National Institute for Health and Care Excellence

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Draft for consultation

Type 2 diabetes in adults: management (medicines update)

[E2.1] Evidence reviews for initial pharmacological management of type 2 diabetes: appendices E to I

NICE guideline GID-NG10336

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

August 2025

Draft for Consultation

This evidence review was developed by NICE

Disclaimer

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

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ISBN:

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E.1 Model 5: People with type 2 diabetes at high risk of cardiovascular disease (no other comorbidities)

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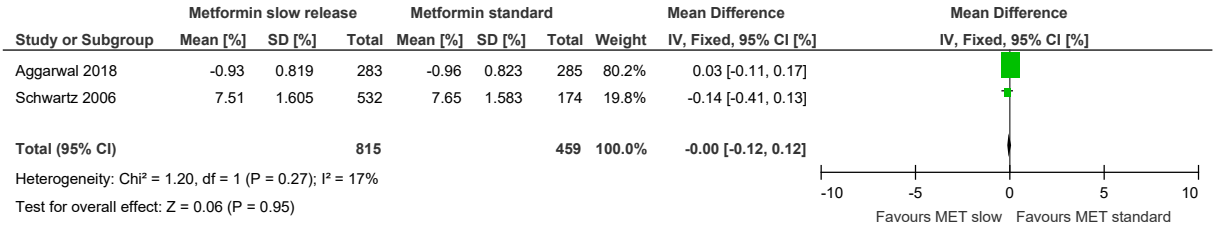
E.1.1 Metformin hydrochloride slow release compared to metformin hydrochloride standard release

Figure 1: HbA1c change (%, lower values are better, change scores and final values) at end of follow-up



E.1.2 Metformin compared to placebo

Figure 2: All-cause mortality at end of follow-up

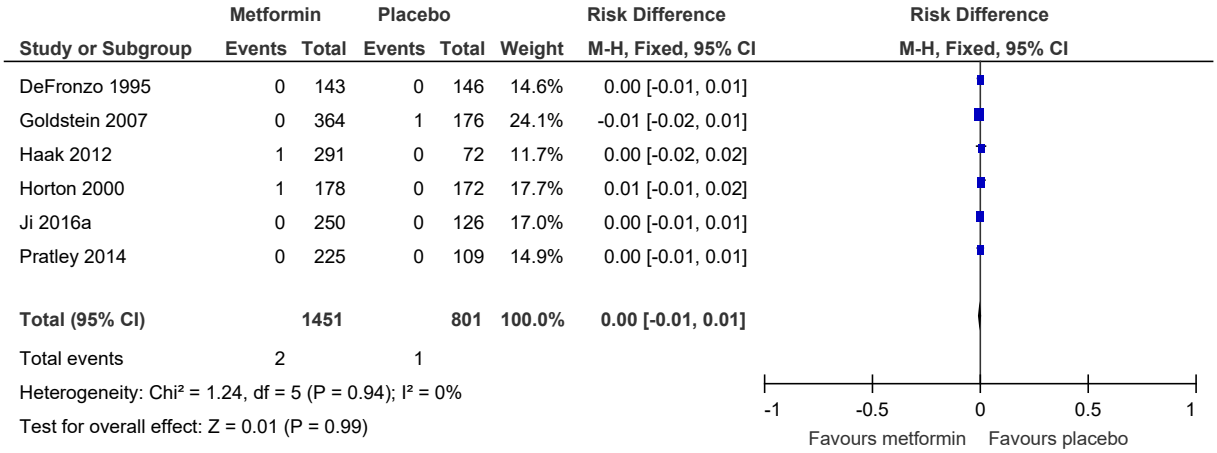


Figure 3: Cardiovascular mortality at end of follow-up

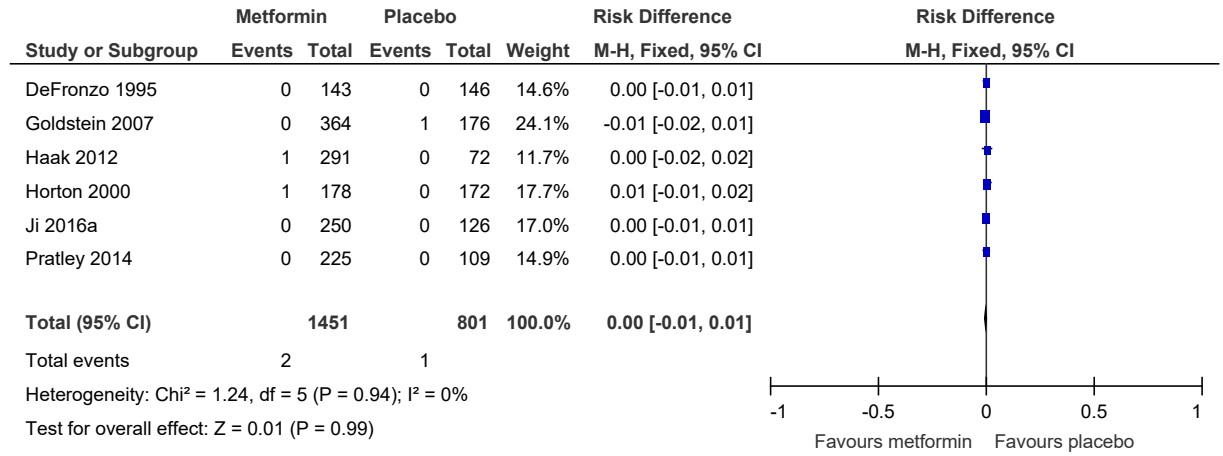


Figure 4: Hypoglycaemia episodes at end of follow-up

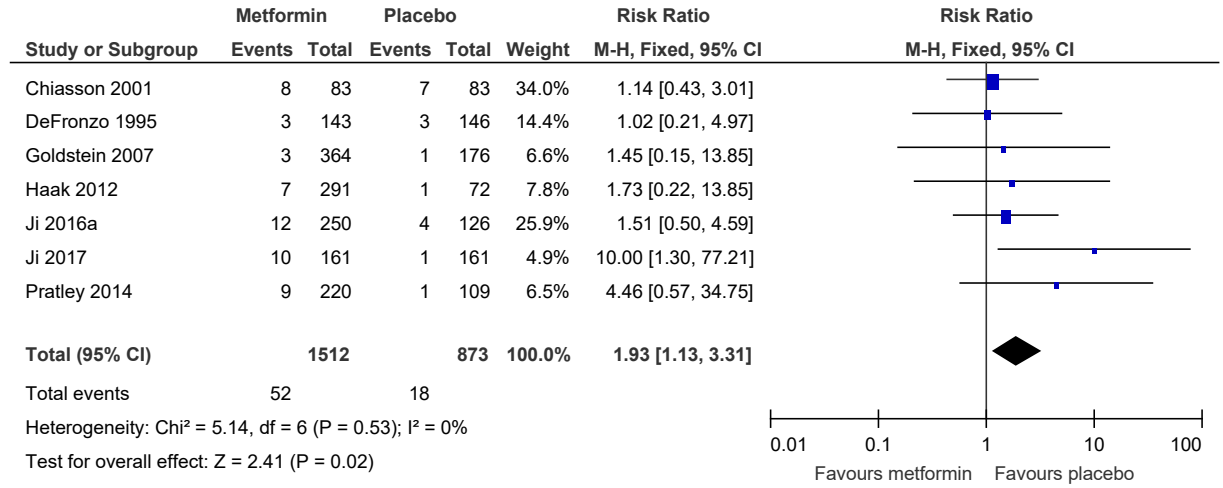


Figure 5: Severe hypoglycaemia at end of follow-up

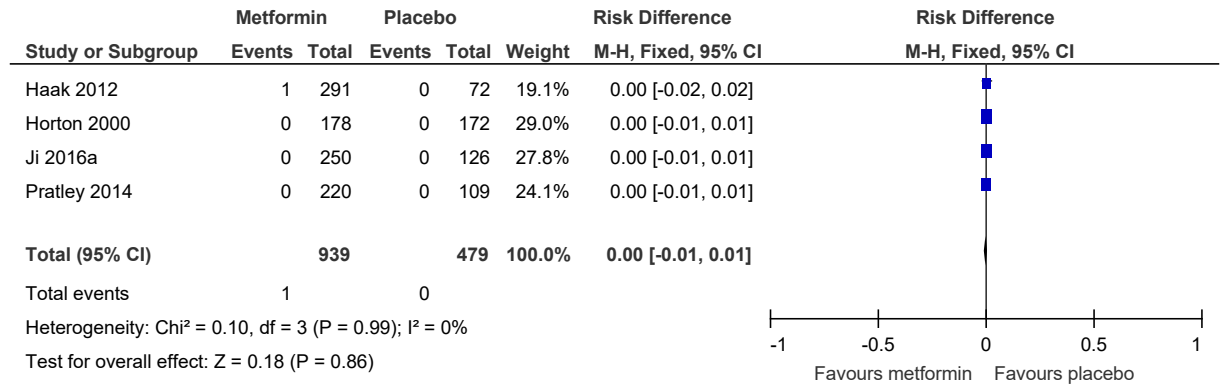
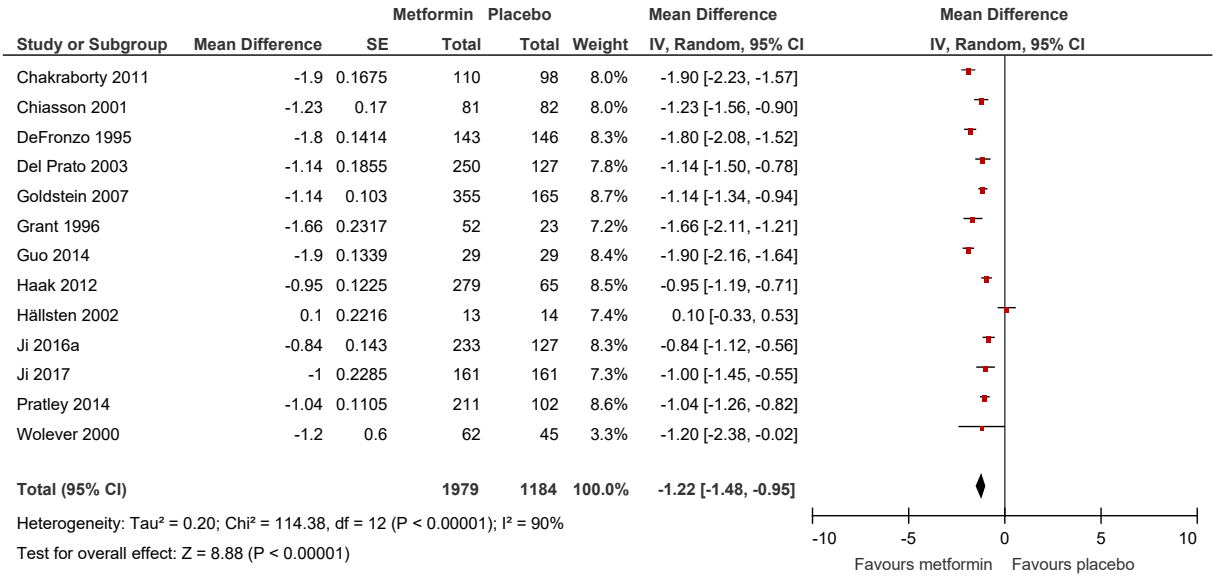


Figure 6: HbA1c change (%, lower values are better, change scores and final values) at end of follow-up



Note: Heterogeneity was not explained by sensitivity analysis, nor subgroup analysis by NAFLD subgroups.

Figure 7: Weight change (kg, lower values are better, change scores and final value) at end of follow

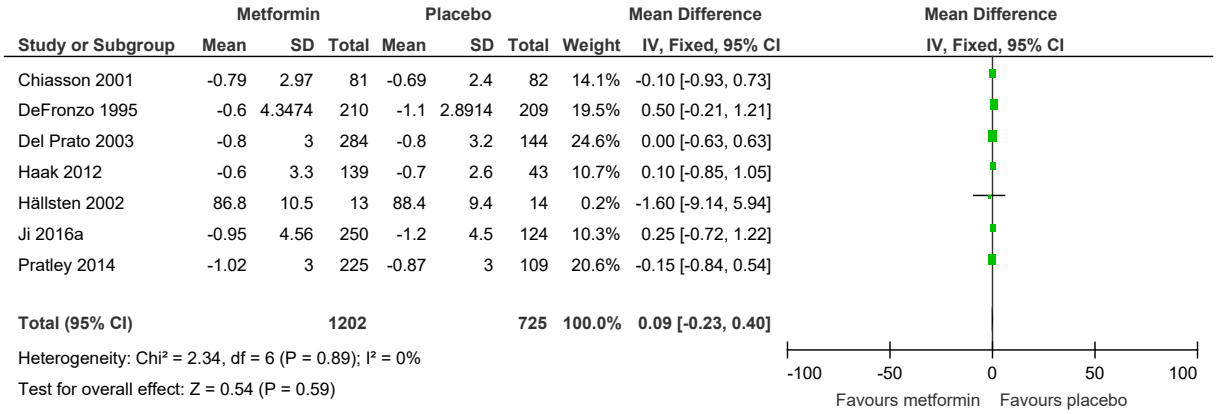
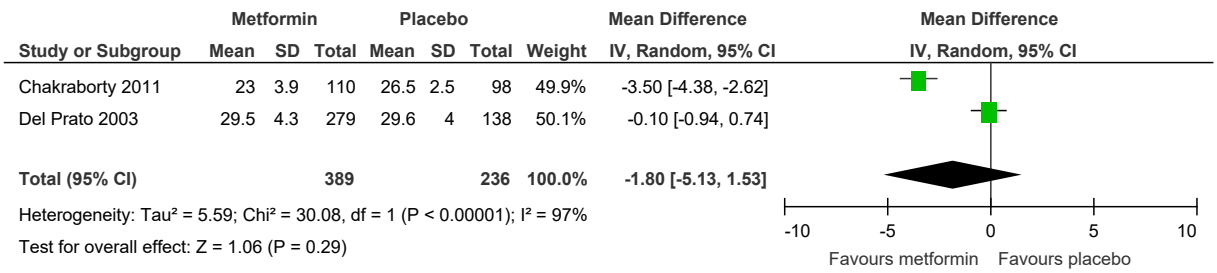


Figure 8: BMI final values (kg/m2, lower values are better) at end of follow-up



E.1.113 Metformin compared to insulin

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

E.1.2 DPP-4 inhibitors

E.1.251 Alogliptin compared to metformin

Figure 9: Hypoglycaemia episodes at end of follow-up

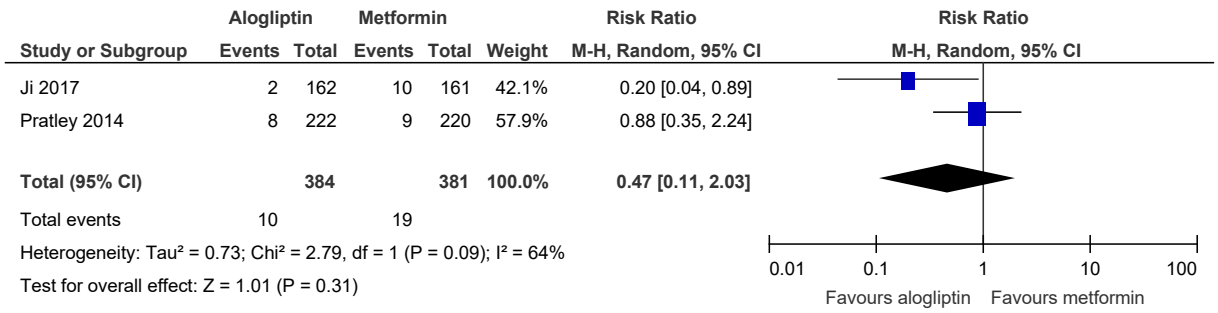
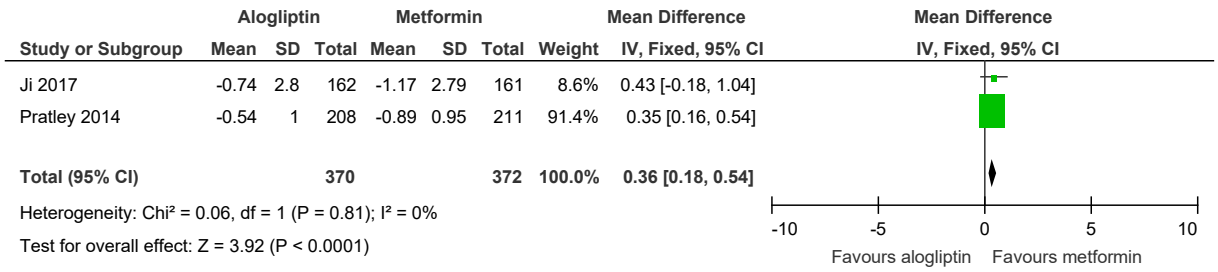


Figure 10: HbA1c change (%, lower values are better, change scores) at end of follow-up



E.1.232 Alogliptin compared to placebo

Figure 11: All-cause mortality at end of follow-up

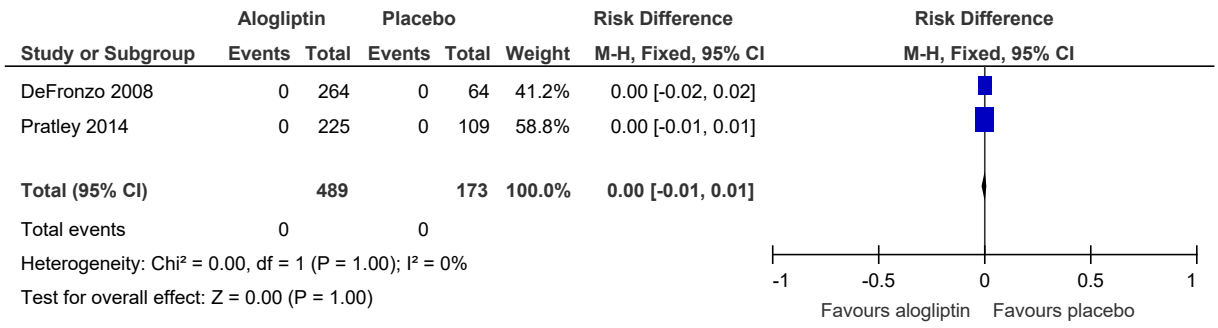


Figure 12: Hypoglycaemia episodes at end of follow-up

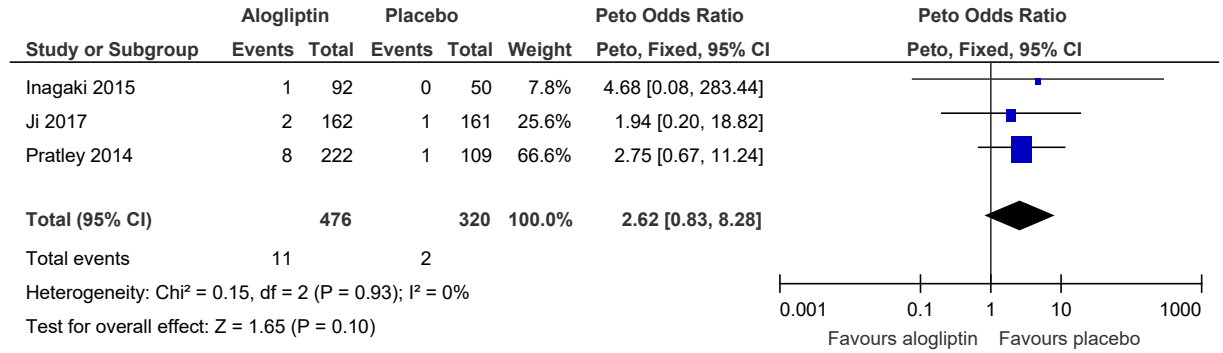


Figure 13: Severe hypoglycaemic episodes at end of follow-up

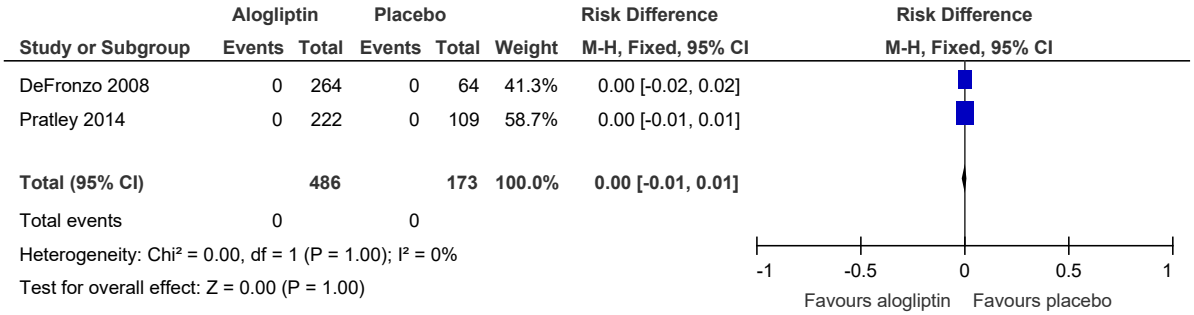


Figure 14: HbA1c change (%, lower values are better, change scores) at end of follow-up

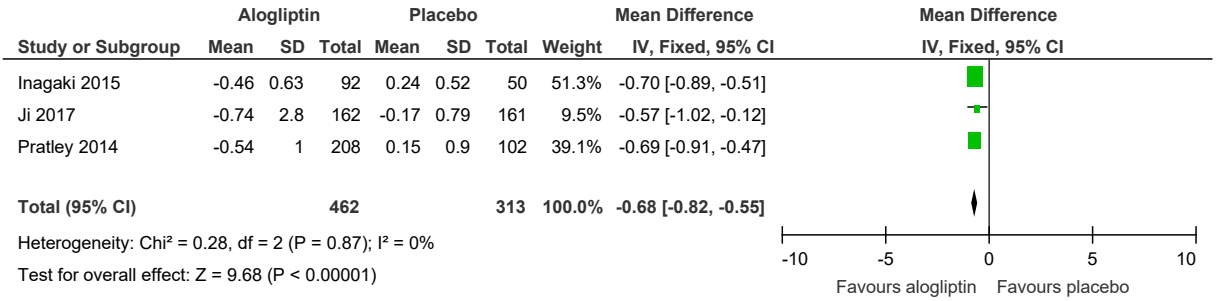
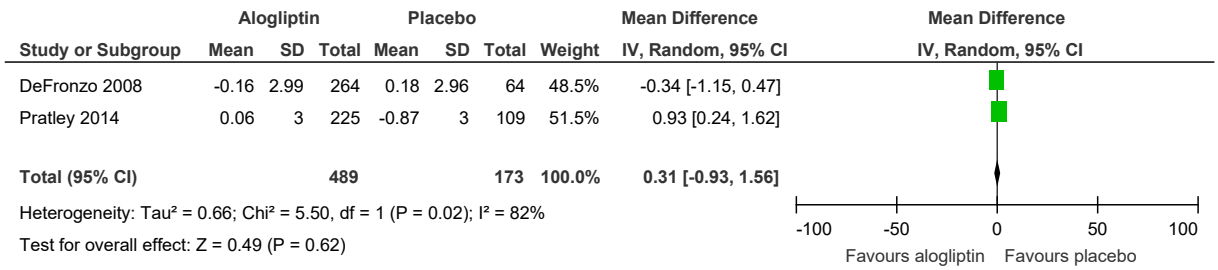


Figure 15: Weight change (kg, lower values are better, change scores) at end of follow-up



E.1.253 Linagliptin compared to metformin

Figure 16: Hypoglycaemia episodes at end of follow-up

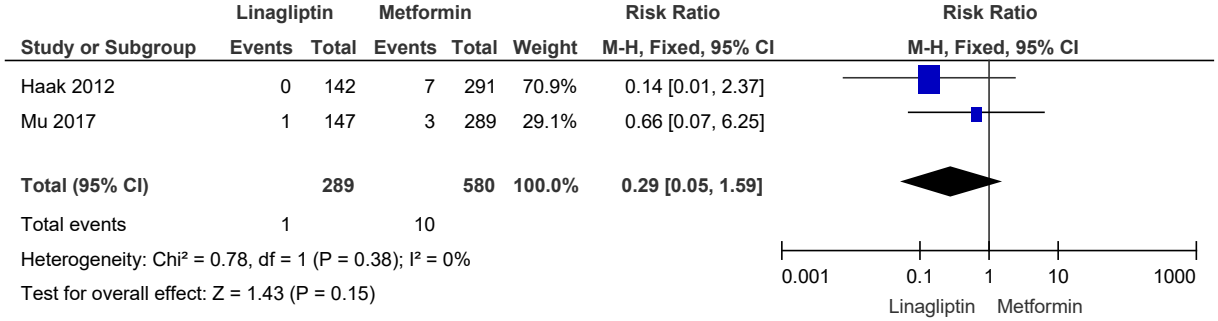


Figure 17: Severe hypoglycaemic episodes at end of follow-up

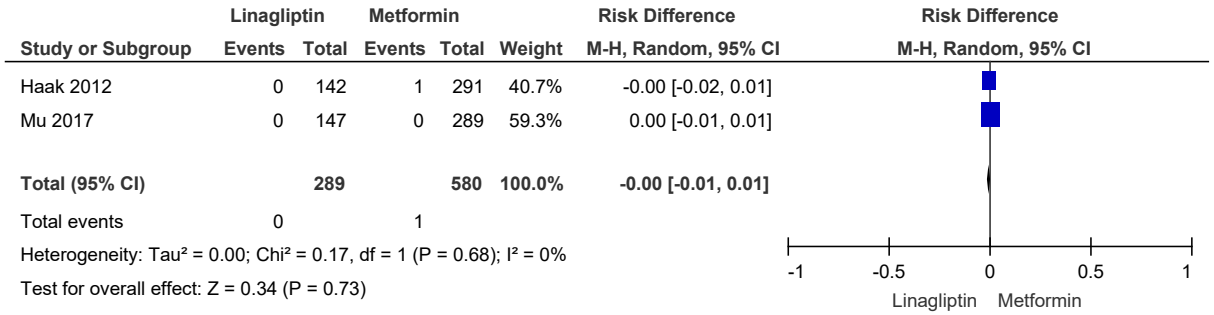


Figure 18: HbA1c change (%, lower values are better, change scores) at end of follow-up

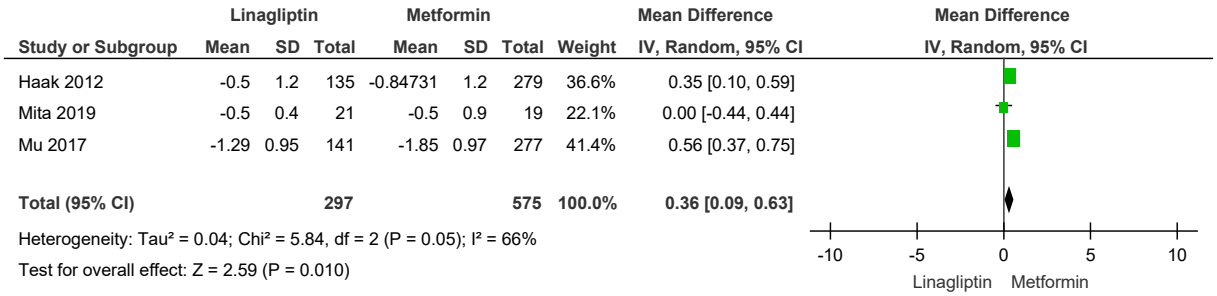
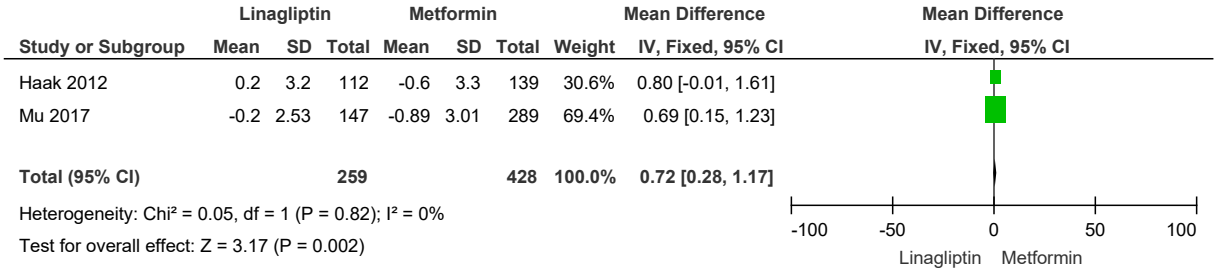


Figure 19: Weight change (kg, lower values are better, change scores) at end of follow-up



E.1.2.4 Linagliptin compared to placebo

Figure 20: Hypoglycaemia episodes at end of follow-up

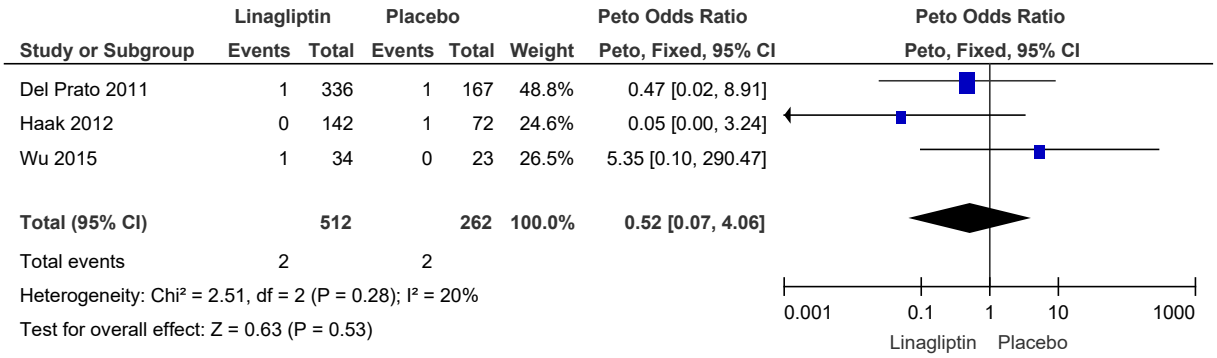


Figure 21: Severe hypoglycaemic episodes at end of follow-up

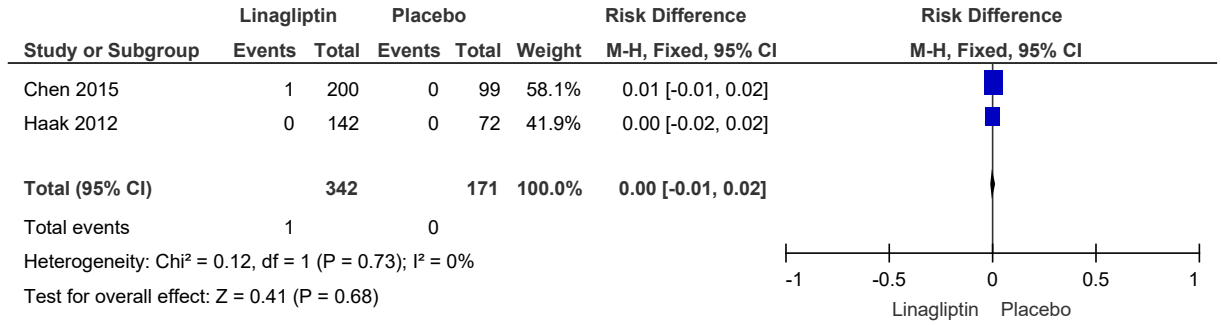
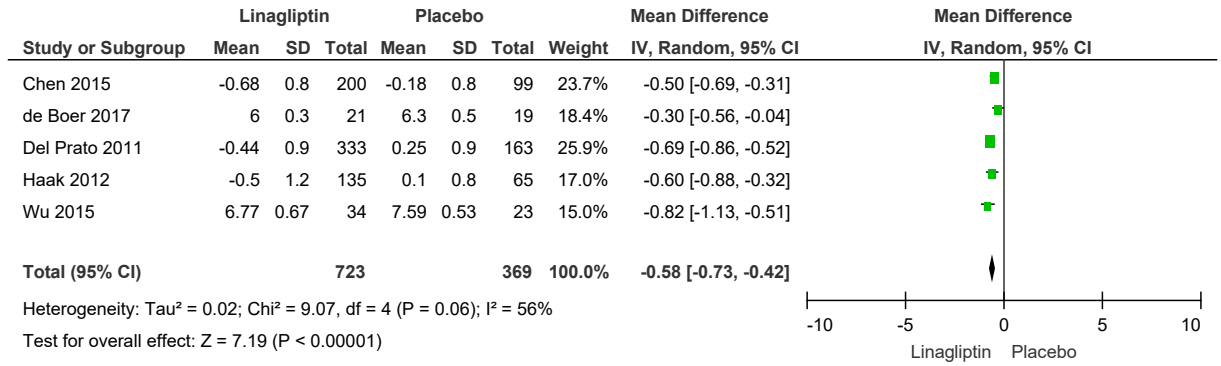
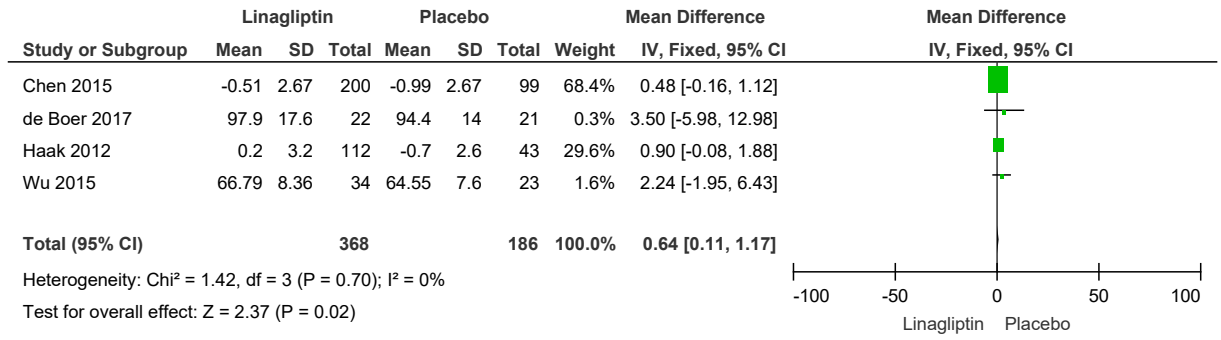


Figure 22: HbA1c change (%, lower values are better, change score) at end of follow-up



Note: Heterogeneity was not explained by sensitivity analysis, nor subgroup analysis by eGFR and NAFLD subgroups.

Figure 23: Weight change (kg, lower values are better, change score) at end of follow-up



E.1.215 Saxagliptin compared to metformin

Figure 24: All-cause mortality at end of follow-up

Study or Subgroup	Saxagliptin Events	Saxagliptin Total	Metformin Events	Metformin Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Dou 2018	1	214	0	210	12.6%	7.25 [0.14, 365.55]
Pfützner 2011A	2	335	5	328	87.4%	0.41 [0.09, 1.83]
Total (95% CI)		**549**		**538**	**100.0%**	**0.59 [0.15, 2.38]**
Total events	3		5			

Heterogeneity: Chi² = 1.80, df = 1 (P = 0.18); I² = 44%

Test for overall effect: Z = 0.74 (P = 0.46)

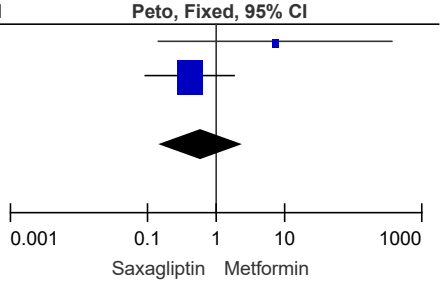


Figure 25: Hypoglycaemia episodes at end of follow-up

Study or Subgroup	Saxagliptin Events	Saxagliptin Total	Metformin Events	Metformin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Dou 2018	3	214	4	210	16.7%	0.74 [0.17, 3.25]
Pfützner 2011A	7	335	20	328	83.3%	0.34 [0.15, 0.80]
Total (95% CI)		**549**		**538**	**100.0%**	**0.41 [0.20, 0.84]**
Total events	10		24			

Heterogeneity: Chi² = 0.77, df = 1 (P = 0.38); I² = 0%

Test for overall effect: Z = 2.42 (P = 0.02)

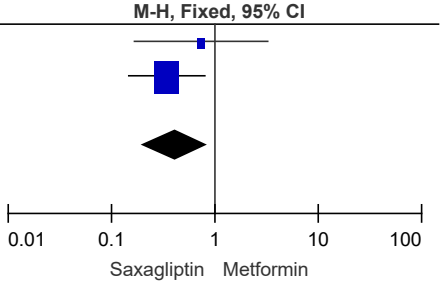


Figure 26: Severe hypoglycaemic episodes at end of follow-up

Study or Subgroup	Saxagliptin Events	Saxagliptin Total	Metformin Events	Metformin Total	Weight	Risk Difference M-H, Random, 95% CI
Dou 2018	0	214	0	210	55.4%	0.00 [-0.01, 0.01]
Pfützner 2011A	0	335	2	328	44.6%	-0.01 [-0.02, 0.00]
Total (95% CI)		**549**		**538**	**100.0%**	**-0.00 [-0.01, 0.00]**
Total events	0		2			

Heterogeneity: Tau² = 0.00; Chi² = 0.84, df = 1 (P = 0.36); I² = 0%

Test for overall effect: Z = 0.78 (P = 0.44)

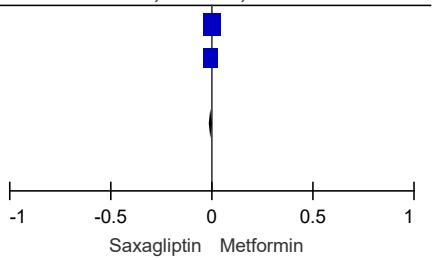


Figure 27: HbA1c change (%, lower values are better, change scores) at end of follow-up

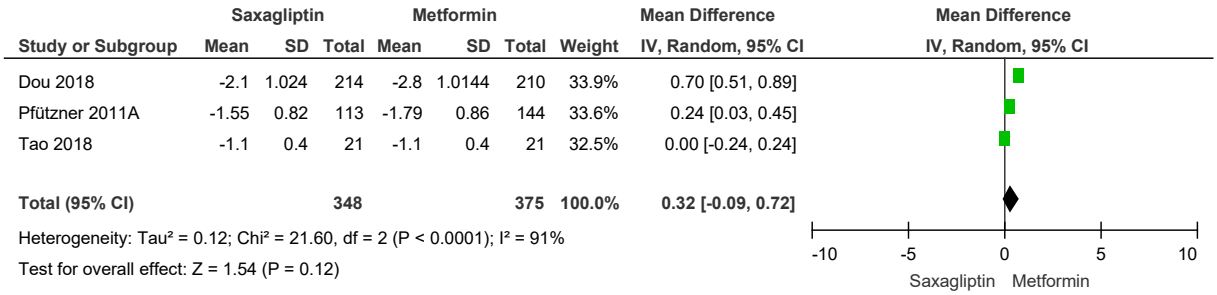


Figure 28: Weight change (kg, lower values are better, change scores) at end of follow-up

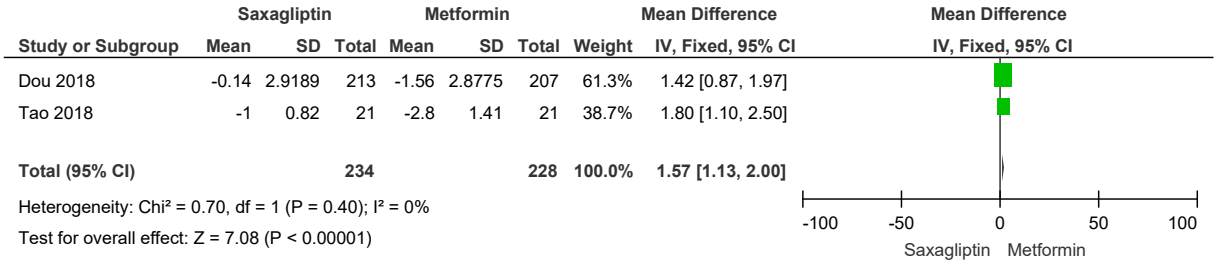
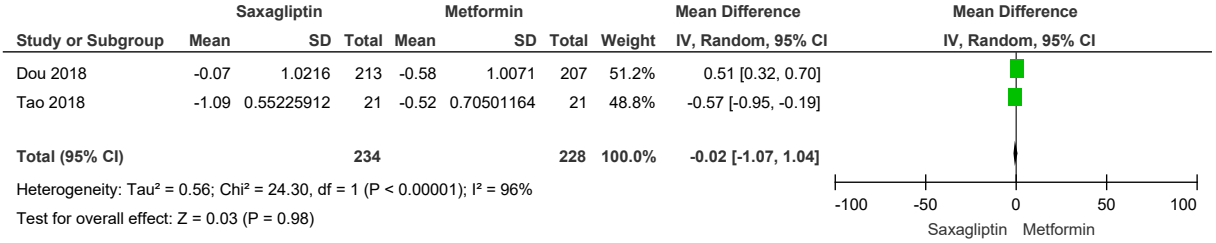


Figure 29: BMI change (kg/m2, lower values are better, change scores) at end of follow-up



E.1.216 Saxagliptin compared to placebo

Figure 30: All-cause mortality at end of follow-up

Study or Subgroup	Saxagliptin Events	Saxagliptin Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Frederich 2012	1	291	0	74	18.1%	0.00 [-0.02, 0.02]
Kumar 2014	0	107	0	106	16.3%	0.00 [-0.02, 0.02]
Pan 2012A	1	284	0	284	43.5%	0.00 [-0.01, 0.01]
Rosenstock 2009A	0	306	0	95	22.2%	0.00 [-0.02, 0.02]
Total (95% CI)		**988**		**559**	**100.0%**	**0.00 [-0.01, 0.01]**
Total events	2		0			

Heterogeneity: Chi² = 0.22, df = 3 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.59 (P = 0.56)

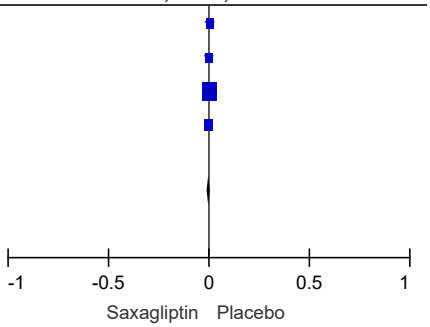


Figure 31: Cardiovascular mortality at end of follow-up

Study or Subgroup	Saxagliptin Events	Saxagliptin Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Frederich 2012	0	291	0	74	31.9%	0.00 [-0.02, 0.02]
Kumar 2014	0	107	0	106	28.8%	0.00 [-0.02, 0.02]
Rosenstock 2009A	0	306	0	95	39.2%	0.00 [-0.02, 0.02]
Total (95% CI)		**704**		**275**	**100.0%**	**0.00 [-0.01, 0.01]**
Total events	0		0			

Heterogeneity: Chi² = 0.00, df = 2 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)

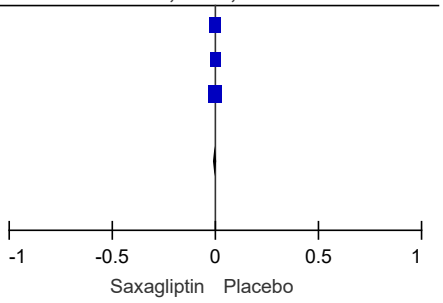


Figure 32: Hypoglycaemia episodes at end of follow-up

Study or Subgroup	Saxagliptin Events	Saxagliptin Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
Kumar 2014	0	107	0	106	28.9%	0.00 [-0.02, 0.02]
Pan 2012A	5	284	2	284	29.1%	0.01 [-0.01, 0.03]
Rosenstock 2009A	0	306	0	95	42.0%	0.00 [-0.02, 0.02]
Total (95% CI)		**697**		**485**	**100.0%**	**0.00 [-0.01, 0.01]**
Total events	5		2			

Heterogeneity: Tau² = 0.00; Chi² = 1.18, df = 2 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.62 (P = 0.54)

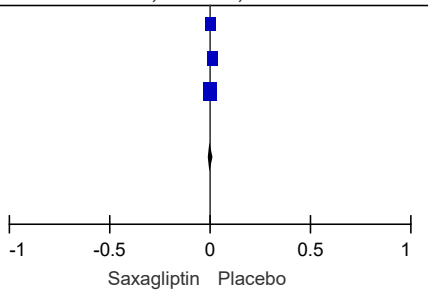


Figure 33: HbA1c change (%, lower values are better, change scores) at end of follow-up

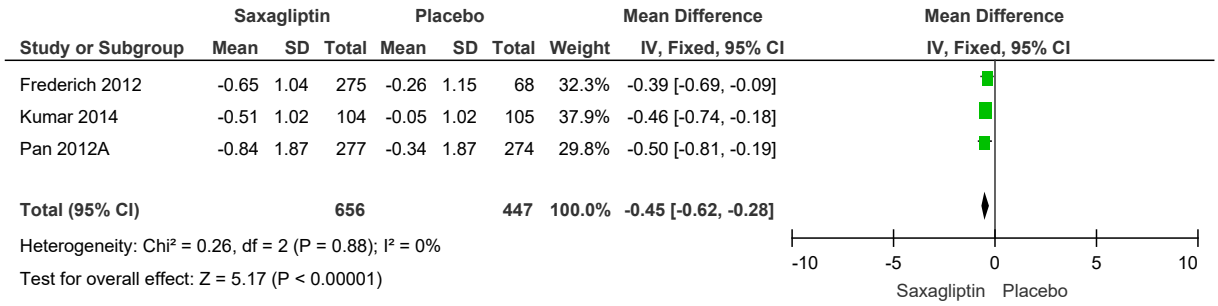
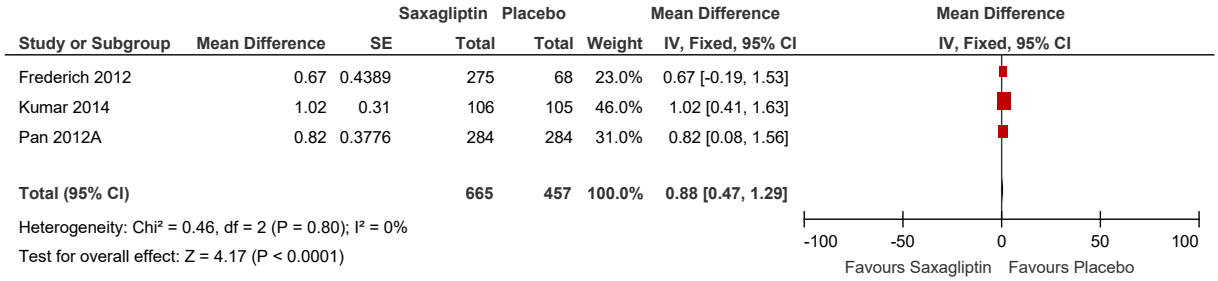


Figure 34: Weight change (kg, lower values are better, change scores) at end of follow-up



E.1.27 Sitagliptin compared to metformin

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

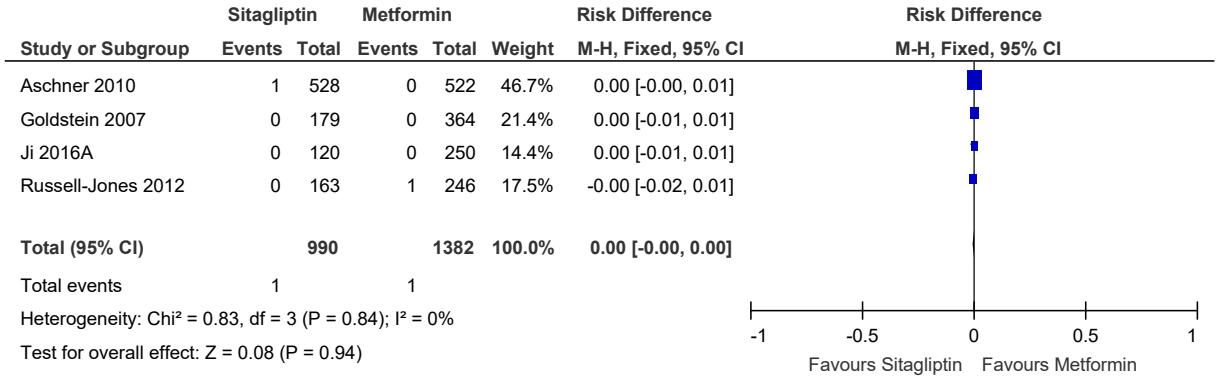


Figure 36: Cardiovascular mortality at end of follow-up

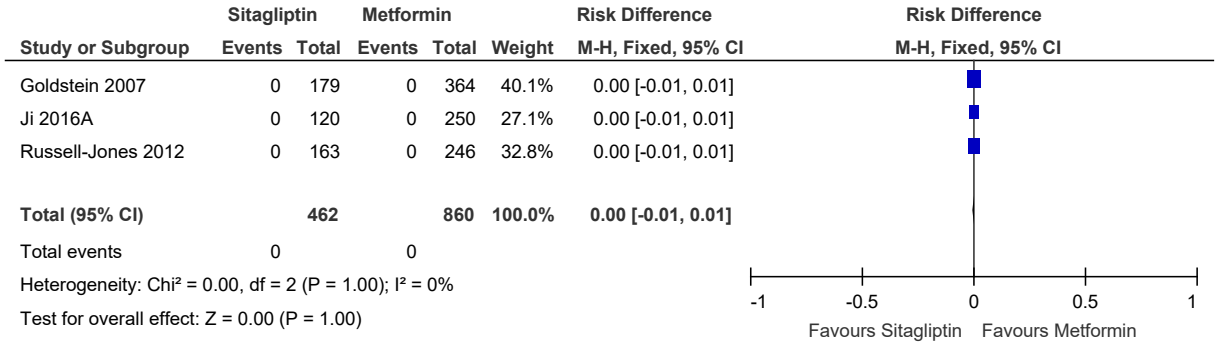


Figure 37: Hypoglycaemia episodes at end of follow-up

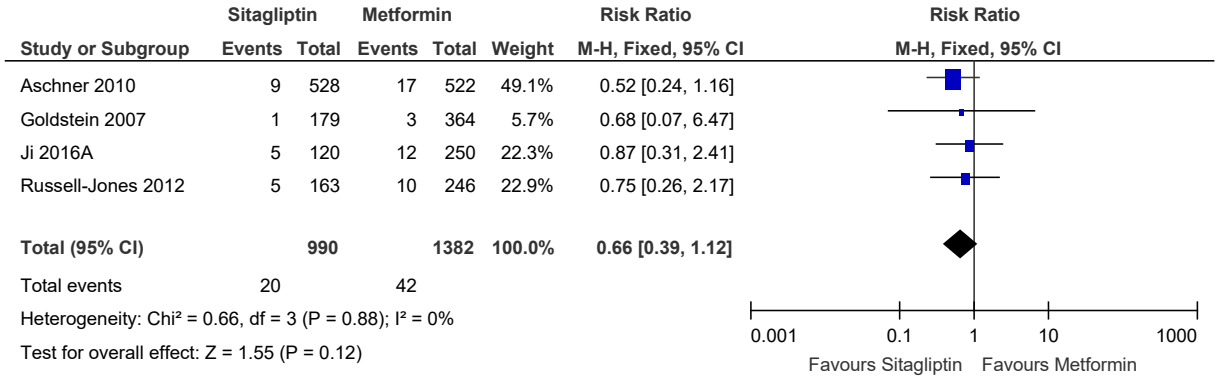


Figure 38: Severe hypoglycaemic episodes at end of follow-up

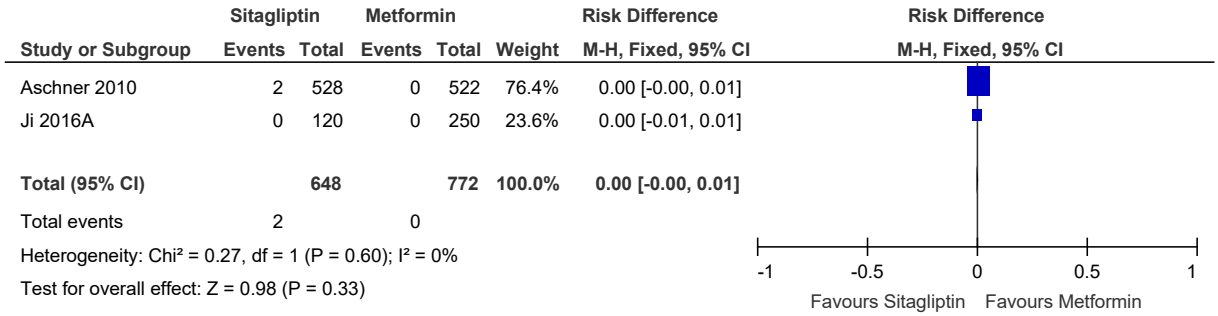


Figure 39: HbA1c change (%, lower values are better, change scores and final values) at end of follow-up

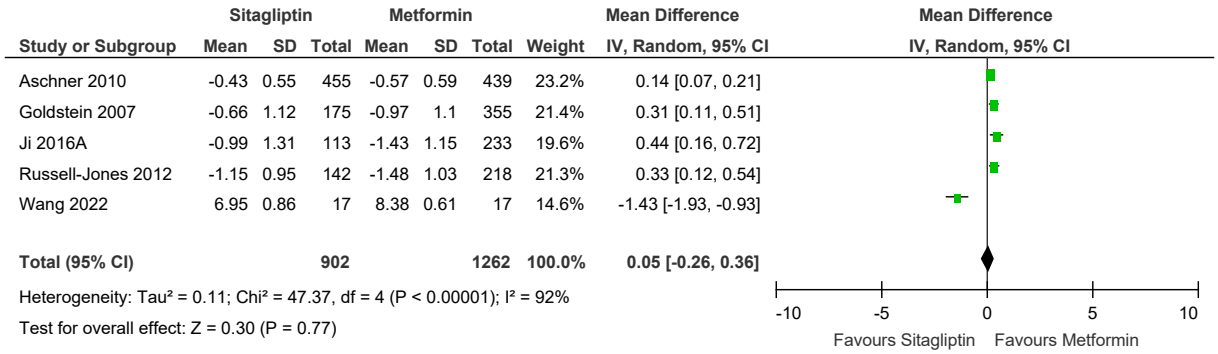
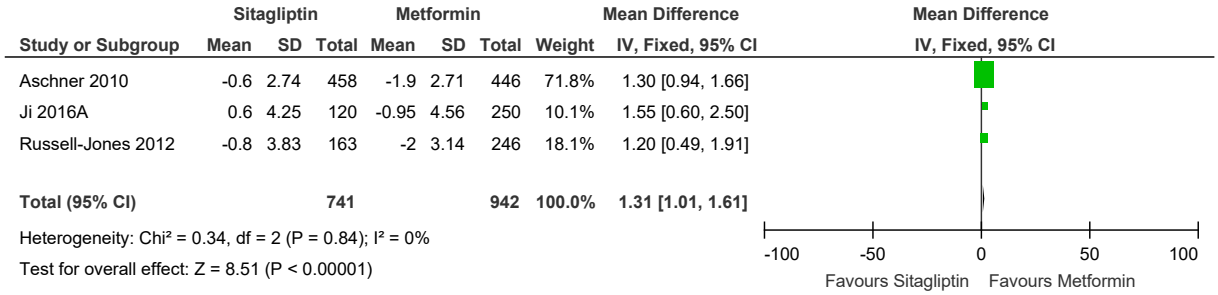


Figure 40: Weight change (kg, higher values are better, change scores) at end of follow-up



