National Institute for Health and Care Excellence

Final

Type 2 diabetes in adults: management

[F6] Evidence reviews for subsequent pharmacological management of type 2 diabetes

NICE guideline

Evidence reviews underpinning recommendations 1.9.1 to 1.9.5, 1.10.1 to 1.18.4, 1.19.1 to 1.19.2, 1.20.1 to 1.20.2, 1.21.3 to 1.31.1 and recommendations for research in the NICE guideline

February 2026

Final

This evidence review was developed by NICE

Disclaimer

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

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

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K.1 Adding

K.1.1 Metformin

K.1.1.1 Adding metformin compared to adding placebo

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

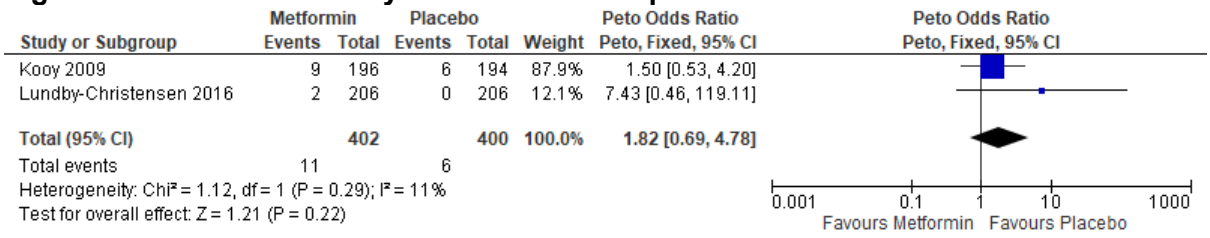


Figure 2: Hypoglycaemia episodes at end of follow up

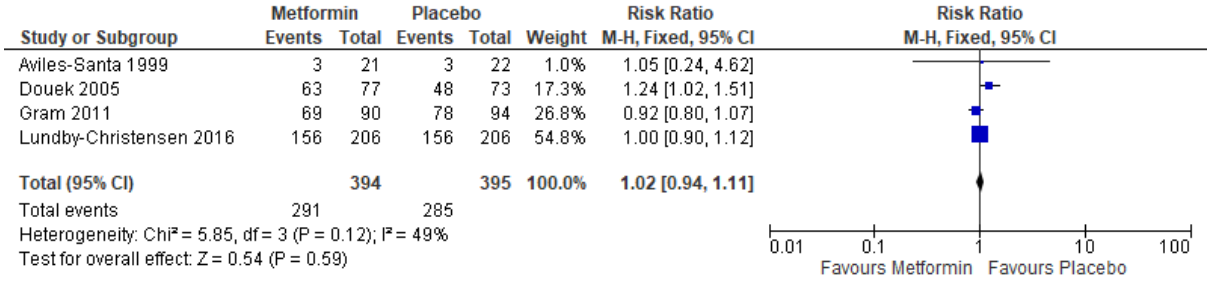


Figure 3: Severe hypoglycaemic episodes at end of follow up

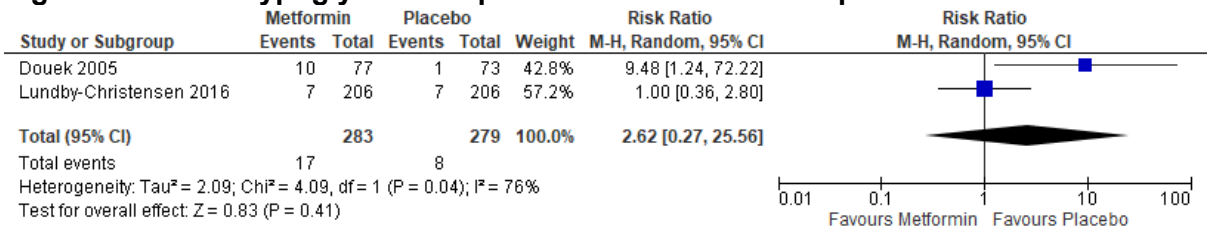
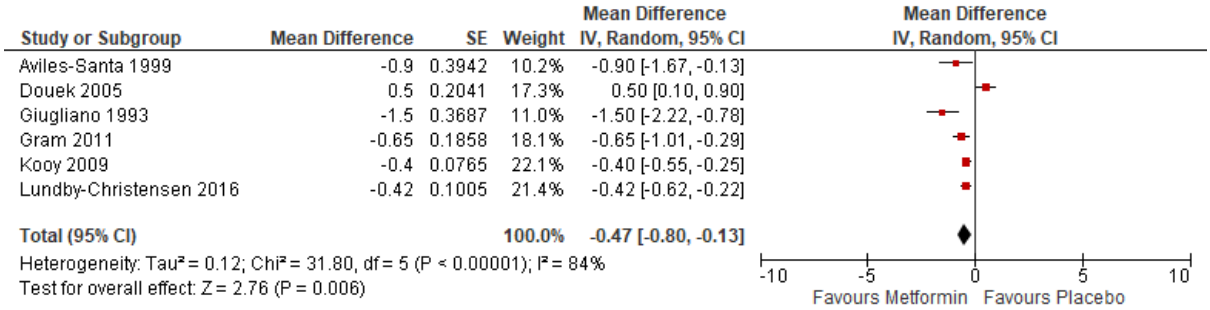
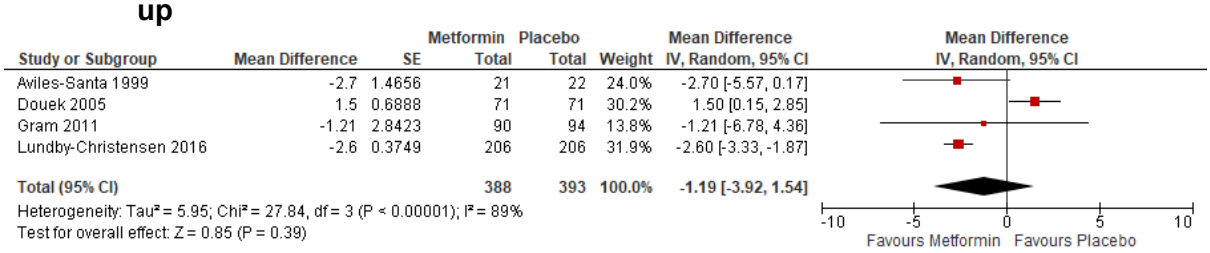


Figure 4: HbA1c change (%, lower values are better, mean difference) at end of follow up



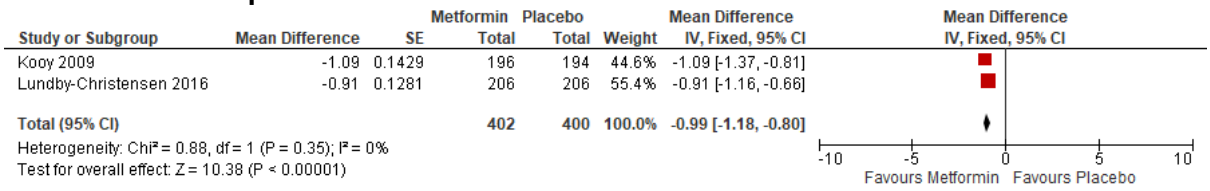
Note: Heterogeneity was not explained by sensitivity analysis, nor subgroup analysis by obesity and onset subgroups.

Figure 5: Weight change (kg, lower values are better, mean difference) at end of follow up



Note: Heterogeneity was not explained by sensitivity analysis. Subgroup analysis was not possible for any subgroup.

Figure 6: BMI change (kg/m², lower values are better, mean difference) at end of follow up



K.1.1.2 Adding metformin compared to adding insulin

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

K.1.2 DPP-4 inhibitors

K.1.2.1 Adding alogliptin compared to adding placebo

Figure 7: All-cause mortality at end of follow up

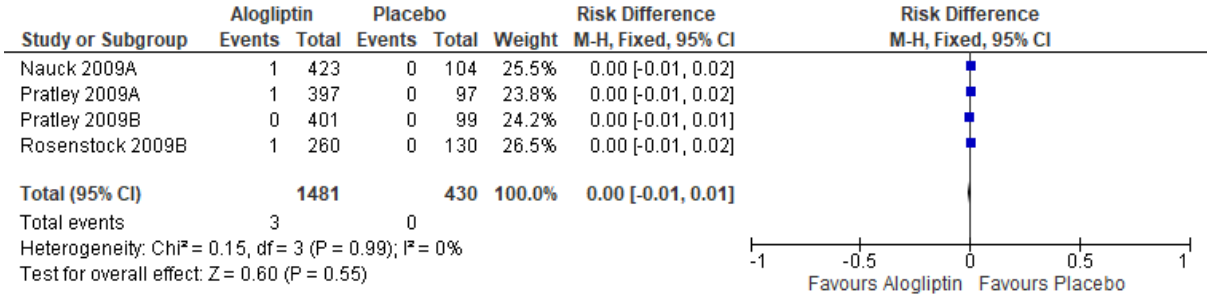


Figure 8: Cardiovascular mortality at end of follow up

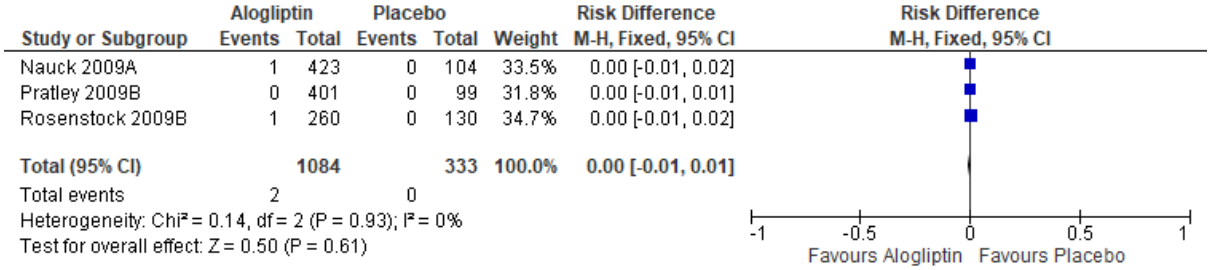


Figure 9: Hypoglycaemia episodes at end of follow up

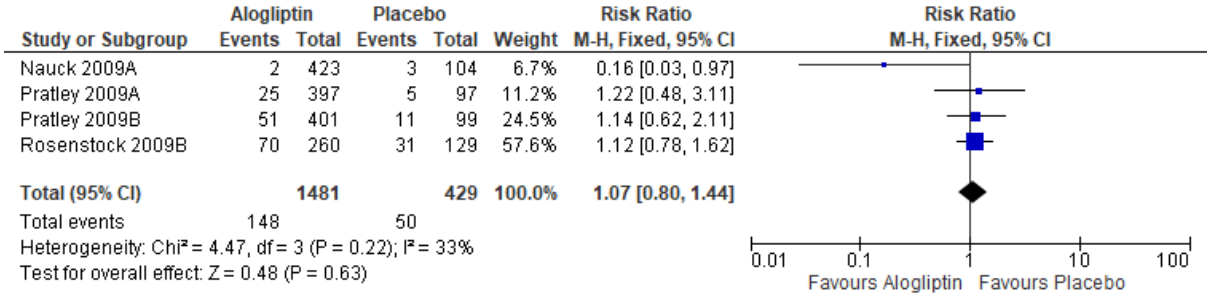


Figure 10: Severe hypoglycaemic episodes at end of follow up

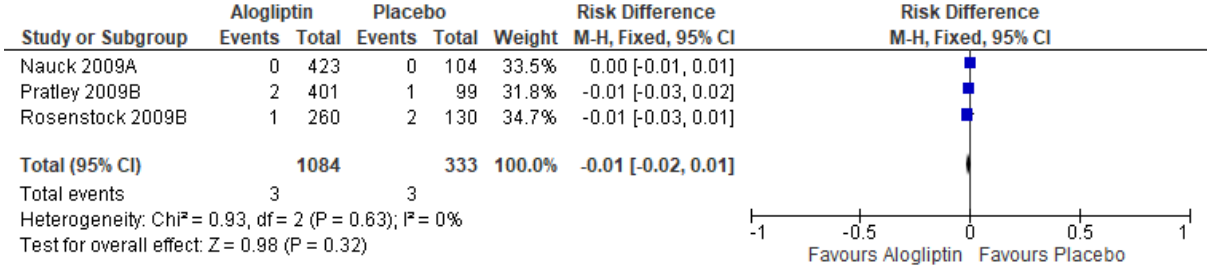
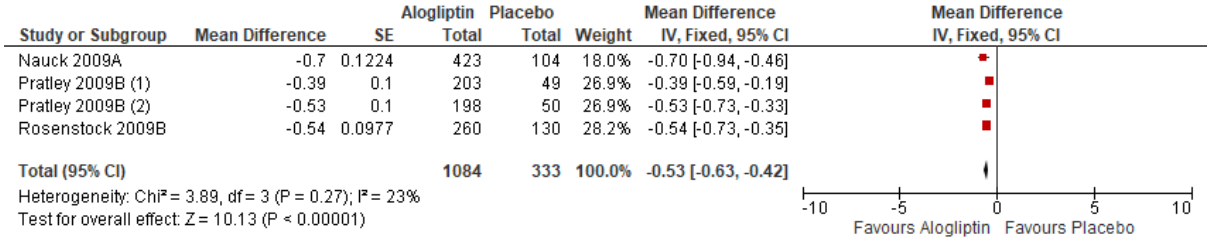
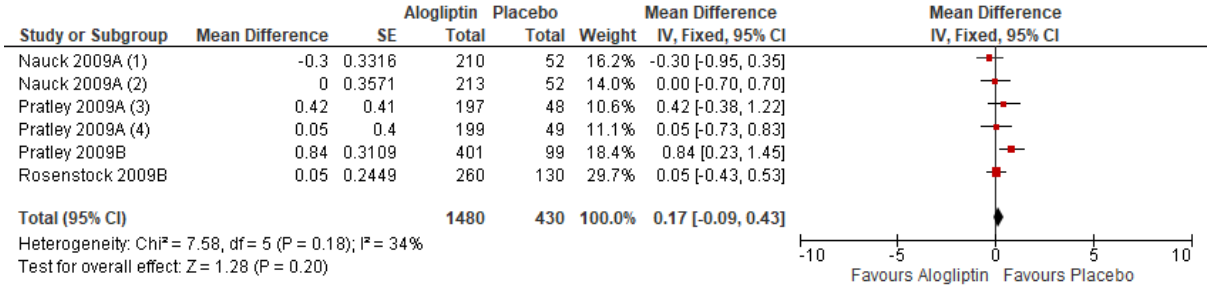


Figure 11: HbA1c change (%, lower values are better, change scores) at end of follow up



Footnotes
(1) Data for alogliptin 12.5 mg. N for placebo arm has been halved.
(2) Data for alogliptin 25 mg. N for placebo arm has been halved.

Figure 12: Weight change (kg, lower values are better, change scores) at end of follow up



Footnotes
(1) Data for alogliptin 25 mg daily compared to placebo. N for placebo arm has been halved.
(2) Data for alogliptin 12.5 mg daily compared to placebo. N for placebo arm has been halved.
(3) Data for alogliptin 12.5 mg. N for placebo arm has been halved
(4) Data for alogliptin 25 mg. N for placebo arm has been halved

K.1.2.2 Adding linagliptin compared to adding placebo

Figure 13: All-cause mortality at end of follow up

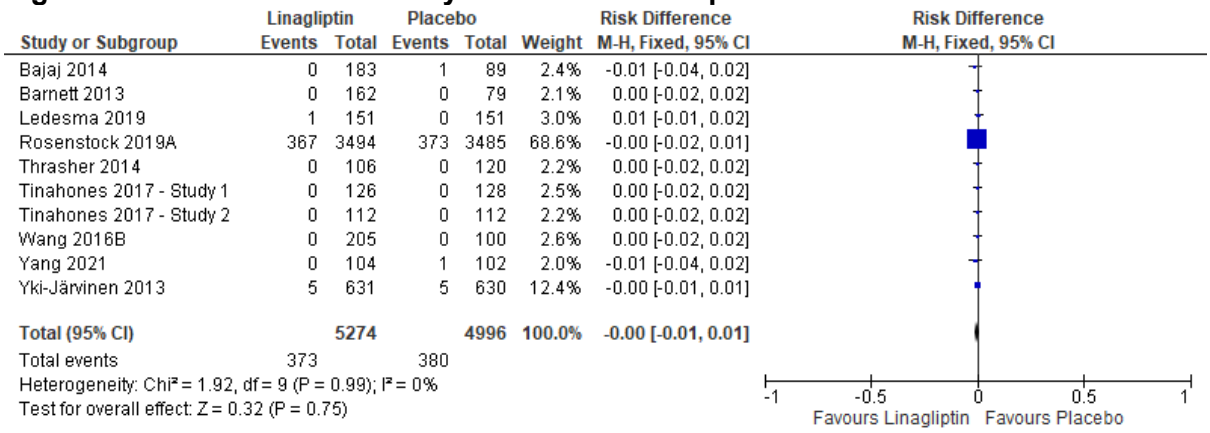


Figure 14: Cardiovascular mortality at end of follow up

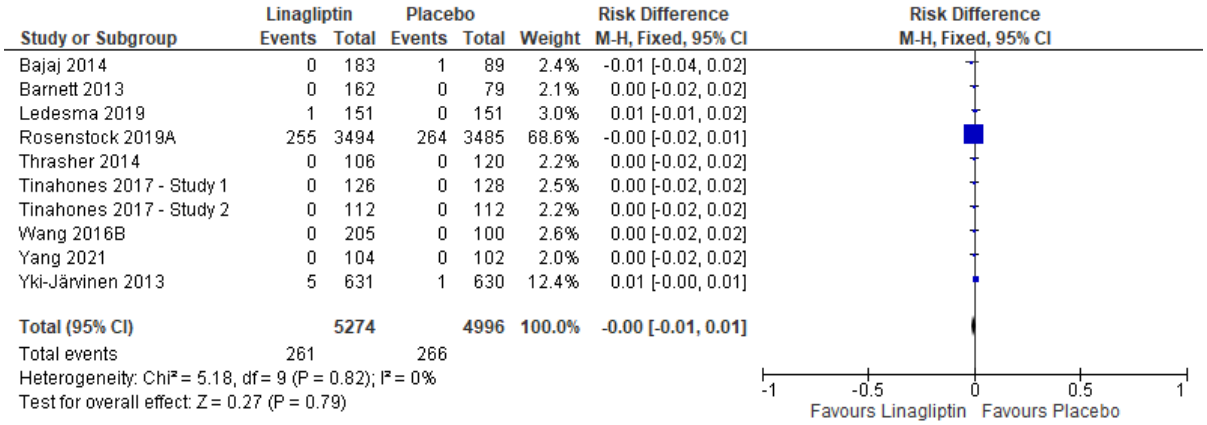


Figure 15: 4-point MACE at end of follow up

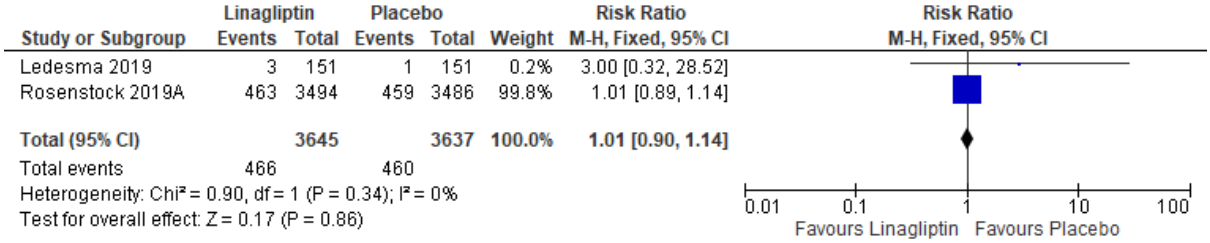


Figure 16: 5-point MACE at end of follow up

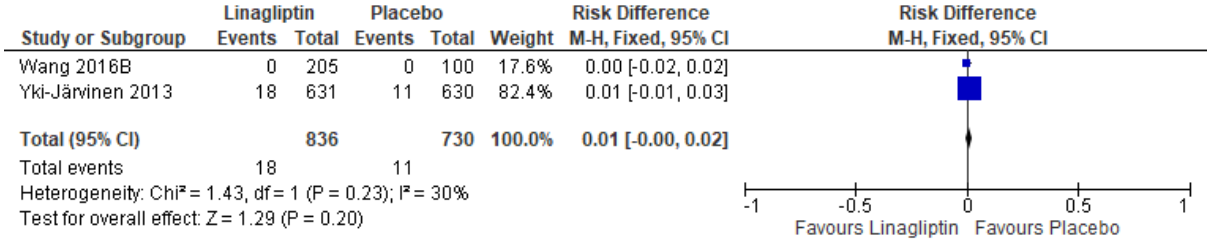


Figure 17: Non-fatal stroke at end of follow up

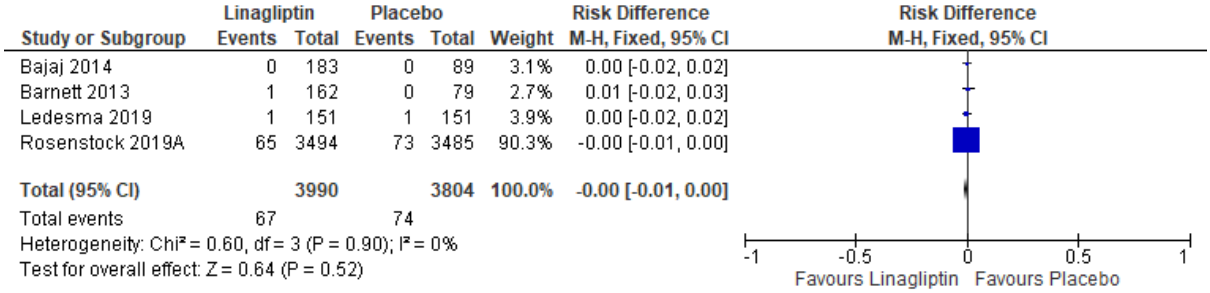


Figure 18: Non-fatal myocardial infarction at end of follow up

Study or Subgroup	Linagliptin Events	Linagliptin Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Ledesma 2019	1	151	0	151	3.9%	0.01 [-0.01, 0.02]
Rosenstock 2019A	156	3494	135	3485	89.8%	0.01 [-0.00, 0.02]
Thrasher 2014	1	106	0	120	2.9%	0.01 [-0.02, 0.03]
Wang 2016B	0	205	0	100	3.5%	0.00 [-0.02, 0.02]
Total (95% CI)		**3956**		**3856**	**100.0%**	**0.01 [-0.00, 0.01]**
Total events	158		135			

Heterogeneity: Chi² = 0.65, df = 3 (P = 0.89); I² = 0%
Test for overall effect: Z = 1.35 (P = 0.18)

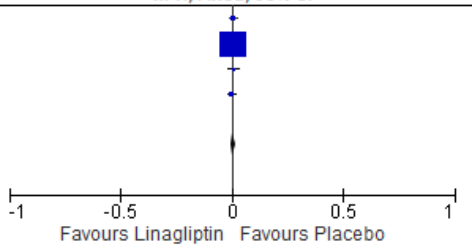


Figure 19: Unstable angina at end of follow up

Study or Subgroup	Linagliptin Events	Linagliptin Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Bajaj 2014	0	183	0	89	3.2%	0.00 [-0.02, 0.02]
Barnett 2013	1	162	0	79	2.9%	0.01 [-0.02, 0.03]
Rosenstock 2019A	42	3494	47	3484	93.9%	-0.00 [-0.01, 0.00]
Total (95% CI)		**3839**		**3652**	**100.0%**	**-0.00 [-0.01, 0.00]**
Total events	43		47			

Heterogeneity: Chi² = 0.44, df = 2 (P = 0.80); I² = 0%
Test for overall effect: Z = 0.47 (P = 0.64)

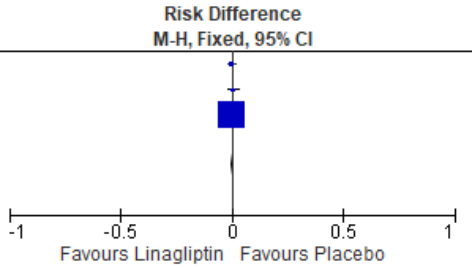


Figure 20: Hospitalisation for heart failure at end of follow up

Study or Subgroup	Linagliptin Events	Linagliptin Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Bajaj 2014	0	183	0	89	3.1%	0.00 [-0.02, 0.02]
Ledesma 2019	1	151	2	151	3.9%	-0.01 [-0.03, 0.02]
Rosenstock 2019A	209	3494	226	3485	89.6%	-0.01 [-0.02, 0.01]
Wang 2016B	0	205	0	100	3.5%	0.00 [-0.02, 0.02]
Total (95% CI)		**4033**		**3825**	**100.0%**	**-0.00 [-0.01, 0.01]**
Total events	210		228			

Heterogeneity: Chi² = 0.70, df = 3 (P = 0.87); I² = 0%
Test for overall effect: Z = 0.91 (P = 0.36)

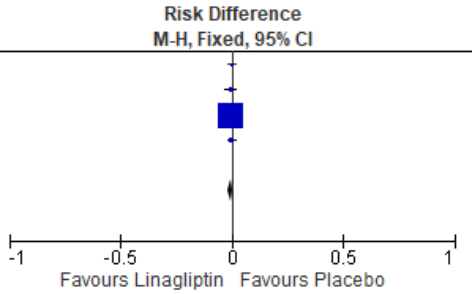


Figure 21: Development of end stage kidney disease at end of follow up

Study or Subgroup	Linagliptin Events	Linagliptin Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Rosenstock 2019A	63	3494	64	3485	96.3%	-0.00 [-0.01, 0.01]
Wang 2016B	0	205	0	100	3.7%	0.00 [-0.02, 0.02]
Total (95% CI)		**3699**		**3585**	**100.0%**	**-0.00 [-0.01, 0.01]**
Total events	63		64			

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.10 (P = 0.92)

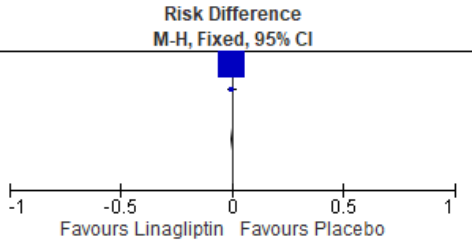


Figure 22: Diabetic ketoacidosis at end of follow up

Study or Subgroup	Linagliptin Events	Linagliptin Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Tinahones 2017 - Study 1	0	126	0	128	53.1%	0.00 [-0.02, 0.02]
Tinahones 2017 - Study 2	0	112	0	112	46.9%	0.00 [-0.02, 0.02]
Total (95% CI)		**238**		**240**	**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)

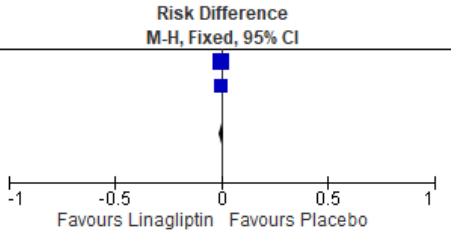
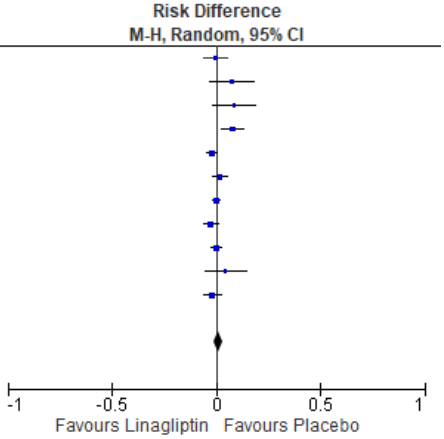


Figure 23: Hypoglycaemia episodes at end of follow up

Study or Subgroup	Linagliptin Events	Linagliptin Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
Bajaj 2014	10	183	5	89	7.4%	-0.00 [-0.06, 0.06]
Barnett 2013	39	162	13	79	3.3%	0.08 [-0.03, 0.18]
Ledesma 2019	52	151	39	151	3.4%	0.09 [-0.02, 0.19]
Owens 2011	180	792	39	263	8.3%	0.08 [0.03, 0.13]
Taskinen 2011	3	523	5	177	13.1%	-0.02 [-0.05, 0.00]
Thrasher 2014	3	106	1	120	11.2%	0.02 [-0.02, 0.06]
Tinahones 2017 - Study 1	0	126	0	128	14.8%	0.00 [-0.02, 0.02]
Tinahones 2017 - Study 2	0	112	3	112	11.4%	-0.03 [-0.06, 0.01]
Wang 2016B	2	205	1	100	13.4%	-0.00 [-0.02, 0.02]
Yang 2021	18	104	13	102	3.8%	0.05 [-0.05, 0.14]
Yki-Järvinen 2013	107	631	118	630	9.9%	-0.02 [-0.06, 0.02]
Total (95% CI)		**3095**		**1951**	**100.0%**	**0.01 [-0.01, 0.03]**
Total events	414		237			

