13 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 7.8 month(s)											
2	RCT	serious[1]	not serious	serious[2]	very serious[7]	NA	2/1454	0/513	RD 0.00 (-0.00, 0.01)	1 more per 1000 (3 fewer to 6 more)	very low
hba1c change (%, lower values are better, mean difference) at end of follow up Mean follow-up: 9 month(s)											
1 (frias 2021)	RCT	serious[1]	not serious	NA[5]	serious[8]	NA	1408	468	MD -0.33 (-0.51, -0.16)	MD 0.33 lower (0.51 lower to 0.16 lower)	low
hba1c change (mmol/mol, lower values are better, change scores) at end of follow up Mean follow-up: 6.5 month(s)											
1 (heise 2022)	RCT	serious[1]	not serious	NA[5]	serious[9]	NA	41	43	MD -4.50 (-6.99, -2.01)	MD 4.50 lower (6.99 lower to 2.01 lower)	low
weight change (kg, lower values are better, mean difference) at end of follow up Mean follow-up: 8.4 month(s)											
2	RCT	serious[1]	not serious	very serious[10]	not serious	NA	1449	511	MD -3.82 (-5.24, -2.41)	MD 3.82 lower (5.24 lower to 2.41 lower)	very low

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

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

3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.79 (0.8-0.9 = serious, <0.8 = very serious).

4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.74 (0.8-0.9 = serious, <0.8 = very serious).

5. Only one study so no inconsistency

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

7. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.38 (0.8-0.9 = serious, <0.8 = very serious).

8. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

9. 95% confidence intervals cross one end of the defined MIDs (-5.50, 5.50)

10. I2 > 75%

L.1.5 SGLT2 inhibitors

L.1.5.1 Adding canagliflozin compared to adding placebo

Table 42: 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 Mean follow-up: 9.9 month(s)											
6	RCT	very serious[1]	not serious	serious[2]	very serious[3]	NA	3/1930	0/867	RD 0.00 (-0.00, 0.01)	2 more per 1000 (3 fewer to 6 more)	very low
all-cause mortality at end of follow up Mean follow-up: 43 month(s)											
1 (mahaffey 2018)	RCT	not serious	not serious	NA[4]	serious[5]	NA	5795	4347	HR 0.87 (0.75, 1.01)	Not estimable	moderate
cardiovascular mortality at end of follow up Mean follow-up: 10.7 month(s)											

5	RCT	very serious[1]	not serious	serious[2]	very serious[6]	NA	2/1195	0/684	RD 0.00 (-0.00, 0.01)	2 more per 1000 (4 fewer to 7 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 43 month(s)											
1 (mahaffey 2018)	RCT	not serious	not serious	NA[4]	serious[5]	NA	5795	4347	HR 0.87 (0.71, 1.06)	Not estimable	moderate
3-point mace at end of follow up Mean follow-up: 43 month(s)											
1 (mahaffey 2018)	RCT	not serious	not serious	NA[4]	serious[5]	NA	5795	4347	HR 0.85 (0.75, 0.97)	Not estimable	moderate
non-fatal stroke at end of follow up Mean follow-up: 43 month(s)											
1 (mahaffey 2018)	RCT	not serious	not serious	NA[4]	serious[5]	NA	5795	4347	HR 0.90 (0.71, 1.15)	Not estimable	moderate
non-fatal myocardial infaRCTion at end of follow up Mean follow-up: 43 month(s)											
1 (mahaffey 2018)	RCT	not serious	not serious	NA[4]	serious[5]	NA	5795	4347	HR 0.85 (0.69, 1.05)	Not estimable	moderate
hospitalisation for heart failure at end of follow up Mean follow-up: 43 month(s)											
1 (mahaffey 2018)	RCT	not serious	not serious	NA[4]	serious[5]	NA	5795	4347	HR 0.67 (0.52, 0.87)	Not estimable	moderate
persistent signs of worsening kidney disease at end of follow up Mean follow-up: 43 month(s)											

1 (mahaffey 2018)	RCT	not serious	not serious	NA[4]	not serious	NA	5795	4347	HR 0.73 (0.67, 0.79)	Not estimable	high
development of end stage kidney disease at end of follow up Mean follow-up: 43 month(s)											
1 (mahaffey 2018)	RCT	not serious	not serious	NA[4]	very serious [7]	NA	5795	4347	HR 0.77 (0.30, 1.97)	Not estimable	low
cardiac arrhythmia at end of follow up Mean follow-up: 43 month(s)											
1 (mahaffey 2018)	RCT	not serious	not serious	NA[4]	serious [5]	NA	125/5795	84/4347	RR 1.12 (0.85, 1.47)	2 more per 1000 (3 fewer to 9 more)	moderate
cardiac arrhythmia at end of follow up Mean follow-up: 43 month(s)											
1 (mahaffey 2018)	RCT	not serious	not serious	NA[4]	serious [5]	NA	5795	4347	HR 0.84 (0.64, 1.12)	Not estimable	moderate
diabetic ketoacidosis at end of follow up Mean follow-up: 5.8 month(s)											
2	RCT	very serious[1]	not serious	not serious	not serious	NA	0/178	0/176	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (16 fewer to 16 more)	low
diabetic ketoacidosis at end of follow up Mean follow-up: 43 month(s)											
1 (mahaffey 2018)	RCT	not serious	not serious	NA[4]	very serious [7]	NA	1447	2039	HR 1.57 (0.40, 6.16)	Not estimable	low
hypoglycaemia episodes at end of follow up Mean follow-up: 11.9 month(s)											
4	RCT	very serious[1]	not serious	serious [2]	not serious	NA	205/968	73/569	RD 0.04 (-0.03, 0.12)	45 more per 1000	very low

										(32 fewer to 121 more)	
hypoglycaemia episodes at end of follow up Mean follow-up: 43 month(s)											
1 (mahaffey 2018)	RCT	not serious	not serious	NA[4]	very serious[7]	NA	1447	2039	HR 1.04 (0.78, 1.39)	Not estimable	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 14 month(s)											
3	RCT	serious[8]	serious[9]	serious[2]	very serious[10]	NA	13/898	9/501	RD -0.01 (-0.02, 0.01)	5 fewer per 1000 (20 fewer to 9 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 12.7 month(s)											
8	RCT	very serious[1]	not serious	very serious[11]	not serious	NA	7672	5152	MD -0.71 (-0.87, -0.54)	MD 0.71 lower (0.87 lower to 0.54 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12.1 month(s)											
7	RCT	very serious[1]	not serious	very serious[11]	serious[12]	NA	7253	4991	MD -2.16 (-2.67, -1.65)	MD 2.16 lower (2.67 lower to 1.65 lower)	very low
weight change (%, lower values are better, change scores) Mean follow-up: 24 month(s)											

1 (bode 2013)	RCT	serious[8]	not serious	NA[4]	serious[13]	NA	425	170	MD -2.93 (-3.89, -1.97)	MD 2.93 lower (3.89 lower to 1.97 lower)	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. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.55 (0.8-0.9 = serious, <0.8 = very serious).

4. Only one study so no inconsistency

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

6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.43 (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. >33.3% of the studies in the meta-analysis were at moderate risk of bias

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

10. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.11 (0.8-0.9 = serious, <0.8 = very serious).

11. I2 > 75%

12. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

13. 95% confidence intervals cross one end of the defined MIDs (-3.00, 3.00)

L.1.5.2 Adding canagliflozin compared to adding sitagliptin

Table 43: Clinical evidence profile: Adding canagliflozin 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
all-cause mortality at end of follow up Mean follow-up: 12 month(s)											
2	RCT	very serious[1]	not serious	serious[2]	very serious[3]	NA	3/1112	1/744	PETO OR 2.03 (0.27, 15.26)	1 more per 1000 (3 fewer to 5 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)											
1 (schernthaner 2013)	RCT	very serious[1]	not serious	NA[4]	very serious[3]	NA	2/377	0/378	PETO OR 2.03 (0.27, 15.26)	5 more per 1000 (2 fewer to 13 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 12 month(s)											
2	RCT	very serious[1]	not serious	serious[5]	serious[6]	NA	213/1112	169/744	RR 1.22 (0.81, 1.86)	51 more per 1000 (44 fewer to 196 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											
2	RCT	very serious[1]	not serious	not serious	very serious[3]	NA	16/1112	14/744	RR 1.10 (0.54, 2.21)	2 more per 1000 (9 fewer to 23 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
2	RCT	very serious[1]	not serious	very serious[7]	serious[8]	NA	1102	732	MD -0.22 (-0.51, 0.07)	MD 0.22 lower (0.51 lower to 0.07 higher)	very low

weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
2	RCT	not serious	not serious	not serious	serious[9]	NA	1102	733	MD -2.31 (-2.77, -1.86)	MD 2.31 lower (2.77 lower to 1.86 lower)	moderate

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 both ends of the defined MIDs (0.80, 1.25)

4. Only one study so no inconsistency

5. I2 between 50% and 75%

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

7. I2 > 75%

8. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

9. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

L.1.5.3 Adding canagliflozin compared to adding semaglutide

Table 44: Clinical evidence profile: Adding canagliflozin compared to adding semaglutide

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: 12 month(s)											
1 (lingvay 2019)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	0/394	1/392	PETO OR 0.13 (0.00, 6.79)	3 fewer per 1000 (8 fewer to 2 more)	low

cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)											
1 (lingvay 2019)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	0/394	1/392	PETO OR 0.13 (0.00, 6.79)	3 fewer per 1000 (8 fewer to 2 more)	low
acute kidney injury at end of follow up Mean follow-up: 12 month(s)											
1 (lingvay 2019)	RCT	not serious	not serious	NA[1]	serious[3]	NA	0/394	4/392	PETO OR 0.13 (0.02, 0.95)	10 fewer per 1000 (20 fewer to 0 more)	moderate
hypoglycaemia episodes at end of follow up Mean follow-up: 12 month(s)											
1 (lingvay 2019)	RCT	not serious	not serious	NA[1]	serious[3]	NA	32/394	53/392	RR 0.60 (0.40, 0.91)	54 fewer per 1000 (82 fewer to 12 fewer)	moderate
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											
1 (lingvay 2019)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	0/394	1/392	PETO OR 0.13 (0.00, 6.79)	3 fewer per 1000 (8 fewer to 2 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (lingvay 2019)	RCT	not serious	not serious	NA[1]	serious[4]	NA	394	394	MD 0.50 (0.38, 0.62)	MD 0.50 higher (0.38 higher to 0.62 higher)	moderate

weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (lingvay 2019)	RCT	not serious	not serious	NA[1]	not serious	NA	394	394	MD 1.10 (0.41, 1.79)	MD 1.10 higher (0.41 higher to 1.79 higher)	high

1. Only one study so no inconsistency

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

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)

L.1.5.4 Adding dapagliflozin compared to adding placebo

Table 45: 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
health-related quality of life - overall (eq-5d, -0.59-1.0, higher values are better, change scores) at end of follow up Mean follow-up: 17.8 month(s)											
2	RCT	serious[1]	not serious	not serious	very serious[2]	NA	176	178	MD 0.00 (-0.03, 0.04)	MD 0.00 higher (0.03 lower to 0.04 higher)	very low
all-cause mortality at end of follow up Mean follow-up: 17.2 month(s)											

11	RCT	serious[1]	not serious	serious[3]	not serious	NA	540/11353	572/10061	RD -0.00 (-0.01, 0.00)	4 fewer per 1000 (10 fewer to 3 more)	low
all-cause mortality at end of follow up Mean follow-up: 50.4 month(s)											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[4]	not serious	NA	8582	8578	HR 0.98 (0.82, 1.17)	Not estimable	moderate
cardiovascular mortality at end of follow up Mean follow-up: 18.9 month(s)											
7	RCT	serious[1]	not serious	serious[3]	very serious[5]	NA	252/10596	251/9445	RD -0.00 (-0.00, 0.00)	0 fewer per 1000 (5 fewer to 4 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 50.4 month(s)											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[4]	not serious	NA	8582	8578	HR 0.92 (0.82, 1.04)	Not estimable	moderate
3-point mace at end of follow up Mean follow-up: 50.4 month(s)											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[4]	not serious	NA	756/8582	803/8578	RR 0.94 (0.86, 1.03)	6 fewer per 1000 (13 fewer to 3 more)	moderate
3-point mace at end of follow up Mean follow-up: 50.4 month(s)											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[4]	not serious	NA	8582	8578	HR 0.93 (0.84, 1.03)	Not estimable	moderate
non-fatal stroke at end of follow up Mean follow-up: 30.8 month(s)											
2	RCT	serious[1]	not serious	serious[3]	not serious	NA	236/9032	231/8724	PETO OR 1.02 (0.85, 1.23)	0 fewer per 1000 (5 fewer to 4 more)	low

non-fatal stroke at end of follow up Mean follow-up: 50.4 month(s)											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[4]	not serious	NA	8582	8578	HR 1.01 (0.84, 1.21)	Not estimable	moderate
non-fatal myocardial infarction at end of follow up Mean follow-up: 50.4 month(s)											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[4]	serious[6]	NA	393/8582	441/8578	RR 0.89 (0.78, 1.02)	6 fewer per 1000 (11 fewer to 1 more)	low
non-fatal myocardial infarction at end of follow up Mean follow-up: 50.4 month(s)											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[4]	serious[6]	NA	8582	8578	HR 0.89 (0.77, 1.02)	Not estimable	low
unstable angina at end of follow up Mean follow-up: 50.4 month(s)											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[4]	not serious	NA	243/8582	238/8578	RR 1.02 (0.86, 1.22)	1 more per 1000 (4 fewer to 6 more)	moderate
hospitalisation for heart failure at end of follow up Mean follow-up: 50.4 month(s)											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[4]	serious[6]	NA	212/8582	286/8578	RR 0.74 (0.62, 0.88)	9 fewer per 1000 (13 fewer to 4 fewer)	low
hospitalisation for heart failure at end of follow up Mean follow-up: 50.4 month(s)											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[4]	serious[6]	NA	8582	8578	HR 0.73 (0.61, 0.88)	Not estimable	low
acute kidney injury at end of follow up Mean follow-up: 50.4 month(s)											

1 (wiviott 2019)	RCT	serious[1]	not serious	NA[4]	serious[6]	NA	125/8582	175/8578	RR 0.71 (0.57, 0.90)	6 fewer per 1000 (9 fewer to 2 fewer)	low
acute kidney injury at end of follow up Mean follow-up: 50.4 month(s)											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[4]	serious[6]	NA	8582	8578	HR 0.69 (0.55, 0.87)	Not estimable	low
persistent signs of worsening kidney disease at end of follow up Mean follow-up: 27.2 month(s)											
4	RCT	serious[1]	not serious	not serious	not serious	NA	149/10051	230/9058	RR 0.57 (0.46, 0.71)	11 fewer per 1000 (14 fewer to 7 fewer)	moderate
persistent signs of worsening kidney disease at end of follow up Mean follow-up: 50.4 month(s)											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[4]	not serious	NA	8582	8578	HR 0.54 (0.43, 0.67)	Not estimable	moderate
development of end stage kidney disease at end of follow up Mean follow-up: 20.5 month(s)											
3	RCT	serious[1]	not serious	serious[3]	not serious	NA	7/9018	20/8856	RD -0.00 (-0.00, -0.00)	1 fewer per 1000 (3 fewer to 0 more)	low
development of end stage kidney disease at end of follow up Mean follow-up: 50.4 month(s)											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[4]	not serious	NA	8582	8578	HR 0.31 (0.13, 0.78)	Not estimable	moderate
death from renal causes at end of follow up Mean follow-up: 50.4 month(s)											

1 (wiviott 2019)	RCT	serious[1]	not serious	NA[4]	very serious[7]	NA	10/8582	6/8578	PETO OR 1.65 (0.62, 4.39)	0 more per 1000 (0 more to 1 more)	very low
death from renal causes at end of follow up Mean follow-up: 50.4 month(s)											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[4]	very serious[7]	NA	8582	8578	HR 0.60 (0.22, 1.65)	Not estimable	very low
cardiac arrhythmia at end of follow up Mean follow-up: 50.4 month(s)											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[4]	serious[6]	NA	94/8582	121/8578	RR 0.78 (0.59, 1.01)	3 fewer per 1000 (6 fewer to 0 more)	low
diabetic ketoacidosis at end of follow up Mean follow-up: 22.6 month(s)											
3	RCT	serious[1]	not serious	serious[3]	not serious	NA	27/8753	12/8745	RD 0.00 (0.00, 0.00)	2 more per 1000 (0 more to 3 more)	low
diabetic ketoacidosis at end of follow up Mean follow-up: 50.4 month(s)											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[4]	serious[6]	NA	8582	8578	HR 2.18 (1.10, 4.30)	Not estimable	low
progression of liver disease at end of follow up Mean follow-up: 50.4 month(s)											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[4]	very serious[7]	NA	82/8582	87/8578	PETO OR 0.94 (0.70, 1.27)	1 fewer per 1000 (4 fewer to 2 more)	very low
progression of liver disease at end of follow up Mean follow-up: 50.4 month(s)											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[4]	serious[6]	NA	8582	8578	HR 0.92 (0.68, 1.25)	Not estimable	low

hypoglycaemia episodes at end of follow up Mean follow-up: 13.7 month(s)											
11	RCT	serious[1]	not serious	serious[3]	not serious	NA	501/2803	181/1517	RD 0.01 (-0.01, 0.03)	13 more per 1000 (8 fewer to 34 more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 17.2 month(s)											
11	RCT	serious[1]	not serious	serious[3]	not serious	NA	62/11353	84/10061	RD -0.00 (-0.00, 0.00)	2 fewer per 1000 (5 fewer to 0 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 15.8 month(s)											
12	RCT	serious[1]	not serious	very serious[8]	serious[9]	NA	10903	9811	MD -0.54 (-0.62, -0.45)	MD 0.54 lower (0.62 lower to 0.45 lower)	very low
hba1c change (mmol/mol, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (brown 2020)	RCT	not serious	not serious	NA[4]	serious[10]	NA	32	34	MD -5.49 (-10.13, -0.85)	MD 5.49 lower (10.13 lower to 0.85 lower)	moderate
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 14.5 month(s)											
13	RCT	very serious[11]	not serious	serious[12]	not serious	NA	10679	9867	MD -1.80 (-2.12, -1.49)	MD 1.80 lower (2.12 lower to 1.49 lower)	very low

bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 8.8 month(s)											
2	RCT	not serious	not serious	serious[12]	very serious[13]	NA	82	84	MD -0.45 (-2.85, 1.94)	MD 0.45 lower (2.85 lower to 1.94 higher)	very low

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

2. 95% confidence intervals cross both ends of the defined MIDs (-0.03, 0.03)

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

4. Only one study so no inconsistency

5. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.43 (0.8-0.9 = serious, <0.8 = very serious).