E.1.28 Sitagliptin compared to placebo

Figure 41: All-cause mortality at end of follow up

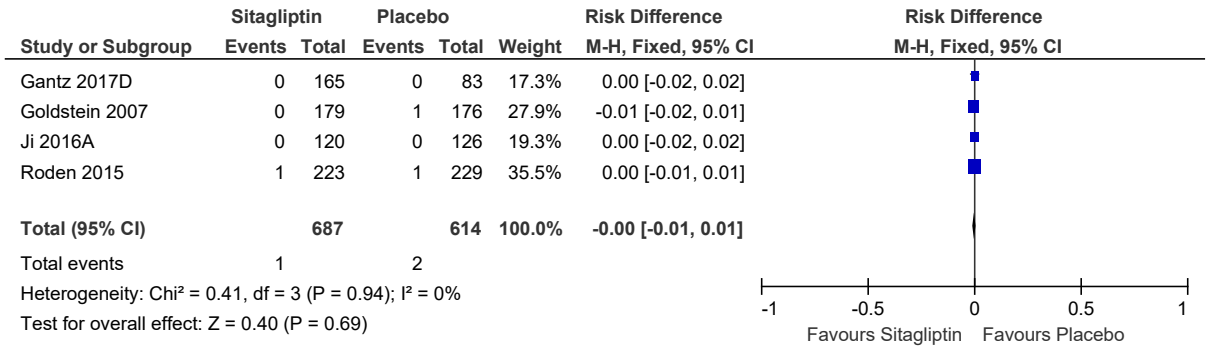


Figure 42: Cardiovascular mortality at end of follow-up

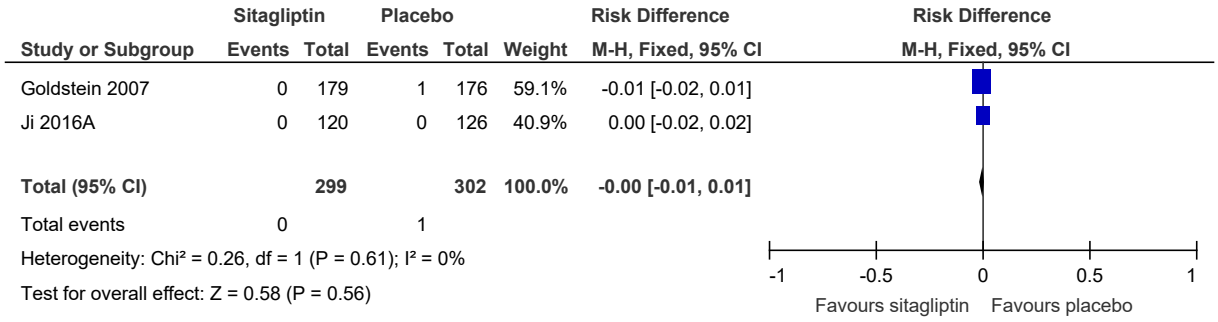


Figure 43: Hypoglycaemia episodes at end of follow-up

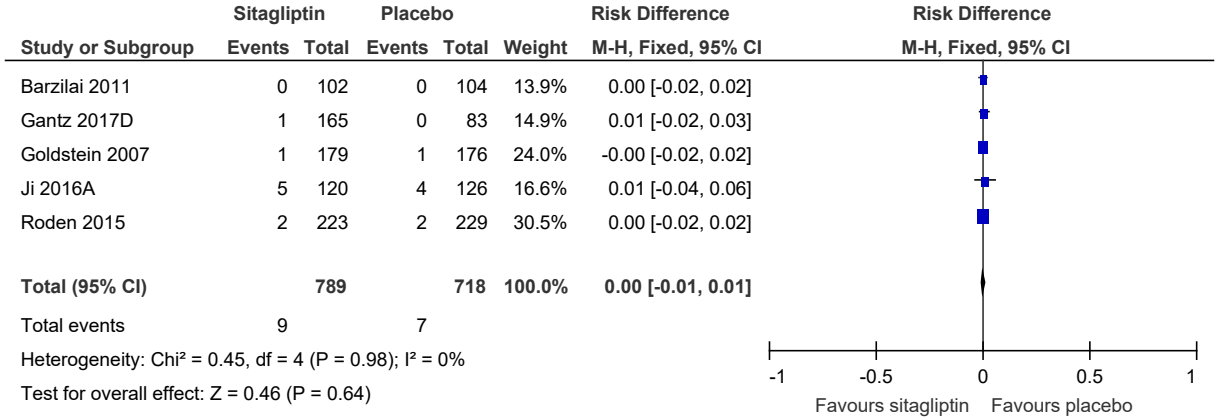


Figure 44: Severe hypoglycaemic episodes at end of follow-up

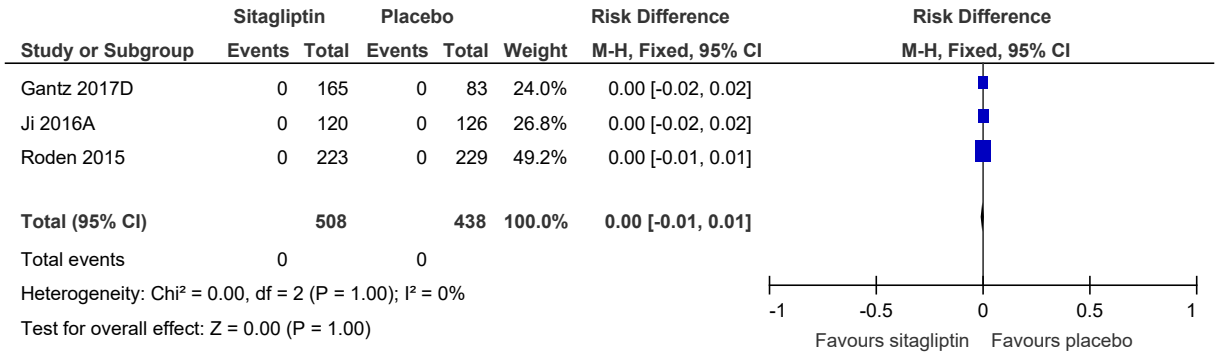
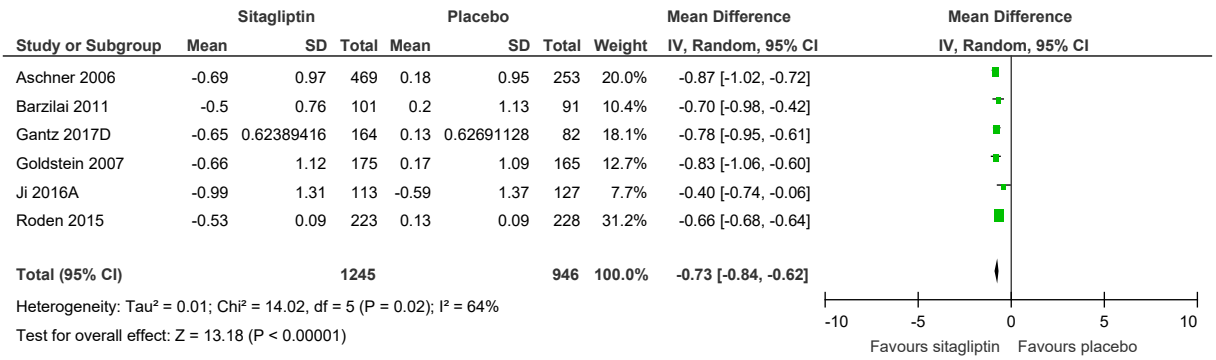
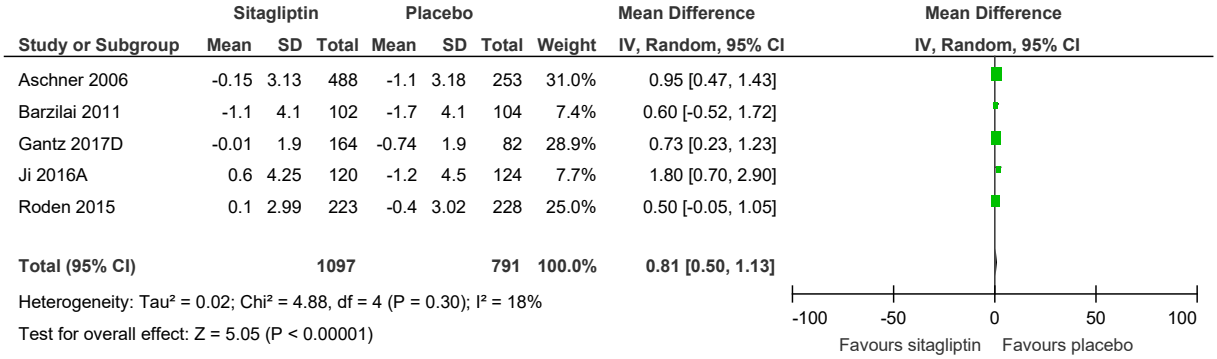


Figure 45: HbA1c change (%, lower values are better, change scores) at end of follow-up



Note: Heterogeneity was not explained by sensitivity analysis, nor subgroup analysis by eGFR subgroups.

Figure 46: Weight change (kg, lower values are better, change scores) at end of follow-up



E.1.219 Vildagliptin compared to metformin

Figure 47: All-cause mortality at end of follow up

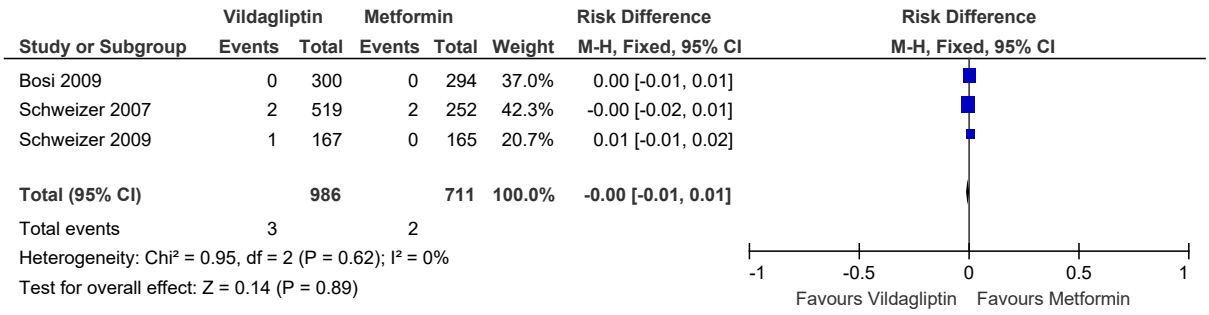


Figure 48: Non-fatal myocardial infarction at end of follow up

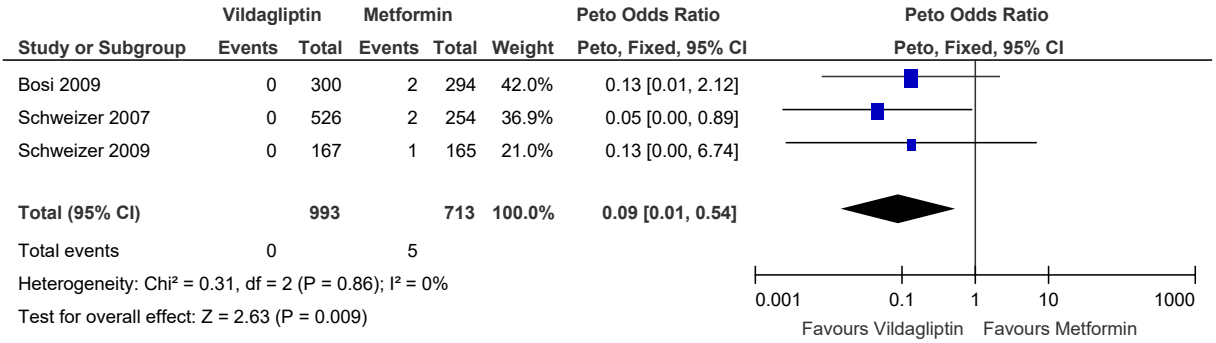


Figure 49: Hypoglycaemia episodes at end of follow-up

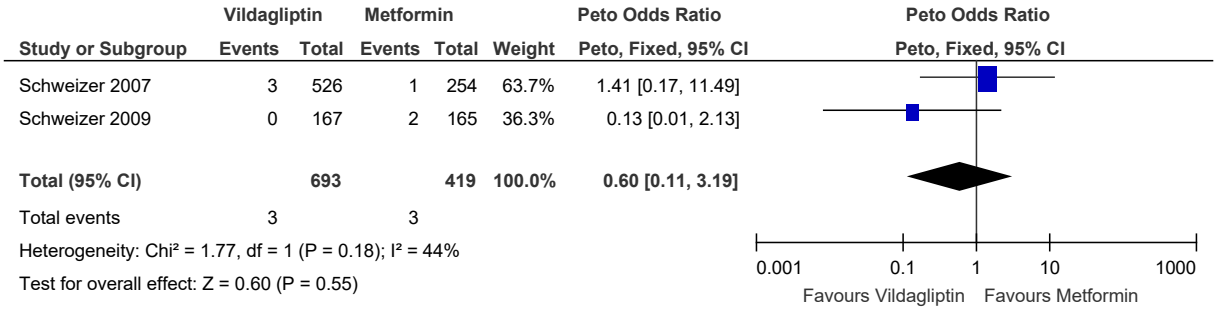


Figure 50: Severe hypoglycaemic episodes at end of follow up

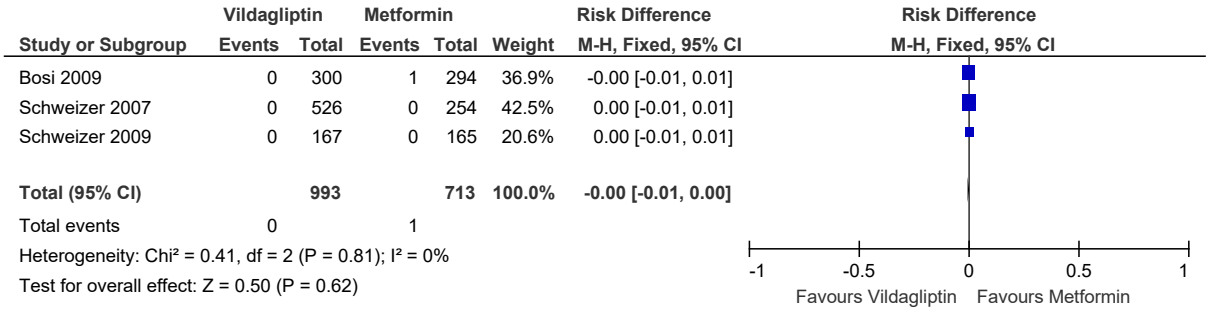


Figure 51: HbA1c change (%, lower values are better, change scores) at end of follow-up

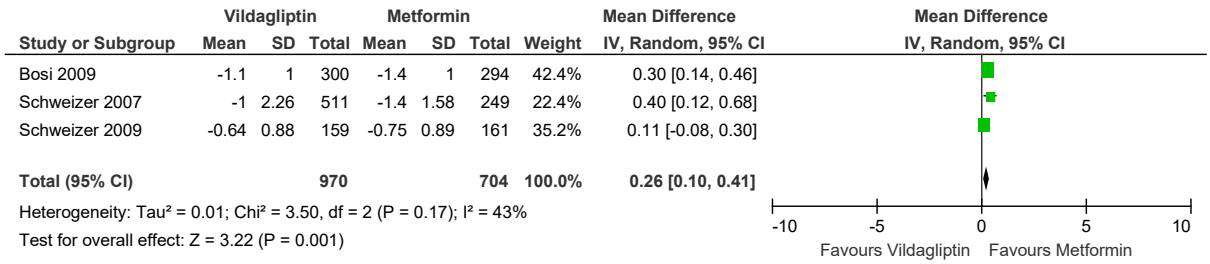
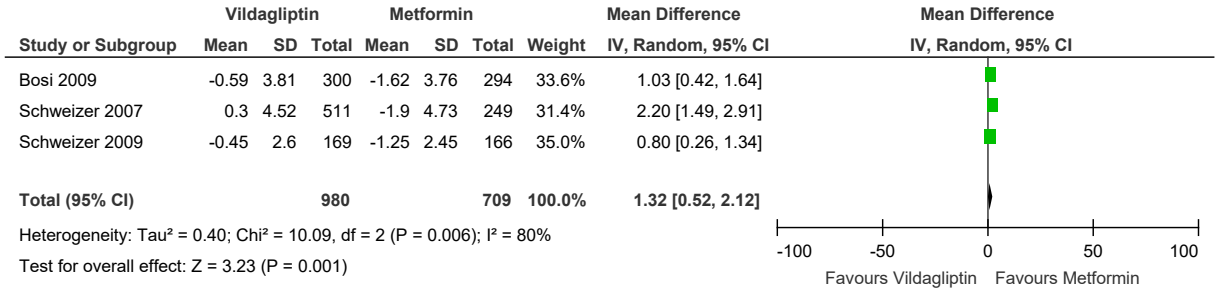


Figure 52: Weight change (kg, lower values are better, change scores) at end of follow-up



E.1.2.10 Vildagliptin compared to placebo

Figure 53: HbA1c change (%, lower values are better, change scores) at end of follow-up

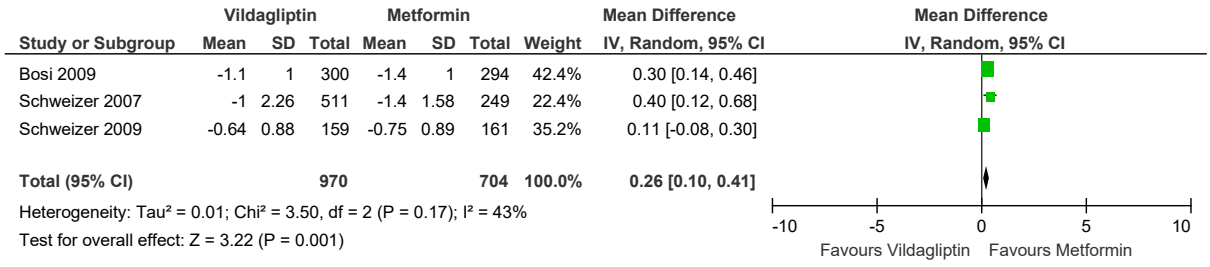
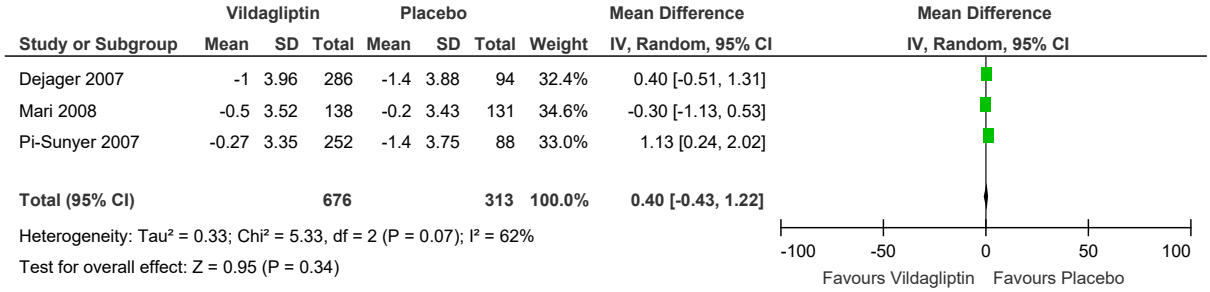


Figure 54: Weight change (kg, lower values are better, change scores) at end of follow-up



E.1.3 GLP-1 receptor agonist

E.1.3.1 Dulaglutide compared to placebo

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

E.1.3.2 Dulaglutide compared to metformin

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

E.1.3.3 Exenatide compared to metformin

Figure 55: Hypoglycaemia episodes at end of follow-up

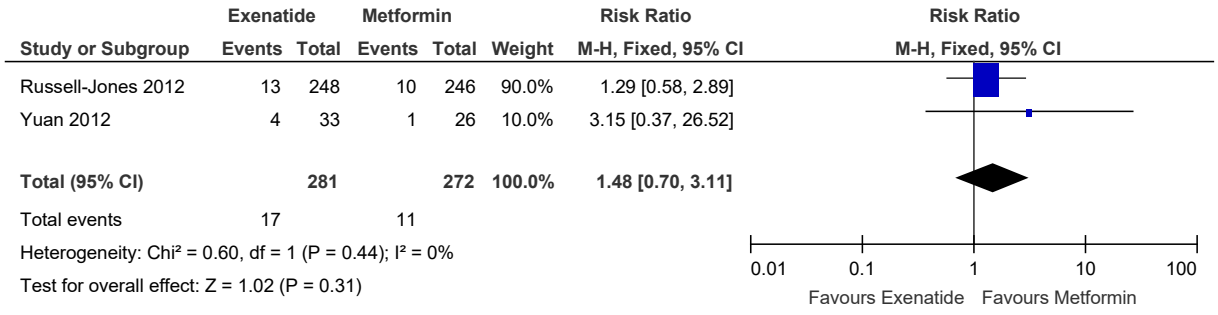


Figure 56: HbA1c change (%, lower values are better, change scores) at end of follow-up

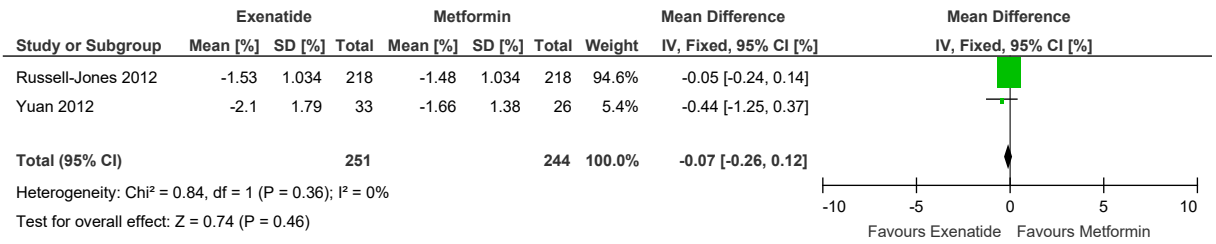
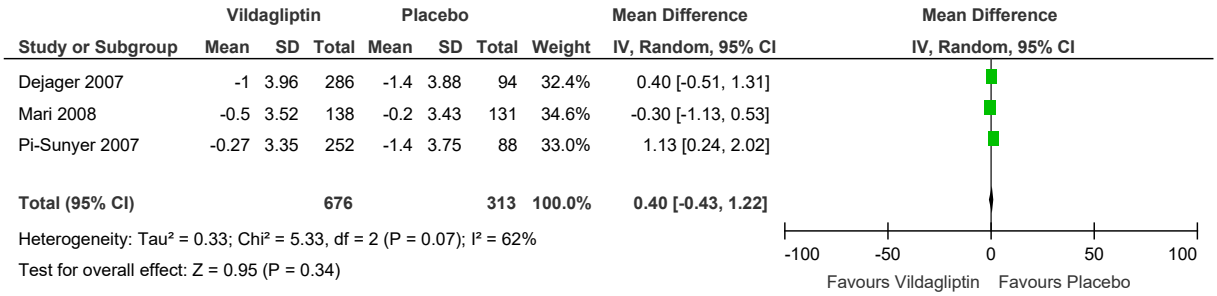


Figure 57: Weight change (kg, lower values are better, change scores) at end of follow-up



E.1.3.4 Exenatide compared to sitagliptin

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

E.1.3.5 Exenatide compared to pioglitazone

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

E.1.3.6 Exenatide compared to insulin

Figure 58: Hypoglycaemia episodes at end of follow-up

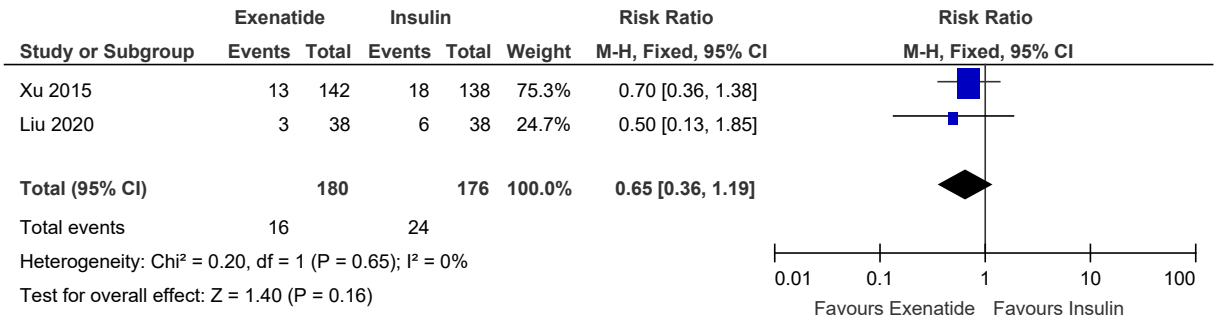


Figure 59: Severe hypoglycaemic episodes at end of follow-up

Study or Subgroup	Favours Exenatide Events	Total	Insulin Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Liu 2020	0	38	0	38	21.4%	0.00 [-0.05, 0.05]
Xu 2015	0	142	0	138	78.6%	0.00 [-0.01, 0.01]
Total (95% CI)		**180**		**176**	**100.0%**	**0.00 [-0.02, 0.02]**
Total events	0		0			

Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%

Test for overall effect: Z = 0.00 (P = 1.00)

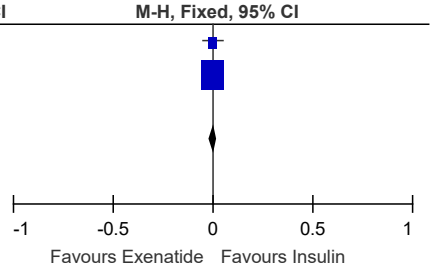


Figure 60: HbA1c change (%, lower values are better, change scores) at end of follow-up

Study or Subgroup	Mean Difference	SE	Exenatide Total	Insulin Total	Weight	Mean Difference IV, Random, 95% CI
Liu 2020	-0.65	0.184	35	36	47.7%	-0.65 [-1.01, -0.29]
Xu 2015	-0.1	0.1416	110	114	52.3%	-0.10 [-0.38, 0.18]
Total (95% CI)			**145**	**150**	**100.0%**	**-0.36 [-0.90, 0.18]**

Heterogeneity: Tau² = 0.12; Chi² = 5.61, df = 1 (P = 0.02); I² = 82%

Test for overall effect: Z = 1.32 (P = 0.19)

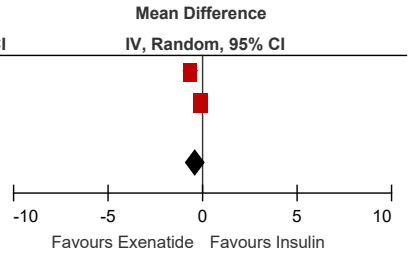


Figure 61: Weight change (kg, lower values are better, change scores) at end of follow-up

Study or Subgroup	Mean Difference	SE	Exenatide Total	Insulin Total	Weight	Mean Difference IV, Fixed, 95% CI
Liu 2020	-3.75	0.923	35	36	22.7%	-3.75 [-5.56, -1.94]
Xu 2015	-4.5	0.5002	110	114	77.3%	-4.50 [-5.48, -3.52]
Total (95% CI)			**145**	**150**	**100.0%**	**-4.33 [-5.19, -3.47]**

Heterogeneity: Chi² = 0.51, df = 1 (P = 0.47); I² = 0%

Test for overall effect: Z = 9.85 (P < 0.00001)

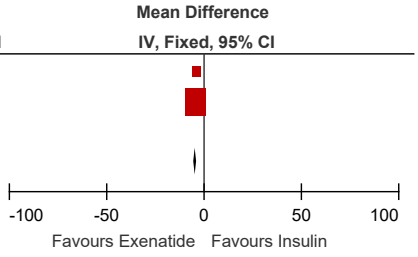
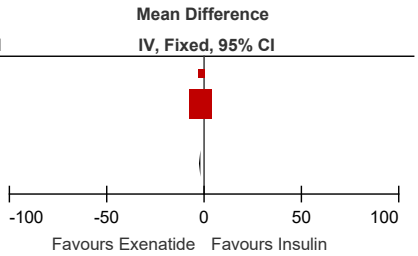


Figure 62: BMI change (kg/m2, lower values are better, change scores) at end of follow-up

Study or Subgroup	Mean Difference	SE	Exenatide Total	Insulin Total	Weight	Mean Difference IV, Fixed, 95% CI
Liu 2020	-1.38	0.339	35	36	14.9%	-1.38 [-2.04, -0.72]
Xu 2015	-1.7	0.1417	110	114	85.1%	-1.70 [-1.98, -1.42]
Total (95% CI)			**145**	**150**	**100.0%**	**-1.65 [-1.91, -1.40]**

Heterogeneity: Chi² = 0.76, df = 1 (P = 0.38); I² = 0%

Test for overall effect: Z = 12.64 (P < 0.00001)



E.1.317 Exenatide compared to placebo

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

E.1.348 Liraglutide compared to metformin

Figure 63: HbA1c change (%, lower values are better, change scores) at end of follow-up

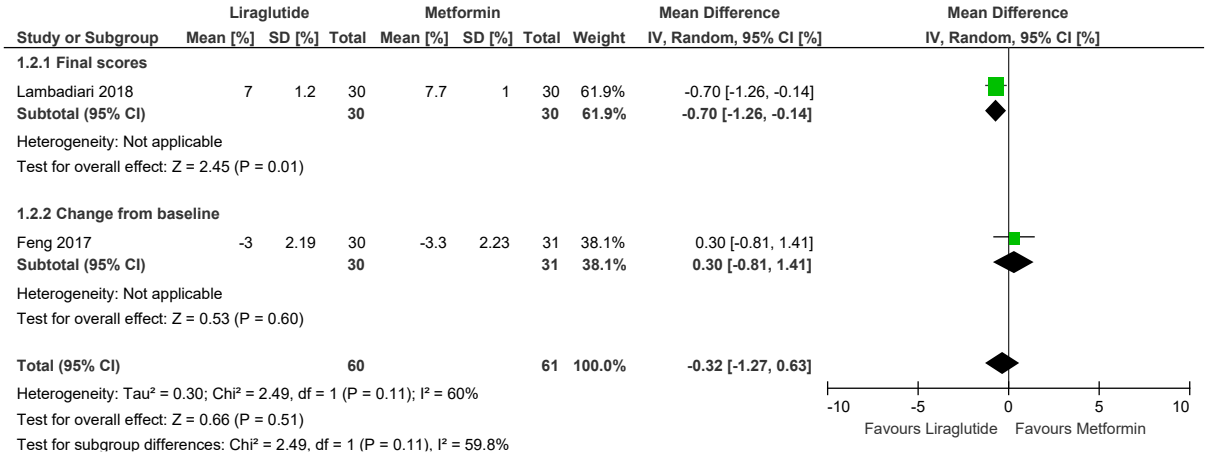


Figure 64: Weight change (kg, lower values are better, final values) at end of follow-up

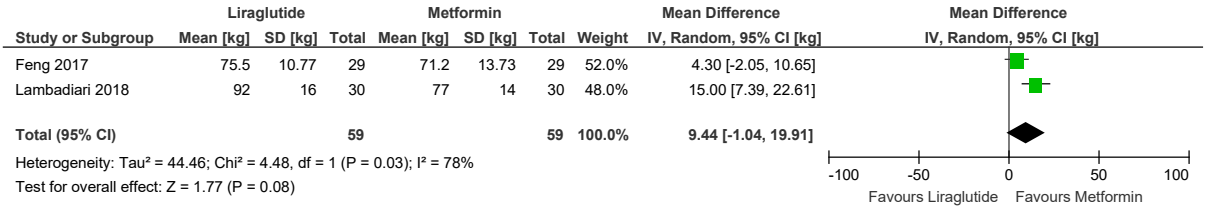
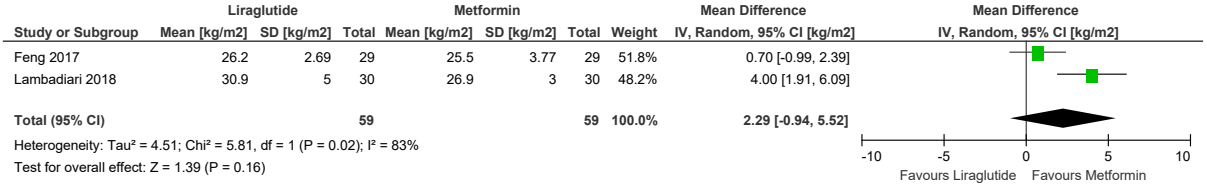


Figure 65: BMI change (kg/m2, lower values are better, final values) at end of follow-up



E.1.3.9 Liraglutide compared to dulaglutide

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

E.1.3.10 Liraglutide compared to gliclazide

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

E.1.3.11 Liraglutide compared to glimepiride

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

E.1.3.12 Liraglutide compared to placebo

Figure 66: All-cause mortality at end of follow-up

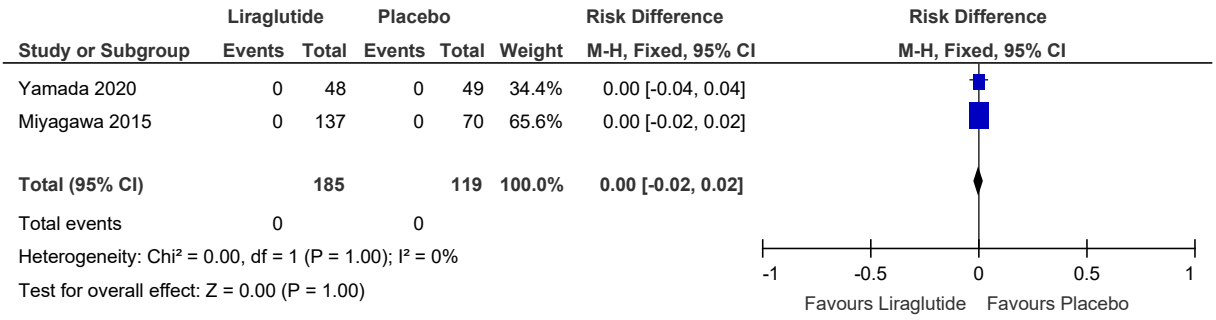


Figure 67: Cardiovascular mortality at end of follow-up

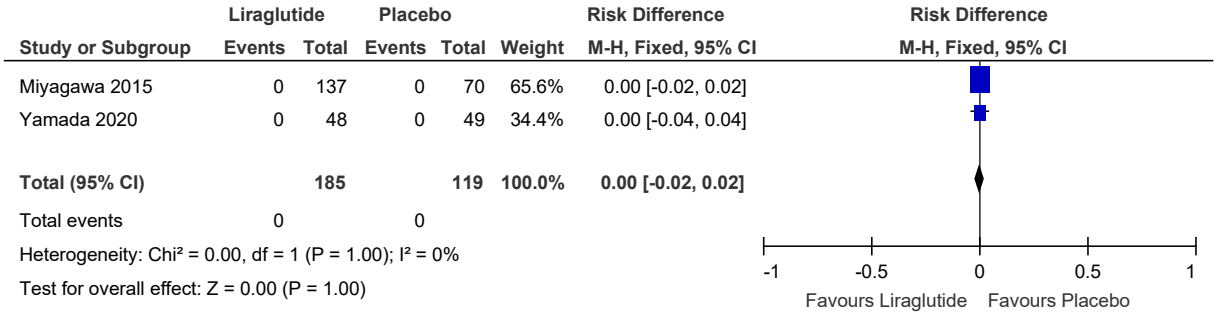


Figure 68: Hypoglycaemia episodes at end of follow-up

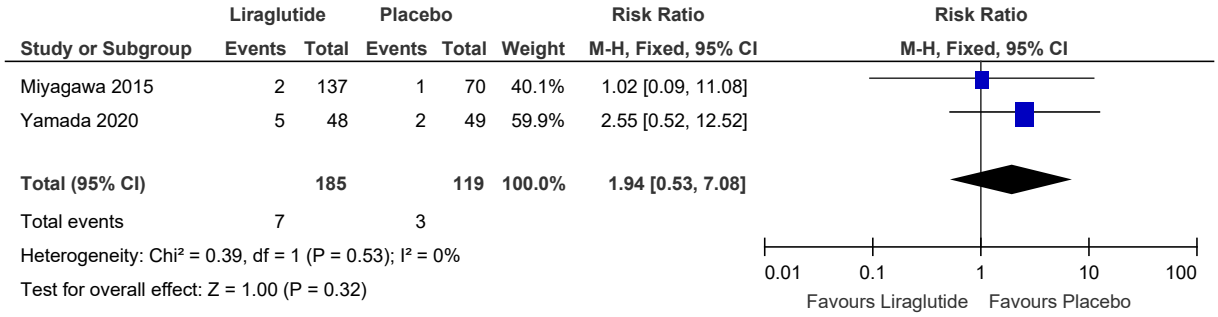


Figure 69: Severe hypoglycaemic episodes at end of follow-up

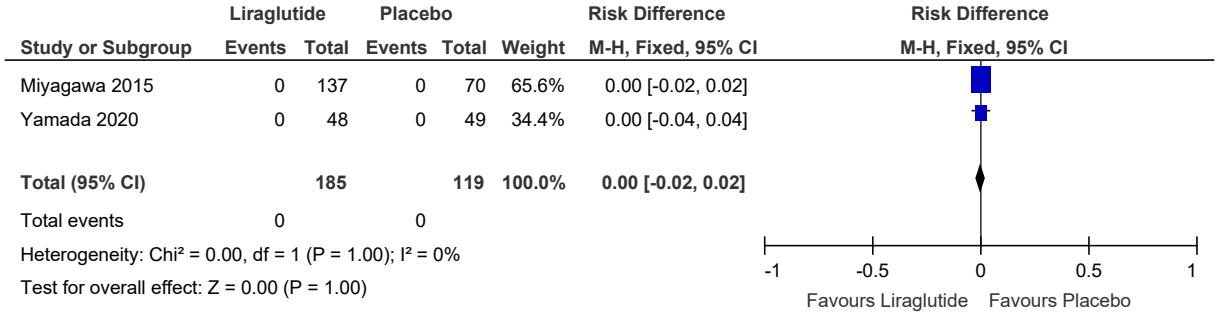
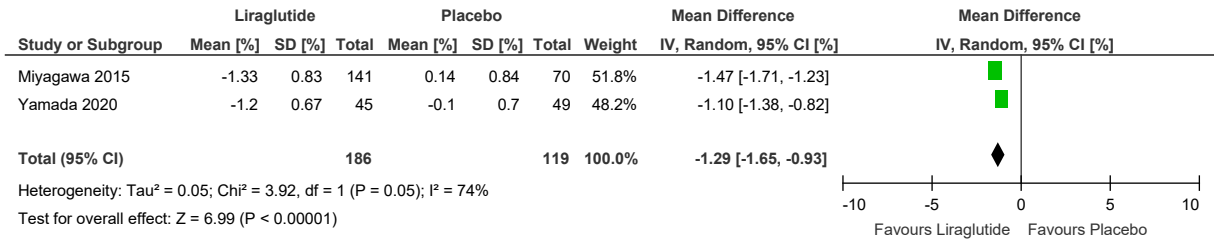


Figure 70: HbA1c change (%, lower values are better, change scores) at end of follow-up



E.1.3.13 Liraglutide compared to sitagliptin

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

E.1.3.14 Semaglutide compared to liraglutide

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

E.1.3.15 Semaglutide compared to sitagliptin

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

E.1.3.16 Semaglutide compared to placebo

Figure 71: All-cause mortality at end of follow-up

Study or Subgroup	Semaglutide Events	Semaglutide Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Aroda 2019B	1	525	0	178	52.0%	0.00 [-0.01, 0.01]
Sorli 2017	0	259	0	129	33.7%	0.00 [-0.01, 0.01]
Yamada 2020	0	146	0	49	14.3%	0.00 [-0.03, 0.03]
Total (95% CI)		**930**		**356**	**100.0%**	**0.00 [-0.01, 0.01]**
Total events	1		0			

Heterogeneity: Chi² = 0.07, df = 2 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.26 (P = 0.80)

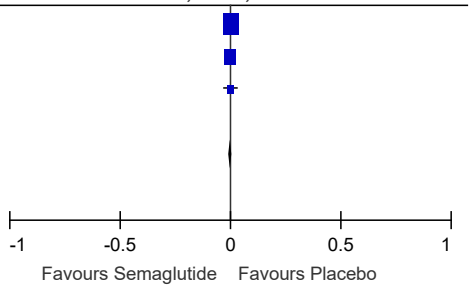


Figure 72: Cardiovascular mortality at end of follow-up

Study or Subgroup	Semaglutide Events	Semaglutide Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Aroda 2019B	1	525	0	178	52.0%	0.00 [-0.01, 0.01]
Sorli 2017	0	259	0	129	33.7%	0.00 [-0.01, 0.01]
Yamada 2020	0	146	0	49	14.3%	0.00 [-0.03, 0.03]
Total (95% CI)		**930**		**356**	**100.0%**	**0.00 [-0.01, 0.01]**
Total events	1		0			

Heterogeneity: Chi² = 0.07, df = 2 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.26 (P = 0.80)

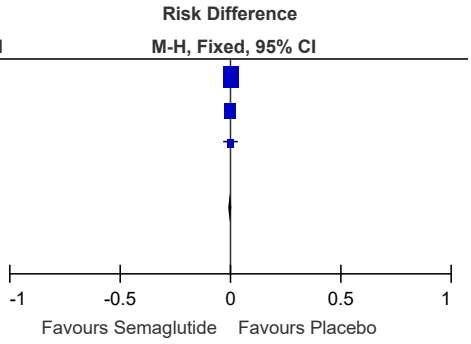


Figure 73: Non-fatal stroke at end of follow-up

Study or Subgroup	Semaglutide Events	Semaglutide Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Aroda 2019B	0	525	2	178	52.0%	-0.01 [-0.03, 0.01]
Sorli 2017	1	258	0	129	33.6%	0.00 [-0.01, 0.02]
Yamada 2020	0	146	0	49	14.4%	0.00 [-0.03, 0.03]
Total (95% CI)		**929**		**356**	**100.0%**	**-0.00 [-0.02, 0.01]**
Total events	1		2			

Heterogeneity: Chi² = 2.03, df = 2 (P = 0.36); I² = 2%
Test for overall effect: Z = 0.80 (P = 0.42)

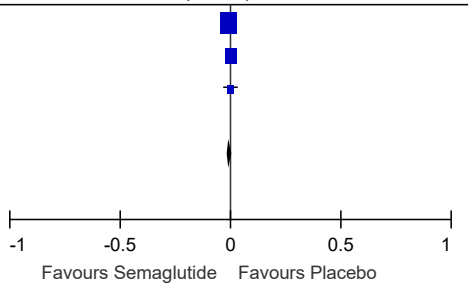


Figure 74: Non-fatal myocardial infarction at end of follow-up

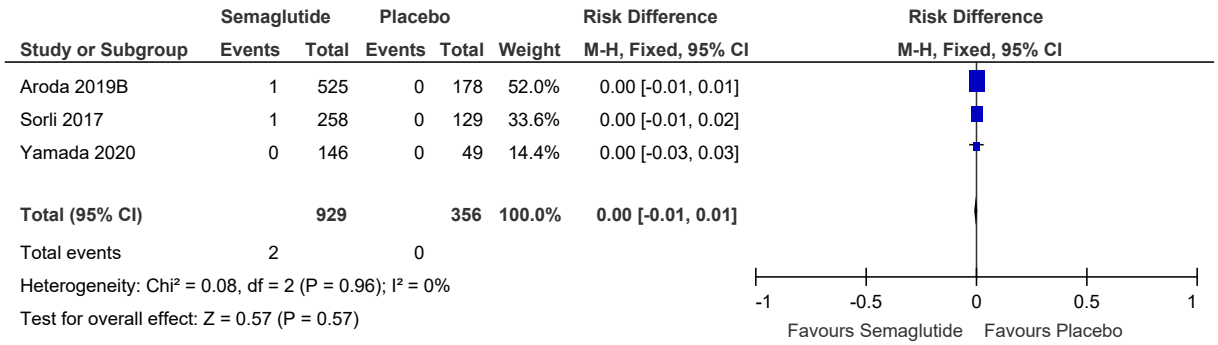


Figure 75: Acute kidney injury at end of follow-up

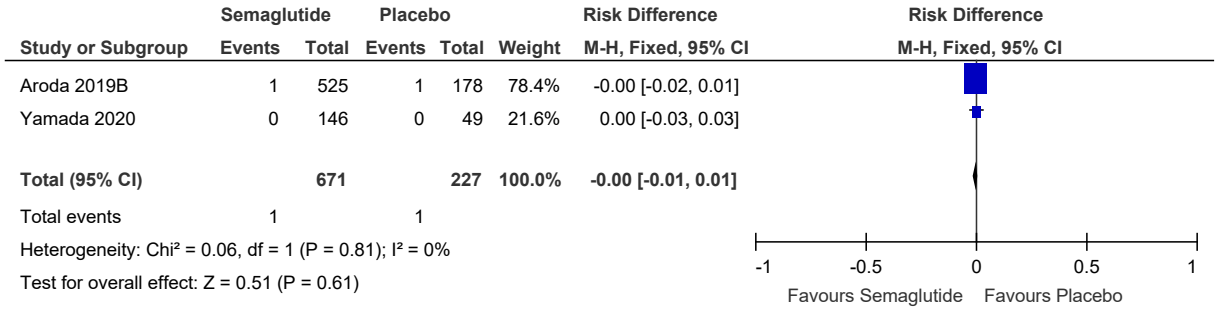


Figure 76: Hypoglycaemia episodes at end of follow-up

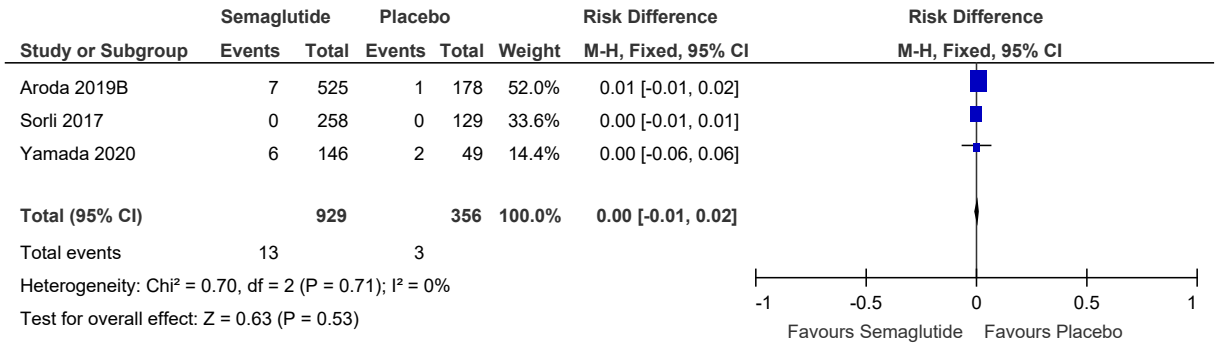


Figure 77: Severe hypoglycaemic episodes at end of follow-up

Study or Subgroup	Semaglutide Events	Semaglutide Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Aroda 2019B	1	525	0	178	52.0%	0.00 [-0.01, 0.01]
Sorli 2017	0	258	2	129	33.6%	-0.02 [-0.04, 0.01]
Yamada 2020	0	146	0	49	14.4%	0.00 [-0.03, 0.03]
Total (95% CI)		**929**		**356**	**100.0%**	**-0.00 [-0.01, 0.01]**
Total events	1		2			

Heterogeneity: Chi² = 2.71, df = 2 (P = 0.26); I² = 26%

Test for overall effect: Z = 0.80 (P = 0.42)

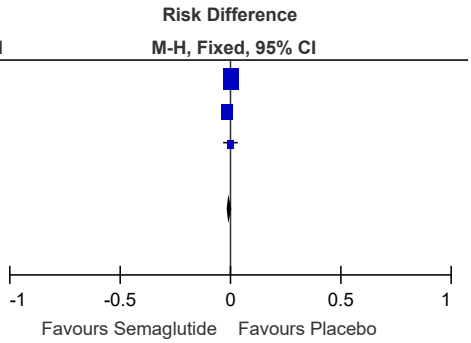
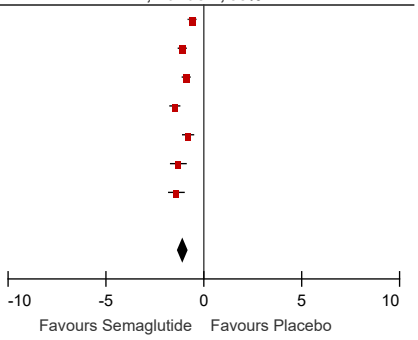


Figure 78: HbA1c change (%, lower values are better, change scores) at end of follow-up

Study or Subgroup	Mean Difference	SE	Semaglutide Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Aroda 2019B (1)	-0.6	0.102	175	60	15.6%	-0.60 [-0.80, -0.40]
Aroda 2019B (2)	-1.1	0.102	175	59	15.6%	-1.10 [-1.30, -0.90]
Aroda 2019B (3)	-0.9	0.102	175	59	15.6%	-0.90 [-1.10, -0.70]
Sorli 2017	-1.48	0.127	258	129	14.8%	-1.48 [-1.73, -1.23]
Yamada 2020 (4)	-0.8	0.1414	46	17	14.3%	-0.80 [-1.08, -0.52]
Yamada 2020 (5)	-1.3	0.2016	49	16	12.0%	-1.30 [-1.70, -0.90]
Yamada 2020 (6)	-1.4	0.2021	47	16	12.0%	-1.40 [-1.80, -1.00]
Total (95% CI)			**925**	**356**	**100.0%**	**-1.06 [-1.31, -0.82]**

Heterogeneity: Tau² = 0.09; Chi² = 39.71, df = 6 (P < 0.00001); I² = 85%

Test for overall effect: Z = 8.46 (P < 0.00001)



Footnotes

(1) 3 mg semaglutide v placebo

(2) 14 mg semaglutide v placebo

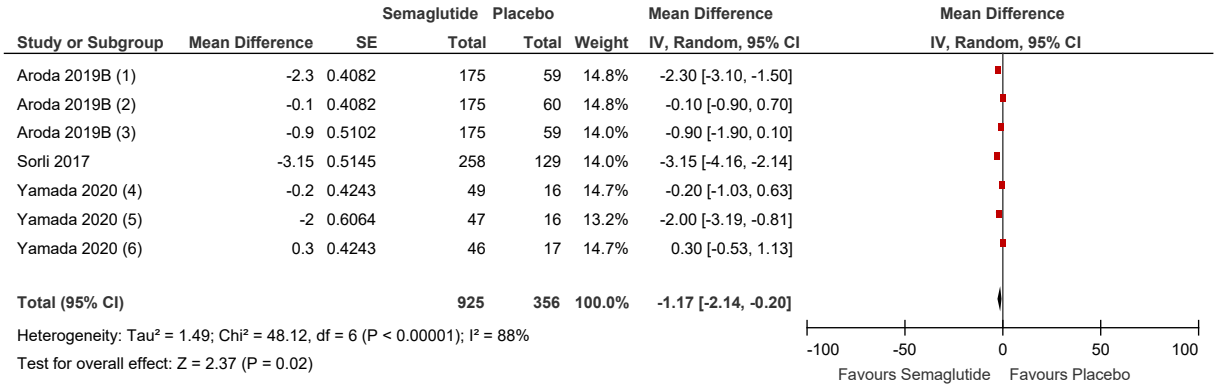
(3) 7 mg semaglutide v placebo

(4) 3 mg semagluitde v placebo

(5) 7 mg semaglutide v placebo

(6) 14 mg semaglutide v placebo

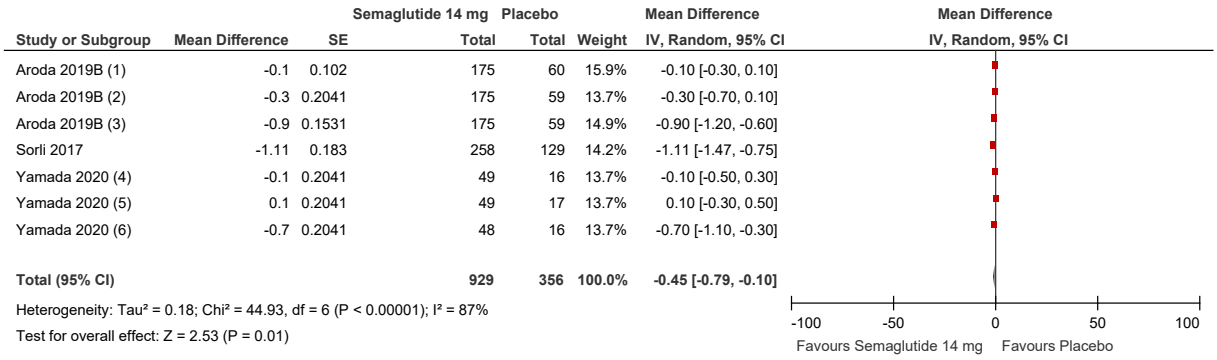
Figure 79: Weight change (kg, lower values are better, change scores) at end of follow-up



Footnotes

(1) 14 mg semaglutide v placebo
(2) 3 mg semagluitde v placebo
(3) 7 mg semaglutide v placebo
(4) 7 mg semaglutide v placebo
(5) 14 mg semaglutide v placebo
(6) 3 mg semaglutide v placebo

Figure 80: BMI change (kg/m2, lower values are better, change scores) at end of follow-up



Footnotes

(1) 3 mg semaglutide v placebo
(2) 7 mg semaglutide v placebo
(3) 14 mg semaglutide v placebo
(4) 7 mg semaglutide v placebo
(5) 3 mg semaglutide v placebo
(6) 14 mg semaglutide v placebo

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

E.1.41 Tirzepatide compared to dulaglutide

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

E.1.5 SGLT2 inhibitors

E.1.5.1 Canagliflozin compared to metformin

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

E.1.5.2 Canagliflozin compared to placebo

Figure 81: Hypoglycaemia episodes at follow-up

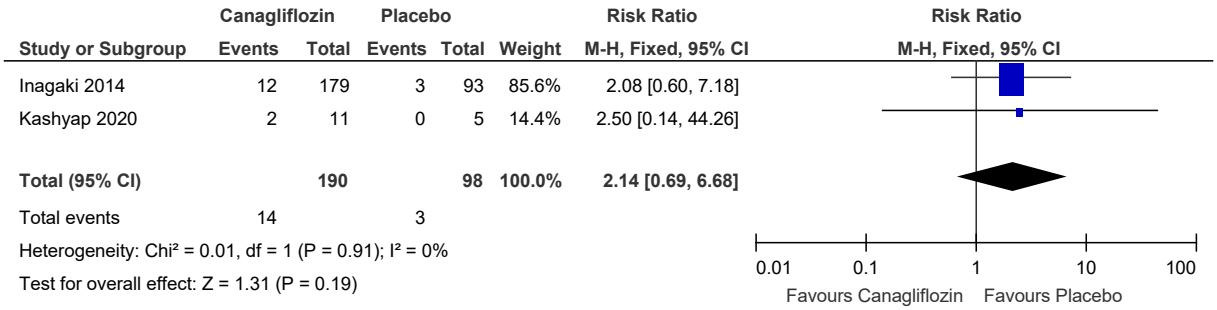


Figure 82: HbA1c change (%, lower values are better, change scores) at end of follow-up