Heterogeneity: Tau² = 0.00; Chi² = 34.59, df = 10 (P = 0.0001); I² = 71%
Test for overall effect: Z = 0.74 (P = 0.46)



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

Figure 24: Severe hypoglycaemic episodes

Study or Subgroup	Linagliptin Events	Linagliptin Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Bajaj 2014	0	183	0	89	5.3%	0.00 [-0.02, 0.02]
Barnett 2013	1	162	0	79	4.7%	0.01 [-0.02, 0.03]
Ledesma 2019	2	151	1	151	6.7%	0.01 [-0.02, 0.03]
Owens 2011	5	792	2	263	17.5%	-0.00 [-0.01, 0.01]
Taskinen 2011	0	523	0	177	11.7%	0.00 [-0.01, 0.01]
Thrasher 2014	0	106	0	120	5.0%	0.00 [-0.02, 0.02]
Tinahones 2017 - Study 1	0	126	0	128	5.6%	0.00 [-0.02, 0.02]
Tinahones 2017 - Study 2	0	112	1	112	5.0%	-0.01 [-0.03, 0.02]
Wang 2016B	0	205	0	100	6.0%	0.00 [-0.02, 0.02]
Yang 2021	0	104	0	102	4.6%	0.00 [-0.02, 0.02]
Yki-Järvinen 2013	2	631	4	630	28.0%	-0.00 [-0.01, 0.00]
Total (95% CI)		**3095**		**1951**	**100.0%**	**-0.00 [-0.01, 0.00]**
Total events	10		8			

Heterogeneity: Chi² = 1.68, df = 10 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.37 (P = 0.71)

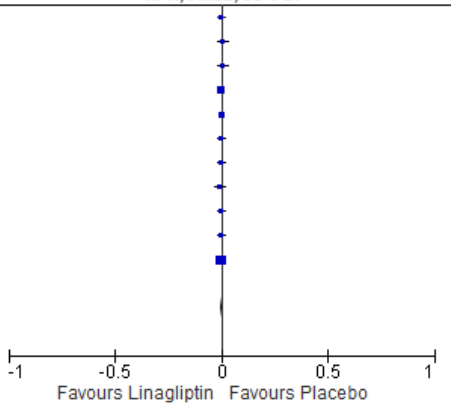
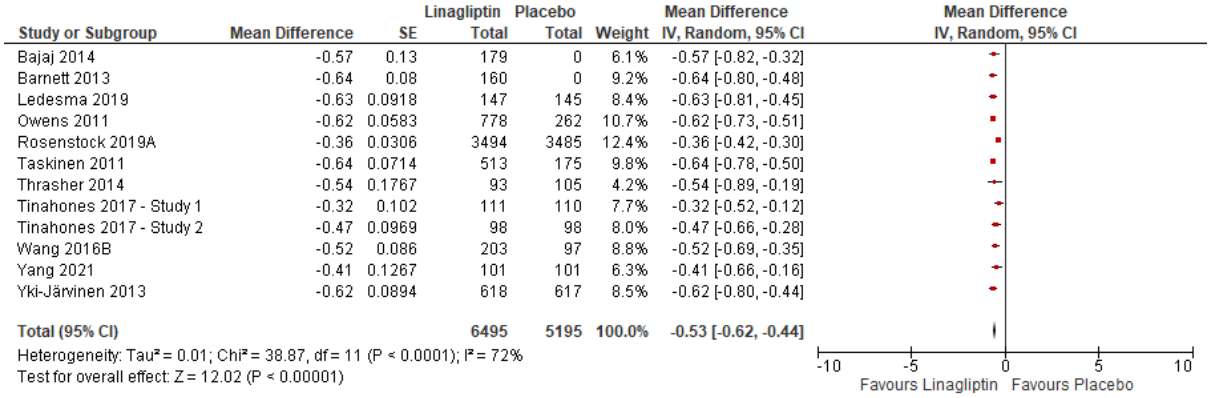
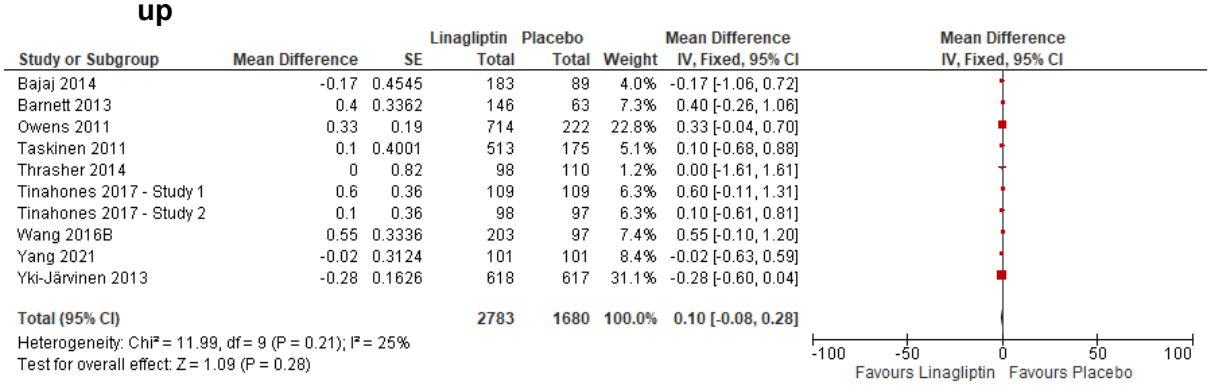


Figure 25: HbA1c change (%, lower values are better, change scores) at end of follow up



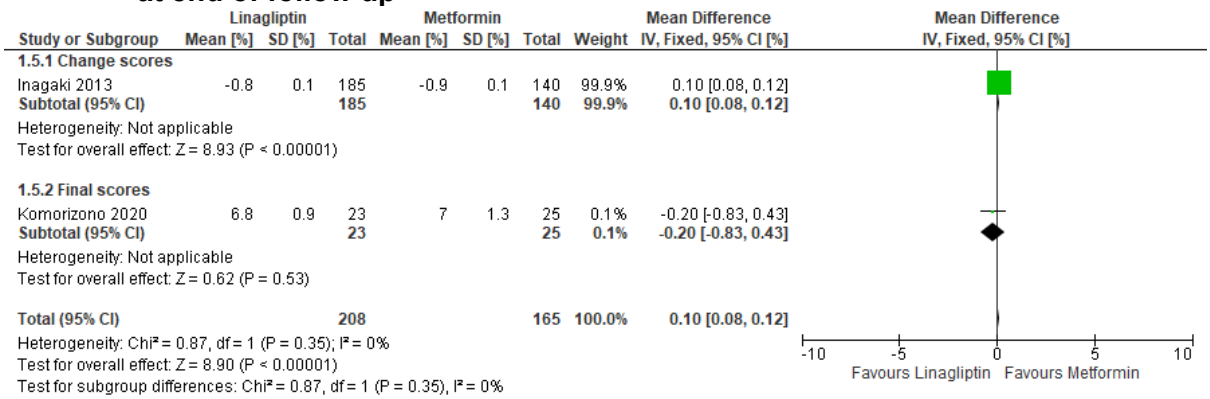
Note: Heterogeneity was not explained by sensitivity analysis, nor subgroup analysis by eGFR subgroup.

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



K.1.2.3 Adding linagliptin compared to adding metformin

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



K.1.2.4 Adding saxagliptin compared to adding placebo

Figure 28: All-cause mortality at end of follow up

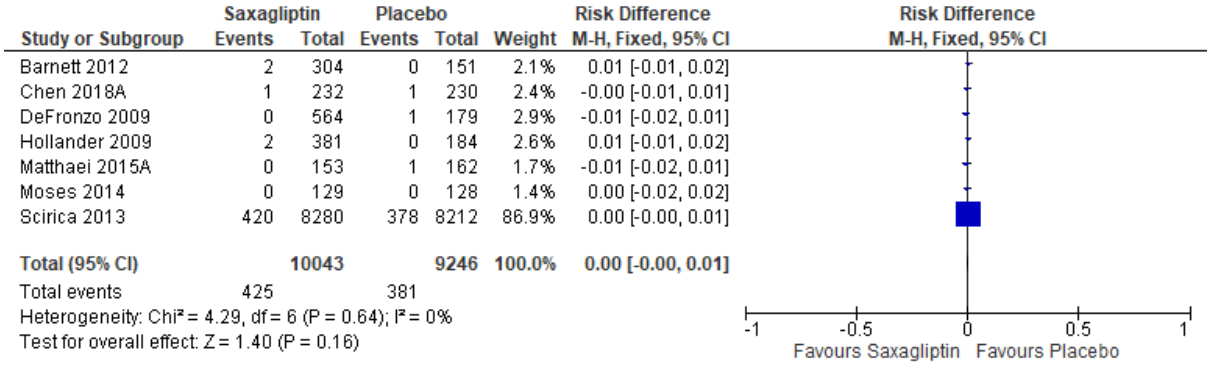


Figure 29: Cardiovascular mortality at end of follow up

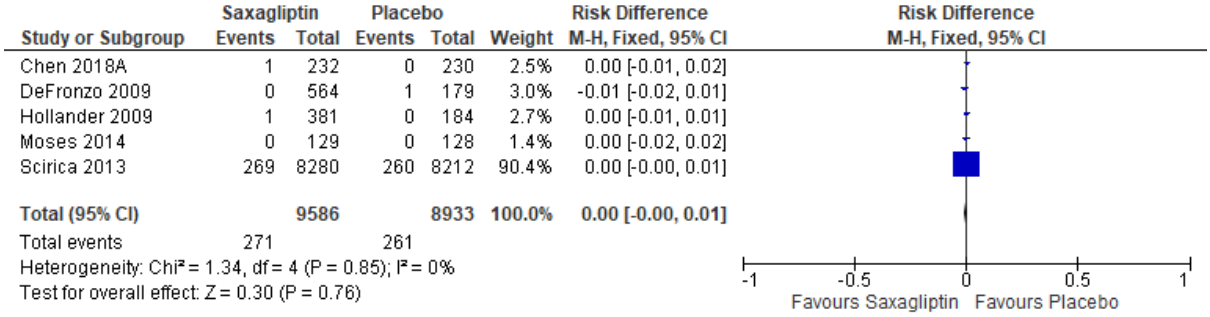


Figure 30: Non-fatal stroke at end of follow up

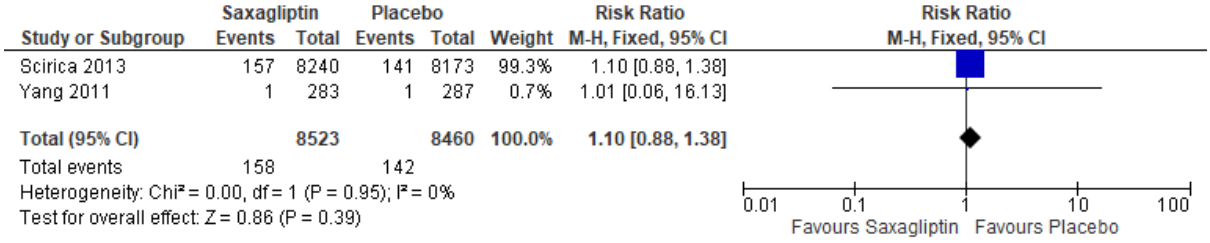


Figure 31: Non-fatal myocardial infarction at end of follow up

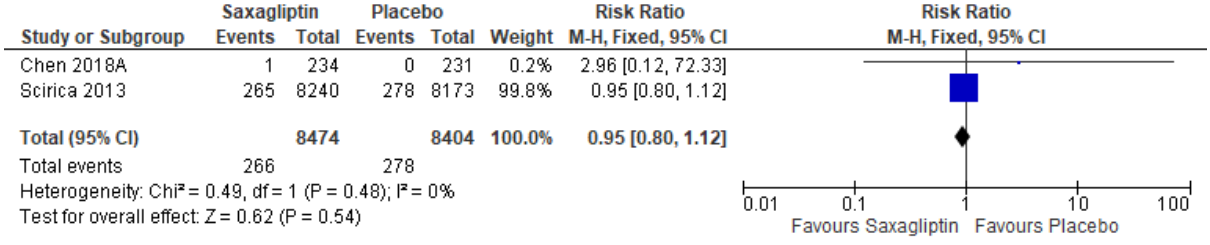
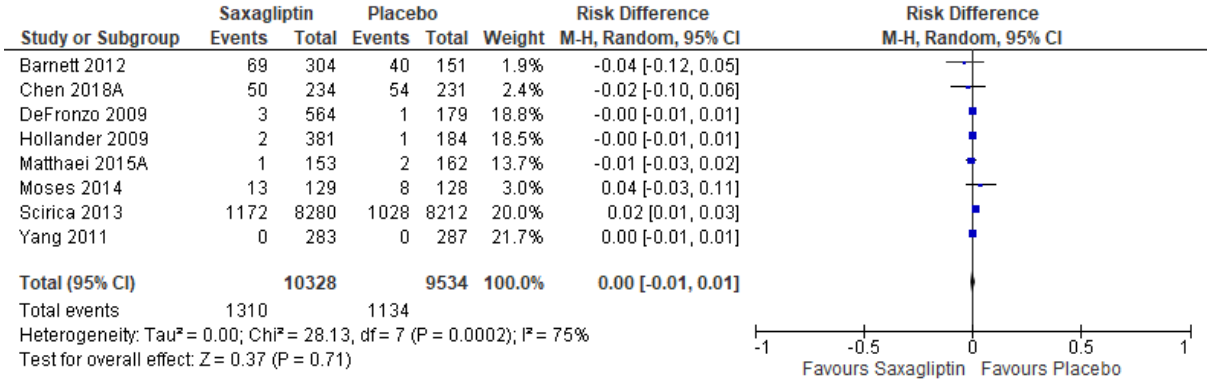


Figure 32: Hypoglycaemia episodes at end of follow up



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

Figure 33: Severe hypoglycaemic episodes at end of follow up

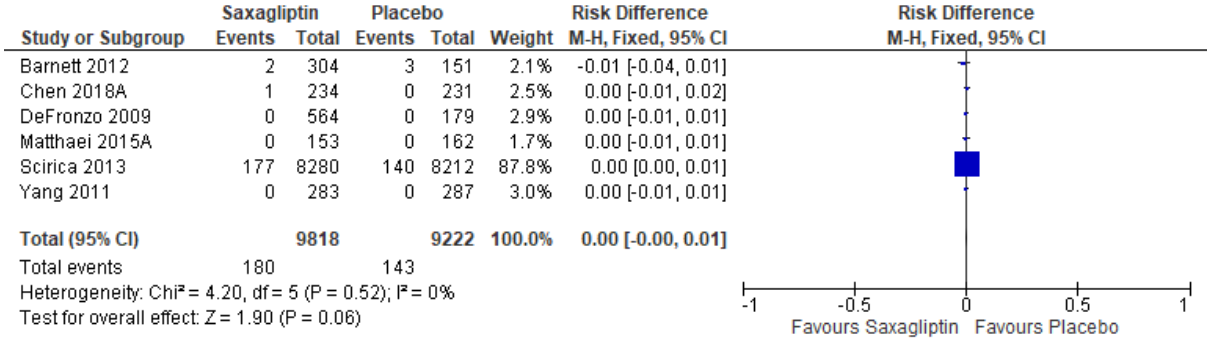
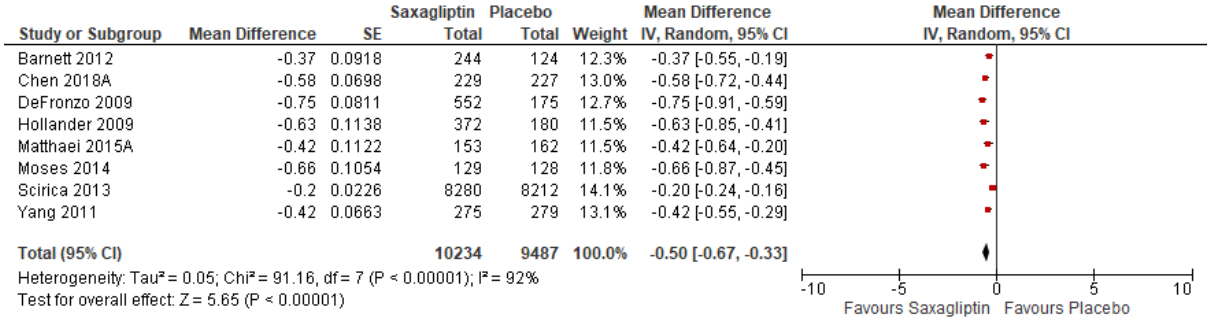
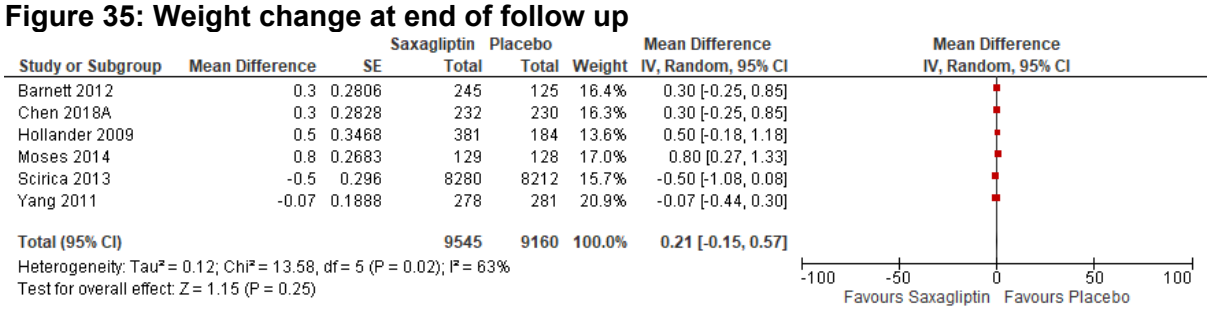


Figure 34: HbA1c change at end of follow up



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

Figure 35: Weight change at end of follow up

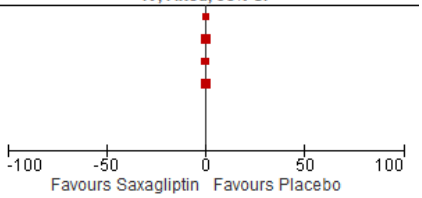


Note: Heterogeneity was not explained by sensitivity analysis, nor subgroup analysis by eGFR subgroup.

Figure 36: BMI change at end of follow up

Study or Subgroup	Mean Difference	SE	Saxagliptin Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Barnett 2012	0.13	0.1	245	125	16.0%	0.13 [-0.07, 0.33]
Chen 2018A	0.08	0.0715	232	229	31.3%	0.08 [-0.06, 0.22]
Scirica 2013	-0.1	0.0865	8280	8212	21.4%	-0.10 [-0.27, 0.07]
Yang 2011	-0.02	0.0714	278	281	31.4%	-0.02 [-0.16, 0.12]
Total (95% CI)			**9035**	**8847**	**100.0%**	**0.02 [-0.06, 0.10]**

Heterogeneity: Chi² = 4.15, df = 3 (P = 0.25); I² = 28%
Test for overall effect: Z = 0.45 (P = 0.65)



K.1.2.5 Adding sitagliptin compared to adding placebo

Figure 37: All-cause mortality at end of follow up

Study or Subgroup	Sitagliptin Events	Sitagliptin Total	Placebo Events	Placebo Total	Weight	Risk Difference IV, Fixed, 95% CI
Ba 2017	0	248	0	249	11.3%	0.00 [-0.01, 0.01]
Dobs 2013	0	170	0	92	2.4%	0.00 [-0.02, 0.02]
Fonseca 2013	0	157	1	156	2.3%	-0.01 [-0.02, 0.01]
Hermansen 2007 - Stratum 1	0	106	0	106	2.1%	0.00 [-0.02, 0.02]
Hermansen 2007 - Stratum 2	1	116	0	113	1.2%	0.01 [-0.02, 0.03]
Lavalle-Gonzalez 2013A	0	366	0	183	9.8%	0.00 [-0.01, 0.01]
Mathieu 2015B	2	329	1	329	6.6%	0.00 [-0.01, 0.01]
Moses 2017	0	210	1	212	4.1%	-0.00 [-0.02, 0.01]
Nauck 2014 Sitagliptin v Placebo	0	315	0	177	8.7%	0.00 [-0.01, 0.01]
Raz 2008	0	96	1	94	0.8%	-0.01 [-0.04, 0.02]
Rosenstock 2006	0	175	0	178	5.7%	0.00 [-0.01, 0.01]
Roussel 2019	0	373	2	370	8.4%	-0.01 [-0.01, 0.00]
Seino 2021	0	70	0	71	0.9%	0.00 [-0.03, 0.03]
Shankar 2017A	0	234	0	233	10.0%	0.00 [-0.01, 0.01]
Vilsboll 2010	0	322	0	319	18.7%	0.00 [-0.01, 0.01]
Yang 2012	0	196	0	198	7.1%	0.00 [-0.01, 0.01]
Total (95% CI)		**3483**		**3080**	**100.0%**	**-0.00 [-0.00, 0.00]**
Total events	3		6			

Heterogeneity: Chi² = 3.55, df = 15 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.43 (P = 0.67)

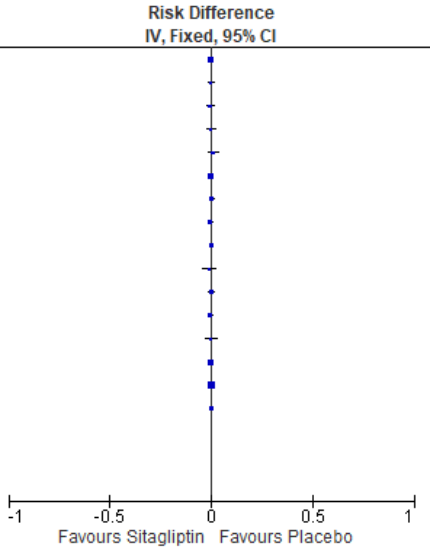


Figure 38: Cardiovascular mortality at end of follow up

Study or Subgroup	Sitagliptin Events	Sitagliptin Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Ba 2017	0	248	0	249	11.5%	0.00 [-0.01, 0.01]
Dobs 2013	0	170	0	92	5.5%	0.00 [-0.02, 0.02]
Hermansen 2007 - Stratum 1	0	106	0	106	4.9%	0.00 [-0.02, 0.02]
Nauck 2014 Sitagliptin v Placebo	0	315	0	177	10.5%	0.00 [-0.01, 0.01]
Raz 2008	0	96	1	94	4.4%	-0.01 [-0.04, 0.02]
Rosenstock 2006	0	175	0	178	8.2%	0.00 [-0.01, 0.01]
Roussel 2019	0	373	2	370	17.2%	-0.01 [-0.01, 0.00]
Seino 2021	0	70	0	71	3.3%	0.00 [-0.03, 0.03]
Shankar 2017A	0	234	0	233	10.8%	0.00 [-0.01, 0.01]
Vilsboll 2010	0	322	0	319	14.8%	0.00 [-0.01, 0.01]
Yang 2012	0	196	0	198	9.1%	0.00 [-0.01, 0.01]
Total (95% CI)		**2305**		**2087**	**100.0%**	**-0.00 [-0.00, 0.00]**
Total events	0		3			

Heterogeneity: Chi² = 1.86, df = 10 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.80 (P = 0.42)

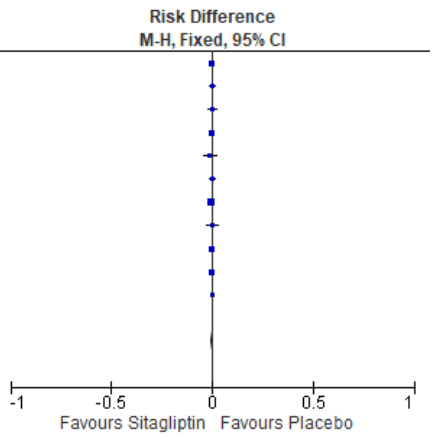


Figure 39: Non-fatal myocardial infarction at end of follow up

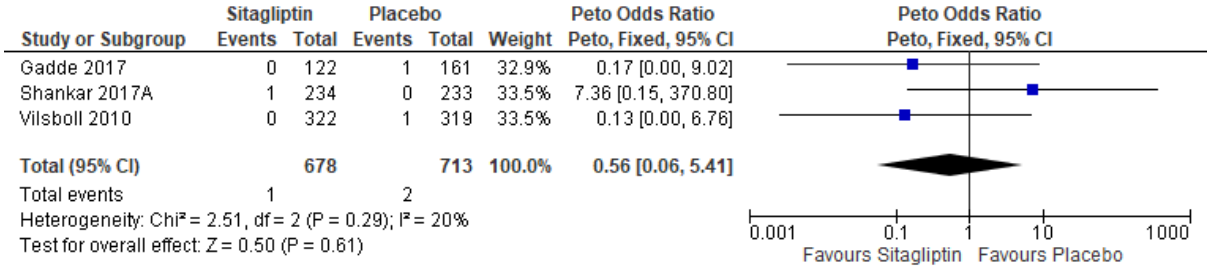


Figure 40: Unstable angina at end of follow up

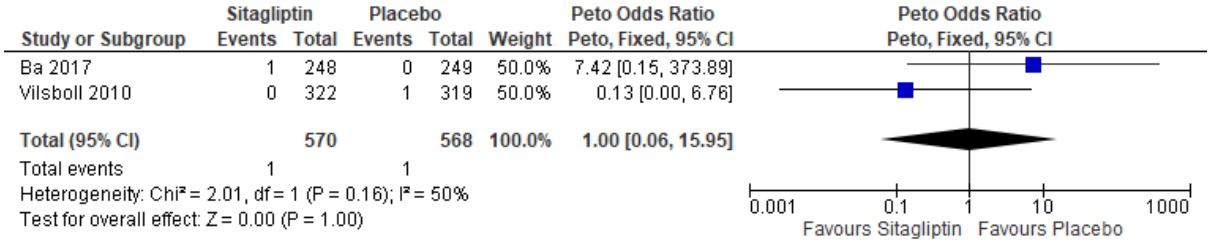
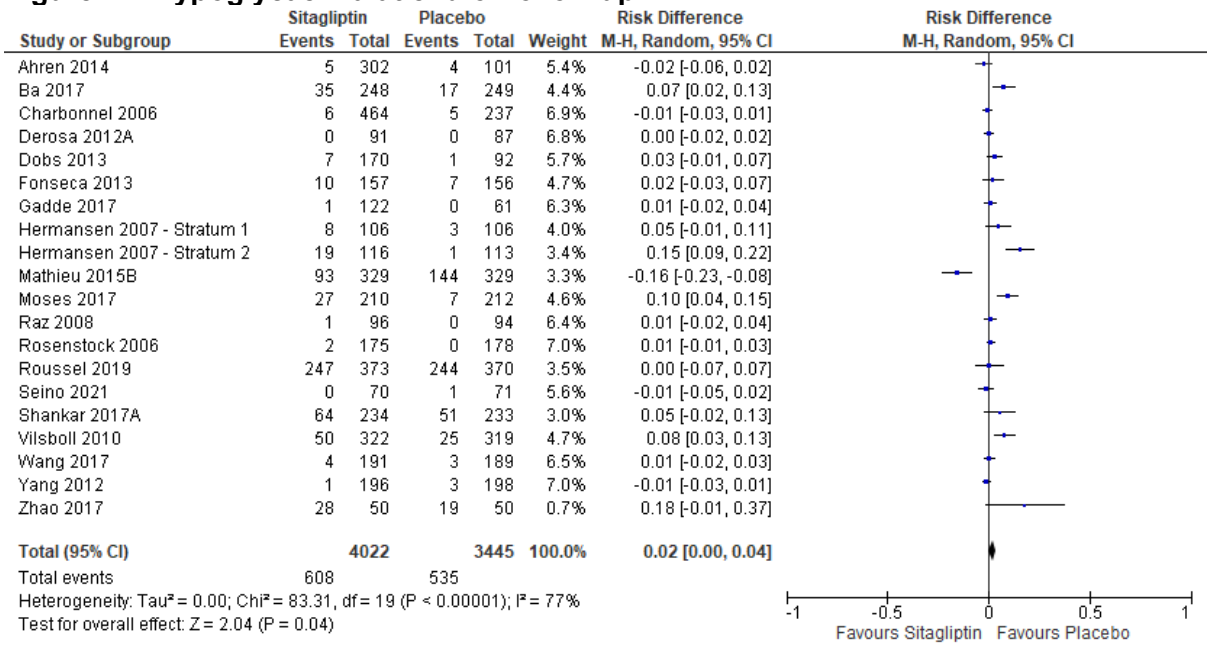