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. I2 > 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 (-5.50, 5.50)

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

12. I2 between 50% and 75%

13. 95% confidence intervals cross both ends of the defined MIDs (-0.80, 0.80)

L.1.5.5 Adding dapagliflozin compared to adding exenatide

Table 46: Clinical evidence profile: Adding dapagliflozin compared to adding exenatide

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: 24 month(s)											
1 (frias 2016)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	2/233	1/230	PETO OR 1.93 (0.20, 18.63)	4 more per 1000 (10 fewer to 19 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 24 month(s)											
1 (frias 2016)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	1/233	1/230	PETO OR 0.99 (0.06, 15.83)	0 fewer per 1000 (12 fewer to 12 more)	very low
acute kidney injury at end of follow up Mean follow-up: 24 month(s)											
1 (frias 2016)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	3/233	2/230	RR 1.48 (0.25, 8.78)	4 more per 1000 (15 fewer to 23 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 24 month(s)											
1 (frias 2016)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	1/233	0/230	PETO OR 7.29 (0.14, 367.65)	4 more per 1000 (4 fewer to 13 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 24 month(s)											

1 (frias 2016)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/233	0/230	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 24 month(s)											
1 (frias 2016)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	230	227	MD 0.23 (-0.10, 0.56)	MD 0.23 higher (0.10 lower to 0.56 higher)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 24 month(s)											
1 (frias 2016)	RCT	very serious[1]	not serious	NA[2]	serious[5]	NA	230	227	MD -2.22 (-3.55, -0.89)	MD 2.22 lower (3.55 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 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 (-2.40, 2.40)

L.1.5.6 Adding dapagliflozin compared to adding liraglutide

Table 47: Clinical evidence profile: Adding dapagliflozin compared to adding liraglutide

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: 5.5 month(s)											
1 (jiang 2021b)	RCT	very serious[1]	serious[2]	NA[3]	serious[4]	NA	0/79	0/77	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (25 fewer to 25 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 5.5 month(s)											
1 (jiang 2021b)	RCT	very serious[1]	serious[2]	NA[3]	serious[4]	NA	0/79	0/77	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (25 fewer to 25 more)	very low
non-fatal myocardial infarction at end of follow up Mean follow-up: 5.5 month(s)											
1 (hao 2022)	RCT	very serious[1]	not serious	NA[3]	serious[4]	NA	0/166	0/143	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (13 fewer to 13 more)	very low
unstable angina at end of follow up Mean follow-up: 5.5 month(s)											
1 (hao 2022)	RCT	very serious[1]	not serious	NA[3]	very serious[5]	NA	2/166	2/143	RR 0.86 (0.12, 6.04)	2 fewer per 1000 (12 fewer to 70 more)	very low
hospitalisation for heart failure at end of follow up Mean follow-up: 5.5 month(s)											
1 (hao 2022)	RCT	very serious[1]	not serious	NA[3]	serious[4]	NA	0/166	0/143	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (13 fewer to 13 more)	very low
diabetic ketoacidosis at end of follow up Mean follow-up: 5.5 month(s)											

1 (jiang 2021b)	RCT	very serious[1]	serious[2]	NA[3]	serious[4]	NA	0/79	0/77	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (25 fewer to 25 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 5.5 month(s)											
1 (hao 2022)	RCT	very serious[1]	not serious	NA[3]	very serious[5]	NA	29/166	21/143	RR 1.19 (0.71, 1.99)	28 more per 1000 (42 fewer to 146 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.5 month(s)											
2	RCT	very serious[1]	not serious	not serious	not serious	NA	0/245	0/220	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
1 (hao 2022)	RCT	very serious[1]	not serious	NA[3]	serious[6]	NA	166	143	MD 0.36 (-0.01, 0.73)	MD 0.36 higher (0.01 lower to 0.73 higher)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
2	RCT	very serious[1]	not serious	not serious	not serious	NA	245	220	MD -0.24 (-1.92, 1.43)	MD 0.24 lower (1.92 lower to 1.43 higher)	low

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

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

3. Only one study so no inconsistency

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

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

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

L.1.5.7 Adding dapagliflozin compared to adding saxagliptin

Table 48: Clinical evidence profile: Adding dapagliflozin compared to adding saxagliptin

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: 5.5 month(s)											
2	RCT	not serious	not serious	serious[1]	very serious[2]	NA	2/472	0/471	RD 0.00 (-0.00, 0.01)	4 more per 1000 (4 fewer to 13 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 5.5 month(s)											
2	RCT	not serious	not serious	serious[1]	very serious[2]	NA	2/472	0/471	RD 0.00 (-0.00, 0.01)	4 more per 1000 (4 fewer to 13 more)	very low
persistent signs of worsening kidney disease at end of follow up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2015a)	RCT	serious[3]	not serious	NA[4]	not serious	NA	0/179	0/176	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (11 fewer to 11 more)	moderate
diabetic ketoacidosis at end of follow up Mean follow-up: 5.5 month(s)											

1 (rosenstock 2019d)	RCT	not serious	not serious	NA[4]	not serious	NA	0/293	0/295	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	high
hypoglycaemia episodes at end of follow up Mean follow-up: 5.5 month(s)											
2	RCT	not serious	not serious	not serious	very serious[5]	NA	2/472	5/471	PETO OR 0.42 (0.10, 1.87)	6 fewer per 1000 (17 fewer to 5 more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.5 month(s)											
2	RCT	not serious	not serious	serious [1]	very serious[6]	NA	0/472	1/471	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (9 fewer to 5 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
2	RCT	not serious	not serious	very serious [7]	not serious	NA	431	431	MD -0.12 (-0.50, 0.25)	MD 0.12 lower (0.50 lower to 0.25 higher)	low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2015a)	RCT	serious[3]	not serious	NA[4]	serious[8]	NA	152	145	MD -2.40 (-3.10, -1.70)	MD 2.40 lower (3.10 lower to 1.70 lower)	low

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

2. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.52 (0.8-0.9 = serious, <0.8 = very serious).

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

4. Only one study so no inconsistency

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

6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.29 (0.8-0.9 = serious, <0.8 = very serious).

7. I2 > 75%

8. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

L.1.5.8 Adding dapagliflozin compared to adding sitagliptin

Table 49: Clinical evidence profile: Adding dapagliflozin 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
all-cause mortality at end of follow up Mean follow-up: 5.5 month(s)											
1 (scott 2018)	RCT	not serious	not serious	NA[1]	not serious	NA	0/306	0/307	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	high
cardiovascular mortality at end of follow up Mean follow-up: 5.5 month(s)											
1 (scott 2018)	RCT	not serious	not serious	NA[1]	not serious	NA	0/306	0/307	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	high
hospitalisation for heart failure at end of follow up											

Mean follow-up: 24 month(s)											
1 (hong 2023)	RCT	serious[2]	not serious	NA[1]	very serious[3]	NA	0/26	0/26	RD 0.00 (-0.07, 0.07)	0 fewer per 1000 (72 fewer to 72 more)	very low
diabetic ketoacidosis at end of follow up Mean follow-up: 5.5 month(s)											
1 (lee 2022)	RCT	very serious[4]	not serious	NA[1]	very serious[3]	NA	0/30	0/30	RD 0.00 (-0.06, 0.06)	0 fewer per 1000 (63 fewer to 63 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 14.8 month(s)											
2	RCT	not serious	not serious	not serious	very serious[5]	NA	20/332	21/333	RR 0.95 (0.53, 1.72)	3 fewer per 1000 (30 fewer to 46 more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 14.8 month(s)											
2	RCT	not serious	not serious	not serious	very serious[5]	NA	3/332	2/333	PETO OR 1.50 (0.26, 8.74)	3 more per 1000 (10 fewer to 16 more)	low
hba1c change (%, lower values are better, change and final scores) at end of follow up Mean follow-up: 11.7 month(s)											
3	RCT	not serious	not serious	not serious	not serious	NA	361	362	MD 0.05 (-0.21, 0.31)	MD 0.05 higher (0.21 lower to 0.31 higher)	high
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											

1 (lee 2022)	RCT	very serious[4]	not serious	NA[1]	serious[6]	NA	30	30	MD -1.59 (-2.70, -0.48)	MD 1.59 lower (2.70 lower to 0.48 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
1 (lee 2022)	RCT	very serious[4]	not serious	NA[1]	serious[7]	NA	30	30	MD -1.59 (-2.70, -0.48)	MD 1.59 lower (2.70 lower to 0.48 lower)	very low

1. Only one study so no inconsistency

2. >33.3% of the studies in the meta-analysis were at moderate risk of bias

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

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

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

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)

L.1.5.9 Adding empagliflozin compared to adding placebo

Table 50: 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

health-related quality of life - overall (eq-5d-5l, higher values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (yabe 2023)	RCT	not serious	not serious	NA[1]	serious[2]	NA	65	64	MD 0.05 (0.01, 0.09)	MD 0.05 higher (0.01 higher to 0.09 higher)	moderate
all-cause mortality at end of follow up Mean follow-up: 13.1 month(s)											
9	RCT	very serious[3]	not serious	serious[4]	very serious[5]	NA	7/2447	3/1295	RD 0.00 (-0.00, 0.01)	1 more per 1000 (4 fewer to 5 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 11.6 month(s)											
5	RCT	very serious[3]	not serious	serious[4]	very serious[6]	NA	2/1356	0/711	RD 0.00 (-0.00, 0.01)	1 more per 1000 (4 fewer to 7 more)	very low
non-fatal stroke at end of follow up Mean follow-up: 12 month(s)											
1 (kawamori 2018)	RCT	not serious	not serious	NA[1]	very serious[7]	NA	0/182	1/93	PETO OR 0.05 (0.00, 3.27)	11 fewer per 1000 (32 fewer to 10 more)	low
unstable angina at end of follow up Mean follow-up: 12 month(s)											
1 (sone 2019)	RCT	not serious	not serious	NA[1]	very serious[7]	NA	0/176	1/90	PETO OR 0.05 (0.00, 3.28)	11 fewer per 1000 (33 fewer to 11 more)	low
hospitalisation for heart failure at end of follow up Mean follow-up: 12 month(s)											

1 (kawamori 2018)	RCT	not serious	not serious	NA[1]	serious[8]	NA	0/182	0/93	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (17 fewer to 17 more)	moderate
acute kidney injury at end of follow up Mean follow-up: 8.8 month(s)											
2	RCT	not serious	not serious	serious[4]	very serious[9]	NA	3/328	0/166	RD 0.01 (-0.01, 0.03)	9 more per 1000 (8 fewer to 26 more)	very low
persistent signs of worsening kidney disease at end of follow up Mean follow-up: 8.9 month(s)											
2	RCT	not serious	not serious	not serious	serious[8]	NA	0/145	0/141	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (19 fewer to 19 more)	moderate
diabetic ketoacidosis at end of follow up Mean follow-up: 10.1 month(s)											
7	RCT	not serious	not serious	serious[4]	very serious[10]	NA	0/1195	1/677	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (9 fewer to 5 more)	very low
progression of liver disease at end of follow up Mean follow-up: 12 month(s)											
1 (yabe 2023)	RCT	not serious	not serious	NA[1]	very serious[7]	NA	2/65	0/64	PETO OR 7.39 (0.46, 119.47)	31 more per 1000 (11 fewer to 73 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 11.7 month(s)											
12	RCT	not serious	not serious	serious[4]	not serious	NA	517/2895	247/1581	RR 1.08 (0.96, 1.22)	13 more per 1000 (7 fewer to 34 more)	moderate
severe hypoglycaemic episodes at end of follow up											

Mean follow-up: 11.8 month(s)											
9	RCT	very serious[3]	not serious	serious[4]	very serious[5]	NA	9/2260	4/1203	RD 0.00 (-0.00, 0.01)	0 more per 1000 (5 fewer to 6 more)	very low
hba1c change (%, lower values are better, change scores and final values) at end of follow up Mean follow-up: 11.3 month(s)											
14	RCT	not serious	not serious	very serious[11]	serious[12]	NA	2471	1314	MD -0.74 (-0.99, -0.49)	MD 0.74 lower (0.99 lower to 0.49 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 10.6 month(s)											
14	RCT	not serious	not serious	very serious[11]	serious[13]	NA	2526	1340	MD -2.22 (-2.62, -1.81)	MD 2.22 lower (2.62 lower to 1.81 lower)	very low
bmi change (kg/m2, lower values are better, change scores and final values) at end of follow up Mean follow-up: 8.8 month(s)											
2	RCT	not serious	not serious	not serious	serious[14]	NA	100	102	MD -0.58 (-0.92, -0.24)	MD 0.58 lower (0.92 lower to 0.24 lower)	moderate

1. Only one study so no inconsistency

2. 95% confidence intervals cross one end of the defined MIDs (-0.03, 0.03)

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

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 = 0.07 (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 = 0.44 (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. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.

9. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.57 (0.8-0.9 = serious, <0.8 = very serious).

10. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.38 (0.8-0.9 = serious, <0.8 = very serious).

11. I2 > 75%

12. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

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

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

L.1.5.10 Adding empagliflozin compared to adding insulin

Table 51: Clinical evidence profile: Adding empagliflozin 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
hba1c change (%, lower values are better, final scores) at end of follow up Mean follow-up: 12 month(s)											

1 (ikonomidis 2020)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	40	40	MD 0.00 (-0.50, 0.50)	MD 0.00 lower (0.50 lower to 0.50 higher)	very low
weight change (kg, lower values are better, final scores) at end of follow up Mean follow-up: 12 month(s)											
1 (ikonomidis 2020)	RCT	serious[1]	not serious	NA[2]	serious[4]	NA	40	40	MD -2.90 (-7.07, 1.27)	MD 2.90 lower (7.07 lower to 1.27 higher)	low
bmi change (kg/m2, lower values are better, final scores) at end of follow up Mean follow-up: 12 month(s)											
1 (ikonomidis 2020)	RCT	serious[1]	not serious	NA[2]	serious[5]	NA	40	40	MD -1.20 (-2.32, -0.08)	MD 1.20 lower (2.32 lower to 0.08 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 (-0.50, 0.50)

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

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

L.1.5.11 Adding empagliflozin compared to adding linagliptin

Table 52: 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
all-cause mortality at end of follow up Mean follow-up: 5.5 month(s)											

1 (liu 2021)	RCT	not serious	not serious	NA[1]	serious[2]	NA	0/53	0/53	RD 0.00 (-0.04, 0.04)	0 fewer per 1000 (36 fewer to 36 more)	moderate
cardiovascular mortality at end of follow up Mean follow-up: 5.5 month(s)											
1 (liu 2021)	RCT	not serious	not serious	NA[1]	serious[2]	NA	0/53	0/53	RD 0.00 (-0.04, 0.04)	0 fewer per 1000 (36 fewer to 36 more)	moderate
diabetic ketoacidosis at end of follow up Mean follow-up: 5.5 month(s)											
1 (liu 2021)	RCT	not serious	not serious	NA[1]	very serious[3]	NA	1/53	0/53	PETO OR 7.39 (0.15, 372.38)	19 more per 1000 (18 fewer to 56 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 5.5 month(s)											
1 (liu 2021)	RCT	not serious	not serious	NA[1]	very serious[3]	NA	5/53	5/53	RR 1.00 (0.31, 3.25)	0 fewer per 1000 (65 fewer to 213 more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.5 month(s)											
1 (liu 2021)	RCT	not serious	not serious	NA[1]	serious[2]	NA	0/53	0/53	RD 0.00 (-0.04, 0.04)	0 fewer per 1000 (36 fewer to 36 more)	moderate
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
1 (liu 2021)	RCT	not serious	not serious	NA[1]	serious[4]	NA	51	53	MD -0.95 (-1.41, -0.49)	MD 0.95 lower	moderate

										(1.41 lower to 0.49 lower)	
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
1 (liu 2021)	RCT	not serious	not serious	NA[1]	serious[5]	NA	51	53	MD -1.70 (-2.58, -0.82)	MD 1.70 lower (2.58 lower to 0.82 lower)	moderate

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. 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 (-2.40, 2.40)

L.1.5.12 Adding empagliflozin compared to adding liraglutide

Table 53: Clinical evidence profile: Adding empagliflozin compared to adding liraglutide

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.5 month(s)											
1 (nakaguchi 2020)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	0/31	0/30	RD 0.00 (-0.06, 0.06)	0 fewer per 1000 (62 fewer to 62 more)	low
hba1c change (%, lower values are better, change and final scores) at end of follow up											

Mean follow-up: 8.8 month(s)											
2	RCT	not serious	not serious	very serious[3]	serious[4]	NA	71	70	MD 0.46 (-0.41, 1.33)	MD 0.46 higher (0.41 lower to 1.33 higher)	very low
weight change (kg, lower values are better, final scores) at end of follow up Mean follow-up: 8.8 month(s)											
2	RCT	not serious	not serious	not serious	not serious	NA	71	70	MD -0.34 (-1.30, 0.61)	MD 0.34 lower (1.30 lower to 0.61 higher)	high
bmi change (kg/m2, lower values are better, final scores) at end of follow up Mean follow-up: 8.8 month(s)											
2	RCT	not serious	not serious	serious[5]	serious[6]	NA	71	70	MD -0.51 (-1.55, 0.53)	MD 0.51 lower (1.55 lower to 0.53 higher)	low

1. Only one study so no inconsistency

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

3. I2 > 75%

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

5. I2 between 50% and 75%

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

L.1.5.13 Adding empagliflozin compared to adding semaglutide

Table 54: Clinical evidence profile: Adding empagliflozin compared to adding semaglutide

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 mental component (sf36, higher values are better, change scores) at end of follow-up Mean follow-up: 12 month(s)											
1 (rodbard 2019)	RCT	serious[1]	not serious	NA[2]	not serious	NA	409	409	MD -0.20 (-1.33, 0.93)	MD 0.20 lower (1.33 lower to 0.93 higher)	moderate
health-related quality of life - subscale physical component (sf-36, higher values are better, change scores) at end of follow-up Mean follow-up: 12 month(s)											
1 (rodbard 2019)	RCT	serious[1]	not serious	NA[2]	not serious	NA	410	409	MD 1.00 (0.12, 1.88)	MD 1.00 higher (0.12 higher to 1.88 higher)	moderate
all-cause mortality at end of follow up Mean follow-up: 12 month(s)											
1 (rodbard 2019)	RCT	not serious	not serious	NA[2]	very serious[3]	NA	1/409	0/410	PETO OR 7.41 (0.15, 373.30)	2 more per 1000 (2 fewer to 7 more)	low
cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)											
1 (rodbard 2019)	RCT	not serious	not serious	NA[2]	very serious[3]	NA	1/409	0/410	PETO OR 7.41	2 more per 1000	low

									(0.15, 373.30)	(2 fewer to 7 more)	
hospitalisation for heart failure at end of follow up Mean follow-up: 12 month(s)											
1 (rodbard 2019)	RCT	not serious	not serious	NA[2]	very serious[3]	NA	1/409	2/410	PETO OR 0.51 (0.05, 4.95)	2 fewer per 1000 (11 fewer to 6 more)	low
acute kidney injury at end of follow up Mean follow-up: 12 month(s)											
1 (rodbard 2019)	RCT	not serious	not serious	NA[2]	very serious[3]	NA	1/409	2/410	PETO OR 0.51 (0.05, 4.95)	2 fewer per 1000 (11 fewer to 6 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 12 month(s)											
1 (rodbard 2019)	RCT	not serious	not serious	NA[2]	very serious[3]	NA	39/409	45/410	RR 0.87 (0.58, 1.30)	14 fewer per 1000 (46 fewer to 33 more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											
1 (rodbard 2019)	RCT	not serious	not serious	NA[2]	very serious[3]	NA	1/409	1/410	RR 1.00 (0.06, 15.97)	0 more per 1000 (2 fewer to 37 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (rodbard 2019)	RCT	not serious	not serious	NA[2]	not serious	NA	410	411	MD 0.40 (0.30, 0.50)	MD 0.40 higher (0.30 higher to 0.50 higher)	high
weight change (kg, lower values are better, change scores) at end of follow up											

Mean follow-up: 12 month(s)											
1 (rodbard 2019)	RCT	not serious	not serious	NA[2]	not serious	NA	410	411	MD 0.20 (-0.50, 0.90)	MD 0.20 higher (0.50 lower to 0.90 higher)	high
bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (rodbard 2019)	RCT	not serious	not serious	NA[2]	not serious	NA	410	411	MD 0.10 (-0.15, 0.35)	MD 0.10 higher (0.15 lower to 0.35 higher)	high

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)

L.1.5.14 Adding empagliflozin compared to adding sitagliptin

Table 55: 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 (mmol/mol, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)											
1 (nesti 2022)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	22	22	MD -1.70 (-3.20, -0.20)	MD 1.70 lower (3.20 lower to 0.20 lower)	low

weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)											
1 (nesti 2022)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	22	22	MD 0.30 (-4.26, 4.86)	MD 0.30 higher (4.26 lower to 4.86 higher)	very low

1. Largest proportion of 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 (-2.40, 2.40)

L.1.5.15 Adding empagliflozin compared to adding vildagliptin

Table 56: Clinical evidence profile: Adding empagliflozin 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
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
1 (khan 2022)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	53	54	MD -0.15 (-0.61, 0.31)	MD 0.15 lower (0.61 lower to 0.31 higher)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
1 (khan 2022)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	53	54	MD -0.12 (-1.44, 1.20)	MD 0.12 lower (1.44 lower to 1.20 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 (-0.50, 0.50)

L.1.5.16 Adding ertugliflozin compared to adding placebo

Table 57: 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 Mean follow-up: 8 month(s)											
3	RCT	not serious	not serious	not serious	not serious	NA	0/1060	0/529	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (5 fewer to 5 more)	high
cardiovascular mortality at end of follow up Mean follow-up: 8 month(s)											
3	RCT	not serious	not serious	not serious	not serious	NA	0/1060	0/529	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (5 fewer to 5 more)	high
diabetic ketoacidosis at end of follow up Mean follow-up: 12 month(s)											
1 (dagogo-jack 2017)	RCT	not serious	not serious	NA[1]	not serious	NA	0/309	0/153	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (10 fewer to 10 more)	high
hypoglycaemia episodes at end of follow up Mean follow-up: 8 month(s)											

3	RCT	not serious	not serious	not serious	serious[2]	NA	66/1060	20/529	RR 1.65 (1.01, 2.69)	25 more per 1000 (0 more to 64 more)	moderate
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											
1 (dagogo-jack 2017)	RCT	not serious	not serious	NA[1]	very serious[3]	NA	0/309	1/153	PETO OR 0.05 (0.00, 3.14)	7 fewer per 1000 (19 fewer to 6 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 8 month(s)											
3	RCT	not serious	not serious	not serious	not serious	NA	1060	529	MD -0.73 (-0.81, -0.64)	MD 0.73 lower (0.81 lower to 0.64 lower)	high
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 8 month(s)											
2	RCT	not serious	not serious	not serious	not serious	NA	648	320	MD -1.94 (-2.26, -1.62)	MD 1.94 lower (2.26 lower to 1.62 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)

L.1.5.17 Adding ertugliflozin compared to adding sitagliptin

Table 58: Clinical evidence profile: Adding ertugliflozin 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
all-cause mortality at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	1/498	0/247	PETO OR 4.46 (0.07, 286.95)	2 more per 1000 (2 fewer to 6 more)	low
cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	1/498	0/247	PETO OR 4.46 (0.07, 286.95)	2 more per 1000 (2 fewer to 6 more)	low
diabetic ketoacidosis at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RCT	not serious	not serious	NA[1]	not serious	NA	0/498	0/247	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	high
hypoglycaemia episodes at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RCT	very serious[3]	not serious	NA[1]	very serious[2]	NA	15/498	7/247	RR 1.06 (0.44, 2.57)	2 more per 1000 (16 fewer to 45 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											