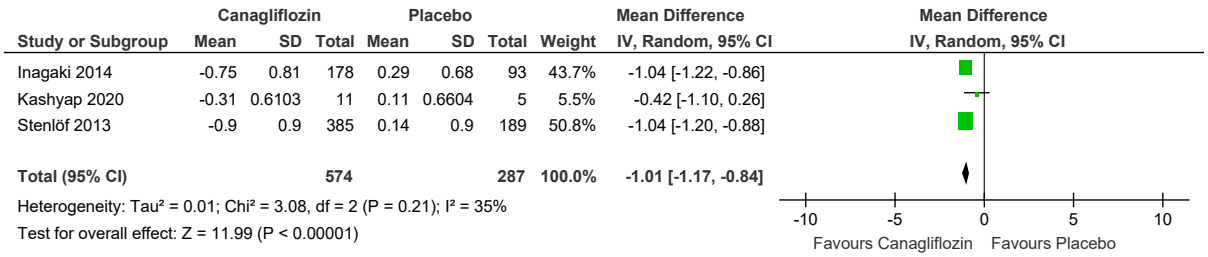
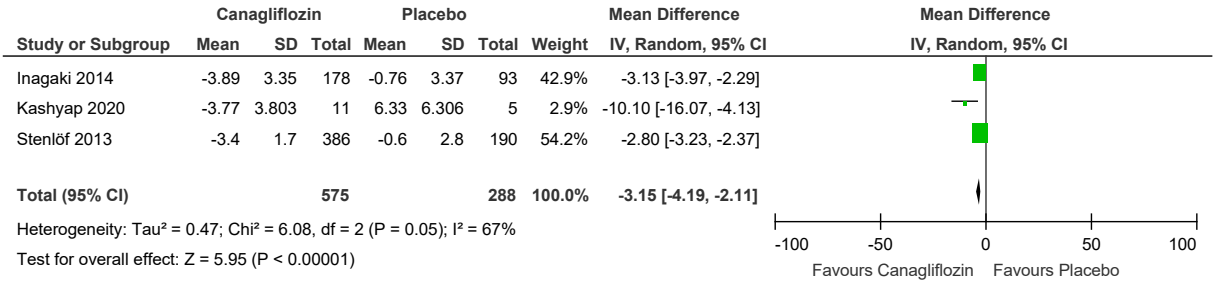


Figure 83: Weight change (kg, lower values are better, change scores) at end of follow-up



E.1.513 Dapagliflozin compared to metformin

Figure 84: All-cause mortality at end of follow-up

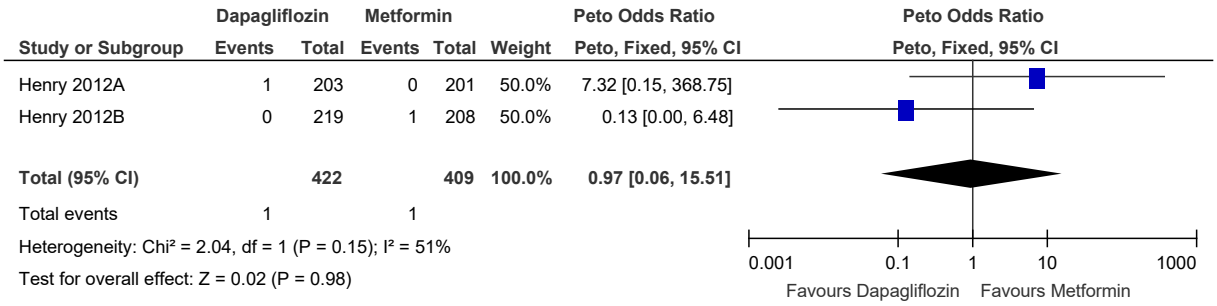


Figure 85: Cardiovascular mortality at end of follow-up

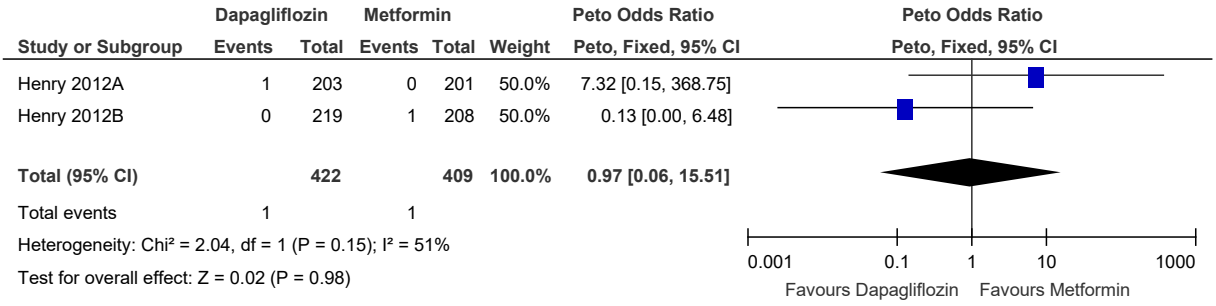


Figure 86: Hypoglycaemia episodes at end of follow-up

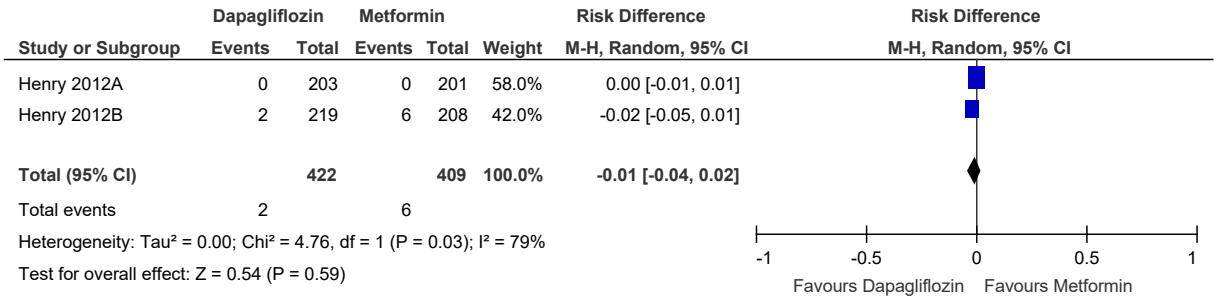


Figure 87: Severe hypoglycaemic episodes at end of follow-up

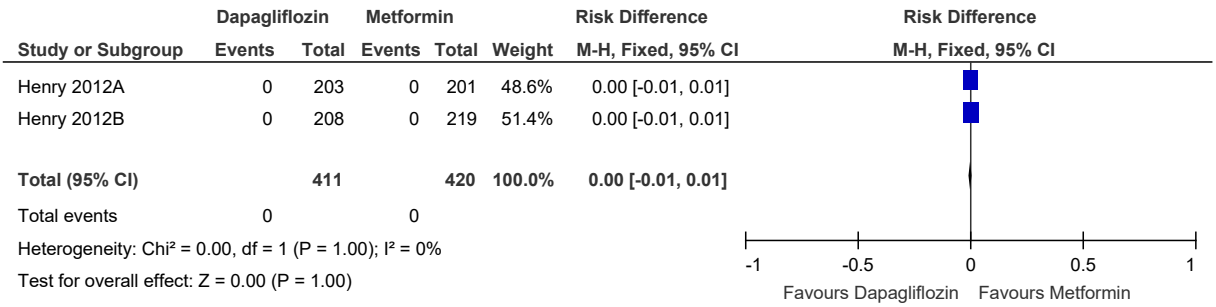


Figure 88: HbA1c change (%, lower values are better, change scores) at end of follow-up

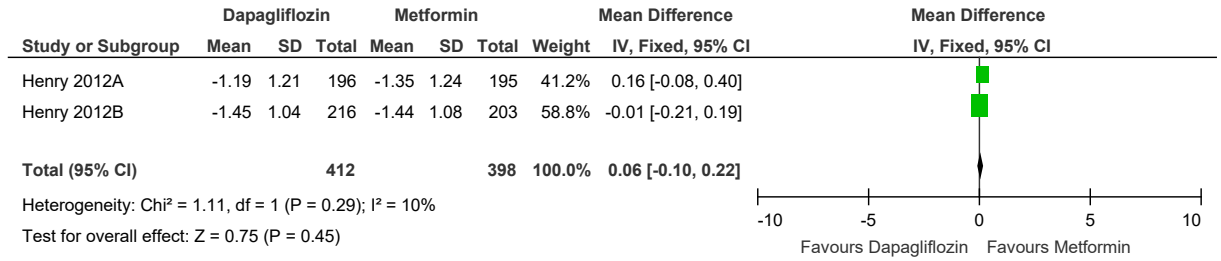
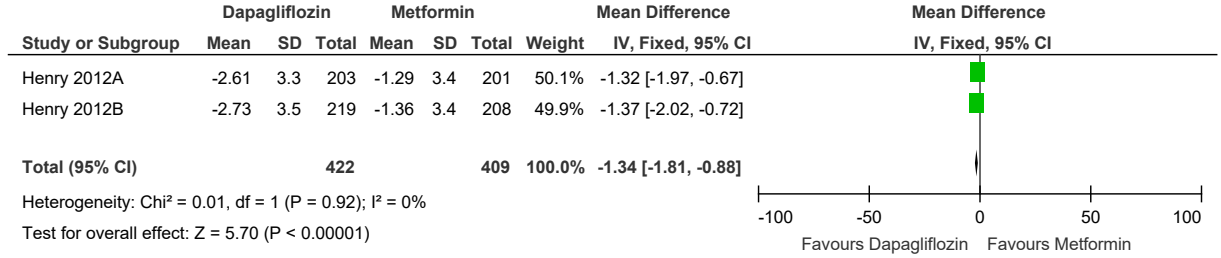


Figure 89: Weight change (kg, lower values are better, change scores) at end of follow-up



E.1.5.4 Dapagliflozin compared to placebo

Figure 90: All-cause mortality at end of follow-up

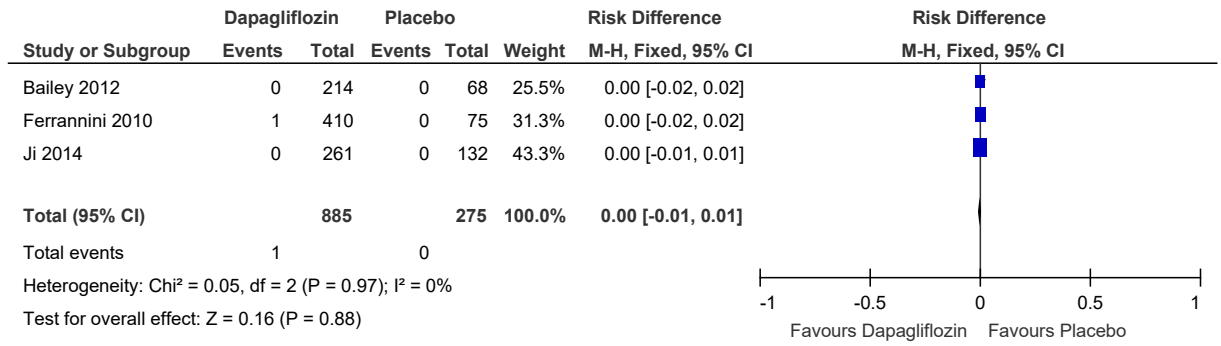


Figure 91: Persistent signs of worsening kidney disease at end of follow-up

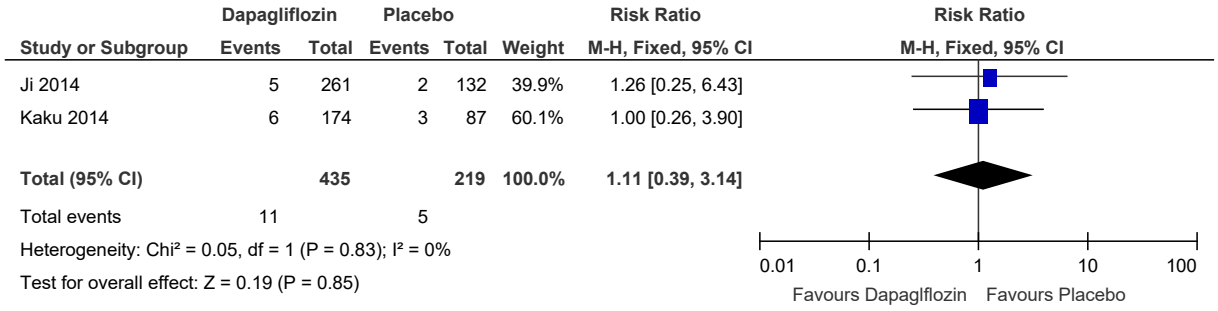


Figure 92: Hypoglycaemia episodes at end of follow-up

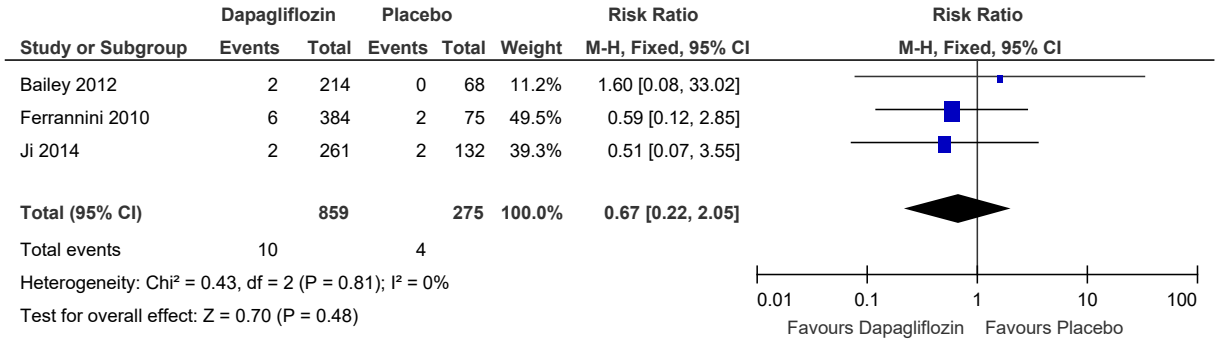
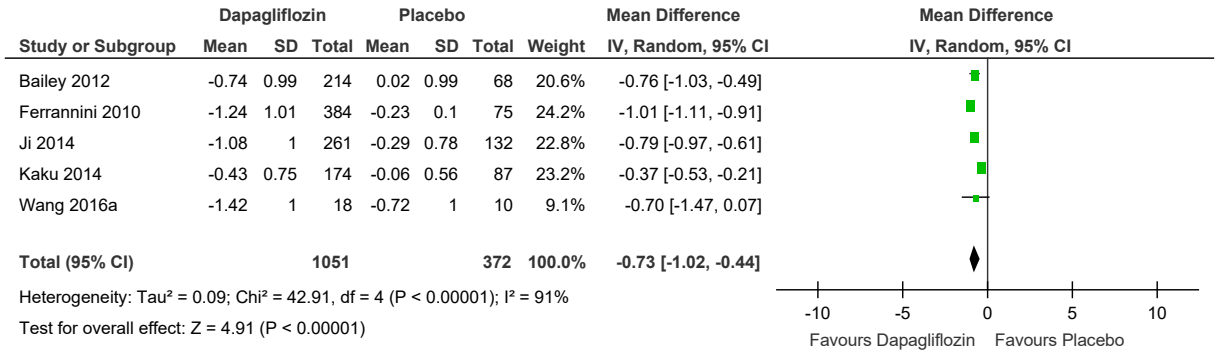
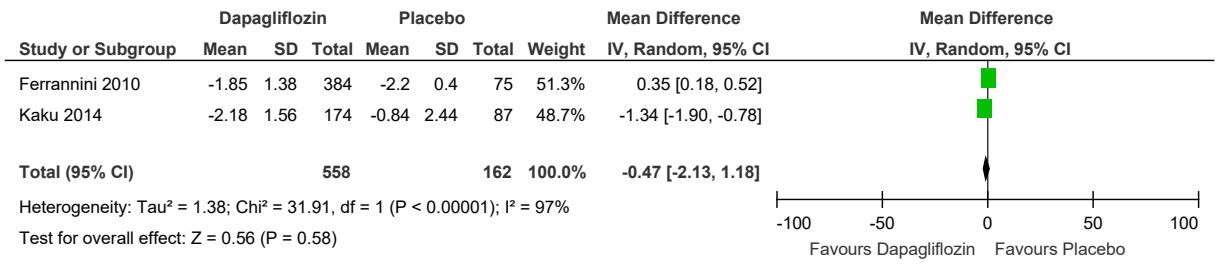


Figure 93: HbA1c change (%, lower values are better, change scores) at end of follow-up



Note: Heterogeneity was not explained by sensitivity analysis, nor subgroup analysis by eGFR subgroups.

Figure 94: Weight change (kg, lower values are better, change scores) at end of follow-up



E.1.5 Empagliflozin compared to metformin

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

E.1.6 Empagliflozin compared to linagliptin

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

E.1.7 Empagliflozin compared to sitagliptin

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

E.1.8 Empagliflozin compared to placebo

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

E.1.6 Sulfonylureas

E.1.1 Gliclazide compared to metformin

Figure 95: Hypoglycaemia episodes at end of follow-up

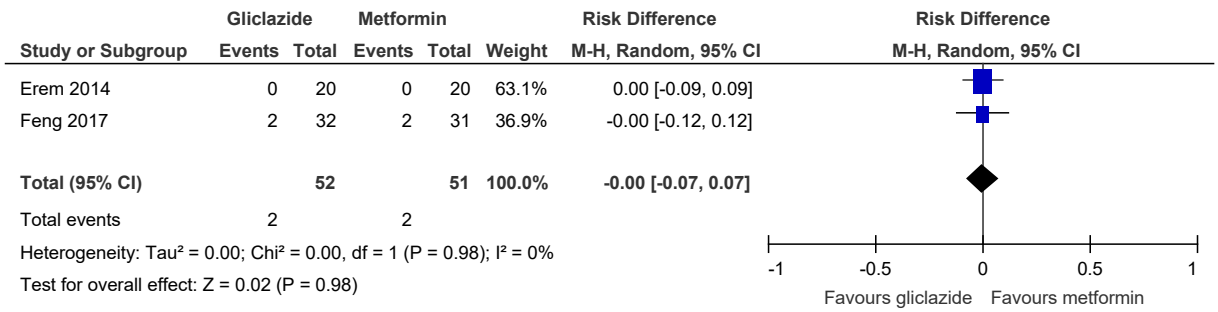


Figure 96: HbA1c change (%, lower values are better, change score and final values) at end of follow-up

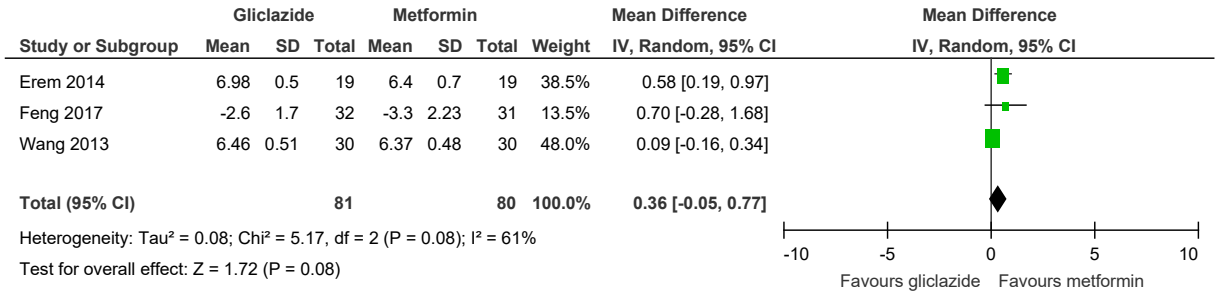


Figure 97: Weight change (kg, lower values are better, final values) at end of follow-up

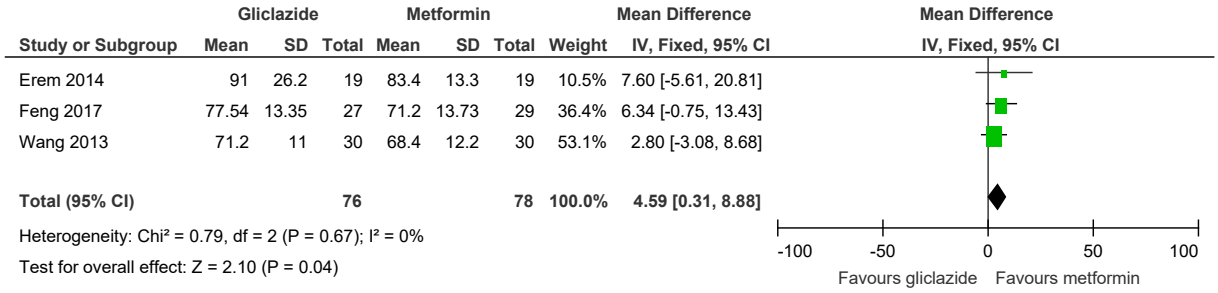
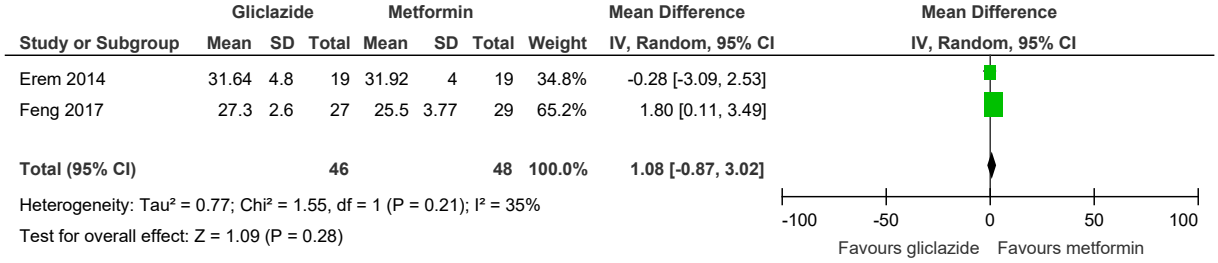


Figure 98: BMI change (kg/m2, lower values are better, final values) at end of follow-up



E.1.612 Gliclazide compared to vildagliptin

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

E.1.613 Glimepiride compared to metformin

Figure 99: Hypoglycaemia episodes at end of follow-up

Study or Subgroup	Glimepiride Events	Glimepiride Total	Metformin Events	Metformin Total	Weight	Risk Difference M-H, Random, 95% CI
Derosa 2004	0	81	0	83	34.7%	0.00 [-0.02, 0.02]
Yamanouchi 2005	1	37	0	39	32.9%	0.03 [-0.04, 0.10]
Yoon 2011a	23	118	4	114	32.4%	0.16 [0.08, 0.24]
Total (95% CI)		**236**		**236**	**100.0%**	**0.06 [-0.11, 0.23]**
Total events	24		4			

Heterogeneity: Tau² = 0.02; Chi² = 53.65, df = 2 (P < 0.00001); I² = 96%
Test for overall effect: Z = 0.70 (P = 0.48)

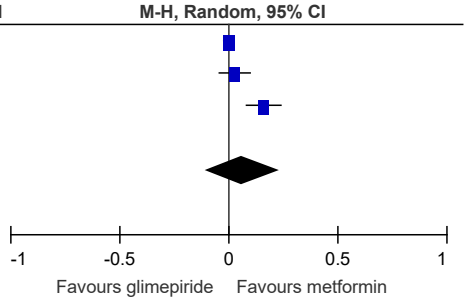


Figure 100: HbA1c change (%, lower values are better, change score and final value) at end of follow-up

Study or Subgroup	Glimepiride Mean	Glimepiride SD	Glimepiride Total	Metformin Mean	Metformin SD	Metformin Total	Weight	Mean Difference IV, Fixed, 95% CI
Derosa 2004	-1.6	13.68	81	-1.4	12.12	83	0.2%	-0.20 [-4.16, 3.76]
Yamanouchi 2005	7.7	0.9	37	7.8	1	39	21.4%	-0.10 [-0.53, 0.33]
Yoon 2011a	-0.89	0.76	118	-0.92	0.96	114	78.4%	0.03 [-0.19, 0.25]
Total (95% CI)			**236**			**236**	**100.0%**	**0.00 [-0.20, 0.20]**

Heterogeneity: Chi² = 0.29, df = 2 (P = 0.87); I² = 0%
Test for overall effect: Z = 0.02 (P = 0.99)

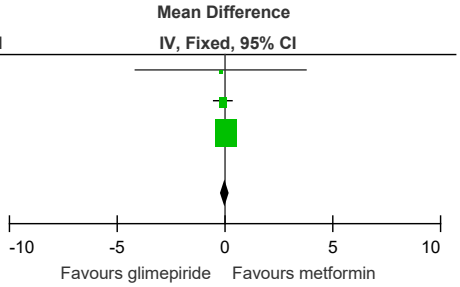
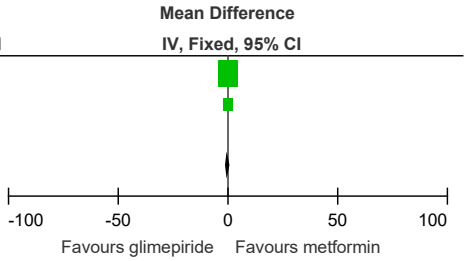


Figure 101: BMI change (kg/m2, lower values are better, change score and final value) at end of follow-up

Study or Subgroup	Glimepiride Mean	Glimepiride SD	Glimepiride Total	Metformin Mean	Metformin SD	Metformin Total	Weight	Mean Difference IV, Fixed, 95% CI
Derosa 2004	-0.7	3.69	81	-0.6	3.67	83	72.8%	-0.10 [-1.23, 1.03]
Yamanouchi 2005	25.4	4	37	25.5	4.2	39	27.2%	-0.10 [-1.94, 1.74]
Total (95% CI)			**118**			**122**	**100.0%**	**-0.10 [-1.06, 0.86]**

Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.20 (P = 0.84)



E.1.634 Glimepiride compared to dulaglutide

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

E.1.665 Glimepiride compared to saxagliptin

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

E.1.626 Glimepiride compared to sitagliptin

Figure 102: All-cause mortality at end of follow-up

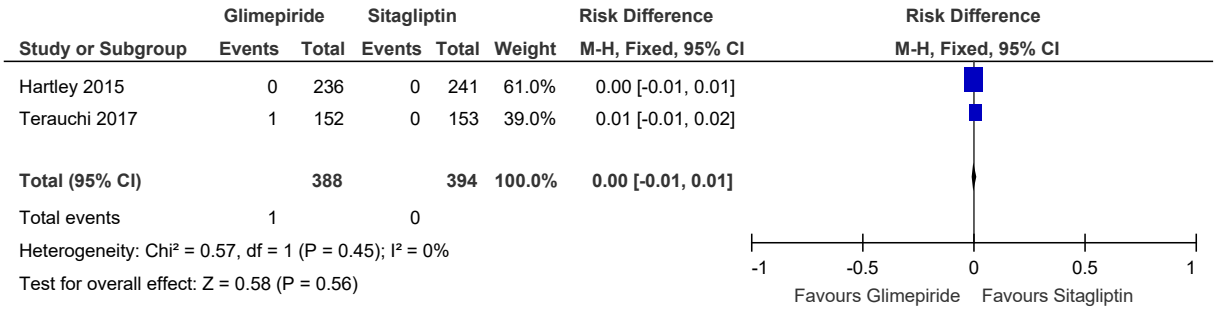


Figure 103: Progression of liver disease at end of follow-up

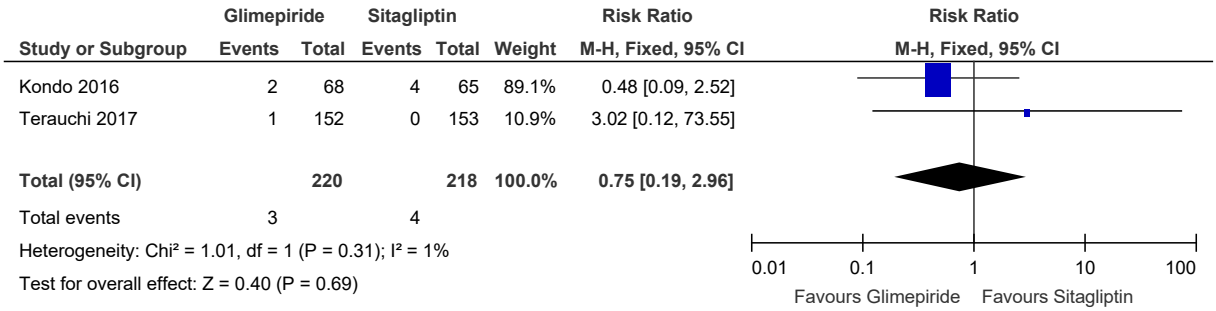


Figure 104: Hypoglycaemia episodes at end of follow-up

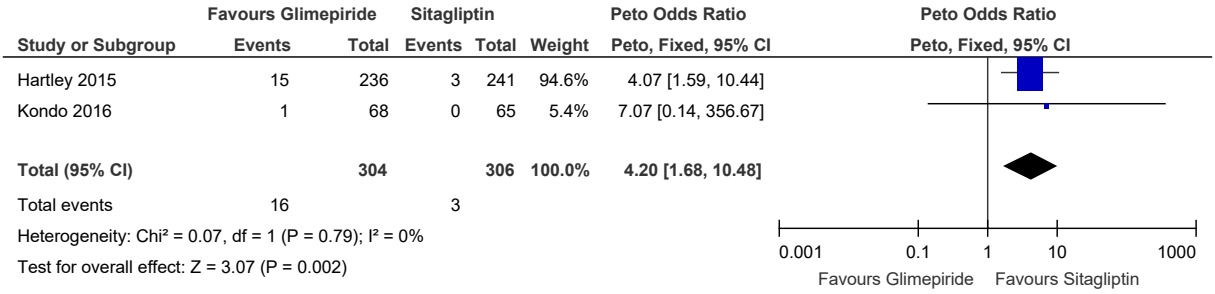


Figure 105: Severe hypoglycaemic episodes at end of follow-up

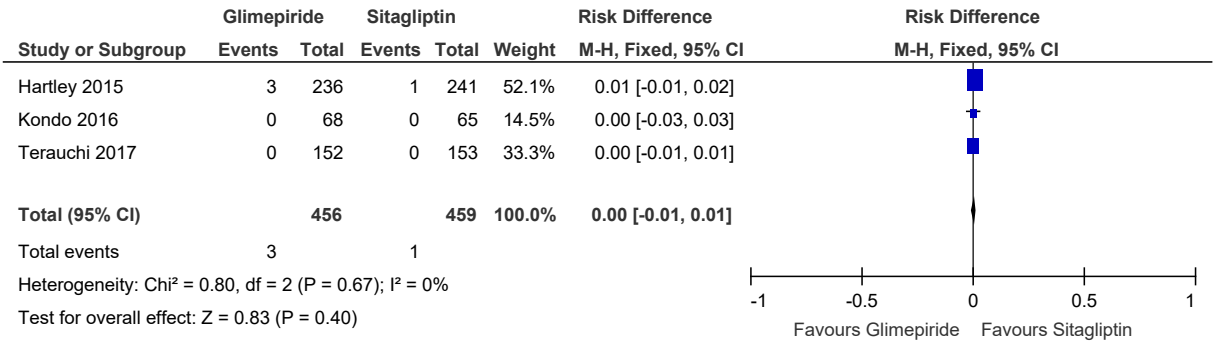


Figure 106: HbA1c change (%, lower values are better, change scores and final value) at end of follow up

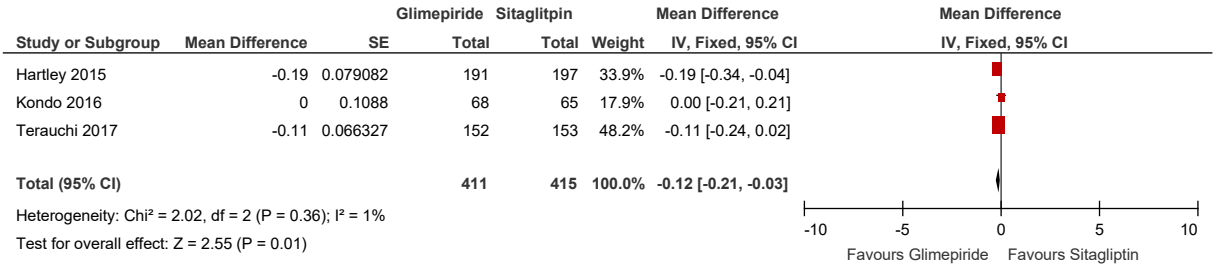
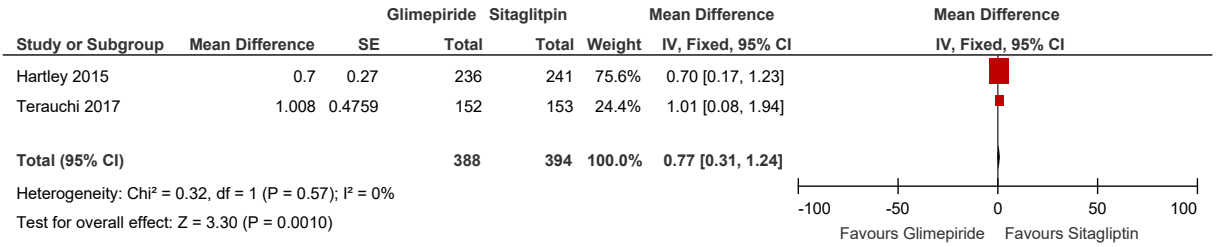


Figure 107: Weight change (kg, lower values are better, change scores) at end of follow-up



E.1.627 Glimepiride compared to canagliflozin

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

E.1.618 Glipizide compared to metformin

Figure 108: HbA1c change (%, lower values are better, change score and final value) at end of follow-up

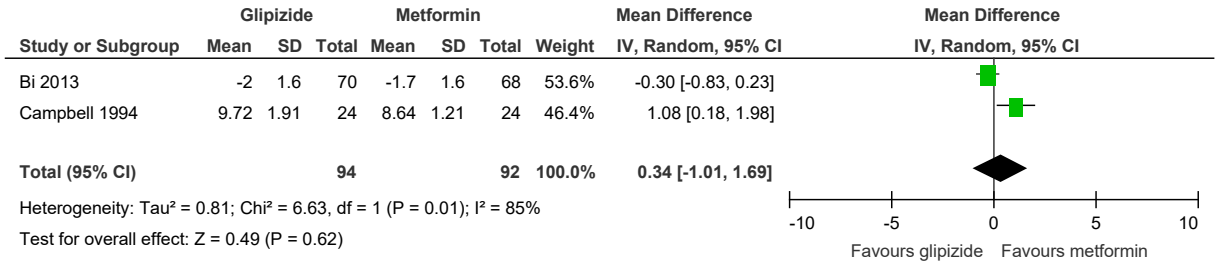
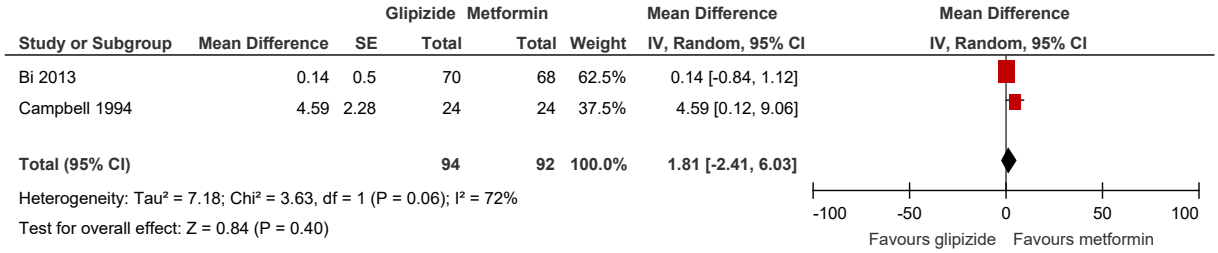


Figure 109: Weight change (kg, lower values are better, change score) at end of follow-up



E.1.619 Glipizide compared to sitagliptin

Figure 110: All-cause mortality at end of follow-up

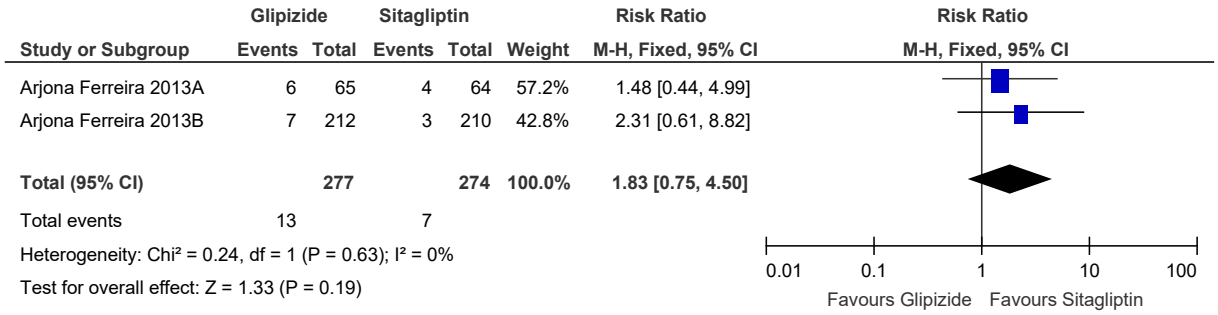


Figure 111: Hospitalisation for heart failure at end of follow-up

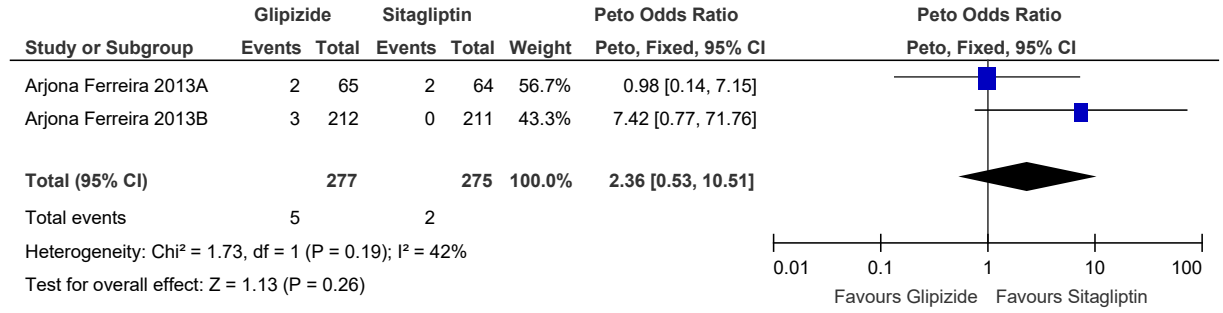


Figure 112: Severe hypoglycaemic episodes at end of follow-up

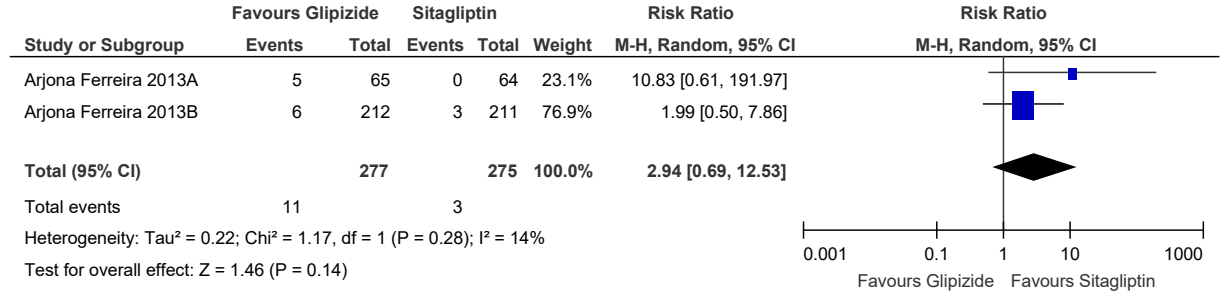


Figure 113: HbA1c change (%, lower values are better, change scores) at end of follow-up

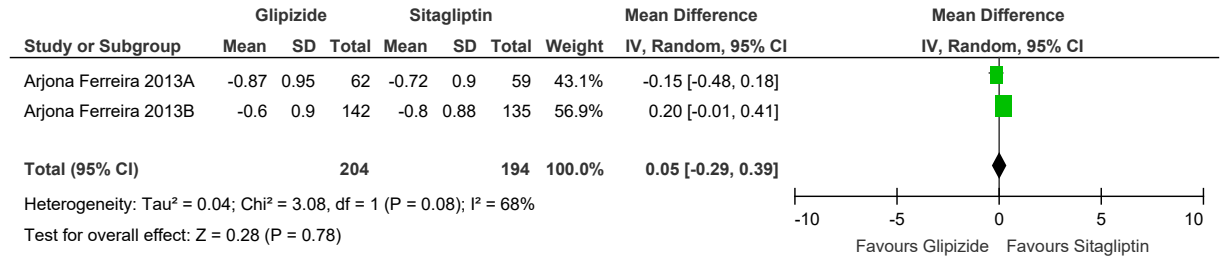
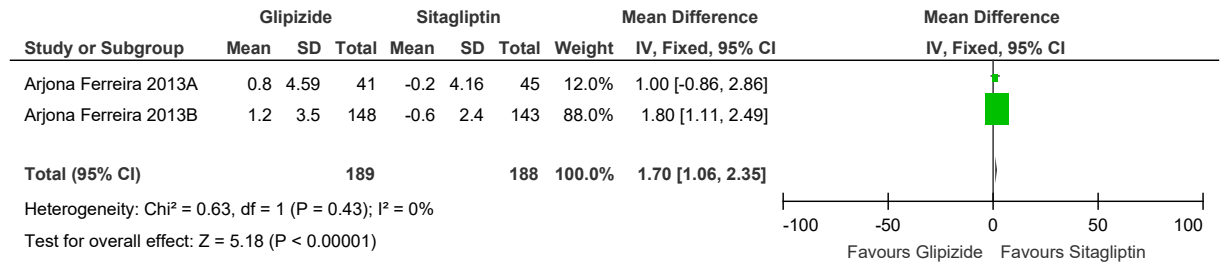
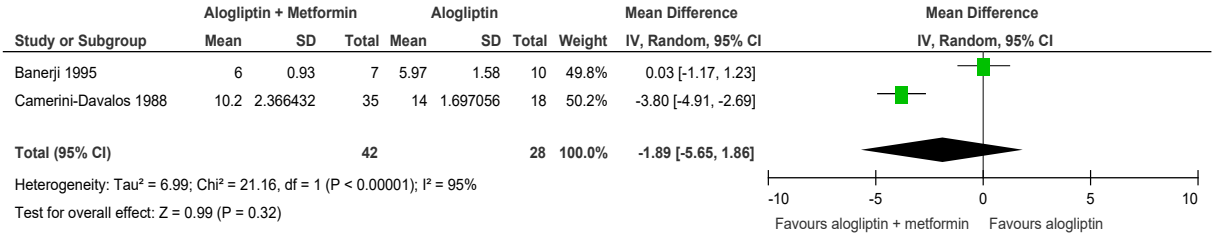


Figure 114: Weight change (kg, lower values are better, change scores) at end of follow-up



E.1.6.10 Glipizide compared to placebo

Figure 115: HbA1c change (%, lower values are better, final value) at end of follow-up



E.1.6.11 Tolbutamide compared to insulin

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

E.1.6.12 Tolbutamide compared to placebo

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

E.1.7 Thiazolidinediones

E.1.7.1 Pioglitazone compared to metformin

Figure 116: All-cause mortality at end of follow up

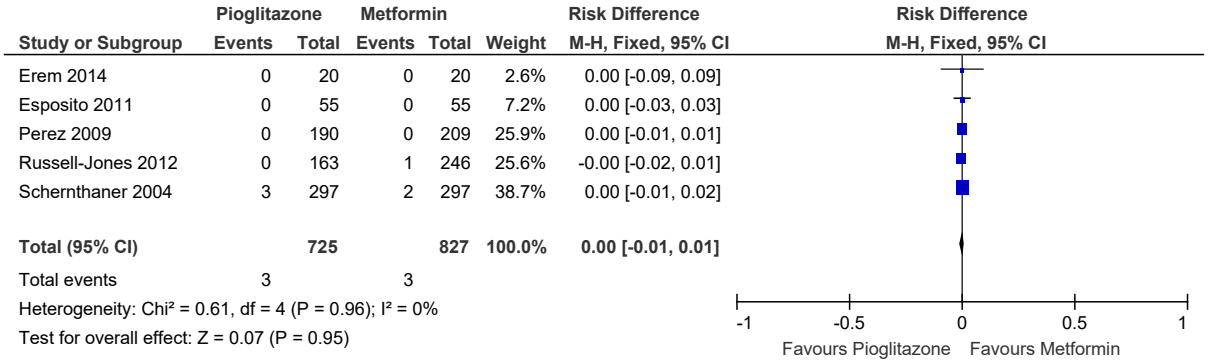
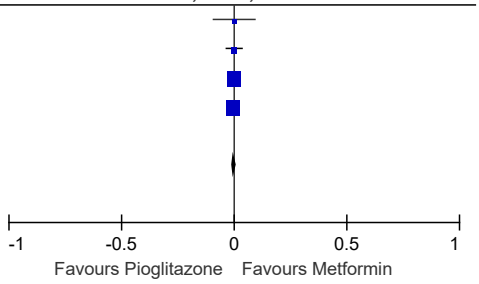


Figure 117: Cardiovascular mortality at end of follow up

Study or Subgroup	Pioglitazone Events	Pioglitazone Total	Metformin Events	Metformin Total	Weight	Risk Difference M-H, Fixed, 95% CI
Erem 2014	0	20	0	20	4.3%	0.00 [-0.09, 0.09]
Esposito 2011	0	55	0	55	11.7%	0.00 [-0.03, 0.03]
Perez 2009	0	190	0	209	42.3%	0.00 [-0.01, 0.01]
Russell-Jones 2012	0	163	1	246	41.7%	-0.00 [-0.02, 0.01]
Total (95% CI)		**428**		**530**	**100.0%**	**-0.00 [-0.01, 0.01]**
Total events	0		1			

Heterogeneity: Chi² = 0.26, df = 3 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.37 (P = 0.71)

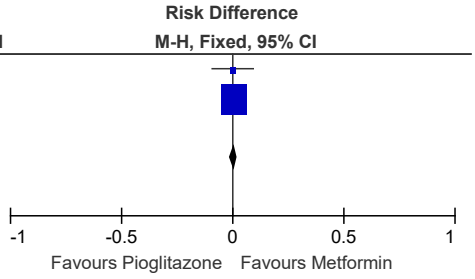


1

Figure 118: Non-fatal myocardial infarction at end of follow up

Study or Subgroup	Pioglitazone Events	Pioglitazone Total	Metformin Events	Metformin Total	Weight	Risk Difference M-H, Fixed, 95% CI
Erem 2014	0	20	0	20	9.1%	0.00 [-0.09, 0.09]
Perez 2009	1	190	0	209	90.9%	0.01 [-0.01, 0.02]
Total (95% CI)		**210**		**229**	**100.0%**	**0.00 [-0.01, 0.02]**
Total events	1		0			

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.90); I² = 0%
Test for overall effect: Z = 0.60 (P = 0.55)

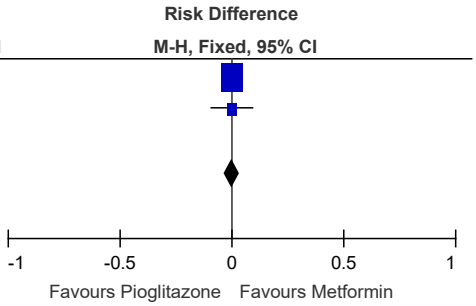


2

3 **Figure 119: Hospitalisation for heart failure at end of follow-up**

Study or Subgroup	Pioglitazone Events	Pioglitazone Total	Metformin Events	Metformin Total	Weight	Risk Difference M-H, Fixed, 95% CI
Esposito 2011	0	55	0	55	73.3%	0.00 [-0.03, 0.03]
Erem 2014	0	20	0	20	26.7%	0.00 [-0.09, 0.09]
Total (95% CI)		**75**		**75**	**100.0%**	**0.00 [-0.04, 0.04]**
Total events	0		0			

Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)



4

5

Figure 120: Hypoglycaemia episodes at end of follow up

Study or Subgroup	Pioglitazone Events	Pioglitazone Total	Metformin Events	Metformin Total	Weight	Risk Difference M-H, Fixed, 95% CI
DeRosa 2009	0	69	0	67	13.0%	0.00 [-0.03, 0.03]
Erem 2014	0	20	0	20	3.8%	0.00 [-0.09, 0.09]
Perez 2009	1	190	3	209	38.2%	-0.01 [-0.03, 0.01]
Russell-Jones 2012	6	163	10	246	37.6%	-0.00 [-0.04, 0.03]
Yamanouchi 2005	0	38	0	39	7.4%	0.00 [-0.05, 0.05]
Total (95% CI)		**480**		**581**	**100.0%**	**-0.00 [-0.02, 0.01]**
Total events	7		13			

Heterogeneity: Chi² = 0.35, df = 4 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.56 (P = 0.58)

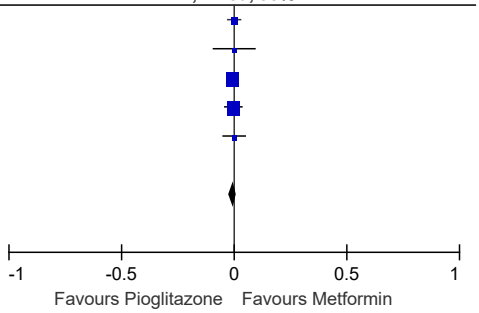


Figure 121: HbA1c change (%, lower values are better, change scores and final values) at end of follow-up

Study or Subgroup	Mean Difference	SE	Pioglitazone Total	Metformin Total	Weight	Mean Difference IV, Random, 95% CI
Derosa 2009	0.3	0.1041	69	67	22.2%	0.30 [0.10, 0.50]
Erem 2014	0.06	0.2057	19	19	10.7%	0.06 [-0.34, 0.46]
Esposito 2011	0	0.0953	55	55	23.6%	0.00 [-0.19, 0.19]
Pavo 2003	0.2	0.185	105	100	12.4%	0.20 [-0.16, 0.56]
Russell-Jones 2012	-0.15	0.1063	137	218	21.8%	-0.15 [-0.36, 0.06]
Yamanouchi 2005	0.1	0.2279	38	39	9.3%	0.10 [-0.35, 0.55]
Total (95% CI)			**423**	**498**	**100.0%**	**0.07 [-0.08, 0.23]**

Heterogeneity: Tau² = 0.02; Chi² = 10.21, df = 5 (P = 0.07); I² = 51%
Test for overall effect: Z = 0.92 (P = 0.36)

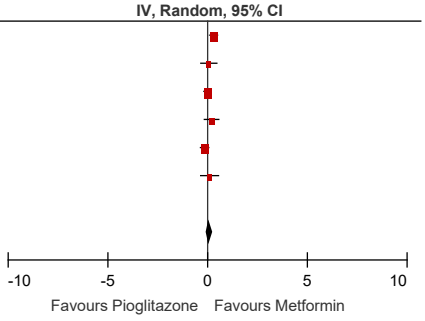


Figure 122: Weight change (kg, lower values are better, change scores and final values) end of follow-up

Study or Subgroup	Pioglitazone Mean [kg]	Pioglitazone SD [kg]	Pioglitazone Total	Metformin Mean [kg]	Metformin SD [kg]	Metformin Total	Weight	Mean Difference IV, Random, 95% CI [kg]
Erem 2014	76.8	14.7	19	83.4	13.3	19	3.3%	-6.60 [-15.51, 2.31]
Esposito 2011	1.4	0.9	55	-0.2	0.2	55	25.1%	1.60 [1.36, 1.84]
Pavo 2003	0.7	4.099	105	-2.4	4	100	22.9%	3.10 [1.99, 4.21]
Roden 2005	2.09	4.887	597	-2.64	4.887	597	24.6%	4.73 [4.18, 5.28]
Russell-Jones 2012	1.5	3.83	163	-2	3.137	246	24.2%	3.50 [2.79, 4.21]
Total (95% CI)			**939**			**1017**	**100.0%**	**2.90 [1.16, 4.64]**

Heterogeneity: Tau² = 3.11; Chi² = 122.27, df = 4 (P < 0.00001); I² = 97%
Test for overall effect: Z = 3.27 (P = 0.001)

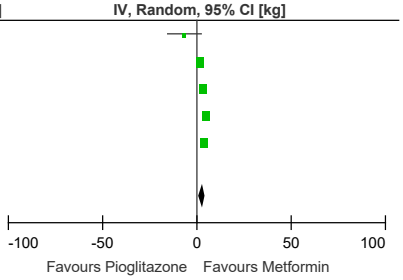
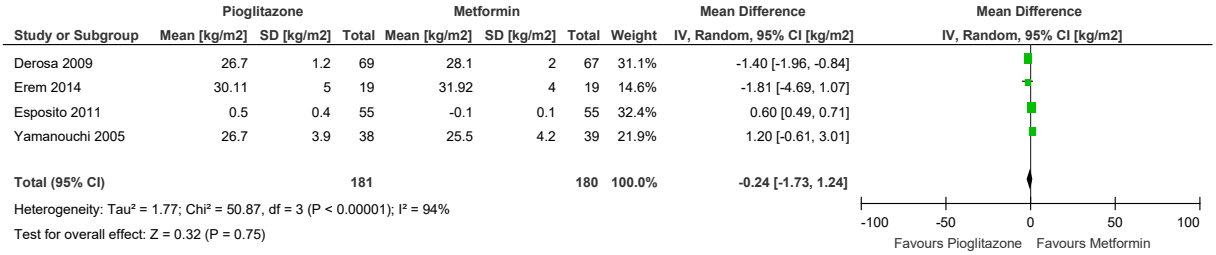


Figure 123: BMI change (kg/m2, lower values are better, change scores and final values) end of follow-up



E.1.752 Pioglitazone compared to linagliptin

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

E.1.783 Pioglitazone compared to sitagliptin

Figure 124: All-cause mortality at end of follow up

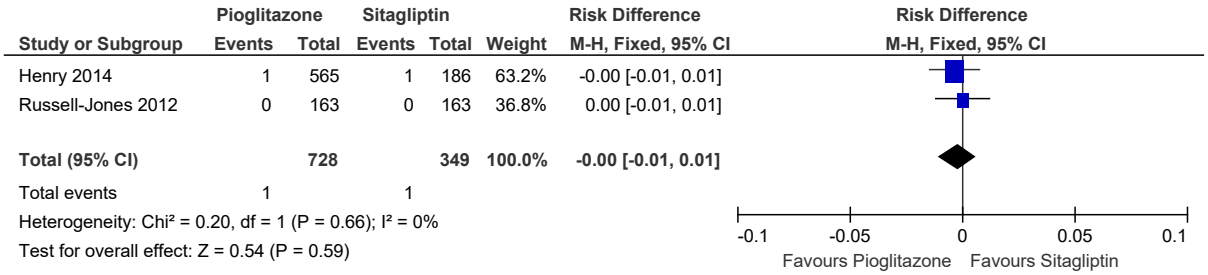


Figure 125: Cardiovascular mortality at end of follow-up

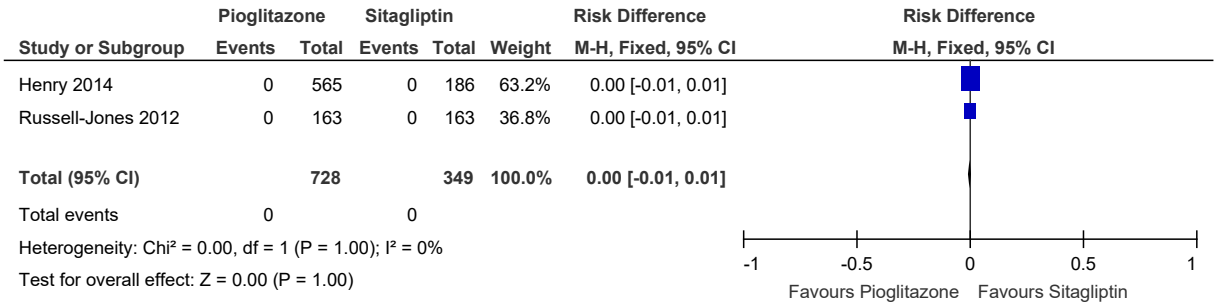


Figure 126: Hypoglycaemia episodes at end of follow-up

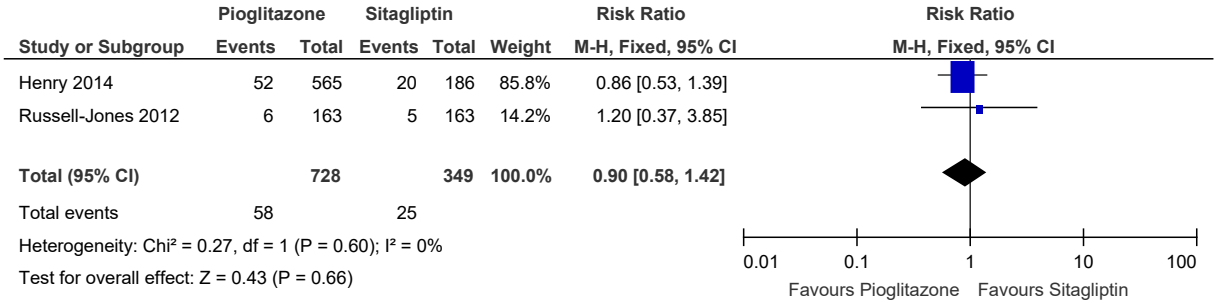


Figure 127: HbA1c change (%, lower values are better, change score) at end of follow-up