Figure 41: Hypoglycaemia at end of follow up



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

Figure 42: Severe hypoglycaemic episodes at end of follow up

Study or Subgroup	Sitagliptin Events	Sitagliptin Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Ahren 2014	1	302	0	302	9.8%	0.00 [-0.01, 0.01]
Ba 2017	13	248	2	249	8.1%	0.04 [0.01, 0.07]
Dobs 2013	0	170	0	92	3.9%	0.00 [-0.02, 0.02]
Fonseca 2013	0	157	2	156	5.1%	-0.01 [-0.03, 0.01]
Gadde 2017	0	122	0	61	2.6%	0.00 [-0.02, 0.02]
Guzman 2017	0	41	0	68	1.7%	0.00 [-0.04, 0.04]
Hermansen 2007 - Stratum 1	0	106	0	106	3.4%	0.00 [-0.02, 0.02]
Hermansen 2007 - Stratum 2	0	116	0	113	3.7%	0.00 [-0.02, 0.02]
Mathieu 2015B	10	329	13	329	10.7%	-0.01 [-0.04, 0.02]
Moses 2017	1	210	0	212	6.8%	0.00 [-0.01, 0.02]
Nauck 2014 Sitagliptin v Placebo	0	315	0	177	7.4%	0.00 [-0.01, 0.01]
Rosenstock 2006	0	175	0	178	5.7%	0.00 [-0.01, 0.01]
Roussel 2019	11	373	18	370	12.1%	-0.02 [-0.05, 0.01]
Seino 2021	0	70	0	71	2.3%	0.00 [-0.03, 0.03]
Vilsboll 2010	2	322	1	319	10.4%	0.00 [-0.01, 0.01]
Yang 2012	0	196	0	198	6.4%	0.00 [-0.01, 0.01]
Total (95% CI)		**3252**		**3001**	**100.0%**	**0.00 [-0.01, 0.01]**
Total events	38		36			

Heterogeneity: Chi² = 13.15, df = 15 (P = 0.59); I² = 0%
Test for overall effect: Z = 0.21 (P = 0.84)

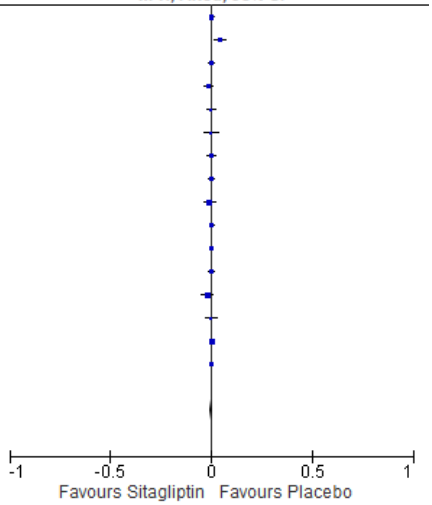
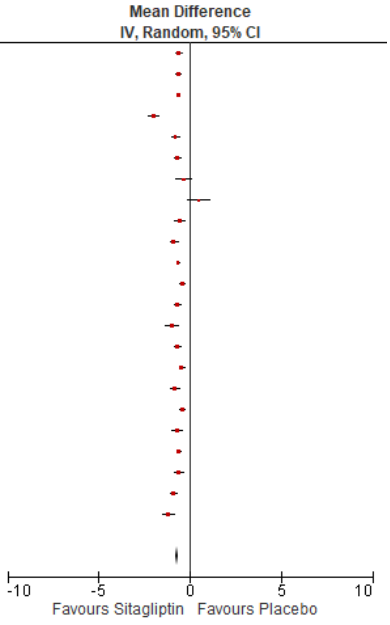


Figure 43: HbA1c change (%, lower values are better, mean difference) at end of follow up

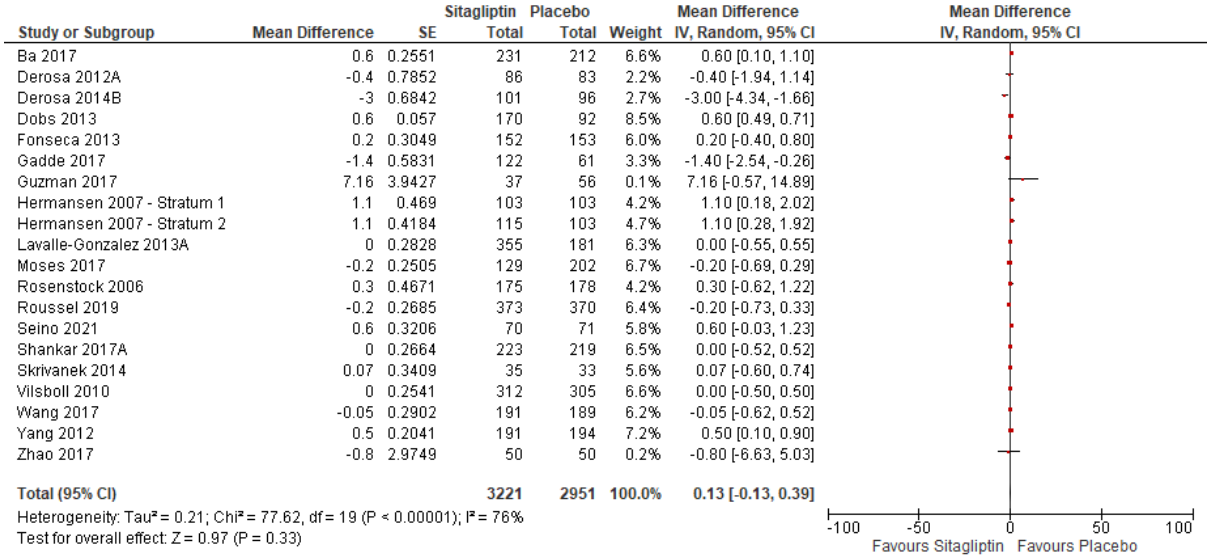
Study or Subgroup	Mean Difference	SE	Sitagliptin Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Ba 2017	-0.61	0.0816	243	236	4.9%	-0.61 [-0.77, -0.45]
Charbonnel 2006	-0.65	0.0882	453	224	4.8%	-0.65 [-0.82, -0.48]
Derosa 2012A	-0.6	0.0245	86	83	5.6%	-0.60 [-0.65, -0.55]
Derosa 2014B	-2	0.136	101	96	3.9%	-2.00 [-2.27, -1.73]
Dobs 2013	-0.8	0.102	168	88	4.6%	-0.80 [-1.00, -0.60]
Fonseca 2013	-0.7	0.0917	152	153	4.7%	-0.70 [-0.88, -0.52]
Gadde 2017	-0.35	0.2302	122	61	2.5%	-0.35 [-0.80, 0.10]
Guzman 2017	0.48	0.314	7	11	1.7%	0.48 [-0.14, 1.10]
Hermansen 2007 - Stratum 1	-0.57	0.1298	103	103	4.1%	-0.57 [-0.82, -0.32]
Hermansen 2007 - Stratum 2	-0.89	0.11	115	109	4.4%	-0.89 [-1.11, -0.67]
Lavalle-Gonzalez 2013A	-0.66	0.04	354	181	5.5%	-0.66 [-0.74, -0.58]
Mathieu 2015B	-0.41	0.0684	329	329	5.1%	-0.41 [-0.54, -0.28]
Moses 2017	-0.68	0.0915	129	202	4.7%	-0.68 [-0.86, -0.50]
Raz 2008	-1	0.1816	95	92	3.2%	-1.00 [-1.36, -0.64]
Rosenstock 2006	-0.7	0.0931	163	174	4.7%	-0.70 [-0.88, -0.52]
Roussel 2019	-0.46	0.0707	373	370	5.1%	-0.46 [-0.60, -0.32]
Seino 2021	-0.83	0.1134	70	71	4.3%	-0.83 [-1.05, -0.61]
Shankar 2017A	-0.4	0.0718	223	219	5.1%	-0.40 [-0.54, -0.26]
Skrivanek 2014	-0.71	0.1526	25	28	3.6%	-0.71 [-1.01, -0.41]
Vilsboll 2010	-0.6	0.051	312	305	5.4%	-0.60 [-0.70, -0.50]
Wang 2017	-0.62	0.1231	191	189	4.2%	-0.62 [-0.86, -0.38]
Yang 2012	-0.9	0.102	191	194	4.6%	-0.90 [-1.10, -0.70]
Zhao 2017	-1.2	0.1703	50	50	3.4%	-1.20 [-1.53, -0.87]
Total (95% CI)			**4055**	**3568**	**100.0%**	**-0.71 [-0.80, -0.61]**

Heterogeneity: Tau² = 0.04; Chi² = 180.05, df = 22 (P < 0.00001); I² = 88%
Test for overall effect: Z = 14.50 (P < 0.00001)



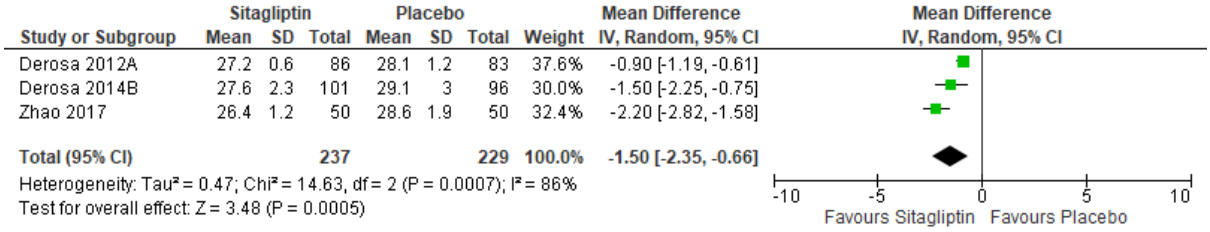
Note: Heterogeneity was not explained by sensitivity analysis, nor subgroup analysis by eGFR, NAFLD, and obesity subgroups.

Figure 44: Weight change (kg, lower values are better, mean difference) at end of follow up



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

Figure 45: BMI change (kg/m^2, lower values are better, final values) at end of follow up



K.1.2.6 Adding sitagliptin compared to adding metformin

Figure 46: HbA1c change (%, lower values are better, change and final scores) at end of follow up

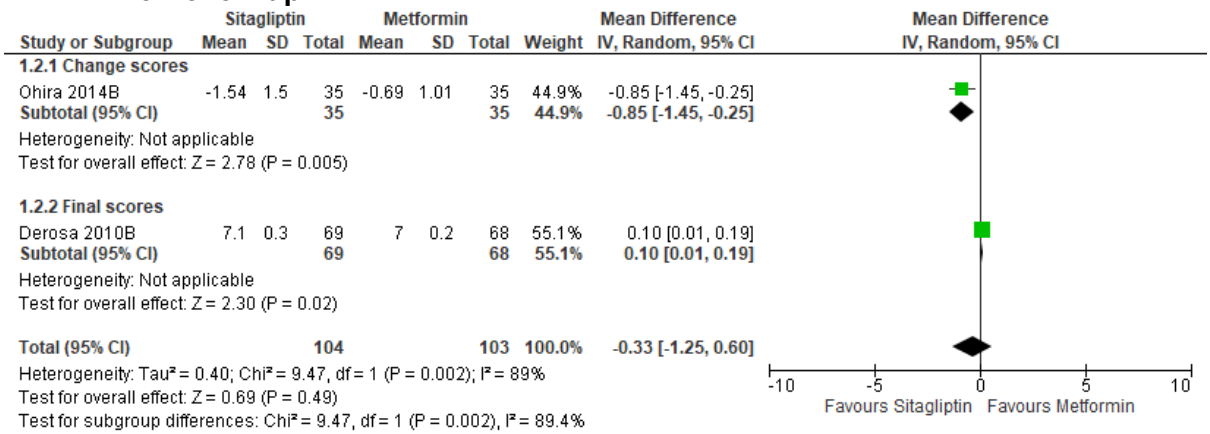


Figure 47: Weight change (kg, lower values are better, change and final scores) at end of follow up

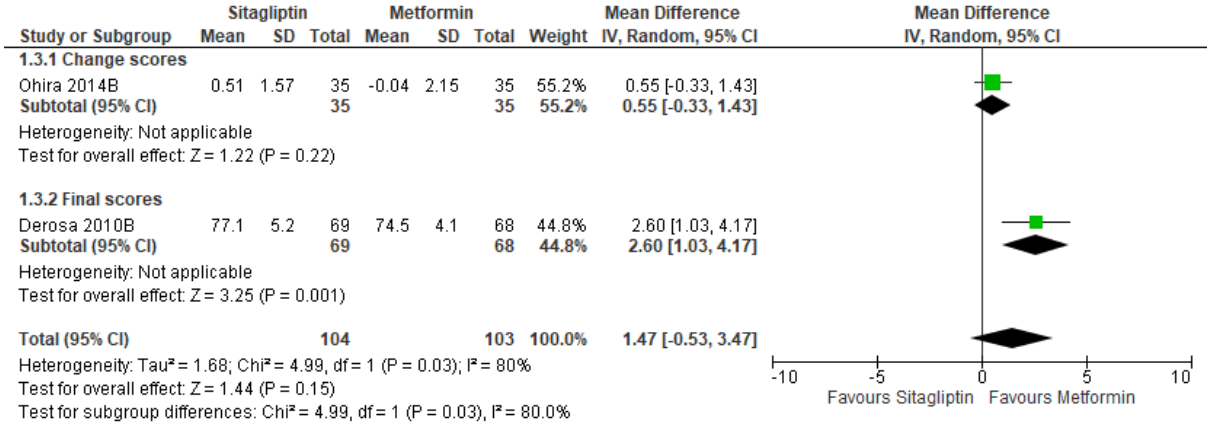
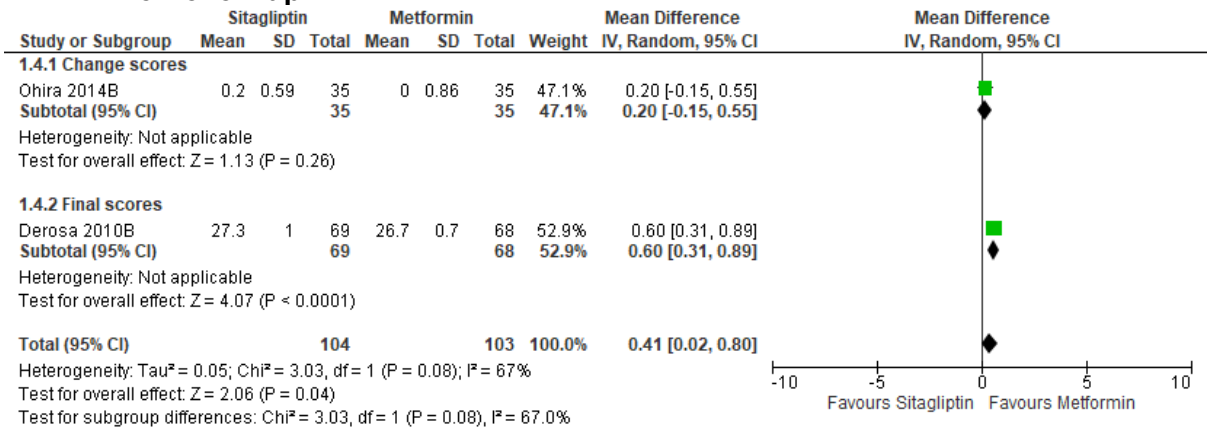


Figure 48: BMI change (kg/m^2, lower values are better, change and final scores) at end of follow up



K.1.2.7 Adding sitagliptin compared to adding insulin

Figure 49: All-cause mortality at end of follow up

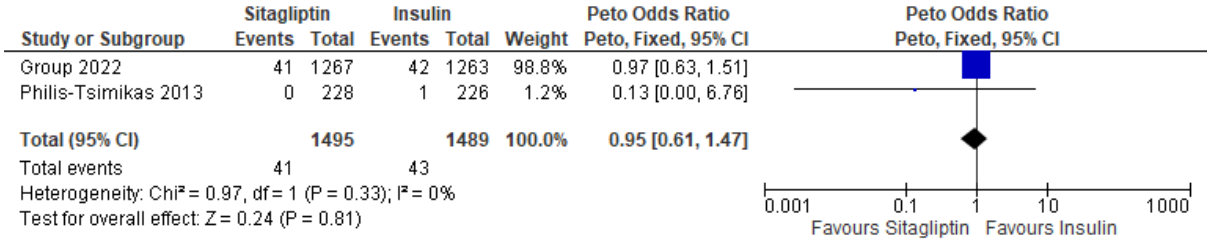


Figure 50: Unstable angina at end of follow up

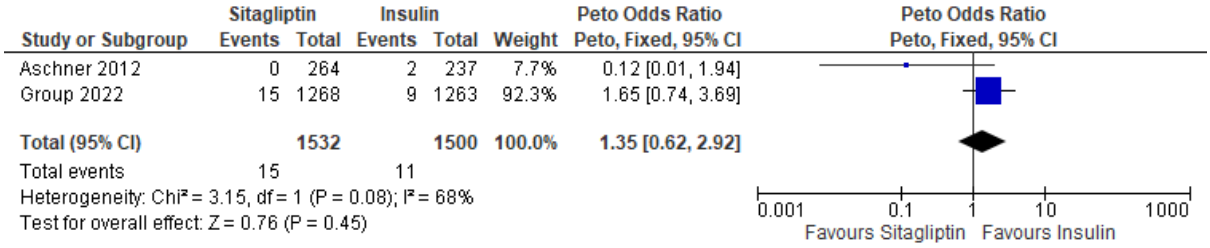
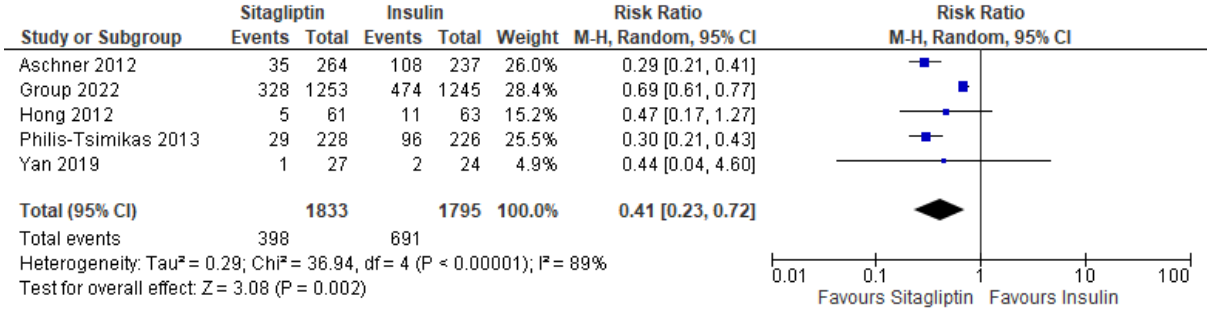


Figure 51: Hypoglycaemia episodes at end of follow up



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

Figure 52: At night hypoglycaemic episodes at end of follow up

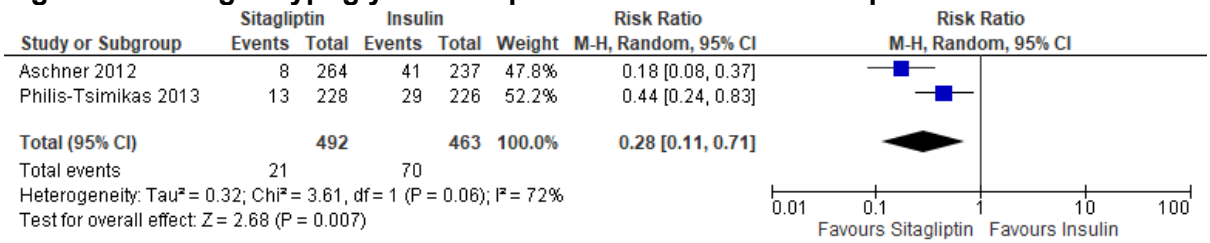


Figure 53: Severe hypoglycaemic episodes at end of follow up

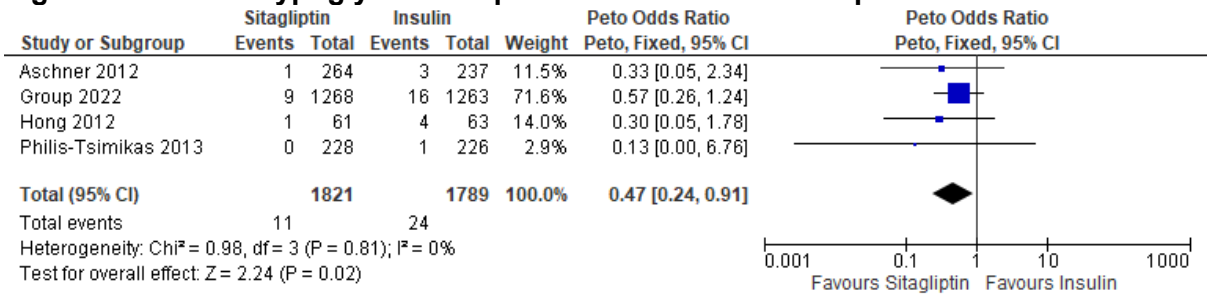
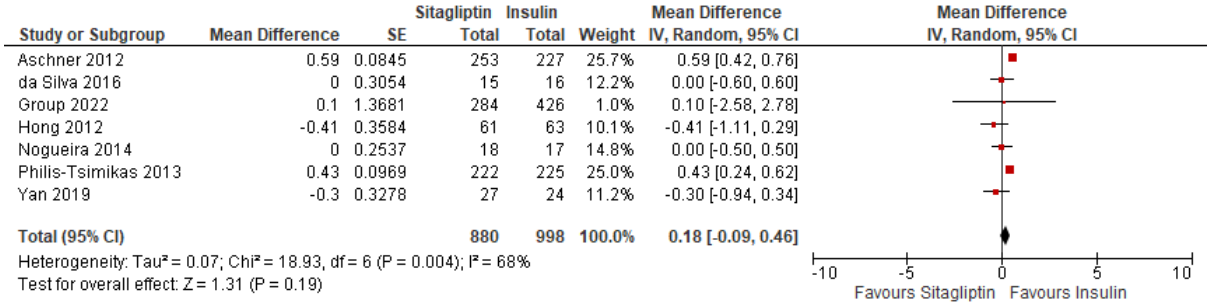
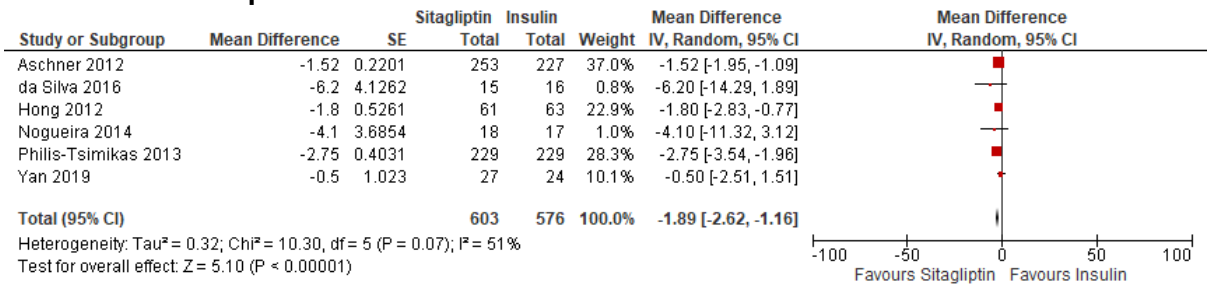


Figure 54: HbA1c change (%, lower values are better, mean difference) at end of follow up



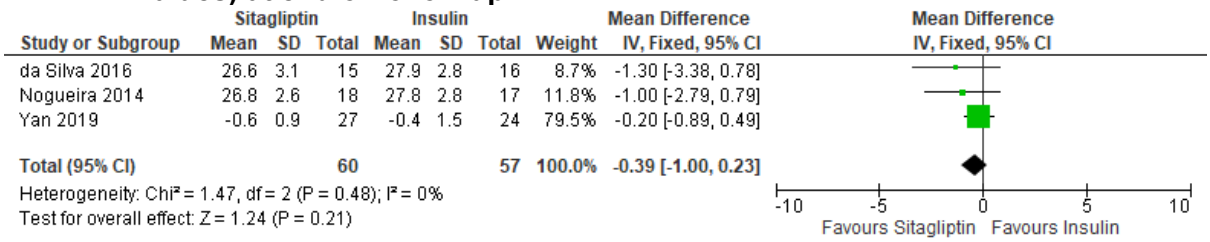
Note: Heterogeneity was not explained by sensitivity analysis, nor subgroup analysis by eGFR, NAFLD, and obesity subgroups.