1 (pratley 2018a)	RCT	very serious[3]	not serious	NA[1]	very serious[2]	NA	2/498	0/247	PETO OR 4.47 (0.24, 85.11)	4 more per 1000 (2 fewer to 10 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RCT	very serious[3]	not serious	NA[1]	not serious	NA	498	247	MD -0.10 (-0.28, 0.08)	MD 0.10 lower (0.28 lower to 0.08 higher)	low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RCT	very serious[3]	not serious	NA[1]	serious[4]	NA	498	247	MD -2.70 (-3.41, -1.99)	MD 2.70 lower (3.41 lower to 1.99 lower)	very low

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

L.1.6 Sulfonylureas

L.1.6.1 Adding gliclazide compared to adding vildagliptin

Table 59: Clinical evidence profile: Adding gliclazide 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 Mean follow-up: 12 month(s)											
2	RCT	serious[1]	not serious	serious[2]	very serious[3]	NA	2/514	1/531	RR 1.70 (0.23, 12.67)	1 more per 1000 (1 fewer to 22 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)											
1 (vianna 2018)	RCT	serious[1]	not serious	NA[4]	very serious[3]	NA	1/21	0/21	PETO OR 7.39 (0.15, 372.38)	48 more per 1000 (43 fewer to 139 more)	very low
non-fatal stroke at end of follow up Mean follow-up: 12 month(s)											
1 (vianna 2018)	RCT	serious[1]	not serious	NA[4]	very serious[3]	NA	0/21	1/21	PETO OR 0.14 (0.00, 6.82)	48 fewer per 1000 (139 fewer to 43 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											
1 (vianna 2018)	RCT	serious[1]	not serious	NA[4]	very serious[5]	NA	0/21	0/21	RD 0.00 (-0.09, 0.09)	0 fewer per 1000 (88 fewer to 88 more)	very low
hypoglycaemia episodes at end of follow up											

Mean follow-up: 12 month(s)											
1 (vianna 2018)	RCT	serious[1]	not serious	NA[4]	serious[5]	NA	7/21	2/21	RR 3.50 (0.82, 14.93)	238 more per 1000 (17 fewer to 1326 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
2	RCT	very serious[6]	not serious	not serious	not serious	NA	414	407	MD -0.07 (-0.23, 0.09)	MD 0.07 lower (0.23 lower to 0.09 higher)	low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 8.8 month(s)											
2	RCT	very serious[6]	not serious	not serious	not serious	NA	512	532	MD 1.22 (0.47, 1.97)	MD 1.22 higher (0.47 higher to 1.97 higher)	low

1. >33.3% of the studies in the meta-analysis were at moderate 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 both ends of the defined MIDs (0.80, 1.25)

4. Only one study so no inconsistency

5. 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. >33.3% of the studies in the meta-analysis were at high risk of bias

L.1.6.2 Adding glimepiride compared to adding placebo

Table 60: Clinical evidence profile: Adding glimepiride 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 - overall health utilities index mark 3 (higher values are better, change scores) at end of follow-up Mean follow-up: 6 month(s)											
1 (roberts 2005)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	82	77	MD 0.03 (-0.02, 0.08)	MD 0.03 higher (0.02 lower to 0.08 higher)	very low
all-cause mortality at end of follow up Mean follow-up: 5.8 month(s)											
2	RCT	very serious[1]	not serious	not serious	serious[4]	NA	0/154	0/146	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (18 fewer to 18 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 5.8 month(s)											
2	RCT	very serious[1]	not serious	not serious	serious[4]	NA	0/154	0/146	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (18 fewer to 18 more)	very low
non-fatal stroke at end of follow up Mean follow-up: 5.5 month(s)											
1 (riddle 1998)	RCT	very serious[1]	not serious	NA[2]	very serious[5]	NA	1/70	0/62	PETO OR 6.59 (0.13, 334.58)	14 more per 1000 (13 fewer to 42 more)	very low
non-fatal myocardial infarction at end of follow up Mean follow-up: 5.8 month(s)											
2	RCT	very serious[1]	not serious	serious[6]	very serious[5]	NA	1/154	3/146	RR 0.41 (0.06, 2.72)	12 fewer per 1000 (19 fewer to 35 more)	very low
death from renal causes at end of follow up Mean follow-up: 24 month(s)											

1 (nauck 2009b)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/242	0/121	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (13 fewer to 13 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 14.9 month(s)											
4	RCT	very serious[1]	not serious	very serious[7]	serious[8]	NA	164/703	23/368	RR 3.75 (1.25, 11.25)	172 more per 1000 (15 more to 641 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 14.9 month(s)											
4	RCT	very serious[1]	not serious	serious[6]	very serious[9]	NA	1/703	1/569	RD -0.00 (-0.01, 0.01)	1 fewer per 1000 (9 fewer to 8 more)	very low
hba1c change (%, lower values are better, change scores and final values) at end of follow up Mean follow-up: 10.6 month(s)											
4	RCT	very serious[1]	not serious	very serious[7]	serious[10]	NA	419	275	MD -0.69 (-1.10, -0.29)	MD 0.69 lower (1.10 lower to 0.29 lower)	very low
weight change (kg, lower values are better, change scores and final values) at end of follow up Mean follow-up: 5.8 month(s)											
2	RCT	very serious[1]	not serious	very serious[7]	very serious[11]	NA	152	139	MD -0.24 (-8.30, 7.81)	MD 0.24 lower (8.30 lower to 7.81 higher)	very low
bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)											
1 (roberts 2005)	RCT	very serious[1]	not serious	NA[2]	serious[12]	NA	82	77	MD 1.09 (0.65, 1.53)	MD 1.09 higher (0.65 higher to 1.53 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 (-0.05, 0.05)

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

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

6. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)7. I2 > 75%

8. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

9. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.04 (0.8-0.9 = serious, <0.8 = very serious).

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

11. 95% confidence intervals cross both ends of the defined MIDs (-2.40, 2.40)

12. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

L.1.6.3 Adding glimepiride compared to adding metformin

Table 61: Clinical evidence profile: Adding glimepiride compared to adding metformin

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 (park 2014)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	20/34	15/33	RR 1.29 (0.81, 2.07)	134 more per 1000 (86 fewer to 485 more)	very low
at night hypoglycaemic episodes at end of follow up Mean follow-up: 5.5 month(s)											
1 (park 2014)	RCT	very serious[1]	not serious	NA[2]	very serious[4]	NA	6/34	3/33	RR 1.94 (0.53, 7.13)	86 more per 1000	very low

										(43 fewer to 557 more)	
severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.5 month(s)											
1 (park 2014)	RCT	very serious[1]	not serious	NA[2]	very serious[5]	NA	0/34	0/33	RD 0.00 (-0.06, 0.06)	0 fewer per 1000 (56 fewer to 56 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
1 (park 2014)	RCT	very serious[1]	not serious	NA[2]	very serious[6]	NA	32	32	MD 0.05 (-0.52, 0.62)	MD 0.05 higher (0.52 lower to 0.62 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 (0.80, 1.25)

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 both ends of the defined MIDs (-0.50, 0.50)

L.1.6.4 Adding glimepiride compared to adding insulin

Table 62: 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
health-realted quality of life - subscale mental component (sf-36, higher values are better, change scores) at end of follow up Mean follow-up: 24 month(s)											
1 (group 2022)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	1222	1209	MD 0.18 (-0.42, 0.78)	MD 0.18 higher (0.42 lower to 0.78 higher)	low
health-realted quality of life - subscale physical component (sf-36, higher values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (group 2022)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	1222	1209	MD 0.00 (-0.55, 0.55)	MD 0.00 lower (0.55 lower to 0.55 higher)	low
all-cause mortality at end of follow up Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	serious[3]	not serious	NA[2]	very serious[4]	NA	43/1251	41/1261	RR 1.06 (0.69, 1.61)	2 more per 1000 (10 fewer to 20 more)	very low
all-cause mortality at end of follow up Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	serious[3]	not serious	NA[2]	very serious[4]	NA	1247	1257	HR 1.04 (0.68, 1.58)	Not estimable	very low
cardiovascular mortality at end of follow up											

Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	serious[3]	not serious	NA[2]	very serious[4]	NA	16/1244	21/1255	RR 0.77 (0.40, 1.47)	4 fewer per 1000 (10 fewer to 8 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	serious[3]	not serious	NA[2]	very serious[4]	NA	1247	1257	HR 0.78 (0.40, 1.48)	Not estimable	very low
3-point mace at end of follow up Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	serious[3]	not serious	NA[2]	very serious[4]	NA	59/1244	65/1255	RR 0.92 (0.65, 1.29)	4 fewer per 1000 (18 fewer to 15 more)	very low
3-point mace at end of follow up Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	serious[3]	not serious	NA[2]	very serious[4]	NA	1247	1257	HR 0.92 (0.65, 1.30)	Not estimable	very low
4-point mace at end of follow up Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	very serious[1]	not serious	NA[2]	very serious[4]	NA	67/1254	71/1263	RR 0.95 (0.69, 1.31)	3 fewer per 1000 (18 fewer to 18 more)	very low
unstable angina at end of follow up Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	very serious[1]	not serious	NA[2]	very serious[4]	NA	12/1254	15/1268	RR 0.81 (0.38, 1.72)	2 fewer per 1000 (7 fewer to 9 more)	very low
hospitalisation for heart failure at end of follow up Mean follow-up: 60 month(s)											

1 (group 2022)	RCT	serious[3]	not serious	NA[2]	very serious[4]	NA	30/1244	26/1255	RR 1.16 (0.69, 1.96)	3 more per 1000 (6 fewer to 20 more)	very low
hospitalisation for heart failure at end of follow up Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	serious[3]	not serious	NA[2]	very serious[4]	NA	1247	1264	HR 1.16 (0.69, 1.96)	Not estimable	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 54 month(s)											
2	RCT	very serious[1]	not serious	not serious	not serious	NA	673/1265	484/1283	RR 1.41 (1.29, 1.54)	155 more per 1000 (110 more to 203 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	1231	1245	HR 1.61 (1.43, 1.81)	Not estimable	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 54 month(s)											
2	RCT	very serious[1]	not serious	serious[5]	very serious[6]	NA	28/1288	16/1301	RD 0.01 (-0.00, 0.02)	9 more per 1000 (1 fewer to 19 more)	very low
hba1c change (%, lower values are better, change scores and final values) at end of follow up Mean follow-up: 35.5 month(s)											
2	RCT	very serious[1]	not serious	not serious	very serious[7]	NA	344	464	MD 0.00 (-0.56, 0.57)	MD 0.00 higher (0.56 lower to 0.57 higher)	very low
weight change (kg, lower values are better, change scores) at end of follow up											

Mean follow-up: 11 month(s)											
1 (moon 2014)	RCT	very serious[1]	not serious	NA[2]	serious[8]	NA	34	38	MD -1.70 (-3.05, -0.35)	MD 1.70 lower (3.05 lower to 0.35 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. >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. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.75 (0.8-0.9 = serious, <0.8 = very serious).

7. 95% confidence intervals cross both ends of the defined MIDs (-0.50, 0.50)

8. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

L.1.6.5 Adding glimepiride compared to adding canagliflozin

Table 63: Clinical evidence profile: Adding glimepiride compared to adding canagliflozin

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: 24 month(s)											
1 (cefalu 2013)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	2/482	2/968	RR 2.01 (0.28, 14.21)	2 more per 1000 (1 fewer to 27 more)	low

cardiovascular mortality at end of follow up Mean follow-up: 24 month(s)											
1 (cefalu 2013)	RCT	not serious	not serious	NA[1]	serious[3]	NA	2/482	0/968	PETO OR 20.30 (1.07, 385.05)	4 more per 1000 (2 fewer to 10 more)	moderate
death from renal causes at end of follow up Mean follow-up: 24 month(s)											
1 (cefalu 2013)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	0/482	1/968	PETO OR 0.22 (0.00, 14.33)	1 fewer per 1000 (3 fewer to 1 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 24 month(s)											
1 (cefalu 2013)	RCT	not serious	not serious	NA[1]	not serious	NA	197/482	71/968	RR 5.57 (4.35, 7.14)	335 more per 1000 (245 more to 451 more)	high
severe hypoglycaemic episodes at end of follow up Mean follow-up: 24 month(s)											
1 (cefalu 2013)	RCT	not serious	not serious	NA[1]	not serious	NA	16/482	4/968	RR 8.03 (2.70, 23.90)	29 more per 1000 (7 more to 95 more)	high
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 24 month(s)											
1 (cefalu 2013,cefalu 2013)	RCT	very serious[4]	not serious	NA[1]	not serious	NA	482	968	MD 0.14 (0.05, 0.22)	MD 0.14 higher (0.05 higher to 0.22 higher)	low

weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 24 month(s)											
1 (cefalu 2013,cefalu 2013)	RCT	very serious[4]	not serious	NA[1]	not serious	NA	482	968	MD 5.15 (4.76, 5.54)	MD 5.15 higher (4.76 higher to 5.54 higher)	low

1. Only one study so no inconsistency

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

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

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

L.1.6.6 Adding glimepiride compared to adding dapagliflozin

Table 64: Clinical evidence profile: Adding glimepiride 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 Mean follow-up: 12 month(s)											
1 (park 2023)	RCT	not serious	not serious	NA[1]	serious[2]	NA	0/61	0/60	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (32 fewer to 32 more)	moderate
cardiovascular mortality at end of follow up											

Mean follow-up: 12 month(s)											
1 (park 2023)	RCT	not serious	not serious	NA[1]	serious[2]	NA	0/61	0/60	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (32 fewer to 32 more)	moderate
hospitalisation for heart failure at end of follow up **Mean follow-up: 12 month(s)**											
1 (muller-wieland 2018)	RCT	not serious	not serious	NA[1]	very serious[3]	NA	1/312	0/313	PETO OR 7.41 (0.15, 373.58)	3 more per 1000 (3 fewer to 9 more)	low
hypoglycaemia episodes at end of follow up **Mean follow-up: 10.2 month(s)**											
3	RCT	not serious	not serious	serious[4]	not serious	NA	22/403	3/404	PETO OR 4.87 (2.18, 10.84)	47 more per 1000 (24 more to 71 more)	moderate
severe hypoglycaemic episodes at end of follow up **Mean follow-up: 12 month(s)**											
1 (muller-wieland 2018)	RCT	not serious	not serious	NA[1]	not serious	NA	0/312	0/313	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	high
hba1c change (%, lower values are better, change scores)											

Mean follow-up: 10.2 month(s)											
3	RCT	not serious	not serious	very serious[5]	serious[6]	NA	394	397	MD 0.14 (-0.29, 0.57)	MD 0.14 higher (0.29 lower to 0.57 higher)	very low
weight change (kg, lower values are better, change score) at end of follow up **Mean follow-up: 10.2 month(s)**											
3	RCT	not serious	not serious	very serious[5]	very serious[7]	NA	397	399	MD 1.59 (-4.00, 7.18)	MD 1.59 higher (4.00 lower to 7.18 higher)	very low
bmi change (kg/m2, lower values are better, change scores) at end of follow up **Mean follow-up: 12 month(s)**											
1 (park 2023)	RCT	not serious	not serious	NA[1]	not serious	NA	56	56	MD 1.37 (1.00, 1.74)	MD 1.37 higher (1.00 higher to 1.74 higher)	high

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

5. I2 > 75%

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

7. 95% confidence intervals cross both ends of the defined MIDs (-2.40, 2.40)

L.1.6.7 Adding glimepiride compared to adding empagliflozin

Table 65: Clinical evidence profile: Adding glimepiride compared to adding empagliflozin

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: 48 month(s)**											
1 (ridderstrale 2014)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	5/780	5/765	RR 0.98 (0.29, 3.37)	0 fewer per 1000 (5 fewer to 16 more)	low
hypoglycaemia episodes at end of follow up **Mean follow-up: 48 month(s)**											
1 (ridderstrale 2014)	RCT	not serious	not serious	NA[1]	not serious	NA	189/780	19/765	RR 9.76 (6.15, 15.47)	217 more per 1000 (128 more to 359 more)	high
hba1c change (%, lower values are better, change scores) at end of follow up **Mean follow-up: 48 month(s)**											
1 (ridderstrale 2014)	RCT	not serious	not serious	NA[1]	not serious	NA	780	765	MD 0.11 (0.03, 0.19)	MD 0.11 higher (0.03 higher to 0.19 higher)	high

weight change (kg, lower values are better, change scores) at end of follow up **Mean follow-up: 48 month(s)**											
1 (ridderstrale 2014)	RCT	not serious	not serious	NA[1]	not serious	NA	780	765	MD 4.61 (4.18, 5.04)	MD 4.61 higher (4.18 higher to 5.04 higher)	high

1. Only one study so no inconsistency

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

L.1.6.8 Adding glimepiride compared to adding ertugliflozin

Table 66: Clinical evidence profile: Adding glimepiride compared to adding ertugliflozin

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: 12 month(s)**											
1 (hollander 2018)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	0/437	6/888	PETO OR 0.22 (0.04, 1.23)	7 fewer per 1000 (12 fewer to 1 fewer)	very low
cardiovascular mortality at end of follow up **Mean follow-up: 12 month(s)**											
1 (hollander 2018)	RCT	very serious[1]	not serious	NA[2]	very serious[4]	NA	0/435	1/880	PETO OR 0.22 (0.00, 14.46)	1 fewer per 1000 (3 fewer to 1 more)	very low
acute kidney injury at end of follow up **Mean follow-up: 12 month(s)**											

1 (hollander 2018)	RCT	very serious[1]	not serious	NA[2]	very serious[4]	NA	0/437	1/888	RR 0.68 (0.03, 16.57)	0 fewer per 1000 (1 fewer to 18 more)	very low
diabetic ketoacidosis at end of follow up Mean follow-up: 12 month(s)											
1 (hollander 2018)	RCT	very serious[1]	not serious	NA[2]	very serious[4]	NA	0/437	1/888	PETO OR 0.22 (0.00, 14.54)	1 fewer per 1000 (3 fewer to 1 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 12 month(s)											
1 (hollander 2018)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	84/437	37/888	RR 4.61 (3.19, 6.67)	151 more per 1000 (91 more to 236 more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											
1 (hollander 2018)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	10/437	2/888	RR 10.16 (2.24, 46.17)	21 more per 1000 (3 more to 102 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (hollander 2018)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	437	888	MD -0.10 (-0.17, -0.03)	MD 0.10 lower (0.17 lower to 0.03 lower)	low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											

1 (hollander 2018)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	437	888	MD 4.10 (3.67, 4.53)	MD 4.10 higher (3.67 higher to 4.53 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)

L.1.6.9 Adding glimepiride compared to adding exenatide

Table 67: Clinical evidence profile: Adding glimepiride compared to adding exenatide

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: 36 month(s)											
1 (gallwitz 2012b)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	5/508	5/511	RR 1.01 (0.29, 3.45)	0 more per 1000 (7 fewer to 24 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 24 month(s)											
2	RCT	not serious	not serious	serious[3]	not serious	NA	341/562	186/568	RR 1.84 (1.62, 2.10)	276 more per 1000 (202 more to 360 more)	high
at night hypoglycaemic episodes at end of follow up Mean follow-up: 36 month(s)											

1 (gallwitz 2012b)	RCT	not serious	not serious	NA[1]	serious 4	NA	82/508	53/511	RR 1.56 (1.13, 2.15)	58 more per 1000 (13 more to 119 more)	moderate
severe hypoglycaemic episodes at end of follow up Mean follow-up: 36 month(s)											
1 (gallwitz 2012b)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	0/508	1/511	PETO OR 0.14 (0.00, 6.86)	2 fewer per 1000 (6 fewer to 2 more)	low
hba1c change (%, lower values are better, change scores and final values) at end of follow up Mean follow-up: 24 month(s)											
2	RCT	not serious	not serious	very serious[5]	not serious	NA	246	234	MD 0.03 (-0.04, 0.10)	MD 0.03 higher (0.04 lower to 0.10 higher)	low
weight change (kg, lower values are better, change scores and final values) at end of follow up Mean follow-up: 24 month(s)											
2	RCT	not serious	not serious	very serious[5]	not serious	NA	560	560	MD -4.03 (-4.61, -3.45)	MD 4.03 lower (4.61 lower to 3.45 lower)	low
bmi change (kg/m2, lower values are better, change scores and final values) at end of follow up Mean follow-up: 24 month(s)											
2	RCT	not serious	not serious	not serious	not serious	NA	560	0	MD 1.79 (1.53, 2.04)	MD 1.79 higher (1.53 higher to 2.04 higher)	high

1. Only one study so no inconsistency

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

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

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

5. I2 > 75%

L.1.6.10 Adding glimepiride compared to adding gliclazide

Table 68: Clinical evidence profile: Adding glimepiride compared to adding gliclazide