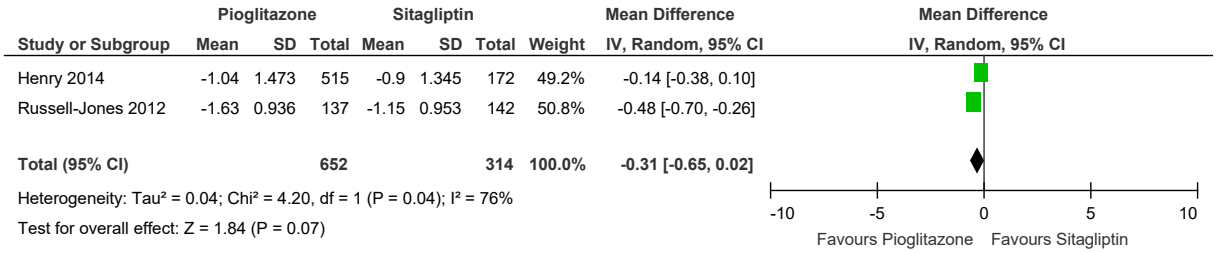
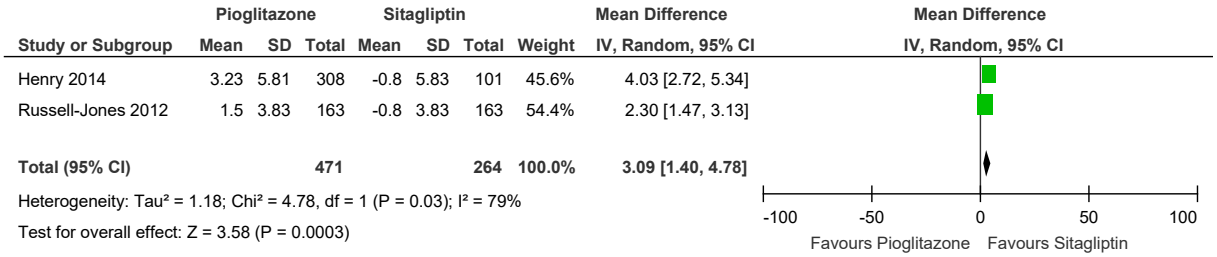


Figure 128: Weight change (kg, lower values are better, change score) at end of follow-up



E.1.24 Pioglitazone compared to vildagliptin

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

E.1.715 Pioglitazone compared to exenatide

Figure 129: All-cause mortality at end of follow-up

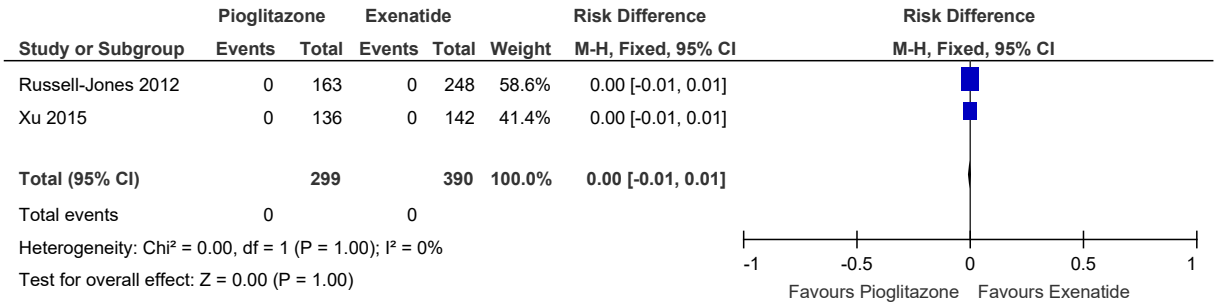


Figure 130: Cardiovascular mortality at end of follow-up

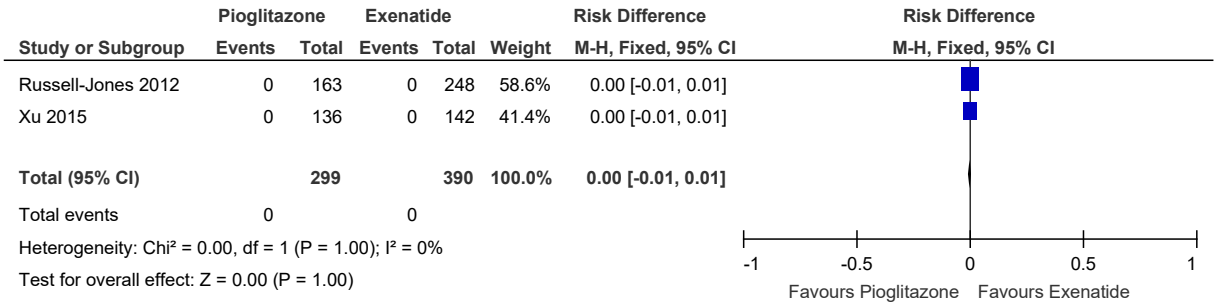


Figure 131: Hypoglycaemia episodes at end of follow-up

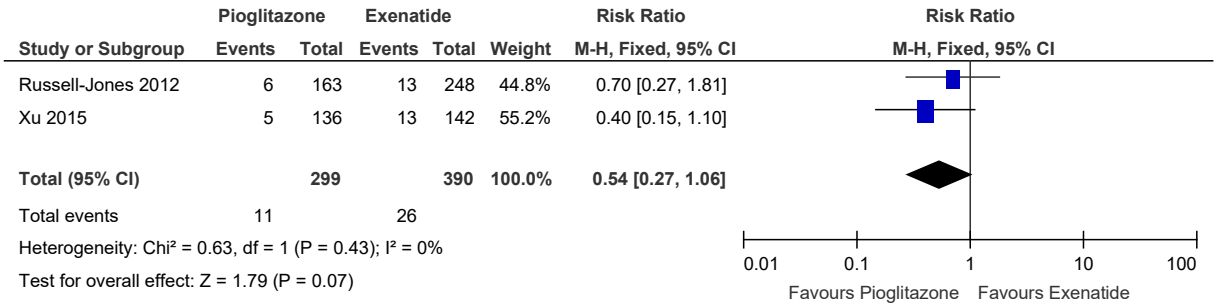


Figure 132: HbA1c change (%, lower values are better, change scores) at end of follow-up

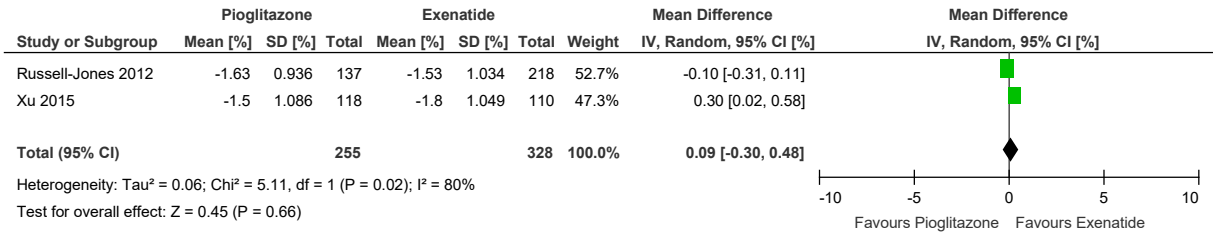
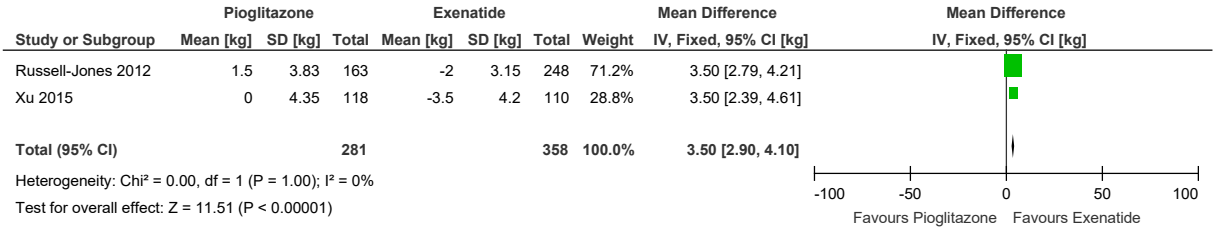


Figure 133: Weight change (kg, lower values are better, change scores at end of follow-up



E.1.766 Pioglitazone compared to liraglutide

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

E.1.797 Pioglitazone compared to gliclazide

Figure 134: Hypoglycaemia episodes at end of follow-up

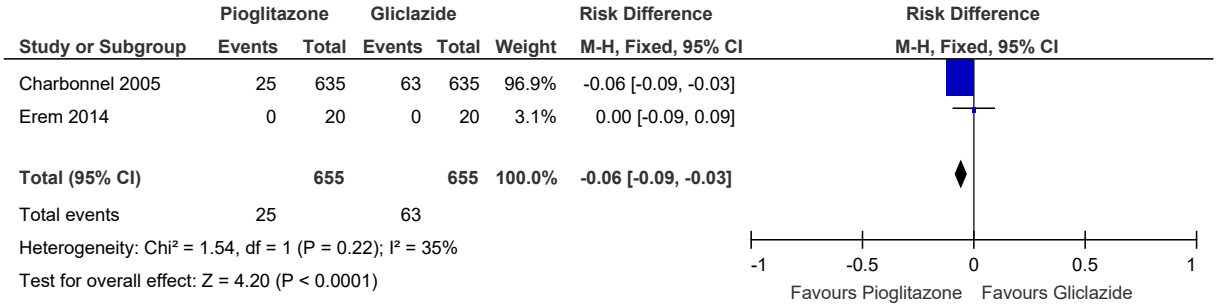


Figure 135: HbA1c change (%, lower values are better, change scores) at end of follow-up

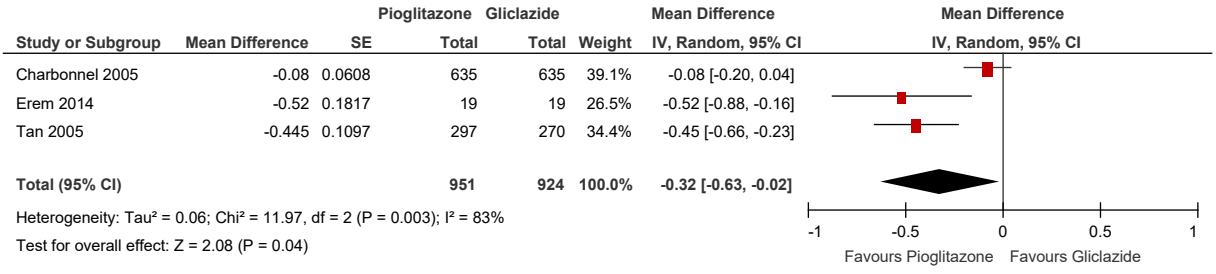
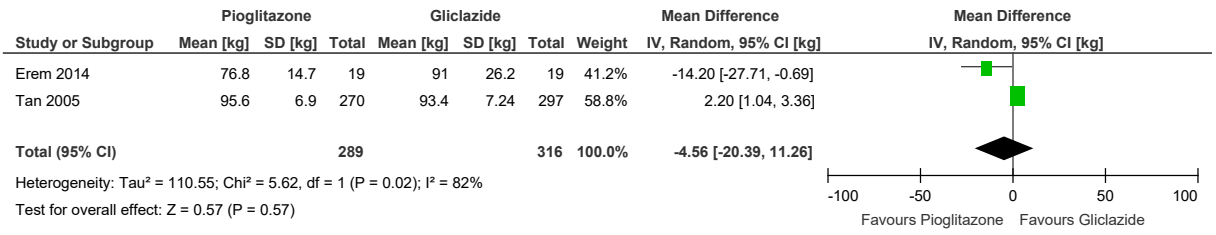


Figure 136: Weight change (kg, lower values are better, change scores) at end of follow-up



E.1.758 Pioglitazone compared to glimepiride

Figure 137: Hypoglycaemia episodes at follow-up

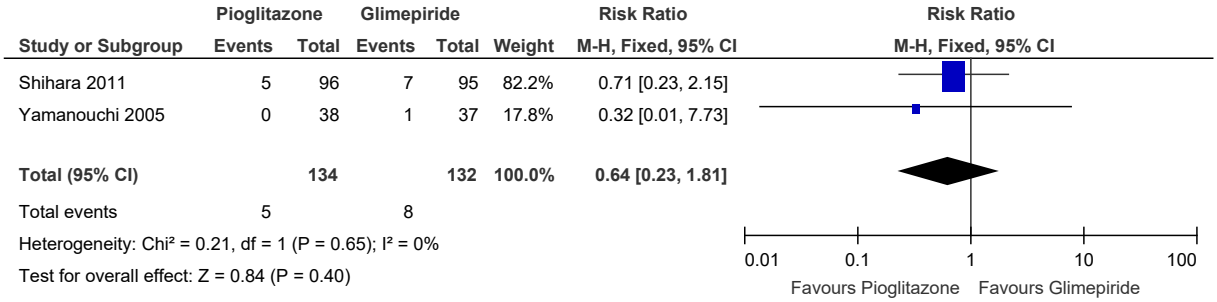
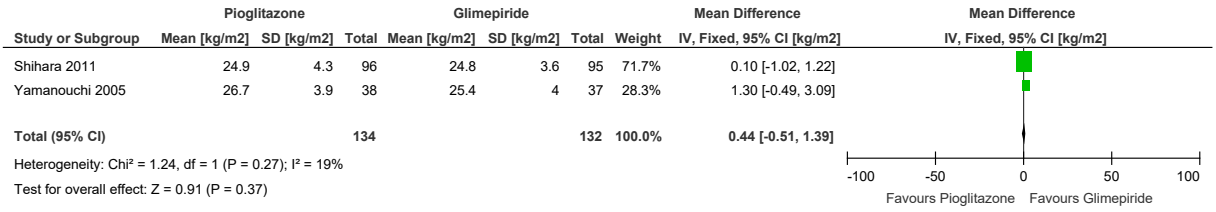


Figure 138: BMI change (kg/m2, lower values are better, final values) at end of follow-up



E.1.759 Pioglitazone compared to insulin

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

E.1.7.10 Pioglitazone compared to placebo

Figure 139: All-cause mortality at end of follow-up

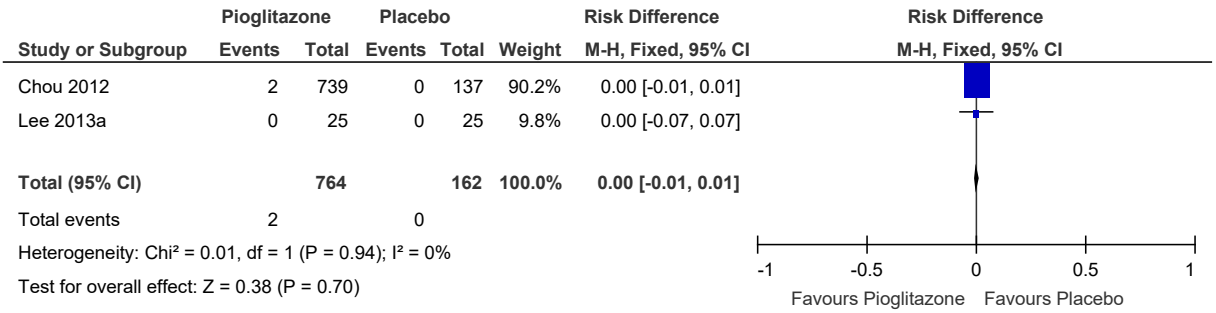


Figure 140: Non-fatal stroke at end of follow-up

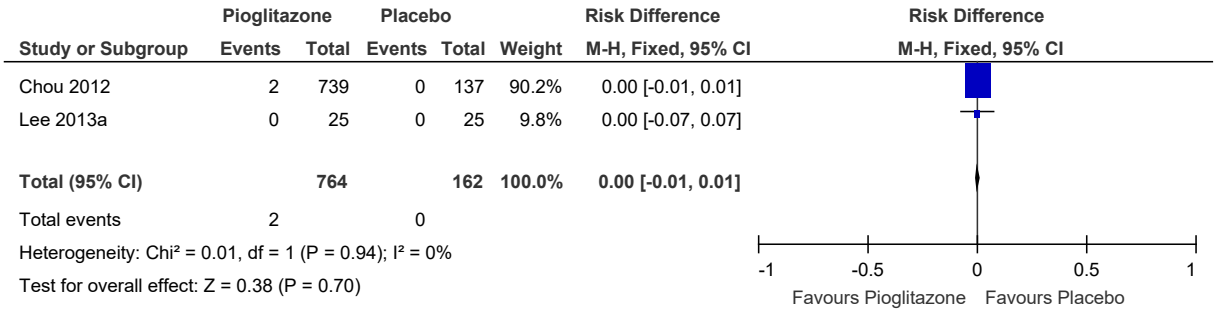


Figure 141: Non-fatal myocardial infarction at end of follow-up

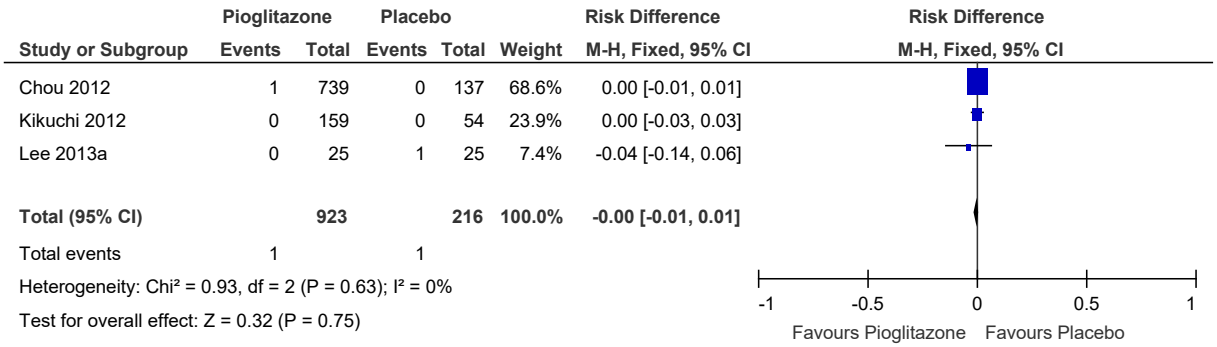


Figure 142: Hypoglycaemia episodes at end of follow-up

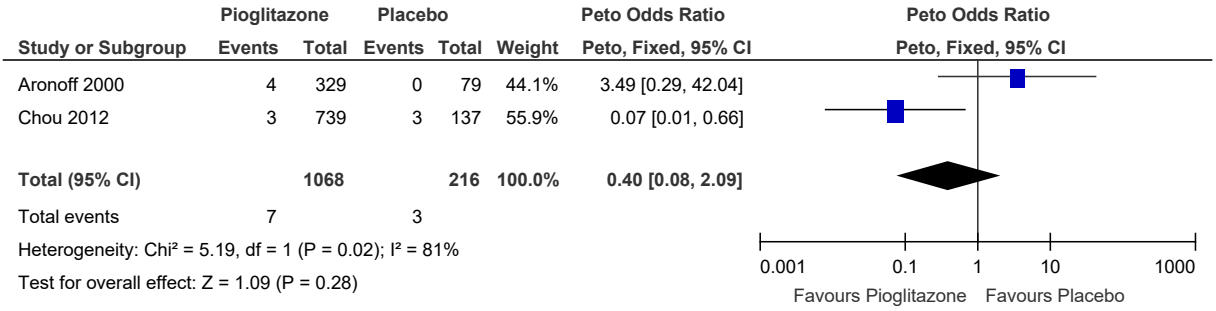


Figure 143: HbA1c change (%, lower values are better, change scores) at end of follow-up

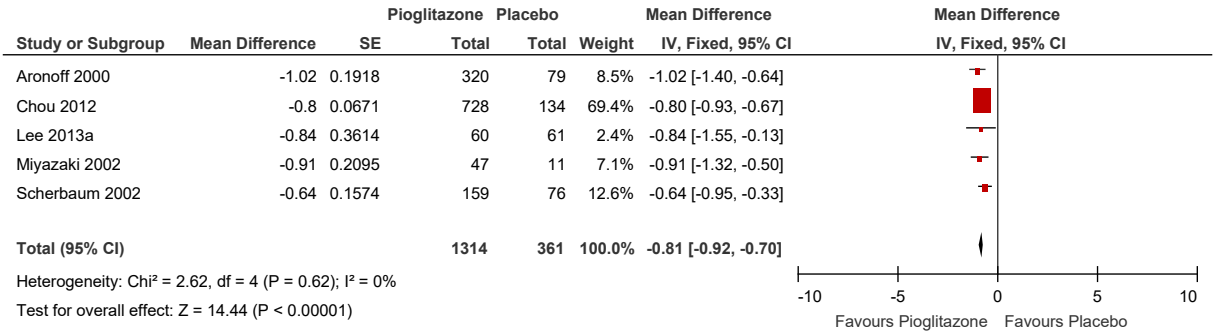
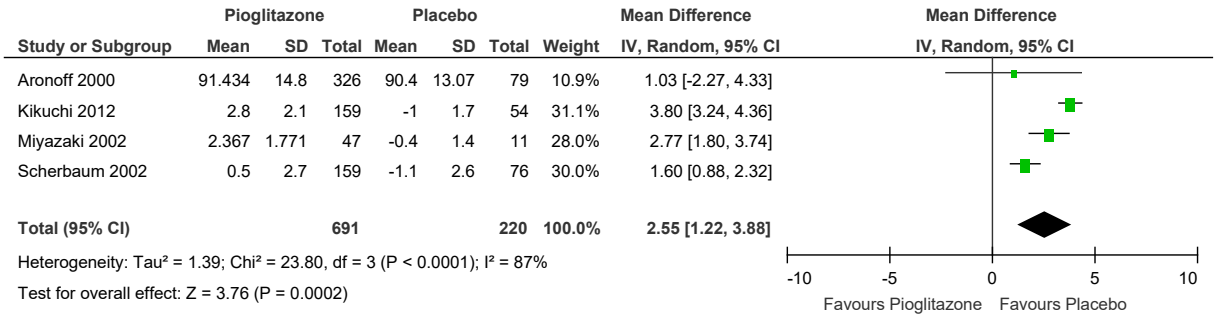


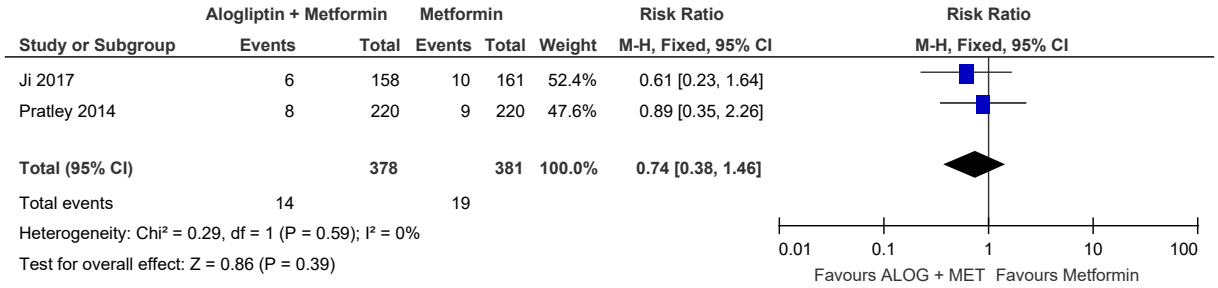
Figure 144: Weight change (kg, lower values are better, change scores and final values) at end of follow-up



E.1.8 Combinations

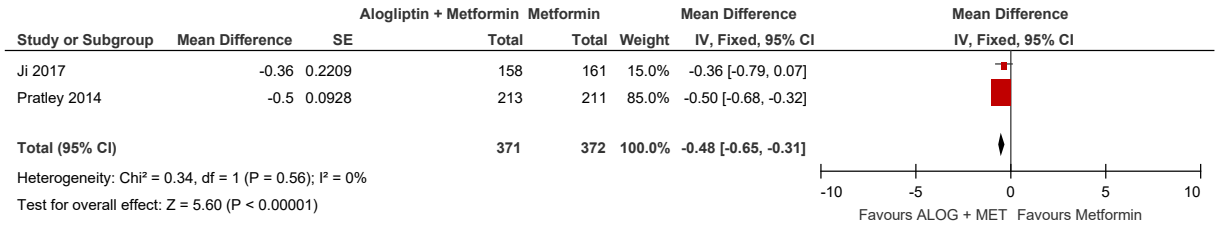
E.1.8.1 Alogliptin + metformin compared to metformin

Figure 145: Hypoglycaemia episodes at end of follow-up



E.1.8.2 Alogliptin + metformin compared to alogliptin

Figure 146: HbA1c change (%, lower values are better, change scores and final values) at end of follow-up



E.1.8.2 Alogliptin + metformin compared to alogliptin

Figure 147: Hypoglycaemia episodes at end of follow-up

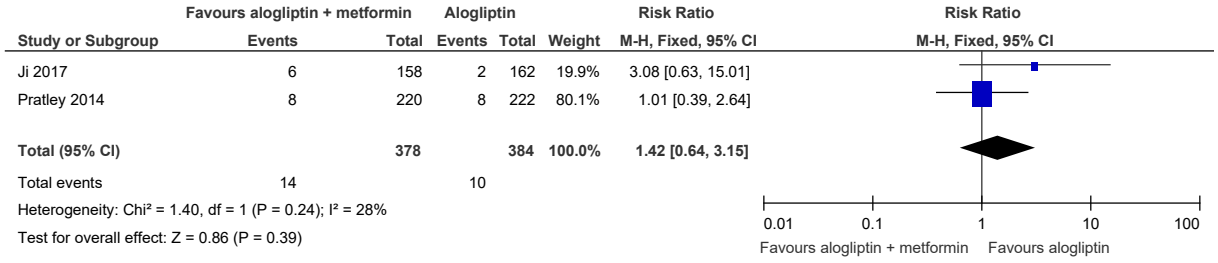
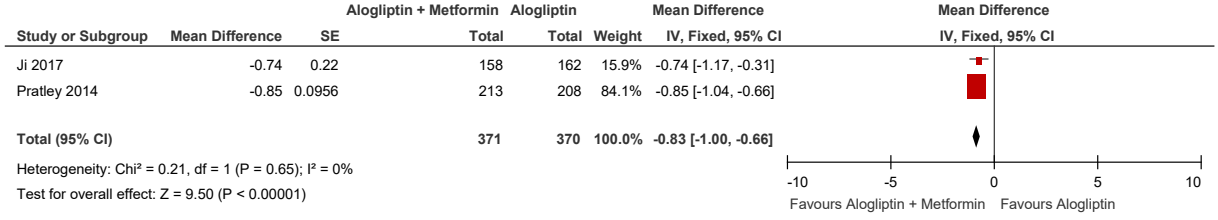
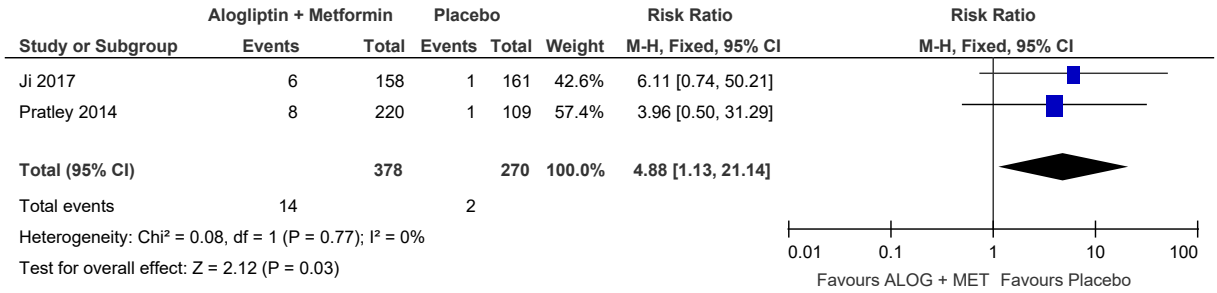


Figure 148: HbA1c change (%, lower values are better, change scores) at end of follow-up



E.1.823 Alogliptin + metformin compared to placebo

Figure 149: Hypoglycaemia episodes at end of follow-up



E.1.864 Linagliptin + metformin compared to metformin

Figure 150: Hypoglycaemia episodes at end follow-up

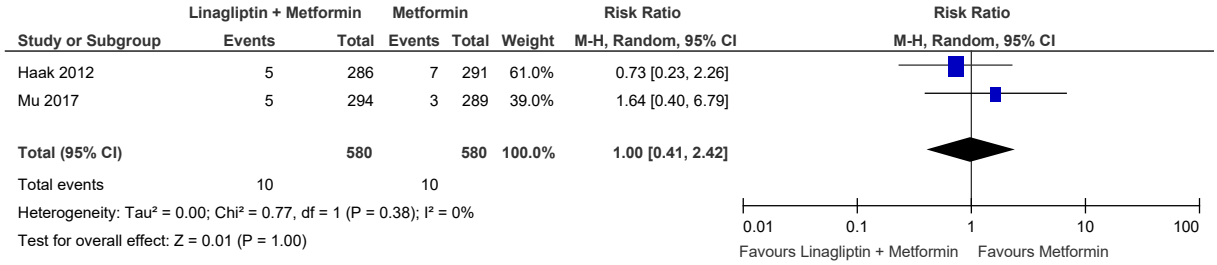


Figure 151: Severe hypoglycaemic episodes at end follow-up

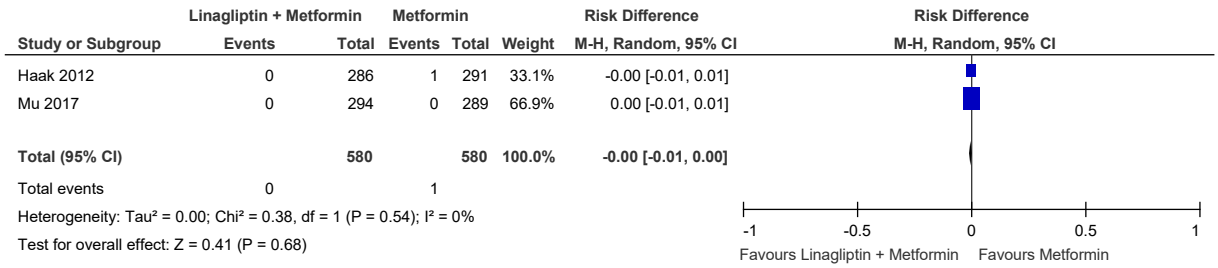


Figure 152: HbA1c change (%, lower vales are better, change scores) at end of follow-up

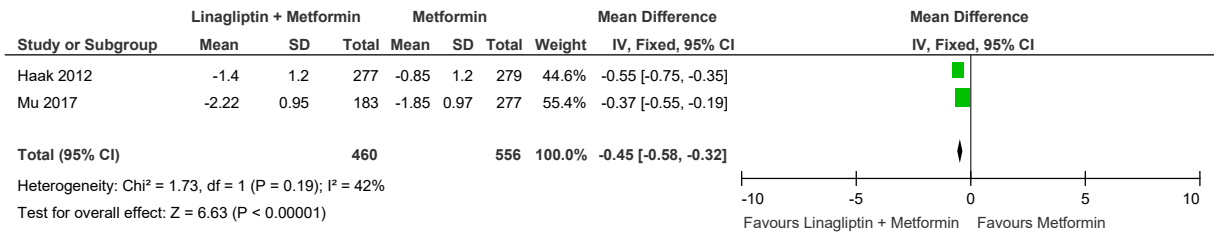
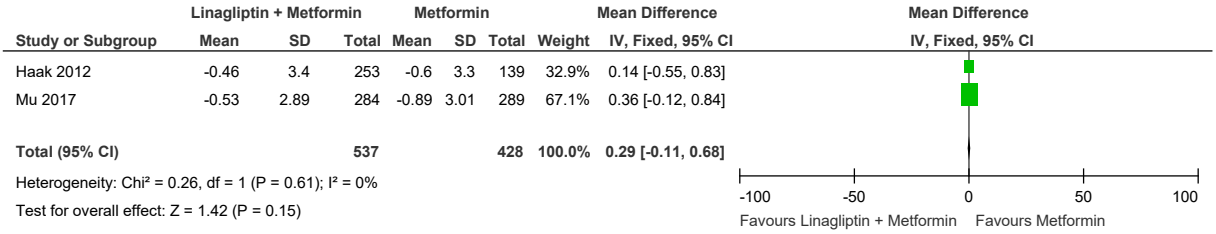


Figure 153: Weight change (kg, lower vales are better, change scores) at end of follow-up



E.1.865 Linagliptin + metformin compared to linagliptin

Figure 154: All-cause mortality at end of follow-up

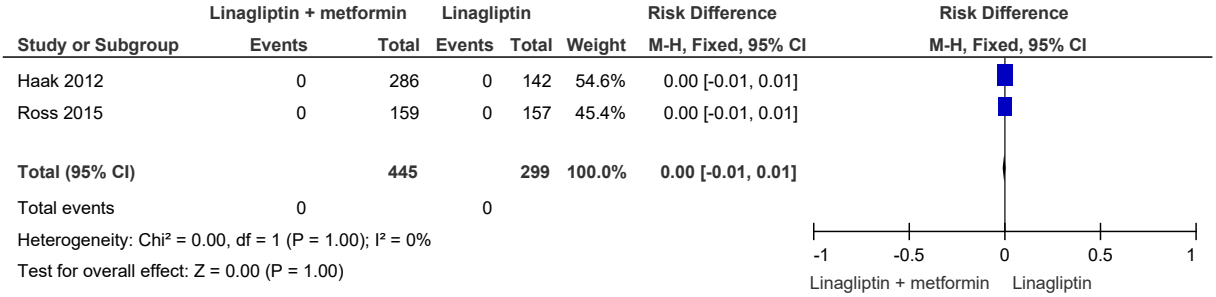


Figure 155: Cardiovascular mortality at end of follow-up

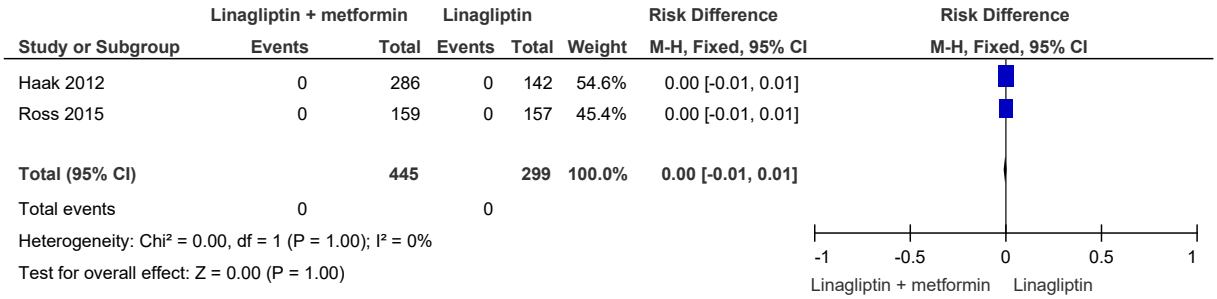


Figure 156: Hospitalisation for heart failure at end of follow-up

Study or Subgroup	Linagliptin + metformin Events	Total	Linagliptin Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Mu 2017	0	294	0	147	55.4%	0.00 [-0.01, 0.01]
Ross 2015	0	159	0	157	44.6%	0.00 [-0.01, 0.01]
Total (95% CI)		**453**		**304**	**100.0%**	**0.00 [-0.01, 0.01]**
Total events	0		0			

Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%

Test for overall effect: Z = 0.00 (P = 1.00)

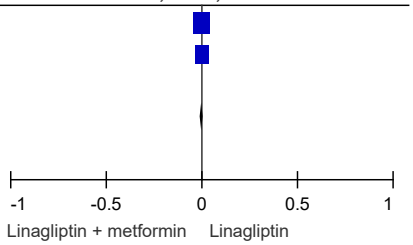


Figure 157: Hypoglycaemia episodes at end of follow-up

Study or Subgroup	Linagliptin + metformin Events	Total	Linagliptin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Haak 2012	5	286	0	142	9.5%	5.48 [0.31, 98.43]
Mu 2017	5	294	1	147	19.0%	2.50 [0.29, 21.20]
Ross 2015	3	159	5	157	71.5%	0.59 [0.14, 2.44]
Total (95% CI)		**739**		**446**	**100.0%**	**1.42 [0.52, 3.87]**
Total events	13		6			

Heterogeneity: Chi² = 2.57, df = 2 (P = 0.28); I² = 22%

Test for overall effect: Z = 0.68 (P = 0.50)

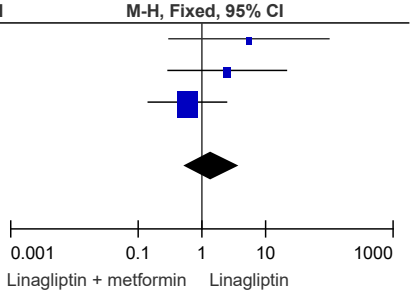


Figure 158: Severe hypoglycaemic episodes at end of follow-up

Study or Subgroup	Linagliptin + metformin Events	Total	Linagliptin Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Haak 2012	0	286	0	142	34.9%	0.00 [-0.01, 0.01]
Mu 2017	0	294	0	147	36.0%	0.00 [-0.01, 0.01]
Ross 2015	0	159	0	157	29.1%	0.00 [-0.01, 0.01]
Total (95% CI)		**739**		**446**	**100.0%**	**0.00 [-0.01, 0.01]**
Total events	0		0			

Heterogeneity: Chi² = 0.00, df = 2 (P = 1.00); I² = 0%

Test for overall effect: Z = 0.00 (P = 1.00)

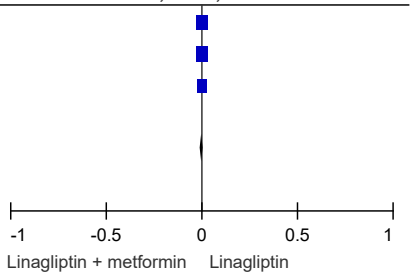


Figure 159: HbA1c change (%, lower values are better, change scores) at end of follow-up

Study or Subgroup	Linagliptin + metformin Mean	SD	Total	Linagliptin Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Haak 2012	-1.40217	1.2	277	-0.5	1.2	135	33.9%	-0.90 [-1.15, -0.66]
Mu 2017	-2.22	0.95	183	-1.29	0.95	141	47.4%	-0.93 [-1.14, -0.72]
Ross 2015	-2.72	1.484318	153	-1.8	1.469694	150	18.7%	-0.92 [-1.25, -0.59]
Total (95% CI)			**613**			**426**	**100.0%**	**-0.92 [-1.06, -0.77]**

Heterogeneity: Chi² = 0.03, df = 2 (P = 0.99); I² = 0%

Test for overall effect: Z = 12.53 (P < 0.00001)

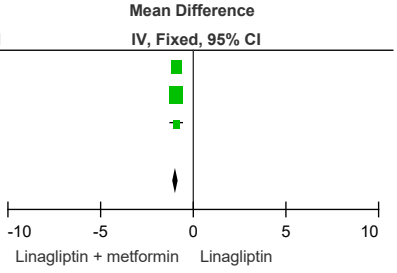
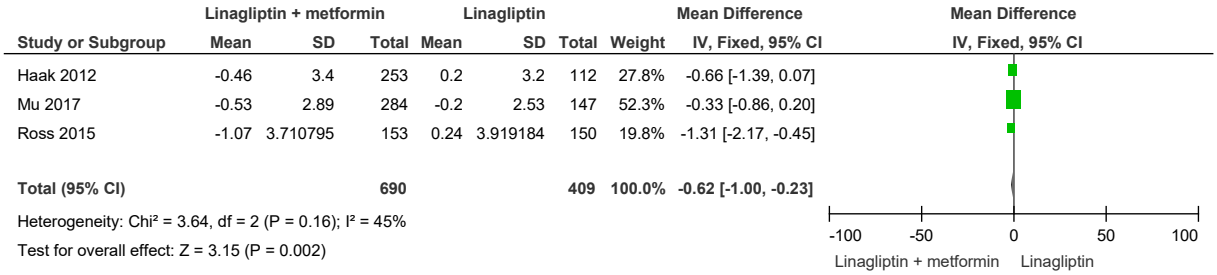


Figure 160:Weight change (kg, lower values are better, change scores) at end of follow-up



E.1.866 Linagliptin + metformin compared to placebo

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

E.1.897 Saxagliptin + metformin compared to metformin

Figure 161: All-cause mortality at end of follow up

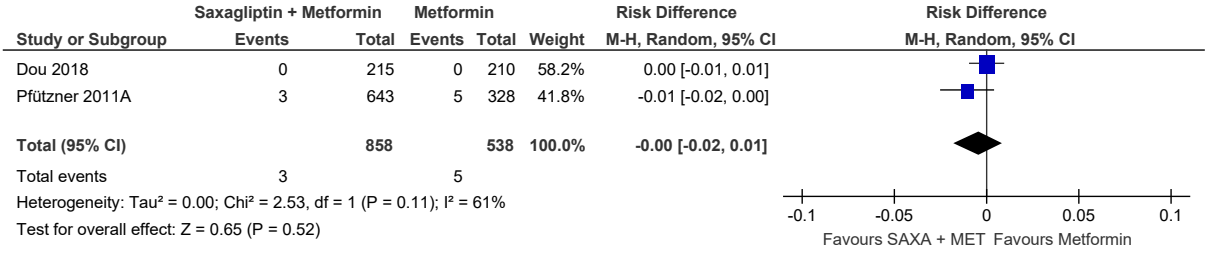


Figure 162: Hypoglycaemia episodes at end of follow-up

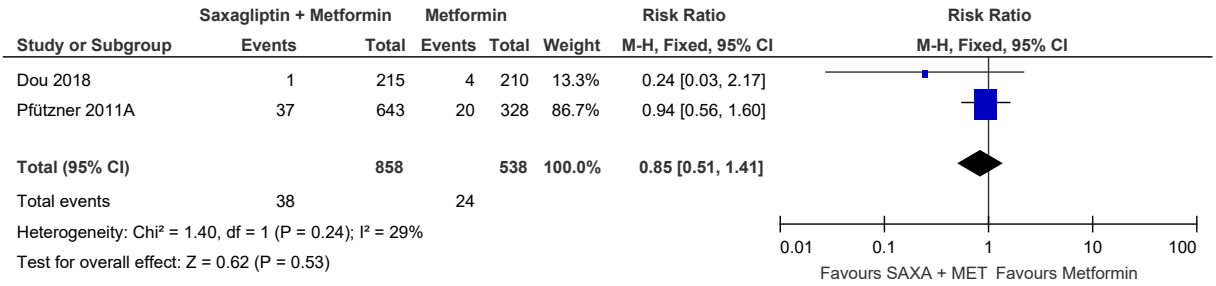


Figure 163: Severe hypoglycaemic episodes at end of follow up

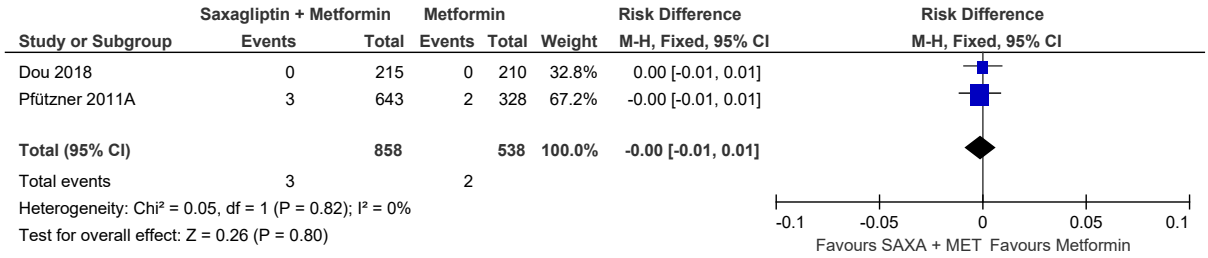


Figure 164: HbA1c change (%, lower values are better, change scores) at end of follow-up

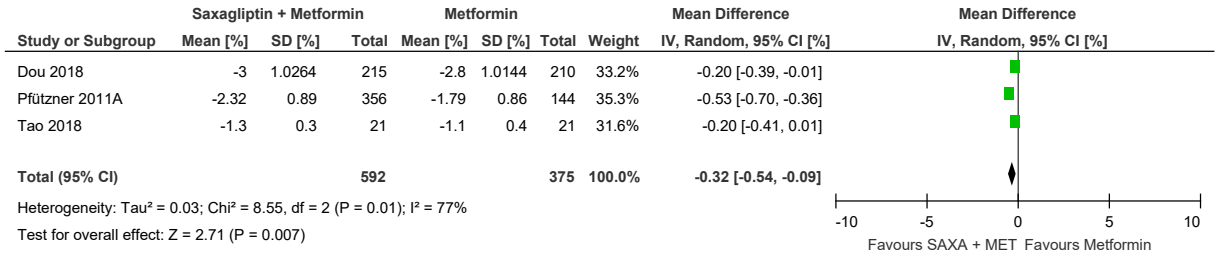


Figure 165: Weight change (kg, lower values are better, change scores) at end of follow-up

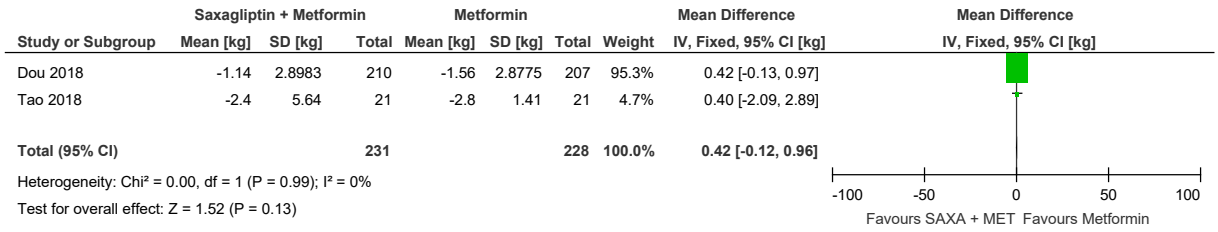
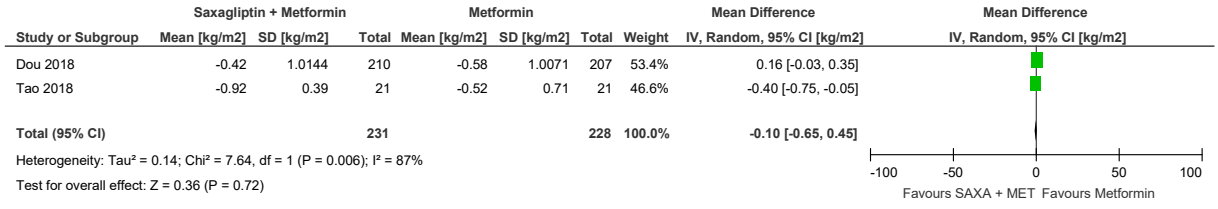


Figure 166: BMI change (kg/m2, lower values are better, change scores) at end of follow-up



E.1.818 Saxagliptin + metformin compared to saxagliptin

Figure 167: All-cause mortality at end of follow-up

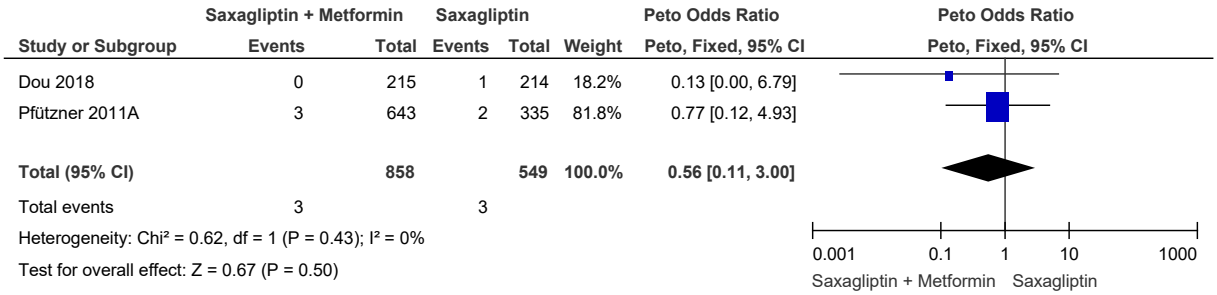


Figure 168: Hypoglycaemia episodes at end of follow-up

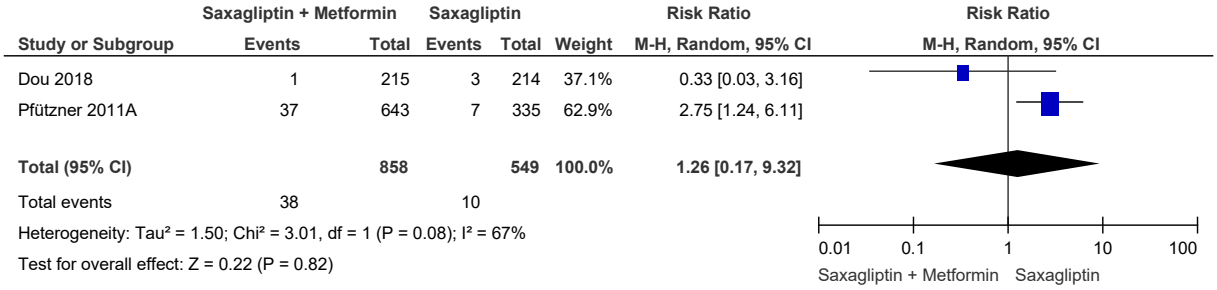


Figure 169: Severe hypoglycaemic episodes at end of follow up

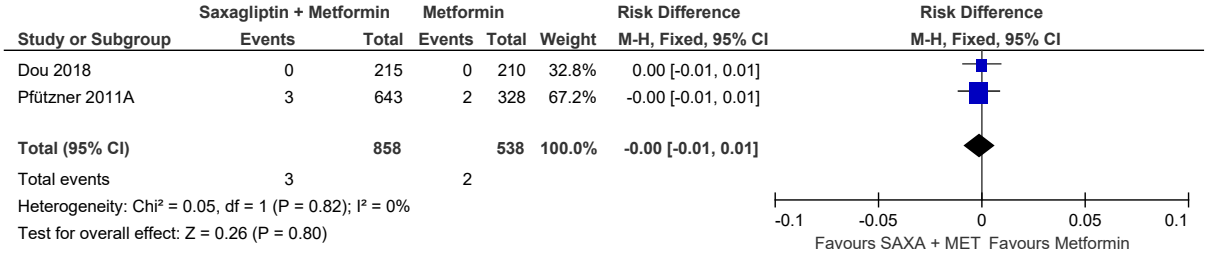
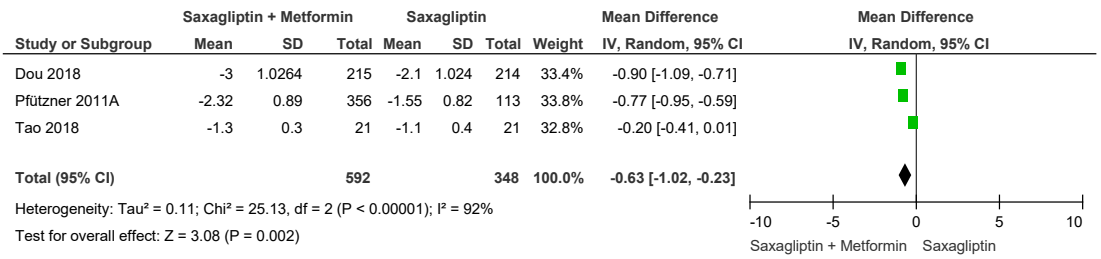
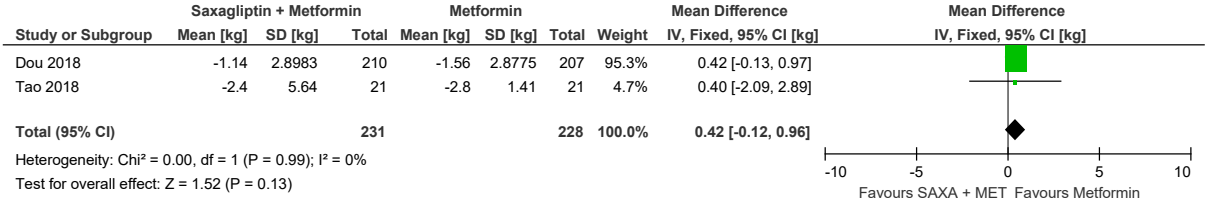


Figure 170: HbA1c change (%, lower values are better, change score) at end of follow-up



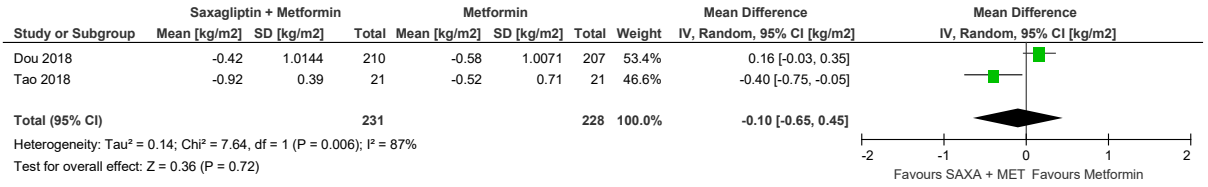
1

Figure 171: Weight change (kg, lower values are better, final values) at end of follow-up



2

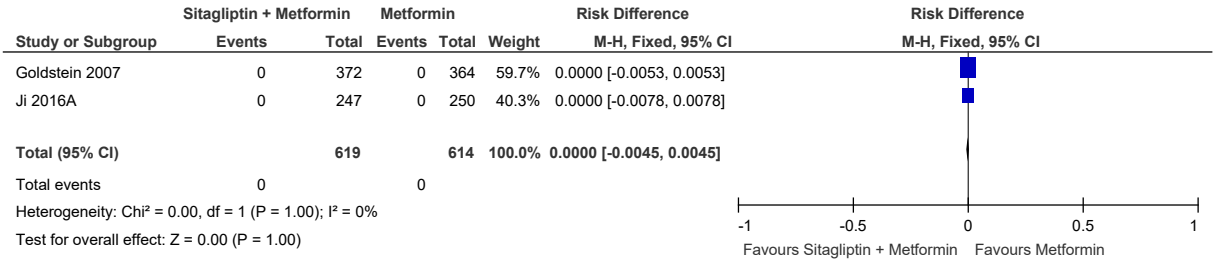
Figure 172: BMI change (kg/m2, lower values are better, final values) at end of follow-up



3

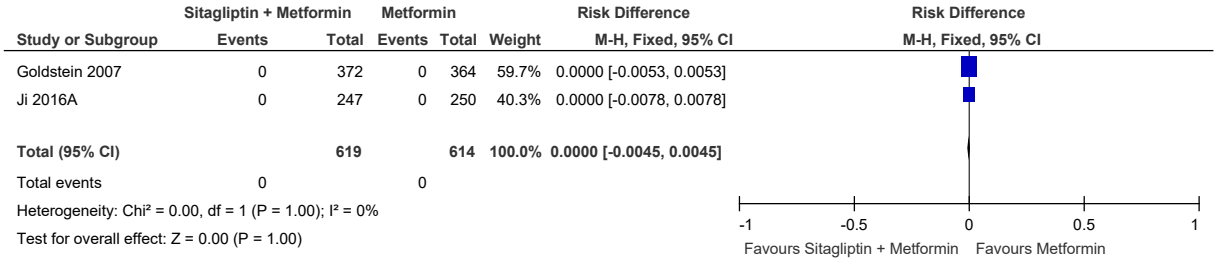
E.1.8.9 Sitagliptin + metformin compared to metformin