Figure 55: Weight change (kg, lower values are better, mean difference) at end of follow up



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

Figure 56: BMI change (kg/m^2, lower values are better, change scores and final values) at end of follow up



K.1.2.8 Adding vildagliptin compared to adding placebo

Figure 57: All-cause mortality at end of follow up

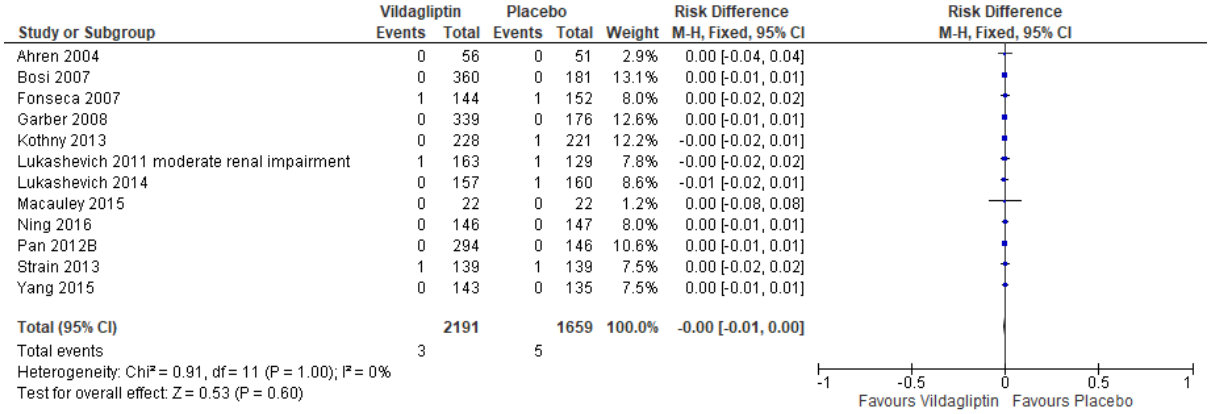


Figure 58: Cardiovascular mortality at end of follow up

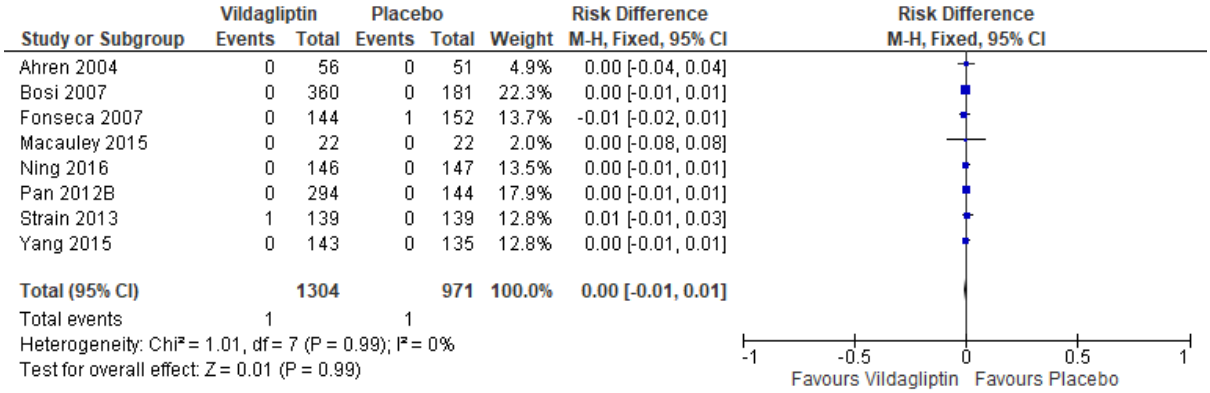


Figure 59: Non-fatal stroke at end of follow up

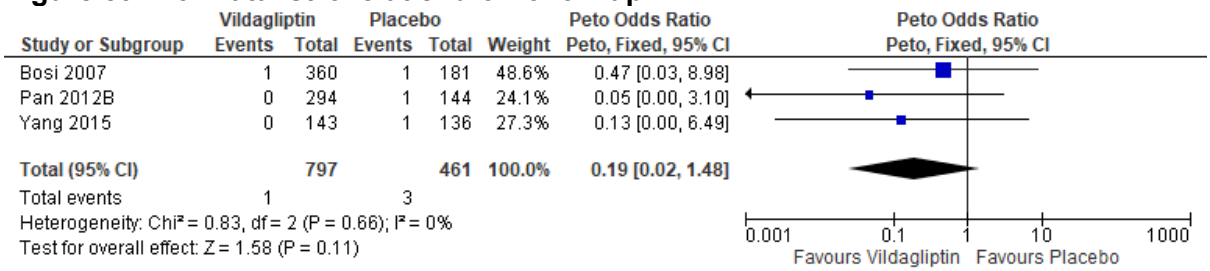


Figure 60: Hypoglycaemia episodes at end of follow up

Study or Subgroup	Vildagliptin Events	Vildagliptin Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Bosi 2007	2	360	1	181	9.6%	0.00 [-0.01, 0.01]
Derosa 2012B	0	84	0	83	3.3%	0.00 [-0.02, 0.02]
Fonseca 2007	33	144	45	152	5.9%	-0.07 [-0.17, 0.03]
Garber 2007	1	305	3	158	8.3%	-0.02 [-0.04, 0.01]
Garber 2008	8	339	1	176	9.3%	0.02 [-0.00, 0.04]
Goodman 2009	2	248	0	122	6.5%	0.01 [-0.01, 0.02]
Kothny 2013	19	228	16	221	9.0%	0.01 [-0.04, 0.06]
Lukashevich 2011 moderate renal impairment	32	122	15	89	4.1%	0.09 [-0.02, 0.20]
Lukashevich 2014	8	157	3	160	6.3%	0.03 [-0.01, 0.07]
Macauley 2015	1	22	0	22	0.9%	0.05 [-0.07, 0.16]
Ning 2016	4	146	8	147	5.9%	-0.03 [-0.07, 0.02]
Pan 2012B	1	294	0	144	7.7%	0.00 [-0.01, 0.02]
Strain 2013	3	139	1	139	5.6%	0.01 [-0.01, 0.04]
Su 2014	2	300	0	300	12.0%	0.01 [-0.00, 0.02]
Yang 2015	0	143	0	135	5.6%	0.00 [-0.01, 0.01]
Total (95% CI)		**3031**		**2229**	**100.0%**	**0.00 [-0.01, 0.01]**
Total events	116		93			

Heterogeneity: Chi² = 15.48, df = 14 (P = 0.35); I² = 10%
Test for overall effect: Z = 0.85 (P = 0.39)

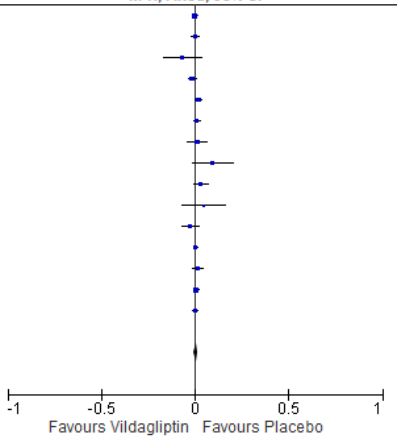


Figure 61: Severe hypoglycaemic episodes at end of follow up

Study or Subgroup	Vildagliptin Events	Vildagliptin Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Bosi 2007	0	360	0	181	11.4%	0.00 [-0.01, 0.01]
Fonseca 2007	0	144	4	152	7.0%	-0.03 [-0.05, 0.00]
Garber 2007	0	305	0	158	9.9%	0.00 [-0.01, 0.01]
Garber 2008	0	339	1	176	11.0%	-0.01 [-0.02, 0.01]
Goodman 2009	0	248	0	122	7.7%	0.00 [-0.01, 0.01]
Kothny 2013	2	228	2	221	10.6%	-0.00 [-0.02, 0.02]
Li 2017	0	17	0	16	0.8%	0.00 [-0.11, 0.11]
Lukashevich 2011 moderate renal impairment	2	122	3	89	4.9%	-0.02 [-0.06, 0.03]
Lukashevich 2014	1	157	0	160	7.5%	0.01 [-0.01, 0.02]
Ning 2016	0	146	1	147	6.9%	-0.01 [-0.03, 0.01]
Pan 2012B	1	294	0	144	9.2%	0.00 [-0.01, 0.02]
Strain 2013	0	139	0	139	6.6%	0.00 [-0.01, 0.01]
Yang 2015	0	143	0	135	6.6%	0.00 [-0.01, 0.01]
Total (95% CI)		**2642**		**1840**	**100.0%**	**-0.00 [-0.01, 0.00]**
Total events	6		11			

Heterogeneity: Chi² = 6.94, df = 12 (P = 0.86); I² = 0%
Test for overall effect: Z = 1.20 (P = 0.23)

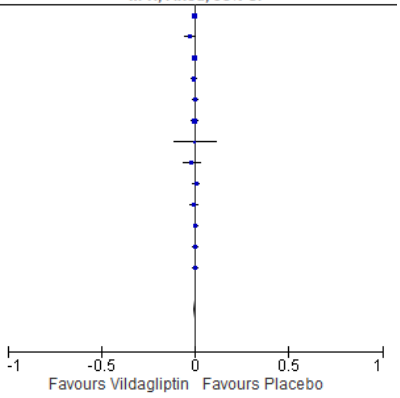
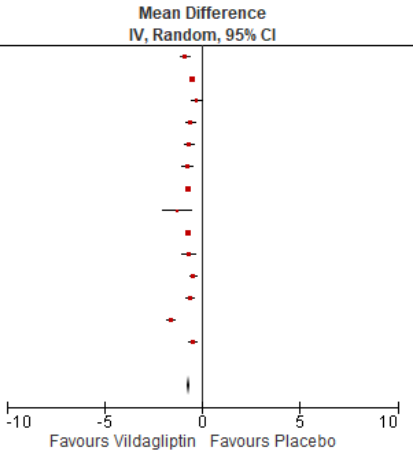


Figure 62: HbA1c change (%, lower values are better, mean difference) at end of follow up

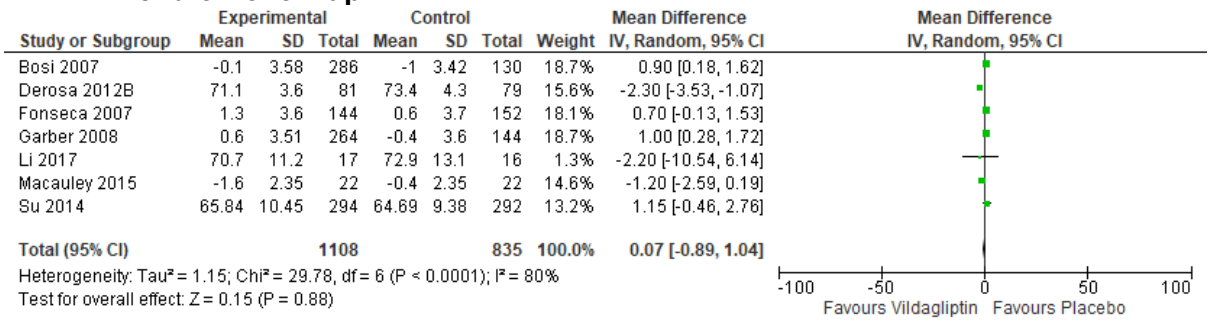
Study or Subgroup	Mean Difference	SE	Vildagliptin Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Bosi 2007	-0.9	0.1226	286	130	5.7%	-0.90 [-1.14, -0.66]
Derosa 2012B	-0.5	0.0251	81	79	12.9%	-0.50 [-0.55, -0.45]
Fonseca 2007	-0.3	0.1412	140	149	4.8%	-0.30 [-0.58, -0.02]
Garber 2007	-0.6	0.1228	305	158	5.7%	-0.60 [-0.84, -0.36]
Garber 2008	-0.675	0.1119	264	144	6.3%	-0.68 [-0.89, -0.46]
Goodman 2009	-0.77	0.1345	248	122	5.1%	-0.77 [-1.03, -0.51]
Kothny 2013	-0.7	0.0094	228	221	13.6%	-0.70 [-0.72, -0.68]
Li 2017	-1.3	0.3785	17	16	0.9%	-1.30 [-2.04, -0.56]
Macauley 2015	-0.7	0.0094	22	22	13.6%	-0.70 [-0.72, -0.68]
Ning 2016	-0.7	0.1697	146	147	3.7%	-0.70 [-1.03, -0.37]
Pan 2012B	-0.45	0.0981	292	144	7.2%	-0.45 [-0.64, -0.26]
Strain 2013	-0.6	0.1071	137	137	6.6%	-0.60 [-0.81, -0.39]
Su 2014	-1.61	0.1004	294	292	7.0%	-1.61 [-1.81, -1.41]
Yang 2015	-0.5	0.1	141	133	7.1%	-0.50 [-0.70, -0.30]
Total (95% CI)			**2601**	**1894**	**100.0%**	**-0.69 [-0.77, -0.62]**

Heterogeneity: Tau² = 0.01; Chi² = 167.84, df = 13 (P < 0.00001); I² = 92%
Test for overall effect: Z = 18.20 (P < 0.00001)



Note: Heterogeneity was not explained by sensitivity analysis, nor subgroup analysis by ACR, eGFR, Frailty, NAFLD, obesity and early onset subgroups.

Figure 63: Weight change (kg, lower values are better, change and final scores) at end of follow up



Note: Heterogeneity was not explained by sensitivity analysis, nor subgroup analysis by ACR, eGFR, Frailty, NAFLD, obesity and early onset subgroups.

K.1.2.9 Adding vildagliptin compared to adding metformin

Figure 64: Hypoglycaemia episodes at end of follow up

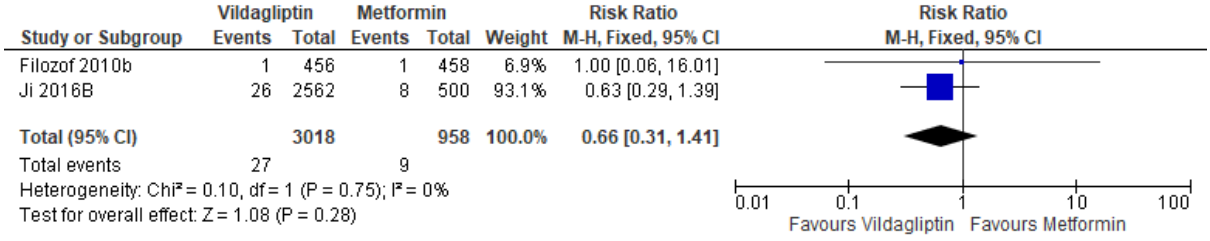
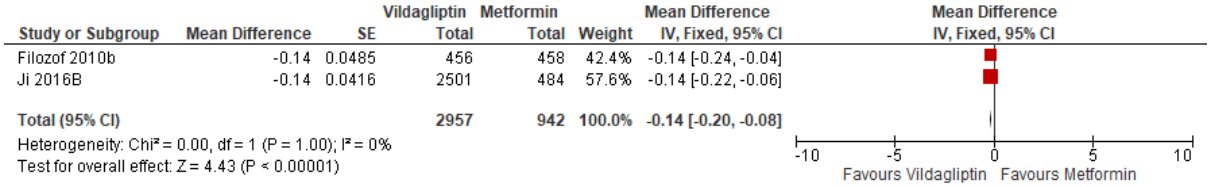


Figure 65: HbA1c change (%, lower values are better, change and final scores) at end of follow up



K.1.2.10 Adding vildagliptin compared to adding insulin

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

K.1.2.11 Adding vildagliptin compared to adding saxagliptin

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

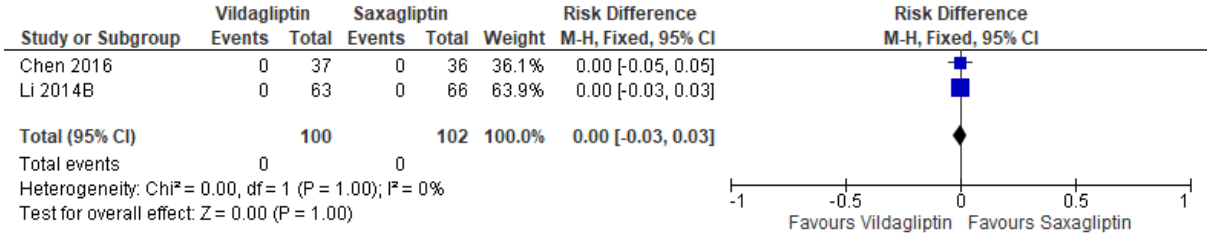


Figure 67: Cardiovascular mortality at end of follow up

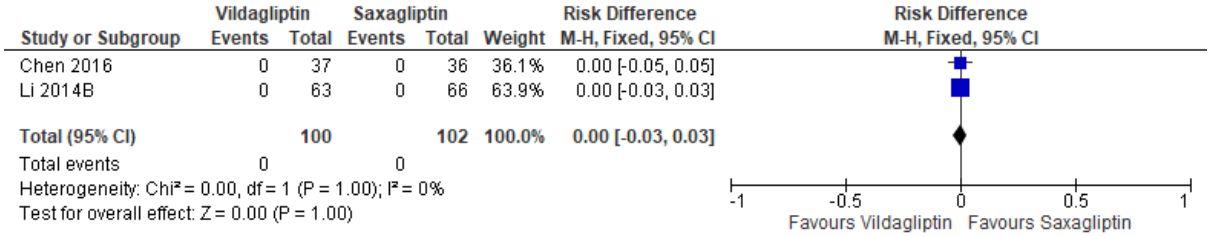


Figure 68: Hypoglycaemia episodes at end of follow up

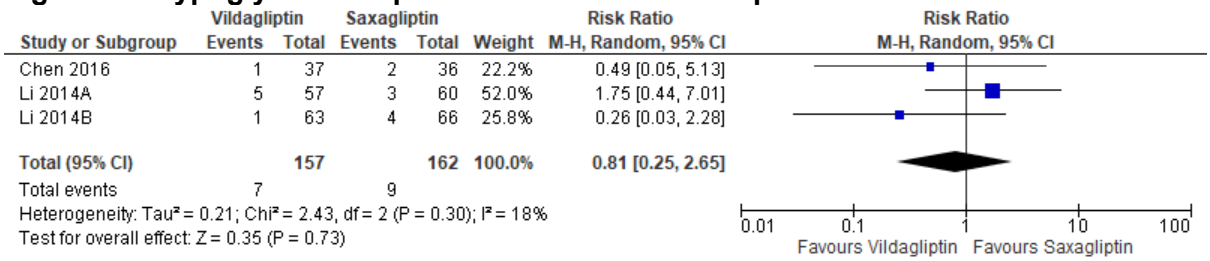


Figure 69: Severe hypoglycaemic episodes at end of follow up

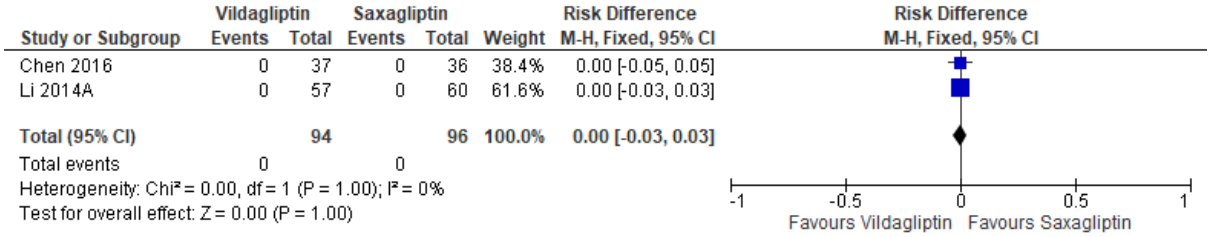


Figure 70: HbA1c change (%, lower values are better, change scores) at end of follow up

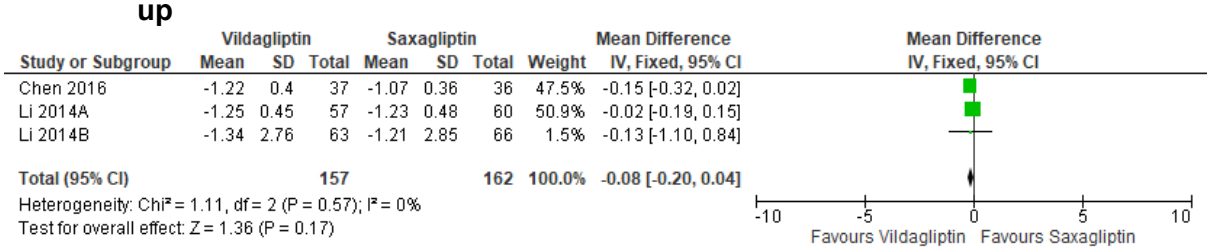
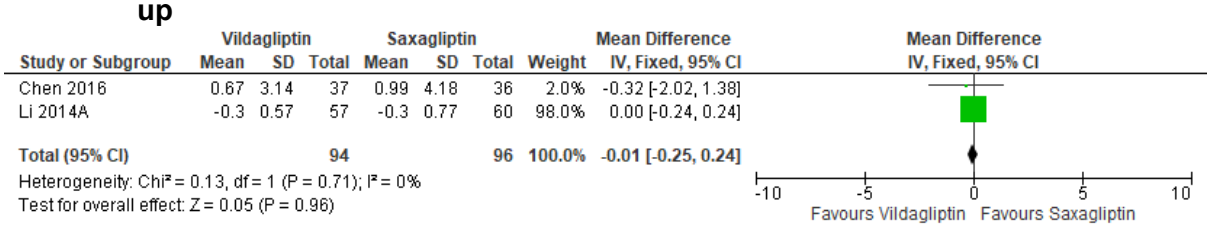


Figure 71: BMI change (kg/m^2, lower values are better, change scores) at end of follow up



K.1.3 GLP-1 receptor agonist

K.1.3.1 Adding dulaglutide compared to adding placebo

Figure 72: All-cause mortality at end of follow up

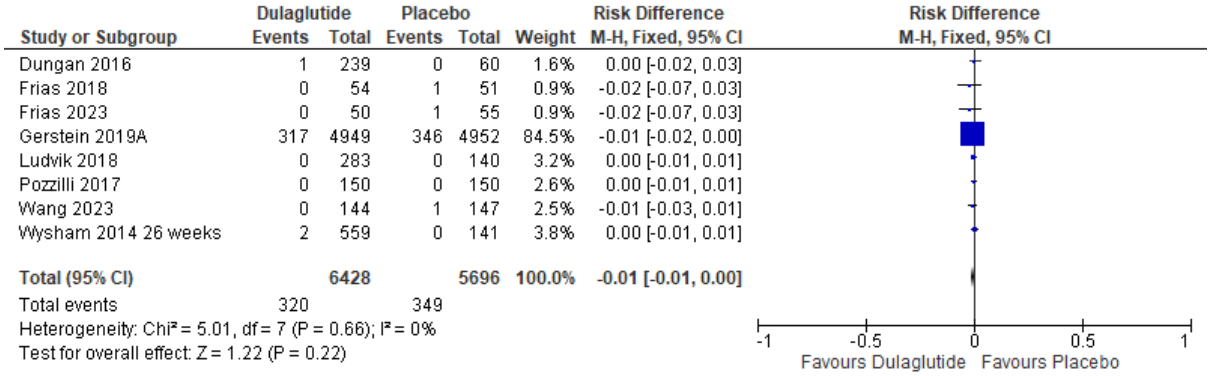


Figure 73: Cardiovascular mortality at end of follow up

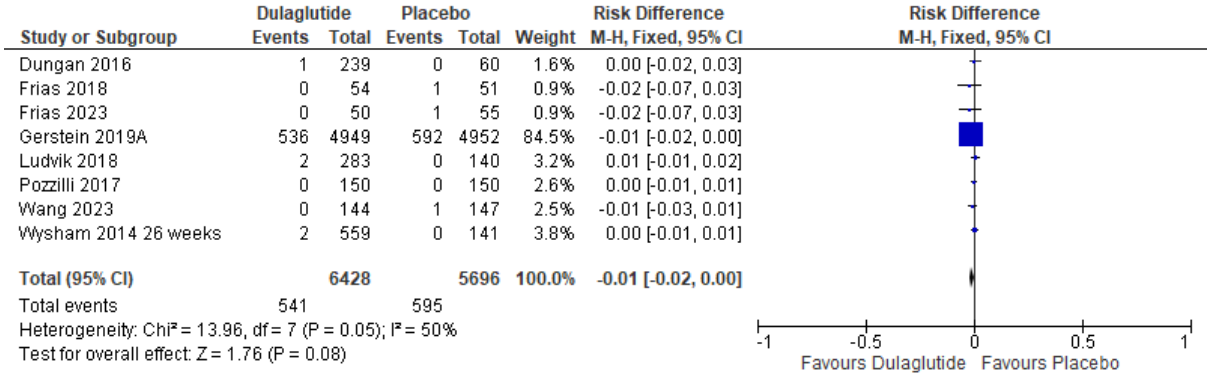


Figure 74: Non-fatal stroke at end of follow up

Study or Subgroup	Dulaglutide Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Dungan 2016	1	239	0	60	0.5%	0.76 [0.03, 18.49]
Gerstein 2019A	135	4949	175	4952	99.3%	0.77 [0.62, 0.96]
Pozzilli 2017	2	150	0	150	0.3%	5.00 [0.24, 103.28]
Total (95% CI)		**5338**		**5162**	**100.0%**	**0.78 [0.63, 0.98]**
Total events	138		175			

Heterogeneity: Chi² = 1.46, df = 2 (P = 0.48); I² = 0%
Test for overall effect: Z = 2.18 (P = 0.03)

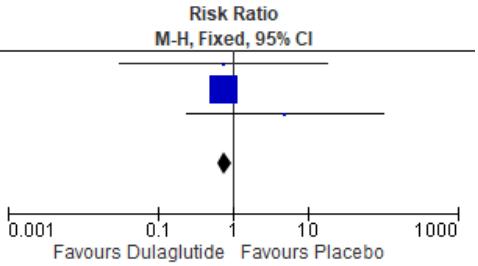


Figure 75: Non-fatal myocardial infarction at end of follow up

Study or Subgroup	Dulaglutide Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gerstein 2019A	205	4949	212	4952	98.2%	0.97 [0.80, 1.17]
Ludvik 2018	0	283	2	140	1.5%	0.10 [0.00, 2.05]
Pozzilli 2017	1	150	0	150	0.2%	3.00 [0.12, 73.06]
Total (95% CI)		**5382**		**5242**	**100.0%**	**0.96 [0.80, 1.16]**
Total events	206		214			

Heterogeneity: Chi² = 2.65, df = 2 (P = 0.27); I² = 25%
Test for overall effect: Z = 0.44 (P = 0.66)

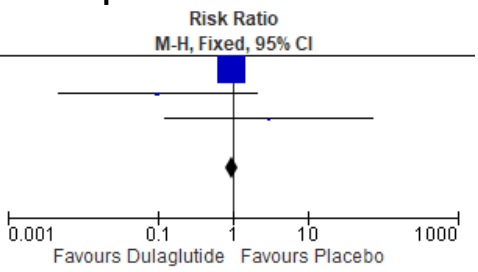


Figure 76: Unstable angina at end of follow up

Study or Subgroup	Dulaglutide Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gerstein 2019A	88	4949	77	4952	96.2%	1.14 [0.84, 1.55]
Ludvik 2018	0	283	1	140	2.5%	0.17 [0.01, 4.04]
Pozzilli 2017	1	150	1	150	1.3%	1.00 [0.06, 15.84]
Total (95% CI)		**5382**		**5242**	**100.0%**	**1.12 [0.83, 1.51]**
Total events	89		79			

Heterogeneity: Chi² = 1.40, df = 2 (P = 0.50); I² = 0%
Test for overall effect: Z = 0.73 (P = 0.47)

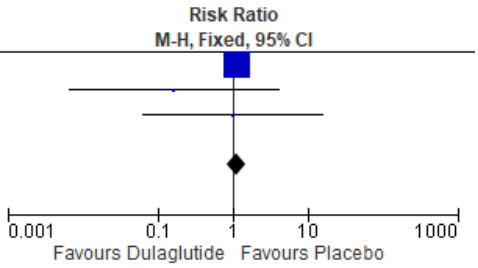


Figure 77: Acute kidney injury at end of follow up

Study or Subgroup	Dulaglutide Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gerstein 2019A	60	4949	67	4952	99.3%	0.90 [0.63, 1.27]
Wang 2023	1	144	0	147	0.7%	3.06 [0.13, 74.55]
Total (95% CI)		**5093**		**5099**	**100.0%**	**0.91 [0.65, 1.29]**
Total events	61		67			

Heterogeneity: Chi² = 0.56, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.53 (P = 0.60)

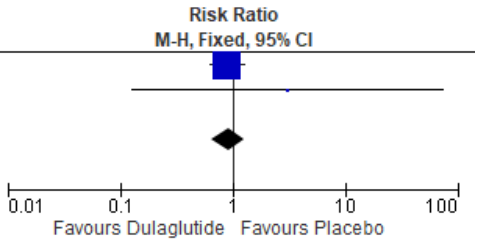


Figure 78: Cardiac arrhythmia at end of follow up

Study or Subgroup	Dulaglutide Events	Dulaglutide Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Frias 2023	0	50	0	55	1.0%	0.00 [-0.04, 0.04]
Gerstein 2019A	216	4949	192	4952	99.0%	0.00 [-0.00, 0.01]
Total (95% CI)		**4999**		**5007**	**100.0%**	**0.00 [-0.00, 0.01]**
Total events	216		192			

Heterogeneity: Chi² = 0.07, df = 1 (P = 0.80); I² = 0%
Test for overall effect: Z = 1.22 (P = 0.22)

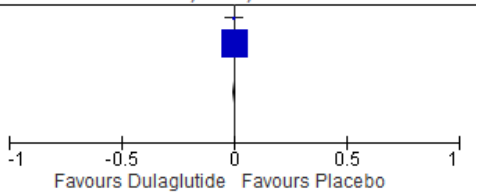


Figure 79: Diabetic ketoacidosis at end of follow up

Study or Subgroup	Dulaglutide Events	Dulaglutide Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Frias 2023	0	50	0	55	21.9%	0.00 [-0.04, 0.04]
Ludvik 2018	0	283	0	140	78.1%	0.00 [-0.01, 0.01]
Total (95% CI)		**333**		**195**	**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)

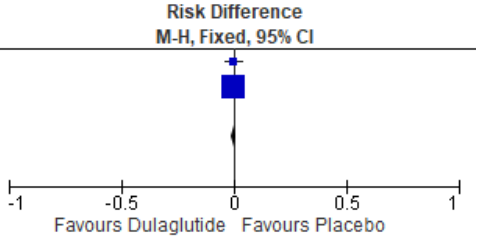


Figure 80: Hypoglycaemia episodes at end of follow up

Study or Subgroup	Dulaglutide Events	Dulaglutide Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Dungan 2016	50	239	2	60	3.1%	6.28 [1.57, 25.07]
Frias 2018	2	54	2	51	2.0%	0.94 [0.14, 6.46]
Frias 2023	2	50	2	55	1.8%	1.10 [0.16, 7.52]
Ludvik 2018	10	283	4	140	5.2%	1.24 [0.39, 3.87]
Pozzilli 2017	53	150	45	150	43.7%	1.18 [0.85, 1.63]
Wang 2023	42	144	46	147	44.2%	0.93 [0.66, 1.32]
Total (95% CI)		**920**		**603**	**100.0%**	**1.22 [0.97, 1.54]**
Total events	159		101			

Heterogeneity: Chi² = 7.83, df = 5 (P = 0.17); I² = 36%
Test for overall effect: Z = 1.72 (P = 0.08)

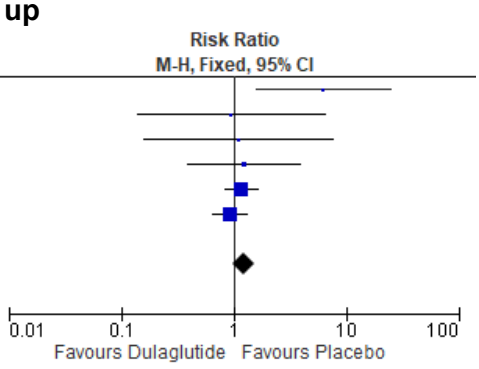


Figure 81: At night hypoglycaemic episodes at end of follow up

Study or Subgroup	Dulaglutide Events	Dulaglutide Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Dungan 2016	16	239	1	60	2.5%	4.02 [0.54, 29.69]
Pozzilli 2017	42	150	43	150	67.8%	0.98 [0.68, 1.40]
Wang 2023	11	144	19	147	29.7%	0.59 [0.29, 1.20]
Total (95% CI)		**533**		**357**	**100.0%**	**0.94 [0.68, 1.29]**
Total events	69		63			

Heterogeneity: Chi² = 3.73, df = 2 (P = 0.16); I² = 46%
Test for overall effect: Z = 0.39 (P = 0.70)

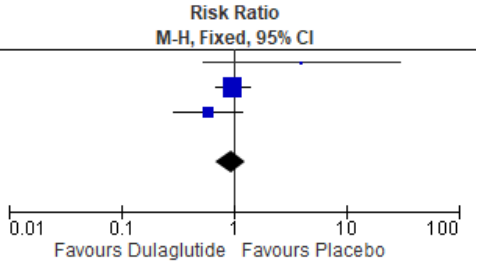


Figure 82: Severe hypoglycaemic episodes at end of follow up

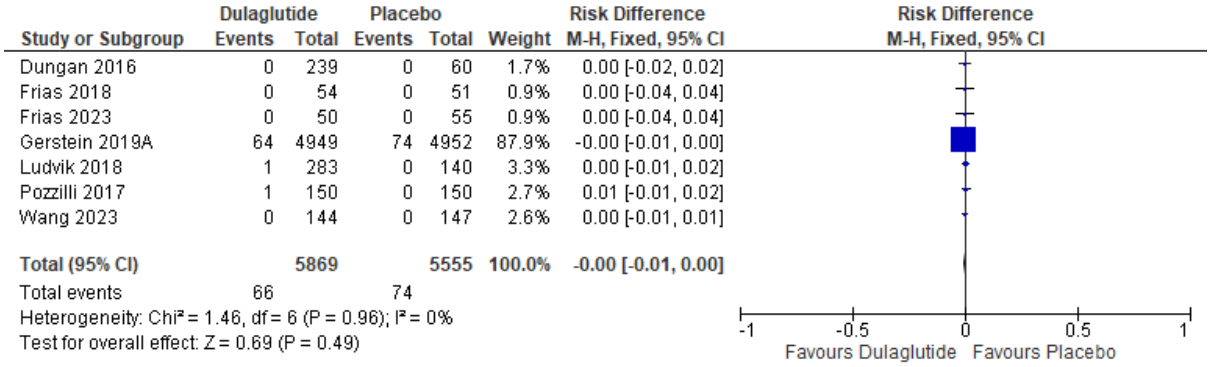
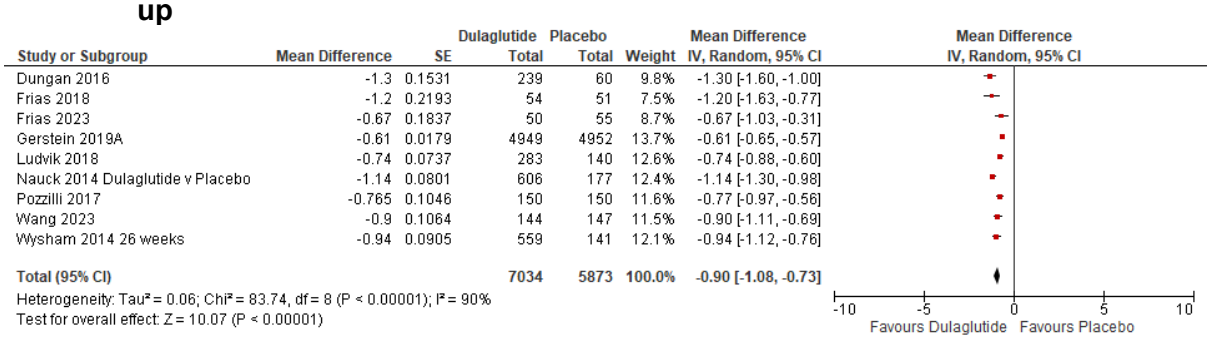


Figure 83: HbA1c change (%, lower values are better, change scores) at end of follow up



Note: Heterogeneity was not explained by sensitivity analysis, nor subgroup analysis by ACR, eGFR, obesity and early onset subgroups.