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: 5.5 month(s)											
1 (xu 2017)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/549	0/550	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (4 fewer to 4 more)	low
cardiovascular mortality at end of follow up Mean follow-up: 5.5 month(s)											
1 (xu 2017)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/549	0/550	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (4 fewer to 4 more)	low
non-fatal stroke at end of follow up Mean follow-up: 5.5 month(s)											
1 (xu 2017)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/549	0/550	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (4 fewer to 4 more)	low
non-fatal myocardial infaRCTion at end of follow up Mean follow-up: 5.5 month(s)											

1 (xu 2017)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/549	2/550	PETO OR 0.14 (0.01, 2.17)	4 fewer per 1000 (9 fewer to 1 more)	very low
diabetic ketoacidosis at end of follow up Mean follow-up: 5.5 month(s)											
1 (xu 2017)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/549	1/550	PETO OR 0.14 (0.00, 6.83)	2 fewer per 1000 (5 fewer to 2 more)	very low
falls requiring hospitalisation at end of follow-up Mean follow-up: 5.5 month(s)											
1 (xu 2017)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/549	0/550	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (4 fewer to 4 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 5.5 month(s)											
1 (xu 2017)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	49/549	20/550	RR 2.45 (1.48, 4.07)	53 more per 1000 (17 more to 112 more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.5 month(s)											
1 (xu 2017)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	1/549	0/550	RR 3.01 (0.12, 73.62)	0 fewer per 1000 (0 more to 0 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
1 (xu 2017)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	414	418	MD 0.05 (-0.11, 0.21)	MD 0.05 higher (0.11 lower to 0.21 higher)	low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
1 (xu 2017)	RCT	not serious	not serious	NA[2]	not serious	NA	549	550	MD 0.24 (0.05, 0.43)	MD 0.24 higher (0.05 higher to 0.43 higher)	high

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)

L.1.6.11 Adding glimepiride compared to adding linagliptin

Table 69: Clinical evidence profile: Adding glimepiride 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
all-cause mortality at end of follow up Mean follow-up: 49.8 month(s)											
2	RCT	not serious	not serious	not serious	serious[1]	NA	340/3785	312/3799	RR 1.09 (0.95, 1.27)	8 more per 1000 (4 fewer to 22 more)	moderate
all-cause mortality at end of follow up Mean follow-up: 75.6 month(s)											
1 (rosenstock 2019b)	RCT	not serious	not serious	NA[2]	serious[1]	NA	3023	3010	HR 1.10 (0.94, 1.28)	Not estimable	moderate
cardiovascular mortality at end of follow up Mean follow-up: 49.8 month(s)											
2	RCT	not serious	not serious	not serious	not serious	NA	170/3785	171/3799	RR 1.00 (0.81, 1.23)	0 fewer per 1000 (8 fewer to 10 more)	high
cardiovascular mortality at end of follow up Mean follow-up: 75.6 month(s)											
1 (rosenstock 2019b)	RCT	not serious	not serious	NA[2]	not serious	NA	3023	3010	HR 1.00 (0.81, 1.23)	Not estimable	high

4-point mace at end of follow up Mean follow-up: 75.6 month(s)											
1 (rosenstock 2019b)	RCT	not serious	not serious	NA[2]	not serious	NA	401/3010	398/3023	RR 1.01 (0.89, 1.15)	2 more per 1000 (15 fewer to 20 more)	high
4-point mace at end of follow up Mean follow-up: 75.6 month(s)											
1 (rosenstock 2019b)	RCT	not serious	not serious	NA[2]	not serious	NA	3010	3023	HR 1.01 (0.88, 1.16)	Not estimable	high
non-fatal stroke at end of follow up Mean follow-up: 49.8 month(s)											
2	RCT	not serious	not serious	serious[3]	very serious[4]	NA	115/3785	94/3799	RR 1.73 (0.58, 5.14)	18 more per 1000 (10 fewer to 103 more)	very low
non-fatal stroke at end of follow up Mean follow-up: 75.6 month(s)											
1 (rosenstock 2019b)	RCT	not serious	not serious	NA[2]	serious[1]	NA	3010	3023	HR 1.15 (0.87, 1.52)	Not estimable	moderate
non-fatal myocardial infarction at end of follow up Mean follow-up: 24 month(s)											
1 (gallwitz 2012a)	RCT	not serious	not serious	NA[2]	very serious[4]	NA	10/775	6/776	RR 1.67 (0.61, 4.57)	5 more per 1000 (3 fewer to 28 more)	low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 75.6 month(s)											
1 (rosenstock 2019b)	RCT	not serious	not serious	NA[2]	very serious[4]	NA	142	145	HR 0.99 (0.78, 1.26)	Not estimable	low
unstable angina at end of follow up Mean follow-up: 49.8 month(s)											

2	RCT	not serious	not serious	not serious	very serious[4]	NA	59/3785	63/3799	RR 0.94 (0.66, 1.34)	1 fewer per 1000 (6 fewer to 6 more)	low
unstable angina at end of follow-up Mean follow-up: 75.6 month(s)											
1 (rosenstock 2019b)	RCT	not serious	not serious	NA[2]	very serious[4]	NA	56	60	HR 0.93 (0.65, 1.33)	Not estimable	low
hospitalisation for heart failure at end of follow up Mean follow-up: 49.8 month(s)											
2	RCT	not serious	not serious	not serious	serious[1]	NA	94/3785	115/3799	RR 0.82 (0.63, 1.07)	5 fewer per 1000 (11 fewer to 2 more)	moderate
hospitalisation for heart failure at end of follow-up Mean follow-up: 75.6 month(s)											
1 (rosenstock 2019b)	RCT	not serious	not serious	NA[2]	serious[1]	NA	92	112	HR 0.83 (0.63, 1.09)	Not estimable	moderate
falls requiring hospitalisation at end of follow up Mean follow-up: 24 month(s)											
1 (gallwitz 2012a)	RCT	not serious	not serious	NA[2]	very serious[4]	NA	2/775	3/776	RR 0.67 (0.11, 3.98)	1 fewer per 1000 (3 fewer to 12 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 49.8 month(s)											
2	RCT	not serious	not serious	very serious[5]	not serious	NA	1412/3785	378/3799	RR 4.05 (3.00, 5.45)	303 more per 1000 (199 more to 443 more)	low

hypoglycaemia episodes at end of follow up Mean follow-up: 75.6 month(s)											
1 (rosenstock 2019b)	RCT	not serious	not serious	NA[2]	not serious	NA	3010	3023	HR 4.35 (3.85, 4.91)	Not estimable	high
severe hypoglycaemic episodes at end of follow up Mean follow-up: 49.8 month(s)											
2	RCT	not serious	not serious	not serious	not serious	NA	77/3785	11/3799	RR 7.03 (3.74, 13.20)	17 more per 1000 (8 more to 35 more)	high
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 75.6 month(s)											
1 (rosenstock 2019b)	RCT	not serious	not serious	NA[2]	not serious	NA	3010	3023	HR 5.63 (4.76, 6.67)	Not estimable	high
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 49.8 month(s)											
2	RCT	not serious	not serious	very serious[5]	not serious	NA	3765	3787	MD -0.09 (-0.30, 0.11)	MD 0.09 lower (0.30 lower to 0.11 higher)	low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 49.8 month(s)											
2	RCT	not serious	not serious	very serious[5]	serious[6]	NA	3786	3798	MD 2.10 (0.96, 3.24)	MD 2.10 higher (0.96 higher to 3.24 higher)	very low

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

2. Only one study so no inconsistency

3. I2 between 50% and 75%

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

5. I2 > 75%

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

L.1.6.12 Adding glimepiride compared to adding liraglutide

Table 70: Clinical evidence profile: Adding glimepiride compared to adding liraglutide

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 mental component (sf36, higher values are better, change scores) at end of follow up Mean follow-up: 24 month(s)											
1 (group 2022)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	1222	1218	MD 0.33 (-0.25, 0.91)	MD 0.33 higher (0.25 lower to 0.91 higher)	low
health-related quality of life - subscale physical component (sf36, higher values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (group 2022)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	1222	1218	MD -0.89 (-1.44, -0.34)	MD 0.89 lower (1.44 lower to 0.34 lower)	low
all-cause mortality at end of follow up Mean follow-up: 60 month(s)											

1 (group 2022)	RCT	serious[3]	not serious	NA[2]	serious[4]	NA	43/1254	27/1262	RR 1.60 (1.00, 2.58)	13 more per 1000 (0 more to 34 more)	low
all-cause mortality at end of follow up Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	serious[3]	not serious	NA[2]	serious[4]	NA	1254	1262	HR 1.61 (1.00, 2.59)	Not estimable	low
cardiovascular mortality at end of follow up Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	serious[3]	not serious	NA[2]	very serious[5]	NA	16/1247	9/1251	RR 1.78 (0.79, 4.02)	6 more per 1000 (2 fewer to 22 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	serious[3]	not serious	NA[2]	very serious[5]	NA	1247	1251	HR 1.78 (0.79, 4.01)	Not estimable	very low
3-point mace at end of follow up Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	serious[3]	not serious	NA[2]	serious[4]	NA	59/1247	48/1251	RR 1.23 (0.85, 1.79)	9 more per 1000 (6 fewer to 30 more)	low
3-point mace at end of follow-up Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	serious[3]	not serious	NA[2]	serious[4]	NA	1247	1251	HR 1.24 (0.85, 1.81)	Not estimable	low
4-point mace at end of follow-up Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	67/1254	54/1262	RR 1.25 (0.88, 1.77)	11 more per 1000 (5 fewer to 33 more)	very low

hospitalisation for heart failure at end of follow up Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	serious[3]	not serious	NA[2]	serious[4]	NA	30/1244	14/1249	RR 2.15 (1.15, 4.04)	13 more per 1000 (2 more to 34 more)	low
hospitalisation for heart failure at end of follow-up Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	serious[3]	not serious	NA[2]	serious[4]	NA	1254	1262	HR 2.16 (1.14, 4.09)	Not estimable	low
unstable angina at end of follow up Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	very serious[1]	not serious	NA[2]	very serious[5]	NA	12/1254	7/1262	RR 1.73 (0.68, 4.37)	4 more per 1000 (2 fewer to 19 more)	very low
death from renal causes at end of follow up Mean follow-up: 24 month(s)											
1 (nauck 2009b)	RCT	very serious[1]	not serious	NA[2]	very serious[5]	NA	0/242	1/724	PETO OR 0.26 (0.00, 24.26)	1 fewer per 1000 (4 fewer to 1 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 42 month(s)											
2	RCT	very serious[1]	not serious	very serious[6]	very serious[5]	NA	660/1473	344/1957	RR 1.17 (0.32, 4.24)	29 more per 1000 (119 fewer to 569 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	1231	1233	HR 2.64 (2.32, 3.00)	Not estimable	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 42 month(s)											

2	RCT	very serious[1]	not serious	not serious	serious[4]	NA	28/1496	13/1986	RR 2.27 (1.18, 4.37)	8 more per 1000 (1 more to 22 more)	very low
hba1c change (%, lower values are better, change scores and final values) at end of follow up Mean follow-up: 42 month(s)											
2	RCT	very serious[1]	not serious	not serious	not serious	NA	552	1061	MD 0.00 (-0.23, 0.23)	MD 0.00 higher (0.23 lower to 0.23 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. >33.3% of the studies in the meta-analysis were at moderate risk of bias

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

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

6. I2 > 75%

L.1.6.13 Adding glimepiride compared to adding saxagliptin

Table 71: Clinical evidence profile: Adding glimepiride compared to adding saxagliptin

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: 12 month(s)											

1 (schernthaner 2015a)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	1/359	1/359	RR 1.00 (0.06, 15.93)	0 fewer per 1000 (3 fewer to 42 more)	very low
cardiovascular mortality at end of follow up **Mean follow-up: 12 month(s)**											
1 (schernthaner 2015a)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	0/359	1/359	PETO OR 0.14 (0.00, 6.82)	3 fewer per 1000 (8 fewer to 3 more)	very low
non-fatal myocardial infaRCTion at end of follow up **Mean follow-up: 11 month(s)**											
1 (gu 2019)	RCT	not serious	not serious	NA[2]	very serious[3]	NA	1/188	0/191	PETO OR 7.51 (0.15, 378.42)	5 more per 1000 (5 fewer to 16 more)	low
hypoglycaemia episodes at end of follow up **Mean follow-up: 11.5 month(s)**											
2	RCT	serious[1]	not serious	not serious	not serious	NA	149/547	27/550	RR 5.54 (3.74, 8.18)	223 more per 1000 (135 more to 353 more)	moderate
severe hypoglycaemic episodes at end of follow up **Mean follow-up: 11 month(s)**											

1 (gu 2019)	RCT	not serious	not serious	NA[2]	very serious[3]	NA	1/188	1/191	RR 1.02 (0.06, 16.12)	0 more per 1000 (5 fewer to 79 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up **Mean follow-up: 11 month(s)**											
1 (gu 2019)	RCT	not serious	not serious	NA[2]	not serious	NA	187	186	MD -0.06 (-0.23, 0.11)	MD 0.06 lower (0.23 lower to 0.11 higher)	high
weight change (kg, lower values are better, change scores) at end of follow up **Mean follow-up: 11.5 month(s)**											
2	RCT	serious[1]	not serious	not serious	not serious	NA	472	475	MD 1.70 (1.32, 2.08)	MD 1.70 higher (1.32 higher to 2.08 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)

L.1.6.14 Adding glimepiride compared to adding sitagliptin

Table 72: Clinical evidence profile: Adding glimepiride 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

all-cause mortality at end of follow up Mean follow-up: 33.5 month(s)											
2	RCT	serious[1]	not serious	serious[2]	very serious[3]	NA	44/1770	41/1781	RR 1.08 (0.71, 1.64)	2 more per 1000 (7 fewer to 15 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 33.5 month(s)											
2	RCT	serious[1]	not serious	serious[2]	very serious[3]	NA	17/1763	21/1778	RR 0.82 (0.44, 1.54)	2 fewer per 1000 (7 fewer to 6 more)	very low
3-point mace at end of follow up Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	serious[1]	not serious	NA[4]	serious[5]	NA	59/1244	69/1262	RR 0.87 (0.62, 1.22)	7 fewer per 1000 (21 fewer to 12 more)	low
non-fatal stroke at end of follow up Mean follow-up: 5.5 month(s)											
1 (xiao 2016)	RCT	very serious[6]	not serious	NA[4]	very serious[7]	NA	0/18	0/23	RD 0.00 (-0.09, 0.09)	0 fewer per 1000 (92 fewer to 92 more)	very low
non-fatal myocardial infarction at end of follow up Mean follow-up: 5.5 month(s)											
1 (xiao 2016)	RCT	very serious[6]	not serious	NA[4]	very serious[7]	NA	0/18	0/23	RD 0.00 (-0.09, 0.09)	0 fewer per 1000 (92 fewer to 92 more)	very low
hospitalisation for heart failure at end of follow up Mean follow-up: 32.8 month(s)											
2	RCT	serious[1]	not serious	serious[2]	very serious[8]	NA	30/1262	30/1285	RD 0.00 (-0.01, 0.01)	0 more per 1000	very low

										(12 fewer to 12 more)	
hypoglycaemia episodes at end of follow up Mean follow-up: 12.2 month(s)											
3	RCT	not serious	not serious	serious[9]	not serious	NA	146/824	43/1031	RR 4.17 (1.73, 10.03)	132 more per 1000 (30 more to 377 more)	moderate
severe hypoglycaemic episodes at end of follow up Mean follow-up: 24.1 month(s)											
4	RCT	very serious[6]	not serious	serious[2]	not serious	NA	39/2285	11/2299	RR 3.12 (1.59, 6.11)	10 more per 1000 (3 more to 24 more)	very low
hba1c change (%, lower values are better, change scores and final values) at end of follow up Mean follow-up: 6 month(s)											
3	RCT	very serious[6]	not serious	very serious[10]	serious[11]	NA	732	745	MD 0.18 (-0.17, 0.53)	MD 0.18 higher (0.17 lower to 0.53 higher)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)											
3	RCT	very serious[6]	not serious	very serious[10]	serious[12]	NA	739	752	MD 1.52 (0.48, 2.56)	MD 1.52 higher (0.48 higher to 2.56 higher)	very low
bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											

1 (kesavadev 2017)	RCT	very serious 6	not serious	NA[4]	not serious	NA	205	213	MD 0.39 (0.15, 0.63)	MD 0.39 higher (0.15 higher to 0.63 higher)	low

1. >33.3% of the studies in the meta-analysis were at moderate 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 both ends 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 (0.80, 1.25)

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

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

8. 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).

9. I2 between 50% and 75%

10. I2 > 75%

11. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

12. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

L.1.6.15 Adding glimepiride compared to adding vildagliptin

Table 73: Clinical evidence profile: Adding glimepiride 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 Mean follow-up: 9 month(s)											
2	RCT	serious[1]	not serious	not serious	very serious[2]	NA	9/2929	9/2942	RR 1.00 (0.40, 2.53)	0 more per 1000 (2 fewer to 5 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)											
1 (ferrannini 2009)	RCT	very serious[3]	not serious	NA[4]	very serious[2]	NA	1/1383	2/1389	RR 0.50 (0.05, 5.53)	1 fewer per 1000 (1 fewer to 7 more)	very low
cardiac arrhythmia at end of follow up Mean follow-up: 12 month(s)											
1 (ferrannini 2009)	RCT	very serious[3]	not serious	NA[4]	very serious[2]	NA	5/1383	3/1389	RR 1.67 (0.40, 6.99)	1 more per 1000 (1 fewer to 13 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 9 month(s)											
2	RCT	serious[1]	not serious	not serious	not serious	NA	505/2929	58/2942	RR 8.75 (6.70, 11.42)	153 more per 1000 (112 more to 205 more)	moderate
severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.8 month(s)											
2	RCT	serious[1]	not serious	serious[5]	not serious	NA	15/1568	0/1575	RD 0.01 (0.00, 0.01)	10 more per 1000	low

										(4 more to 15 more)	
hba1c change (%, lower values are better, change values and final scores) at end of follow up Mean follow-up: 11.9 month(s)											
4	RCT	very serious[3]	not serious	not serious	not serious	NA	2720	2785	MD -0.13 (-0.21, -0.05)	MD 0.13 lower (0.21 lower to 0.05 lower)	low
weight change (kg, lower values are better, change scores and final values) at end of follow up Mean follow-up: 11.8 month(s)											
3	RCT	very serious[3]	not serious	not serious	not serious	NA	1648	1667	MD 1.50 (1.23, 1.78)	MD 1.50 higher (1.23 higher to 1.78 higher)	low
bmi change (kg/m2, lower values are better, final values) at end of follow up Mean follow-up: 6 month(s)											
1 (derosa 2014a)	RCT	very serious[3]	not serious	NA[4]	serious[6]	NA	70	83	MD 0.60 (0.13, 1.07)	MD 0.60 higher (0.13 higher to 1.07 higher)	very low

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

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. Only one study so no inconsistency

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

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

L.1.6.16 Adding glipizide compared to adding placebo

Table 74: Clinical evidence profile: Adding glipizide 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: 6 month(s)											
1 (wilding 2013b)	RCT	serious[1]	not serious	NA[2]	serious[3]	NA	0/93	0/87	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (22 fewer to 22 more)	low
cardiovascular mortality at end of follow up Mean follow-up: 6 month(s)											
1 (wilding 2013b)	RCT	serious[1]	not serious	NA[2]	serious[3]	NA	0/93	0/87	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (22 fewer to 22 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 6 month(s)											
1 (wilding 2013b)	RCT	serious[1]	not serious	NA[2]	not serious	NA	6/93	0/87	PETO OR 7.32 (1.44, 37.16)	65 more per 1000 (15 more to 115 more)	moderate
severe hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)											
1 (wilding 2013b)	RCT	serious[1]	not serious	NA[2]	serious[4]	NA	1/93	1/87	RR 0.94 (0.06, 14.73)	1 fewer per 1000	low

										(11 fewer to 158 more)	
hba1c change (%, lower values are better, final values) at end of follow up Mean follow-up: 36 month(s)											
1 (camerini-davalos 1994)	RCT	very serious[5]	not serious	NA[2]	serious[4]	NA	34	27	MD -0.90 (-1.78, -0.02)	MD 0.90 lower (1.78 lower to 0.02 lower)	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. 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)

5. >33.3% of the studies in the meta-analysis were at high risk of bias

L.1.6.17 Adding glipizide compared to adding metformin

Table 75: Clinical evidence profile: Adding glipizide compared to adding metformin

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, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (vähätalo 2007)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	15	26	MD 0.50 (-0.34, 1.34)	MD 0.50 higher (0.34 lower to 1.34 higher)	very low

weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (vähätalo 2007)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	15	26	MD 1.30 (-1.35, 3.95)	MD 1.30 higher (1.35 lower to 3.95 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 one end of the defined MIDs (-2.40, 2.40)

L.1.6.18 Adding glipizide compared to adding alogliptin

Table 76: Clinical evidence profile: Adding glipizide compared to adding alogliptin

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: 24 month(s)											
1 (del prato 2014)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	5/869	6/1751	RR 1.68 (0.51, 5.49)	2 more per 1000 (2 fewer to 15 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 24 month(s)											
1 (del prato 2014)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	4/869	4/1751	RR 2.01 (0.51, 8.04)	2 more per 1000	very low