Figure 173: All-cause mortality at end of follow-up



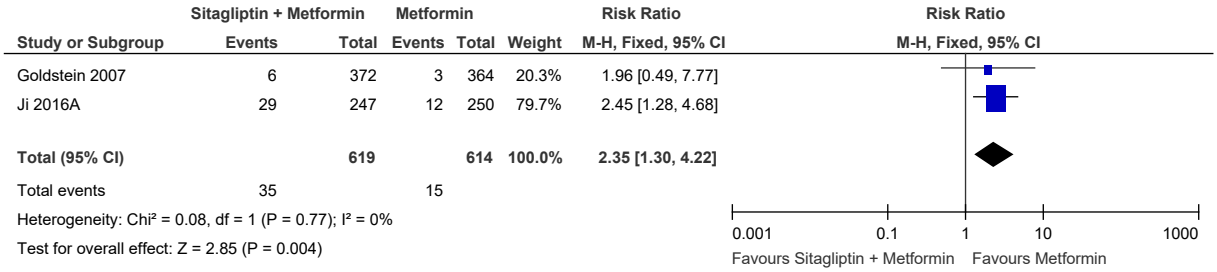
5

Figure 174: Cardiovascular mortality at end of follow-up



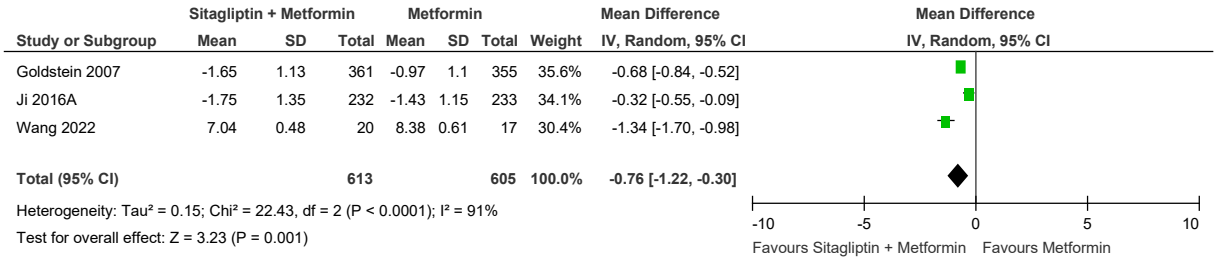
6

Figure 175: Hypoglycaemia episodes at end of follow-up



1

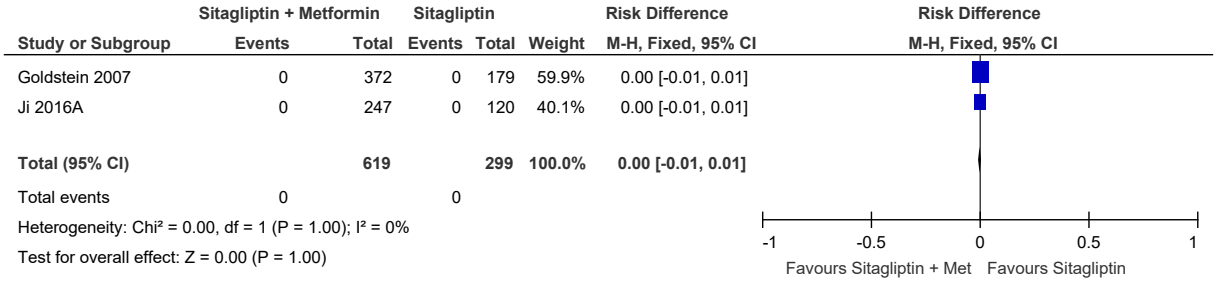
Figure 176: HbA1c change (%, lower values are better, change scores and final value) at end of follow-up



2

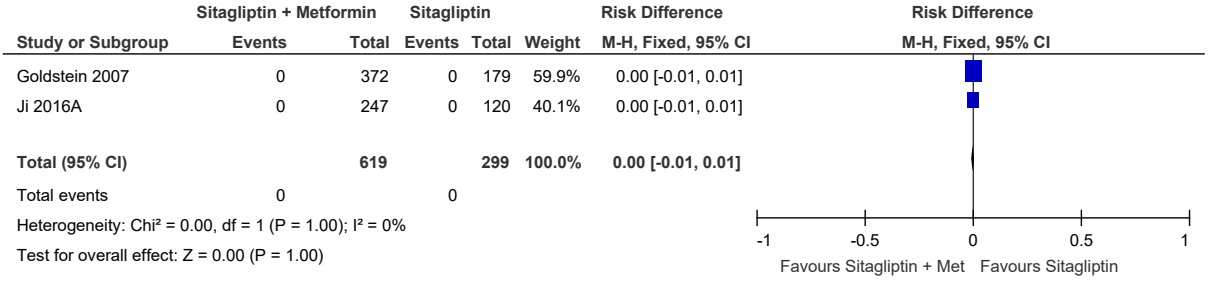
E.1.8.10 Sitagliptin + metformin compared to sitagliptin

Figure 177: All-cause mortality at end of follow-up



4

Figure 178: Cardiovascular mortality at end of follow-up



5

Figure 179: Hypoglycaemia episodes at end of follow-up

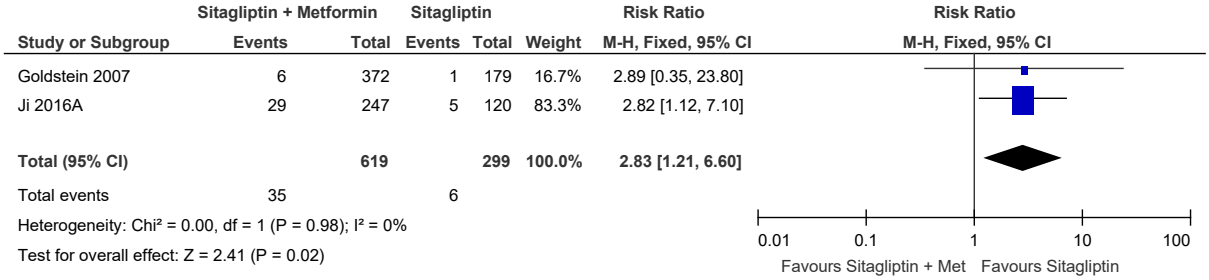
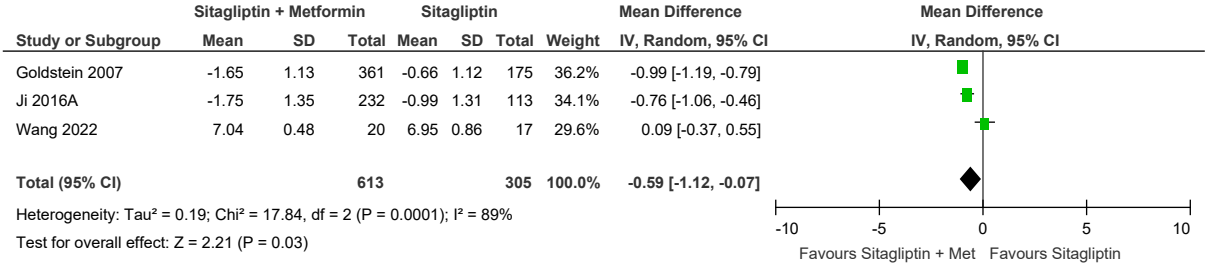


Figure 180: HbA1c change (%, lower values are better, change scores and final value) at end of follow-up



E.1.8.1 Sitagliptin + metformin compared to glimepiride

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

E.1.8.2 Sitagliptin + metformin compared to pioglitazone

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

E.1.8.3 Sitagliptin + metformin compared to placebo

Figure 181: All-cause mortality at end of follow up

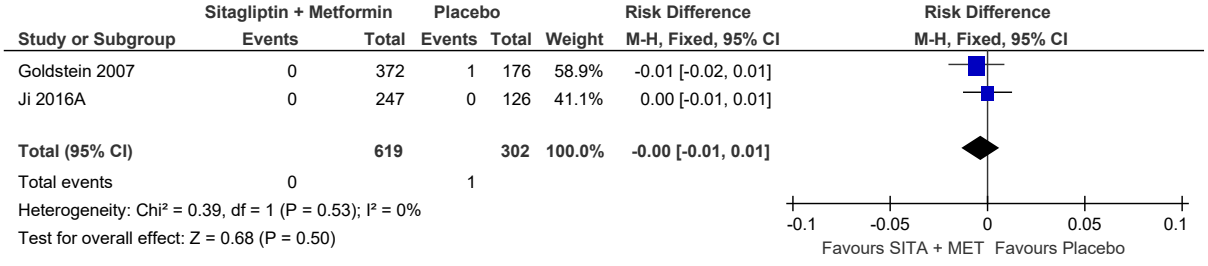
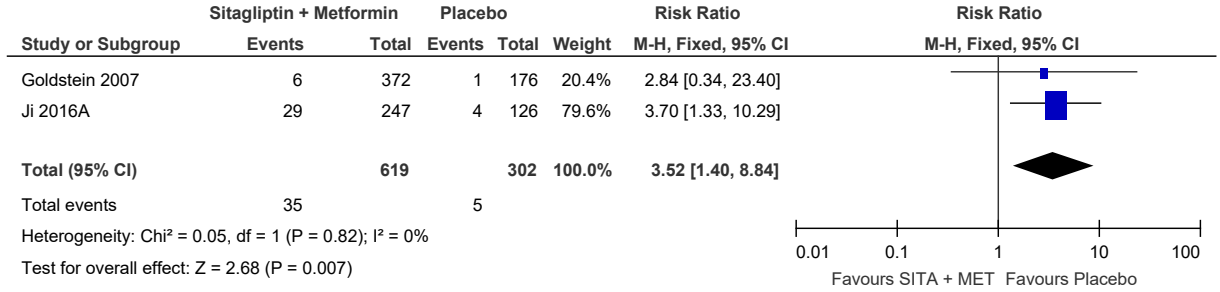


Figure 182: Cardiovascular mortality at end of follow up

1

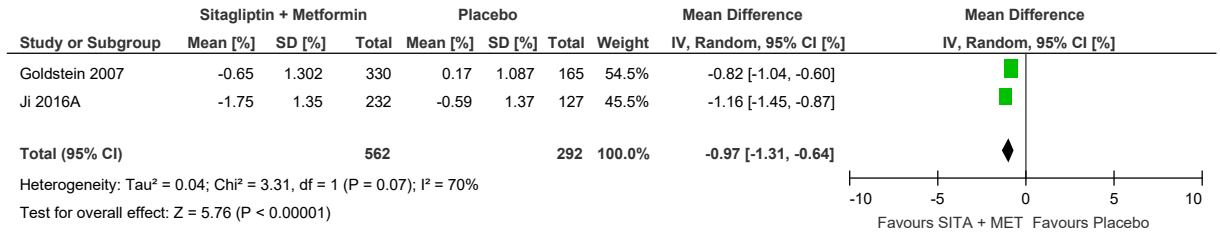
2 **Figure 183: Hypoglycaemia episodes at end of follow-up**



3

4

5 **Figure 184: HbA1c change (%, lower values are better, change scores) at end of**
6 **follow-up**

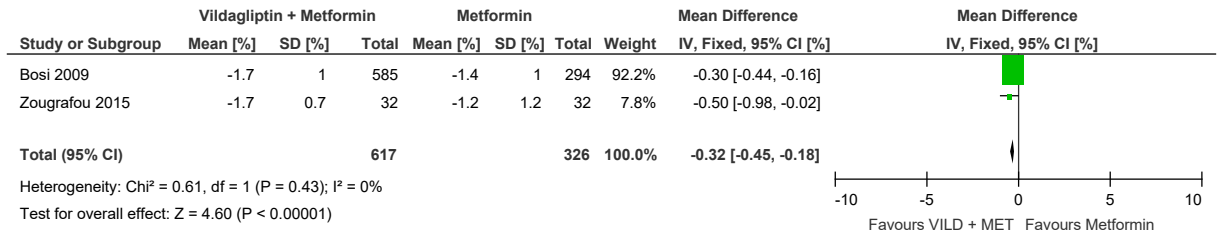


7

8

E.1.8.14 Vildagliptin + metformin compared to metformin

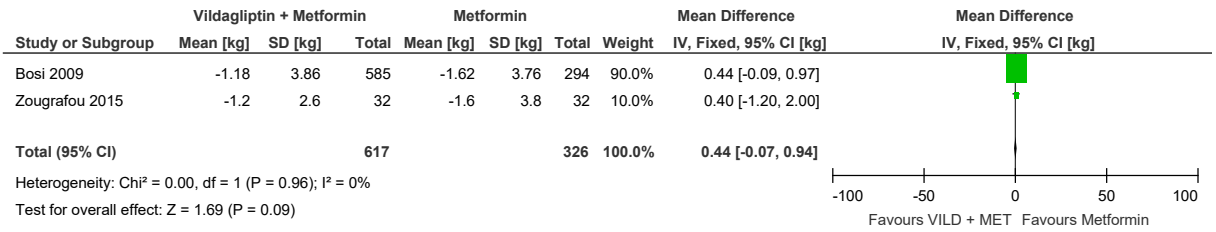
10 **Figure 185: HbA1c change (%, lower values are better, change scores) at end of**
11 **follow-up**



12

13

Figure 186: Weight change (kg, lower values are better, change scores) at end of follow-up



E.1.8.15 Vildagliptin + metformin compared to vildagliptin

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

E.1.8.16 Canagliflozin + metformin compared to canagliflozin

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

E.1.8.17 Canagliflozin + metformin compared to metformin

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

E.1.8.18 Dapagliflozin + metformin compared to dapagliflozin

Figure 187: All-cause mortality at end of follow-up

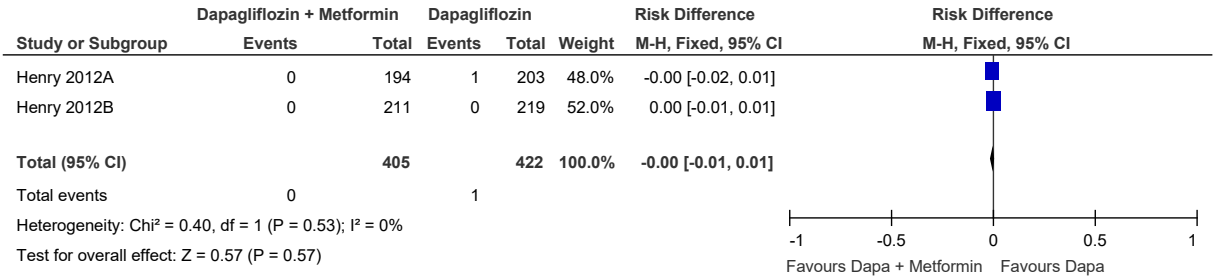


Figure 188: Cardiovascular mortality at end of follow-up

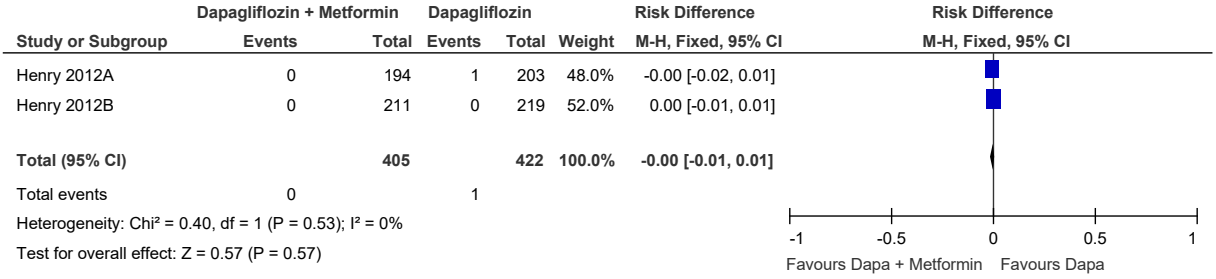


Figure 189: Hypoglycaemia episodes at end of follow-up

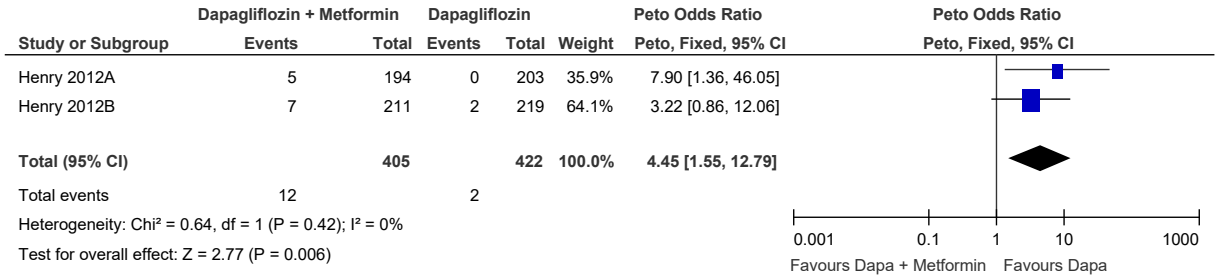


Figure 190: Severe hypoglycaemic episodes at end of follow-up

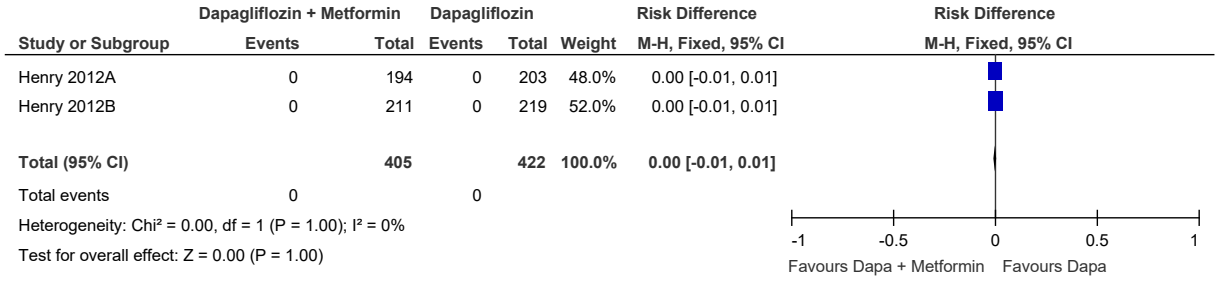


Figure 191: HbA1c change (%, lower values are better, change scores) at end of follow-up

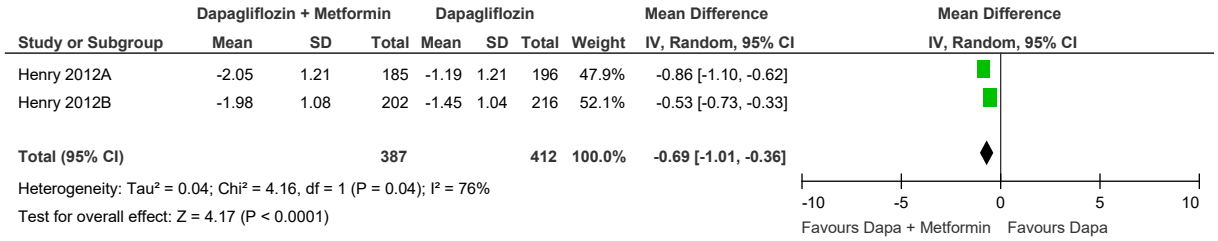
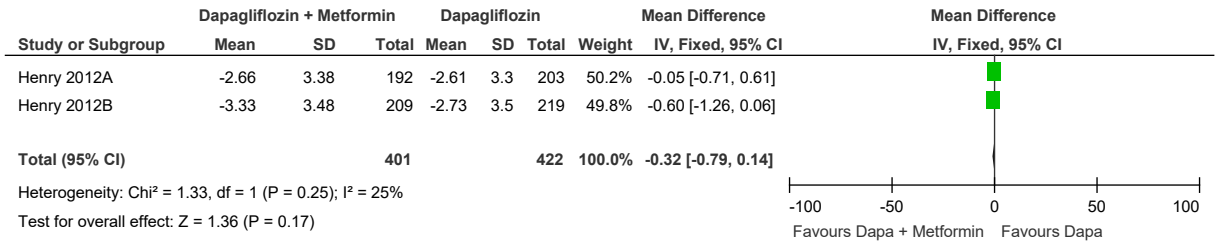


Figure 192: Weight change (kg, lower values are better, change scores) at end of follow-up



E.1.8.19 Dapagliflozin + metformin compared to metformin

Figure 193: All-cause mortality at end of follow-up

Study or Subgroup	Dapagliflozin + Metformin Events	Total	Metformin Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Henry 2012A	0	194	0	201	48.5%	0.00 [-0.01, 0.01]
Henry 2012B	0	211	1	208	51.5%	-0.00 [-0.02, 0.01]
Total (95% CI)		**405**		**409**	**100.0%**	**-0.00 [-0.01, 0.01]**
Total events	0		1			

Heterogeneity: Chi² = 0.36, df = 1 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.58 (P = 0.56)

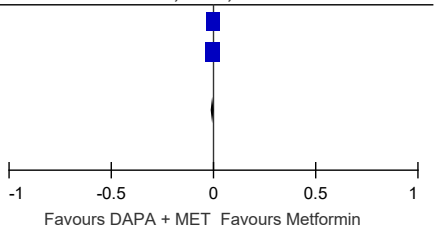


Figure 194: Cardiovascular mortality at end of follow-up

Study or Subgroup	Dapagliflozin + Metformin Events	Total	Metformin Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Henry 2012A	0	194	0	201	48.5%	0.00 [-0.01, 0.01]
Henry 2012B	0	211	1	208	51.5%	-0.00 [-0.02, 0.01]
Total (95% CI)		**405**		**409**	**100.0%**	**-0.00 [-0.01, 0.01]**
Total events	0		1			

Heterogeneity: Chi² = 0.36, df = 1 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.58 (P = 0.56)

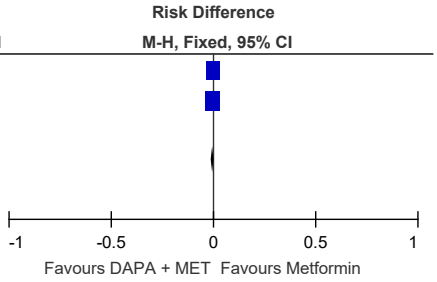


Figure 195: Hypoglycaemia episodes at end of follow-up

Study or Subgroup	Dapagliflozin + Metformin Events	Total	Metformin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Henry 2012A	5	194	0	201	6.5%	11.39 [0.63, 204.70]
Henry 2012B	7	211	6	208	80.2%	1.15 [0.39, 3.36]
Zhou 2022	2	75	1	75	13.3%	2.00 [0.19, 21.59]
Total (95% CI)		**480**		**484**	**100.0%**	**1.93 [0.81, 4.60]**
Total events	14		7			

Heterogeneity: Chi² = 2.35, df = 2 (P = 0.31); I² = 15%
Test for overall effect: Z = 1.48 (P = 0.14)

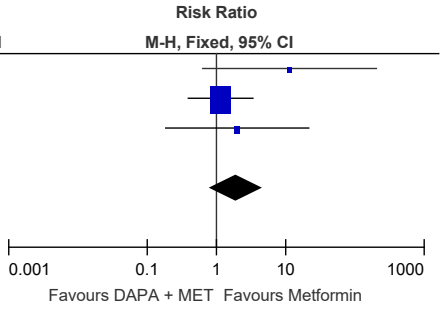


Figure 196: Severe hypoglycaemic episodes at end of follow-up

Study or Subgroup	Dapagliflozin + Metformin Events	Total	Metformin Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Henry 2012A	0	194	0	201	48.5%	0.00 [-0.01, 0.01]
Henry 2012B	0	211	0	208	51.5%	0.00 [-0.01, 0.01]
Total (95% CI)		**405**		**409**	**100.0%**	**0.00 [-0.01, 0.01]**
Total events	0		0			

Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)

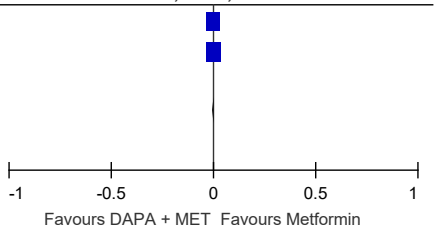


Figure 197: HbA1c change (%, lower values are better, change scores and final values) at end of follow-up

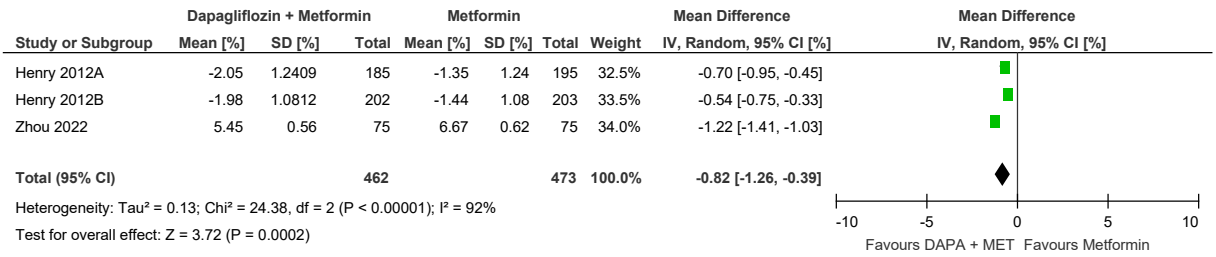
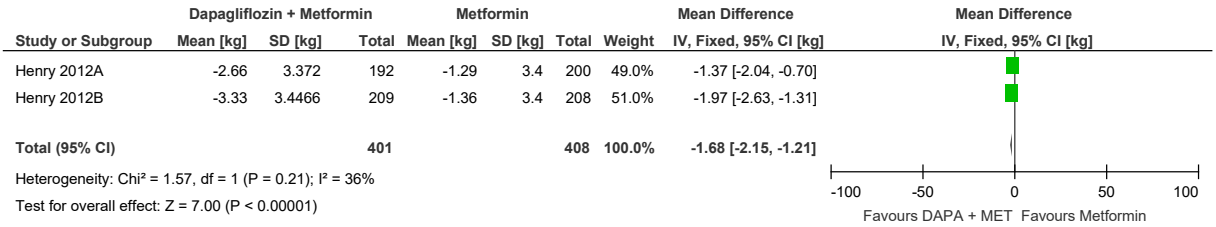


Figure 198: Weight change (kg, lower values are better, change scores and final values) at end of follow-up



E.1.8.20 Empagliflozin + metformin compared to metformin

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

E.1.8.21 Empagliflozin + metformin compared to empagliflozin

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

E.1.8.22 Empagliflozin + linagliptin compared to empagliflozin

Figure 199: All-cause mortality at end of follow-up

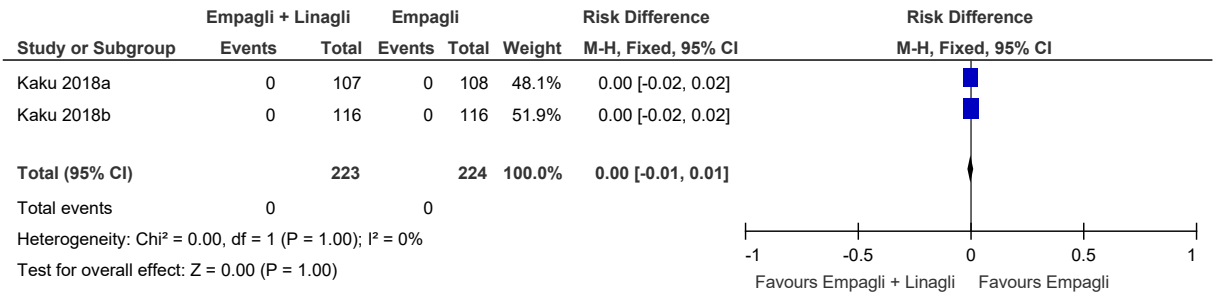


Figure 200: Non-fatal myocardial infarction at end of follow-up

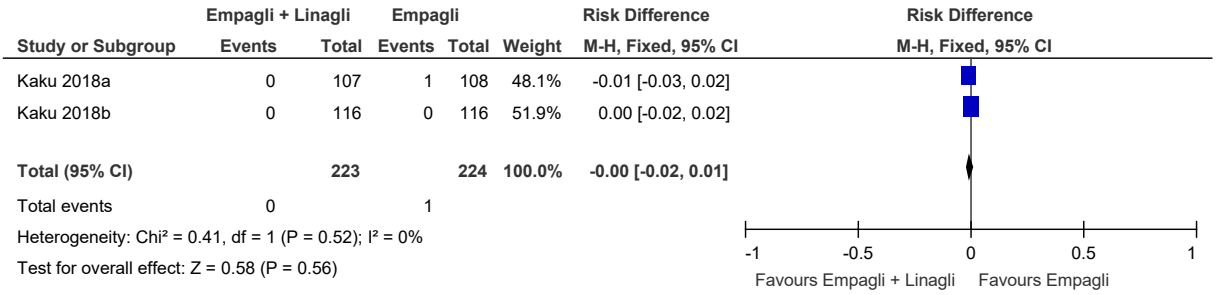


Figure 201: Severe hypoglycaemic events at end of follow-up

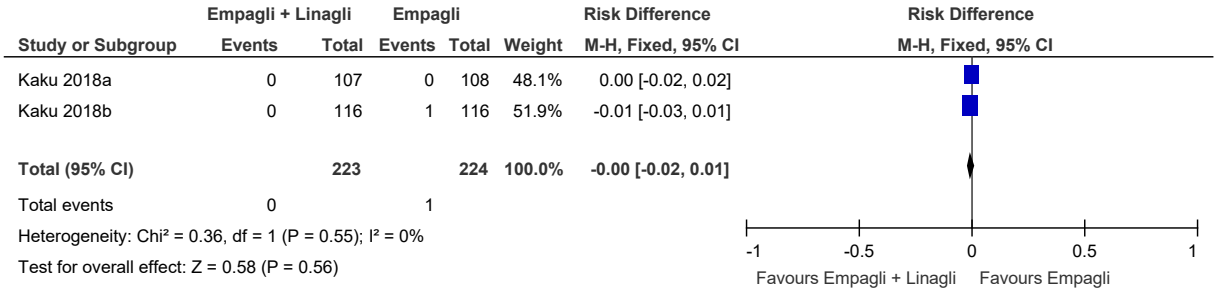
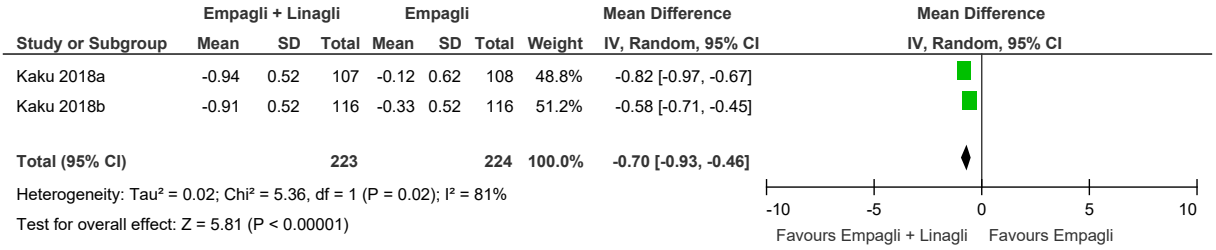


Figure 202: HbA1c change (%, lower values are better, change scores) at end of follow-up



E.1.8.13 Empagliflozin + linagliptin compared to linagliptin

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

E.1.8.14 Gliclazide + saxagliptin compared to saxagliptin + metformin

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

E.1.8.25 Pioglitazone + metformin compared to pioglitazone

Figure 203: Hypoglycaemia episodes at end of follow-up

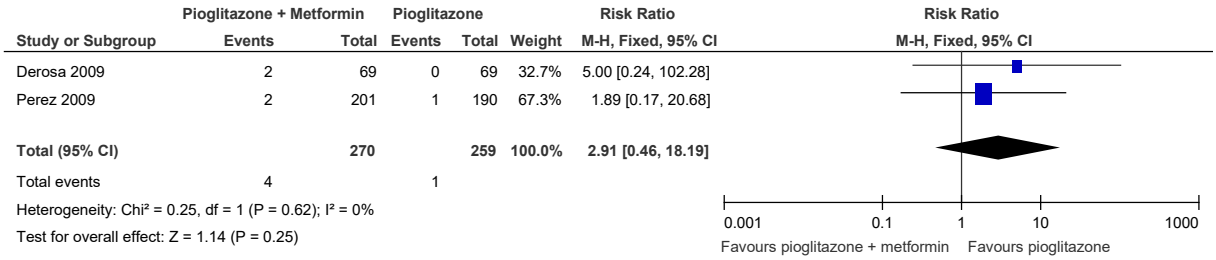
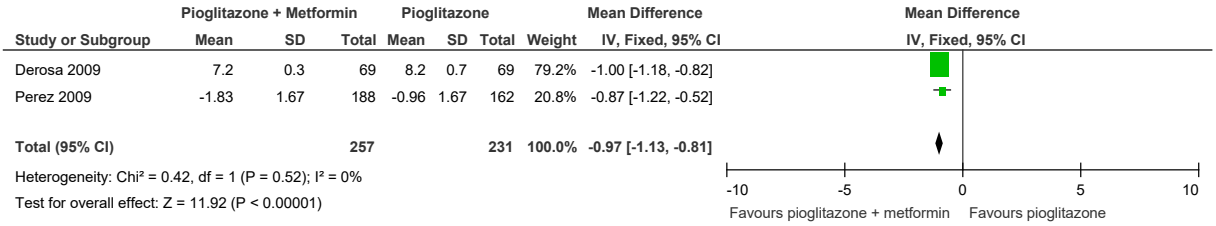


Figure 204: HbA1c change (%, lower values are better, change score and final value) at end of follow-up



E.1.8.26 Glimepiride + metformin compared to canagliflozin + metformin

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

E.1.8.27 Glimepiride + metformin compared to metformin

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

E.1.8.28 Glimepiride + metformin compared to pioglitazone

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

E.1.8.29 Pioglitazone + metformin compared to metformin

Figure 205: Hypoglycaemia episodes at end of follow-up

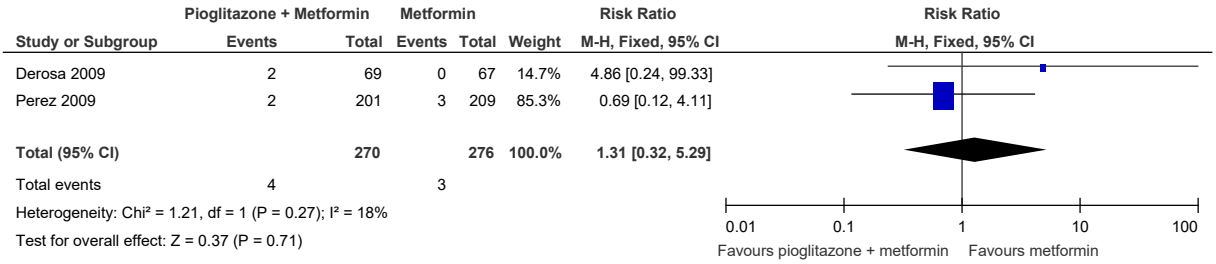
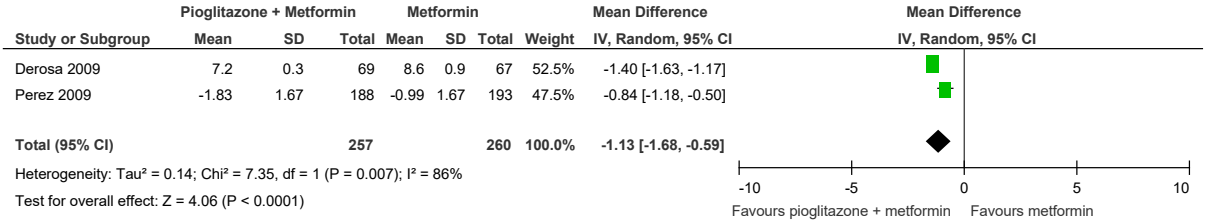


Figure 206: HbA1c change (%, lower values are better, change score and final value) at end of follow-up



E.1.8.30 Pioglitazone + metformin compared to glimepiride + metformin

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

E.1.8.31 Pioglitazone + alogliptin compared to alogliptin

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

E.1.8.32 Pioglitazone + alogliptin compared to pioglitazone

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

E.1.8.33 Pioglitazone + linagliptin compared to linagliptin

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

E.1.8.34 Pioglitazone + linagliptin compared to pioglitazone

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

E.1.8.35 Pioglitazone + sitagliptin compared to pioglitazone

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

E.1.8.36 Pioglitazone + vildagliptin compared to pioglitazone

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

E.1.8.37 Pioglitazone + vildagliptin compared to vildagliptin

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

Appendix F GRADE tables

F.1 Model 5: People with type 2 diabetes at high risk of cardiovascular disease (no other comorbidities)

F.1.1 Biguanides

F.1.1.1 Metformin hydrochloride slow release compared to metformin hydrochloride standard release

Table 1: Clinical evidence profile: Metformin hydrochloride slow release compared to metformin hydrochloride 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 Mean follow-up: 5.5 month(s)											
1 (aggarwal 2018)	RCT	serious [1]	not serious	NA[2]	very serious[3]	NA	1/283	0/285	PETO OR 7.44 (0.15, 375.04)	4 more per 1000 (3 fewer to 10 more)	very low
hypoglycaemia episodes Mean follow-up: 5.5 month(s)											
1 (aggarwal 2018)	RCT	serious [1]	not serious	NA[2]	very serious[3]	NA	0/283	3/285	PETO OR 0.14 (0.01, 1.31)	11 fewer per 1000 (22 fewer to 1 more)	very low
hba1c change Mean follow-up: 5.5 month(s)											
2	RCT	serious [1]	not serious	serious[4]	not serious	NA	815	459	MD -0.00 (-0.12, 0.12)	MD 0.00 lower (0.12 lower to 0.12 higher)	low

weight change Mean follow-up: 5.5 month(s)											
1 (aggarwal 2018)	RCT	serious [1]	not serious	NA[2]	not serious	NA	235	236	MD 0.15 (-0.53, 0.83)	MD 0.15 higher (0.53 lower to 0.83 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 by 1 or 2 increments due to heterogeneity, unexplained by subgroup analysis

F.1.1.2 Metformin compared to placebo

Table 2: Clinical evidence profile: Metformin compared 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
all-cause mortality at end of follow-up Mean follow-up: 5.9 month(s)											
6	RCT	very serious[1]	not serious	serious[2]	very serious[3]	NA	2/1451	1/801	RD 0.00 (-0.01, 0.01)	0 more per 1000 (6 fewer to 6 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 5.9 month(s)											
6	RCT	very serious[1]	not serious	serious[2]	very serious[3]	NA	2/1451	1/801	RD 0.00 (-0.01, 0.01)	0 more per 1000 (6 fewer to 6 more)	very low
non-fatal myocardial infarction at end of follow-up											

Mean follow-up: 6 month(s)											
1 (pratley 2014)	RCT	very serious[1]	not serious	NA[4]	serious[5]	NA	0/225	0/109	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	very low
hospitalisation for heart failure at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RCT	very serious[1]	not serious	NA[4]	serious[5]	NA	0/225	0/109	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	very low
diabetic ketoacidosis at end of follow-up Mean follow-up: 5.5 month(s)											
1 (goldstein 2007)	RCT	very serious[1]	not serious	NA[4]	very serious[6]	NA	0/364	1/176	PETO OR 0.05 (0.00, 3.04)	6 fewer per 1000 (17 fewer to 5 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 6.2 month(s)											
7	RCT	very serious[1]	not serious	not serious	serious[7]	NA	52/1512	18/873	RR 1.93 (1.13, 3.31)	19 more per 1000 (3 more to 48 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.8 month(s)											
4	RCT	very serious[1]	not serious	serious[2]	very serious[8]	NA	1/939	0/479	RD 0.00 (-0.01, 0.01)	1 more per 1000 (6 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: 6.3 month(s)											
13	RCT	very serious[1]	not serious	very serious[9]	not serious	NA	1979	1184	MD -1.22 (-1.48, -0.95)	MD 1.22 lower	very low

										(1.48 lower to 0.95 lower)	
weight change (kg, lower values are better, change scores and final value) at end of follow-up Mean follow-up: 6.4 month(s)											
7	RCT	very serious[1]	not serious	not serious	not serious	NA	1202	725	MD 0.09 (-0.23, 0.40)	MD 0.09 higher (0.23 lower to 0.40 higher)	low
bmi change (kg/m2, lower values are better, final values) at end of follow-up Mean follow-up: 5.8 month(s)											
2	RCT	very serious[1]	not serious	very serious[9]	very serious[10]	NA	389	236	MD -1.80 (-5.13, 1.53)	MD 1.80 lower (5.13 lower to 1.53 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 = 0.03 (0.8-0.9 = serious, <0.8 = very serious).

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 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 = 0.23 (0.8-0.9 = serious, <0.8 = very serious).

9. I2 > 75%

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

F.1.1.3 Metformin compared to insulin

Table 3: Clinical evidence profile: Metformin compared to insulin

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
hypoglycaemia episodes at end of follow-up Mean follow-up: 8.4 month(s)											
1 (pistrosch 2013)	RCT	very serious [1]	not serious	NA[2]	serious[3]	NA	4/36	14/39	RR 0.31 (0.11, 0.85)	248 fewer per 1000 (319 fewer to 52 fewer)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 8.4 month(s)											
1 (pistrosch 2013)	RCT	very serious [1]	not serious	NA[2]	serious[4]	NA	0/36	0/39	RD 0.00 (-0.05, 0.05)	0 fewer per 1000 (51 fewer to 51 more)	very low
hba1c change (%, lower values are better, change scores) Mean follow-up: 8.4 month(s)											
1 (pistrosch 2013)	RCT	very serious [1]	not serious	NA[2]	not serious	NA	36	39	MD 0.20 (-0.05, 0.45)	MD 0.20 higher (0.05 lower to 0.45 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. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.

F.1.2 DPP-4 inhibitors

F.1.2.1 Alogliptin compared to placebo

Table 4: Clinical evidence profile: Alogliptin v 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)											
2	RCT	very serious[1]	not serious	not serious	not serious	NA	0/489	0/173	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	low
cardiovascular mortality at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	0/225	0/109	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	very low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RCT	very serious[1]	not serious	NA[2]	very serious[4]	NA	1/225	0/109	PETO OR 4.41 (0.07, 288.47)	4 more per 1000 (4 fewer to 13 more)	very low
hospitalisation for heart failure at end of follow-up											

Mean follow-up: 6 month(s)											
1 (pratley 2014)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	0/225	0/109	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.8 month(s)											
3	RCT	very serious[1]	not serious	serious[5]	serious[6]	NA	11/476	2/320	PETO OR 2.62 (0.83, 8.28)	17 more per 1000 (1 more to 33 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 6 month(s)											
2	RCT	very serious[1]	not serious	not serious	not serious	NA	0/486	0/173	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.8 month(s)											
3	RCT	not serious	not serious	not serious	not serious	NA	462	313	MD -0.68 (-0.82, -0.55)	MD 0.68 lower (0.82 lower to 0.55 lower)	high
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)											
2	RCT	very serious[1]	not serious	very serious[7]	not serious	NA	489	173	MD 0.31 (-0.93, 1.56)	MD 0.31 higher (0.93 lower to 1.56 higher)	very low

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

2. Only one study so no inconsistency

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

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

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, 1.25)

7. I2 > 75%

F.1.2.2 Alogliptin compared to metformin

Table 5: Clinical evidence profile: Alogliptin compared to 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: 6 month(s)											
1 (pratley 2014)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/225	0/225	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	low
cardiovascular mortality at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/225	0/225	RD 0.00 (-0.01, 0.01)	0 fewer per 1000	low

										(9 fewer to 9 more)	
non-fatal myocardial infarction at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	1/225	0/225	PETO OR 7.39 (0.15, 372.38)	4 more per 1000 (4 fewer to 13 more)	very low
hospitalisation for heart failure at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/225	0/225	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: 5.8 month(s)											
2	RCT	very serious[1]	not serious	serious[4]	very serious[3]	NA	10/384	19/381	RR 0.47 (0.11, 2.03)	26 fewer per 1000 (44 fewer to 51 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/222	0/220	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.8 month(s)											
2	RCT	very serious[1]	not serious	not serious	serious[5]	NA	370	372	MD 0.36 (0.18, 0.54)	MD 0.36 higher (0.18 higher to 0.54 higher)	very low

weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	225	225	MD 1.08 (0.53, 1.63)	MD 1.08 higher (0.53 higher to 1.63 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. I2 between 50% and 75%

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

F.1.2.3 Linagliptin compared to metformin

Table 6: Clinical evidence profile: linagliptin compared to 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: 6 month(s)											
1 (haak 2012)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/142	1/291	PETO OR 0.23 (0.00, 14.69)	3 fewer per 1000 (10 fewer to 3 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 6 month(s)											

1 (haak 2012)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/142	1/291	PETO OR 0.23 (0.00, 14.69)	3 fewer per 1000 (10 fewer to 3 more)	very low
4-point mace at end of follow-up Mean follow-up: 5.5 month(s)											
1 (mu 2017)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/147	1/289	PETO OR 0.22 (0.00, 13.98)	3 fewer per 1000 (10 fewer to 3 more)	very low
hospitalisation for heart failure at end of follow-up Mean follow-up: 5.5 month(s)											
1 (mu 2017)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/147	0/289	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (10 fewer to 10 more)	low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.8 month(s)											
2	RCT	very serious[1]	not serious	not serious	very serious[3]	NA	1/289	10/580	RR 0.29 (0.05, 1.59)	12 fewer per 1000 (16 fewer to 10 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.8 month(s)											
2	RCT	very serious[1]	not serious	serious[4]	very serious[5]	NA	0/289	1/580	RD -0.00 (-0.01, 0.01)	1 fewer per 1000 (9 fewer to 7 more)	very low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.7 month(s)											
3	RCT	very serious[1]	not serious	serious[6]	serious[7]	NA	297	575	MD 0.36 (0.09, 0.63)	MD 0.36 higher (0.09 higher to 0.63 higher)	very low

weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 5.8 month(s)											
2	RCT	very serious[1]	not serious	not serious	not serious	NA	259	428	MD 0.72 (0.28, 1.17)	MD 0.72 higher (0.28 higher to 1.17 higher)	low
bmi change (kg/m2, lower values are better, change and final scores) at end of follow up Mean follow-up: 5.5 month(s)											
1 (mita 2019)	RCT	very serious[1]	not serious	NA[2]	very serious[8]	NA	20	18	MD 0.00 (-0.83, 0.83)	MD 0.00 lower (0.83 lower to 0.83 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. 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 = 0.23 (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 (-0.50, 0.50)

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

F.1.2.4 Linagliptin compared to placebo

Table 7: Clinical evidence profile: linagliptin v 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 (haak 2012)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	0/142	0/72	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (21 fewer to 21 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 6 month(s)											
1 (haak 2012)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	0/142	0/72	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (21 fewer to 21 more)	very low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 5.5 month(s)											
1 (chen 2015)	RCT	serious[4]	not serious	NA[2]	very serious[5]	NA	0/200	1/99	PETO OR 0.05 (0.00, 3.14)	10 fewer per 1000 (30 fewer to 10 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.7 month(s)											
3	RCT	very serious[1]	not serious	serious[6]	very serious[5]	NA	2/512	2/262	PETO OR 0.52 (0.07, 4.06)	4 fewer per 1000 (16 fewer to 8 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.8 month(s)											

2	RCT	serious[4]	not serious	serious[6]	very serious[7]	NA	1/342	0/171	RD 0.00 (-0.01, 0.02)	3 more per 1000 (11 fewer to 17 more)	very low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.7 month(s)											
5	RCT	very serious[1]	not serious	serious[8]	serious[9]	NA	723	369	MD -0.58 (-0.73, -0.42)	MD 0.58 lower (0.73 lower to 0.42 lower)	very low
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 5.7 month(s)											
4	RCT	serious[4]	not serious	not serious	not serious	NA	368	186	MD 0.64 (0.11, 1.17)	MD 0.64 higher (0.11 higher to 1.17 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. 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 moderate risk of bias

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. 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).

8. I2 between 50% and 75%

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

F.1.2.5 Saxagliptin compared to metformin

Table 8: Clinical evidence profile: Saxaglitpin compared to 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: 11.8 month(s)											
2	RCT	very serious[1]	not serious	serious[2]	very serious[3]	NA	3/549	5/538	PETO OR 0.59 (0.15, 2.38)	4 fewer per 1000 (14 fewer to 6 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 18 month(s)											
1 (pfützner 2011a)	RCT	very serious[1]	not serious	NA[4]	very serious[3]	NA	2/335	4/328	RR 0.49 (0.09, 2.65)	6 fewer per 1000 (11 fewer to 20 more)	very low
non-fatal stroke at end of follow-up Mean follow-up: 5.5 month(s)											
1 (dou 2018)	RCT	very serious[1]	not serious	NA[4]	very serious[3]	NA	1/214	1/210	RR 0.98 (0.06, 15.59)	0 fewer per 1000 (4 fewer to 69 more)	very low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 5.5 month(s)											
1 (dou 2018)	RCT	very serious[1]	not serious	NA[4]	very serious[3]	NA	0/214	1/210	PETO OR 0.13 (0.00, 6.69)	5 fewer per 1000 (14 fewer to 5 more)	very low
persistent signs of worsening kidney disease at end of follow-up Mean follow-up: 5.5 month(s)											

1 (dou 2018)	RCT	very serious[1]	not serious	NA[4]	very serious[3]	NA	0/214	1/210	PETO OR 0.13 (0.00, 6.69)	5 fewer per 1000 (14 fewer to 5 more)	very low
progression of liver disease at end of follow-up Mean follow-up: 5.5 month(s)											
1 (dou 2018)	RCT	very serious[1]	not serious	NA[4]	very serious[3]	NA	1/214	0/210	PETO OR 7.25 (0.14, 365.55)	5 more per 1000 (4 fewer to 14 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 11.8 month(s)											
2	RCT	very serious[1]	not serious	not serious	serious[5]	NA	10/549	24/538	RR 0.41 (0.20, 0.84)	26 fewer per 1000 (36 fewer to 7 fewer)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 11.8 month(s)											
2	RCT	very serious[1]	not serious	serious[2]	very serious[6]	NA	0/549	2/538	RD -0.00 (-0.01, 0.00)	3 fewer per 1000 (10 fewer to 4 more)	very low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
3	RCT	very serious[1]	not serious	very serious[7]	serious[8]	NA	348	375	MD 0.32 (-0.09, 0.72)	MD 0.32 higher (0.09 lower to 0.72 higher)	very low
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	very serious[1]	not serious	not serious	not serious	NA	234	228	MD 1.57 (1.13, 2.00)	MD 1.57 higher	low

										(1.13 higher to 2.00 higher)	
bmi change (kg/m2, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	very serious[1]	not serious	very serious[7]	very serious[9]	NA	234	228	MD -0.02 (-1.07, 1.04)	MD 0.02 lower (1.07 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. 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. 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).

7. I2 > 75%

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

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

F.1.2.6 Saxagliptin compared to placebo

Table 9: Clinical evidence profile: Saxagliptin compared 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

all-cause mortality at end of follow-up Mean follow-up: 5.5 month(s)											
4	RCT	very serious[1]	not serious	serious[2]	very serious[3]	NA	2/988	0/559	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)											
3	RCT	very serious[1]	not serious	not serious	not serious	NA	0/704	0/275	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (10 fewer to 10 more)	low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)											
3	RCT	very serious[1]	not serious	serious[2]	very serious[4]	NA	5/697	2/485	RD 0.00 (-0.01, 0.01)	3 more per 1000 (7 fewer to 13 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)											
1 (pan 2012a)	RCT	very serious[1]	not serious	NA[5]	not serious	NA	0/284	0/284	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
3	RCT	very serious[1]	not serious	not serious	serious[6]	NA	656	447	MD -0.45 (-0.62, -0.28)	MD 0.45 lower (0.62 lower to 0.28 lower)	very low
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											

3	RCT	very serious[1]	not serious	not serious	not serious	NA	665	457	MD 0.88 (0.47, 1.29)	MD 0.88 higher (0.47 higher to 1.29 higher)	low
bmi change (kg/m2, lower values are better, change score) at end of follow-up											
1 (kumar 2014)	RCT	serious[7]	not serious	NA[5]	not serious	NA	105	106	MD 0.40 (0.16, 0.64)	MD 0.40 higher (0.16 higher to 0.64 higher)	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. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.42 (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 = 0.17 (0.8-0.9 = serious, <0.8 = very serious).

5. Only one study so no inconsistency

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

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

F.1.2.7 Sitagliptin compared to metformin

Table 10: Clinical evidence profile: Sitagliptin compared to metformin

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, -0.11-1, higher values are better, change score) at end of follow-up Mean follow-up: 6 month(s)											
1 (russell-jones 2012)	RCT	not serious	not serious	NA[1]	serious[2]	NA	149	227	MD -0.01 (-0.04, 0.02)	MD 0.01 lower (0.04 lower to 0.02 higher)	moderate
all-cause mortality at end of follow-up Mean follow-up: 5.6 month(s)											
4	RCT	serious[3]	not serious	serious[4]	very serious[5]	NA	1/990	1/1382	RD 0.00 (-0.00, 0.00)	0 more per 1000 (4 fewer to 4 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 5.7 month(s)											
3	RCT	very serious[6]	not serious	not serious	not serious	NA	0/462	0/860	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 5.5 month(s)											
1 (aschner 2010)	RCT	serious[3]	not serious	NA[1]	very serious[7]	NA	0/528	1/522	PETO OR 0.13 (0.00, 6.74)	2 fewer per 1000 (6 fewer to 2 more)	very low
cardiac arrhythmia at end of follow-up Mean follow-up: 5.5 month(s)											
1 (aschner 2010)	RCT	serious[3]	not serious	NA[1]	very serious[7]	NA	0/528	1/522	PETO OR 0.13 (0.00, 6.74)	2 fewer per 1000 (6 fewer to 2 more)	very low
diabetic ketoacidosis at end of follow-up Mean follow-up: 5.5 month(s)											
1 (goldstein 2007)	RCT	serious[3]	not serious	NA[1]	not serious	NA	0/179	0/364	RD 0.00 (-0.01, 0.01)	0 fewer per 1000	moderate

										(9 fewer to 9 more)	
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.6 month(s)											
4	RCT	serious[3]	not serious	not serious	serious[8]	NA	20/990	42/1382	RR 0.66 (0.39, 1.12)	10 fewer per 1000 (18 fewer to 4 more)	low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	serious[3]	not serious	serious[4]	very serious[9]	NA	2/648	0/772	RD 0.00 (-0.00, 0.01)	3 more per 1000 (3 fewer to 9 more)	very low
hba1c change (%, lower values are better, change scores and final value) at end of follow-up Mean follow-up: 5.6 month(s)											
5	RCT	serious[3]	not serious	very serious[10]	not serious	NA	902	1262	MD 0.05 (-0.26, 0.36)	MD 0.05 higher (0.26 lower to 0.36 higher)	very low
weight change (kg, higher values are better, change scores) at end of follow-up Mean follow-up: 5.7 month(s)											
3	RCT	serious[3]	not serious	not serious	not serious	NA	741	942	MD 1.31 (1.01, 1.61)	MD 1.31 higher (1.01 higher to 1.61 higher)	moderate
bmi change (kg/m2, lower values are better, final value) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (wang 2022)	RCT	very serious[6]	not serious	NA[1]	very serious[11]	NA	17	17	MD -1.36 (-3.58, 0.86)	MD 1.36 lower	very low

										(3.58 lower to 0.86 higher)	

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 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 = 0.05 (0.8-0.9 = serious, <0.8 = very serious).

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

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

8. 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 = 0.55 (0.8-0.9 = serious, <0.8 = very serious).