Figure 84: Weight change (kg, lower values are better, change scores) at end of follow up

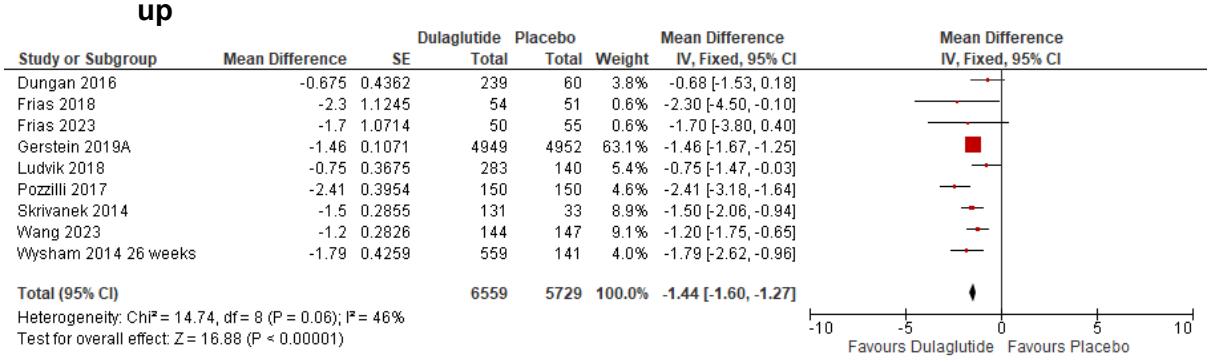
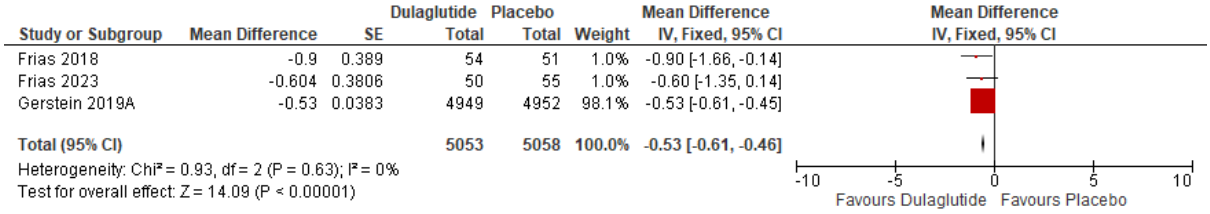


Figure 85: BMI change (kg/m^2, lower values are better, change scores) at end of follow up



K.1.3.2 Adding dulaglutide compared to adding insulin

Figure 86: All-cause mortality at end of follow up

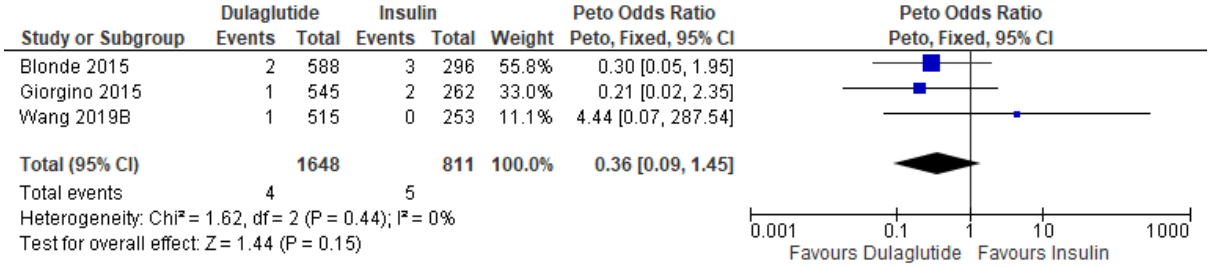


Figure 87: Hypoglycaemia episodes at end of follow up

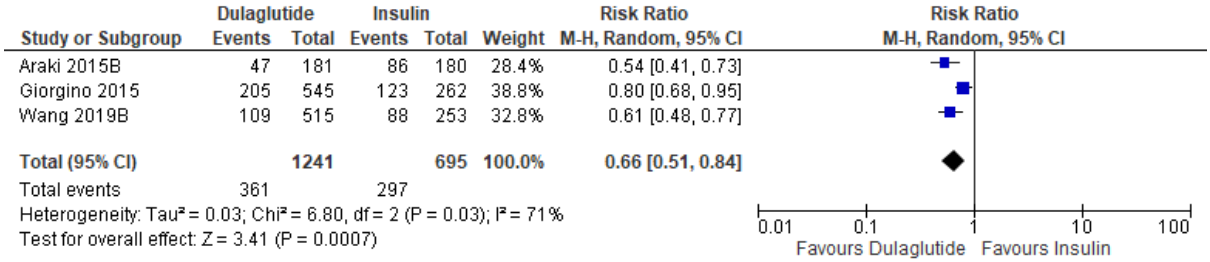


Figure 88: At night hypoglycaemic episodes at end of follow yp

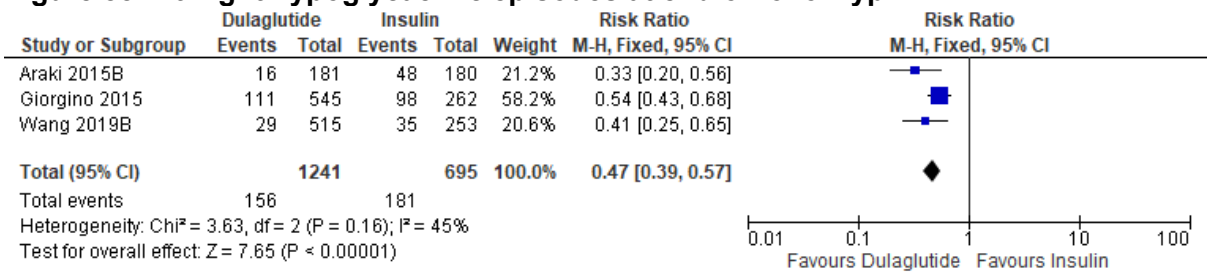
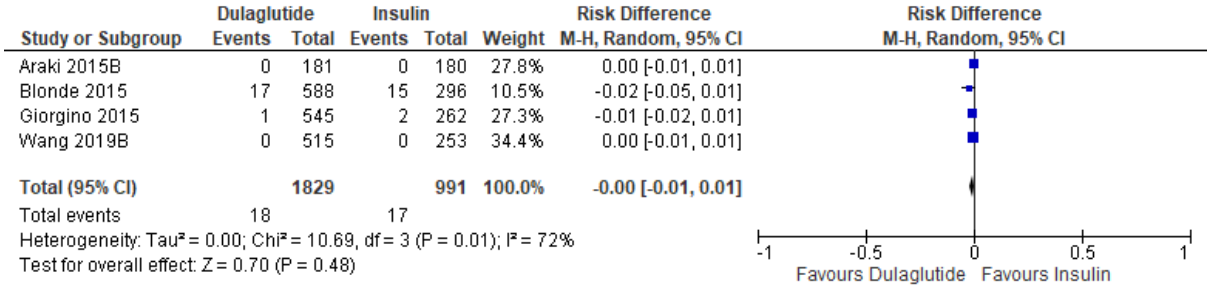
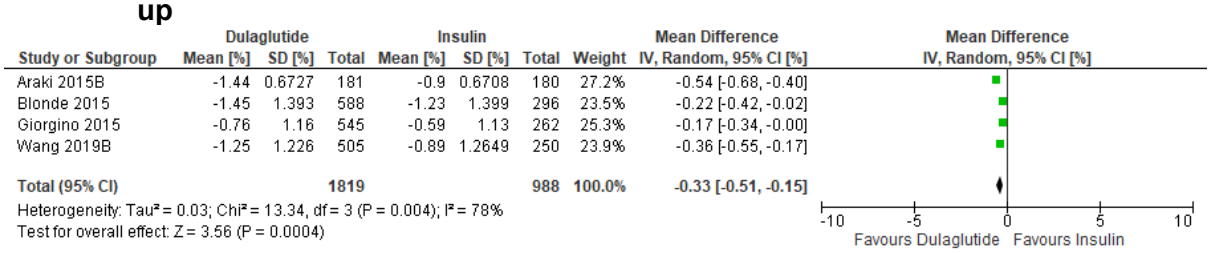


Figure 89: Severe hypoglycaemic episodes at end of follow up



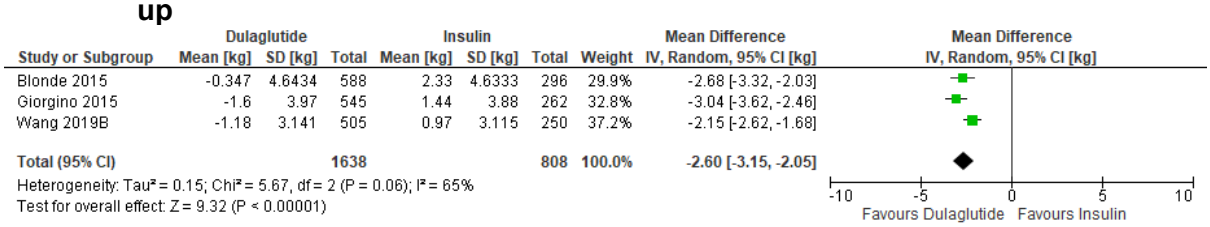
Note: Heterogeneity was not explained by sensitivity analysis, nor subgroup analysis by eGFR subgroup.

Figure 90: 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 subgroup.

Figure 91: Weight change (kg, lower values are better, change scores) at end of follow up



K.1.3.3 Adding dulaglutide compared to adding exenatide

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

K.1.3.4 Adding dulaglutide compared to adding sitagliptin

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

K.1.3.5 Adding exenatide compared to adding placebo

Figure 92: All-cause mortality at end of follow up

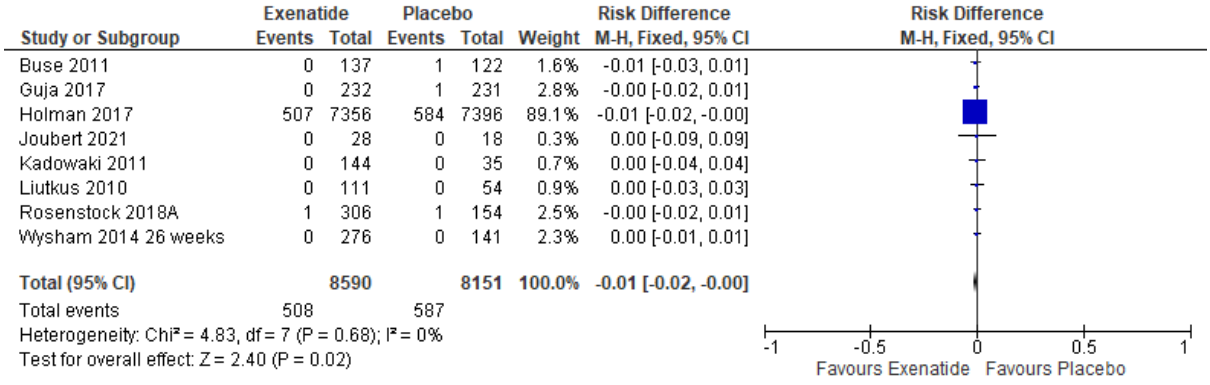


Figure 93: Cardiovascular mortality at end of follow up

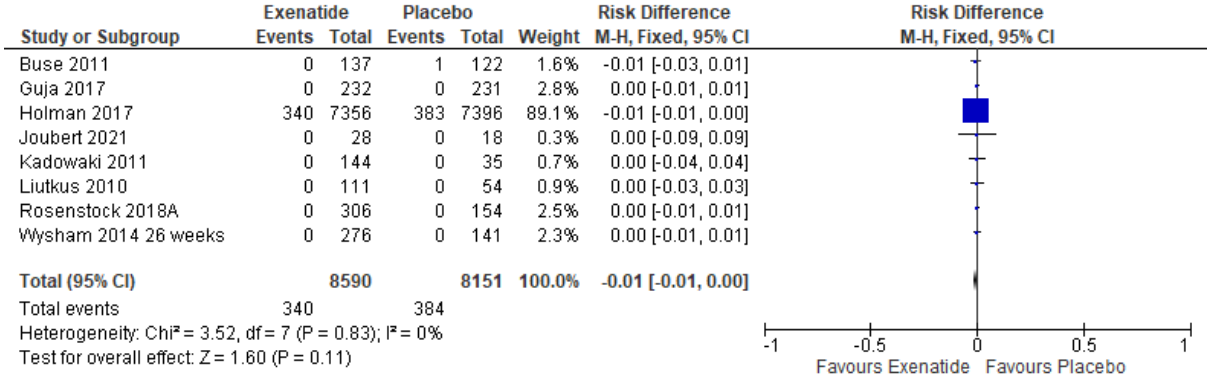


Figure 94: Non-fatal myocardial infarction at end of follow up

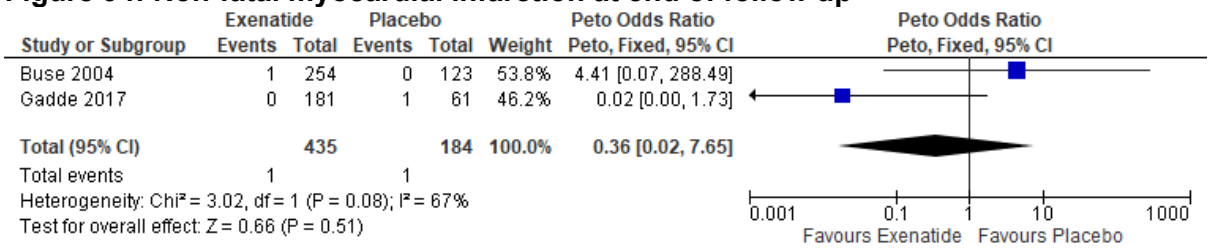


Figure 95: Hospitalisation for heart failure at end of follow up

Figure 96: Diabetic ketoacidosis at end of follow up

Study or Subgroup	Exenatide Events	Exenatide Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Harreiter 2021	0	16	0	14	21.0%	0.00 [-0.12, 0.12]
Kadowaki 2011	1	144	0	35	79.0%	0.01 [-0.03, 0.05]
Total (95% CI)		**160**		**49**	**100.0%**	**0.01 [-0.04, 0.05]**
Total events	1		0			

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.91); I² = 0%
Test for overall effect: Z = 0.25 (P = 0.80)

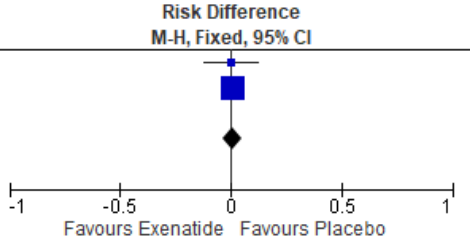
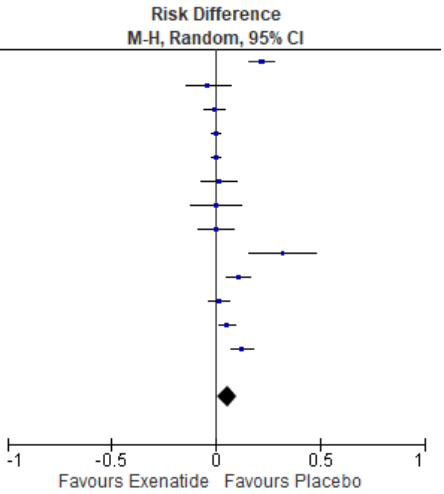


Figure 97: Hypoglycaemia episodes at end of follow up

Study or Subgroup	Exenatide Events	Exenatide Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
Buse 2004	64	254	4	123	8.1%	0.22 [0.16, 0.28]
Buse 2011	34	137	35	122	6.2%	-0.04 [-0.15, 0.07]
DeFronzo 2005	11	223	6	113	8.5%	-0.00 [-0.05, 0.05]
Derosa 2012C	0	86	0	85	9.3%	0.00 [-0.02, 0.02]
Gadde 2017	0	181	0	61	9.3%	0.00 [-0.02, 0.02]
Guja 2017	81	232	77	231	7.1%	0.02 [-0.07, 0.10]
Harreiter 2021	0	16	0	14	5.7%	0.00 [-0.12, 0.12]
Joubert 2021	0	28	0	18	7.1%	0.00 [-0.09, 0.09]
Kadowaki 2011	79	144	8	35	4.4%	0.32 [0.16, 0.48]
Kendall 2005	114	486	31	247	8.3%	0.11 [0.05, 0.16]
Liutkus 2010	4	111	1	54	8.5%	0.02 [-0.03, 0.07]
Rosenstock 2018A	24	306	4	154	8.9%	0.05 [0.01, 0.09]
Wysham 2014 26 weeks	44	276	5	141	8.4%	0.12 [0.07, 0.18]
Total (95% CI)		**2480**		**1398**	**100.0%**	**0.06 [0.01, 0.10]**
Total events	455		171			

Heterogeneity: Tau² = 0.01; Chi² = 133.04, df = 12 (P < 0.00001); I² = 91%
Test for overall effect: Z = 2.37 (P = 0.02)



Note: Heterogeneity was not explained by sensitivity analysis

Figure 98: Severe hypoglycaemic episodes at end of follow up

Study or Subgroup	Exenatide Events	Exenatide Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Buse 2004	0	254	0	123	1.9%	0.00 [-0.01, 0.01]
Buse 2011	0	137	1	122	1.5%	-0.01 [-0.03, 0.01]
DeFronzo 2005	0	223	0	113	1.7%	0.00 [-0.01, 0.01]
Gadde 2017	0	181	0	61	1.0%	0.00 [-0.02, 0.02]
Guja 2017	0	232	0	231	2.6%	0.00 [-0.01, 0.01]
Harreiter 2021	0	16	0	14	0.2%	0.00 [-0.12, 0.12]
Holman 2017	247	7356	219	7396	84.1%	0.00 [-0.00, 0.01]
Joubert 2021	0	28	0	18	0.2%	0.00 [-0.09, 0.09]
Kadowaki 2011	0	144	0	35	0.6%	0.00 [-0.04, 0.04]
Kendall 2005	1	486	0	247	3.7%	0.00 [-0.01, 0.01]
Rosenstock 2018A	0	306	0	154	2.3%	0.00 [-0.01, 0.01]
Total (95% CI)		**9363**		**8514**	**100.0%**	**0.00 [-0.00, 0.01]**
Total events	248		220			

Heterogeneity: Chi² = 2.83, df = 10 (P = 0.99); I² = 0%
Test for overall effect: Z = 1.34 (P = 0.18)

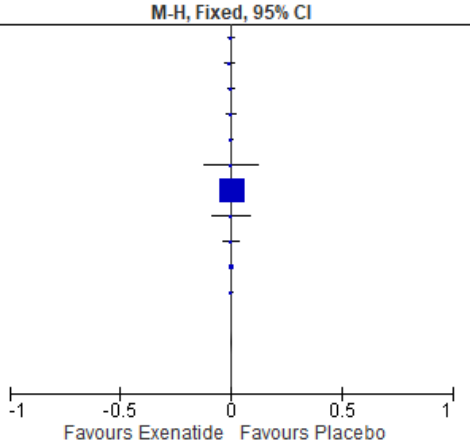
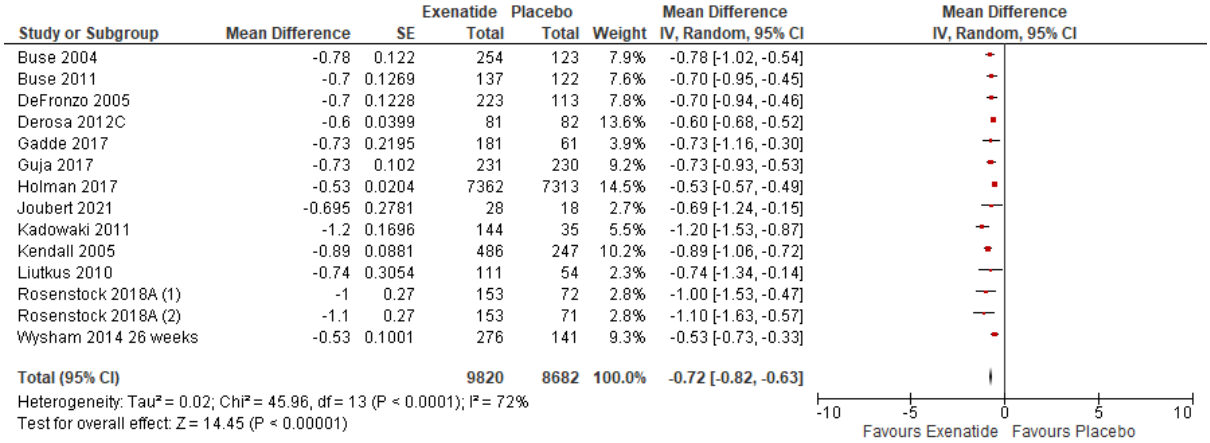


Figure 99: HbA1c change (%, lower values are better, change scores) at end of follow up



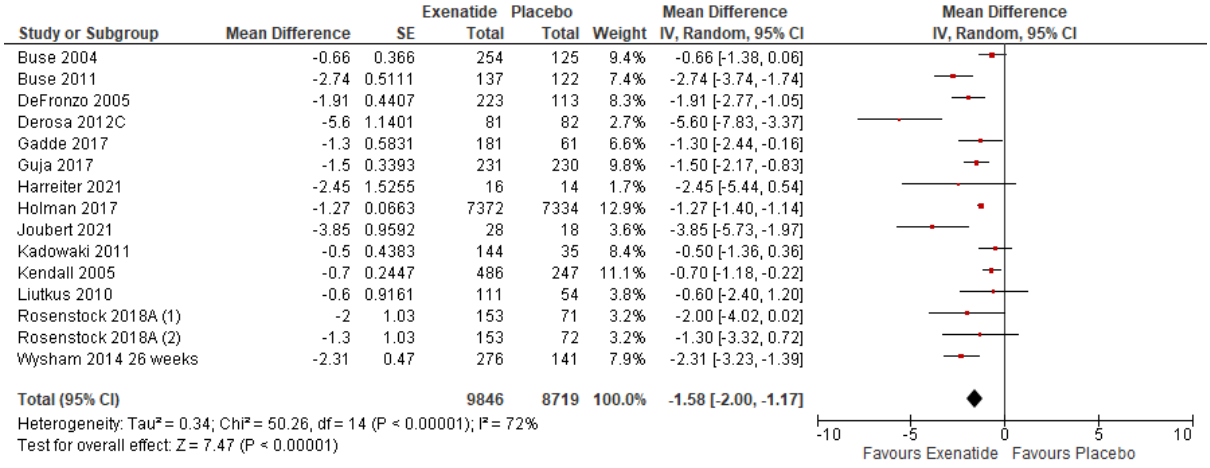
Study or Subgroup	Mean Difference	SE	Exenatide Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Buse 2004	-0.78	0.122	254	123	7.9%	-0.78 [-1.02, -0.54]
Buse 2011	-0.7	0.1269	137	122	7.6%	-0.70 [-0.95, -0.45]
DeFronzo 2005	-0.7	0.1228	223	113	7.8%	-0.70 [-0.94, -0.46]
Derosa 2012C	-0.6	0.0399	81	82	13.6%	-0.60 [-0.68, -0.52]
Gadde 2017	-0.73	0.2195	181	61	3.9%	-0.73 [-1.16, -0.30]
Guja 2017	-0.73	0.102	231	230	9.2%	-0.73 [-0.93, -0.53]
Holman 2017	-0.53	0.0204	7362	7313	14.5%	-0.53 [-0.57, -0.49]
Joubert 2021	-0.695	0.2781	28	18	2.7%	-0.69 [-1.24, -0.15]
Kadowaki 2011	-1.2	0.1696	144	35	5.5%	-1.20 [-1.53, -0.87]
Kendall 2005	-0.89	0.0881	486	247	10.2%	-0.89 [-1.06, -0.72]
Liutkus 2010	-0.74	0.3054	111	54	2.3%	-0.74 [-1.34, -0.14]
Rosenstock 2018A (1)	-1	0.27	153	72	2.8%	-1.00 [-1.53, -0.47]
Rosenstock 2018A (2)	-1.1	0.27	153	71	2.8%	-1.10 [-1.63, -0.57]
Wysham 2014 26 weeks	-0.53	0.1001	276	141	9.3%	-0.53 [-0.73, -0.33]
Total (95% CI)			**9820**	**8682**	**100.0%**	**-0.72 [-0.82, -0.63]**

Heterogeneity: Tau² = 0.02; Chi² = 45.96, df = 13 (P < 0.0001); I² = 72%
Test for overall effect: Z = 14.45 (P < 0.00001)

Footnotes
(1) 40 mcg daily arm. N placebo was halved
(2) 60 mcg daily arm. N placebo was halved

Note: Heterogeneity was not explained by sensitivity analysis, nor subgroup analysis by obesity or eGFR subgroup

Figure 100: Weight change (kg, lower values are better, change scores) at end of follow up



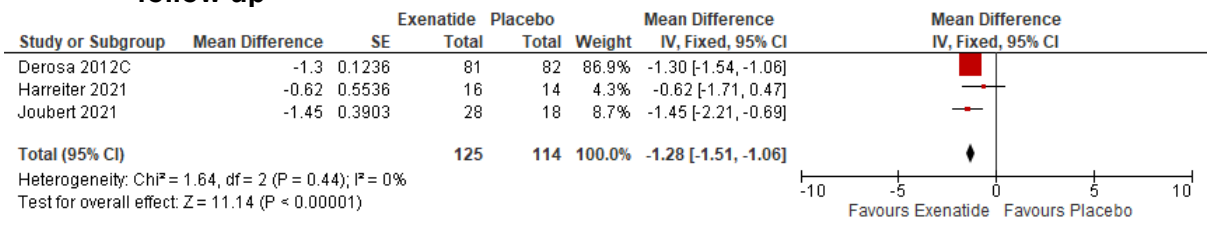
Study or Subgroup	Mean Difference	SE	Exenatide Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Buse 2004	-0.66	0.366	254	125	9.4%	-0.66 [-1.38, 0.06]
Buse 2011	-2.74	0.5111	137	122	7.4%	-2.74 [-3.74, -1.74]
DeFronzo 2005	-1.91	0.4407	223	113	8.3%	-1.91 [-2.77, -1.05]
Derosa 2012C	-5.6	1.1401	81	82	2.7%	-5.60 [-7.83, -3.37]
Gadde 2017	-1.3	0.5831	181	61	6.6%	-1.30 [-2.44, -0.16]
Guja 2017	-1.5	0.3393	231	230	9.8%	-1.50 [-2.17, -0.83]
Harreiter 2021	-2.45	1.5255	16	14	1.7%	-2.45 [-5.44, 0.54]
Holman 2017	-1.27	0.0663	7372	7334	12.9%	-1.27 [-1.40, -1.14]
Joubert 2021	-3.85	0.9592	28	18	3.6%	-3.85 [-5.73, -1.97]
Kadowaki 2011	-0.5	0.4383	144	35	8.4%	-0.50 [-1.36, 0.36]
Kendall 2005	-0.7	0.2447	486	247	11.1%	-0.70 [-1.18, -0.22]
Liutkus 2010	-0.6	0.9161	111	54	3.8%	-0.60 [-2.40, 1.20]
Rosenstock 2018A (1)	-2	1.03	153	71	3.2%	-2.00 [-4.02, 0.02]
Rosenstock 2018A (2)	-1.3	1.03	153	72	3.2%	-1.30 [-3.32, 0.72]
Wysham 2014 26 weeks	-2.31	0.47	276	141	7.9%	-2.31 [-3.23, -1.39]
Total (95% CI)			**9846**	**8719**	**100.0%**	**-1.58 [-2.00, -1.17]**

Heterogeneity: Tau² = 0.34; Chi² = 50.26, df = 14 (P < 0.00001); I² = 72%
Test for overall effect: Z = 7.47 (P < 0.00001)

Footnotes
(1) 60 mcg daily arm. N for placebo arm was halved
(2) 40 mcg daily arm. N for placebo arm was halved.