										(1 fewer to 16 more)	
3-point mace at end of follow up Mean follow-up: 24 month(s)											
1 (del prato 2014)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	11/869	14/1751	RR 1.58 (0.72, 3.47)	5 more per 1000 (2 fewer to 20 more)	very low
non-fatal stroke at end of follow up Mean follow-up: 24 month(s)											
1 (del prato 2014)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	3/869	5/1751	RR 1.21 (0.29, 5.05)	1 more per 1000 (2 fewer to 12 more)	very low
non-fatal myocardial infaRCTion at end of follow up Mean follow-up: 24 month(s)											
1 (del prato 2014)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	4/869	5/1751	RR 1.61 (0.43, 5.99)	2 more per 1000 (2 fewer to 14 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 24 month(s)											
1 (del prato 2014)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	202/869	34/1751	RR 11.97 (8.40, 17.06)	213 more per 1000 (144 more to 312 more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 24 month(s)											
1 (del prato 2014)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	5/869	1/1751	RR 10.07 (1.18, 86.10)	5 more per 1000 (0 more to 49 more)	very low

hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 24 month(s)											
1 (del prato 2014)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	336	753	MD 0.11 (0.02, 0.20)	MD 0.11 higher (0.02 higher to 0.20 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. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

L.1.6.19 Adding glipizide compared to adding dapagliflozin

Table 77: Clinical evidence profile: Adding glipizide 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 Mean follow-up: 48 month(s)											
1 (nauck 2011)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	5/408	2/406	RR 2.49 (0.49, 12.75)	7 more per 1000 (3 fewer to 58 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 12 month(s)											

1 (nauck 2011)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	147/408	7/406	RR 20.90 (9.91, 44.05)	343 more per 1000 (154 more to 742 more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											
1 (nauck 2011)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	3/408	0/406	PETO OR 7.39 (0.77, 71.24)	7 more per 1000 (1 fewer to 16 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 48 month(s)											
1 (nauck 2011)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	401	400	MD 0.30 (0.08, 0.52)	MD 0.30 higher (0.08 higher to 0.52 higher)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 48 month(s)											
1 (nauck 2011)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	401	400	MD 4.38 (3.45, 5.31)	MD 4.38 higher (3.45 higher to 5.31 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. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

L.1.6.20 Adding glipizide compared to adding saxagliptin

Table 78: Clinical evidence profile: Adding glipizide compared to adding saxagliptin

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: 24 month(s)											
1 (göke 2010)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	2/430	4/428	RD -0.00 (-0.02, 0.01)	5 fewer per 1000 (16 fewer to 6 more)	low
cardiovascular mortality at end of follow up Mean follow-up: 24 month(s)											
1 (göke 2010)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	2/430	1/428	RD 0.00 (-0.01, 0.01)	2 more per 1000 (6 fewer to 10 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 24 month(s)											
1 (göke 2010)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	39/430	0/428	PETO OR 8.07 (4.25, 15.33)	91 more per 1000 (64 more to 118 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 24 month(s)											
1 (göke 2010)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	423	423	MD 0.06 (-0.05, 0.17)	MD 0.06 higher (0.05 lower to 0.17 higher)	low

weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 24 month(s)											
1 (göke 2010)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	426	424	MD 2.80 (2.25, 3.35)	MD 2.80 higher (2.25 higher to 3.35 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 (-2.40, 2.40)

L.1.6.21 Adding glipizide compared to adding sitagliptin

Table 79: Clinical evidence profile: Adding glipizide 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
all-cause mortality at end of follow up Mean follow-up: 24 month(s)											
1 (nauck 2007b)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	8/584	1/588	RR 8.05 (1.01, 64.20)	12 more per 1000 (0 more to 107 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 24 month(s)											
1 (nauck 2007b)	RCT	very serious[1]	not serious	NA[2]	very serious[4]	NA	3/584	0/588	PETO OR 7.47 (0.78, 71.91)	5 more per 1000 (1 fewer to 11 more)	very low

hypoglycaemia episodes at end of follow up Mean follow-up: 24 month(s)											
1 (nauck 2007b)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	448/584	31/588	RR 14.55 (10.30, 20.56)	714 more per 1000 (490 more to 1031 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 24 month(s)											
1 (nauck 2007b)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	584	588	HR 20.00 (11.11, 33.33)	Not estimable	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 24 month(s)											
1 (nauck 2007b)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	22/584	2/588	RR 11.08 (2.62, 46.89)	34 more per 1000 (5 more to 156 more)	low
severe hypoglycaemia episodes at end of follow-up Mean follow-up: 24 month(s)											
1 (nauck 2007b)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	584	588	HR 12.50 (2.13, 100)	Not estimable	low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 24 month(s)											
1 (nauck 2007b)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	559	576	MD -0.02 (-0.14, 0.10)	MD 0.02 lower (0.14 lower to 0.10 higher)	low
weight change (kg, lower values are better, change scores) at end of follow up											

Mean follow-up: 24 month(s)											
1 (nauck 2007b)	RCT	very serious[1]	not serious	NA[2]	serious[5]	NA	559	576	MD 2.30 (1.38, 3.22)	MD 2.30 higher (1.38 higher to 3.22 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 (0.80, 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 (-2.40, 2.40)

L.1.7 Thiazolidinediones

L.1.7.1 Adding pioglitazone compared to adding placebo

Table 80: 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 Mean follow-up: 7 month(s)											
6	RCT	very serious[1]	not serious	serious[2]	very serious[3]	NA	5/1168	6/1166	RD -0.00 (-0.01, 0.00)	2 fewer per 1000	very low

										(8 fewer to 5 more)	
cardiovascular mortality at end of follow up Mean follow-up: 6 month(s)											
4	RCT	very serious[1]	not serious	serious[2]	very serious[4]	NA	1/749	1/904	RD 0.00 (-0.01, 0.01)	0 more per 1000 (6 fewer to 6 more)	very low
3-point mace at end of follow up Mean follow-up: 8.7 month(s)											
2	RCT	very serious[1]	not serious	serious[5]	serious[6]	NA	45/619	15/656	RR 1.36 (0.38, 4.88)	8 more per 1000 (14 fewer to 89 more)	very low
non-fatal stroke at end of follow up Mean follow-up: 5.4 month(s)											
1 (punthakee 2012)	RCT	very serious[1]	not serious	NA[7]	very serious[8]	NA	2/392	2/541	PETO OR 1.39 (0.19, 10.15)	1 more per 1000 (7 fewer to 10 more)	very low
non-fatal myocardial infarction at end of follow up Mean follow-up: 5.7 month(s)											
2	RCT	serious[9]	not serious	serious[2]	very serious[8]	NA	5/494	7/647	RR 0.81 (0.27, 2.42)	2 fewer per 1000 (8 fewer to 15 more)	very low
hospitalisation for heart failure at end of follow up Mean follow-up: 6.2 month(s)											
2	RCT	very serious[1]	not serious	serious[2]	very serious[10]	NA	2/537	1/695	RD 0.00 (-0.00, 0.01)	2 more per 1000 (4 fewer to 9 more)	very low
persistent signs of worsening kidney disease at end of follow up Mean follow-up: 5.4 month(s)											

1 (punthakee 2012)	RCT	very serious[1]	not serious	NA[7]	serious[6]	NA	8/392	20/541	RR 0.55 (0.25, 1.24)	17 fewer per 1000 (28 fewer to 9 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 7.3 month(s)											
7	RCT	very serious[1]	not serious	very serious[11]	serious[6]	NA	232/742	107/598	RR 2.10 (1.12, 3.95)	198 more per 1000 (21 more to 529 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 8.7 month(s)											
2	RCT	very serious[1]	not serious	not serious	serious[6]	NA	5/669	0/656	PETO OR 6.33 (0.98, 40.83)	7 more per 1000 (1 more to 14 more)	very low
hba1c change (%, lower values are better, change scores and final values) at end of follow up Mean follow-up: 7.2 month(s)											
12	RCT	very serious[1]	not serious	very serious[11]	serious[12]	NA	1384	1373	MD -0.70 (-0.91, -0.48)	MD 0.70 lower (0.91 lower to 0.48 lower)	very low
weight change (kg, lower values are better, change scores and final values) at end of follow up Mean follow-up: 7.2 month(s)											
9	RCT	very serious[1]	not serious	serious[5]	not serious	NA	1149	1230	MD 3.55 (2.54, 4.55)	MD 3.55 higher (2.54 higher to 4.55 higher)	very low
bmi change (kg/m2, lower values are better, final values) at end of follow up Mean follow-up: 5.8 month(s)											

4	RCT	very serious[1]	not serious	not serious	serious[13]	NA	538	678	MD 1.03 (0.42, 1.65)	MD 1.03 higher (0.42 higher to 1.65 higher)	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. 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).

4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.04 (0.8-0.9 = serious, <0.8 = very serious).

5. I2 between 50% and 75%

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

7. Only one study so no inconsistency

8. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

9. >33.3% of the studies in the meta-analysis were at moderate risk of bias

10. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.2 (0.8-0.9 = serious, <0.8 = very serious).

11. I2 > 75%

12. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

13. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

L.1.7.2 Adding pioglitazone compared to adding metformin

Table 81: Clinical evidence profile: Adding pioglitazone compared to adding metformin

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: 12 month(s)											
2	RCT	very serious[1]	not serious	serious[2]	very serious[3]	NA	1/351	3/351	PETO OR 0.36 (0.05, 2.60)	6 fewer per 1000 (17 fewer to 5 more)	very low
unstable angina at end of follow up Mean follow-up: 12 month(s)											
1 (morikawa 2011)	RCT	very serious[1]	not serious	NA[4]	very serious[3]	NA	1/32	0/31	PETO OR 7.16 (0.14, 361.11)	31 more per 1000 (29 fewer to 92 more)	very low
hospitalisation for heart failure at end of follow up Mean follow-up: 5.5 month(s)											
1 (van der meer 2009)	RCT	very serious[1]	not serious	NA[4]	serious[5]	NA	0/39	0/39	RD 0.00 (-0.05, 0.05)	0 fewer per 1000 (49 fewer to 49 more)	very low
persistent signs of worsening kidney disease at end of follow up Mean follow-up: 12 month(s)											
1 (morikawa 2011)	RCT	very serious[1]	not serious	NA[4]	very serious[3]	NA	2/32	6/31	RR 0.32 (0.07, 1.48)	131 fewer per 1000 (180 fewer to 93 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 15 month(s)											

2	RCT	very serious[1]	not serious	not serious	serious[6]	NA	44/359	59/362	RR 0.75 (0.53, 1.08)	40 fewer per 1000 (77 fewer to 13 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											
1 (hanefeld 2004)	RCT	very serious[1]	not serious	NA[4]	not serious	NA	0/319	0/320	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	low
hba1c change (%, lower values are better, change scores and final values) at end of follow up Mean follow-up: 11 month(s)											
7	RCT	very serious[1]	not serious	not serious	not serious	NA	525	525	MD 0.10 (-0.02, 0.22)	MD 0.10 higher (0.02 lower to 0.22 higher)	low
weight change (kg, lower values are better, change scores and final values) at end of follow up Mean follow-up: 9.8 month(s)											
3	RCT	very serious[1]	not serious	not serious	serious[7]	NA	377	382	MD 2.47 (-0.96, 5.89)	MD 2.47 higher (0.96 lower to 5.89 higher)	very low
bmi change (kg/m2, lower values are better, final values) at end of follow up Mean follow-up: 9.8 month(s)											
3	RCT	very serious[1]	not serious	very serious[8]	very serious[9]	NA	150	103	MD 0.80 (-1.56, 3.17)	MD 0.80 higher (1.56 lower to 3.17 higher)	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 both ends of the defined MIDs (0.80, 1.25)

4. Only one study so no inconsistency

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 (0.80, 1.25)

7. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

8. I2 > 75%

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

L.1.7.3 Adding pioglitazone compared to adding insulin

Table 82: Clinical evidence profile: Adding pioglitazone 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 Mean follow-up: 8.2 month(s)											
2	RCT	very serious[1]	not serious	not serious	serious[2]	NA	7/140	14/134	RR 0.47 (0.24, 0.93)	56 fewer per 1000 (80 fewer to 7 fewer)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 8.2 month(s)											
2	RCT	very serious[1]	not serious	serious[3]	very serious[4]	NA	1/140	4/134	RD -0.02 (-0.06, 0.01)	23 fewer per 1000 (58 fewer to 12 more)	very low

hba1c change (%, lower values are better, change scores and final values) at end of follow up Mean follow-up: 7.5 month(s)											
3	RCT	very serious[1]	not serious	not serious	serious[5]	NA	155	149	MD 0.57 (0.32, 0.81)	MD 0.57 higher (0.32 higher to 0.81 higher)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
1 (hartemann-heurtier 2009)	RCT	very serious[1]	not serious	NA[6]	serious[7]	NA	14	13	MD 1.30 (-0.75, 3.35)	MD 1.30 higher (0.75 lower to 3.35 higher)	very low
bmi change (kg/m2, lower values are better, final values) at end of follow up Mean follow-up: 6 month(s)											
1 (dorkhan 2009)	RCT	very serious[1]	not serious	NA[6]	very serious[8]	NA	15	15	MD -0.60 (-4.93, 3.73)	MD 0.60 lower (4.93 lower to 3.73 higher)	very low

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

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

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

4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.51 (0.8-0.9 = serious, <0.8 = very serious).

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

6. Only one study so no inconsistency

7. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

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

L.1.7.4 Adding pioglitazone compared to adding dapagliflozin

Table 83: Clinical evidence profile: Adding pioglitazone 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
hypoglycaemia episodes at end of follow up Mean follow-up: 6.5 month(s)											
1 (kinoshita 2020)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	0/33	0/33	RD 0.00 (-0.06, 0.06)	0 fewer per 1000 (57 fewer to 57 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 6.5 month(s)											
1 (kinoshita 2020)	RCT	not serious	not serious	NA[1]	not serious	NA	33	32	MD 0.04 (-0.38, 0.46)	MD 0.04 higher (0.38 lower to 0.46 higher)	high
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6.5 month(s)											
1 (kinoshita 2020)	RCT	not serious	not serious	NA[1]	not serious	NA	33	32	MD 5.30 (4.32, 6.28)	MD 5.30 higher	high

										(4.32 higher to 6.28 higher)	

1. Only one study so no inconsistency

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

L.1.7.5 Adding pioglitazone compared to adding empagliflozin

Figure 1: Clinical evidence profile: Adding pioglitazone compared to adding empagliflozin

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
non-fatal stroke at end of follow up Mean follow-up: 5.5 month(s)											
1 (attaran 2023)	RCT	serious[1]	not serious	NA 2	very serious[3]	NA	0/36	1/37	PETO OR 0.14 (0.00, 7.01)	27 fewer per 1000 (79 fewer to 25 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 5.5 month(s)											
2	RCT	serious[1]	not serious	serious[4]	very serious[5]	NA	2/91	0/95	RD 0.02 (-0.05, 0.08)	18 more per 1000 (47 fewer to 83 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.5 month(s)											
2	RCT	serious[1]	not serious	not serious	serious[6]	NA	0/91	0/95	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (30 fewer to 30 more)	low

hba1c change (%, lower values are better, change scores and final values) at end of follow up Mean follow-up: 5.5 month(s)											
2	RCT	serious[1]	not serious	not serious	not serious	NA	91	95	MD 0.07 (-0.20, 0.35)	MD 0.07 higher (0.20 lower to 0.35 higher)	moderate
bmi change (kg/m2, lower values are better, change scores and final values) at end of follow up Mean follow-up: 5.5 month(s)											
2	RCT	serious[1]	not serious	not serious	not serious	NA	91	95	MD 1.73 (1.32, 2.14)	MD 1.73 higher (1.32 higher to 2.14 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. 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 = 0.53 (0.8-0.9 = serious, <0.8 = very serious).

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

L.1.7.6 Adding pioglitazone compared to adding exenatide

Table 84: Clinical evidence profile: Adding pioglitazone compared to adding exenatide

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 (eq-5d, higher values better, change scores) at end of follow-up Mean follow-up: 6 month(s)											
1 (bergenstal 2010)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	130	129	MD -0.02 (-0.08, 0.04)	MD 0.02 lower (0.08 lower to 0.04 higher)	very low
all-cause mortality at end of follow up Mean follow-up: 6 month(s)											
1 (bergenstal 2010)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	0/165	0/160	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 6 month(s)											
1 (bergenstal 2010)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	0/165	0/160	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	very low
unstable angina at end of follow up Mean follow-up: 6 month(s)											
1 (bergenstal 2010)	RCT	very serious[1]	not serious	NA[2]	very serious[5]	NA	1/165	0/160	PETO OR 7.17 (0.14, 361.44)	6 more per 1000 (6 fewer to 18 more)	very low
acute kidney injury at end of follow up Mean follow-up: 6 month(s)											

1 (bergenstal 2010)	RCT	very serious[1]	not serious	NA[2]	very serious[5]	NA	1/165	0/160	PETO OR 7.17 (0.14, 361.44)	6 more per 1000 (6 fewer to 18 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 6 month(s)											
1 (bergenstal 2010)	RCT	very serious[1]	not serious	NA[2]	very serious[5]	NA	1/165	2/160	PETO OR 0.50 (0.05, 4.80)	6 fewer per 1000 (27 fewer to 14 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)											
1 (bergenstal 2010)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	0/165	0/160	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)											
1 (bergenstal 2010)	RCT	serious[6]	not serious	NA[2]	serious[7]	NA	165	160	MD 0.30 (0.05, 0.55)	MD 0.30 higher (0.05 higher to 0.55 higher)	low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)											
1 (bergenstal 2010)	RCT	serious[6]	not serious	NA[2]	not serious	NA	165	160	MD 5.10 (4.26, 5.94)	MD 5.10 higher (4.26 higher to 5.94 higher)	moderate

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 (-0.03, 0.03)

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

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

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

7. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

L.1.7.7 Adding pioglitazone compared to adding gliclazide

Table 85: Clinical evidence profile: Adding pioglitazone compared to adding gliclazide

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: 12 month(s)											
1 (matthews 2005)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/317	2/313	PETO OR 0.13 (0.01, 2.13)	6 fewer per 1000 (15 fewer to 2 more)	very low
non-fatal myocardial infaRCTion at end of follow up Mean follow-up: 12 month(s)											
1 (matthews 2005)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	1/317	0/313	PETO OR 7.30 (0.14, 367.74)	3 more per 1000 (3 fewer to 9 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 24 month(s)											
1 (matthews 2005)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	7/317	36/313	RR 0.19 (0.09, 0.42)	93 fewer per 1000 (105 fewer to 66 fewer)	low

severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											
1 (matthews 2005)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/317	0/313	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 24 month(s)											
1 (matthews 2005)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	317	313	MD -0.12 (-0.31, 0.07)	MD 0.12 lower (0.31 lower to 0.07 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)

L.1.7.8 Adding pioglitazone compared to adding glimepiride

Table 86: Clinical evidence profile: Adding pioglitazone 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
all-cause mortality at end of follow up Mean follow-up: 18 month(s)											
1 (mazzone 2006)	RCT	very serious[1]	serious[2]	NA[3]	very serious[4]	NA	1/230	0/228	PETO OR 7.33 (0.15, 369.17)	4 more per 1000 (4 fewer to 13 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 18 month(s)											

1 (mazzone 2006)	RCT	very serious[1]	serious[2]	NA[3]	not serious	NA	0/230	0/228	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	very low
3-point mace at end of follow up Mean follow-up: 18 month(s)											
1 (mazzone 2006)	RCT	very serious[1]	serious[2]	NA[3]	very serious[4]	NA	0/230	2/228	PETO OR 0.13 (0.01, 2.14)	9 fewer per 1000 (21 fewer to 3 more)	very low
non-fatal stroke at end of follow up Mean follow-up: 11.8 month(s)											
2	RCT	very serious[1]	serious[2]	serious[5]	very serious[4]	NA	1/261	1/260	PETO OR 1.01 (0.06, 16.18)	0 fewer per 1000 (11 fewer to 11 more)	very low
non-fatal myocardial infarction at end of follow up Mean follow-up: 11.8 month(s)											
2	RCT	very serious[1]	serious[2]	not serious	very serious[4]	NA	0/261	2/260	PETO OR 0.14 (0.01, 2.19)	8 fewer per 1000 (18 fewer to 3 more)	very low
unstable angina at end of follow up Mean follow-up: 18 month(s)											
1 (mazzone 2006)	RCT	very serious[1]	serious[2]	NA[3]	not serious	NA	0/230	0/228	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	very low
hospitalisation for heart failure at end of follow up Mean follow-up: 8.2 month(s)											
5	RCT	very serious[1]	not serious	serious[5]	very serious[6]	NA	5/657	2/638	RD 0.00 (-0.01, 0.01)	4 more per 1000 (6 fewer to 15 more)	very low
acute kidney injury at end of follow up											

Mean follow-up: 5.5 month(s)											
1 (pfützner 2011b)	RCT	serious[7]	not serious	NA[3]	very serious[4]	NA	0/142	1/146	PETO OR 0.14 (0.00, 7.01)	7 fewer per 1000 (20 fewer to 7 more)	very low
falls requiring hospitalisation at end of follow up **Mean follow-up: 6 month(s)**											
1 (kim 2020)	RCT	serious[7]	not serious	NA[3]	very serious[4]	NA	2/69	0/66	PETO OR 7.18 (0.44, 116.06)	29 more per 1000 (11 fewer to 69 more)	very low
hypoglycaemia episodes at end of follow up **Mean follow-up: 8.5 month(s)**											
7	RCT	very serious[1]	not serious	very serious[8]	serious[9]	NA	81/753	140/738	RR 0.49 (0.24, 0.99)	98 fewer per 1000 (145 fewer to 2 fewer)	very low
severe hypoglycaemic episodes at end of follow up **Mean follow-up: 5.8 month(s)**											
3	RCT	very serious[1]	not serious	not serious	not serious	NA	0/285	0/264	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	low
hba1c change (%, lower values are better, change scores and final values) at end of follow up **Mean follow-up: 6.9 month(s)**											
12	RCT	very serious[1]	not serious	serious[10]	not serious	NA	801	778	MD -0.07 (-0.19, 0.05)	MD 0.07 lower (0.19 lower to 0.05 higher)	very low
weight change (kg, lower values are better, change scores and final values) at end of follow up											

Mean follow-up: 8.2 month(s)											
8	RCT	very serious[1]	not serious	serious[10]	not serious	NA	663	656	MD 0.88 (0.02, 1.74)	MD 0.88 higher (0.02 higher to 1.74 higher)	very low
bmi change (kg/m2, lower values are better, change scores and final values) at end of follow up Mean follow-up: 7.6 month(s)											
7	RCT	very serious[1]	not serious	not serious	not serious	NA	441	419	MD 0.32 (-0.14, 0.79)	MD 0.32 higher (0.14 lower to 0.79 higher)	low

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

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

3. Only one study so no inconsistency

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

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

6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.34 (0.8-0.9 = serious, <0.8 = very serious).