10. I2 > 75%

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

F.1.2.8 Sitagliptin compared to placebo

Table 11: Clinical evidence profile: Sitagliptin compared 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
all-cause mortality at end of follow-up Mean follow-up: 8.5 month(s)											

4	RCT	serious[1]	not serious	serious[2]	very serious[3]	NA	1/687	2/614	RD -0.00 (-0.01, 0.01)	1 fewer per 1000 (9 fewer to 6 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	very serious[4]	not serious	serious[2]	very serious[5]	NA	0/299	1/302	RD -0.00 (-0.01, 0.01)	3 fewer per 1000 (15 fewer to 8 more)	very low
diabetic ketoacidosis at end of follow-up Mean follow-up: 5.5 month(s)											
1 (goldstein 2007)	RCT	very serious[4]	not serious	NA[6]	very serious[7]	NA	0/179	1/176	PETO OR 0.13 (0.00, 6.71)	6 fewer per 1000 (17 fewer to 5 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 7.9 month(s)											
5	RCT	very serious[4]	not serious	serious[2]	very serious 8	NA	9/789	7/718	RD 0.00 (-0.01, 0.01)	3 more per 1000 (8 fewer to 14 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 9.5 month(s)											
3	RCT	serious[1]	not serious	not serious	not serious	NA	0/508	0/438	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	moderate
hba1c change (%, lower values are better, change scores) at end of follow-up Mean follow-up: 7.5 month(s)											
6	RCT	serious[1]	not serious	serious[9]	not serious	NA	1245	946	MD -0.73 (-0.84, -0.62)	MD 0.73 lower	low

										(0.84 lower to 0.62 lower)	
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 7.9 month(s)											
5	RCT	serious[1]	not serious	not serious	not serious	NA	1097	791	MD 0.81 (0.50, 1.13)	MD 0.81 higher (0.50 higher to 1.13 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 = 0.16 (0.8-0.9 = serious, <0.8 = very serious).

4. >33.3% of the studies in the meta-analysis were at high 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 = 0.29 (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. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.06 (0.8-0.9 = serious, <0.8 = very serious).

9. I2 between 50% and 75%

F.1.2.9 Vildagliptin compared to metformin

Table 12: Clinical evidence profile: Vildagliptin compared to 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: 7.8 month(s)											
3	RCT	serious[1]	not serious	serious[2]	very serious[3]	NA	3/986	2/711	RD -0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 5 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 5.5 month(s)											
1 (schweizer 2009)	RCT	serious[1]	not serious	NA[4]	very serious[5]	NA	1/167	0/165	PETO OR 7.30 (0.14, 367.98)	6 more per 1000 (6 fewer to 18 more)	very low
non-fatal myocardial infarction at end of follow up Mean follow-up: 7.8 month(s)											
3	RCT	serious[1]	not serious	not serious	not serious	NA	0/993	5/713	PETO OR 0.09 (0.01, 0.54)	7 fewer per 1000 (13 fewer to 1 fewer)	moderate
cardiac arrhythmia at end of follow-up Mean follow-up: 5.5 month(s)											
1 (schweizer 2009)	RCT	serious[1]	not serious	NA[4]	very serious[5]	NA	1/167	1/165	PETO OR 0.99 (0.06, 15.86)	0 fewer per 1000 (17 fewer to 17 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 8.8 month(s)											

2	RCT	very serious[6]	not serious	serious[2]	very serious[5]	NA	3/693	3/419	PETO OR 0.60 (0.11, 3.19)	3 fewer per 1000 (12 fewer to 7 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 7.8 month(s)											
3	RCT	very serious[6]	not serious	serious[2]	very serious[7]	NA	0/993	1/713	RD -0.00 (-0.01, 0.00)	1 fewer per 1000 (5 fewer to 4 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow-up Mean follow-up: 7.8 month(s)											
3	RCT	serious[1]	not serious	not serious	not serious	NA	970	704	MD 0.26 (0.10, 0.41)	MD 0.25 higher (0.14 higher to 0.37 higher)	moderate
weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 7.8 month(s)											
3	RCT	serious[1]	not serious	very serious[8]	not serious	NA	980	709	MD 1.32 (0.52, 2.12)	MD 1.32 higher (0.52 higher to 2.12 higher)	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 = 0.03 (0.8-0.9 = serious, <0.8 = very serious).

4. Only one study so no inconsistency

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 high risk of bias

7. 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).

8. I2 > 75%

F.1.2.10 Vildagliptin compared to placebo

Table 13: Clinical evidence profile: Vildagliptin compared 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
all-cause mortality at end of follow-up Mean follow-up: 12 month(s)											
1 (mari 2008)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/156	1/150	PETO OR 0.13 (0.00, 6.56)	7 fewer per 1000 (20 fewer to 6 more)	very low
hypoglycaemia episodes at end follow-up Mean follow-up: 12 month(s)											
1 (mari 2008)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/153	1/149	PETO OR 0.13 (0.00, 6.64)	7 fewer per 1000 (20 fewer to 6 more)	very low
severe hypoglycaemic episodes at end follow-up Mean follow-up: 12 month(s)											
1 (mari 2008)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	0/149	0/153	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (13 fewer to 13 more)	very low

hba1c change (%, lower values are better, change scores) at the end of follow-up Mean follow-up: 8.8 month(s)											
4	RCT	very serious[1]	not serious	not serious	serious[5]	NA	720	361	MD -0.48 (-0.67, -0.29)	MD 0.48 lower (0.67 lower to 0.29 lower)	very low
weight change (kg, lower values are better, change scores) at the end of follow-up Mean follow-up: 8.8 month(s)											
3	RCT	very serious[1]	not serious	serious[6]	not serious	NA	676	313	MD 0.40 (-0.43, 1.22)	MD 0.40 higher (0.43 lower to 1.22 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 both ends of the defined MIDs (0.80, 1.25)

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

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

6. I2 between 50% and 75%

F.1.3 GLP-1 receptor agonist

F.1.3.1 Dulaglutide compared to placebo

Table 14: Clinical evidence profile: dulaglutide v placebo

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
hr-qol - subscale convenience/flexibility (pam-d21-j, 0-100, higher values are better, final value) at end of follow-up Mean follow-up: 6 month(s)											
1 (miyagawa 2015)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	280	70	MD 6.73 (0.34, 13.12)	MD 6.73 higher (0.34 higher to 13.12 higher)	very low
hr-qol - subscale perceived effectiveness (pam-d21-j, 0-100, higher values are better, final value) at end of follow-up Mean follow-up: 6 month(s)											
1 (miyagawa 2015)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	280	70	MD 50.79 (20.80, 80.78)	MD 50.79 higher (20.80 higher to 80.78 higher)	very low
hr-qol - subscale emotional effects (pam-d21-j, 0-100, higher values are better, final value) at end of follow-up Mean follow-up: 6 month(s)											
1 (miyagawa 2015)	RCT	very serious[1]	not serious	NA[2]	serious[5]	NA	280	70	MD 3.71 (0.40, 7.02)	MD 3.71 higher (0.40 higher to 7.02 higher)	very low

hr-qol - subscale physical effects (pam-d21-j, 0-100, higher values are better, final value) at end of follow-up Mean follow-up: 6 month(s)											
1 (miyagawa 2015)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	280	70	MD -0.95 (-2.71, 0.81)	MD 0.95 lower (2.71 lower to 0.81 higher)	low
hr-qol - subscale satisfaction (idmq-j, 0-100, higher values are better, final value) at end of follow-up Mean follow-up: 6 month(s)											
1 (miyagawa 2015)	RCT	very serious[1]	not serious	NA[2]	serious[6]	NA	280	70	MD 32.05 (13.12, 50.98)	MD 32.05 higher (13.12 higher to 50.98 higher)	very low
hr-qol - subscale ease of use (idmq-j, 0-100, higher values are better, final value) at end of follow-up Mean follow-up: 6 month(s)											
1 (miyagawa 2015)	RCT	very serious[1]	not serious	NA[2]	serious[7]	NA	280	70	MD 12.94 (5.30, 20.58)	MD 12.94 higher (5.30 higher to 20.58 higher)	very low
hr-qol - subscale lifestyle impact (idmq-j, 0-100, higher values are better, final value) at end of follow-up Mean follow-up: 6 month(s)											
1 (miyagawa 2015)	RCT	very serious[1]	not serious	NA[2]	serious[8]	NA	280	70	MD 10.12 (4.14, 16.10)	MD 10.12 higher (4.14 higher to 16.10 higher)	very low
hr-qol - subscale blood glucose control (idmq-j, 0-100, higher values are better, final value) at end of follow-up Mean follow-up: 6 month(s)											

1 (miyagawa 2015)	RCT	very serious[1]	not serious	NA[2]	serious[9]	NA	280	70	MD 34.43 (14.11, 54.75)	MD 34.43 higher (14.11 higher to 54.75 higher)	very low
all-cause mortality at end of follow-up Mean follow-up: 12 month(s)											
1 (miyagawa 2015)	RCT	serious[10]	not serious	NA[2]	serious[11]	NA	0/280	0/70	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: 12 month(s)											
1 (miyagawa 2015)	RCT	serious[10]	not serious	NA[2]	serious[11]	NA	0/280	0/70	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	low
hypoglycaemia episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (miyagawa 2015)	RCT	serious[10]	not serious	NA[2]	very serious[12]	NA	6/280	1/70	RR 1.50 (0.18, 12.26)	7 more per 1000 (12 fewer to 161 more)	very low
at night hypoglycaemic episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (miyagawa 2015)	RCT	serious[10]	not serious	NA[2]	very serious[12]	NA	2/280	0/70	PETO OR 3.50 (0.11, 112.54)	7 more per 1000 (3 fewer to 17 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (miyagawa 2015)	RCT	serious[10]	not serious	NA[2]	serious[11]	NA	0/280	0/70	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	low
hba1c change (%, lower values are better, change scores) at end of follow-up											

Mean follow-up: 6 month(s)											
1 (miyagawa 2015)	RCT	serious[10]	not serious	NA[2]	not serious	NA	281	70	MD -1.57 (-1.79, -1.35)	MD 1.57 lower (1.79 lower to 1.35 lower)	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 one end of the defined MIDs (-12.20, 12.20)

4. 95% confidence intervals cross one end of the defined MIDs (-57.30, 57.30)

5. 95% confidence intervals cross one end of the defined MIDs (-6.30, 6.30)

6. 95% confidence intervals cross one end of the defined MIDs (-36.20, 36.20)

7. 95% confidence intervals cross one end of the defined MIDs (-14.60, 14.60)

8. 95% confidence intervals cross one end of the defined MIDs (-11.40, 11.40)

9. 95% confidence intervals cross one end of the defined MIDs (-38.80, 38.80)

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

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

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

F.1.3.2 Dulaglutide v 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 (umpierrez 2014)	RCT	serious[1]	not serious	NA[2]	not serious	NA	0/539	0/268	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	moderate
cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)											
1 (umpierrez 2014)	RCT	serious[1]	not serious	NA[2]	not serious	NA	0/539	0/268	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	moderate
hypoglycaemia episodes at end of follow up Mean follow-up: 12 month(s)											
1 (umpierrez 2014)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	63/539	34/268	RR 0.92 (0.62, 1.36)	10 fewer per 1000 (48 fewer to 46 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											
1 (umpierrez 2014)	RCT	serious[1]	not serious	NA[2]	not serious	NA	0/539	0/269	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	moderate
hba1c change (%, lower values are better, change scores and final values) at end of follow up Mean follow-up: 12 month(s)											
1 (umpierrez 2014)	RCT	serious[1]	not serious	NA[2]	not serious	NA	539	268	MD -0.18 (-0.33, -0.04)	MD 0.18 lower (0.33 lower to 0.04 lower)	moderate
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (umpierrez 2014)	RCT	serious[1]	not serious	NA[2]	not serious	NA	539	268	MD 0.40 (-0.18, 0.97)	MD 0.40 higher	moderate

										(0.18 lower to 0.97 higher)	

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)

F.1.3.3 Exenatide compared to metformin

Table 15: Clinical evidence profile: exenatide compared to metformin

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, 0-100, higher values are better, change scores) at end of follow-up Mean follow-up: 6 month(s)											
1 (russell-jones 2012)	RCT	not serious	not serious	NA[1]	not serious	NA	232	227	MD 0.00 (-0.03, 0.03)	MD 0.00 lower (0.03 lower to 0.03 higher)	high
all-cause mortality at end of follow-up Mean follow-up: 6 month(s)											
1 (russell-jones 2012)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	0/248	1/246	PETO OR 0.13 (0.00, 6.77)	4 fewer per 1000 (12 fewer to 4 more)	low
cardiovascular mortality at end of follow-up Mean follow-up: 6 month(s)											

1 (russell-jones 2012)	RCT	not serious	not serious	NA[1]	not serious	NA	0/248	0/246	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	high
hypoglycaemia episodes at end of follow-up Mean follow-up: 6 month(s)											
2	RCT	not serious	not serious	not serious	very serious[2]	NA	17/281	11/272	RR 1.48 (0.70, 3.11)	19 more per 1000 (12 fewer to 85 more)	low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (yuan 2012)	RCT	very serious[3]	not serious	NA[1]	very serious[4]	NA	0/33	0/26	RD 0.00 (-0.06, 0.06)	0 fewer per 1000 (65 fewer to 65 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow-up Mean follow-up: 6 month(s)											
2	RCT	not serious	not serious	not serious	not serious	NA	251	244	MD -0.07 (-0.26, 0.12)	MD 0.07 lower (0.26 lower to 0.12 higher)	high
weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 6 month(s)											
2	RCT	not serious	not serious	very serious[5]	serious[6]	NA	281	272	MD -0.98 (-2.93, 0.97)	MD 0.98 lower (2.93 lower to 0.97 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 (yuan 2012)	RCT	very serious[3]	not serious	NA[1]	not serious	NA	33	26	MD -1.41 (-1.81, -1.01)	MD 1.41 lower (1.81 lower to 1.01 lower)	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. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.

5. I2 > 75%

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

F.1.3.4 Exenatide compared to sitagliptin

Table 16: Clinical evidence profile: exenatide compared to 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, 0-100, higher values are better, change scores) at end of follow-up Mean follow-up: 6 month(s)											
1 (russell-jones 2012)	RCT	not serious	not serious	NA[1]	serious[2]	NA	232	149	MD 0.01 (-0.02, 0.04)	MD 0.01 higher (0.02 lower to 0.04 higher)	moderate
all-cause mortality at end of follow-up Mean follow-up: 6 month(s)											

1 (russell-jones 2012)	RCT	not serious	not serious	NA[1]	not serious	NA	0/248	0/163	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (10 fewer to 10 more)	high
cardiovascular mortality at end of follow-up Mean follow-up: 6 month(s)											
1 (russell-jones 2012)	RCT	not serious	not serious	NA[1]	not serious	NA	0/248	0/163	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: 6 month(s)											
1 (russell-jones 2012)	RCT	not serious	not serious	NA[1]	very serious[3]	NA	13/248	5/163	RR 1.71 (0.62, 4.70)	22 more per 1000 (12 fewer to 114 more)	low
hba1c change (%, lower values are better, change scores) at end of follow-up Mean follow-up: 6 month(s)											
1 (russell-jones 2012)	RCT	not serious	not serious	NA[1]	serious[4]	NA	218	142	MD -0.38 (-0.59, -0.17)	MD 0.38 lower (0.59 lower to 0.17 lower)	moderate
weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 6 month(s)											
1 (russell-jones 2012)	RCT	not serious	not serious	NA[1]	not serious	NA	248	163	MD -1.20 (-1.91, -0.49)	MD 1.20 lower (1.91 lower to 0.49 lower)	high

1. Only one study so no inconsistency

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

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)

F.1.3.5 Exenatide compared to pioglitazone

Table 17: Clinical evidence profile: exenatide compared to pioglitazone

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 at end of follow-up Mean follow-up: 6 month(s)											
1 (russell-jones 2012)	RCT	not serious	not serious	NA[1]	serious[2]	NA	248	163	MD 0.04 (0.01, 0.07)	MD 0.04 higher (0.01 higher to 0.07 higher)	moderate
all-cause mortality at end of follow-up Mean follow-up: 6 month(s)											
1 (russell-jones 2012)	RCT	not serious	not serious	NA[1]	not serious	NA	0/248	0/163	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (10 fewer to 10 more)	high
cardiovascular mortality at end of follow-up Mean follow-up: 6 month(s)											
1 (russell-jones 2012)	RCT	not serious	not serious	NA[1]	not serious	NA	0/248	0/163	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: 6 month(s)											
1 (russell-jones 2012)	RCT	not serious	not serious	NA[1]	very serious[3]	NA	13/248	6/163	RR 1.42 (0.55, 3.67)	16 more per 1000	low

										(16 fewer to 98 more)	
hba1c change (%, lower values are better, change scores) at end of follow-up Mean follow-up: 6 month(s)											
1 (russell-jones 2012)	RCT	not serious	not serious	NA[1]	not serious	NA	248	163	MD 0.10 (-0.09, 0.29)	MD 0.10 higher (0.09 lower to 0.29 higher)	high
weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 6 month(s)											
1 (russell-jones 2012)	RCT	not serious	not serious	NA[1]	not serious	NA	248	163	MD -3.50 (-4.21, -2.79)	MD 3.50 lower (4.21 lower to 2.79 lower)	high

1. Only one study so no inconsistency

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

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

F.1.3.6 Exenatide compared to insulin

Table 18: Clinical evidence profile: exenatide compared to insulin

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
all-cause mortality at end of follow-up Mean follow-up: 11.1 month(s)											

1 (xu 2015)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	0/142	0/138	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 11.1 month(s)											
1 (xu 2015)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	0/142	0/138	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 8.3 month(s)											
2	RCT	very serious[1]	not serious	not serious	serious[4]	NA	16/180	24/176	RR 0.65 (0.36, 1.19)	47 fewer per 1000 (87 fewer to 25 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 8.3 month(s)											
2	RCT	very serious[1]	not serious	not serious	not serious	NA	0/180	0/176	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (16 fewer to 16 more)	low
hba1c change (%, lower values are better, change scores) at end of follow-up [%] Mean follow-up: 8.3 month(s)											
2	RCT	very serious[1]	not serious	very serious[5]	serious[6]	NA	145	150	MD -0.36 (-0.90, 0.18)	MD 0.36 lower (0.90 lower to 0.18 higher)	very low
hba1c change (%, lower values are better, change scores and final values) at end of follow-up [%] Mean follow-up: 8.3 month(s)											
2	RCT	very serious[1]	not serious	very serious[5]	serious[6]	NA	145	150	MD -0.36 (-0.90, 0.18)	MD 0.36 lower	very low

										(0.90 lower to 0.18 higher)	
hba1c change (%, lower values are better, change scores and final values) at end of follow-up [%] Mean follow-up: 8.3 month(s)											
2	RCT	very serious[1]	not serious	very serious[5]	serious[6]	NA	145	150	MD -0.36 (-0.90, 0.18)	MD 0.36 lower (0.90 lower to 0.18 higher)	very low
weight change (kg, lower values are better, change scores) at end of follow-up [kg] Mean follow-up: 8.3 month(s)											
2	RCT	very serious[1]	not serious	not serious	not serious	NA	145	150	MD -4.33 (-5.19, -3.47)	MD 4.33 lower (5.19 lower to 3.47 lower)	low
bmi change (kg/m2, lower values are better, change scores) at end of follow-up [kg/m2] Mean follow-up: 8.3 month(s)											
2	RCT	very serious[1]	not serious	not serious	not serious	NA	145	150	MD -1.65 (-1.91, -1.40)	MD 1.65 lower (1.91 lower to 1.40 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 one end of the defined MIDs (0.80, 1.25)

5. I2 > 75%

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

F.1.3.7 Exenatide compared to placebo

Table 19: Clinical evidence profile: exenatide compared 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
all-cause mortality at end of follow-up Mean follow-up: 5.5 month(s)											
1 (moretto 2008)	RCT	serious[1]	not serious	NA[2]	serious[3]	NA	0/155	0/77	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: 5.5 month(s)											
1 (moretto 2008)	RCT	serious[1]	not serious	NA[2]	serious[3]	NA	0/155	0/77	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)											
1 (moretto 2008)	RCT	serious[1]	not serious	NA[2]	very serious[4]	NA	7/155	1/77	RR 3.48 (0.44, 27.76)	32 more per 1000 (7 fewer to 348 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)											
1 (moretto 2008)	RCT	serious[1]	not serious	NA[2]	serious[3]	NA	0/155	0/77	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	low

hba1c change (%, lower values are better, change scores) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (moretto 2008)	RCT	serious[1]	not serious	NA[2]	serious[5]	NA	155	77	MD -0.60 (-0.84, -0.36)	MD 0.60 lower (0.84 lower to 0.36 lower)	low
weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (moretto 2008)	RCT	serious[1]	not serious	NA[2]	not serious	NA	155	77	MD -1.55 (-2.27, -0.83)	MD 1.55 lower (2.27 lower to 0.83 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. 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)

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

F.1.3.8 Liraglutide compared to metformin

Table 20: Clinical evidence profile: liraglutide compared to 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 (feng 2017)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/30	2/31	RR 0.21 (0.01, 4.13)	51 fewer per 1000 (64 fewer to 202 more)	very low
hba1c change (%, 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	serious[4]	very serious[5]	NA	60	61	MD -0.32 (-1.27, 0.63)	MD -0.32 lower (-1.27 lower to 0.63 higher)	very low
weight change (kg, lower values are better, final values) at end of follow-up **Mean follow-up: 5.8 month(s)**											
2	RCT	very serious[1]	not serious	very serious[6]	serious[8]	NA	59	59	MD 9.44 (-1.04, 19.91)	MD 9.44 higher (-1.04 lower to 19.91 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)**											
2	RCT	very serious[1]	not serious	very serious[6]	very serious[7]	NA	59	59	MD 2.29 (-0.94, 5.52)	MD 2.29 higher (-0.94 lower to 5.52 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 between 50% and 75%

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

6. I2 > 75%

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

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

F.1.3.9 Liraglutide compared to dulaglutide

Table 21: Clinical evidence profile: Liraglutide compared 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
health-related quality of life - subscale convenience/flexibility (pam-d21-j, 0-100, higher values are better, change scores) at end of follow-up Mean follow-up: 6 month(s)											
1 (miyagawa 2015)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	137	280	MD -5.64 (-10.58, -0.70)	MD 5.64 lower (10.58 lower to 0.70 lower)	low
health-related quality of life - subscale perceived effectiveness (pam-d21-j, 0-100, higher values are better, change scores) at end of follow-up Mean follow-up: 6 month(s)											
1 (miyagawa 2015)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	137	280	MD -0.43 (-5.74, 4.88)	MD 0.43 lower (5.74 lower to 4.88 higher)	low

health-related quality of life - subscale emotional effects (pam-d21-j, 0-100, higher values are better, change scores) at end of follow-up Mean follow-up: 6 month(s)											
1 (miyagawa 2015)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	137	280	MD -2.36 (-4.93, 0.21)	MD 2.36 lower (4.93 lower to 0.21 higher)	low
health-related quality of life - subscale physical effects (pam-d21-j, 0-100, higher values are better, change scores) at end of follow-up Mean follow-up: 6 month(s)											
1 (miyagawa 2015)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	137	280	MD -0.66 (-2.01, 0.69)	MD 0.66 lower (2.01 lower to 0.69 higher)	low
health-related quality of life - subscale satisfaction (idmq-j, 0-100, higher values are better, change scores) at end of follow-up Mean follow-up: 6 month(s)											
1 (miyagawa 2015)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	137	280	MD -5.71 (-10.14, -1.28)	MD 5.71 lower (10.14 lower to 1.28 lower)	low
health-related quality of life - subscale ease of use (idmq-j, 0-100, higher values are better, change scores) at end of follow-up Mean follow-up: 6 month(s)											
1 (miyagawa 2015)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	137	280	MD 0.73 (-3.03, 4.49)	MD 0.73 higher (3.03 lower to 4.49 higher)	low

health-related quality of life - subscale lifestyle impact (idmq-j, 0-100, higher values are better, change scores) at end of follow-up Mean follow-up: 6 month(s)											
1 (miyagawa 2015)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	137	280	MD 4.21 (-0.04, 8.46)	MD 4.21 higher (0.04 lower to 8.46 higher)	low
health-related quality of life - subscale blood glucose control (idmq-j, 0-100, higher values are better, change scores) at end of follow-up Mean follow-up: 6 month(s)											
1 (miyagawa 2015)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	137	280	MD -2.04 (-5.90, 1.82)	MD 2.04 lower (5.90 lower to 1.82 higher)	low
all-cause mortality at end of follow-up Mean follow-up: 12 month(s)											
1 (miyagawa 2015)	RCT	serious[3]	not serious	NA[2]	not serious	NA	0/137	0/280	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (11 fewer to 11 more)	moderate
cardiovascular mortality at end of follow-up Mean follow-up: 12 month(s)											
1 (miyagawa 2015)	RCT	serious[3]	not serious	NA[2]	not serious	NA	0/137	0/280	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (11 fewer to 11 more)	moderate
hypoglycaemia episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (miyagawa 2015)	RCT	serious[3]	not serious	NA[2]	very serious[4]	NA	4/137	8/280	RR 1.02 (0.31, 3.33)	1 more per 1000	very low

										(20 fewer to 67 more)	
at night hypoglycaemic episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (miyagawa 2015)	RCT	serious[3]	not serious	NA[2]	very serious[4]	NA	1/137	2/280	RR 1.02 (0.09, 11.17)	0 more per 1000 (6 fewer to 73 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (miyagawa 2015)	RCT	serious[3]	not serious	NA[2]	not serious	NA	0/137	0/280	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (11 fewer to 11 more)	moderate
hba1c change (%, lower values are better, change scores) at end of follow-up Mean follow-up: 6 month(s)											
1 (miyagawa 2015)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	137	280	MD 0.20 (0.00, 0.40)	MD 0.20 higher (0.00 higher to 0.40 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 both ends of the defined MIDs (0.80, 1.25)

F.1.3.10 Liraglutide compared to gliclazide

Table 22: Clinical evidence profile: liraglutide compared to gliclazide

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 (feng 2017)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/30	2/32	PETO OR 0.14 (0.01, 2.29)	63 fewer per 1000 (146 fewer to 21 more)	very low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (feng 2017)	RCT	very serious[1]	not serious	NA[2]	very serious[4]	NA	30	32	MD -0.40 (-1.38, 0.58)	MD 0.40 lower (1.38 lower to 0.58 higher)	very low
weight change (kg, lower values are better, final value) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (feng 2017)	RCT	very serious[1]	not serious	NA[2]	very serious[5]	NA	29	27	MD -2.04 (-8.42, 4.34)	MD 2.04 lower (8.42 lower to 4.34 higher)	very low
bmi change (kg/m2, lower values are better, final value) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (feng 2017)	RCT	very serious[1]	not serious	NA[2]	serious[6]	NA	29	27	MD -1.10 (-2.49, 0.29)	MD 1.10 lower (2.49 lower to 0.29 higher)	very low

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

2. Only one study so no inconsistency

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

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

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

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

F.1.3.11 Liraglutide compared to glimepiride

Table 23: Clinical evidence profile: liraglutide compared 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
hba1c change (%, lower values are better, change score) 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	178	94	MD -0.51 (-0.84, -0.18)	MD 0.51 lower (0.84 lower to 0.18 lower)	very low

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

2. Only one study so no inconsistency

3. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

F.1.3.12 Liraglutide compared to placebo

Table 24: Clinical evidence profile: Liraglutide compared 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
all-cause mortality at end of follow-up Mean follow-up: 12 month(s)											
2	RCT	very serious[1]	not serious	not serious	serious[2]	NA	0/185	0/119	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 12 month(s)											
2	RCT	serious[3]	not serious	not serious	serious[2]	NA	0/185	0/119	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: 12 month(s)											
1 (yamada 2020)	RCT	very serious[1]	not serious	NA[4]	serious[2]	NA	0/48	0/49	RD 0.00 (-0.04, 0.04)	0 fewer per 1000 (39 fewer to 39 more)	very low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 12 month(s)											
1 (yamada 2020)	RCT	very serious[1]	not serious	NA[4]	serious[2]	NA	0/48	0/49	RD 0.00 (-0.04, 0.04)	0 fewer per 1000 (39 fewer to 39 more)	very low
unstable angina at end of follow-up Mean follow-up: 12 month(s)											
1 (yamada 2020)	RCT	very serious[1]	not serious	NA[4]	serious[2]	NA	0/48	0/49	RD 0.00 (-0.04, 0.04)	0 fewer per 1000	very low

										(39 fewer to 39 more)	
acute kidney injury at end of follow-up Mean follow-up: 12 month(s)											
1 (yamada 2020)	RCT	very serious[1]	not serious	NA[4]	serious[2]	NA	0/48	0/49	RD 0.00 (-0.04, 0.04)	0 fewer per 1000 (39 fewer to 39 more)	very low
cardiac arrhythmia at end of follow-up Mean follow-up: 12 month(s)											
1 (yamada 2020)	RCT	very serious[1]	not serious	NA[4]	serious[2]	NA	0/48	0/49	RD 0.00 (-0.04, 0.04)	0 fewer per 1000 (39 fewer to 39 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 9 month(s)											
2	RCT	very serious[1]	not serious	not serious	very serious[5]	NA	7/185	3/119	RR 1.94 (0.53, 7.08)	24 more per 1000 (12 fewer to 153 more)	very low
at night hypoglycaemic episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (miyagawa 2015)	RCT	serious[3]	not serious	NA[4]	serious[2]	NA	0/137	0/70	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (22 fewer to 22 more)	low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 9 month(s)											
2	RCT	serious[3]	not serious	not serious	serious[2]	NA	0/185	0/119	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	low
hba1c change (%, lower values are better, change scores) at end of follow-up											

Mean follow-up: 9 month(s)											
2	RCT	serious[3]	not serious	serious[6]	not serious	NA	186	119	MD -1.29 (-1.65, -0.93)	MD 1.29 lower (1.65 lower to 0.93 lower)	low
weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 12 month(s)											
1 (yamada 2020)	RCT	very serious[1]	not serious	NA[4]	not serious	NA	45	49	MD 0.60 (-0.25, 1.45)	MD 0.60 higher (0.25 lower to 1.45 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. >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 between 50% and 75%

F.1.3.13 Liraglutide compared to sitagliptin

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
hba1c change (%, lower values are better, final values) at end of follow up Mean follow-up: 6 month(s)											
1 (suzuki 2014)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	24	16	MD -0.60 (-1.57, 0.37)	MD 0.60 lower (1.57 lower to 0.37 higher)	very low

weight change (kg, lower values are better, final values) at end of follow up Mean follow-up: 6 month(s)											
1 (suzuki 2014)	RCT	very serious[1]	not serious	NA[2]	very serious[4]	NA	24	16	MD -0.90 (-15.40, 13.60)	MD 0.90 lower (15.40 lower to 13.60 higher)	very low

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

2. Only one study so no inconsistency

3. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

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

F.1.3.14 Semaglutide compared to liraglutide

Table 25: Clinical evidence profile: Semaglutide compared 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 - subscale physical component (sf-36v2 acute, 0-100, higher values are better, change scores) at end of follow-up Mean follow-up: 12 month(s)											
1 (yamada 2020,yamada 2020,yamada 2020)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	142	49	MD -1.02 (-2.02, -0.01)	MD 1.02 lower (2.02 lower to 0.01 lower)	very low
health-related quality of life - subscale mental component (sf-36v2 acute, 0-100, higher values are better, change scores) at end of follow-up Mean follow-up: 12 month(s)											

1 (yamada 2020,yamada 2020,yamada 2020)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	140	49	MD -0.57 (-2.07, 0.93)	MD 0.57 lower (2.07 lower to 0.93 higher)	low
all-cause mortality at end of follow-up Mean follow-up: 12 month(s)											
1 (yamada 2020)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	0/146	0/48	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (30 fewer to 30 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 12 month(s)											
1 (yamada 2020)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	0/146	0/48	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (30 fewer to 30 more)	very low
non-fatal stroke at end of follow-up Mean follow-up: 12 month(s)											
1 (yamada 2020)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	0/146	0/48	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (30 fewer to 30 more)	very low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 12 month(s)											
1 (yamada 2020)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	0/146	0/48	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (30 fewer to 30 more)	very low
unstable angina at end of follow-up Mean follow-up: 12 month(s)											

1 (yamada 2020)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	0/146	0/48	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (30 fewer to 30 more)	very low
acute kidney injury at end of follow-up Mean follow-up: 12 month(s)											
1 (yamada 2020)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	0/146	0/48	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (30 fewer to 30 more)	very low
cardiac arrhythmia at end of follow-up Mean follow-up: 12 month(s)											
1 (yamada 2020)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	0/146	0/48	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (30 fewer to 30 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 12 month(s)											
1 (yamada 2020)	RCT	very serious[1]	not serious	NA[2]	serious[5]	NA	6/146	5/48	RR 0.39 (0.13, 1.23)	63 fewer per 1000 (91 fewer to 24 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 12 month(s)											
1 (yamada 2020)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	0/146	0/48	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 scores) at end of follow-up Mean follow-up: 12 month(s)											

1 (yamada 2020)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	142	45	MD -0.07 (-0.30, 0.16)	MD 0.07 lower (0.30 lower to 0.16 higher)	low
weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 12 month(s)											
1 (yamada 2020)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	142	45	MD -1.22 (-1.94, -0.50)	MD 1.22 lower (1.94 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. 95% confidence intervals cross one end of the defined MIDs (-2.00, 2.00)

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)

F.1.3.15 Semaglutide compared to sitagliptin

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
hba1c change (%, lower values are better, change scores) at end of follow up ~ Mean follow-up: 7 month(s)											
1 (seino 2018)	RCT	not serious	not serious	NA[1]	not serious	NA	305	103	MD -1.35 (-1.63, -1.07)	MD 1.35 lower (1.63 lower to 1.07 lower)	high

weight change (kg, lower values are better, change score) at end of follow up ~ Mean follow-up: 7 month(s)											
1 (seino 2018)	RCT	not serious	not serious	NA[1]	Serious[2]	NA	305	103	MD -3.05 (-3.88, -2.22)	MD 3.05 lower (3.88 lower to 2.22 lower)	moderate
bmi change (kg/m2, lower values are better, change score) at end of follow up ~ Mean follow-up: 7 month(s)											
1 (seino 2018)	RCT	not serious	not serious	NA[1]	not serious	NA	305	103	MD -1.10 (-1.38, -0.82)	MD 1.10 lower (1.38 lower to 0.82 lower)	high
severe hypoglycaemic episodes at end of follow up ~ Mean follow-up: 8 month(s)											
1 (seino 2018)	RCT	not serious	not serious	NA[1]	not serious	NA	0/305	0/103	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	high

1. Only one study so no inconsistency

2. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

F.1.3.16 Semaglutide compared to placebo

Table 26: Clinical evidence profile: Semaglutide compared 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
health-related quality of life - subscale physical component (sf-36v2 acute, 0-100, higher values are better, change scores) at end of follow-up Mean follow-up: 12 month(s)											
1 (yamada 2020,yamada 2020,yamada 2020)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	142	49	MD -0.76 (-1.72, 0.21)	MD 0.76 lower	low

										(1.72 lower to 0.21 higher)	
health-related quality of life - subscale mental component (sf-36v2 acute, 0-100, higher values are better, change scores) at end of follow-up Mean follow-up: 12 month(s)											
1 (yamada 2020,yamada 2020,yamada 2020)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	142	49	MD 1.73 (0.31, 3.15)	MD 1.73 higher (0.31 higher to 3.15 higher)	very low
all-cause mortality at end of follow-up Mean follow-up: 8.1 month(s)											
3	RCT	not serious	not serious	serious[5]	very serious[6]	NA	1/930	0/356	RD 0.00 (-0.01, 0.01)	1 more per 1000 (7 fewer to 8 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 8.1 month(s)											
3	RCT	not serious	not serious	serious[5]	very serious[6]	NA	1/930	0/356	RD 0.00 (-0.01, 0.01)	1 more per 1000 (7 fewer to 8 more)	very low
non-fatal stroke at end of follow-up Mean follow-up: 8.1 month(s)											
3	RCT	not serious	not serious	serious[5]	very serious[7]	NA	1/929	2/356	RD -0.00 (-0.02, 0.01)	5 fewer per 1000 (16 fewer to 7 more)	very low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 8.1 month(s)											
3	RCT	not serious	serious[8]	serious[5]	very serious[9]	NA	2/929	0/356	RD 0.00 (-0.01, 0.01)	2 more per 1000 (6 fewer to 10 more)	very low
unstable angina at end of follow-up											

Mean follow-up: 12 month(s)											
1 (yamada 2020)	RCT	very serious[1]	not serious	NA[2]	serious[10]	NA	0/146	0/49	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (29 fewer to 29 more)	very low
hospitalisation for heart failure at end of follow-up Mean follow-up: 5.5 month(s)											
1 (aroda 2019b)	RCT	not serious	not serious	NA[2]	not serious	NA	0/525	0/178	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	high
acute kidney injury at end of follow-up Mean follow-up: 8.8 month(s)											
2	RCT	not serious	not serious	serious[5]	very serious[11]	NA	1/671	1/227	RD -0.00 (-0.01, 0.01)	3 fewer per 1000 (14 fewer to 8 more)	very low
cardiac arrhythmia at end of follow-up Mean follow-up: 12 month(s)											
1 (yamada 2020)	RCT	very serious[1]	not serious	NA[2]	serious[10]	NA	0/146	0/49	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (29 fewer to 29 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 8.1 month(s)											
3	RCT	not serious	not serious	serious[5]	very serious[12]	NA	13/929	3/356	RD 0.00 (-0.01, 0.02)	4 more per 1000 (9 fewer to 17 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 8.1 month(s)											
3	RCT	not serious	not serious	serious[5]	very serious[7]	NA	1/929	2/356	RD -0.00 (-0.01, 0.01)	4 fewer per 1000 (15 fewer to 6 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	very serious[1]	not serious	very serious[13]	not serious	NA	927	356	MD -1.07 (-1.31, -0.83)	MD 1.07 lower (1.31 lower to 0.83 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 9.1 month(s)											
3	RCT	very serious[1]	not serious	very serious[13]	not serious	NA	925	356	MD -1.17 (-2.14, -0.20)	MD 1.17 lower (2.14 lower to 0.20 lower)	very low
bmi change (kg/m2, lower values are better, change scores) at end of follow-up Mean follow-up: 9.1 month(s)											
3	RCT	very serious[1]	not serious	very serious[13]	not serious	NA	929	356	MD -0.45 (-0.79, -0.10)	MD 0.45 lower (0.79 lower to 0.10 lower)	very low

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

2. Only one study so no inconsistency

3. 95% confidence intervals cross one end of the defined MIDs (-3.00, 3.00)

4. 95% confidence intervals cross one end of the defined MIDs (-4.53, 4.53)

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 = 0.22 (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 = 0.51 (0.8-0.9 = serious, <0.8 = very serious).

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

9. 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).

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

11. 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).

12. 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).

13. I2 > 75%

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

F.1.4.1 Tirzepatide compared to dulaglutide

Table 27: Clinical evidence profile: Tirzepatide compared 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
all-cause mortality at end of follow-up Mean follow-up: 12 month(s)											
1 (inagaki 2022)	RCT	serious[1]	not serious	NA[2]	not serious	NA	0/477	0/159	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	moderate
cardiovascular mortality at end of follow-up Mean follow-up: 12 month(s)											

1 (inagaki 2022)	RCT	serious[1]	not serious	NA[2]	not serious	NA	0/477	0/159	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	moderate
3-point mace at end of follow-up Mean follow-up: 12 month(s)											
1 (inagaki 2022)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	4/477	2/159	RR 0.67 (0.12, 3.61)	4 fewer per 1000 (11 fewer to 33 more)	very low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 12 month(s)											
1 (inagaki 2022)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	1/477	0/159	PETO OR 3.79 (0.04, 350.61)	2 more per 1000 (2 fewer to 6 more)	very low
unstable angina at end of follow-up Mean follow-up: 12 month(s)											
1 (inagaki 2022)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	1/477	1/159	RR 0.33 (0.02, 5.30)	4 fewer per 1000 (6 fewer to 27 more)	very low
cardiac arrhythmia at end of follow-up Mean follow-up: 12 month(s)											
1 (inagaki 2022)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	1/477	1/159	RR 0.33 (0.02, 5.30)	4 fewer per 1000 (6 fewer to 27 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 12 month(s)											
1 (inagaki 2022)	RCT	serious[1]	not serious	NA[2]	not serious	NA	1/477	11/159	RR 0.03 (0.00, 0.23)	67 fewer per 1000 (69 fewer to 53 fewer)	moderate
severe hypoglycaemic episodes at end of follow-up											

1 (inagaki 2022)	RCT	serious[1]	not serious	NA[2]	not serious	NA	0/477	0/159	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: 12 month(s)											
1 (inagaki 2022)	RCT	serious[1]	not serious	NA[2]	not serious	NA	477	159	MD -1.30 (-1.53, -1.07)	MD 1.30 lower (1.53 lower to 1.07 lower)	moderate
weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 12 month(s)											
1 (inagaki 2022)	RCT	serious[1]	not serious	NA[2]	not serious	NA	477	159	MD -7.84 (-8.76, -6.92)	MD 7.84 lower (8.76 lower to 6.92 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)

F.1.5 SGLT2 inhibitors

F.1.5.1 Canagliflozin compared to metformin

Table 28: Clinical evidence profile: Canagliflozin v 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 (rosenstock 2016)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/475	1/237	PETO OR 0.05 (0.00, 3.17)	4 fewer per 1000 (12 fewer to 4 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/475	1/237	PETO OR 0.05 (0.00, 3.17)	4 fewer per 1000 (12 fewer to 4 more)	very low
non-fatal stroke at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	1/475	0/237	PETO OR 4.48 (0.07, 286.61)	2 more per 1000 (2 fewer to 6 more)	very low
unstable angina at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/475	0/237	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	low
cardiac arrhythmia at end of follow-up Mean follow-up: 5.5 month(s)											

1 (rosenstock 2016)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	1/475	0/237	PETO OR 4.48 (0.07, 286.61)	2 more per 1000 (2 fewer to 6 more)	very low
diabetic ketoacidosis at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	1/475	0/237	PETO OR 4.48 (0.07, 286.61)	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)											
1 (rosenstock 2016)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	16/475	11/237	RR 0.73 (0.34, 1.54)	13 fewer per 1000 (31 fewer to 25 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/475	1/237	PETO OR 0.05 (0.00, 3.17)	4 fewer per 1000 (12 fewer to 4 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	464	230	MD -0.10 (-0.27, 0.07)	MD 0.10 lower (0.27 lower to 0.07 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 2016)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	472	237	MD -1.35 (-2.07, -0.63)	MD 1.35 lower (2.07 lower to 0.63 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)

F.1.5.2 Canagliflozin compared to placebo

Table 29: Clinical evidence profile: canagliflozin compared 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
all-cause mortality at end of follow-up Mean follow-up: 6 month(s)											
1 (stenlöf 2013)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	1/392	1/192	RR 0.49 (0.03, 7.79)	3 fewer per 1000 (5 fewer to 35 more)	low
cardiovascular mortality at end of follow-up Mean follow-up: 6 month(s)											
1 (stenlöf 2013)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	0/392	1/192	PETO OR 0.05 (0.00, 3.10)	5 fewer per 1000 (15 fewer to 5 more)	low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.8 month(s)											

2	RCT	very serious[3]	not serious	not serious	very serious[2]	NA	14/190	3/98	RR 2.14 (0.69, 6.68)	35 more per 1000 (10 fewer to 174 more)	very low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.8 month(s)											
3	RCT	serious[4]	not serious	not serious	not serious	NA	574	287	MD -1.01 (-1.17, -0.84)	MD 1.01 lower (1.17 lower to 0.84 lower)	moderate
weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 5.8 month(s)											
3	RCT	serious[4]	not serious	serious[5]	serious[6]	NA	575	288	MD -3.15 (-4.19, -2.11)	MD 3.15 lower (4.19 lower to 2.11 lower)	very low
bmi change (kg/m2, lower values are better, change scores) at end of follow-up Mean follow-up: 6 month(s)											
1 (kashyap 2020)	RCT	very serious[3]	not serious	NA[1]	not serious	NA	11	5	MD -2.89 (-4.54, -1.24)	MD 2.89 lower (4.54 lower to 1.24 lower)	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. >33.3% of the studies in the meta-analysis were at moderate risk of bias

5. I2 between 50% and 75%

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

F.1.5.3 Dapagliflozin compared to metformin

Table 30: Clinical evidence profile: dapagliflozin compared to 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)											
2	RCT	not serious	not serious	serious[1]	very serious[2]	NA	1/422	1/409	PETO OR 0.97 (0.06, 15.51)	0 fewer per 1000 (7 fewer to 7 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	1/422	1/409	PETO OR 0.97 (0.06, 15.51)	0 fewer per 1000 (7 fewer to 7 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	not serious	not serious	serious[1]	very serious[3]	NA	2/422	6/409	RD -0.01 (-0.04, 0.02)	8 fewer per 1000 (38 fewer to 22 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)											

2	RCT	not serious	not serious	not serious	not serious	NA	0/411	0/420	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: 5.5 month(s)											
2	RCT	not serious	not serious	not serious	not serious	NA	412	398	MD 0.06 (-0.10, 0.22)	MD 0.06 higher (0.10 lower to 0.22 higher)	high
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	422	409	MD -1.34 (-1.81, -0.88)	MD 1.34 lower (1.81 lower to 0.88 lower)	high

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. 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).

F.1.5.4 Dapagliflozin compared to placebo

Table 31: Clinical evidence profile: dapagliflozin compared 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
all-cause mortality at end of follow-up											

Mean follow-up: 5.7 month(s)											
3	RCT	serious[1]	not serious	serious[2]	very serious[3]	NA	1/885	0/275	RD 0.00 (-0.01, 0.01)	1 more per 1000 (9 fewer to 10 more)	very low
persistent signs of worsening kidney disease at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	not serious	not serious	not serious	very serious[4]	NA	11/435	5/219	RR 1.11 (0.39, 3.14)	2 more per 1000 (14 fewer to 49 more)	low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.7 month(s)											
3	RCT	serious[1]	not serious	not serious	very serious[4]	NA	10/859	4/275	RR 0.67 (0.22, 2.05)	5 fewer per 1000 (11 fewer to 15 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow-up Mean follow-up: 5.6 month(s)											
5	RCT	serious[1]	not serious	very serious[5]	serious[6]	NA	1051	372	MD -0.73 (-1.02, -0.44)	MD 0.73 lower (1.02 lower to 0.44 lower)	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	serious[1]	not serious	very serious[5]	not serious	NA	558	162	MD -0.47 (-2.13, 1.18)	MD 0.47 lower (2.13 lower to 1.18 higher)	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 = 0.21 (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 > 75%

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

F.1.5.5 Empagliflozin compared to metformin

Table 32: Clinical evidence profile: empagliflozin compared to 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 (hadjadj 2016)	RCT	not serious	not serious	NA[1]	not serious	NA	0/339	0/341	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 (hadjadj 2016)	RCT	not serious	not serious	NA[1]	not serious	NA	0/339	0/341	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: 5.5 month(s)											

1 (hadjadj 2016)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	2/339	2/341	RR 1.01 (0.14, 7.10)	0 more per 1000 (5 fewer to 36 more)	low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (hadjadj 2016)	RCT	not serious	not serious	NA[1]	not serious	NA	285	269	MD 0.15 (-0.02, 0.32)	MD 0.15 higher (0.02 lower to 0.32 higher)	high

1. Only one study so no inconsistency

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

F.1.5.6 Empagliflozin compared to linagliptin

Table 33: Clinical evidence profile: empagliflozin v 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: 12 month(s)											
1 (lewin 2015)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	3/270	0/135	PETO OR 4.52 (0.41, 50.09)	11 more per 1000 (1 fewer to 24 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 12 month(s)											
1 (lewin 2015)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	1/270	0/135	PETO OR 4.48 (0.07, 286.49)	4 more per 1000 (4 fewer to 11 more)	very low

hypoglycaemia episodes at end of follow-up Mean follow-up: 12 month(s)											
1 (lewin 2015)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	5/270	1/135	RR 2.50 (0.30, 21.19)	11 more per 1000 (5 fewer to 150 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 12 month(s)											
1 (lewin 2015)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/270	0/135	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (11 fewer to 11 more)	low
hba1c change (%, lower values are better, change scores) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (lewin 2015)	RCT	serious[4]	not serious	NA[2]	not serious	NA	265	133	MD -0.23 (-0.39, -0.07)	MD 0.23 lower (0.39 lower to 0.07 lower)	moderate
weight change (kg, lower values are better) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (lewin 2015)	RCT	not serious	not serious	NA[2]	serious[5]	NA	266	133	MD -1.40 (-4.82, 2.02)	MD 1.40 lower (4.82 lower to 2.02 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 (0.80, 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 (-2.40, 2.40)

F.1.5.7 Empagliflozin compared to sitagliptin

Table 34: Clinical evidence profile: empagliflozin compared to 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: 17.5 month(s)											
1 (roden 2015)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	1/447	1/223	RR 0.50 (0.03, 7.94)	2 fewer per 1000 (4 fewer to 31 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 17.5 month(s)											
1 (roden 2015)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	4/447	2/223	RR 1.00 (0.18, 5.41)	0 fewer per 1000 (7 fewer to 40 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 17.5 month(s)											
1 (roden 2015)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	1/447	0/223	PETO OR 4.48 (0.07, 286.62)	2 more per 1000 (2 fewer to 7 more)	very low
hba1c change (%, lower values are better) at end of follow-up Mean follow-up: 17.5 month(s)											
1 (roden 2015)	RCT	serious[1]	not serious	NA[2]	not serious	NA	448	223	MD -0.18 (-0.20, -0.16)	MD 0.18 lower (0.20 lower to 0.16 lower)	moderate
weight change (kg, lower values are better) at end of follow-up											

Mean follow-up: 17.5 month(s)											
1 (roden 2015)	RCT	serious[1]	not serious	NA[2]	serious[4]	NA	448	223	MD -2.45 (-2.93, -1.97)	MD 2.45 lower (2.93 lower to 1.97 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 (-2.40, 2.40)

F.1.5.8 Empagliflozin compared to placebo

Table 35: Clinical evidence profile: empagliflozin compared 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
all-cause mortality at end of follow-up Mean follow-up: 17.5 month(s)											
1 (roden 2015)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	1/447	1/229	RR 0.51 (0.03, 8.15)	2 fewer per 1000 (4 fewer to 31 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 17.5 month(s)											
1 (roden 2015)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	4/447	2/229	RR 1.02 (0.19, 5.55)	0 more per 1000 (7 fewer to 40 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 17.5 month(s)											

1 (roden 2015)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	1/447	0/229	PETO OR 4.54 (0.07, 285.28)	2 more per 1000 (2 fewer to 7 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow-up Mean follow-up: 11.5 month(s)											
2	RCT	serious[1]	not serious	very serious[4]	serious[5]	NA	490	270	MD -0.52 (-1.16, 0.11)	MD 0.52 lower (1.16 lower to 0.11 higher)	very low
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	serious[6]	NA	490	270	MD -2.04 (-2.49, -1.60)	MD 2.04 lower (2.49 lower to 1.60 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. 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)

F.1.6 Sulfonylureas

F.1.6.1 Gliclazide compared to metformin

Table 36: Clinical evidence profile: gliclazide compared to metformin

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
cardiovascular mortality at end of follow-up Mean follow-up: 12 month(s)											
1 (erem 2014)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/20	0/20	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: 12 month(s)											
1 (erem 2014)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/20	0/20	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: 12 month(s)											
1 (erem 2014)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/20	0/20	RD 0.00 (-0.09, 0.09)	0 fewer per 1000 (92 fewer to 92 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 8.8 month(s)											
2	RCT	very serious[1]	not serious	serious[4]	very serious[5]	NA	2/52	2/51	RD -0.00 (-0.07, 0.07)	1 fewer per 1000 (74 fewer to 72 more)	very low
severe hypoglycaemic episodes at end of follow-up											

Mean follow-up: 12 month(s)											
1 (erem 2014)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/20	0/20	RD 0.00 (-0.09, 0.09)	0 fewer per 1000 (92 fewer to 92 more)	very low
hba1c change (%, lower values are better, change score and final values) at end of follow-up Mean follow-up: 7.8 month(s)											
3	RCT	very serious[1]	not serious	serious[6]	serious[7]	NA	81	80	MD 0.36 (-0.05, 0.77)	MD 0.36 higher (0.05 lower to 0.77 higher)	very low
weight change (kg, lower values are better, final values) at end of follow-up Mean follow-up: 7.8 month(s)											
3	RCT	very serious[1]	not serious	not serious	serious[8]	NA	76	78	MD 4.59 (0.31, 8.88)	MD 4.59 higher (0.31 higher to 8.88 higher)	very low
bmi change (kg/m2, lower values are better, final values) at end of follow-up Mean follow-up: 8.8 month(s)											
2	RCT	very serious[1]	not serious	not serious	very serious[9]	NA	46	48	MD 1.08 (-0.87, 3.02)	MD 1.08 higher (0.87 lower to 3.02 higher)	very low

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

2. Only one study so no inconsistency

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

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

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

6. I2 between 50% and 75%

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 (-2.40, 2.40)

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

F.1.6.2 Gliclazide compared to vildagliptin

Table 37: Clinical evidence profile: glizlacide compared to 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 end of follow-up Mean follow-up: 24 month(s)											
1 (foley 2009)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	9/546	6/546	RR 1.50 (0.54, 4.19)	5 more per 1000 (5 fewer to 35 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow-up Mean follow-up: 24 month(s)											
1 (foley 2009)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	546	546	MD 0.13 (-0.07, 0.33)	MD 0.13 higher (0.07 lower to 0.33 higher)	low
weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 24 month(s)											

1 (foley 2009)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	546	546	MD 0.80 (0.25, 1.35)	MD 0.80 higher (0.25 higher to 1.35 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)

F.1.6.3 Glimepiride compared to metformin

Table 38: Clinical evidence profile: glimepiride compared to 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: 11.7 month(s)											
3	RCT	very serious[1]	not serious	serious[2]	not serious	NA	24/236	4/236	RD 0.06 (-0.11, 0.23)	61 more per 1000 (109 fewer to 230 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 12 month(s)											
1 (derosa 2004)	RCT	very serious[1]	not serious	NA[3]	serious[4]	NA	0/81	0/83	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (24 fewer to 24 more)	very low
hba1c change (%, lower values are better, change score and final value) at end of follow-up Mean follow-up: 11.7 month(s)											

3	RCT	very serious[1]	not serious	not serious	not serious	NA	236	236	MD 0.00 (-0.20, 0.20)	MD 0.00 higher (0.20 lower to 0.20 higher)	low
bmi change (kg/m2, lower values are better, change score and final value) at end of follow-up Mean follow-up: 12 month(s)											
2	RCT	very serious[1]	not serious	not serious	very serious[5]	NA	118	122	MD -0.10 (-1.06, 0.86)	MD 0.10 lower (1.06 lower to 0.86 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. 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, 0.80)

F.1.6.4 Glimepiride compared to dulaglutide

Table 39: Clinical evidence profile: glimepiride compared 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
all-cause mortality at end of follow-up Mean follow-up: 6 month(s)											

1 (chen 2018b)	RCT	very serious [1]	not serious	NA[2]	very serious[3]	NA	0/243	1/492	PETO OR 0.22 (0.00, 14.47)	2 fewer per 1000 (6 fewer to 2 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 6 month(s)											
1 (chen 2018b)	RCT	very serious [1]	not serious	NA[2]	not serious	NA	0/243	0/492	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	low
non-fatal stroke at end of follow-up Mean follow-up: 6 month(s)											
1 (chen 2018b)	RCT	very serious [1]	not serious	NA[2]	very serious[3]	NA	0/243	1/492	PETO OR 0.22 (0.00, 14.47)	2 fewer per 1000 (6 fewer to 2 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (chen 2018b)	RCT	very serious [1]	not serious	NA[2]	not serious	NA	38/243	23/492	RR 3.35 (2.04, 5.48)	110 more per 1000 (49 more to 210 more)	low
at night hypoglycaemic episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (chen 2018b)	RCT	very serious [1]	not serious	NA[2]	not serious	NA	9/243	2/492	RR 9.11 (1.98, 41.84)	33 more per 1000 (4 more to 166 more)	low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (chen 2018b)	RCT	very serious 1	not serious	NA[2]	not serious	NA	0/243	0/492	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: 6 month(s)											
1 (chen 2018b)	RCT	very serious [1]	not serious	NA[2]	serious[4]	NA	242	478	MD 0.45 (0.28, 0.62)	MD 0.45 higher (0.28 higher to 0.62 higher)	very low
weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 6 month(s)											
1 (chen 2018b)	RCT	very serious [1]	not serious	NA[2]	serious[5]	NA	242	478	MD 2.01 (1.55, 2.47)	MD 2.01 higher (1.55 higher to 2.47 higher)	very low

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

2. Only one study so no inconsistency

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

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

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

F.1.6.5 Glimepiride compared to saxagliptin

Table 40: Clinical evidence profile: glimepiride compared to saxagliptin

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 value) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (li 2019a)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	33	30	MD 0.01 (-0.25, 0.27)	MD 0.01 higher (0.25 lower to 0.27 higher)	low
bmi change (kg/m2, lower values are better, final value) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (li 2019a)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	33	30	MD -1.04 (-2.85, 0.77)	MD 1.04 lower (2.85 lower to 0.77 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 one end of the defined MIDs (-0.80, 0.80)

F.1.6.6 Glimepiride compared to sitagliptin

Table 41: Clinical evidence profile: glimepiride compared to 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: 15.5 month(s)											
2	RCT	not serious	not serious	serious[1]	very serious[2]	NA	1/388	0/394	RD 0.00 (-0.01, 0.01)	3 more per 1000 (6 fewer to 11 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 7 month(s)											

1 (hartley 2015)	RCT	not serious	not serious	NA[3]	not serious	NA	0/236	0/241	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	high
persistent signs of worsening kidney disease at end of follow-up Mean follow-up: 12 month(s)											
1 (kondo 2016)	RCT	very serious[4]	not serious	NA[3]	serious[5]	NA	0/68	3/65	PETO OR 0.13 (0.01, 1.23)	46 fewer per 1000 (97 fewer to 5 more)	very low
progression of liver disease at end of follow-up Mean follow-up: 18 month(s)											
2	RCT	very serious[4]	not serious	not serious	very serious[6]	NA	3/220	4/218	RR 0.75 (0.19, 2.96)	5 fewer per 1000 (15 fewer to 36 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 9.5 month(s)											
2	RCT	not serious	not serious	serious[1]	not serious	NA	16/304	3/306	PETO OR 4.20 (1.68, 10.48)	43 more per 1000 (15 more to 70 more)	moderate
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 14.3 month(s)											
3	RCT	not serious	not serious	serious[1]	very serious[7]	NA	3/456	1/459	RD 0.00 (-0.01, 0.01)	4 more per 1000 (6 fewer to 15 more)	very low
hba1c change (%, lower values are better, change scores and final value) at end of follow-up Mean follow-up: 10.3 month(s)											
3	RCT	very serious[4]	not serious	not serious	not serious	NA	411	415	MD -0.12 (-0.21, -0.03)	MD 0.12 lower	low

										(0.21 lower to 0.03 lower)	
weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 15.5 month(s)											
2	RCT	not serious	not serious	not serious	not serious	NA	388	394	MD 0.77 (0.31, 1.24)	MD 0.77 higher (0.31 higher to 1.24 higher)	high
bmi change (kg/m2, lower values are better, final value) at end of follow-up Mean follow-up: 12 month(s)											
1 (kondo 2016)	RCT	very serious[4]	not serious	NA[3]	not serious	NA	68	65	MD 0.00 (-0.36, 0.36)	MD 0.00 lower (0.36 lower to 0.36 higher)	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 = 0.29 (0.8-0.9 = serious, <0.8 = very serious).