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

Figure 101: BMI change (kg/m², lower values are better, change scores) at end of follow up



Study or Subgroup	Mean Difference	SE	Exenatide Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Derosa 2012C	-1.3	0.1236	81	82	86.9%	-1.30 [-1.54, -1.06]
Harreiter 2021	-0.62	0.5536	16	14	4.3%	-0.62 [-1.71, 0.47]
Joubert 2021	-1.45	0.3903	28	18	8.7%	-1.45 [-2.21, -0.69]
Total (95% CI)			**125**	**114**	**100.0%**	**-1.28 [-1.51, -1.06]**

Heterogeneity: Chi² = 1.64, df = 2 (P = 0.44); I² = 0%
Test for overall effect: Z = 11.14 (P < 0.00001)

K.1.3.6 Adding exenatide compared to adding insulin

Figure 102: Health-related quality of life – overall (EQ5D, -0.59-1.0, higher values are better, change scores) at end of follow up

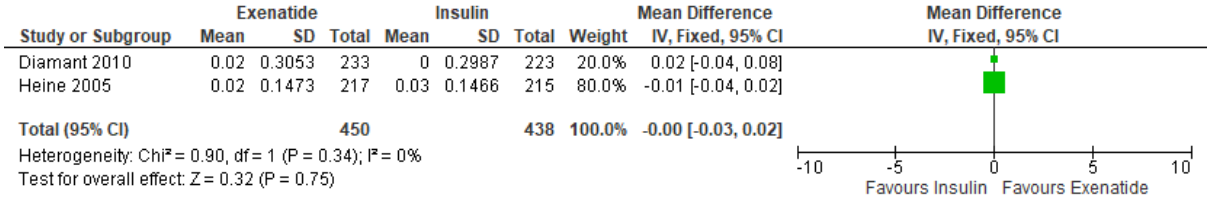


Figure 103: Health-related quality of life – overall (IWQoL, 0-100, higher values are better, change scores) at end of follow up

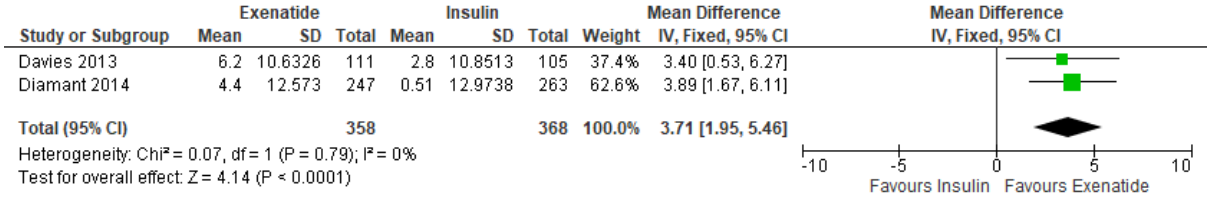


Figure 104: All-cause mortality at end of follow up

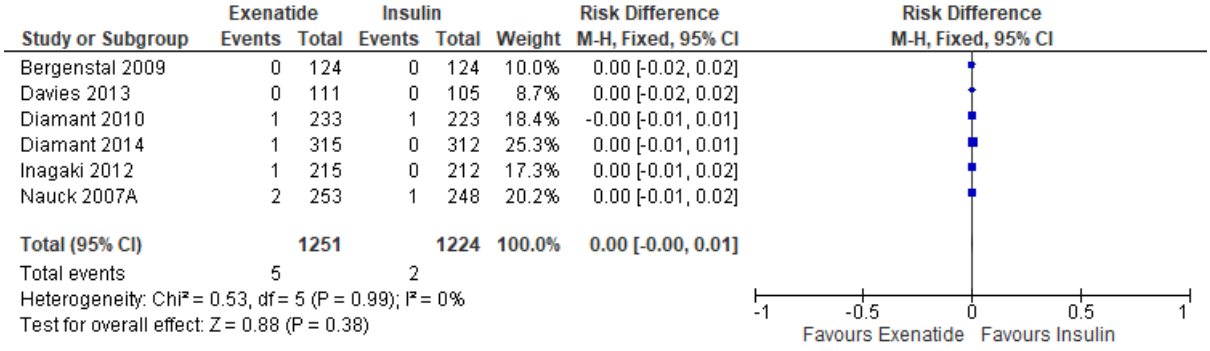


Figure 105: Cardiovascular mortality at end of follow up

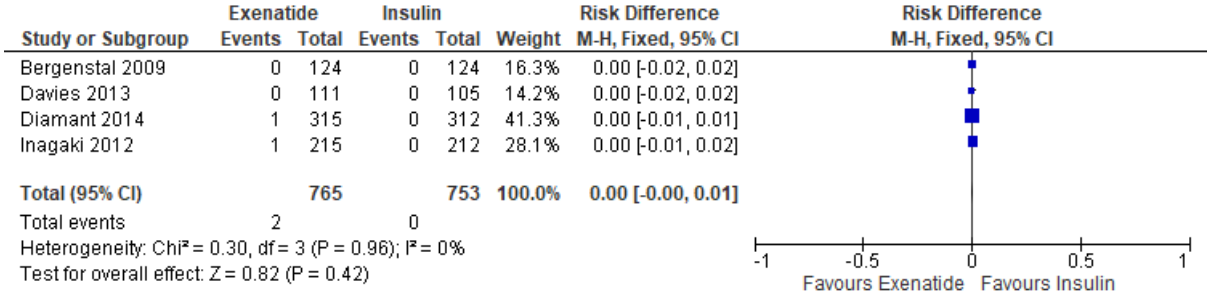


Figure 106: Hypoglycaemia episodes at end of follow up

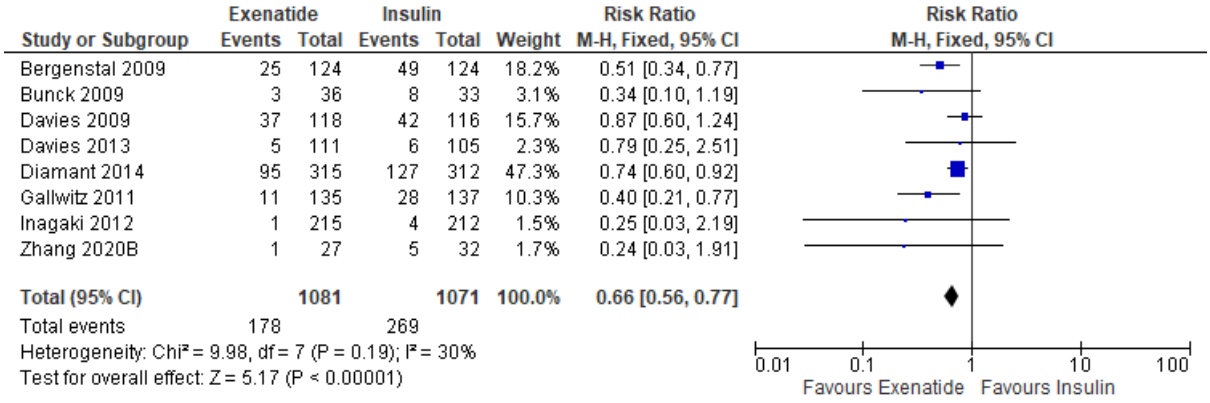
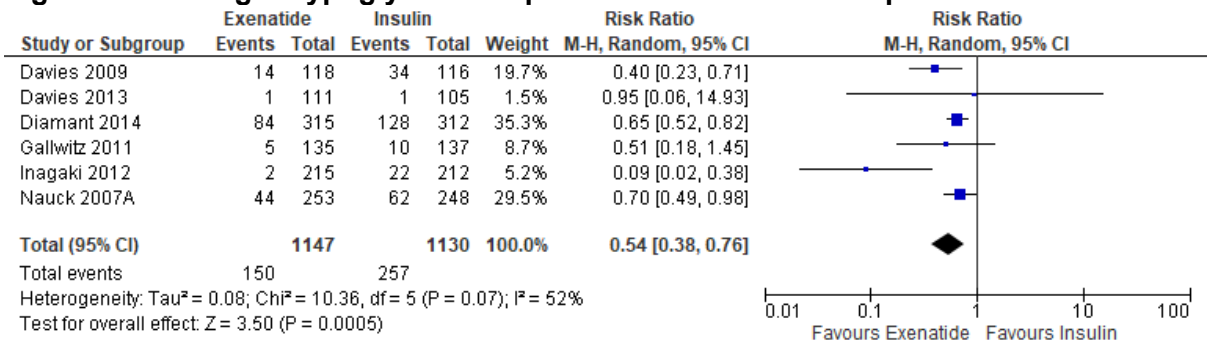


Figure 107: At night hypoglycaemic episodes at end of follow up



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

Figure 108: Severe hypoglycaemic episodes at end of follow up

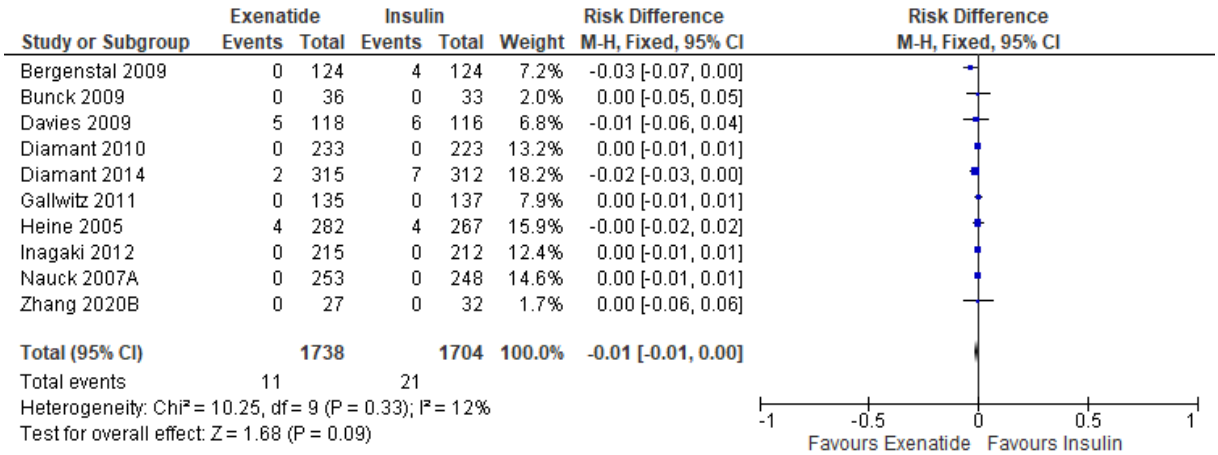
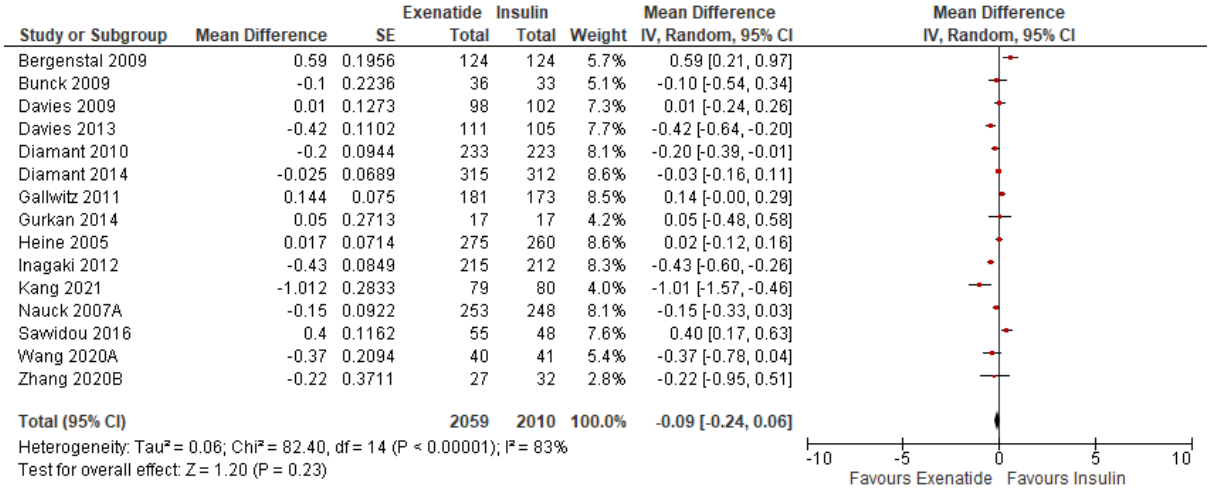
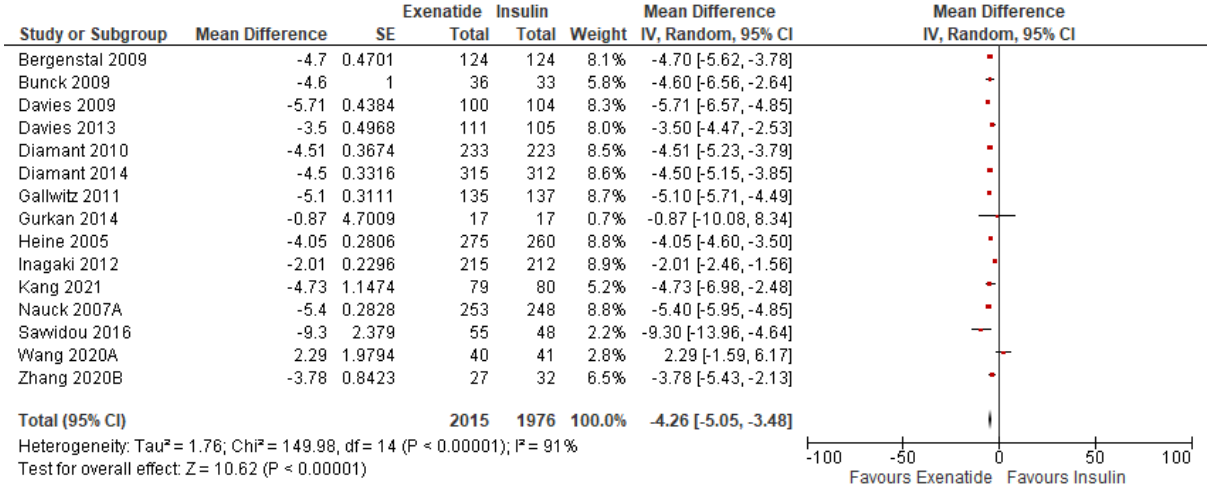


Figure 109: HbA1c change (%, lower values are better, change and final scores) at end of follow up



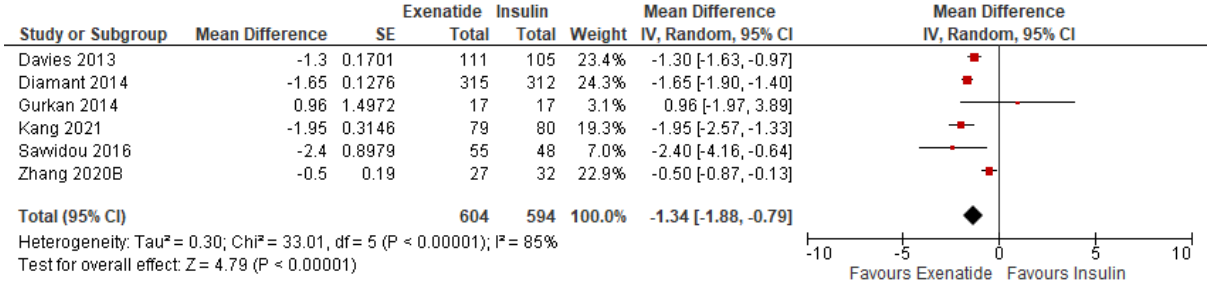
Note: Heterogeneity was not explained by sensitivity analysis, nor subgroup analysis by obesity subgroup.

Figure 110: Weight change (kg, lower values are better, change and final scores) at end of follow up



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

Figure 111: BMI change (kg/m^2, lower values are better, change and final scores) at end of follow up



Note: Heterogeneity was not explained by sensitivity analysis. Subgroup analysis was not possible for this outcome.

K.1.3.7 Adding exenatide compared to adding liraglutide

Figure 112: Hypoglycaemia episodes at end of follow up

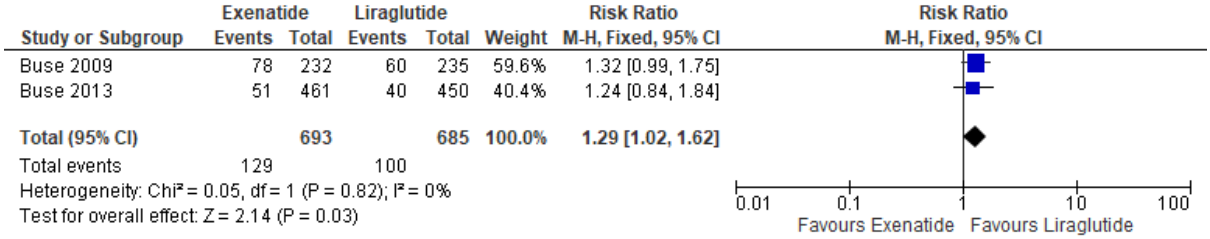


Figure 113: Severe hypoglycaemic episodes at end of follow up

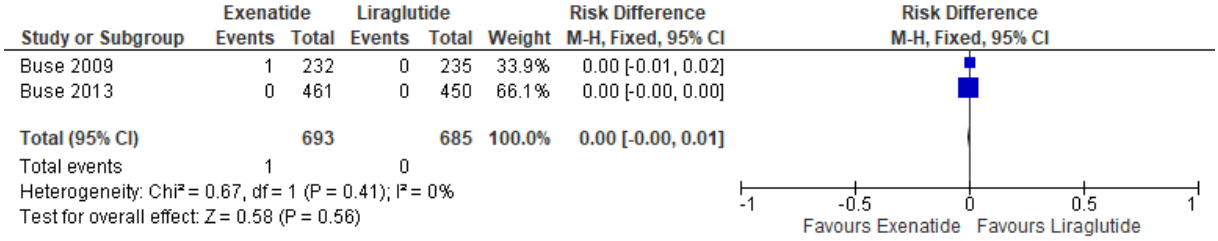


Figure 114: HbA1c change (%, lower values are better, change scores) at end of follow up

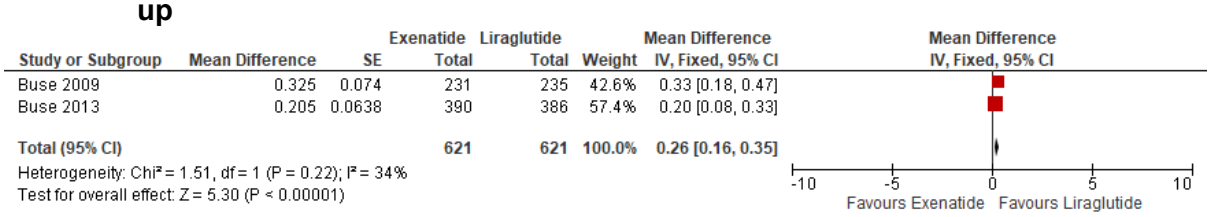
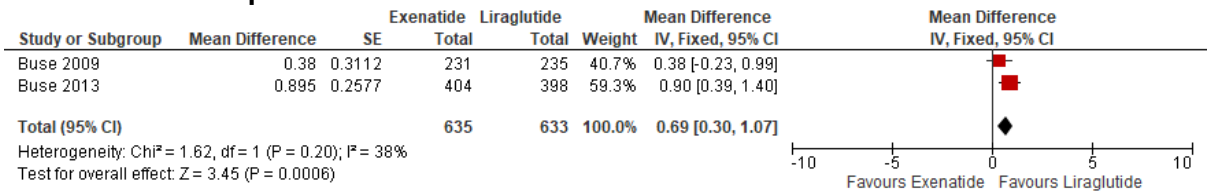


Figure 115: Weight change (kg, lower values are better, change scores) at end of follow up



K.1.3.8 Adding exenatide compared to adding sitagliptin

Figure 116: Hypoglycaemia episodes at end of follow up

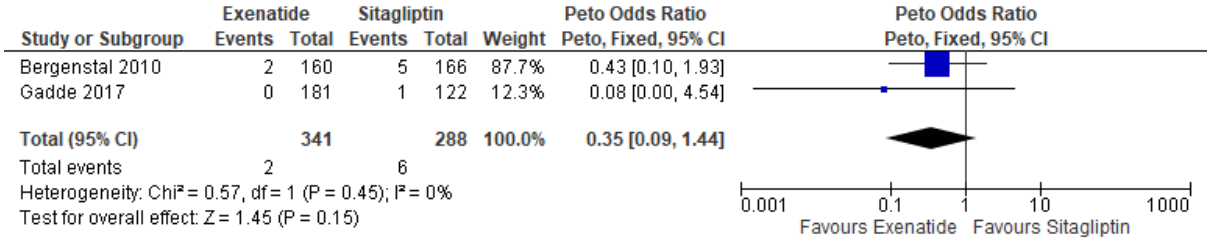


Figure 117: Severe hypoglycaemic episodes at end of follow up

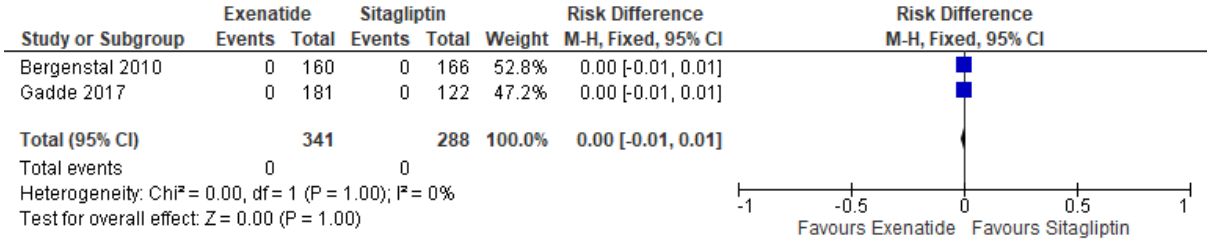


Figure 118: HbA1c change (%, lower values are better, change scores) at end of follow up

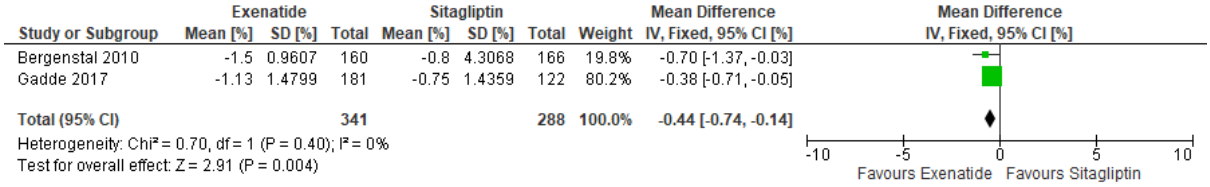
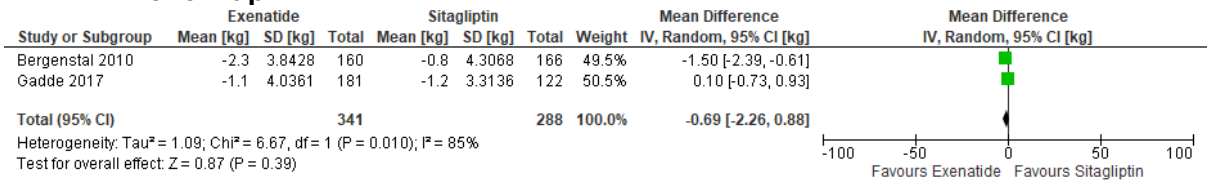


Figure 119: Weight change (kg, lower values are better, change scores) at end of follow up



K.1.3.9 Adding liraglutide compared to adding placebo

Figure 120: Health-related quality of life – subscale physical functioning (SF-36 physical function subscale, higher value are better, change scores) at end of follow-up