7. >33.3% of the studies in the meta-analysis were at moderate risk of bias

8. I2 > 75%

9. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

10. I2 between 50% and 75%

L.1.7.9 Adding pioglitazone compared to adding glipizide

Table 87: Clinical evidence profile: Adding pioglitazone compared to adding glipizide

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 end of follow up Mean follow-up: 5.5 month(s)											
1 (xiao 2015)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	34	36	MD 0.58 (0.34, 0.82)	MD 0.58 higher (0.34 higher to 0.82 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)

L.1.7.10 Adding pioglitazone compared to adding sitagliptin

Table 88: Clinical evidence profile: Adding pioglitazone 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
health-related quality of life - overall (eq-5d, higher values are better, change scores) at end of follow-up Mean follow-up: 6 month(s)											
1 (bergenstal 2010)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	130	139	MD -0.03 (-0.09, 0.03)	MD 0.03 lower	very low

										(0.09 lower to 0.03 higher)	
all-cause mortality at end of follow up Mean follow-up: 6 month(s)											
1 (bergenstal 2010)	RCT	very serious[1]	not serious	NA[2]	very serious[4]	NA	0/165	1/166	PETO OR 0.14 (0.00, 6.86)	6 fewer per 1000 (18 fewer to 6 more)	very low
unstable angina at end of follow up Mean follow-up: 6 month(s)											
1 (bergenstal 2010)	RCT	very serious[1]	not serious	NA[2]	very serious[4]	NA	1/165	0/166	PETO OR 7.43 (0.15, 374.66)	6 more per 1000 (6 fewer to 18 more)	very low
acute kidney injury at end of follow up Mean follow-up: 6 month(s)											
1 (bergenstal 2010)	RCT	very serious[1]	not serious	NA[2]	very serious[4]	NA	1/165	0/166	PETO OR 7.43 (0.15, 374.66)	6 more per 1000 (6 fewer to 18 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 5.7 month(s)											
3	RCT	serious[5]	not serious	not serious	very serious[4]	NA	8/290	13/291	RR 0.62 (0.26, 1.45)	17 fewer per 1000 (33 fewer to 20 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.7 month(s)											
3	RCT	very serious[1]	not serious	not serious	not serious	NA	0/290	0/291	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 7.2 month(s)											

4	RCT	serious[5]	not serious	very serious[6]	not serious	NA	391	396	MD -0.12 (-0.37, 0.14)	MD 0.12 lower (0.37 lower to 0.14 higher)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 7.2 month(s)											
4	RCT	serious[5]	not serious	very serious[6]	not serious	NA	391	396	MD 1.62 (1.52, 1.73)	MD 1.62 higher (1.52 higher to 1.73 higher)	very low
bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (khaloo 2019)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	110	112	MD 3.50 (2.62, 4.38)	MD 3.50 higher (2.62 higher to 4.38 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 (-0.03, 0.03)

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 moderate risk of bias

6. I2 > 75%

L.1.7.11 Adding pioglitazone compared to adding vildagliptin

Table 89: Clinical evidence profile: Adding pioglitazone 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
non-fatal stroke at end of follow up Mean follow-up: 12 month(s)											
1 (bolli 2008)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	2/280	1/295	RR 2.11 (0.19, 23.11)	4 more per 1000 (3 fewer to 75 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 12 month(s)											
1 (bolli 2008)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	1/280	1/295	RR 1.05 (0.07, 16.76)	0 more per 1000 (3 fewer to 53 more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											
1 (bolli 2008)	RCT	not serious	not serious	NA[1]	not serious	NA	0/280	0/295	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	high
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (bolli 2008)	RCT	not serious	not serious	NA[1]	not serious	NA	281	295	MD 0.00 (-0.18, 0.18)	MD 0.00 lower (0.18 lower to 0.18 higher)	high

weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (bolli 2008)	RCT	not serious	not serious	NA[1]	serious[3]	NA	281	295	MD 2.40 (1.69, 3.11)	MD 2.40 higher (1.69 higher to 3.11 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. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

L.1.8 Insulin combinations

L.1.8.1 Adding insulin degludec/liraglutide compared to adding placebo

Table 90: Clinical evidence profile: Adding insulin degludec/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 Mean follow-up: 6 month(s)											
1 (rodbard 2017)	RCT	not serious	not serious	NA[2]	very serious[4]	NA	1/288	0/146	PETO OR 4.51 (0.07, 285.77)	3 more per 1000 (3 fewer to 10 more)	low
non-fatal myocardial infaRCTion at end of follow up Mean follow-up: 6 month(s)											

1 (rodbard 2017)	RCT	not serious	not serious	NA[2]	very serious[4]	NA	1/288	0/146	PETO OR 4.51 (0.07, 285.77)	3 more per 1000 (3 fewer to 10 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 6 month(s)											
1 (rodbard 2017)	RCT	not serious	not serious	NA[2]	not serious	NA	120/288	25/146	RR 2.43 (1.66, 3.57)	245 more per 1000 (113 more to 439 more)	high
at night hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)											
1 (rodbard 2017)	RCT	not serious	not serious	NA[2]	serious[5]	NA	34/288	10/146	RR 1.72 (0.88, 3.39)	50 more per 1000 (8 fewer to 164 more)	moderate
severe hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)											
1 (rodbard 2017)	RCT	not serious	not serious	NA[2]	very serious[4]	NA	2/288	0/146	PETO OR 4.53 (0.24, 85.38)	7 more per 1000 (3 fewer to 17 more)	low
hba1c change (%, lower values are better, mean difference) at end of follow up Mean follow-up: 6 month(s)											
1 (rodbard 2017)	RCT	serious[1]	not serious	NA[2]	not serious	NA	289	146	MD -1.02 (-1.18, -0.86)	MD 1.02 lower (1.18 lower to 0.86 lower)	moderate
weight change (kg, lower values are better, mean difference) at end of follow up Mean follow-up: 6 month(s)											

1 (rodbard 2017)	RCT	very serious[3]	not serious	NA[2]	not serious	NA	289	146	MD 1.48 (0.90, 2.06)	MD 1.48 higher (0.90 higher to 2.06 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. >33.3% of the studies in the meta-analysis were at high risk of bias

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 (0.80, 1.25)

L.1.8.2 Adding insulin degludec/liraglutide compared to adding insulin

Table 91: Clinical evidence profile: Adding insulin degludec/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
health-related quality of life - overall eq-5d-5l index score (higher scores are better, final values) at end of follow up Mean follow-up: 6 month(s)											
1 (watada 2019)	RCT	serious[1]	not serious	NA[2]	serious[3]	NA	105	105	MD 0.03 (-0.00, 0.06)	MD 0.03 higher (0.00 lower to 0.06 higher)	low
health-related quality of life - subscale mental component (sf-36 v2, 0-100, higher scores are better, change scores and final values) at end of follow up Mean follow-up: 6 month(s)											

2	RCT	very serious[4]	not serious	very serious[5]	serious[6]	NA	516	512	MD 0.57 (-1.91, 3.05)	MD 0.57 higher (1.91 lower to 3.05 higher)	very low
health-related quality of life - subscale physical component (sf-36 v2, 0-100, higher scores are better, change scores and final values) at end of follow up Mean follow-up: 6 month(s)											
2	RCT	very serious[4]	not serious	very serious[5]	serious[7]	NA	515	512	MD 0.55 (-1.81, 2.92)	MD 0.55 higher (1.81 lower to 2.92 higher)	very low
all-cause mortality at end of follow up Mean follow-up: 8.6 month(s)											
9	RCT	not serious	not serious	serious[8]	very serious[9]	NA	4/2932	7/2180	RD -0.00 (-0.00, 0.00)	2 fewer per 1000 (5 fewer to 2 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 8.6 month(s)											
9	RCT	not serious	not serious	serious[8]	very serious[10]	NA	2/2932	5/2180	RD -0.00 (-0.00, 0.00)	2 fewer per 1000 (5 fewer to 2 more)	very low
3-point mace at end of follow up Mean follow-up: 8 month(s)											
3	RCT	not serious	not serious	not serious	very serious[11]	NA	9/1343	5/774	PETO OR 1.11 (0.37, 3.32)	0 more per 1000 (7 fewer to 7 more)	low
non-fatal stroke at end of follow up Mean follow-up: 8.9 month(s)											

6	RCT	not serious	not serious	serious[8]	very serious[11]	NA	7/1732	4/1398	PETO OR 1.21 (0.36, 4.11)	1 more per 1000 (3 fewer to 5 more)	very low
non-fatal myocardial infarction at end of follow up Mean follow-up: 9.4 month(s)											
7	RCT	not serious	not serious	serious[8]	very serious[11]	NA	9/2405	5/1835	PETO OR 1.48 (0.51, 4.30)	1 more per 1000 (2 fewer to 4 more)	very low
unstable angina at end of follow up Mean follow-up: 12 month(s)											
3	RCT	very serious[4]	not serious	serious[8]	very serious[11]	NA	5/1119	1/936	PETO OR 3.47 (0.69, 17.50)	3 more per 1000 (1 fewer to 8 more)	very low
hospitalisation for heart failure at end of follow up Mean follow-up: 15 month(s)											
2	RCT	very serious[4]	not serious	serious[8]	very serious[11]	NA	1/758	2/757	PETO OR 0.51 (0.05, 4.93)	1 fewer per 1000 (6 fewer to 3 more)	very low
acute kidney injury at end of follow up Mean follow-up: 6 month(s)											
1 (philis-tsimikas 2019)	RCT	not serious	not serious	NA 2	very serious[11]	NA	0/209	1/210	PETO OR 0.14 (0.00, 6.85)	5 fewer per 1000 (14 fewer to 5 more)	low
persistent signs of worsening kidney disease at end of follow up Mean follow-up: 6 month(s)											
1 (philis-tsimikas 2019)	RCT	not serious	not serious	NA[2]	very serious[11]	NA	0/209	1/210	PETO OR 0.14 (0.00, 6.85)	5 fewer per 1000 (14 fewer to 5 more)	low
development of end stage kidney disease at end of follow up Mean follow-up: 24 month(s)											

1 (aroda 2019a)	RCT	very serious[4]	not serious	NA[2]	very serious[11]	NA	1/506	0/504	PETO OR 7.36 (0.15, 370.92)	2 more per 1000 (2 fewer to 6 more)	very low
cardiac arrhythmia at end of follow up Mean follow-up: 15 month(s)											
2	RCT	very serious[4]	not serious	serious[8]	very serious[11]	NA	2/758	2/757	PETO OR 1.00 (0.14, 7.11)	0 fewer per 1000 (5 fewer to 5 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 7 month(s)											
6	RCT	not serious	not serious	not serious	serious[12]	NA	561/2033	473/1285	RR 0.78 (0.70, 0.86)	82 fewer per 1000 (109 fewer to 52 fewer)	moderate
at night hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)											
3	RCT	not serious	serious[13]	serious[14]	serious[12]	NA	29/812	69/631	RR 0.47 (0.20, 1.09)	58 fewer per 1000 (87 fewer to 10 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.9 month(s)											
6	RCT	not serious	not serious	serious[8]	very serious[15]	NA	16/1062	20/1176	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (14 fewer to 9 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 6.5 month(s)											
11	RCT	serious[1]	not serious	very serious[5]	serious[16]	NA	3121	2551	MD -0.65 (-0.82, -0.48)	MD 0.65 lower (0.82 lower to	very low

										0.48 lower)	
hba1c change (mmol/mol, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)											
1 (wang 2022b)	RCT	not serious	not serious	NA[2]	serious[17]	NA	361	179	MD -6.50 (-7.96, -5.04)	MD 6.50 lower (7.96 lower to 5.04 lower)	moderate
weight change (kg, lower values are better, change scores and final values) at end of follow up Mean follow-up: 8 month(s)											
12	RCT	not serious	not serious	very serious[5]	serious[18]	NA	3736	2982	MD -2.21 (-2.79, -1.63)	MD 2.21 lower (2.79 lower to 1.63 lower)	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 one end of the defined MIDs (-0.03, 0.03)

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

5. I2 > 75%

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 (-2.00, 2.00)

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

9. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.5 (0.8-0.9 = serious, <0.8 = very serious).

10. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.56 (0.8-0.9 = serious, <0.8 = very serious).

11. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

12. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

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

14. I2 between 50% and 75%

15. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.07 (0.8-0.9 = serious, <0.8 = very serious).

16. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

17. 95% confidence intervals cross one end of the defined MIDs (-5.50, 5.50)

18. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

L.1.8.3 Adding insulin degludec/liraglutide compared to adding liraglutide

Table 92: Clinical evidence profile: Adding insulin degludec/liraglutide compared to adding liraglutide

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: 9 month(s)											
2	RCT	not serious	not serious	serious[1]	very serious[2]	NA	2/1194	0/594	RD 0.00 (-0.00, 0.01)	2 more per 1000 (3 fewer to 6 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)											

1 (gough 2014)	RCT	not serious	not serious	NA[3]	very serious[4]	NA	2/833	0/414	PETO OR 4.47 (0.24, 84.97)	2 more per 1000 (1 fewer to 6 more)	low
3-point mace at end of follow up Mean follow-up: 12 month(s)											
1 (gough 2014)	RCT	not serious	not serious	NA[3]	very serious[4]	NA	4/833	1/414	RR 1.99 (0.22, 17.73)	2 more per 1000 (2 fewer to 40 more)	low
non-fatal stroke at end of follow up Mean follow-up: 6 month(s)											
1 (wang 2022b)	RCT	not serious	not serious	NA[3]	very serious[4]	NA	2/361	4/180	RR 0.25 (0.05, 1.35)	17 fewer per 1000 (21 fewer to 8 more)	low
non-fatal myocardial infaRCTion at end of follow up Mean follow-up: 12 month(s)											
1 (gough 2014)	RCT	not serious	not serious	NA[3]	very serious[4]	NA	2/833	1/414	RR 0.99 (0.09, 10.93)	0 fewer per 1000 (2 fewer to 24 more)	low
unstable angina at end of follow up Mean follow-up: 6 month(s)											
1 (wang 2022b)	RCT	not serious	not serious	NA[3]	not serious	NA	0/361	0/180	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	high
hypoglycaemia episodes at end of follow up Mean follow-up: 8 month(s)											
3	RCT	not serious	not serious	very serious[5]	not serious	NA	389/1461	35/865	RR 8.77 (3.03, 25.43)	315 more per 1000 (82 more to 988 more)	low
at night hypoglycaemic episodes at end of follow up											

Mean follow-up: 6 month(s)											
1 (wang 2022b)	RCT	not serious	serious[6]	NA[3]	very serious[4]	NA	5/361	0/180	PETO OR 4.53 (0.70, 29.28)	14 more per 1000 (2 more to 26 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)											
1 (gough 2014)	RCT	not serious	not serious	NA[3]	very serious[4]	NA	3/825	0/414	PETO OR 4.50 (0.41, 49.66)	4 more per 1000 (0 more to 8 more)	low
hba1c change (%, lower values are better, mean difference) at end of follow up Mean follow-up: 9 month(s)											
2	RCT	not serious	not serious	not serious	serious[7]	NA	1195	688	MD -0.54 (-0.62, -0.45)	MD 0.54 lower (0.62 lower to 0.45 lower)	moderate
hba1c change (mmol/mol, lower values are better, mean difference) at end of follow up Mean follow-up: 6 month(s)											
1 (wang 2022b)	RCT	not serious	not serious	NA[3]	serious[8]	NA	361	180	MD -6.87 (-8.32, -5.42)	MD 6.87 lower (8.32 lower to 5.42 lower)	moderate
weight change (kg, lower values are better, mean difference) at end of follow up Mean follow-up: 8 month(s)											
3	RCT	not serious	not serious	very serious[5]	serious[9]	NA	1470	867	MD 2.96 (2.17, 3.75)	MD 2.96 higher (2.17 higher to 3.75 higher)	very low

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

2. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.41 (0.8-0.9 = serious, <0.8 = very serious).

3. Only one study so no inconsistency

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

5. I2 > 75%

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

7. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

8. 95% confidence intervals cross one end of the defined MIDs (-5.50, 5.50)

9. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

L.1.8.4 Adding insulin glargine/lixisenatide compared to adding insulin

Table 93: Clinical evidence profile: Adding insulin glargine/lixisenatide 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 Mean follow-up: 6.3 month(s)											
7	RCT	serious[1]	not serious	serious[2]	very serious[3]	NA	4/2070	5/2073	RD -0.00 (-0.00, 0.00)	0 fewer per 1000 (4 fewer to 3 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 6.3 month(s)											
7	RCT	serious[1]	not serious	serious[2]	very serious[4]	NA	50/2070	46/2073	RD 0.00 (-0.01, 0.01)	2 more per 1000 (7 fewer to 11 more)	very low

non-fatal stroke at end of follow up Mean follow-up: 7 month(s)											
1 (rosenstock 2016b)	RCT	serious[1]	not serious	NA[5]	very serious[6]	NA	0/469	1/467	PETO OR 0.13 (0.00, 6.79)	2 fewer per 1000 (6 fewer to 2 more)	very low
non-fatal myocardial infaRCTion at end of follow up Mean follow-up: 7 month(s)											
1 (rosenstock 2016b)	RCT	serious[1]	not serious	NA[5]	not serious	NA	0/469	0/467	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (4 fewer to 4 more)	moderate
unstable angina at end of follow up Mean follow-up: 7 month(s)											
1 (rosenstock 2016b)	RCT	serious[1]	not serious	NA[5]	very serious[6]	NA	1/469	1/467	PETO OR 1.00 (0.06, 15.94)	0 fewer per 1000 (6 fewer to 6 more)	very low
hospitalisation for heart failure at end of follow up Mean follow-up: 7 month(s)											
1 (rosenstock 2016b)	RCT	serious[1]	not serious	NA[5]	very serious[6]	NA	0/469	2/467	PETO OR 0.13 (0.01, 2.15)	4 fewer per 1000 (10 fewer to 2 more)	very low
death from renal causes at end of follow up Mean follow-up: 6.9 month(s)											
1 (yuan 2022)	RCT	not serious	not serious	NA[5]	not serious	NA	0/211	0/212	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	high
hypoglycaemia episodes at end of follow up Mean follow-up: 6.3 month(s)											

7	RCT	not serious	not serious	serious [2]	not serious	NA	399/2069	397/2073	RR 1.01 (0.90, 1.12)	1 more per 1000 (19 fewer to 24 more)	moderate
severe hypoglycaemic episodes at end of follow up Mean follow-up: 6.3 month(s)											
7	RCT	serious [1]	not serious	serious [2]	very serious [7]	NA	7/2069	6/2073	RD 0.00 (-0.00, 0.00)	0 more per 1000 (3 fewer to 4 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 6.3 month(s)											
7	RCT	not serious	not serious	very serious [8]	serious [9]	NA	2068	2070	MD -0.50 (-0.64, -0.35)	MD 0.50 lower (0.64 lower to 0.35 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6.3 month(s)											
7	RCT	not serious	not serious	not serious	not serious	NA	2068	2070	MD -1.16 (-1.32, -0.99)	MD 1.16 lower (1.32 lower to 0.99 lower)	high

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

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

3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.07 (0.8-0.9 = serious, <0.8 = very serious).