3. Only one study so no inconsistency

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

5. 95% confidence intervals cross one end of the defined MIDs (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 = 0.3 (0.8-0.9 = serious, <0.8 = very serious).

F.1.6.7 Glipizide compared to metformin

Table 42: Clinical evidence profile: glipizide compared to 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 (campbell 1994)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/24	0/24	RD 0.00 (-0.08, 0.08)	0 fewer per 1000 (78 fewer to 78 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 12 month(s)											
1 (campbell 1994)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/24	0/24	RD 0.00 (-0.08, 0.08)	0 fewer per 1000 (78 fewer to 78 more)	very low
hba1c change (%, lower values are better, change score and final value) at end of follow-up Mean follow-up: 8.8 month(s)											
2	RCT	very serious[1]	not serious	very serious[4]	very serious[5]	NA	94	92	MD 0.34 (-1.01, 1.69)	MD 0.34 higher (1.01 lower to 1.69 higher)	very low
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	very serious[1]	not serious	serious[6]	very serious[7]	NA	94	92	MD 1.81 (-2.41, 6.03)	MD 1.81 higher (2.41 lower to 6.03 higher)	very low

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Only one study so no inconsistency
3. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
4. I2 > 75%
5. 95% confidence intervals cross both ends of the defined MIDs (-0.50, 0.50)
6. I2 between 50% and 75%
7. 95% confidence intervals cross both ends of the defined MIDs (-2.40, 2.40)

F.1.6.8 Glipizide compared to sitagliptin

Table 43: Clinical evidence profile: glipizide compared to 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: 12.4 month(s)											
2	RCT	serious[1]	not serious	not serious	very serious[2]	NA	13/277	7/274	RR 1.83 (0.75, 4.50)	21 more per 1000 (6 fewer to 89 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 12.4 month(s)											
1 (arjona ferreira 2013b)	RCT	serious[1]	not serious	NA[3]	very serious[2]	NA	3/212	2/210	RR 1.49 (0.25, 8.80)	5 more per 1000 (7 fewer to 74 more)	very low
non-fatal stroke at end of follow-up Mean follow-up: 12.4 month(s)											

1 (arjona ferreira 2013b)	RCT	serious[1]	not serious	NA[3]	very serious[2]	NA	1/212	2/210	RR 0.50 (0.05, 5.42)	5 fewer per 1000 (9 fewer to 42 more)	very low
hospitalisation for heart failure at end of follow-up Mean follow-up: 12.4 month(s)											
2	RCT	serious[1]	not serious	serious[4]	very serious[2]	NA	5/277	2/275	PETO OR 2.36 (0.53, 10.51)	11 more per 1000 (8 fewer to 29 more)	very low
development of end stage kidney disease at end of follow-up Mean follow-up: 12.4 month(s)											
1 (arjona ferreira 2013b)	RCT	serious[1]	not serious	NA[3]	very serious[2]	NA	1/210	2/212	RR 0.50 (0.05, 5.52)	5 fewer per 1000 (9 fewer to 43 more)	very low
diabetic ketoacidosis at end of follow-up Mean follow-up: 12.4 month(s)											
1 (arjona ferreira 2013b)	RCT	serious[1]	not serious	NA[3]	very serious[2]	NA	0/212	1/210	PETO OR 0.13 (0.00, 6.76)	5 fewer per 1000 (14 fewer to 5 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 12.4 month(s)											
2	RCT	serious[1]	not serious	not serious	very serious[2]	NA	11/277	3/275	RR 2.94 (0.69, 12.53)	21 more per 1000 (3 fewer to 126 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow-up Mean follow-up: 12.4 month(s)											
2	RCT	serious[1]	not serious	serious[5]	not serious	NA	204	194	MD 0.05 (-0.29, 0.39)	MD 0.05 higher	low

										(0.29 lower to 0.39 higher)	
weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 12.4 month(s)											
2	RCT	serious[1]	not serious	not serious	not serious	NA	189	188	MD 1.70 (1.06, 2.35)	MD 1.70 higher (1.06 higher to 2.35 higher)	moderate

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. Only one study so no inconsistency

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

5. I2 between 50% and 75%

F.1.6.9 Glipizide compared to placebo

Table 44: Clinical evidence profile: glipizide compared 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
remission at end of follow-up Mean follow-up: 22 month(s)											
1 (banerji 1995)	RCT	serious[1]	serious[2]	NA[3]	very serious[4]	NA	4/10	4/10	RR 1.00 (0.34, 2.93)	0 fewer per 1000 (263 fewer to 770 more)	very low

hypoglycaemia episodes at end of follow-up Mean follow-up: 15 month(s)											
1 (birkeland 1994)	RCT	very serious[5]	not serious	NA[3]	serious[6]	NA	0/15	4/15	PETO OR 0.11 (0.01, 0.85)	267 fewer per 1000 (491 fewer to 43 fewer)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 22 month(s)											
1 (banerji 1995)	RCT	serious[1]	not serious	NA[3]	very serious[7]	NA	0/10	0/10	RD 0.00 (-0.17, 0.17)	0 fewer per 1000 (174 fewer to 174 more)	very low
hba1c change (%, lower values are better, final value) at end of follow-up Mean follow-up: 23 month(s)											
2	RCT	serious[1]	not serious	very serious[8]	very serious[9]	NA	42	28	MD -1.89 (-5.65, 1.86)	MD 1.89 lower (5.65 lower to 1.86 higher)	very low
bmi change (%, lower values are better, change score) at end of follow-up Mean follow-up: 22 month(s)											
1 (banerji 1995)	RCT	serious[1]	not serious	NA[3]	very serious[10]	NA	10	10	MD -2.52 (-8.35, 3.31)	MD 2.52 lower (8.35 lower to 3.31 higher)	very low

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

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

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

8. I2 > 75%

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

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

F.1.6.10 Tolbutamide compared to insulin

Table 45: Clinical evidence profile: Tolbutamide compared to insulin

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
all-cause mortality at end of follow-up Mean follow-up: 60 month(s)											
1 (goldner 1971)	RCT	very serious [1]	not serious	NA[2]	serious [3]	NA	30/204	38/414	RR 1.60 (1.02, 2.51)	55 more per 1000 (2 more to 138 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 60 month(s)											
1 (goldner 1971)	RCT	very serious [1]	not serious	NA[2]	not serious	NA	26/204	25/414	RR 2.11 (1.25, 3.56)	67 more per 1000 (15 more to 155 more)	low
persistent signs of worsening kidney disease at end of follow-up Mean follow-up: 60 month(s)											

1 (goldner 1971)	RCT	very serious [1]	not serious	NA[2]	very serious [4]	NA	11/188	18/378	RR 1.23 (0.59, 2.55)	11 more per 1000 (19 fewer to 74 more)	very low
cardiac arrhythmia at end of follow-up Mean follow-up: 60 month(s)											
1 (goldner 1971)	RCT	very serious [1]	not serious	NA[2]	very serious [4]	NA	16/193	31/392	RR 1.05 (0.59, 1.87)	4 more per 1000 (33 fewer to 69 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)

F.1.6.11 Tolbutamide compared to placebo

Table 46: Clinical evidence profile: Tolbutamide compared 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
all-cause mortality at end of follow-up Mean follow-up: 60 month(s)											
1 (goldner 1971)	RCT	very serious [1]	not serious	NA[2]	serious [3]	NA	30/204	21/205	RR 1.44 (0.85, 2.42)	45 more per 1000 (15 fewer to 146 more)	very low
cardiovascular mortality at end of follow-up											

Mean follow-up: 60 month(s)											
1 (goldner 1971)	RCT	very serious [1]	not serious	NA[2]	not serious	NA	26/204	10/205	RR 2.61 (1.29, 5.28)	79 more per 1000 (14 more to 209 more)	low
persistent signs of worsening kidney disease at end of follow-up Mean follow-up: 60 month(s)											
1 (goldner 1971)	RCT	very serious [1]	not serious	NA[2]	very serious [4]	NA	11/188	12/184	RR 0.90 (0.41, 1.98)	7 fewer per 1000 (39 fewer to 64 more)	very low
cardiac arrhythmia at end of follow-up Mean follow-up: 60 month(s)											
1 (goldner 1971)	RCT	very serious [1]	not serious	NA[2]	serious [3]	NA	16/193	27/193	RR 0.59 (0.33, 1.06)	57 fewer per 1000 (94 fewer to 9 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)

F.1.7 Thiazolidinedione

F.1.7.1 Pioglitazone compared to metformin

Figure 207: Clinical evidence profile: Pioglitazone compared to metformin

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 - eq5d Mean follow-up: 6 month(s)											
1 (russell-jones 2012)	RCT	not serious	not serious	NA[1]	serious[2]	NA	146	227	MD -0.04 (-0.07, -0.01)	MD 0.04 lower (0.07 lower to 0.01 lower)	moderate
all-cause mortality Mean follow-up: 8.2 month(s)											
5	RCT	not serious	not serious	serious[3]	very serious[4]	NA	3/725	3/827	RD -0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 6 more)	very low
cardiovascular mortality Mean follow-up: 7.2 month(s)											
4	RCT	very serious[5]	not serious	serious[3]	very serious[6]	NA	0/428	1/530	RD -0.00 (-0.01, 0.01)	1 fewer per 1000 (9 fewer to 6 more)	very low
non-fatal myocardial infarction Mean follow-up: 8.8 month(s)											
2	RCT	very serious[5]	not serious	serious[3]	very serious[7]	NA	1/210	0/229	RD 0.01 (-0.01, 0.02)	5 more per 1000 (9 fewer to 19 more)	very low

hospitalisation for heart failure Mean follow-up: 8.8 month(s)											
2	RCT	not serious	not serious	not serious	serious[8]	NA	0/75	0/75	RD 0.00 (-0.04, 0.04)	0 fewer per 1000 (37 fewer to 37 more)	moderate
hypoglycaemia episodes Mean follow-up: 10.1 month(s)											
5	RCT	very serious[5]	not serious	serious[3]	very serious[6]	NA	7/480	13/581	RD -0.01 (-0.02, 0.01)	5 fewer per 1000 (19 fewer to 9 more)	very low
severe hypoglycaemic episodes Mean follow-up: 12 month(s)											
1 (erem 2014)	RCT	very serious[5]	not serious	NA[1]	very serious[8]	NA	0/20	0/20	RD 0.00 (-0.09, 0.09)	0 fewer per 1000 (92 fewer to 92 more)	very low
hba1c change Mean follow-up: 9.7 month(s)											
6	RCT	not serious	not serious	serious[9]	not serious	NA	423	498	MD 0.07 (-0.08, 0.23)	MD 0.07 higher (0.08 lower to 0.23 higher)	moderate
weight change Mean follow-up: 8.6 month(s)											
5	RCT	not serious	not serious	very serious[10]	serious[11]	NA	939	1017	MD 2.90 (1.16, 4.64)	MD 2.90 higher (1.16 higher to 4.64 higher)	very low
bmi change Mean follow-up: 11.1 month(s)											

4	RCT	not serious	not serious	very serious[10][1]	very serious[12][1]	NA	181	180	MD -0.24 (-1.73, 1.24)	MD 0.24 lower (1.73 lower to 1.24 higher)	very low

1. Only one study so no inconsistency

2. 95% confidence intervals cross one end 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. 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. >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 = 0.3 (0.8-0.9 = serious, <0.8 = very serious).

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

9. I2 between 50% and 75%

10. I2 > 75%

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

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

F.1.7.2 Pioglitazone compared to linagliptin

Figure 208: Clinical evidence profile: Pioglitazone compared to linagliptin

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
4-point mace at end of follow-up Mean follow-up: 6.9 month(s)											
1 (nauck 2016)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	2/409	2/135	PETO OR 0.26 (0.03, 2.50)	10 fewer per 1000 (31 fewer to 12 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 6.9 month(s)											
1 (nauck 2016)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	5/409	0/135	PETO OR 3.82 (0.50, 29.27)	12 more per 1000 (2 more to 23 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 6.9 month(s)											
1 (nauck 2016)	RCT	serious[1]	not serious	NA[2]	not serious	NA	0/409	0/135	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (11 fewer to 11 more)	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)

F.1.7.3 Pioglitazone compared to sitagliptin

Table 47: Clinical evidence profile: Pioglitazone compared to 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 at end of follow-up Mean follow-up: 6 month(s)											
1 (russell-jones 2012)	RCT	not serious	not serious	NA[1]	serious[2]	NA	146	149	MD -0.03 (-0.06, -0.00)	MD 0.03 lower (0.06 lower to 0.00 lower)	moderate
all-cause mortality at end of follow-up Mean follow-up: 9 month(s)											
2	RCT	very serious[3]	not serious	serious[4]	very serious[5]	NA	1/728	1/349	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: 9 month(s)											
2	RCT	very serious[3]	not serious	not serious	not serious	NA	0/728	0/349	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	low
non-fatal stroke at end of follow-up Mean follow-up: 12 month(s)											
1 (henry 2014)	RCT	very serious[3]	not serious	NA[1]	very serious[6]	NA	2/568	1/186	RR 0.65 (0.06, 7.18)	2 fewer per 1000 (5 fewer to 33 more)	very low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 12 month(s)											

1 (henry 2014)	RCT	very serious [3]	not serious	NA[1]	not serious	NA	0/568	2/186	PETO OR 0.02 (0.00, 0.43)	11 fewer per 1000 (26 fewer to 4 more)	low
hypoglycaemia episodes at end of follow-up Mean follow-up: 9 month(s)											
2	RCT	very serious [3]	not serious	not serious	very serious [6]	NA	58/728	25/349	RR 0.90 (0.58, 1.42)	7 fewer per 1000 (30 fewer to 30 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 12 month(s)											
1 (henry 2014)	RCT	very serious [3]	not serious	NA[1]	very serious [6]	NA	0/565	1/186	PETO OR 0.02 (0.00, 1.65)	5 fewer per 1000 (16 fewer to 5 more)	very low
hba1c change (%, change score, lower values better) Mean follow-up: 9 month(s)											
2	RCT	not serious	not serious	very serious [7]	serious [8]	NA	652	314	MD -0.31 (-0.65, 0.02)	MD 0.31 lower (0.65 lower to 0.02 higher)	very low
weight change (kg, change score, lower values better) Mean follow-up: 9 month(s)											
2	RCT	not serious	not serious	very serious [7]	serious [9]	NA	471	264	MD 3.09 (1.40, 4.78)	MD 3.09 higher (1.40 higher to 4.78 higher)	very low

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 = 0.11 (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. 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)

F.1.7.4 Pioglitazone compared to vildagliptin

Table 48: Clinical evidence profile: Pioglitazone compared to 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 end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2007a)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/161	1/153	PETO OR 0.13 (0.00, 6.48)	7 fewer per 1000 (19 fewer to 6 more)	very low
hba1c change (%, change score, lower scores better) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2007a)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	157	150	MD -0.30 (-0.58, -0.02)	MD 0.30 lower (0.58 lower to 0.02 lower)	very low
weight change (kg, change score, lower scores better) Mean follow-up: 5.5 month(s)											

1 (rosenstock 2007a)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	157	150	MD 1.30 (0.47, 2.13)	MD 1.30 higher (0.47 higher to 2.13 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)

F.1.7.5 Pioglitazone compared to exenatide

Table 49: Clinical evidence profile: Pioglitazone compared to 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 Mean follow-up: 6 month(s)											
1 (russell-jones 2012)	RCT	not serious	not serious	NA[1]	serious[2]	NA	146	232	MD -0.04 (-0.07, -0.01)	MD 0.04 lower (0.07 lower to 0.01 lower)	moderate
all-cause mortality Mean follow-up: 8.6 month(s)											
2	RCT	not serious	not serious	not serious	not serious	NA	0/299	0/390	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	high
cardiovascular mortality											

Mean follow-up: 8.6 month(s)											
2	RCT	not serious	not serious	not serious	not serious	NA	0/299	0/390	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	high
hypoglycaemia episodes Mean follow-up: 8.6 month(s)											
2	RCT	very serious [3]	not serious	not serious	serious [4]	NA	11/299	26/390	RR 0.54 (0.27, 1.06)	31 fewer per 1000 (49 fewer to 4 more)	very low
severe hypoglycaemic episodes Mean follow-up: 11.1 month(s)											
1 (xu 2015)	RCT	very serious [3]	not serious	NA[1]	serious [5]	NA	0/136	0/142	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	very low
hba1c change Mean follow-up: 8.6 month(s)											
2	RCT	not serious	not serious	very serious[6]	not serious	NA	255	328	MD 0.09 (-0.30, 0.48)	MD 0.09 higher (0.30 lower to 0.48 higher)	low
weight change Mean follow-up: 8.6 month(s)											
2	RCT	not serious	not serious	not serious	not serious	NA	281	358	MD 3.50 (2.90, 4.10)	MD 3.50 higher (2.90 higher to 4.10 higher)	high
bmi change Mean follow-up: 11.1 month(s)											

1 (xu 2015)	RCT	very serious [3]	not serious	NA[1]	not serious	NA	118	110	MD 1.30 (1.02, 1.58)	MD 1.30 higher (1.02 higher to 1.58 higher)	low

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. 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. I2 > 75%

F.1.7.6 Pioglitazone compared to liraglutide

Table 50: Clinical evidence profile: Pioglitazone compared 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
hypoglycaemia episodes Mean follow-up: 5.5 month(s)											
1 (zhang 2020a)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	2/30	1/30	RR 2.00 (0.19, 20.90)	33 more per 1000 (27 fewer to 663 more)	very low
severe hypoglycaemic episodes Mean follow-up: 5.5 month(s)											
1 (zhang 2020a)	RCT	very serious[1]	not serious	NA[2]	very serious[4]	NA	0/30	0/30	RD 0.00 (-0.06, 0.06)	0 fewer per 1000	very low

										(63 fewer to 63 more)	
hba1c change Mean follow-up: 5.5 month(s)											
1 (zhang 2020a)	RCT	very serious[1]	not serious	NA[2]	serious[5]	NA	30	30	MD 0.40 (-0.39, 1.19)	MD 0.40 higher (0.39 lower to 1.19 higher)	very low
weight change Mean follow-up: 5.5 month(s)											
1 (zhang 2020a)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	30	30	MD 9.90 (4.89, 14.91)	MD 9.90 higher (4.89 higher to 14.91 higher)	low
bmi change Mean follow-up: 5.5 month(s)											
1 (zhang 2020a)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	30	30	MD 3.60 (1.78, 5.42)	MD 3.60 higher (1.78 higher to 5.42 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)

F.1.7.7 Pioglitazone compared to gliclazide

Table 51: Clinical evidence profile: Pioglitazone compared to glicazide

cardiovascular mortality											

Mean follow-up: 12 month(s)											
1 (erem 2014)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/20	0/20	RD 0.00 (-0.09, 0.09)	0 fewer per 1000 (92 fewer to 92 more)	very low
non-fatal myocardial infarction Mean follow-up: 12 month(s)											
1 (erem 2014)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/20	0/20	RD 0.00 (-0.09, 0.09)	0 fewer per 1000 (92 fewer to 92 more)	very low
hospitalisation for heart failure Mean follow-up: 12 month(s)											
1 (erem 2014)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/20	0/20	RD 0.00 (-0.09, 0.09)	0 fewer per 1000 (92 fewer to 92 more)	very low
hypoglycaemia episodes Mean follow-up: 12 month(s)											
2	RCT	very serious[1]	not serious	serious[4]	not serious	NA	25/655	63/655	RD -0.06 (-0.09, -0.03)	58 fewer per 1000 (85 fewer to 31 fewer)	very low
severe hypoglycaemic episodes Mean follow-up: 12 month(s)											
1 (erem 2014)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/20	0/20	RD 0.00 (-0.09, 0.09)	0 fewer per 1000 (92 fewer to 92 more)	very low
hba1c change Mean follow-up: 12 month(s)											
3	RCT	very serious[1]	not serious	very serious[5]	serious[6]	NA	951	924	MD -0.32 (-0.63, -0.02)	MD 0.32 lower (0.63 lower to 0.02 lower)	very low
weight change Mean follow-up: 12 month(s)											

2	RCT	very serious[1]	not serious	very serious[5]	very serious[7]	NA	289	316	MD -4.56 (-20.39, 11.26)	MD 4.56 lower (20.39 lower to 11.26 higher)	very low
bmi change Mean follow-up: 12 month(s)											
1 (erem 2014)	RCT	very serious[1]	not serious	NA[2]	very serious[8]	NA	19	19	MD -1.53 (-4.65, 1.59)	MD 1.53 lower (4.65 lower to 1.59 higher)	very low

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

2. Only one study so no inconsistency

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

4. 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)

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

F.1.7.8 Pioglitazone compared to glimepiride

Table 52: Clinical evidence profile: Pioglitazone compared 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 Mean follow-up: 9 month(s)											

2	RCT	serious[1]	not serious	not serious	very serious[2]	NA	5/134	8/132	RR 0.64 (0.23, 1.81)	22 fewer per 1000 (47 fewer to 49 more)	very low
hba1c change Mean follow-up: 12 month(s)											
1 (yamanouchi 2005)	RCT	very serious[3]	not serious	NA[4]	serious[5]	NA	38	37	MD 0.20 (-0.23, 0.63)	MD 0.20 higher (0.23 lower to 0.63 higher)	very low
weight change Mean follow-up: 6 month(s)											
1 (shihara 2011)	RCT	very serious[3]	not serious	NA[4]	very serious[6]	NA	96	95	MD -0.20 (-3.92, 3.52)	MD 0.20 lower (3.92 lower to 3.52 higher)	very low
bmi change Mean follow-up: 9 month(s)											
2	RCT	very serious[3]	not serious	not serious	serious[7]	NA	134	132	MD 0.44 (-0.51, 1.39)	MD 0.44 higher (0.51 lower to 1.39 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. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

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

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

F.1.7.9 Pioglitazone compared to insulin

Figure 209: Clinical evidence profile: Pioglitazone v 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 Mean follow-up: 11.1 month(s)											
1 (xu 2015)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	0/136	0/138	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	very low
cardiovascular mortality Mean follow-up: 11.1 month(s)											
1 (xu 2015)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	0/136	0/142	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	very low
hypoglycaemia episodes Mean follow-up: 11.1 month(s)											
1 (xu 2015)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	5/136	18/138	RR 0.28 (0.11, 0.74)	94 fewer per 1000 (116 fewer to 34 fewer)	low
severe hypoglycaemic episodes Mean follow-up: 11.1 month(s)											
1 (xu 2015)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	0/136	0/138	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	very low
hba1c change											

Mean follow-up: 11.1 month(s)											
1 (xu 2015)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	118	114	MD 0.20 (-0.08, 0.48)	MD 0.20 higher (0.08 lower to 0.48 higher)	low
weight change Mean follow-up: 11.1 month(s)											
1 (xu 2015)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	118	114	MD -1.00 (-1.98, -0.02)	MD 1.00 lower (1.98 lower to 0.02 lower)	low
bmi change Mean follow-up: 11.1 month(s)											
1 (xu 2015)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	118	114	MD -0.40 (-0.68, -0.12)	MD 0.40 lower (0.68 lower to 0.12 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. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.

F.1.7.10 Pioglitazone compared to placebo

Table 53: Clinical evidence profile: Pioglitazone compared 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
all-cause mortality Mean follow-up: 6 month(s)											
2	RCT	serious[1]	not serious	serious[2]	very serious[3]	NA	2/764	0/162	RD 0.00 (-0.01, 0.01)	2 more per 1000	very low

										(10 fewer to 15 more)	
cardiovascular mortality Mean follow-up: 6 month(s)											
1 (chou 2012)	RCT	serious 1	not serious	NA[4]	very serious[5]	NA	1/739	0/137	PETO OR 3.27 (0.01, 721.52)	1 more per 1000 (1 fewer to 4 more)	very low
non-fatal stroke Mean follow-up: 6 month(s)											
2	RCT	serious[1] 1	not serious	serious[2]	very serious[3]	NA	2/764	0/162	RD 0.00 (-0.01, 0.01)	2 more per 1000 (10 fewer to 15 more)	very low
non-fatal myocardial infarction Mean follow-up: 6.2 month(s)											
3	RCT	serious[1]	not serious	serious[2]	very serious[6]	NA	1/923	1/216	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (15 fewer to 11 more)	very low
hospitalisation for heart failure Mean follow-up: 6 month(s)											
1 (chou 2012)	RCT	serious[1]	not serious	NA[4]	very serious[5]	NA	2/739	0/137	PETO OR 3.28 (0.07, 149.08)	3 more per 1000 (1 fewer to 6 more)	very low
hypoglycaemia episodes Mean follow-up: 6 month(s)											
2	RCT	serious[1]	not serious	serious[2]	very serious[5]	NA	7/1068	3/216	PETO OR 0.40 (0.08, 2.09)	7 fewer per 1000 (24 fewer to 9 more)	very low
hba1c change											

Mean follow-up: 6 month(s)											
5	RCT	serious[1]	not serious	not serious	not serious	NA	1314	361	MD -0.81 (-0.92, -0.70)	MD 0.81 lower (0.92 lower to 0.70 lower)	moderate
weight change Mean follow-up: 6.1 month(s)											
4	RCT	very serious[7]	not serious	very serious[8]	serious[9]	NA	691	220	MD 2.55 (1.22, 3.88)	MD 2.55 higher (1.22 higher to 3.88 higher)	very low
bmi change Mean follow-up: 6 month(s)											
1 (miyazaki 2002)	RCT	very serious[7]	not serious	NA[4]	serious[10]	NA	47	11	MD 0.77 (0.45, 1.10)	MD 0.77 higher (0.45 higher to 1.10 higher)	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 = 0.34 (0.8-0.9 = serious, <0.8 = very serious).

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 = 0.35 (0.8-0.9 = serious, <0.8 = very serious).

7. >33.3% of the studies in the meta-analysis were at high 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 one end of the defined MIDs (-0.80, 0.80)

F.1.8 Combinations

F.1.8.1 Alogliptin + metformin compared to metformin

Table 54: Clinical evidence profile: Alogliptin + metformin compared to 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: 6 month(s)											
1 (pratley 2014)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/225	0/225	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	low
cardiovascular mortality at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/225	0/225	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/225	0/225	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	low
hospitalisation for heart failure at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/225	0/225	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: 5.8 month(s)											
2	RCT	very serious[1]	not serious	not serious	very serious[3]	NA	14/378	19/381	RR 0.74 (0.38, 1.46)	13 fewer per 1000 (31 fewer to 23 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RCT	very serious 1	not serious	NA[2]	not serious	NA	0/220	0/220	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	low
hba1c change (%, lower values are better, change scores) at end of follow-up Mean follow-up: 5.8 month(s)											
2	RCT	very serious[1]	not serious	not serious	serious[4]	NA	371	372	MD -0.48 (-0.65, -0.31)	MD 0.48 lower (0.65 lower to 0.31 lower)	very low
weight change (kg, lower values are better, change scores and final values) at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	225	225	MD 0.15 (-0.40, 0.69)	MD 0.15 higher (0.40 lower to 0.69 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)

F.1.8.2 Alogliptin + metformin compared to alogliptin

Table 55: Clinical evidence profile: alogliptin + metformin compared 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
all-cause mortality **Mean follow-up: 6 month(s)**											
1 (pratley 2014)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/225	0/225	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	low
cardiovascular mortality at end of follow-up **Mean follow-up: 6 month(s)**											
1 (pratley 2014)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/225	0/225	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	low
non-fatal myocardial infarction at end of follow-up **Mean follow-up: 6 month(s)**											
1 (pratley 2014)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/225	1/225	PETO OR 0.14 (0.00, 6.82)	4 fewer per 1000 (13 fewer to 4 more)	very low
hospitalisation for heart failure at end of follow-up **Mean follow-up: 6 month(s)**											
1 (pratley 2014)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/225	0/225	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: 5.8 month(s)											
2	RCT	very serious[1]	not serious	not serious	very serious[3]	NA	14/378	10/384	RR 1.42 (0.64, 3.15)	11 more per 1000 (9 fewer to 56 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/220	0/222	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.8 month(s)											
2	RCT	very serious[1]	not serious	not serious	not serious	NA	371	370	MD -0.83 (-1.00, -0.66)	MD 0.83 lower (1.00 lower to 0.66 lower)	low
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	225	225	MD -0.93 (-1.48, -0.38)	MD 0.93 lower (1.48 lower to 0.38 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)

F.1.8.3 Alogliptin + metformin compared to placebo

Table 56: Clinical evidence profile: alogliptin + metformin v 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 (pratley 2014)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	0/225	0/109	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	0/225	0/109	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	very low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	0/225	0/109	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	very low
hospitalisation for heart failure at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	0/225	0/109	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.8 month(s)											
2	RCT	very serious[1]	not serious	not serious	serious[4]	NA	14/378	2/270	RR 4.88 (1.13, 21.14)	29 more per 1000	very low

										(1 more to 149 more)	
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	0/220	0/109	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 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)											
1 (pratley 2014)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	213	102	MD -1.26 (-1.48, -1.04)	MD 1.26 lower (1.48 lower to 1.04 lower)	low
weight change* Mean follow-up: 6 month(s)											
1 (pratley 2014)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	225	109	MD -0.00 (-0.68, 0.68)	MD 0.00 lower (0.68 lower to 0.68 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.

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

F.1.8.4 Linagliptin + metformin v placebo

Table 57: Clinical evidence profile: linagliptin + metformin v 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 (haak 2012)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/286	0/72	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 (haak 2012)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/286	0/72	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	low
hypoglycaemia episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (haak 2012)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	5/286	1/72	RR 1.26 (0.15, 10.61)	4 more per 1000 (12 fewer to 133 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (haak 2012)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/286	0/72	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	low
hba1c change (%, lower values are better, change scores and final values) at end of follow-up Mean follow-up: 6 month(s)											

1 (haak 2012)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	277	65	MD -1.50 (-1.74, -1.26)	MD 1.50 lower (1.74 lower to 1.26 lower)	low
weight change (kg, lower values are better, change scores and final values) at end of follow-up Mean follow-up: 6 month(s)											
1 (haak 2012)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	253	43	MD 0.24 (-0.64, 1.12)	MD 0.24 higher (0.64 lower to 1.12 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)

F.1.8.5 Linagliptin + metformin compared to metformin

Table 58: Clinical evidence profile: Linagliptin + metformin compared to 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: 6 month(s)											
1 (haak 2012)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/286	1/291	PETO OR 0.14 (0.00, 6.94)	3 fewer per 1000 (10 fewer to 3 more)	very low
cardiovascular mortality at end of follow-up											

Mean follow-up: 6 month(s)											
1 (haak 2012)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/286	1/291	PETO OR 0.14 (0.00, 6.94)	3 fewer per 1000 (10 fewer to 3 more)	very low
4-point mace at end of follow-up Mean follow-up: 5.5 month(s)											
1 (mu 2017)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/294	1/289	PETO OR 0.13 (0.00, 6.70)	3 fewer per 1000 (10 fewer to 3 more)	very low
hospitalisation for heart failure at end of follow-up Mean follow-up: 5.5 month(s)											
1 (mu 2017)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/294	0/289	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	low
hypoglycaemia episodes at end follow-up Mean follow-up: 5.8 month(s)											
2	RCT	very serious[1]	not serious	serious[4]	very serious[3]	NA	10/580	10/580	RR 1.00 (0.41, 2.42)	0 fewer per 1000 (10 fewer to 25 more)	very low
severe hypoglycaemic episodes at end follow-up Mean follow-up: 5.8 month(s)											
2	RCT	very serious[1]	not serious	serious[5]	very serious[6]	NA	0/580	1/580	RD -0.00 (-0.01, 0.00)	1 fewer per 1000 (7 fewer to 4 more)	very low
hba1c change (%, lower vales are better, change scores) at end of follow-up Mean follow-up: 5.8 month(s)											
2	RCT	very serious[1]	not serious	not serious	serious[7]	NA	460	556	MD -0.45 (-0.58, -0.32)	MD 0.45 lower	very low

										(0.58 lower to 0.32 lower)	
weight change (kg, lower vales are better, change scores) at end of follow-up Mean follow-up: 5.8 month(s)											
2	RCT	very serious[1]	not serious	not serious	not serious	NA	537	428	MD 0.29 (-0.11, 0.68)	MD 0.29 higher (0.11 lower to 0.68 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. Downgraded by 1 or 2 increments because of heterogeneity, unexplained by subgroup analysis

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).

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

F.1.8.6 Linagliptin + metformin compared to linagliptin

Table 59: Clinical evidence profile: linagliptin + metformin v 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: 5.8 month(s)											

2	RCT	very serious[1]	not serious	not serious	not serious	NA	0/445	0/299	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: 5.8 month(s)											
2	RCT	very serious[1]	not serious	not serious	not serious	NA	0/445	0/299	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	low
4-point mace at end of follow-up Mean follow-up: 5.5 month(s)											
1 (mu 2017)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/294	0/147	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (10 fewer to 10 more)	low
hospitalisation for heart failure at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	very serious[1]	not serious	not serious	not serious	NA	0/453	0/304	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.7 month(s)											
3	RCT	not serious	not serious	not serious	very serious[3]	NA	13/739	6/446	RR 1.42 (0.52, 3.87)	6 more per 1000 (6 fewer to 39 more)	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	0/739	0/446	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	low

hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.7 month(s)											
3	RCT	very serious[1]	not serious	not serious	not serious	NA	613	426	MD -0.92 (-1.06, -0.77)	MD 0.92 lower (1.06 lower to 0.77 lower)	low
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 5.7 month(s)											
3	RCT	very serious[1]	not serious	not serious	not serious	NA	690	409	MD -0.62 (-1.00, -0.23)	MD 0.62 lower (1.00 lower to 0.23 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)

F.1.8.7 Saxagliptin + metformin compared to metformin

Table 60: Clinical evidence profile: Saxagliptin + metformin compared to 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: 11.8 month(s)											
2	RCT	very serious[1]	not serious	serious[2]	very serious[3]	NA	3/858	5/538	RD -0.00 (-0.02, 0.01)	4 fewer per 1000 (18 fewer to 9 more)	very low

cardiovascular mortality at end of follow-up Mean follow-up: 18 month(s)											
1 (pfützner 2011a)	RCT	very serious[1]	not serious	NA[4]	very serious[5]	NA	2/643	4/328	RR 0.26 (0.05, 1.39)	9 fewer per 1000 (12 fewer to 5 more)	very low
non-fatal stroke at end of follow-up Mean follow-up: 5.5 month(s)											
1 (dou 2018)	RCT	very serious[1]	not serious	NA[4]	very serious[5]	NA	0/215	1/210	PETO OR 0.13 (0.00, 6.66)	5 fewer per 1000 (14 fewer to 5 more)	very low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 5.5 month(s)											
1 (dou 2018)	RCT	very serious[1]	not serious	NA[4]	very serious[5]	NA	0/215	1/210	PETO OR 0.13 (0.00, 6.66)	5 fewer per 1000 (14 fewer to 5 more)	very low
persistent signs of worsening kidney disease at end of follow-up Mean follow-up: 5.5 month(s)											
1 (dou 2018)	RCT	very serious[1]	not serious	NA[4]	very serious[5]	NA	0/215	1/210	PETO OR 0.13 (0.00, 6.66)	5 fewer per 1000 (14 fewer to 5 more)	very low
progression of liver disease at end of follow-up Mean follow-up: 5.5 month(s)											
1 (dou 2018)	RCT	very serious[1]	not serious	NA[4]	not serious	NA	0/215	0/210	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: 11.8 month(s)											

2	RCT	very serious[1]	not serious	not serious	very serious[5]	NA	38/858	24/538	RR 0.85 (0.51, 1.41)	7 fewer per 1000 (22 fewer to 18 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 11.8 month(s)											
2	RCT	very serious[1]	not serious	serious[2]	very serious[6]	NA	3/858	2/538	RD -0.00 (-0.01, 0.01)	1 fewer per 1000 (7 fewer to 6 more)	very low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
3	RCT	very serious[1]	not serious	very serious[7]	serious[8]	NA	592	375	MD -0.32 (-0.54, -0.09)	MD 0.32 lower (0.54 lower to 0.09 lower)	very low
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	very serious[1]	not serious	not serious	not serious	NA	231	228	MD 0.42 (-0.12, 0.96)	MD 0.42 higher (0.12 lower to 0.96 higher)	low
bmi change (kg/m2, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	very serious[1]	not serious	very serious[7]	not serious	NA	231	228	MD -0.10 (-0.65, 0.45)	MD 0.10 lower (0.65 lower to 0.45 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 = 0.48 (0.8-0.9 = serious, <0.8 = very serious).

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 = 0.03 (0.8-0.9 = serious, <0.8 = very serious).

7. I2 > 75%

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

F.1.8.8 Saxagliptin + metformin compared to saxagliptin

Table 61: Clinical evidence profile: Saxagliptin + metformin compared to 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: 11.8 month(s)											
2	RCT	very serious[1]	not serious	serious[2]	very serious[3]	NA	3/858	3/549	PETO OR 0.56 (0.11, 3.00)	2 fewer per 1000 (9 fewer to 5 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 18 month(s)											
1 (pfützner 2011a)	RCT	very serious[1]	not serious	NA[4]	very serious[3]	NA	2/643	2/335	RR 0.52 (0.07, 3.68)	3 fewer per 1000 (6 fewer to 16 more)	very low
non-fatal stroke at end of follow-up Mean follow-up: 5.5 month(s)											

1 (dou 2018)	RCT	very serious[1]	not serious	NA[4]	very serious[3]	NA	0/215	1/214	PETO OR 0.13 (0.00, 6.79)	5 fewer per 1000 (14 fewer to 4 more)	very low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 5.5 month(s)											
1 (dou 2018)	RCT	very serious[1]	not serious	NA[4]	not serious	NA	0/215	0/214	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	low
persistent signs of worsening kidney disease at end of follow-up Mean follow-up: 5.5 month(s)											
1 (dou 2018)	RCT	very serious[1]	not serious	NA[4]	not serious	NA	0/215	0/214	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	low
progression of liver disease at end of follow-up Mean follow-up: 5.5 month(s)											
1 (dou 2018)	RCT	very serious[1]	not serious	NA[4]	very serious[3]	NA	0/215	1/214	PETO OR 0.13 (0.00, 6.79)	5 fewer per 1000 (14 fewer to 4 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 11.8 month(s)											
2	RCT	very serious[1]	not serious	serious[5]	very serious[3]	NA	38/858	10/549	RR 1.26 (0.17, 9.32)	5 more per 1000 (15 fewer to 152 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 11.8 month(s)											
2	RCT	very serious[1]	not serious	serious[2]	very serious[6]	NA	3/858	0/549	RD 0.00 (-0.00, 0.01)	3 more per 1000	very low

										(3 fewer to 8 more)	
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
3	RCT	very serious[1]	not serious	very serious[7]	serious[8]	NA	592	348	MD -0.63 (-1.02, -0.23)	MD 0.63 lower (1.02 lower to 0.23 lower)	very low
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	very serious[1]	not serious	serious[9]	not serious	NA	231	234	MD -0.54 (-2.06, 0.98)	MD 0.54 lower (2.06 lower to 0.98 higher)	very low
bmi change (kg/m2, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	very serious[1]	not serious	very serious[7]	not serious	NA	231	234	MD -0.10 (-0.61, 0.41)	MD 0.10 lower (0.61 lower to 0.41 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. 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 = 0.6 (0.8-0.9 = serious, <0.8 = very serious).

7. I2 > 75%

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

9. Downgraded by 1 or 2 increments because of heterogeneity, unexplained by subgroup analysis

F.1.8.9 Sitagliptin + metformin compared to metformin

Table 62: Clinical evidence profile: Sitagliptin + metformin compared to 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 follow-up Mean follow-up: 5.5 month(s)											
2	RCT	very serious[1]	not serious	not serious	not serious	NA	0/619	0/614	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (4 fewer to 4 more)	low
cardiovascular mortality at end follow-up Mean follow-up: 5.5 month(s)											
2	RCT	very serious[1]	not serious	not serious	not serious	NA	0/619	0/614	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (4 fewer to 4 more)	low
diabetic ketoacidosis at end follow-up Mean follow-up: 5.5 month(s)											
1 (goldstein 2007)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/372	0/364	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (5 fewer to 5 more)	low
hypoglycaemia episodes at end follow-up Mean follow-up: 5.5 month(s)											
2	RCT	serious[3]	not serious	not serious	not serious	NA	35/619	15/614	RR 2.35 (1.30, 4.22)	33 more per 1000 (7 more to 79 more)	moderate

severe hypoglycaemic episodes at end follow-up Mean follow-up: 5.5 month(s)											
1 (ji 2016a)	RCT	serious[3]	not serious	NA[2]	not serious	NA	0/247	0/250	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	moderate
hba1c change (%, lower values are better, change scores and final values) at end follow-up Mean follow-up: 5.5 month(s)											
3	RCT	very serious[1]	not serious	very serious[4]	serious[5]	NA	613	605	MD -0.76 (-1.22, -0.30)	MD 0.76 lower (1.22 lower to 0.30 lower)	very low
weight change (kg, lower values are better, change scores) at end follow-up Mean follow-up: 5.5 month(s)											
1 (ji 2016a)	RCT	serious[3]	not serious	NA[2]	not serious	NA	247	250	MD 1.15 (0.40, 1.90)	MD 1.15 higher (0.40 higher to 1.90 higher)	moderate
bmi change (kg/m2, lower values are better, final values) at end follow-up Mean follow-up: 5.5 month(s)											
1 (wang 2022)	RCT	very serious[1]	not serious	NA[2]	very serious[6]	NA	20	17	MD -0.22 (-2.36, 1.92)	MD 0.22 lower (2.36 lower to 1.92 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. >33.3% of the studies in the meta-analysis were at moderate risk of bias

4. I2 > 75%

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

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

F.1.8.10 Sitagliptin + metformin compared to sitagliptin

Table 63: Clinical evidence profile: Sitagliptin + metformin compared to 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)											
2	RCT	serious[1]	not serious	not serious	not serious	NA	0/619	0/299	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	moderate
cardiovascular mortality at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	serious[1]	not serious	not serious	not serious	NA	0/619	0/299	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	moderate
diabetic ketoacidosis at end of follow-up Mean follow-up: 5.5 month(s)											
1 (goldstein 2007)	RCT	serious[1]	not serious	NA[2]	not serious	NA	0/372	0/179	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	moderate
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	serious[1]	not serious	not serious	serious[3]	NA	35/619	6/299	RR 2.83 (1.21, 6.60)	37 more per 1000	low

										(4 more to 112 more)	
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)											
1 (ji 2016a)	RCT	serious[1]	not serious	NA[2]	not serious	NA	0/247	0/120	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (13 fewer to 13 more)	moderate
hba1c change (%, lower values are better, change scores and final value) at end of follow-up Mean follow-up: 5.5 month(s)											
3	RCT	serious[1]	not serious	very serious[4]	serious[5]	NA	613	305	MD -0.59 (-1.12, -0.07)	MD 0.59 lower (1.12 lower to 0.07 lower)	very low
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (ji 2016a)	RCT	serious[1]	not serious	NA[2]	not serious	NA	247	120	MD -0.40 (-1.31, 0.51)	MD 0.40 lower (1.31 lower to 0.51 higher)	moderate
bmi change (kg/m2, lower values are better, final value) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (wang 2022)	RCT	very serious[6]	not serious	NA[2]	very serious[7]	NA	20	17	MD 1.14 (-0.81, 3.09)	MD 1.14 higher (0.81 lower to 3.09 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 (0.80, 1.25)

4. I2 > 75%

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

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

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

F.1.8.11 Sitagliptin + metformin compared to glimepiride

Table 64: Clinical evidence profile: Sitagliptin + metformin compared 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
all-cause mortality at end of follow-up Mean follow-up: 7 month(s)											
1 (kim 2017)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	0/146	0/144	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (13 fewer to 13 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 7 month(s)											
1 (kim 2017)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	8/146	29/144	RR 0.27 (0.13, 0.57)	147 fewer per 1000 (175 fewer to 86 fewer)	low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 7 month(s)											
1 (kim 2017)	RCT	very serious[1]	not serious	NA[2]	very serious[4]	NA	0/146	1/144	PETO OR 0.13 (0.00, 6.73)	7 fewer per 1000	very low

										(21 fewer to 7 more)	
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 7 month(s)											
1 (kim 2017)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	146	144	MD -0.78 (-0.96, -0.60)	MD 0.78 lower (0.96 lower to 0.60 lower)	low
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 7 month(s)											
1 (kim 2017)	RCT	very serious[1]	not serious	NA[2]	serious[5]	NA	146	144	MD -1.72 (-2.74, -0.70)	MD 1.72 lower (2.74 lower to 0.70 lower)	very low

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

2. Only one study so no inconsistency

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

4. 95% confidence intervals cross 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)

F.1.8.12 Sitagliptin + metformin compared to pioglitazone

Table 65: Clinical evidence profile: Sitagliptin + metformin compared to 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: 7.4 month(s)											
1 (wainstein 2012)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	22/261	11/256	RR 1.96 (0.97, 3.96)	41 more per 1000 (1 fewer to 127 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 7.4 month(s)											
1 (wainstein 2012)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/261	0/261	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 7.4 month(s)											
1 (wainstein 2012)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	253	246	MD -0.50 (-0.68, -0.32)	MD 0.50 lower (0.68 lower to 0.32 lower)	very low

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

2. Only one study so no inconsistency

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

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

F.1.8.13 Sitagliptin + metformin compared to placebo

Table 66: Clinical evidence profile: Sitagliptin + metformin compared 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
all-cause mortality at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	serious[1]	not serious	serious[2]	very serious[3]	NA	0/619	1/302	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (12 fewer to 7 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	serious[1]	not serious	serious[2]	very serious[3]	NA	0/619	1/302	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (12 fewer to 7 more)	very low
diabetic ketoacidosis at end of follow-up Mean follow-up: 5.5 month(s)											
1 (goldstein 2007)	RCT	very serious[4]	not serious	NA[5]	very serious[6]	NA	0/372	1/176	PETO OR 0.04 (0.00, 2.96)	6 fewer per 1000 (17 fewer to 5 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	serious[1]	not serious	not serious	not serious	NA	35/619	5/302	RR 3.52 (1.40, 8.84)	42 more per 1000 (7 more to 130 more)	moderate
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)											

1 (ji 2016a)	RCT	serious[1]	not serious	NA[5]	not serious	NA	0/247	0/126	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	moderate
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	very serious[4]	not serious	serious[7]	not serious	NA	562	292	MD -0.97 (-1.31, -0.64)	MD 0.97 lower (1.31 lower to 0.64 lower)	very low
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (ji 2016a)	RCT	serious[1]	not serious	NA[5]	not serious	NA	247	124	MD 1.40 (0.46, 2.34)	MD 1.40 higher (0.46 higher to 2.34 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 = 0.42 (0.8-0.9 = serious, <0.8 = very serious).

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

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%

F.1.8.14 Vildagliptin + metformin compared to metformin

Table 67: Clinical evidence profile: Vildagliptin + metformin compared to 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: 6 month(s)											
1 (bosi 2009)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	1/585	0/294	PETO OR 4.49 (0.07, 286.22)	2 more per 1000 (2 fewer to 5 more)	very low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 6 month(s)											
1 (bosi 2009)	RCT	serious[1]	not serious	NA[2]	serious[4]	NA	0/585	2/294	PETO OR 0.05 (0.00, 0.95)	7 fewer per 1000 (16 fewer to 3 more)	low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (bosi 2009)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	0/585	1/294	PETO OR 0.05 (0.00, 3.20)	3 fewer per 1000 (10 fewer to 3 more)	very low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)											
2	RCT	serious[1]	not serious	not serious	not serious	NA	617	326	MD -0.32 (-0.45, -0.18)	MD 0.32 lower (0.45 lower to 0.18 lower)	moderate
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)											

2	RCT	serious[1]	not serious	not serious	not serious	NA	617	326	MD 0.44 (-0.07, 0.94)	MD 0.44 higher (0.07 lower to 0.94 higher)	moderate
bmi change (kg/m2, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)											
1 (zougrafou 2015)	RCT	very serious[5]	not serious	NA[2]	not serious	NA	32	32	MD 0.20 (-0.35, 0.75)	MD 0.20 higher (0.35 lower to 0.75 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 (0.80, 1.25)

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

F.1.8.15 Vildagliptin + metformin compared to vildagliptin

Table 68: Clinical evidence profile: Vildagliptin + metformin compared to 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 follow-up Mean follow-up: 6 month(s)											
1 (bosi 2009)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	1/585	0/300	PETO OR 4.54 (0.07, 285.24)	2 more per 1000 (2 fewer to 5 more)	very low

non-fatal myocardial infarction at end follow-up Mean follow-up: 6 month(s)											
1 (bosi 2009)	RCT	serious[1]	not serious	NA[2]	not serious	NA	0/585	0/300	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (5 fewer to 5 more)	moderate
severe hypoglycaemic episodes at end follow-up Mean follow-up: 6 month(s)											
1 (bosi 2009)	RCT	serious[1]	not serious	NA[2]	not serious	NA	0/585	0/300	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (5 fewer to 5 more)	moderate
hba1c change (%, lower values are better, change scores) at end follow-up Mean follow-up: 6 month(s)											
1 (bosi 2009)	RCT	serious[1]	not serious	NA[2]	serious[4]	NA	585	300	MD -0.60 (-0.74, -0.46)	MD 0.60 lower (0.74 lower to 0.46 lower)	low
weight change (kg, lower values are better, change scores) at end follow-up Mean follow-up: 6 month(s)											
1 (bosi 2009)	RCT	serious[1]	not serious	NA[2]	not serious	NA	585	300	MD -0.59 (-1.12, -0.06)	MD 0.59 lower (1.12 lower to 0.06 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)

F.1.8.16 Canagliflozin + metformin compared to metformin

Table 69: Clinical evidence profile: Canagliflozin + metformin compared to 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 (rosenstock 2016)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/474	1/237	PETO OR 0.05 (0.00, 3.18)	4 fewer per 1000 (12 fewer to 4 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/474	1/237	PETO OR 0.05 (0.00, 3.18)	4 fewer per 1000 (12 fewer to 4 more)	very low
non-fatal stroke at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	1/474	0/237	PETO OR 4.48 (0.07, 286.49)	2 more per 1000 (2 fewer to 6 more)	very low
unstable angina at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	1/474	0/237	PETO OR 4.48 (0.07, 286.49)	2 more per 1000 (2 fewer to 6 more)	very low
persistent signs of worsening kidney disease at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	4/474	0/237	PETO OR 4.51 (0.56, 36.22)	8 more per 1000 (0 more to 17 more)	very low

cardiac arrhythmia at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/474	0/237	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	low
diabetic ketoacidosis at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/474	0/237	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	23/474	11/237	RR 1.05 (0.52, 2.11)	2 more per 1000 (22 fewer to 51 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/474	1/237	PETO OR 0.05 (0.00, 3.18)	4 fewer per 1000 (12 fewer to 4 more)	very low
hba1c change (%, lower values are better, change scores and final values) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	471	230	MD -0.47 (-0.64, -0.30)	MD 0.47 lower (0.64 lower to 0.30 lower)	very low
weight change (kg, lower values are better, change scores and final values) at end of follow-up Mean follow-up: 5.5 month(s)											

1 (rosenstock 2016)	RCT	very serious[1]	not serious	NA[2]	serious[5]	NA	473	237	MD -1.75 (-2.47, -1.03)	MD 1.75 lower (2.47 lower to 1.03 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)

F.1.8.17 Canagliflozin + metformin compared to canagliflozin

Table 70: Clinical evidence profile: Canagliflozin + metformin v 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: 5.5 month(s)											
1 (rosenstock 2016)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/474	0/475	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 (rosenstock 2016)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/474	0/475	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 (rosenstock 2016)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	1/474	1/475	RR 1.00 (0.06, 15.97)	0 more per 1000 (2 fewer to 32 more)	very low
unstable angina at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	1/474	0/475	PETO OR 7.40 (0.15, 373.17)	2 more per 1000 (2 fewer to 6 more)	very low
cardiac arrhythmia at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/474	1/475	PETO OR 0.14 (0.00, 6.83)	2 fewer per 1000 (6 fewer to 2 more)	very low
diabetic ketoacidosis at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/474	1/475	PETO OR 0.14 (0.00, 6.83)	2 fewer per 1000 (6 fewer to 2 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	23/474	16/475	RR 1.44 (0.77, 2.69)	15 more per 1000 (8 fewer to 57 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/474	0/475	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (4 fewer to 4 more)	low

hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	471	464	MD -0.37 (-0.51, -0.23)	MD 0.37 lower (0.51 lower to 0.23 lower)	very low
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	473	472	MD -0.40 (-0.99, 0.19)	MD 0.40 lower (0.99 lower to 0.19 higher)	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 (0.80, 1.25)

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

F.1.8.18 Dapagliflozin + metformin compared to dapagliflozin

Table 71: Clinical evidence profile: dapagliflozin + metformin compared 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
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	0/405	1/422	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[2]	NA	0/405	1/422	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (10 fewer to 6 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	not serious	not serious	not serious	not serious	NA	12/405	2/422	RR 5.20 (1.35, 20.07)	20 more per 1000 (2 more to 90 more)	high
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	not serious	not serious	not serious	not serious	NA	0/405	0/422	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: 5.5 month(s)											
2	RCT	not serious	not serious	very serious[3]	serious[4]	NA	387	412	MD -0.69 (-1.01, -0.36)	MD 0.69 lower (1.01 lower to 0.36 lower)	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	401	422	MD -0.32 (-0.79, 0.14)	MD 0.32 lower (0.79 lower to 0.14 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 = 0.29 (0.8-0.9 = serious, <0.8 = very serious).