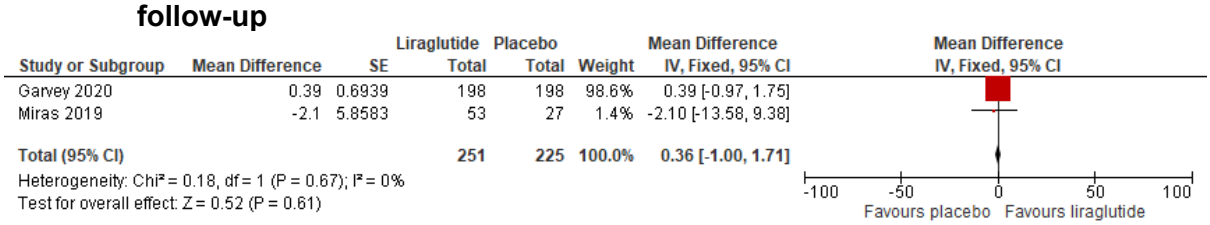
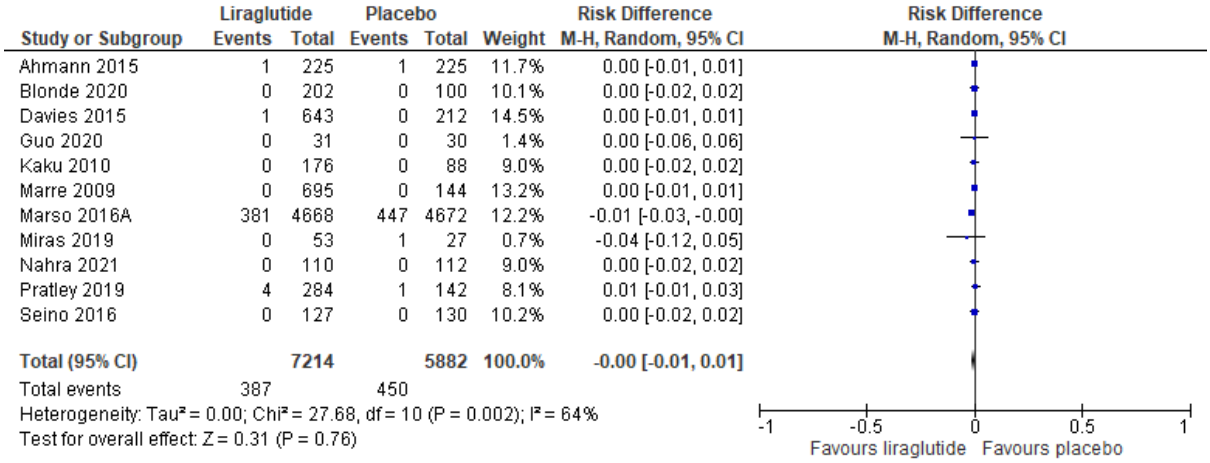
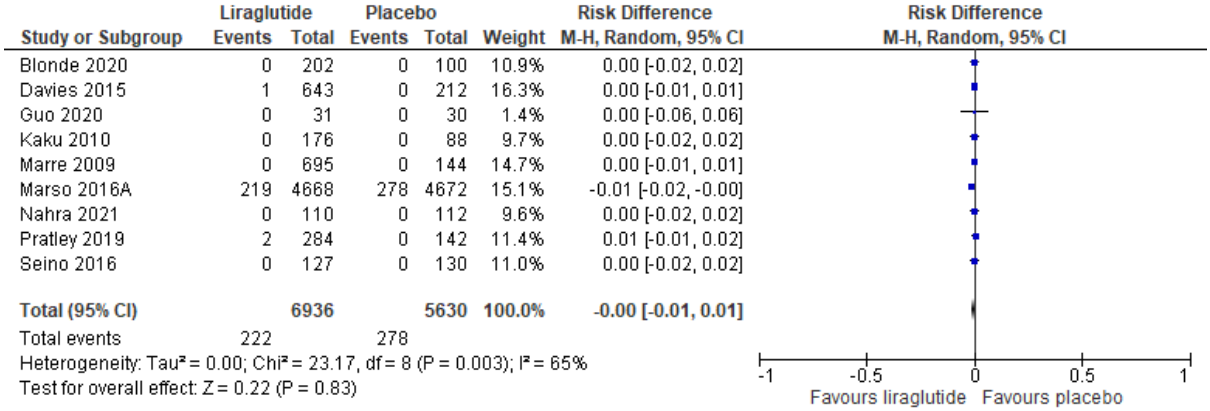


Figure 121: All-cause mortality at end of follow-up



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

Figure 122: Cardiovascular mortality at end of follow-up



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

Figure 123: Non-fatal stroke at end of follow-up

Figure 124: Non-fatal myocardial infarction at end of follow-up

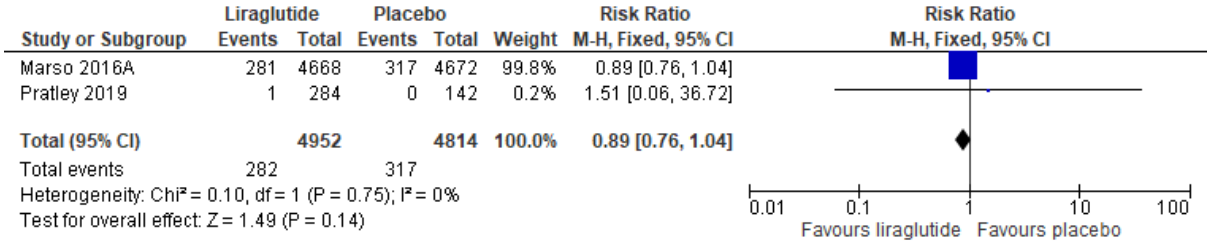


Figure 125: Unstable angina at end of follow-up

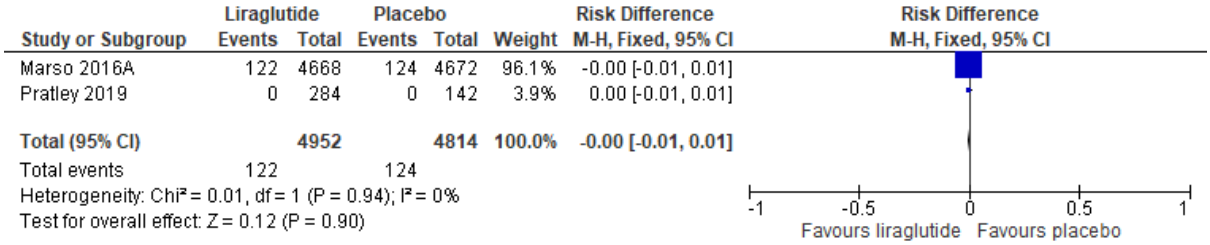


Figure 126: Acute kidney injury at end of follow-up

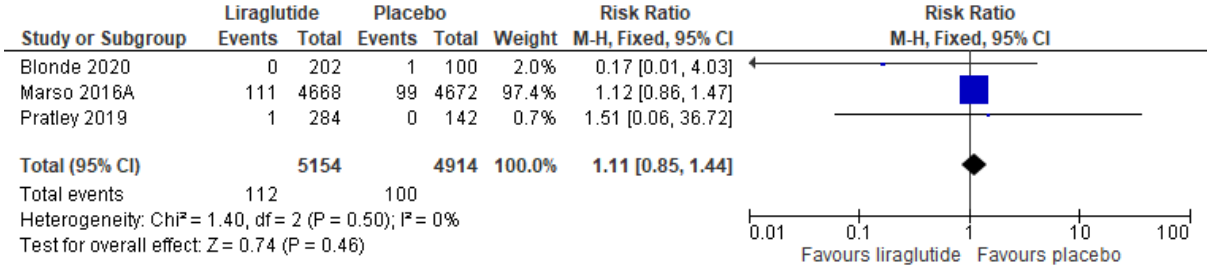


Figure 127: Persistent signs of kidney disease at end of follow-up

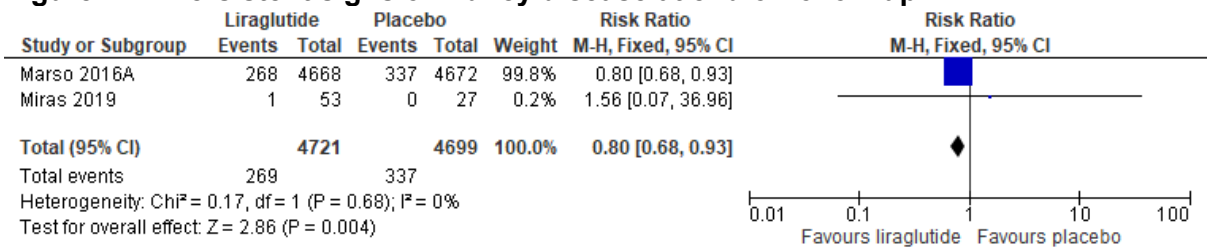


Figure 128: Development of end stage kidney disease at end of follow-up

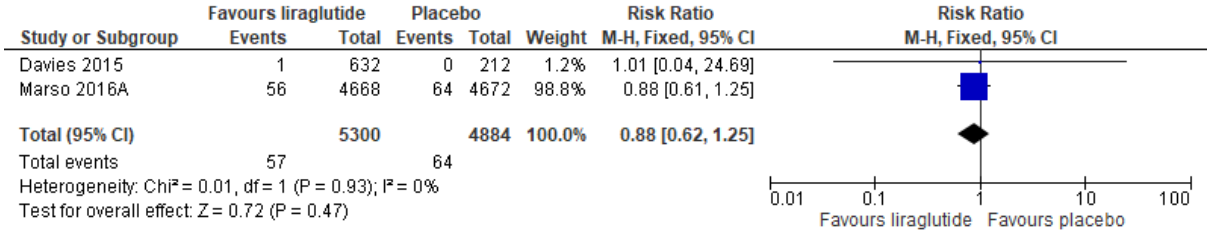


Figure 129: Death from renal cause at end of follow-up

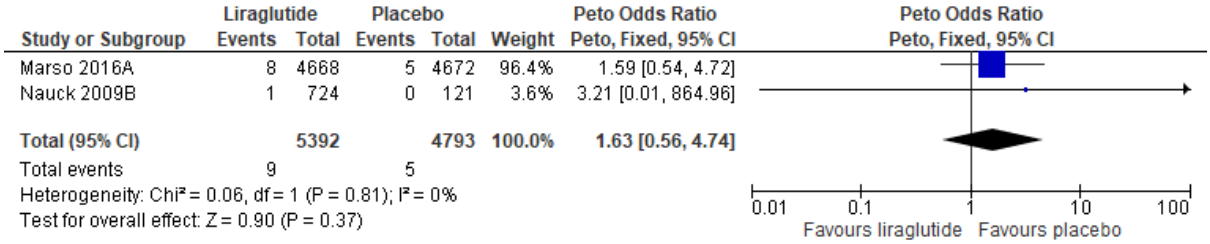
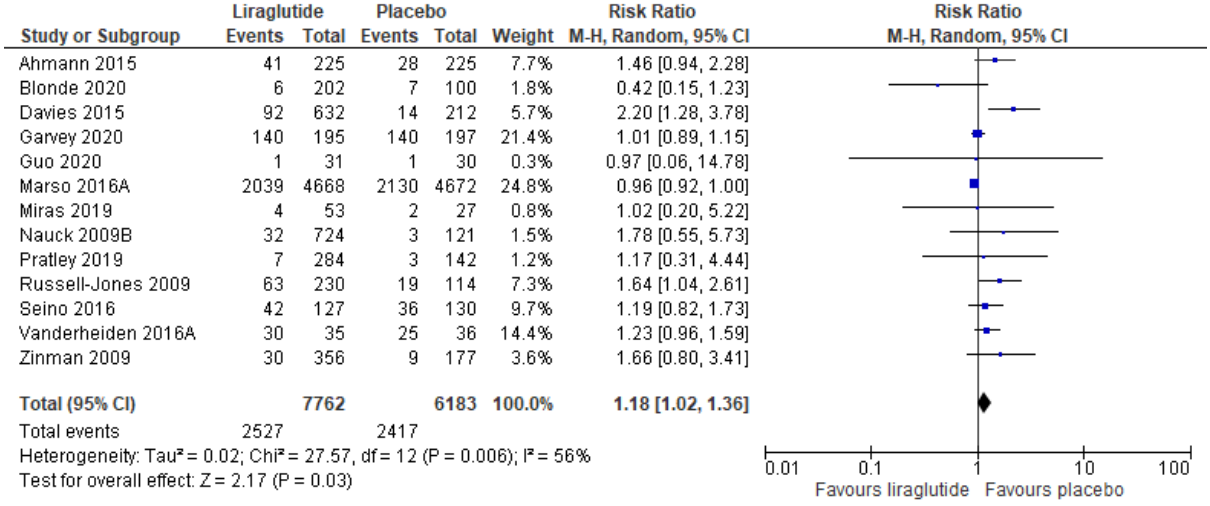


Figure 130: Hypoglycaemia episodes at end of follow-up



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

Figure 131: At night hypoglycaemic episodes at end of follow up

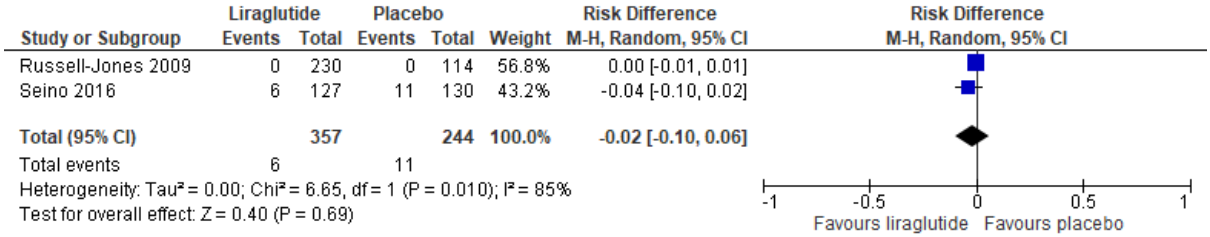


Figure 132: Severe hypoglycaemic episodes at end of follow up

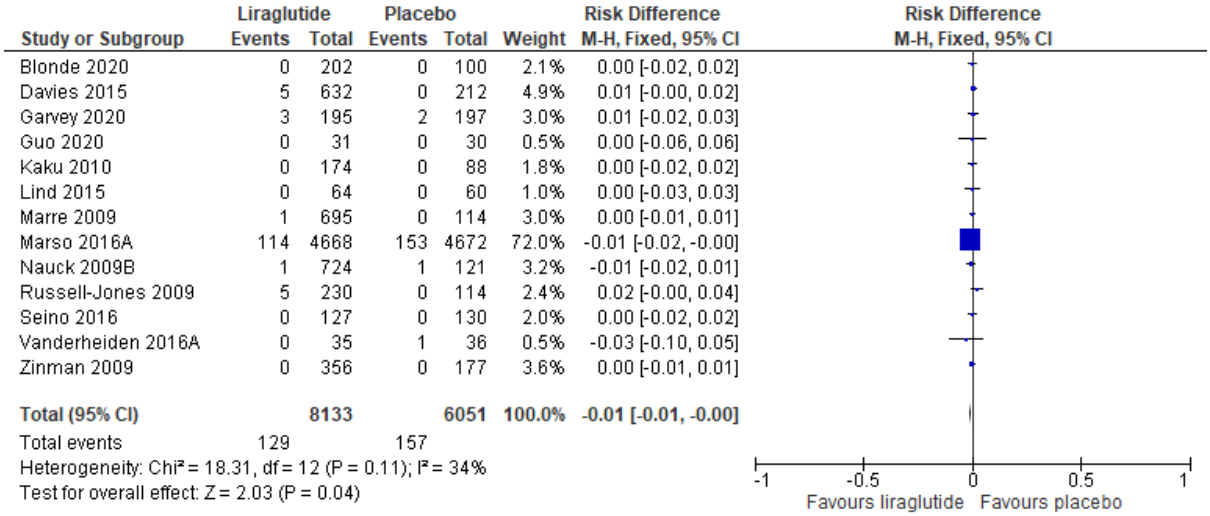
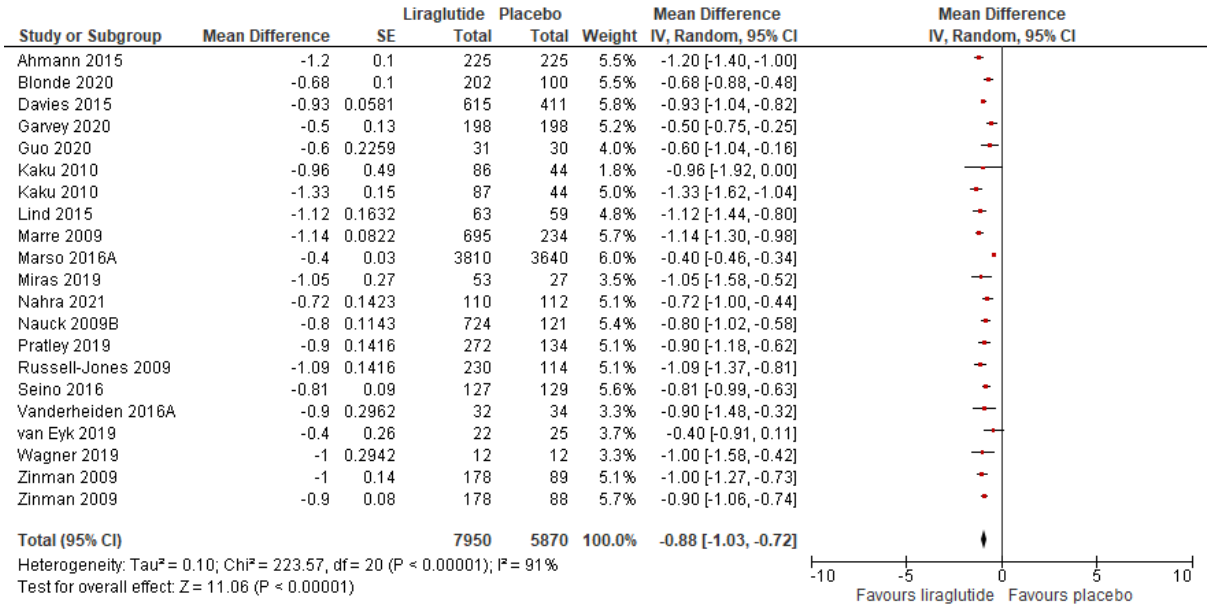
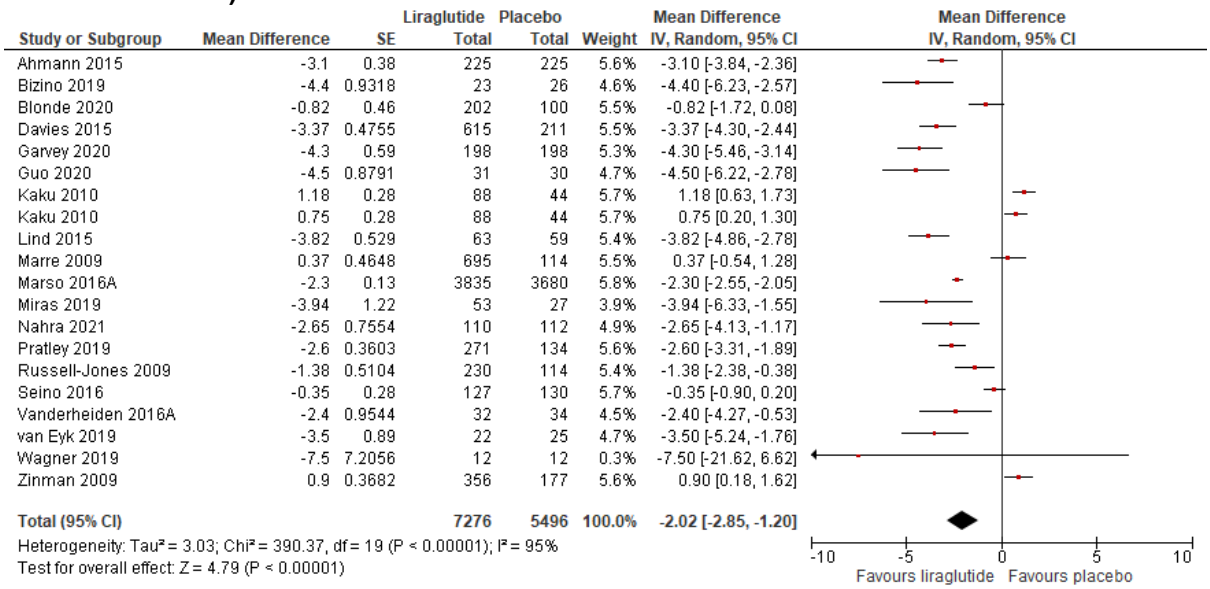


Figure 133: HbA1c change (% lower values are better, change scores and final values) at end of follow up



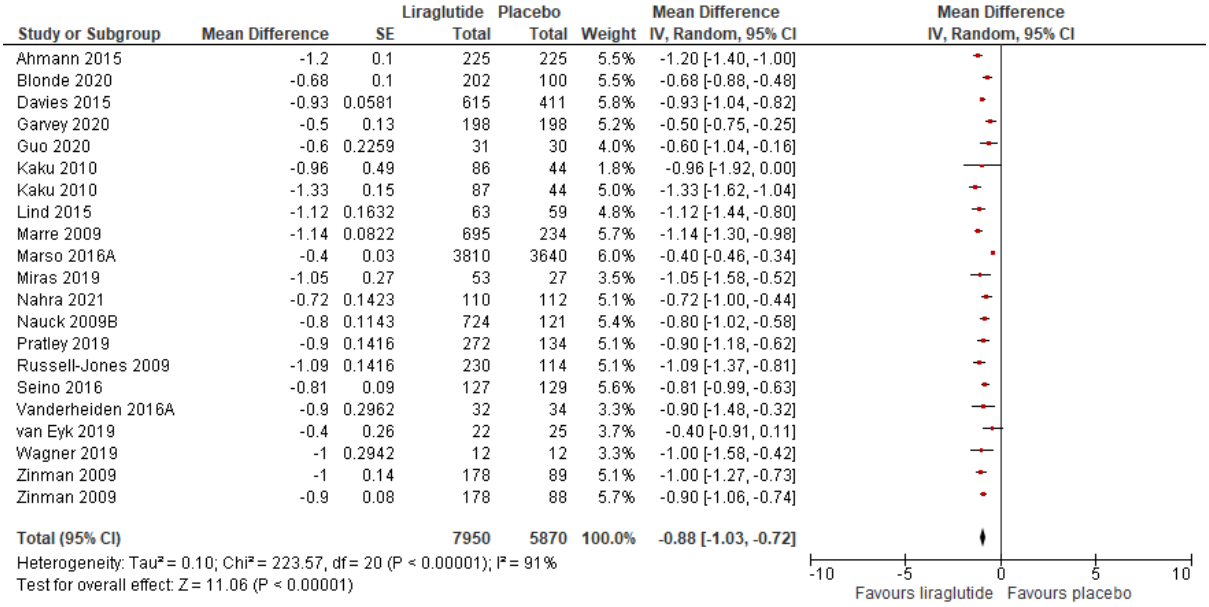
Note: Heterogeneity was not explained by sensitivity analysis, nor subgroup analysis by eGFR, NAFLD and obesity subgroups.

Figure 134: Weight change (kg, lower values are better, change scores and final values)



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

Figure 135: BMI change (kg/m^2, 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 eGFR, NAFLD and obesity subgroups.

K.1.3.10 Adding liraglutide compared to adding insulin

Figure 136: Health-related quality of life - subscale mental component (SF-36, 0-100. higher values are better, change scores) at end of follow-up

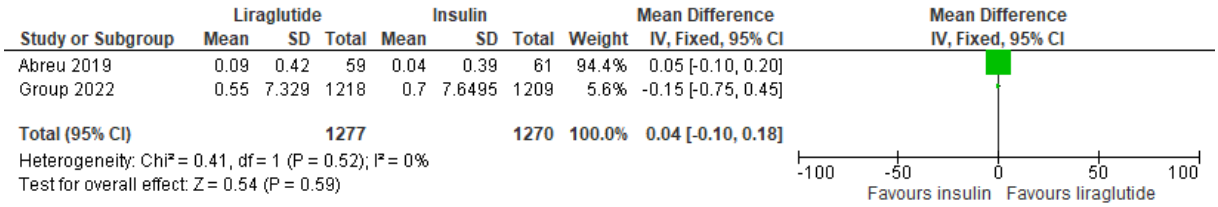


Figure 137: Health-related quality of life -subscale physical component (SF-36, 0, 100, higher values are better, change scores) at end of follow-up

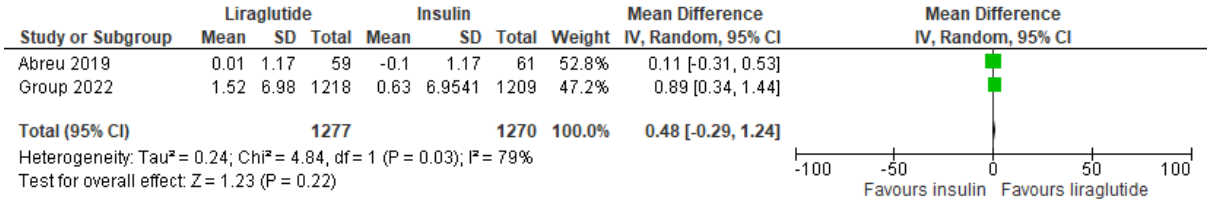
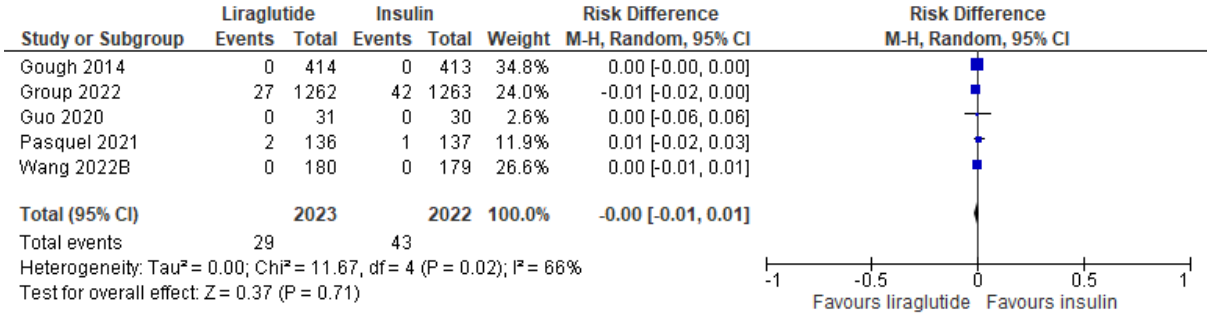
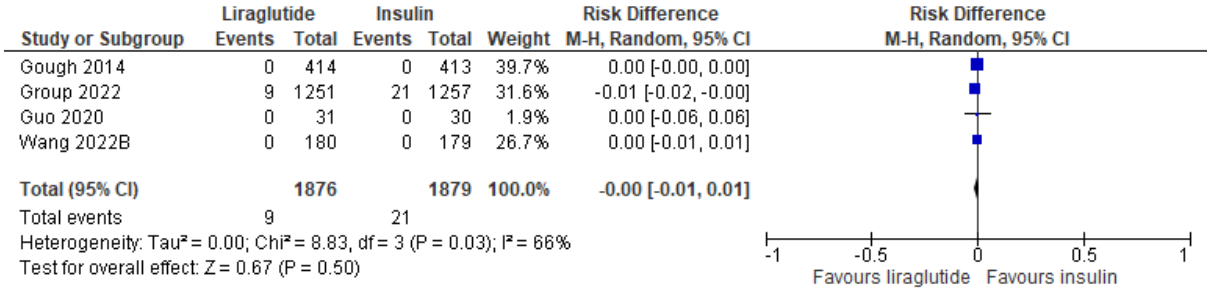


Figure 138: All-cause mortality at end of follow-up



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

Figure 139: Cardiovascular mortality at end of follow-up



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

Figure 140: 3-point MACE at end of follow-up

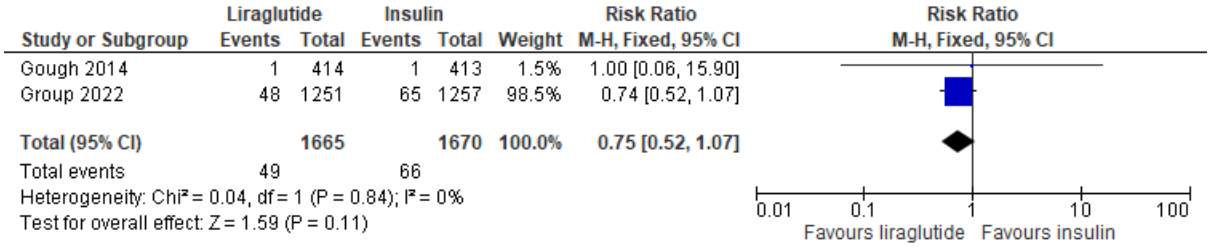


Figure 141: Unstable angina at end of follow-up

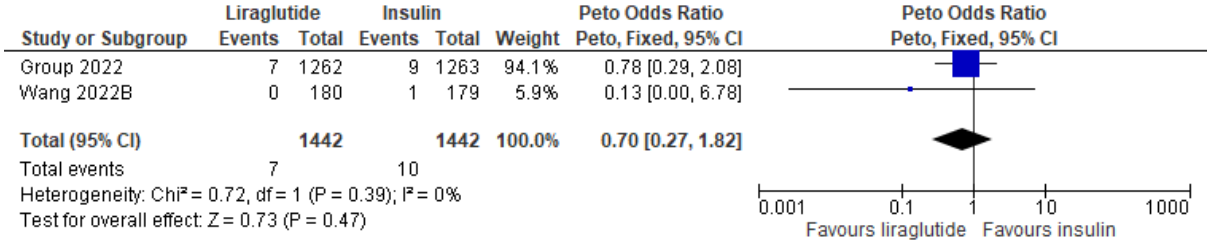


Figure 142: Non-fatal stroke at end of follow-up

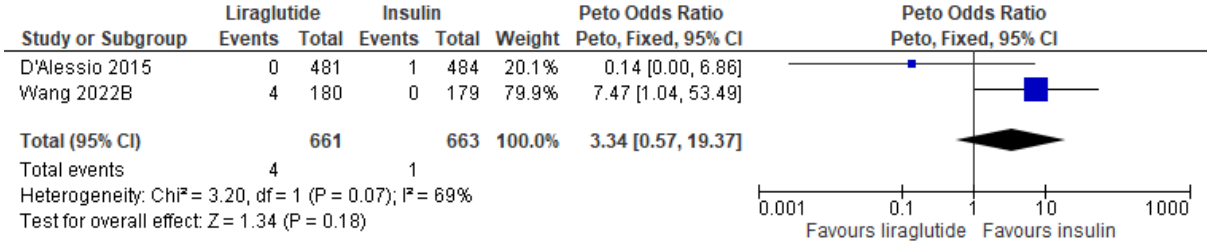
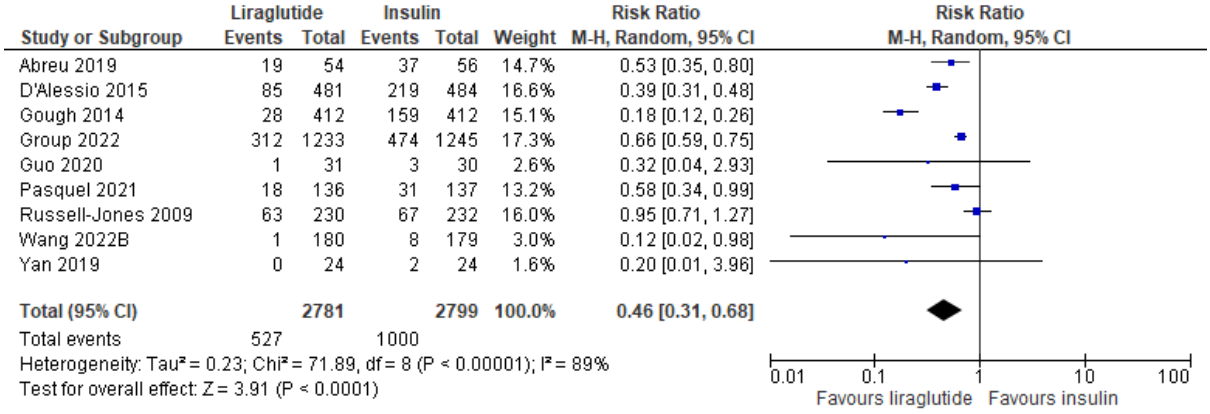