4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.09 (0.8-0.9 = serious, <0.8 = very serious).

5. Only one study so no inconsistency

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

7. 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).

8. I2 > 75%

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

L.1.8.5 Adding insulin glargine/lixisenatide compared to adding lixisenatide

Table 94: Clinical evidence profile: Adding insulin glargine/lixisenatide compared to adding lixisenatide

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: 6.2 month(s)											
2	RCT	serious[1]	not serious	serious[2]	very serious[3]	NA	2/817	1/409	RD -0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 6.2 month(s)											
2	RCT	serious[1]	not serious	serious[2]	very serious[4]	NA	1/817	1/409	PETO OR 0.47 (0.02, 8.90)	1 fewer per 1000 (7 fewer to 4 more)	very low
non-fatal stroke at end of follow up Mean follow-up: 7 month(s)											
1 (rosenstock 2016b)	RCT	serious[1]	not serious	NA[5]	very serious[6]	NA	0/469	1/233	PETO OR 0.05 (0.00, 3.16)	4 fewer per 1000 (13 fewer to 4 more)	very low

non-fatal myocardial infaRCTion at end of follow up Mean follow-up: 7 month(s)											
1 (rosenstock 2016b)	RCT	serious[1]	not serious	NA[5]	not serious	NA	0/469	0/233	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	moderate
unstable angina at end of follow up Mean follow-up: 7 month(s)											
1 (rosenstock 2016b)	RCT	serious[1]	not serious	NA[5]	very serious[6]	NA	1/469	0/233	PETO OR 4.47 (0.07, 286.86)	2 more per 1000 (2 fewer to 6 more)	very low
hospitalisation for heart failure at end of follow up Mean follow-up: 7 month(s)											
1 (rosenstock 2016b)	RCT	serious[1]	not serious	NA[5]	not serious	NA	0/469	0/233	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	moderate
hypoglycaemia episodes at end of follow up Mean follow-up: 6.2 month(s)											
2	RCT	serious[1]	not serious	serious[7]	not serious	NA	291/817	27/409	RR 5.41 (3.71, 7.87)	291 more per 1000 (179 more to 454 more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 6.2 month(s)											
2	RCT	serious[1]	not serious	serious[2]	very serious[4]	NA	1/817	1/409	RD -0.00 (-0.01, 0.01)	1 fewer per 1000 (8 fewer to 5 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up											

Mean follow-up: 6.2 month(s)											
2	RCT	not serious	not serious	very serious [8]	not serious	NA	816	408	MD -0.85 (-1.14, -0.55)	MD 0.85 lower (1.4 lower to 0.55 lower)	low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6.2 month(s)											
2	RCT	serious [1]	not serious	not serious	not serious	NA	643	581	MD 1.83 (1.40, 2.25)	MD 1.83 higher (1.40 higher to 2.25 higher)	moderate

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

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

3. 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).

4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.1 (0.8-0.9 = serious, <0.8 = very serious).

5. Only one study so no inconsistency

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

7. I2 between 50% and 75%

8. I2 > 75%.

L.1.8.6 Adding dapagliflozin + exenatide compared to adding dapagliflozin

Table 95: Clinical evidence profile: Adding dapagliflozin + exenatide 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 Mean follow-up: 24 month(s)											
1 (frias 2016)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	3/231	2/233	RR 1.51 (0.26, 8.97)	4 more per 1000 (6 fewer to 68 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 24 month(s)											
1 (frias 2016)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	1/231	1/233	RR 1.01 (0.06, 16.03)	0 more per 1000 (4 fewer to 65 more)	very low
acute kidney injury at end of follow up Mean follow-up: 24 month(s)											
1 (frias 2016)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/231	3/233	PETO OR 0.14 (0.01, 1.31)	13 fewer per 1000 (27 fewer to 2 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 24 month(s)											
1 (frias 2016)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	4/231	1/233	RR 4.03 (0.45, 35.83)	13 more per 1000 (2 fewer to 149 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 24 month(s)											

1 (frias 2016)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/231	0/233	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 24 month(s)											
1 (frias 2016)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	228	230	MD -0.64 (-0.96, -0.32)	MD 0.64 lower (0.96 lower to 0.32 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 24 month(s)											
1 (frias 2016)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	228	230	MD 0.51 (-0.77, 1.79)	MD 0.51 higher (0.77 lower to 1.79 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. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

L.1.8.7 Adding dapagliflozin + exenatide compared to adding exenatide

Table 96: Clinical evidence profile: Adding dapagliflozin + exenatide compared to adding exenatide

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: 24 month(s)											

1 (frias 2016)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	3/231	1/230	PETO OR 2.72 (0.38, 19.46)	9 more per 1000 (8 fewer to 26 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 24 month(s)											
1 (frias 2016)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	1/231	1/230	PETO OR 1.00 (0.06, 15.97)	0 fewer per 1000 (12 fewer to 12 more)	very low
acute kidney injury at end of follow up Mean follow-up: 24 month(s)											
1 (frias 2016)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/231	2/230	PETO OR 0.13 (0.01, 2.15)	9 fewer per 1000 (21 fewer to 3 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 24 month(s)											
1 (frias 2016)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	4/231	0/230	PETO OR 7.45 (1.04, 53.26)	17 more per 1000 (1 more to 34 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 24 month(s)											
1 (frias 2016)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/231	0/230	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 24 month(s)											

1 (frias 2016)	RCT	very serious[1]	not serious	NA[2]	serious[5]	NA	228	227	MD -0.41 (-0.73, -0.09)	MD 0.41 lower (0.73 lower to 0.09 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 24 month(s)											
1 (frias 2016)	RCT	very serious[1]	not serious	NA[2]	serious[6]	NA	228	227	MD -1.71 (-2.96, -0.46)	MD 1.71 lower (2.96 lower to 0.46 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 (0.80, 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 (-2.40, 2.40)

L.1.8.8 Adding dapagliflozin + saxagliptin compared to adding dapagliflozin

Table 97: 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 Mean follow-up: 5.5 month(s)											

2	RCT	not serious	not serious	serious[1]	very serious[2]	NA	1/472	2/472	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (10 fewer to 6 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 5.5 month(s)											
2	RCT	not serious	not serious	serious[1]	very serious[3]	NA	0/472	2/472	RD -0.00 (-0.01, 0.00)	4 fewer per 1000 (13 fewer to 4 more)	very low
hospitalisation for heart failure at end of follow up Mean follow-up: 12 month(s)											
1 (muller-wieland 2018)	RCT	not serious	not serious	NA[4]	not serious	NA	0/312	0/313	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	high
persistent signs of worsening kidney disease at end of follow up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2015a)	RCT	serious[5]	not serious	NA[4]	not serious	NA	0/179	0/179	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (11 fewer to 11 more)	moderate
diabetic ketoacidosis at end of follow up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2019d)	RCT	not serious	not serious	NA[4]	not serious	NA	0/293	0/293	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	high
hypoglycaemia episodes at end of follow up Mean follow-up: 7.7 month(s)											
3	RCT	not serious	not serious	serious[1]	serious[6]	NA	9/784	3/783	PETO OR 2.74 (0.88, 8.54)	8 more per 1000	low

										(1 fewer to 16 more)	
severe hypoglycaemic episodes at end of follow up Mean follow-up: 7.7 month(s)											
3	RCT	not serious	not serious	serious [1]	very serious [7]	NA	1/784	1/783	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (5 fewer to 5 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 7.7 month(s)											
3	RCT	not serious	not serious	not serious	not serious	NA	753	740	MD -0.37 (-0.46, -0.27)	MD 0.37 lower (0.46 lower to 0.27 lower)	high
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 8.8 month(s)											
2	RCT	not serious	not serious	not serious	not serious	NA	471	463	MD 0.31 (-0.12, 0.74)	MD 0.31 higher (0.12 lower to 0.74 higher)	high

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

2. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.13 (0.8-0.9 = serious, <0.8 = very serious).

3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.52 (0.8-0.9 = serious, <0.8 = very serious).

4. Only one study so no inconsistency

5. >33.3% of the studies in the meta-analysis were at moderate risk of bias

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

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)

L.1.8.9 Adding dapagliflozin + saxagliptin compared to adding glimepiride

Table 98: Clinical evidence profile: Adding dapagliflozin + saxagliptin 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
all-cause mortality at end of follow up Mean follow-up: 36 month(s)											
1 (frias 2020)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	1/227	3/216	PETO OR 0.35 (0.05, 2.48)	9 fewer per 1000 (27 fewer to 8 more)	very low
hospitalisation for heart failure at end of follow up Mean follow-up: 12 month(s)											
2	RCT	not serious	not serious	serious[4]	very serious[5]	NA	0/539	1/528	RD -0.00 (-0.01, 0.00)	2 fewer per 1000 (8 fewer to 4 more)	very low
diabetic ketoacidosis at end of follow up Mean follow-up: 12 month(s)											
1 (frias 2020)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/227	0/216	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 24 month(s)											
2	RCT	very serious[1]	not serious	serious[6]	serious[7]	NA	20/539	66/525	RR 0.22 (0.06, 0.87)	98 fewer per 1000	very low

										(119 fewer to 16 fewer)	
severe hypoglycaemic episodes at end of follow up Mean follow-up: 24 month(s)											
2	RCT	not serious	not serious	serious [4]	very serious [8]	NA	0/539	3/525	RD -0.01 (-0.02, 0.01)	6 fewer per 1000 (24 fewer to 13 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 24 month(s)											
2	RCT	not serious	not serious	serious [6]	serious [9]	NA	529	517	MD -0.34 (-0.65, -0.02)	MD 0.34 lower (0.65 lower to 0.02 lower)	low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 24 month(s)											
2	RCT	not serious	not serious	very serious [10]	serious [11]	NA	536	522	MD -4.12 (-6.12, -2.12)	MD 4.12 lower (6.12 lower to 2.12 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. 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 = 0.3 (0.8-0.9 = serious, <0.8 = very serious).

6. I2 between 50% and 75%

7. 95% confidence intervals cross one end 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 = 0.69 (0.8-0.9 = serious, <0.8 = very serious).

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

10. I2 > 75%

11. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

L.1.8.10 Adding dapagliflozin + saxagliptin compared to adding insulin

Table 99: Clinical evidence profile: Adding dapagliflozin + saxagliptin 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
health-related quality of life - subscale net benefit score (phase v health outcomes information systems diabetes module, higher scores are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (vilsboll 2019)	RCT	not serious	not serious	NA[1]	not serious	NA	324	319	MD 1.10 (-0.84, 3.04)	MD 1.10 higher (0.84 lower to 3.04 higher)	high
health-related quality of life - subscale regimen acceptance score (phase v health outcomes information systems diabetes module, higher scores are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (vilsboll 2019)	RCT	not serious	not serious	NA[1]	not serious	NA	324	319	MD 4.20	MD 4.20 higher	high

									(1.98, 6.42)	(1.98 higher to 6.42 higher)	
health-related quality of life - subscale satisfaction (phase v health outcomes information systems diabetes module, higher scores are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (vilsboll 2019)	RCT	not serious	not serious	NA[1]	not serious	NA	324	319	MD 3.40 (1.46, 5.34)	MD 3.40 higher (1.46 higher to 5.34 higher)	high
all-cause mortality at end of follow up Mean follow-up: 12 month(s)											
1 (vilsboll 2019)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	2/324	0/319	PETO OR 7.30 (0.46, 116.95)	6 more per 1000 (2 fewer to 15 more)	low
cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)											
1 (vilsboll 2019)	RCT	not serious	not serious	NA[1]	not serious	NA	0/324	0/319	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	high
acute kidney injury at end of follow up Mean follow-up: 12 month(s)											
1 (vilsboll 2019)	RCT	not serious	not serious	NA[1]	not serious	NA	0/324	0/319	RR 0.00 (0.00, 0.00)	0 fewer per 1000 (0 more to 0 more)	high
diabetic ketoacidosis at end of follow up Mean follow-up: 12 month(s)											

1 (vilsboll 2019)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	0/324	1/319	PETO OR 0.13 (0.00, 6.72)	3 fewer per 1000 (9 fewer to 3 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 12 month(s)											
1 (vilsboll 2019)	RCT	not serious	not serious	NA[1]	not serious	NA	93/324	147/319	RR 0.62 (0.51, 0.77)	174 fewer per 1000 (228 fewer to 107 fewer)	high
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											
1 (vilsboll 2019)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	0/324	3/319	PETO OR 0.13 (0.01, 1.28)	9 fewer per 1000 (20 fewer to 1 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (vilsboll 2019)	RCT	very serious[3]	not serious	NA[1]	not serious	NA	212	177	MD -0.25 (-0.40, -0.10)	MD 0.25 lower (0.40 lower to 0.10 lower)	low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (vilsboll 2019)	RCT	very serious[3]	not serious	NA[1]	not serious	NA	212	178	MD -4.60 (-5.37, -3.83)	MD 4.60 lower (5.37 lower to	low

										3.83 lower)	

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

L.1.8.11 Adding dapagliflozin + saxagliptin compared to adding saxagliptin

Table 100: Clinical evidence profile: Adding dapagliflozin + saxagliptin compared to adding saxagliptin

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: 5.5 month(s)											
2	RCT	not serious	not serious	serious[1]	very serious[2]	NA	1/472	0/471	RD 0.00 (-0.01, 0.01)	2 more per 1000 (5 fewer to 9 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 5.5 month(s)											
2	RCT	not serious	not serious	not serious	not serious	NA	0/472	0/471	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	high
persistent signs of worsening kidney disease at end of follow up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2015a)	RCT	serious[3]	not serious	NA[4]	not serious	NA	0/179	0/176	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (11 fewer to 11 more)	moderate

diabetic ketoacidosis at end of follow up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2019d)	RCT	not serious	not serious	NA[4]	not serious	NA	0/293	0/295	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	high
hypoglycaemia episodes at end of follow up Mean follow-up: 5.5 month(s)											
2	RCT	not serious	not serious	not serious	very serious[5]	NA	8/472	6/471	RR 1.33 (0.47, 3.81)	4 more per 1000 (7 fewer to 36 more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.5 month(s)											
2	RCT	not serious	not serious	serious[1]	very serious[2]	NA	1/472	0/469	RD 0.00 (-0.01, 0.01)	2 more per 1000 (5 fewer to 9 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
2	RCT	not serious	not serious	very serious[6]	serious[7]	NA	443	431	MD -0.75 (-1.61, 0.12)	MD 0.75 lower (1.61 lower to 0.12 higher)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
2	RCT	not serious	not serious	not serious	not serious	NA	443	433	MD -1.79 (-2.22, -1.36)	MD 1.79 lower (2.22 lower to 1.36 lower)	high

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

2. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.29 (0.8-0.9 = serious, <0.8 = very serious).

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

4. Only one study so no inconsistency

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

6. I2 > 75%

7. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

L.1.8.12 Adding dapagliflozin + saxagliptin compared to adding sitagliptin

Table 101: Clinical evidence profile: Adding dapagliflozin + saxagliptin 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
all-cause mortality at end of follow up Mean follow-up: 12 month(s)											
1 (handelsman 2019)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/232	0/229	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	low
cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)											
1 (handelsman 2019)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/232	0/229	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	low
acute kidney injury at end of follow up Mean follow-up: 12 month(s)											

1 (handelsman 2019)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	1/232	0/229	PETO OR 7.29 (0.14, 367.63)	4 more per 1000 (4 fewer to 13 more)	very low
cardiac arrhythmia at end of follow up Mean follow-up: 12 month(s)											
1 (handelsman 2019)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	1/232	5/229	PETO OR 0.26 (0.05, 1.28)	18 fewer per 1000 (38 fewer to 3 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 12 month(s)											
1 (handelsman 2019)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	12/232	9/229	RR 1.32 (0.57, 3.06)	12 more per 1000 (17 fewer to 81 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											
1 (handelsman 2019)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/232	0/229	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (handelsman 2019)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	232	229	MD -0.48 (-0.72, -0.24)	MD 0.48 lower (0.72 lower to 0.24 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											

1 (handelsman 2019)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	232	229	MD -1.50 (-2.33, -0.67)	MD 1.50 lower (2.33 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. 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)

L.1.8.13 Adding empagliflozin + liraglutide compared to adding empagliflozin

Table 102: Clinical evidence profile: Adding empagliflozin + liraglutide compared to adding empagliflozin

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 scores) at end of follow up Mean follow-up: 12 month(s)											
1 (ikonomidis 2020)	RCT	serious[1]	not serious	NA[2]	serious[3]	NA	40	40	MD -0.70 (-1.12, -0.28)	MD 0.70 lower (1.12 lower to 0.28 lower)	low
weight change (kg, lower values are better, final scores) at end of follow up Mean follow-up: 12 month(s)											
1 (ikonomidis 2020)	RCT	serious[1]	not serious	NA[2]	very serious[4]	NA	40	40	MD 1.10 (-3.07, 5.27)	MD 1.10 higher (3.07 lower to 5.27 higher)	very low
bmi change (kg/m2, lower values are better, final scores) at end of follow up Mean follow-up: 12 month(s)											

1 (ikonomidis 2020)	RCT	serious[1]	not serious	NA[2]	serious[5]	NA	40	40	MD -1.10 (-2.49, 0.29)	MD 1.10 lower (2.49 lower to 0.29 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 one end of the defined MIDs (-0.50, 0.50)

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

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

L.1.8.14 Adding empagliflozin + liraglutide compared to adding insulin

Table 103: Clinical evidence profile: Adding empagliflozin + 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
hba1c change (%, lower values are better, final scores) at end of follow up Mean follow-up: 12 month(s)											
1 (ikonomidis 2020)	RCT	serious[1]	not serious	NA[2]	serious[3]	NA	40	40	MD -0.70 (-1.15, -0.25)	MD 0.70 lower (1.15 lower to 0.25 lower)	low
weight change (kg, lower values are better, final scores) at end of follow up Mean follow-up: 12 month(s)											
1 (ikonomidis 2020)	RCT	serious[1]	not serious	NA[2]	serious[4]	NA	40	40	MD -1.80 (-5.74, 2.14)	MD 1.80 lower (5.74 lower to 2.14 higher)	low
bmi change (kg/m2, lower values are better, final scores) at end of follow up											

Mean follow-up: 12 month(s)											
1 (ikonomidis 2020)	RCT	serious[1]	not serious	NA[2]	serious[5]	NA	40	40	MD -2.30 (-3.85, -0.75)	MD 2.30 lower (3.85 lower to 0.75 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 one end of the defined MIDs (-0.50, 0.50)

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

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

L.1.8.15 Adding empagliflozin + liraglutide compared to adding liraglutide

Table 104: Clinical evidence profile: Adding empagliflozin + liraglutide compared to adding liraglutide

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 scores) at end of follow up Mean follow-up: 12 month(s)											
1 (ikonomidis 2020)	RCT	serious[1]	not serious	NA[2]	serious[3]	NA	40	40	MD -0.30 (-0.67, 0.07)	MD 0.30 lower (0.67 lower to 0.07 higher)	low
weight change (kg, lower values are better, final scores) at end of follow up Mean follow-up: 12 month(s)											
1 (ikonomidis 2020)	RCT	serious[1]	not serious	NA[2]	very serious[4]	NA	40	40	MD 0.40 (-4.25, 5.05)	MD 0.40 higher (4.25 lower to 5.05 higher)	very low

bmi change (kg/m2, lower values are better, final scores) at end of follow up Mean follow-up: 12 month(s)											
1 (ikonomidis 2020)	RCT	serious[1]	not serious	NA[2]	very serious[5]	NA	40	40	MD -0.30 (-1.85, 1.25)	MD 0.30 lower (1.85 lower to 1.25 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 one end of the defined MIDs (-0.50, 0.50)

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

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

L.1.8.16 Adding ertugliflozin + sitagliptin compared to adding ertugliflozin

Table 105: Clinical evidence profile: Adding ertugliflozin + sitagliptin compared to adding ertugliflozin

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: 12 month(s)											
1 (pratley 2018a)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	1/487	1/498	PETO OR 1.02 (0.06, 16.37)	0 more per 1000 (6 fewer to 6 more)	low
cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	0/487	1/498	PETO OR 0.14 (0.00, 6.97)	2 fewer per 1000 (6 fewer to 2 more)	low

diabetic ketoacidosis at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	1/487	0/498	PETO OR 7.56 (0.15, 380.98)	2 more per 1000 (2 fewer to 6 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RCT	very serious[3]	not serious	NA[1]	very serious[2]	NA	22/487	15/498	RR 1.50 (0.79, 2.86)	15 more per 1000 (6 fewer to 56 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RCT	very serious[3]	not serious	NA[1]	very serious[2]	NA	0/487	2/498	PETO OR 0.14 (0.01, 2.21)	4 fewer per 1000 (10 fewer to 2 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RCT	very serious[3]	not serious	NA[1]	serious[4]	NA	487	498	MD -0.50 (-0.64, -0.36)	MD 0.50 lower (0.64 lower to 0.36 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RCT	very serious[3]	not serious	NA[1]	not serious	NA	487	498	MD 0.20 (-0.37, 0.77)	MD 0.20 higher (0.37 lower to 0.77 higher)	low