3. I2 > 75%

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

F.1.8.19 Dapagliflozin + metformin compared to metformin

Table 72: Clinical evidence profile: dapagliflozin + metformin compared to 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)											
2	RCT	not serious	not serious	serious[1]	very serious[2]	NA	0/405	1/409	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (11 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[2]	NA	0/405	1/409	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (11 fewer to 6 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)											

3	RCT	not serious	not serious	not serious	serious[3]	NA	14/480	7/484	RR 1.93 (0.81, 4.60)	13 more per 1000 (3 fewer to 52 more)	moderate
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	not serious	not serious	not serious	not serious	NA	0/405	0/409	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 and final values) at end of follow-up Mean follow-up: 5.5 month(s)											
3	RCT	not serious	not serious	very serious[4]	serious[5]	NA	462	473	MD -0.82 (-1.26, -0.39)	MD 0.82 lower (1.26 lower to 0.39 lower)	very low
weight change (kg, lower values are better, change scores and final values) at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	not serious	not serious	not serious	not serious	NA	401	408	MD -1.68 (-2.15, -1.21)	MD 1.68 lower (2.15 lower to 1.21 lower)	high
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)											
1 (zhou 2022)	RCT	very serious[6]	not serious	NA 7	serious[8]	NA	75	75	MD -0.91 (-1.27, -0.55)	MD 0.91 lower (1.27 lower to 0.55 lower)	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 = 0.29 (0.8-0.9 = serious, <0.8 = very serious).

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

4. I2 > 75%

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

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

7. Only one study so no inconsistency

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

F.1.8.20 Empagliflozin + metformin compared to metformin

Table 73: Clinical evidence profile: empagliflozin + metformin compared to 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 end at of follow-up Mean follow-up: 5.5 month(s)											
1 (hadjadj 2016)	RCT	not serious	not serious	NA[1]	not serious	NA	0/680	0/341	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (5 fewer to 5 more)	high
cardiovascular mortality at end follow-up Mean follow-up: 5.5 month(s)											
1 (hadjadj 2016)	RCT	not serious	not serious	NA[1]	not serious	NA	0/680	0/341	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (5 fewer to 5 more)	high

hypoglycaemia episodes at end follow-up Mean follow-up: 5.5 month(s)											
1 (hadjadj 2016)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	7/680	2/341	RR 1.76 (0.37, 8.40)	4 more per 1000 (4 fewer to 43 more)	low
hba1c change (%, lower vales are better, change scores) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (hadjadj 2016)	RCT	not serious	not serious	NA[1]	serious[3]	NA	569	269	MD -0.54 (-0.69, -0.39)	MD 0.54 lower (0.69 lower to 0.39 lower)	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 (-0.50, 0.50)

F.1.8.21 Empagliflozin + metformin compared to empagliflozin

Table 74: Clinical evidence profile: empagliflozin + metformin compared to 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: 5.5 month(s)											
1 (hadjadj 2016)	RCT	not serious	not serious	NA[1]	not serious	NA	0/680	0/339	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (5 fewer to 5 more)	high
cardiovascular mortality at end of follow-up											

Mean follow-up: 5.5 month(s)											
1 (hadjadj 2016)	RCT	not serious	not serious	NA[1]	not serious	NA	0/680	0/339	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (5 fewer to 5 more)	high
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)											
1 (hadjadj 2016)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	7/680	2/339	RR 1.74 (0.36, 8.35)	4 more per 1000 (4 fewer to 43 more)	low
hba1c change (%, lower values are better, change scores) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (hadjadj 2016)	RCT	not serious	not serious	NA[1]	not serious	NA	569	285	MD -0.69 (-0.83, -0.55)	MD 0.69 lower (0.83 lower to 0.55 lower)	high

1. Only one study so no inconsistency

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

F.1.8.22 Gliclazide + saxagliptin compared to saxagliptin + metformin

Table 75: Clinical evidence profile: Gliclazide + saxagliptin compared to saxagliptin + 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 (chen 2022)	RCT	not serious	not serious	NA[1]	not serious	NA	0/216	0/216	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	high
cardiovascular mortality at end of follow-up Mean follow-up: 5.5 month(s)											
1 (chen 2022)	RCT	not serious	not serious	NA[1]	not serious	NA	0/216	0/216	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: 5.5 month(s)											
1 (chen 2022)	RCT	serious[2]	not serious	NA[1]	serious[3]	NA	23/216	11/216	RR 2.09 (1.05, 4.18)	56 more per 1000 (2 more to 162 more)	low
hba1c change (%, lower values are better, change scores) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (chen 2022)	RCT	not serious	not serious	NA[1]	not serious	NA	216	216	MD 0.10 (-0.11, 0.31)	MD 0.10 higher (0.11 lower to 0.31 higher)	high
bmi change (kg/m2, lower values are better, change scores) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (chen 2022)	RCT	not serious	not serious	NA[1]	very serious[4]	NA	216	216	MD 1.00 (-0.92, 2.92)	MD 1.00 higher (0.92 lower to 2.92 higher)	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. 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, 0.80)

F.1.8.23 Glimepiride + metformin compared to canagliflozin + metformin

Table 76: Clinical evidence profile: glimepiride + metformin compared to canagliflozin + metformin

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (zhou 2021)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	13	12	MD 1.57 (0.80, 2.34)	MD 1.57 higher (0.80 higher to 2.34 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

F.1.8.24 Empagliflozin + linagliptin compared to empagliflozin

Table 77: Clinical evidence profile: empagliflozin + linagliptin compared to 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											
2	RCT	very serious[1]	not serious	not serious	not serious	NA	0/223	0/224	RD 0.00 (-0.01, 0.01)	0 fewer per 1000	low

										(12 fewer to 12 more)	
non-fatal myocardial infarction at end of follow-up											
2	RCT	very serious[1]	not serious	serious[2]	very serious[3]	NA	0/223	1/224	RD -0.00 (-0.02, 0.01)	4 fewer per 1000 (20 fewer to 11 more)	very low
severe hypoglycaemic episodes at end of follow-up											
2	RCT	very serious[1]	not serious	serious[2]	very serious[3]	NA	0/223	1/224	RD -0.00 (-0.02, 0.01)	4 fewer per 1000 (20 fewer to 11 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow-up Mean follow-up: 8.8 month(s)											
2	RCT	very serious[1]	not serious	very serious[4]	serious[5]	NA	223	224	MD -0.70 (-0.93, -0.46)	MD 0.70 lower (0.93 lower to 0.46 lower)	very low

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

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

3. 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).

4. I2 > 75%

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

F.1.8.25 Empagliflozin + linagliptin compared to 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: 12 month(s)											
1 (lewin 2015)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	1/272	0/135	PETO OR 4.47 (0.07, 286.91)	4 more per 1000 (4 fewer to 11 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)											
1 (lewin 2015)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	1/272	0/135	PETO OR 4.47 (0.07, 286.91)	4 more per 1000 (4 fewer to 11 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 12 month(s)											
1 (lewin 2015)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/272	1/135	RR 0.17 (0.01, 4.05)	6 fewer per 1000 (7 fewer to 23 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											
1 (lewin 2015)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/272	0/135	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (11 fewer to 11 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											

1 (lewin 2015)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	245	112	MD -0.48 (-0.64, -0.31)	MD 0.48 lower (0.64 lower to 0.31 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)

F.1.8.26 Glimepiride + metformin compared to metformin

Table 78: Clinical evidence profile: glimepiride + metformin compared to 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: 15 month(s)											
1 (derosa 2009)	RCT	not serious	serious[1]	NA[2]	very serious[3]	NA	3/66	0/67	PETO OR 7.74 (0.79, 75.70)	46 more per 1000 (5 fewer to 96 more)	very low
hba1c change (%, lower values are better, final value) at end of follow-up Mean follow-up: 15 month(s)											
1 (derosa 2009)	RCT	not serious	not serious	NA[2]	not serious	NA	66	67	MD -0.80 (-1.04, -0.56)	MD 0.80 lower (1.04 lower to 0.56 lower)	high

bmi change (kg/m2, lower values are better, final value) at end of follow-up Mean follow-up: 15 month(s)											
1 (derosa 2009)	RCT	not serious	not serious	NA[2]	serious[4]	NA	66	67	MD 0.30 (-0.41, 1.01)	MD 0.30 higher (0.41 lower to 1.01 higher)	moderate

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

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, 0.80)

F.1.8.27 Glimepiride + metformin compared to pioglitazone

Table 79: Clinical evidence profile: glimepiride + metformin compared to 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 follow-up Mean follow-up: 15 month(s)											
1 (derosa 2009)	RCT	not serious	serious[1]	NA[2]	serious[3]	NA	3/66	0/69	PETO OR 7.98 (0.82, 78.04)	46 more per 1000 (5 fewer to 96 more)	low
hba1c change final value at follow-up (%, lower values are better, change scores) Mean follow-up: 15 month(s)											
1 (derosa 2009)	RCT	not serious	not serious	NA[2]	serious[4]	NA	66	69	MD -0.40 (-0.59, -0.21)	MD 0.40 lower (0.59 lower to 0.21 lower)	moderate

bmi change (kg/m2, final values) at end of follow-up Mean follow-up: 15 month(s)											
1 (derosa 2009)	RCT	not serious	not serious	NA[2]	not serious	NA	66	69	MD 1.70 (1.10, 2.30)	MD 1.70 higher (1.10 higher to 2.30 higher)	high

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

2. Only one study so no inconsistency

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

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

F.1.8.28 Pioglitazone + metformin compared to metformin

Table 80: Clinical evidence profile: Pioglitazone + metformin compared to 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 (perez 2009)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/201	0/209	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (10 fewer to 10 more)	low
cardiovascular mortality at end of follow-up Mean follow-up: 5.5 month(s)											
1 (perez 2009)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/201	0/209	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (10 fewer to 10 more)	low

non-fatal myocardial infarction at end of follow-up Mean follow-up: 5.5 month(s)											
1 (perez 2009)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/201	0/209	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (10 fewer to 10 more)	low
hypoglycaemia episodes at end of follow-up Mean follow-up: 10.2 month(s)											
2	RCT	very serious[1]	serious[3]	not serious	very serious[4]	NA	4/270	3/276	RR 1.31 (0.32, 5.29)	3 more per 1000 (7 fewer to 47 more)	very low
hba1c change and final (%, lower values are better, change scores and final values) at end of follow-up Mean follow-up: 10.2 month(s)											
2	RCT	not serious	not serious	very serious[5]	not serious	NA	257	260	MD -1.13 (-1.68, -0.59)	MD 1.13 lower (1.68 lower to 0.59 lower)	low
bmi change final value (kg/m2, lower values are better, change scores) at end of follow-up Mean follow-up: 15 month(s)											
1 (derosa 2009)	RCT	not serious	not serious	NA[2]	serious[6]	NA	69	67	MD -1.20 (-1.77, -0.63)	MD 1.20 lower (1.77 lower to 0.63 lower)	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. 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. I2 > 75%

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

F.1.8.29 Pioglitazone + metformin compared to pioglitazone

Table 81: Clinical evidence profile: Pioglitazone + metformin compared to 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: 5.5 month(s)											
1 (perez 2009)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/201	0/190	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (10 fewer to 10 more)	low
cardiovascular mortality at end of follow-up Mean follow-up: 5.5 month(s)											
1 (perez 2009)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/201	0/190	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (10 fewer to 10 more)	low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 5.5 month(s)											
1 (perez 2009)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/201	1/190	PETO OR 0.13 (0.00, 6.45)	5 fewer per 1000 (16 fewer to 5 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 10.2 month(s)											
2	RCT	very serious[1]	not serious	not serious	very serious[3]	NA	4/270	1/259	RR 2.91 (0.46, 18.19)	7 more per 1000 (2 fewer to 66 more)	very low

hba1c change (%, lower values are better, change scores and final values) at end of follow-up Mean follow-up: 10.2 month(s)											
2	RCT	not serious	not serious	not serious	not serious	NA	257	231	MD -0.97 (-1.13, -0.81)	MD 0.97 lower (1.13 lower to 0.81 lower)	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)

F.1.8.30 Pioglitazone + metformin compared to glimepiride + metformin

Table 82: Clinical evidence profile: Pioglitazone + metformin compared to glimepiride + 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: 15 month(s)											
1 (derosa 2009)	RCT	not serious	serious[1]	NA[2]	very serious[3]	NA	2/69	3/66	RR 0.64 (0.11, 3.70)	16 fewer per 1000 (40 fewer to 123 more)	very low
hba1c change final value (%, lower values are better) at end of follow-up Mean follow-up: 15 month(s)											
1 (derosa 2009)	RCT	not serious	not serious	NA[2]	serious[4]	NA	69	66	MD -0.60 (-0.72, -0.48)	MD 0.60 lower	moderate

										(0.72 lower to 0.48 lower)	
bmi change final value (kg/m2, lower values are better) at end of follow-up Mean follow-up: 15 month(s)											
1 (derosa 2009)	RCT	not serious	not serious	NA[2]	not serious	NA	69	66	MD -1.50 (-2.11, -0.89)	MD 1.50 lower (2.11 lower to 0.89 lower)	high

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

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)

F.1.8.31 Pioglitazone + alogliptin compared to alogliptin

Table 83: Clinical evidence profile: Pioglitazone + alogliptin v alogliptin

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
hba1c change (%, lower values are better, final values) at the end of follow-up Mean follow-up: 6 month(s)											
1 (rosenstock 2010)	RCT	serious[1]	not serious	NA[2]	serious[3]	NA	327	164	MD -0.68 (-0.88, -0.48)	MD 0.68 lower (0.88 lower to 0.48 lower)	low
weight change (kg, lower values are better, final values) at the end of follow-up											

Mean follow-up: 6 month(s)											
1 (rosenstock 2010)	RCT	serious[1]	not serious	NA[2]	not serious	NA	327	164	MD 3.12 (2.42, 3.82)	MD 3.12 higher (2.42 higher to 3.82 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 one end of the defined MIDs (-0.50, 0.50)

F.1.8.32 Pioglitazone + alogliptin compared to pioglitazone

Table 84: Clinical evidence profile: Pioglitazone + alogliptin compared to 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 the end of follow-up Mean follow-up: 6 month(s)											
1 (rosenstock 2010)	RCT	serious[1]	not serious	NA[2]	serious[3]	NA	327	163	MD -0.49 (-0.69, -0.29)	MD 0.49 lower (0.69 lower to 0.29 lower)	low
weight change (kg, lower values are better, final values) at the end of follow-up Mean follow-up: 6 month(s)											
1 (rosenstock 2010)	RCT	serious[1]	not serious	NA[2]	not serious	NA	327	163	MD 0.64 (-0.08, 1.36)	MD 0.64 higher (0.08 lower to 1.36 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 one end of the defined MIDs (-0.50, 0.50)

F.1.8.33 Pioglitazone + linagliptin compared to linagliptin

Table 85: Clinical evidence profile: Pioglitazone + linagliptin compared to Linagliptin

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
4-point MACE at end of follow up **Mean follow-up: 6.9 month(s)**											
1 (nauck 2016)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	2/392	2/135	RR 0.34 (0.05, 2.42)	10 fewer per 1000 (14 fewer to 21 more)	very low
hypoglycaemia episodes at end of follow-up **Mean follow-up: 6.9 month(s)**											
1 (nauck 2016)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	4/392	0/135	PETO OR 3.87 (0.41, 36.73)	10 more per 1000 (0 more to 20 more)	very low
severe hypoglycaemic episodes at end of follow-up											

Mean follow-up: 6.9 month(s)											
1 (nauck 2016)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	1/392	0/135	PETO OR 3.84 (0.04, 341.86)	3 more per 1000 (2 fewer to 8 more)	very low
hba1c change (%, lower values are better, change score) at end of follow-up **Mean follow-up: 6.9 month(s)**											
1 (nauck 2016)	RCT	serious[1]	not serious	NA[2]	serious[4]	NA	371	130	MD -0.67 (-0.86, -0.48)	MD 0.67 lower (0.86 lower to 0.48 lower)	low
weight change (kg, lower values are better, change score) at end of follow-up **Mean follow-up: 6.9 month(s)**											
1 (nauck 2016)	RCT	serious[1]	not serious	NA[2]	serious[5]	NA	272	81	MD 1.63 (0.10, 3.16)	MD 1.63 higher (0.10 higher to 3.16 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)

F.1.8.34 Pioglitazone + linagliptin compared with pioglitazone

Table 86: Clinical evidence profile: Pioglitazone + linagliptin compared to Pioglitazone

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
4-point mace at end of follow up Mean follow-up: 6.9 month(s)											
1 (nauck 2016)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	2/392	2/409	RR 1.04 (0.15, 7.37)	0 more per 1000 (4 fewer to 31 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 6.9 month(s)											
1 (nauck 2016)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	4/392	5/409	RR 0.83 (0.23, 3.09)	2 fewer per 1000 (9 fewer to 25 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 6.9 month(s)											
1 (nauck 2016)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	1/392	0/409	PETO OR 7.72 (0.15, 389.23)	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: 6.9 month(s)											
1 (nauck 2016)	RCT	serious[1]	not serious	NA[2]	not serious	NA	392	409	MD -0.32 (-0.45, -0.19)	MD 0.32 lower (0.45 lower to 0.19 lower)	moderate

weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 6.9 month(s)											
1 (nauck 2016)	RCT	serious[1]	not serious	NA[2]	not serious	NA	272	258	MD -1.21 (-2.26, -0.16)	MD 1.21 lower (2.26 lower to 0.16 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)

F.1.8.35 Pioglitazone + sitagliptin compared to pioglitazone

Table 87: Clinical evidence profile: Pioglitazone + sitagliptin compared to 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: 12.5 month(s)											
1 (yoon 2012)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	1/164	0/153	PETO OR 6.91 (0.14, 349.05)	6 more per 1000 (6 fewer to 18 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 12.5 month(s)											
1 (yoon 2012)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	1/164	0/153	PETO OR 6.91 (0.14, 349.05)	6 more per 1000 (6 fewer to 18 more)	very low

hypoglycaemia episodes at end of follow-up Mean follow-up: 12.5 month(s)											
1 (yoon 2012)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	4/164	0/153	PETO OR 7.04 (0.98, 50.50)	24 more per 1000 (1 more to 48 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 12.5 month(s)											
1 (yoon 2012)	RCT	very serious[1]	not serious	NA[2]	serious[5]	NA	0/164	0/153	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	very low
hba1c change (%, lower values are better) at end of follow-up Mean follow-up: 12.5 month(s)											
1 (yoon 2012)	RCT	very serious[1]	not serious	NA[2]	serious[6]	NA	161	149	MD -0.50 (-0.71, -0.29)	MD 0.50 lower (0.71 lower to 0.29 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 12.5 month(s)											
1 (yoon 2012)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	164	153	MD 0.70 (-0.74, 2.14)	MD 0.70 higher (0.74 lower to 2.14 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)

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)

F.1.8.36 Pioglitazone + vildagliptin compared to pioglitazone

Table 88: Clinical evidence profile: Pioglitazone + sitagliptin compared to 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 the end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2007a)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	1/292	0/161	PETO OR 4.72 (0.08, 283.23)	3 more per 1000 (3 fewer to 10 more)	very low
hba1c change (%, lower values are better, change values) at the end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2007a)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	285	157	MD -0.40 (-0.64, -0.16)	MD 0.40 lower (0.64 lower to 0.16 lower)	very low
weight change (%, lower values are better, change values) at the end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2007a)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	285	157	MD 0.26 (-0.46, 0.98)	MD 0.26 higher (0.46 lower to 0.98 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)

F.1.8.37 Pioglitazone + vildagliptin compared to vildagliptin

Table 89: Clinical evidence profile: Pioglitazone + vildagliptin compared to 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 end follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2007a)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	1/292	1/153	PETO OR 0.50 (0.03, 9.27)	3 fewer per 1000 (18 fewer to 11 more)	very low
hba1c change (%, lower values are better, change scores) at end follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2007a)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	285	150	MD -0.70 (-0.94, -0.46)	MD 0.70 lower (0.94 lower to 0.46 lower)	very low
weight change (kg, lower values are better, change scores) at end follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2007a)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	285	150	MD 1.56 (0.84, 2.28)	MD 1.56 higher (0.84 higher to 2.28 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)

F.1.8.38 Saxagliptin + metformin compared to metformin

Table 90: Clinical evidence profile: Saxagliptin + metformin v metformin

persistent signs of worsening kidney disease at end of follow-up Mean follow-up: 5.5 month(s)											
1 (dou 2018)	RCT	very serious[1]	not serious	NA[4]	very serious[5]	NA	0/215	1/210	PETO OR 0.13 (0.00, 6.66)	5 fewer per 1000 (14 fewer to 5 more)	very low
progression of liver disease at end of follow-up Mean follow-up: 5.5 month(s)											
1 (dou 2018)	RCT	very serious[1]	not serious	NA[4]	not serious	NA	0/215	0/210	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: 11.8 month(s)											
2	RCT	very serious[1]	not serious	not serious	very serious[5]	NA	38/858	24/538	RR 0.85 (0.51, 1.41)	7 fewer per 1000 (22 fewer to 18 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 11.8 month(s)											
2	RCT	very serious[1]	not serious	serious[2]	very serious[6]	NA	3/858	2/538	RD -0.00 (-0.01, 0.01)	1 fewer per 1000 (7 fewer to 6 more)	very low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											

3	RCT	very serious[1]	not serious	very serious[7]	serious[8]	NA	592	375	MD -0.32 (-0.54, -0.09)	MD 0.32 lower (0.54 lower to 0.09 lower)	very low
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	very serious[1]	not serious	not serious	not serious	NA	231	228	MD 0.42 (-0.12, 0.96)	MD 0.42 higher (0.12 lower to 0.96 higher)	low
bmi change (kg/m2, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	very serious[1]	not serious	very serious[7]	not serious	NA	231	228	MD -0.10 (-0.65, 0.45)	MD 0.10 lower (0.65 lower to 0.45 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 = 0.48 (0.8-0.9 = serious, <0.8 = very serious).

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 = 0.03 (0.8-0.9 = serious, <0.8 = very serious).

7. I2 > 75%

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

F.1.9 Saxagliptin + metformin compared to saxagliptin

Table 91: Clinical evidence profile: Saxagliptin + metformin compared to 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: 11.8 month(s)											
2	RCT	very serious[1]	not serious	serious[2]	very serious[3]	NA	3/858	3/549	PETO OR 0.56 (0.11, 3.00)	2 fewer per 1000 (9 fewer to 5 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 18 month(s)											
1 (pfützner 2011a)	RCT	very serious[1]	not serious	NA[4]	very serious[3]	NA	2/643	2/335	RR 0.52 (0.07, 3.68)	3 fewer per 1000 (6 fewer to 16 more)	very low
non-fatal stroke at end of follow-up Mean follow-up: 5.5 month(s)											
1 (dou 2018)	RCT	very serious[1]	not serious	NA[4]	very serious[3]	NA	0/215	1/214	PETO OR 0.13 (0.00, 6.79)	5 fewer per 1000 (14 fewer to 4 more)	very low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 5.5 month(s)											
1 (dou 2018)	RCT	very serious[1]	not serious	NA[4]	not serious	NA	0/215	0/214	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	low
persistent signs of worsening kidney disease at end of follow-up Mean follow-up: 5.5 month(s)											

1 (dou 2018)	RCT	very serious[1]	not serious	NA[4]	not serious	NA	0/215	0/214	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	low
progression of liver disease at end of follow-up Mean follow-up: 5.5 month(s)											
1 (dou 2018)	RCT	very serious[1]	not serious	NA[4]	very serious[3]	NA	0/215	1/214	PETO OR 0.13 (0.00, 6.79)	5 fewer per 1000 (14 fewer to 4 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 11.8 month(s)											
2	RCT	very serious[1]	not serious	serious[5]	very serious[3]	NA	38/858	10/549	RR 1.26 (0.17, 9.32)	5 more per 1000 (15 fewer to 152 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 11.8 month(s)											
2	RCT	very serious[1]	not serious	serious[2]	very serious[6]	NA	3/858	0/549	RD 0.00 (-0.00, 0.01)	3 more per 1000 (3 fewer to 8 more)	very low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
3	RCT	very serious[1]	not serious	very serious[7]	serious[8]	NA	592	348	MD -0.63 (-1.02, -0.23)	MD 0.63 lower (1.02 lower to 0.23 lower)	very low
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	very serious[1]	not serious	not serious	not serious	NA	231	234	MD -0.54 (-2.06, 0.98)	MD 0.54 lower	low

										(2.06 lower to 0.98 higher)	
bmi change (kg/m2, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	very serious[1]	not serious	very serious[7]	not serious	NA	231	234	MD -0.10 (-0.61, 0.41)	MD 0.10 lower (0.61 lower to 0.41 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. 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 = 0.6 (0.8-0.9 = serious, <0.8 = very serious).

7. I2 > 75%

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

F.1.10 Sitagliptin + metformin compared to metformin

Table 92: Clinical evidence profile: Sitagliptin + metformin compared to 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 follow-up Mean follow-up: 5.5 month(s)											

2	RCT	very serious[1]	not serious	not serious	not serious	NA	0/619	0/614	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (4 fewer to 4 more)	low
cardiovascular mortality at end follow-up Mean follow-up: 5.5 month(s)											
2	RCT	very serious[1]	not serious	not serious	not serious	NA	0/619	0/614	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (4 fewer to 4 more)	low
diabetic ketoacidosis at end follow-up Mean follow-up: 5.5 month(s)											
1 (goldstein 2007)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/372	0/364	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (5 fewer to 5 more)	low
hypoglycaemia episodes at end follow-up Mean follow-up: 5.5 month(s)											
2	RCT	serious[3]	not serious	not serious	not serious	NA	35/619	15/614	RR 2.35 (1.30, 4.22)	33 more per 1000 (7 more to 79 more)	moderate
severe hypoglycaemic episodes at end follow-up Mean follow-up: 5.5 month(s)											
1 (ji 2016a)	RCT	serious[3]	not serious	NA[2]	not serious	NA	0/247	0/250	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	moderate
hba1c change (%, lower values are better, change scores and final values) at end follow-up Mean follow-up: 5.5 month(s)											
3	RCT	very serious[1]	not serious	very serious[4]	serious[5]	NA	613	605	MD -0.76 (-1.22, -0.30)	MD 0.76 lower (1.22 lower to 0.30 lower)	very low

weight change (kg, lower values are better, change scores) at end follow-up Mean follow-up: 5.5 month(s)											
1 (ji 2016a)	RCT	serious[3]	not serious	NA[2]	not serious	NA	247	250	MD 1.15 (0.40, 1.90)	MD 1.15 higher (0.40 higher to 1.90 higher)	moderate
bmi change (kg/m2, lower values are better, final values) at end follow-up Mean follow-up: 5.5 month(s)											
1 (wang 2022)	RCT	very serious[1]	not serious	NA[2]	very serious[6]	NA	20	17	MD -0.22 (-2.36, 1.92)	MD 0.22 lower (2.36 lower to 1.92 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. >33.3% of the studies in the meta-analysis were at moderate risk of bias

4. I2 > 75%

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

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

F.1.11 Sitagliptin + metformin compared to sitagliptin

Table 93: Clinical evidence profile: Sitaglipttin + metformin compared to 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)											
2	RCT	serious[1]	not serious	not serious	not serious	NA	0/619	0/299	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	moderate
cardiovascular mortality at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	serious[1]	not serious	not serious	not serious	NA	0/619	0/299	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	moderate
diabetic ketoacidosis at end of follow-up Mean follow-up: 5.5 month(s)											
1 (goldstein 2007)	RCT	serious[1]	not serious	NA[2]	not serious	NA	0/372	0/179	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	moderate
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	serious[1]	not serious	not serious	serious[3]	NA	35/619	6/299	RR 2.83 (1.21, 6.60)	37 more per 1000 (4 more to 112 more)	low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)											
1 (ji 2016a)	RCT	serious[1]	not serious	NA[2]	not serious	NA	0/247	0/120	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (13 fewer to 13 more)	moderate
hba1c change (%, lower values are better, change scores and final value) at end of follow-up Mean follow-up: 5.5 month(s)											
3	RCT	serious[1]	not serious	very serious[4]	serious[5]	NA	613	305	MD -0.59 (-1.12, -0.07)	MD 0.59 lower	very low

										(1.12 lower to 0.07 lower)	
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (ji 2016a)	RCT	serious[1]	not serious	NA[2]	not serious	NA	247	120	MD -0.40 (-1.31, 0.51)	MD 0.40 lower (1.31 lower to 0.51 higher)	moderate
bmi change (kg/m2, lower values are better, final value) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (wang 2022)	RCT	very serious[6]	not serious	NA[2]	very serious[7]	NA	20	17	MD 1.14 (-0.81, 3.09)	MD 1.14 higher (0.81 lower to 3.09 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 (0.80, 1.25)

4. I2 > 75%

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

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

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

F.1.12 Sitagliptin + metformin compared to placebo

Table 94: Clinical evidence profile: Sitagliptin + metformin compared 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
all-cause mortality at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	serious[1]	not serious	serious[2]	very serious[3]	NA	0/619	1/302	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (12 fewer to 7 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	serious[1]	not serious	serious[2]	very serious[3]	NA	0/619	1/302	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (12 fewer to 7 more)	very low
diabetic ketoacidosis at end of follow-up Mean follow-up: 5.5 month(s)											
1 (goldstein 2007)	RCT	very serious[4]	not serious	NA[5]	very serious[6]	NA	0/372	1/176	PETO OR 0.04 (0.00, 2.96)	6 fewer per 1000 (17 fewer to 5 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	serious[1]	not serious	not serious	not serious	NA	35/619	5/302	RR 3.52 (1.40, 8.84)	42 more per 1000 (7 more to 130 more)	moderate
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)											

1 (ji 2016a)	RCT	serious[1]	not serious	NA[5]	not serious	NA	0/247	0/126	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	moderate
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	very serious[4]	not serious	serious[7]	not serious	NA	562	292	MD -0.97 (-1.31, -0.64)	MD 0.97 lower (1.31 lower to 0.64 lower)	very low
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (ji 2016a)	RCT	serious[1]	not serious	NA[5]	not serious	NA	247	124	MD 1.40 (0.46, 2.34)	MD 1.40 higher (0.46 higher to 2.34 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 = 0.42 (0.8-0.9 = serious, <0.8 = very serious).

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

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%

F.1.1 Sitagliptin + metformin compared to metformin

Table 95: Clinical evidence profile: Sitagliptin + metformin compared to 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 follow-up Mean follow-up: 5.5 month(s)											
2	RCT	very serious[1]	not serious	not serious	not serious	NA	0/619	0/614	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (4 fewer to 4 more)	low
cardiovascular mortality at end follow-up Mean follow-up: 5.5 month(s)											
2	RCT	very serious[1]	not serious	not serious	not serious	NA	0/619	0/614	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (4 fewer to 4 more)	low
diabetic ketoacidosis at end follow-up Mean follow-up: 5.5 month(s)											
1 (goldstein 2007)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/372	0/364	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (5 fewer to 5 more)	low
hypoglycaemia episodes at end follow-up Mean follow-up: 5.5 month(s)											
2	RCT	serious[3]	not serious	not serious	not serious	NA	35/619	15/614	RR 2.35 (1.30, 4.22)	33 more per 1000 (7 more to 79 more)	moderate
severe hypoglycaemic episodes at end follow-up Mean follow-up: 5.5 month(s)											
1 (ji 2016a)	RCT	serious[3]	not serious	NA[2]	not serious	NA	0/247	0/250	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	moderate

hba1c change (%, lower values are better, change scores and final values) at end follow-up Mean follow-up: 5.5 month(s)											
3	RCT	very serious[1]	not serious	very serious[4]	serious[5]	NA	613	605	MD -0.76 (-1.22, -0.30)	MD 0.76 lower (1.22 lower to 0.30 lower)	very low
weight change (kg, lower values are better, change scores) at end follow-up Mean follow-up: 5.5 month(s)											
1 (ji 2016a)	RCT	serious[3]	not serious	NA[2]	not serious	NA	247	250	MD 1.15 (0.40, 1.90)	MD 1.15 higher (0.40 higher to 1.90 higher)	moderate
bmi change (kg/m2, lower values are better, final values) at end follow-up Mean follow-up: 5.5 month(s)											
1 (wang 2022)	RCT	very serious[1]	not serious	NA[2]	very serious[6]	NA	20	17	MD -0.22 (-2.36, 1.92)	MD 0.22 lower (2.36 lower to 1.92 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. >33.3% of the studies in the meta-analysis were at moderate risk of bias

4. I2 > 75%

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

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

F.1.2 Sitagliptin + metformin compared to glimepiride

Table 96: Clinical evidence profile: Sitagliptin + metformin compared 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
all-cause mortality at end of follow-up Mean follow-up: 7 month(s)											
1 (kim 2017)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	0/146	0/144	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (13 fewer to 13 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 7 month(s)											
1 (kim 2017)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	8/146	29/144	RR 0.27 (0.13, 0.57)	147 fewer per 1000 (175 fewer to 86 fewer)	low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 7 month(s)											
1 (kim 2017)	RCT	very serious[1]	not serious	NA[2]	very serious[4]	NA	0/146	1/144	PETO OR 0.13 (0.00, 6.73)	7 fewer per 1000 (21 fewer to 7 more)	very low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 7 month(s)											
1 (kim 2017)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	146	144	MD -0.78 (-0.96, -0.60)	MD 0.78 lower (0.96 lower to 0.60 lower)	low
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 7 month(s)											

1 (kim 2017)	RCT	very serious[1]	not serious	NA[2]	serious[5]	NA	146	144	MD -1.72 (-2.74, -0.70)	MD 1.72 lower (2.74 lower to 0.70 lower)	very low

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

2. Only one study so no inconsistency

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

4. 95% confidence intervals cross 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)

F.1.3 Sitagliptin + metformin compared to pioglitazone

Table 97: Clinical evidence profile: Sitagliptin + metformin compared to 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: 7.4 month(s)											
1 (wainstein 2012)	RCT	very serious[1]	not serious	NA[2]	serious[3]	NA	22/261	11/256	RR 1.96 (0.97, 3.96)	41 more per 1000 (1 fewer to 127 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 7.4 month(s)											
1 (wainstein 2012)	RCT	very serious[1]	not serious	NA[2]	not serious	NA	0/261	0/261	RD 0.00 (-0.01, 0.01)	0 fewer per 1000	low

										(7 fewer to 7 more)	
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 7.4 month(s)											
1 (wainstein 2012)	RCT	very serious[1]	not serious	NA[2]	serious[4]	NA	253	246	MD -0.50 (-0.68, -0.32)	MD 0.50 lower (0.68 lower to 0.32 lower)	very low

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

2. Only one study so no inconsistency

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

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

F.1.4 Vilagliptin + metformin compared to metformin

Table 98: Clinical evidence profile: Vildagliptin + metformin compared to 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: 6 month(s)											
1 (bosi 2009)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	1/585	0/294	PETO OR 4.49 (0.07, 286.22)	2 more per 1000 (2 fewer to 5 more)	very low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 6 month(s)											

1 (bosi 2009)	RCT	serious[1]	not serious	NA[2]	serious[4]	NA	0/585	2/294	PETO OR 0.05 (0.00, 0.95)	7 fewer per 1000 (16 fewer to 3 more)	low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (bosi 2009)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	0/585	1/294	PETO OR 0.05 (0.00, 3.20)	3 fewer per 1000 (10 fewer to 3 more)	very low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)											
2	RCT	serious[1]	not serious	not serious	not serious	NA	617	326	MD -0.32 (-0.45, -0.18)	MD 0.32 lower (0.45 lower to 0.18 lower)	moderate
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)											
2	RCT	serious[1]	not serious	not serious	not serious	NA	617	326	MD 0.44 (-0.07, 0.94)	MD 0.44 higher (0.07 lower to 0.94 higher)	moderate
bmi change (kg/m2, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)											
1 (zougrafou 2015)	RCT	very serious[5]	not serious	NA[2]	not serious	NA	32	32	MD 0.20 (-0.35, 0.75)	MD 0.20 higher (0.35 lower to 0.75 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 (0.80, 1.25)

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

F.1.5 Vildagliptin + metformin compared to vildagliptin

Table 99: Clinical evidence profile: Vildagliptin + metformin compared to 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 follow-up Mean follow-up: 6 month(s)											
1 (bosi 2009)	RCT	serious[1]	not serious	NA[2]	very serious[3]	NA	1/585	0/300	PETO OR 4.54 (0.07, 285.24)	2 more per 1000 (2 fewer to 5 more)	very low
non-fatal myocardial infarction at end follow-up Mean follow-up: 6 month(s)											
1 (bosi 2009)	RCT	serious[1]	not serious	NA[2]	not serious	NA	0/585	0/300	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (5 fewer to 5 more)	moderate
severe hypoglycaemic episodes at end follow-up Mean follow-up: 6 month(s)											
1 (bosi 2009)	RCT	serious[1]	not serious	NA[2]	not serious	NA	0/585	0/300	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (5 fewer to 5 more)	moderate
hba1c change (%, lower values are better, change scores) at end follow-up Mean follow-up: 6 month(s)											

1 (bosi 2009)	RCT	serious[1]	not serious	NA[2]	serious[4]	NA	585	300	MD -0.60 (-0.74, -0.46)	MD 0.60 lower (0.74 lower to 0.46 lower)	low
weight change (kg, lower values are better, change scores) at end follow-up Mean follow-up: 6 month(s)											
1 (bosi 2009)	RCT	serious[1]	not serious	NA[2]	not serious	NA	585	300	MD -0.59 (-1.12, -0.06)	MD 0.59 lower (1.12 lower to 0.06 lower)	moderate

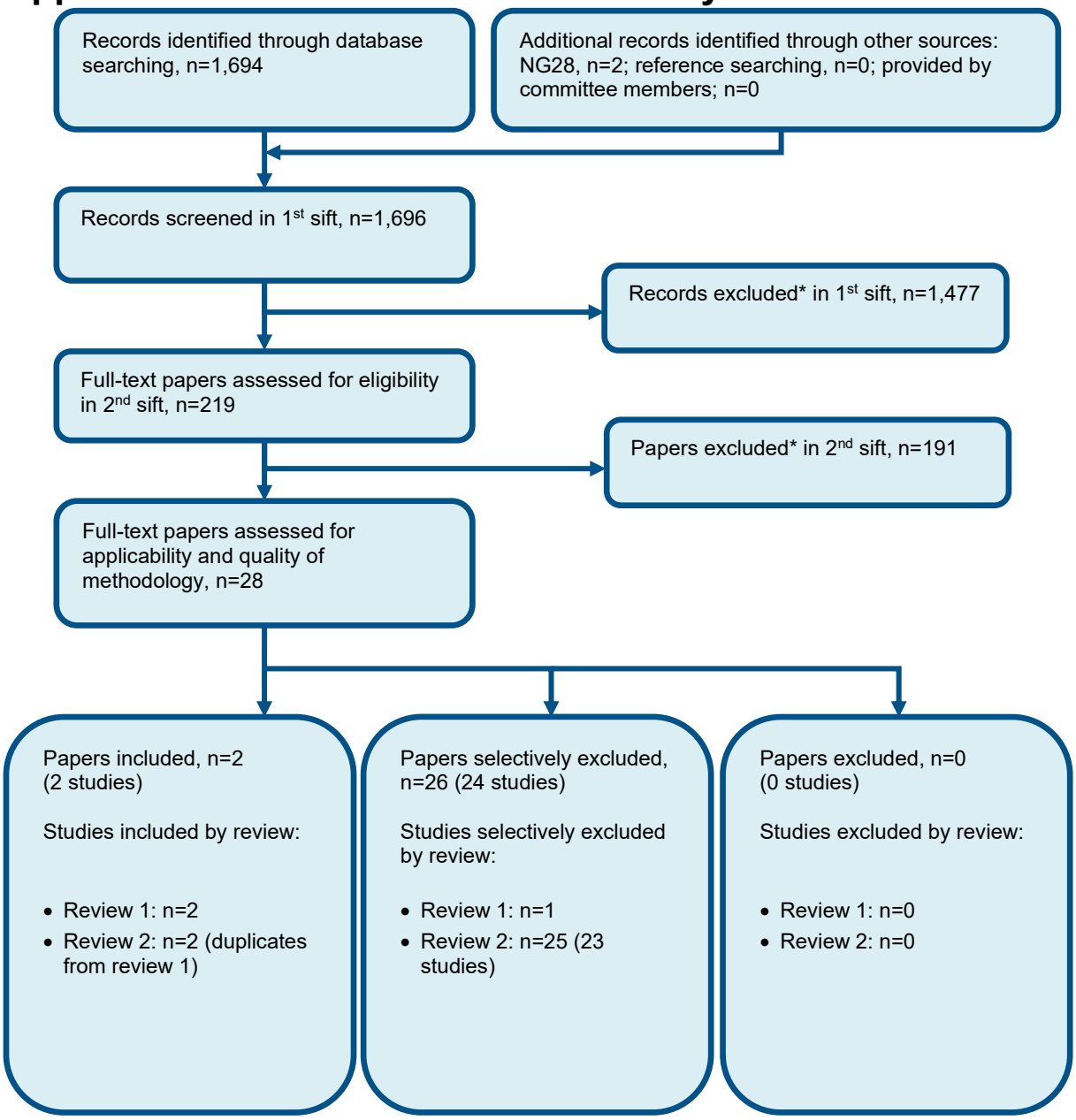
1. >33.3% of the studies in the meta-analysis were at moderate risk of bias

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)

Appendix G Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H Economic evidence tables

Study	National Institute for Health and Care Excellence (NG28) 2015	
Study details	**Population & interventions**	**Cost effectiveness (pa)**

Economic analysis: CUA (health outcome: QALY)

Study design: Individual patient simulation model. Patient population based on real-world UK cohort. Treatment effects based on systematic literature review and network meta-analysis of guideline clinical review results.

Approach to analysis: The UKPDS OM1 was used to conduct modelling analysis. Outcomes of interest included:

1. Ischaemic heart disease
2. Myocardial infarction
3. Heart failure
4. Stroke
5. Amputation
6. Severe vision loss
7. Renal failure

Perspective: UK NHS

Time horizon: lifetime/ 40 years

Treatment effect duration:[a] Treatment effects to HbA1c

Population:
Initial therapy in adults aged 18 years and over with type 2 diabetes.

Cohort settings:
Start age (years): 59.8
Male: 57.1%
HbA1c: 66mmol/mol

Interventions:
Various drug interventions and no treatment were compared to each other – see table to right.

Treatment intensification following failure to control HbA1c levels with initial treatment were based on results for metformin-sulfonylurea. Further intensification was based on results for metformin-NPH insulin.

Intervention in order of cost	Cost[c]	QALYs	Inc. costs versus metformin	Inc. QALYs versus metformin	Cost per QALY gained versus metformin
Metformin	£19,250	9.033			
Repaglinide	£19,298	8.974	£48	-0.059	Dominated
Pioglitazone	£19,412	8.973	£163	-0.060	Dominated
Sulfonylurea	£19,580	8.950	£330	-0.082	Dominated
No treatment (placebo)	£20,043	8.912	£794	-0.121	Dominated
Sitagliptin	£20,457	8.990	£1,207	-0.043	Dominated
Vildagliptin	£20,627	8.954	£1,377	-0.074	Dominated

Currency & cost year:
2012/13 UK pounds[b]

Cost components incorporated:
Drug costs, drug consumables (needles, self-monitoring blood glucose strips and lancets, sharps bins), staff time for GLP-1 and insulin initiation, diabetes-related complications costs

Probability Intervention 2 cost effective versus all other interventions (£20K/30K threshold): 88%/86%

For people who could not take metformin, repaglinide was the most cost-effective initial therapy at a maximum acceptable ICER of £20k in 45% of iterations, followed by pioglitazone (35%).

Analysis of uncertainty: Metformin remained the most cost-effective treatment option when 2-year treatment

were modelled at 1 year and were taken from the NMA. Treatment-related weight gain was assumed to last indefinitely and weight loss to last for one year with an immediate gain within the following year. Hypoglycaemic episode rates remained constant over time. **Discounting:** Costs: 3.5%; Outcomes: 3.5%			effects data for HbA1c and weight change were applied.
Data sources			
Health outcomes: Baseline data for demographic factors (age, sex, ethnicity, duration of diabetes, height, weight), clinical risk factors (HbA1c, SBP, total cholesterol, HDL, smoking status and presence of atrial fibrillation and PAD) and history of diabetes-related complications were taken from The Health Improvement Network (THIN) 2014. Treatment effectiveness data were all taken from NMAs conducted as part of the guideline clinical review and were four: HbA1c, weight change, hypoglycaemic events and treatment discontinuation. Changes in HbA1c were used to predict diabetes related complications. **Quality-of-life weights:** EQ-5D UK tariff valuations taken from the UKPDS RCT. **Cost sources:** Drug unit costs were taken from the NHS June Drug Tariff 2014. Drug consumable costs were based on weighted averages of prescribed usage from the Health and Social Care Information Centre (HSCIC) 2014. Staff costs were taken from the Personal Social Services Research Unit (PSSRU) 2014. Diabetes-related complications costs (except for renal failure costs) were sourced from the UKPDS RCT and inflated to 2012/13 costs. Renal failure costs were taken from a UK study (Lamping 2000).			
Comments			
Source of funding: UK Department of Health and Social Care (DHSC). **Limitations:** Newer GLP-1 agonists and SGLT-2 inhibitors are missing from the analysis. Tirzepatide is also missing from the analysis. The validity of HbA1c as a surrogate marker used to predict cardiovascular outcomes and mortality has been questioned. Sources of costs are dated and do not accurately reflect current NHS conditions. The proportion of hypoglycaemic episodes that are severe (2%) and (therefore incur costs to the NHS) was assumed to be the same across all treatments. **Other:**			
Overall applicability:[c] Directly applicable		**Overall quality:**[d] Potentially serious limitations	

Abbreviations: CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); HbA1c= glycated haemoglobin; HDL= high-density lipoprotein; Inc.= incremental; ICER= incremental cost-effectiveness ratio; NMA= network meta-analysis; NPH= neutral protamine Hagedorn; NR= not reported; OM1= outcomes model 1; pa= probabilistic analysis; PAD= peripheral arterial disease; QALYs= quality-adjusted life years; RCT= randomised controlled trial; SBP= systolic blood pressure; UKPDS= United Kingdom prospective diabetes study

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

Study	National Institute for Health and Care Excellence (NG28) 2022	
Study details	**Population & interventions**	**Cost effectiveness (da)**
Economic analysis: CUA (health outcome: QALY) **Study design:** Two-part model utilising individual patient simulation to predict diabetes-related complications. Health states were assigned according to complications. CVD treatment effects were applied to health states in second part. Patient population based on real-world UK cohort. Treatment effects based on systematic literature review and network meta-analysis of guideline clinical review results. **Approach to analysis:** A two-part model was constructed in R. In the first part, the UKPDS risk equations were used to simulate outcomes for the standard care arm. Treatment effects of CVOT drugs versus standard care were applied in the second part of the model. Outcomes of interest included: 1. Ischaemic heart disease (IHD) 2. Myocardial infarction (MI) 3. Heart failure (HF)	**Population:** Adults aged 18 years and over with type 2 diabetes **Cohort settings:** Start age (years): 58.79 Male: 57% HbA1c: 66mmol/mol **Interventions:** Various CVOT drugs in combination with metformin were compared to metformin alone (standard care) – see table to right. Subgroup analyses were also conducted for those: 1. with a BMI of greater than or equal to 30kg/m2 2. at high risk of a CV event who have not had a prior event 3. who have had a prior CV event 4. combination of numbers 2 and 3 above	**CVOTs as additions (compared to metformin alone)**

Intervention in order of cost	Cost[(c)]	QALYs	Inc. costs versus metformin	Inc. QALYs versus metformin	Cost per QALY gained versus metformin
Metformin	£17,565	9.47			
Pioglitazone + metformin	£19,212	9.373	£1,647	-0.097	Dominated
Alogliptin + metformin	£22,061	9.408	£4,496	-0.062	Dominated
Ertugliflozin + metformin	£22,316	9.668	£4,751	0.198	£24,004
Linagliptin + metformin	£22,813	9.491	£5,248	0.021	£248,971
Sitagliptin + metformin	£23,387	9.503	£5,822	0.033	£177,546
Dapagliflozin + metformin	£23,399	9.837	£5,834	0.367	£15,899
Empagliflozin + metformin	£23,785	9.714	£6,220	0.244	£25,526
Saxagliptin + metformin	£23,806	9.2	£6,241	-0.27	Dominated
Canagliflozin + metformin	£24,485	9.696	£6,920	0.226	£30,664
Lixisenatide + metformin	£26,543	9.179	£8,977	-0.291	Dominated
Semaglutide (injection) + metformin	£30,130	9.943	£12,565	0.473	£26,552
Dulaglutide + metformin	£30,154	9.631	£12,589	0.161	£78,166

4. Stroke
5. Amputation
6. Ulceration
7. Severe vision loss
8. Renal complications

Perspective: UK NHS

Time horizon: lifetime/ 40 years

Treatment effect duration:[(a)]

Discounting: Costs: 3.5%; Outcomes: 3.5%

These have been presented here – see table to right.

Treatment intensification following failure to control HbA1c levels with initial treatment were based on results for metformin-sulfonylurea. Further intensification was based on results for metformin-NPH insulin.

Exenatide + metformin	£30,446	9.534	£12,881	0.064	£202,472
Semaglutide (oral) + metformin	£31,890	9.147	£14,325	-0.323	Dominated
Liraglutide + metformin	£36,478	9.466	£18,913	-0.004	Dominated

Intervention in order of class	**High cardiovascular risk – no prior event**		**High cardiovascular risk –prior event**		**All high cardiovascular risk**		**High BMI**	
Alogliptin + metformin	Dominated	10	Dominated	9	Dominated	10	Dominated	10
Linagliptin + metformin	£180,134	8	Dominated	10	£246,771	8	£197,198	8
Saxagliptin + metformin	Dominated	13	Dominated	12	Dominated	13	Dominated	13
Sitagliptin + metformin	£142,839	9	£106,216	8	£156,778	9	£198,878	9
Dulaglutide + metformin	£67,281	11	£60,963	11	£65,234	11	£80,323	11
Exenatide + metformin	£148,989	12	£127,832	13	£148,364	12	£213,942	12
Liraglutide + metformin	£1,553,519	15	£243,109	15	£1,404,163	15	Dominated	15
Lixisenatide + metformin	Dominated	14	Dominated	14	Dominated	14	Dominated	14
Semaglutide (injection) + metformin	£24,383	6	£21,916	4	£24,671	6	£28,353	6
Semaglutide (oral) + metformin	Dominated	16	Dominated	16	Dominated	16	Dominated	16
Pioglitazone + metformin	Dominated	7	£56,283	6	Dominated	7	Dominated	7

Canagliflozin + metformin	£24,032	4	£24,057	5	£24,225	5	£29,178	5
Dapagliflozin + metformin	£15,124	1	£15,380	1	£15,207	1	£15,193	1
Empagliflozin + metformin	£24,581	5	£21,567	3	£24,633	4	£22,858	4
Ertugliflozin + metformin	£21,725	3	£31,165	7	£21,995	3	£21,675	3

Although metformin alone does not appear in the table above, it ranked 2 in all analyses.

Currency & cost year:
2020/21 UK pounds[(b)]

Cost components incorporated:
Drug costs, drug consumables (needles, self-monitoring blood glucose strips and lancets [for sulfonylureas and insulins only], sharps bins), staff time for GLP-1 and insulin drug class initiation, diabetes-related complications costs

Analysis of uncertainty:

- There were no analyses of uncertainty presented for the addition of CVOT drugs to metformin.

Data sources

Health outcomes: Baseline data for clinical risk factors (age, sex, smoking status, HbA1c, SBP, cholesterol, HDL, LDL, eGFR, WBC count, albuminuria, haemoglobin, and heart rate) as well as prevalence of diabetes-related outcomes were taken from The Health Improvement Network (THIN) 2014. Patients were simulated over 40 years through the UKPDS OM2 model for the standard care arm. Changes in HbA1c were used to predict CV-related outcomes. Relative treatment effectiveness data were all taken from NMAs conducted as part of the guideline clinical review and were: IHD, MI, HF, stroke. Amputation, ulceration, severe vision loss and renal complications were identical between arms. CV mortality and relative severe hypoglycaemic event rates were also taken from NMAs. **Quality-of-life weights:** Baseline utility score was taken from the UKPDS RCT. Disutilities resulting from diabetes-related complications were taken from a systematic review (Beaudet 2014). **Cost sources:** Drug unit costs were taken from the NHS May Drug Tariff 2021. Drug consumable costs were taken from other NICE guidelines: SMBG costs were taken from the diabetes in pregnancy guideline (NG3) and unit costs for needles were taken from the type 1 diabetes guideline (NG17). Staff costs were taken from the Personal Social Services Research Unit (PSSRU) 2020. Diabetes-related complications costs (except for ulceration and renal complications costs) were sourced from the UKPDS post-trial monitoring study (Alva 2015) and inflated to 2020/21 costs. Renal complications costs were taken from the NICE guideline update on chronic kidney disease.

Comments

Source of funding: UK Department of Health and Social Care (DHSC). **Limitations:** Only CVOT drugs are included in the incremental analysis; drug classes such as sulfonylureas and insulin are included as background treatments only. Tirzepatide is also missing from the analysis. Probabilistic analysis was only conducted for the second intensification stage due to a lack of time. The analysis assumes that non-cardiovascular (microvascular) treatment-related outcomes are the same between comparator arms. The timing of treatment intensification does not differ between different treatment options, meaning between-treatment effects on HbA1c are not fully captured. **Other:**

Overall applicability:[c] Directly applicable **Overall quality:**[d] Potentially serious limitations

Abbreviations: CUA= cost–utility analysis; CV= cardiovascular; CVOT= cardiovascular outcome trial; da= deterministic analysis; eGFR= estimated glomerular filtration rate; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); HbA1c= glycated haemoglobin; HDL= high-density lipoprotein; Inc.= incremental; ICER= incremental cost-effectiveness ratio; LDL= low-density lipoprotein; NMA= network meta-analysis; NR= not reported; OM2= outcomes model 2; QALYs= quality-adjusted life years; RCT= randomised controlled trial; SBP= systolic blood pressure; SMBG= self-monitoring blood glucose; UKPDS= United Kingdom prospective diabetes study; WBC= white blood cell

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Directly applicable / Partially applicable / Not applicable

Minor limitations / Potentially serious limitations / Very serious limitations

Appendix I Health economic model

A health economic model was conducted focussing on combinations in addition to metformin modified release oral tablets. This is reported in the health economics analysis report.