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

L.1.8.17 Adding ertugliflozin + sitagliptin compared to adding sitagliptin

Table 106: Clinical evidence profile: Adding ertugliflozin + sitagliptin 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
all-cause mortality at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	1/487	0/247	PETO OR 4.51 (0.07, 285.75)	2 more per 1000 (2 fewer to 6 more)	low
cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RCT	not serious	not serious	NA[1]	not serious	NA	0/487	0/247	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	high
diabetic ketoacidosis at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	1/487	0/247	PETO OR 4.51 (0.07, 285.75)	2 more per 1000 (2 fewer to 6 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 12 month(s)											

1 (pratley 2018a)	RCT	very serious[3]	not serious	NA[1]	very serious[2]	NA	22/487	7/247	RR 1.59 (0.69, 3.68)	17 more per 1000 (9 fewer to 76 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RCT	very serious[3]	not serious	NA[1]	not serious	NA	0/487	0/247	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RCT	very serious[3]	not serious	NA[1]	serious[4]	NA	487	247	MD -0.60 (-0.77, -0.43)	MD 0.60 lower (0.77 lower to 0.43 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RCT	very serious[3]	not serious	NA[1]	serious[5]	NA	487	247	MD -2.50 (-3.23, -1.77)	MD 2.50 lower (3.23 lower to 1.77 lower)	very low

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. 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 (-2.40, 2.40)

L.1.8.18 Adding glimepiride + metformin compared to adding glimepiride

Table 107: Clinical evidence profile: Adding glimepiride + metformin 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
hypoglycaemia episodes at end of follow up Mean follow-up: 5.5 month(s)											
1 (park 2014)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	17/32	20/34	RR 0.90 (0.59, 1.39)	57 fewer per 1000 (243 fewer to 229 more)	very low
at night hypoglycaemic episodes at end of follow up Mean follow-up: 5.5 month(s)											
1 (park 2014)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	3/32	6/34	RR 0.53 (0.14, 1.95)	83 fewer per 1000 (151 fewer to 167 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.5 month(s)											
1 (park 2014)	RCT	very serious[1]	not serious	NA[2]	very serious[4]	NA	0/32	0/34	RD 0.00 (-0.06, 0.06)	0 fewer per 1000 (57 fewer to 57 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
1 (park 2014)	RCT	very serious[1]	not serious	NA[2]	serious[5]	NA	32	32	MD -0.71 (-1.20, -0.22)	MD 0.71 lower	very low

										(1.20 lower to 0.22 lower)	
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
1 (park 2014)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	32	32	MD 0.12 (-1.25, 1.49)	MD 0.12 higher (1.25 lower to 1.49 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 (-0.50, 0.50)

L.1.8.19 Adding glimepiride + metformin compared to adding metformin

Table 108: Clinical evidence profile: Adding glimepiride + metformin compared to adding metformin

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 (park 2014)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	17/32	20/34	RR 0.90 (0.59, 1.39)	57 fewer per 1000 (243 fewer to 229 more)	very low

at night hypoglycaemic episodes at end of follow up Mean follow-up: 5.5 month(s)											
1 (park 2014)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	3/32	6/34	RR 0.53 (0.14, 1.95)	83 fewer per 1000 (151 fewer to 167 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.5 month(s)											
1 (park 2014)	RCT	very serious[1]	not serious	NA[2]	very serious[4]	NA	0/32	0/34	RD 0.00 (-0.06, 0.06)	0 fewer per 1000 (57 fewer to 57 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
1 (park 2014)	RCT	very serious[1]	not serious	NA[2]	serious[5]	NA	32	32	MD -0.71 (-1.20, -0.22)	MD 0.71 lower (1.20 lower to 0.22 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
1 (park 2014)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	32	32	MD 0.12 (-1.25, 1.49)	MD 0.12 higher (1.25 lower to 1.49 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. 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)

L.1.8.20 Adding glimepiride + metformin slow release compared to adding glimepiride + metformin standard release

Table 109: Clinical evidence profile: Adding glimepiride + metformin slow release compared to adding glimepiride + metformin standard release

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: 5.8 month(s)											
1 (kim 2018)	RCT	very serious [1]	not serious	NA[2]	serious [3]	NA	19/86	10/86	RR 1.90 (0.94, 3.85)	105 more per 1000 (7 fewer to 331 more)	very low
at night hypoglycaemic episodes at end of follow up Mean follow-up: 5.8 month(s)											
1 (kim 2018)	RCT	very serious [1]	not serious	NA[2]	very serious [4]	NA	3/86	5/86	RR 0.60 (0.15, 2.43)	23 fewer per 1000 (50 fewer to 83 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 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)

L.1.8.21 Adding liraglutide + metformin compared to adding metformin

Table 110: Clinical evidence profile: Adding liraglutide + metformin compared to adding metformin

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 end of follow up Mean follow-up: 6 month(s)											
1 (iacobellis 2017)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	49	36	MD -0.80 (-1.13, -0.47)	MD 0.80 lower (1.13 lower to 0.47 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 (iacobellis 2017)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	49	36	MD 4.00 (1.92, 6.08)	MD 4.00 higher (1.92 higher to 6.08 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 (-0.50, 0.50)

L.1.8.22 Adding pioglitazone + alogliptin compared to adding pioglitazone

Table 111: Clinical evidence profile: Adding pioglitazone + alogliptin 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 Mean follow-up: 6 month(s)											
1 (defronzo 2012)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/780	1/387	PETO OR 0.05 (0.00, 3.15)	3 fewer per 1000 (8 fewer to 2 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 6 month(s)											
1 (defronzo 2012)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/780	1/387	PETO OR 0.05 (0.00, 3.15)	3 fewer per 1000 (8 fewer to 2 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 6 month(s)											
1 (defronzo 2012)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	10/780	8/387	RR 0.62 (0.25, 1.56)	8 fewer per 1000 (16 fewer to 12 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)											
1 (defronzo 2012)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	1/780	2/387	PETO OR 0.22 (0.02, 2.44)	4 fewer per 1000 (11 fewer to 4 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up											

Mean follow-up: 6 month(s)											
1 (defronzo 2012)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	659	274	MD -0.50 (-0.62, -0.38)	MD 0.50 lower (0.62 lower to 0.38 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)

L.1.8.23 Adding pioglitazone + exenatide compared to adding insulin

Table 112: Clinical evidence profile: Adding pioglitazone + 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 Mean follow-up: 36 month(s)											
1 (abdul-ghani 2017)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	1/146	2/140	PETO OR 0.49 (0.05, 4.75)	7 fewer per 1000 (31 fewer to 16 more)	very low
non-fatal stroke at end of follow up Mean follow-up: 36 month(s)											
1 (abdul-ghani 2017)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	0/146	2/140	PETO OR 0.13 (0.01, 2.07)	14 fewer per 1000 (34 fewer to 5 more)	very low
hospitalisation for heart failure at end of follow up											

Mean follow-up: 36 month(s)											
1 (abdul-ghani 2017)	RCT	serious[1]	not serious	NA[2]	serious[4]	NA	0/146	0/140	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 36 month(s)											
1 (abdul-ghani 2017)	RCT	serious[1]	not serious	NA[2]	serious[4]	NA	99/146	125/140	RR 0.76 (0.67, 0.86)	215 fewer per 1000 (295 fewer to 124 fewer)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 36 month(s)											
1 (abdul-ghani 2017)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	0/146	1/140	PETO OR 0.13 (0.00, 6.54)	7 fewer per 1000 (21 fewer to 7 more)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 36 month(s)											
1 (abdul-ghani 2017)	RCT	serious[1]	not serious	NA[2]	not serious	NA	146	140	MD -4.40 (-4.73, -4.07)	MD 4.40 lower (4.73 lower to 4.07 lower)	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 (0.80, 1.25)

L.1.8.24 Adding pioglitazone + exenatide compared to adding pioglitazone

Table 113: Clinical evidence profile: Adding pioglitazone + exenatide 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
hba1c change (%, lower values are better, final values) at end of follow up Mean follow-up: 12 month(s)											
1 (sathyanarayana 2011)	RCT	very serious[1]	serious[2]	NA[3]	serious[4]	NA	11	10	MD -0.50 (-0.80, -0.20)	MD 0.50 lower (0.80 lower to 0.20 lower)	very low
weight change (kg, lower values are better, final values) at end of follow up Mean follow-up: 12 month(s)											
1 (sathyanarayana 2011)	RCT	very serious[1]	serious[2]	NA[3]	very serious[5]	NA	11	10	MD -1.10 (-6.54, 4.34)	MD 1.10 lower (6.54 lower to 4.34 higher)	very low
bmi change (kg/m2, lower values are better, final values) at end of follow up Mean follow-up: 12 month(s)											
1 (sathyanarayana 2011)	RCT	very serious[1]	serious[2]	NA[3]	not serious	NA	11	10	MD 3.40 (1.83, 4.97)	MD 3.40 higher (1.83 higher to 4.97 higher)	very low

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

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

3. Only one study so no inconsistency

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 (-2.40, 2.40)

L.1.8.25 Adding pioglitazone + metformin compared to adding metformin

Table 114: Clinical evidence profile: Adding pioglitazone + metformin compared to adding metformin

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: 6 month(s)											
1 (hanefeld 2011)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	11/39	9/42	RR 1.32 (0.61, 2.83)	68 more per 1000 (83 fewer to 392 more)	very low
hba1c change (%, lower values are better, final values) at end of follow up Mean follow-up: 6 month(s)											
1 (hanefeld 2011)	RCT	serious[1]	not serious	NA[2]	serious[4]	NA	37	39	MD -0.38 (-0.70, -0.06)	MD 0.38 lower (0.70 lower to 0.06 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. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

L.1.8.26 Adding pioglitazone + metformin compared to adding pioglitazone

Table 115: Clinical evidence profile: Adding pioglitazone + metformin 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
hypoglycaemia episodes at end of follow up Mean follow-up: 6 month(s)											
1 (hanefeld 2011)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	11/39	8/40	RR 1.41 (0.64, 3.13)	82 more per 1000 (73 fewer to 426 more)	very low
hba1c change (%, lower values are better, final values) at end of follow up Mean follow-up: 6 month(s)											
1 (hanefeld 2011)	RCT	serious[1]	not serious	NA[2]	serious[4]	NA	37	37	MD -0.34 (-0.68, -0.00)	MD 0.34 lower (0.68 lower to 0.00 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. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

L.2 Switching

L.2.1 Metformin

L.2.1.1 Switching to metformin slow release compared to staying on metformin standard release

Table 116: Clinical evidence profile: Switching to metformin slow release compared to staying on metformin standard release

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: 6 month(s)											
1 (fujioka 2003)	RCT	very serious [1]	not serious	NA[2]	very serious [3]	NA	1/146	0/75	PETO OR 4.54 (0.07, 285.16)	7 more per 1000 (7 fewer to 20 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 6 month(s)											
1 (fujioka 2003)	RCT	very serious [1]	not serious	NA[2]	very serious [3]	NA	1/146	1/75	RR 0.51 (0.03, 8.10)	6 fewer per 1000 (13 fewer to 95 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)											
1 (fujioka 2003)	RCT	very serious [1]	not serious	NA[2]	serious [4]	NA	0/146	0/75	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 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. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.

L.2.2 DPP-4 inhibitors

L.2.2.1 Switching to sitagliptin compared to switching to placebo

Table 117: Clinical evidence profile: Switching to sitagliptin compared to switching to 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											
1 (retnakaran 2010)	RCT	very serious [1]	serious[2]	NA[3]	very serious [4]	NA	1/10	1/11	RR 1.10 (0.08, 15.36)	9 more per 1000 (84 fewer to 1305 more)	very low

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

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

3. Only one study so no inconsistency

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

L.2.2.2 Switching to vildagliptin compared to switching to alogliptin

Table 118: Clinical evidence profile: Switching to vildagliptin compared to Switching to alogliptin

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 (tanaka 2017)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	68/68	62/62	RR 1.00 (0.97, 1.03)	0 fewer per 1000 (29 fewer to 30 more)	low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)											
1 (tanaka 2017)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	0/68	0/62	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (30 fewer to 30 more)	very low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (tanaka 2017)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	63	62	MD -0.20 (-0.43, 0.03)	MD 0.20 lower (0.43 lower to 0.03 higher)	low
weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (tanaka 2017)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	63	62	MD -0.10 (-0.74, 0.54)	MD 0.10 lower (0.74 lower to 0.54 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. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.

L.2.3 GLP-1 receptor agonist

L.2.3.1 Switching to liraglutide compared to staying on sitagliptin

Table 119: Clinical evidence profile: Switching to liraglutide compared to staying on sitagliptin

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 the end of follow-up Mean follow-up: 5.5 month(s)											
1 (bailey 2016)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	1/204	0/202	PETO OR 7.32 (0.15, 368.77)	5 more per 1000 (5 fewer to 14 more)	very low
hypoglycaemia episodes at the end of follow-up Mean follow-up: 5.5 month(s)											
1 (bailey 2016)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	0/204	3/202	PETO OR 0.13 (0.01, 1.28)	15 fewer per 1000 (32 fewer to 2 more)	very low
severe hypoglycaemic episodes at the end of follow-up Mean follow-up: 5.5 month(s)											
1 (bailey 2016)	RCT	serious[1]	not serious	NA[2]	not serious	NA	0/204	0/202	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (10 fewer to 10 more)	moderate
hba1c change (%, lower values are better, final values) at the end of follow-up Mean follow-up: 5.5 month(s)											
1 (bailey 2016)	RCT	serious[1]	not serious	NA[2]	serious[4]	NA	204	202	MD -0.61 (-0.82, -0.40)	MD 0.61 lower (0.82 lower to 0.40 lower)	low

weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (bailey 2016)	RCT	serious[1]	not serious	NA[2]	not serious	NA	204	202	MD -1.67 (-2.34, -1.00)	MD 1.67 lower (2.34 lower to 1.00 lower)	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. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

L.2.3.2 Switching to semagluitde compared to switching to dulaglutide

Table 120: Clinical evidence profile: Switching to semaglutide compared to switching to 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: 6 month(s)											
1 (lijima 2023)	RCT	serious[1]	not serious	NA 2	very serious[3]	NA	0/16	0/16	RD 0.00 (-0.11, 0.11)	0 fewer per 1000 (114 fewer to 114 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)											

1 (lijima 2023)	RCT	serious[1]	not serious	NA[2]	serious[4]	NA	16	16	MD -0.42 (-0.71, -0.13)	MD 0.42 lower (0.71 lower to 0.13 lower)	low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)											
1 (lijima 2023)	RCT	serious[1]	not serious	NA[2]	serious[5]	NA	16	16	MD -2.50 (-4.70, -0.30)	MD 2.50 lower (4.70 lower to 0.30 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. 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)

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

L.2.3.3 Switching to semaglutide compared to staying on sitagliptin

Table 121: Clinical evidence profile - Switching to semaglutide compared to staying on sitagliptin

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: 12 month(s)											
1 (buse 2020)	RCT	not serious	not serious	NA[1]	serious[2]	NA	0/100	0/97	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	moderate

cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)											
1 (buse 2020)	RCT	not serious	not serious	NA[1]	serious[2]	NA	0/100	0/97	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	moderate
non-fatal myocardial infaRCTion at end of follow up Mean follow-up: 12 month(s)											
1 (buse 2020)	RCT	not serious	not serious	NA[1]	serious[2]	NA	0/100	0/97	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	moderate
hospitalisation for heart failure at end of follow up Mean follow-up: 12 month(s)											
1 (buse 2020)	RCT	not serious	not serious	NA[1]	very serious[3]	NA	0/100	1/97	PETO OR 0.13 (0.00, 6.62)	10 fewer per 1000 (30 fewer to 10 more)	low
acute kidney injury at end of follow up Mean follow-up: 12 month(s)											
1 (buse 2020)	RCT	not serious	not serious	NA[1]	serious[2]	NA	0/100	0/97	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	moderate
at night hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											
1 (buse 2020)	RCT	not serious	not serious	NA[1]	serious[2]	NA	0/100	0/97	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	moderate
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											

1 (buse 2020)	RCT	not serious	not serious	NA[1]	serious[2]	NA	0/100	0/97	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	moderate
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (buse 2020)	RCT	serious[4]	not serious	NA[1]	serious[5]	NA	100	98	MD -0.30 (-0.60, 0.00)	MD 0.30 lower (0.60 lower to 0.00 higher)	low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (buse 2020)	RCT	serious[4]	not serious	NA[1]	serious[6]	NA	100	98	MD -1.50 (-2.85, -0.15)	MD 1.50 lower (2.85 lower to 0.15 lower)	low
bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (buse 2020)	RCT	serious[4]	not serious	NA[1]	serious[7]	NA	100	98	MD -0.40 (-0.90, 0.10)	MD 0.40 lower (0.90 lower to 0.10 higher)	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 one end 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)

L.2.4 SGLT2 inhibitors

L.2.4.1 Switching to canagliflozin compared to switching to liraglutide

Table 122: Clinical evidence profile: Switching to canagliflozin compared to switching to liraglutide

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 (diabetes therapy-related qol, 0-100, higher values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
1 (ando 2021)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	17	17	MD 6.50 (0.14, 12.86)	MD 6.50 higher (0.14 higher to 12.86 higher)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.5 month(s)											
1 (ando 2021)	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)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
1 (ando 2021)	RCT	very serious[1]	not serious	NA[2]	serious[5]	NA	17	17	MD 0.10 (-0.30, 0.50)	MD 0.10 higher (0.30 lower to 0.50 higher)	very low
weight change (kg, lower values are better, change scores) at end of follow up											

Mean follow-up: 5.5 month(s)											
1 (ando 2021)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	17	17	MD 0.20 (-1.89, 2.29)	MD 0.20 higher (1.89 lower to 2.29 higher)	low
bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
1 (ando 2021)	RCT	very serious[1]	not serious	NA[2]	serious[6]	NA	17	17	MD 0.10 (-0.61, 0.81)	MD 0.10 higher (0.61 lower to 0.81 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 (-4.95, 4.95)

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 (-0.80, 0.80)

L.2.1 Sulfonylureas

L.2.1.1 Switching to glimepiride compared to switching to liraglutide

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) at end of follow-up Mean follow-up: 12 month(s)											

1 (garber 2009)	RCT	very serious [1]	not serious	NA[2]	serious[3]	NA	154	320	MD 0.42 (0.21, 0.63)	MD 0.42 higher (0.21 higher to 0.63 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)

L.2.2 Thiazolidinediones

L.2.2.1 Staying on pioglitazone compared to switching to dapagliflozin

Table 123: Clinical evidence profile: Staying on pioglitazone compared to switching to dapagliflozin

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 (cho 2019)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	9/35	7/36	RR 1.32 (0.55, 3.16)	63 more per 1000 (87 fewer to 420 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.5 month(s)											
1 (cho 2019)	RCT	serious[1]	not serious	NA[2]	serious[4]	NA	0/35	0/36	RD 0.00 (-0.05, 0.05)	0 fewer per 1000 (53 fewer to 53 more)	low
hba1c change (%, lower values are better, final values) at end of follow up											

Mean follow-up: 5.5 month(s)											
1 (cho 2019)	RCT	serious[1]	not serious	NA[2]	not serious	NA	35	36	MD 0.10 (-0.25, 0.45)	MD 0.10 higher (0.25 lower to 0.45 higher)	moderate
weight change (kg, lower values are better, final values) at end of follow up Mean follow-up: 5.5 month(s)											
1 (cho 2019)	RCT	serious[1]	not serious	NA[2]	very serious[5]	NA	35	36	MD 3.90 (-2.85, 10.65)	MD 3.90 higher (2.85 lower to 10.65 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 (0.80, 1.25)

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

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

L.2.2.2 Switching to pioglitazone compared to switching to glimepiride

Table 124: Clinical evidence profile: Switching to pioglitazone compared with switching to glimepiride

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: 12 month(s)											
1 (tan 2004)	RCT	not serious	not serious	NA[1]	serious[2]	NA	19/121	38/123	RR 0.51 (0.31, 0.83)	152 fewer per 1000 (213 fewer to 53 fewer)	moderate

hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (tan 2004)	RCT	not serious	not serious	NA[1]	very serious[3]	NA	109	109	MD -0.10 (-1.49, 1.29)	MD 0.10 lower (1.49 lower to 1.29 higher)	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 (-0.50, 0.50)

L.2.3 Combinations

L.2.3.1 Switching to fixed-dose combination glimepiride/metformin slow release compared to staying on fixed-dose combination glimepiride/metformin standard release

Table 125: Clinical evidence profile: Fixed-dose combination glimepiride/metformin slow release compared to staying on fixed-dose combination glimepiride/metformin standard release

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: 5.8 month(s)											
1 (kim 2018)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	19/86	10/86	RR 1.90 (0.94, 3.85)	105 more per 1000 (7 fewer to 331 more)	very low
at night hypoglycaemic episodes at end of follow up Mean follow-up: 5.8 month(s)											

1 (kim 2018)	RCT	very serious [1]	not serious	NA[2]	very serious [4]	NA	3/86	5/86	RR 0.60 (0.15, 2.43)	23 fewer per 1000 (50 fewer to 83 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 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)