Figure 143: Hypoglycaemia episodes at end of follow-up



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

Figure 144: At night hypoglycaemic episodes

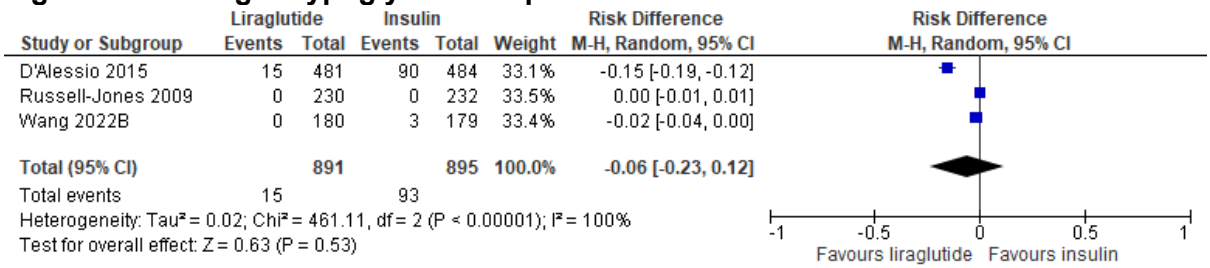


Figure 145: Severe hypoglycaemic episodes at end of follow up

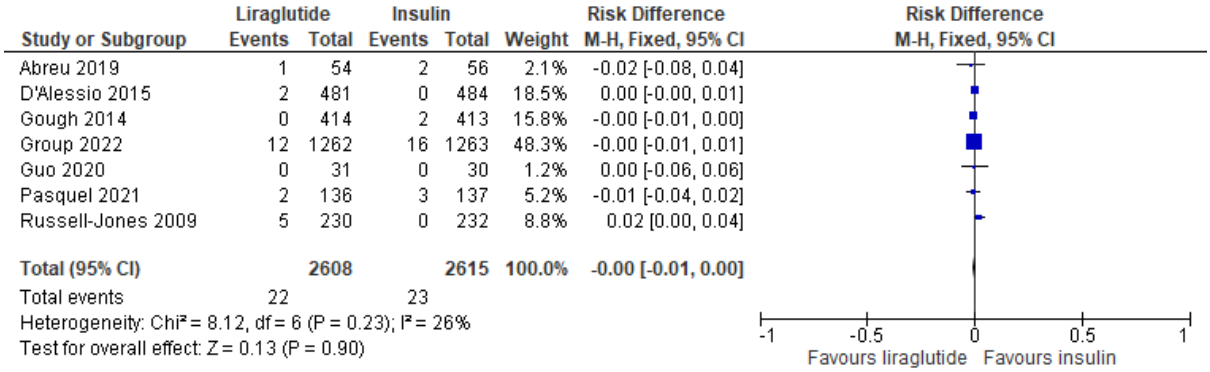
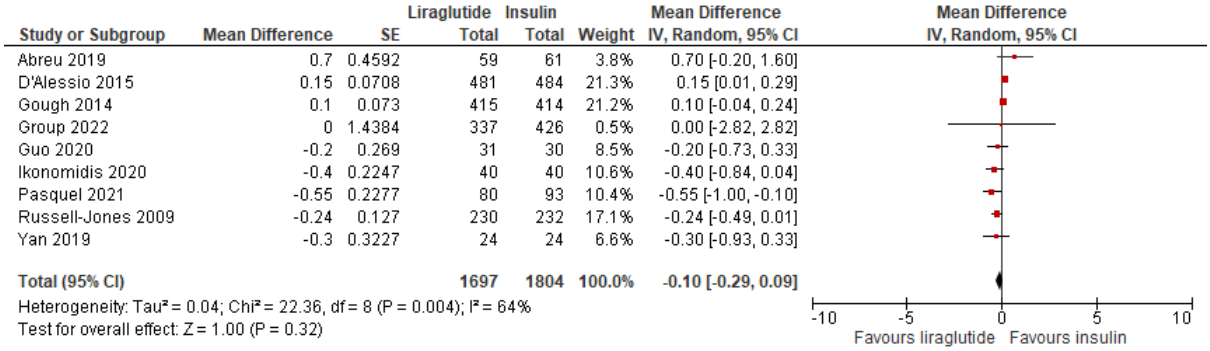


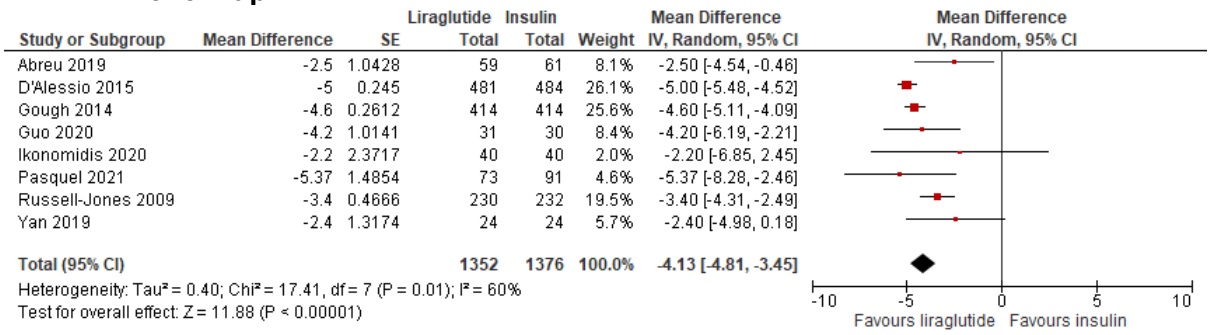
Figure 146: HbA1c change (%, lower values are better, change scores and final values) at end of follow-up

Note: Heterogeneity was not explained by sensitivity analysis, nor subgroup analysis by eGFR, NAFLD, and obesity subgrou



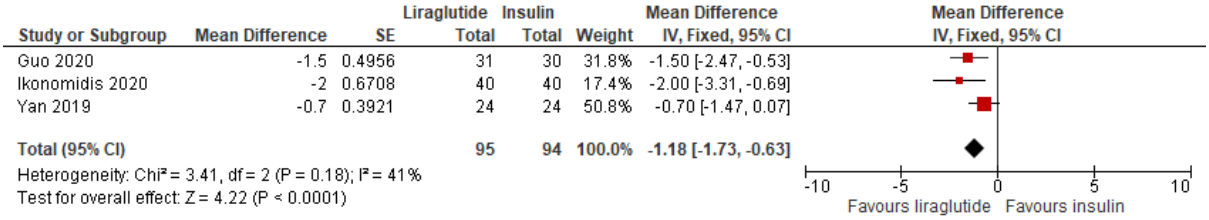
ps.

Figure 147: Weight change (kg, lower values are better, change scores) at end of follow-up



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

Figure 148: BMI change (kg/m^2, lower values are better, change scores and final values) at end of follow-up



K.1.3.11 Adding liraglutide compared to adding dulaglutide

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

K.1.3.12 Adding liraglutide compared to adding saxagliptin

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

K.1.3.13 Adding liraglutide compared to adding sitagliptin

Figure 149: All-cause mortality at end of follow up

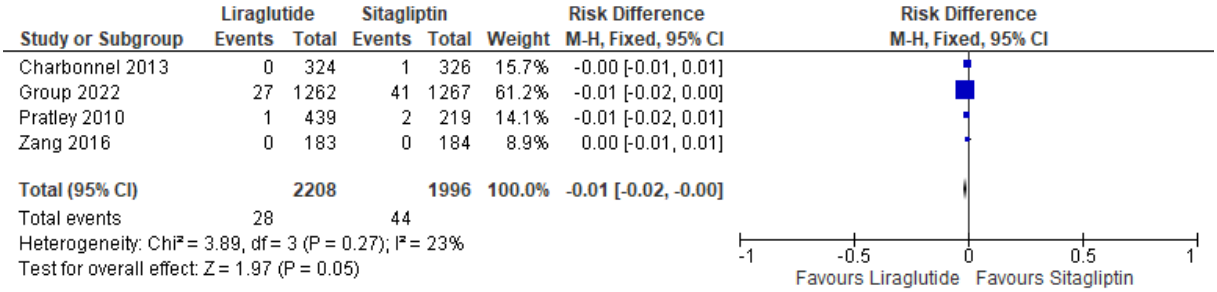


Figure 150: Cardiovascular mortality at end of follow up

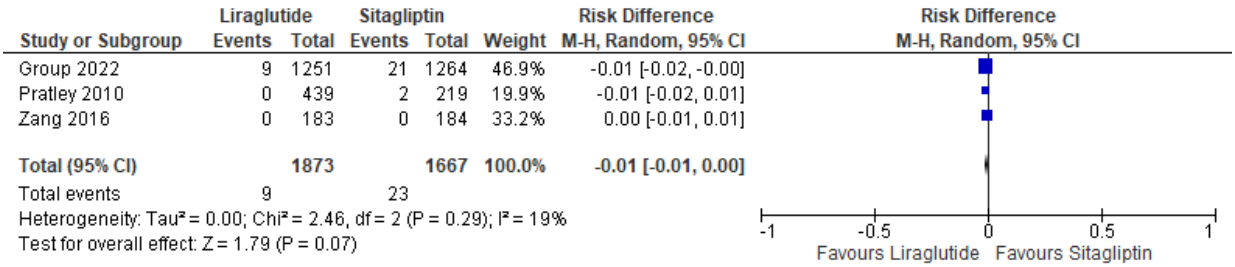
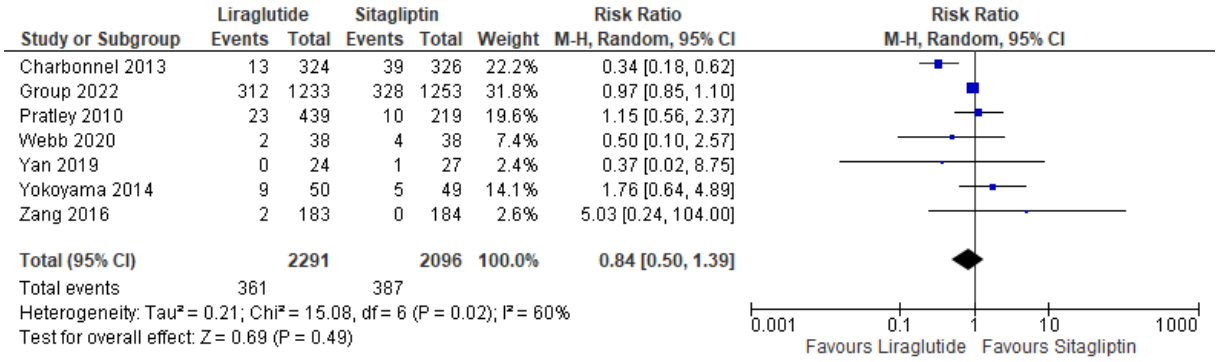


Figure 151: Hypoglycaemia episodes at end of follow up



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

Figure 152: Severe hypoglycaemic episodes at end of follow up

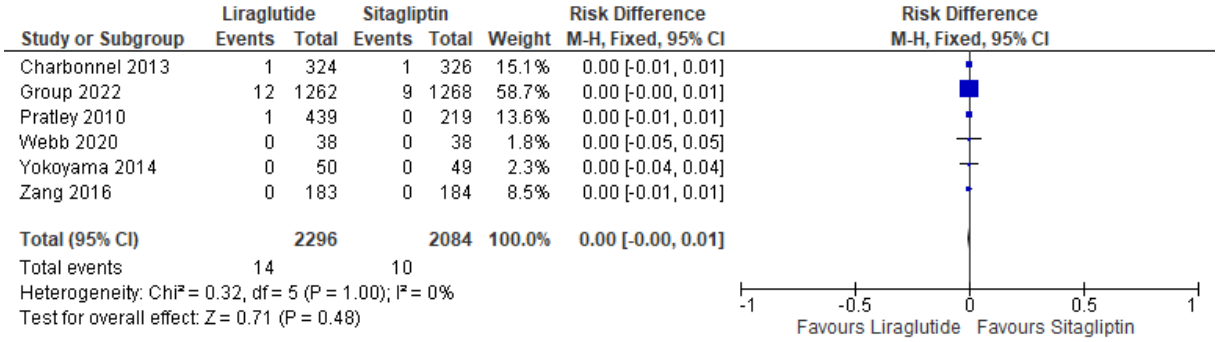
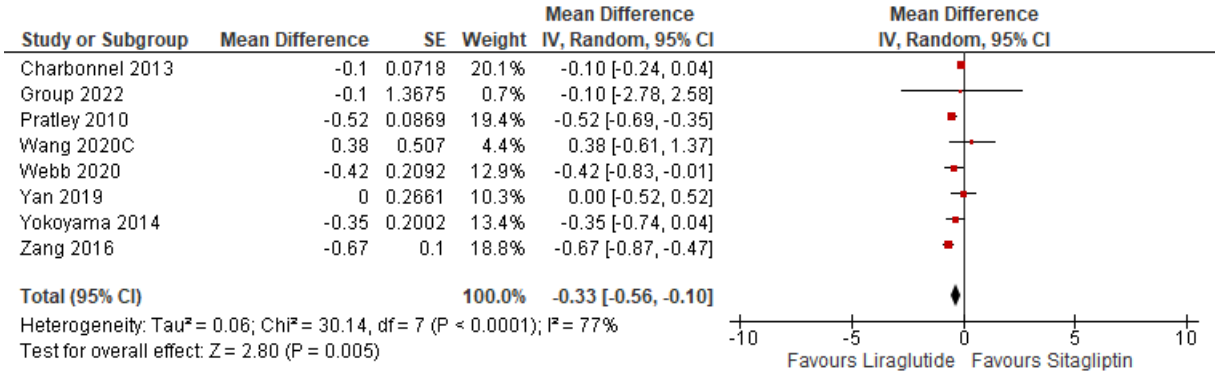
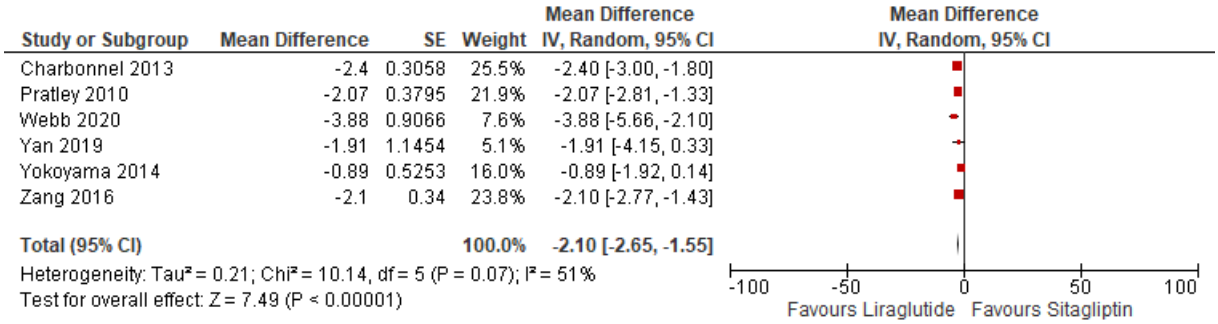


Figure 153: HbA1c change (%, lower values are better, mean difference) at end of follow up



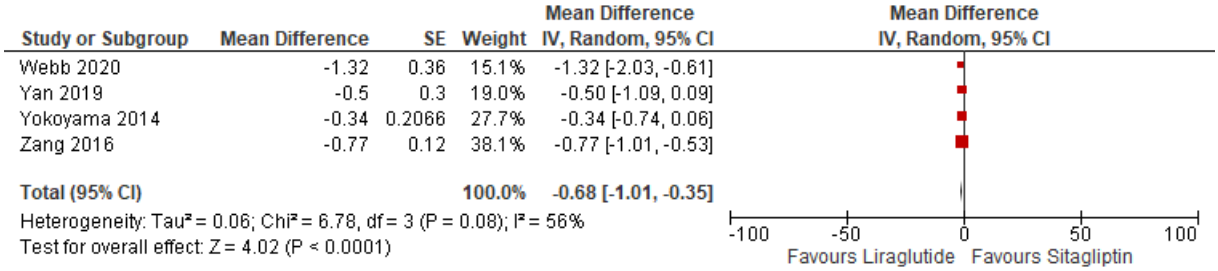
Note: Heterogeneity was not explained by sensitivity analysis, nor subgroup analysis by eGFR, NAFLD, and obesity subgroups.

Figure 154: Weight change (kg, lower values are better, mean difference) at end of follow up



Note: Heterogeneity was not explained by sensitivity analysis, nor subgroup analysis by eGFR, mixed population, NAFLD, obesity and not stated/ unclear subgroup.

Figure 155: BMI change (kg/m^2, lower values are better, mean difference) at end of follow up



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

K.1.3.14 Adding liraglutide compared to adding vildagliptin

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

K.1.3.15 Adding lixisenatide compared to adding placebo

Figure 156: All-cause mortality at end of follow up

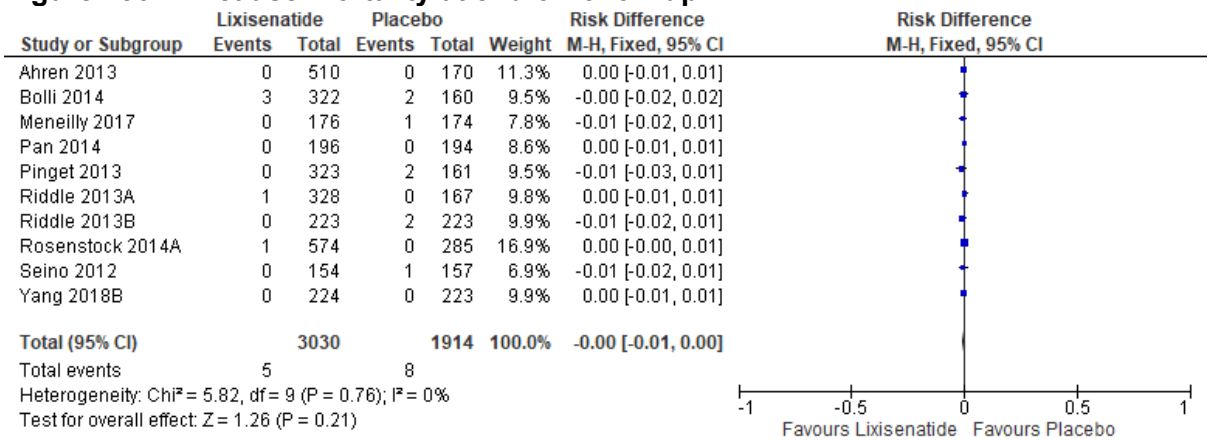


Figure 157: Cardiovascular mortality at end of follow up

Study or Subgroup	Lixisenatide Events	Lixisenatide Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Ahren 2013	0	510	0	170	12.5%	0.00 [-0.01, 0.01]
Meneilly 2017	0	176	0	174	8.6%	0.00 [-0.01, 0.01]
Pan 2014	0	196	0	194	9.5%	0.00 [-0.01, 0.01]
Pinget 2013	0	323	1	161	10.5%	-0.01 [-0.02, 0.01]
Riddle 2013A	1	328	0	167	10.8%	0.00 [-0.01, 0.01]
Riddle 2013B	0	223	1	223	10.9%	-0.00 [-0.02, 0.01]
Rosenstock 2014A	1	574	0	285	18.6%	0.00 [-0.00, 0.01]
Seino 2012	0	154	0	157	7.6%	0.00 [-0.01, 0.01]
Yang 2018B	0	224	0	223	10.9%	0.00 [-0.01, 0.01]
Total (95% CI)		**2708**		**1754**	**100.0%**	**-0.00 [-0.00, 0.00]**
Total events	2		2			

Heterogeneity: Chi² = 1.85, df = 8 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.27 (P = 0.78)

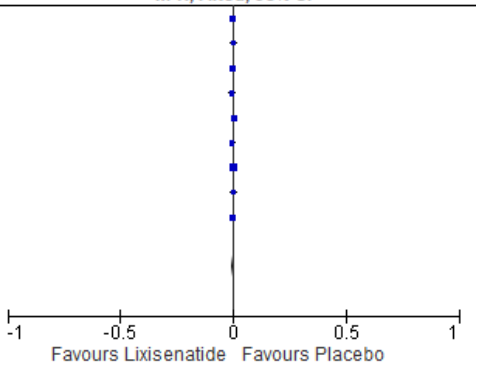


Figure 158: Non-fatal stroke at end of follow up

Study or Subgroup	Lixisenatide Events	Lixisenatide Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Pan 2014	1	196	0	194	33.4%	7.31 [0.15, 368.62]
Seino 2012	2	154	0	157	66.6%	7.58 [0.47, 121.81]
Total (95% CI)		**350**		**351**	**100.0%**	**7.49 [0.78, 72.21]**
Total events	3		0			

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%
Test for overall effect: Z = 1.74 (P = 0.08)

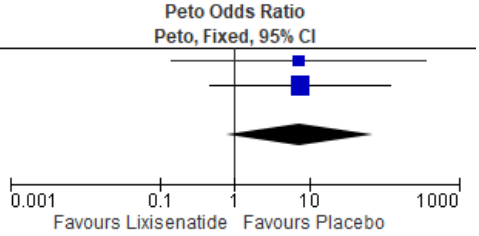


Figure 159: Hypoglycaemia episodes at end of follow up

Study or Subgroup	Lixisenatide Events	Lixisenatide Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ahren 2013	19	510	1	170	0.7%	6.33 [0.85, 46.96]
Bolli 2014	18	322	12	160	7.3%	0.75 [0.37, 1.51]
Meneilly 2017	31	176	18	174	8.3%	1.70 [0.99, 2.93]
Pan 2014	11	196	5	194	2.3%	2.18 [0.77, 6.15]
Pinget 2013	11	323	2	161	1.2%	2.74 [0.61, 12.22]
Riddle 2013A	87	328	35	167	21.2%	1.27 [0.90, 1.79]
Riddle 2013B	45	223	26	223	11.9%	1.73 [1.11, 2.70]
Rosenstock 2014A	88	574	35	285	21.3%	1.25 [0.87, 1.80]
Seino 2012	66	154	37	157	16.7%	1.82 [1.30, 2.54]
Yang 2018B	20	224	20	223	9.1%	1.00 [0.55, 1.80]
Total (95% CI)		**3030**		**1914**	**100.0%**	**1.46 [1.24, 1.71]**
Total events	396		191			

Heterogeneity: Chi² = 12.28, df = 9 (P = 0.20); I² = 27%
Test for overall effect: Z = 4.65 (P < 0.00001)

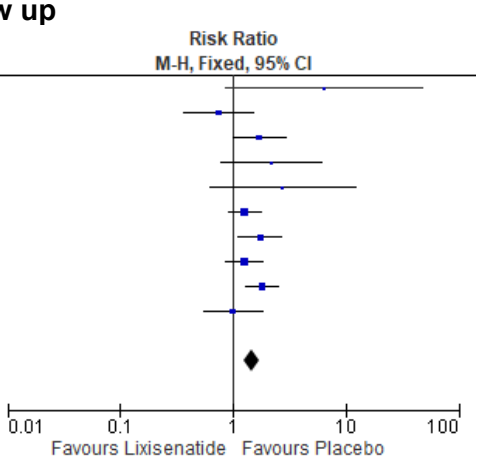


Figure 160: Severe hypoglycaemic episodes at end of follow up

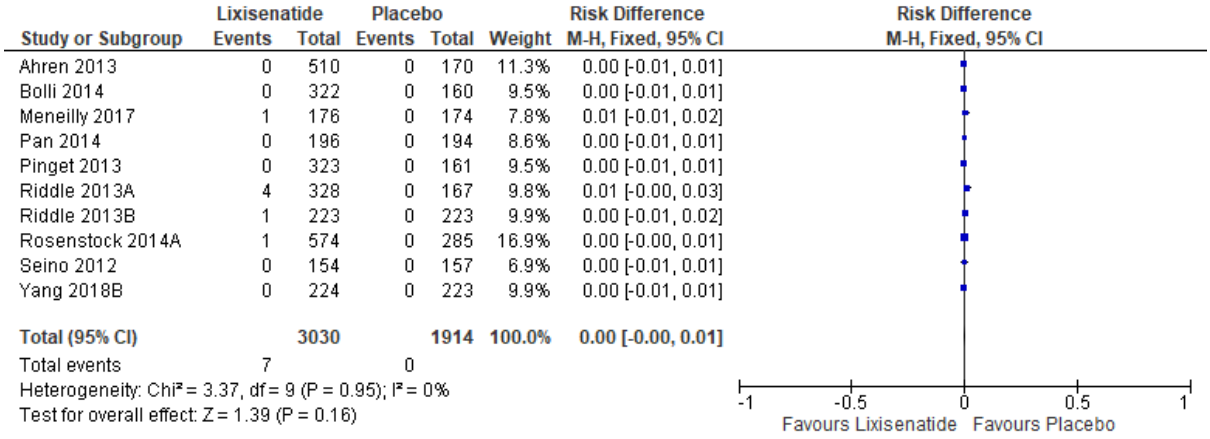
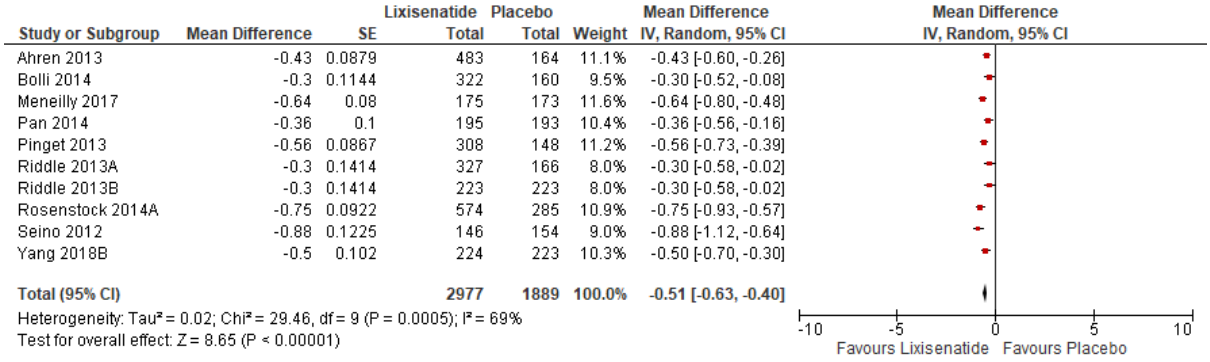
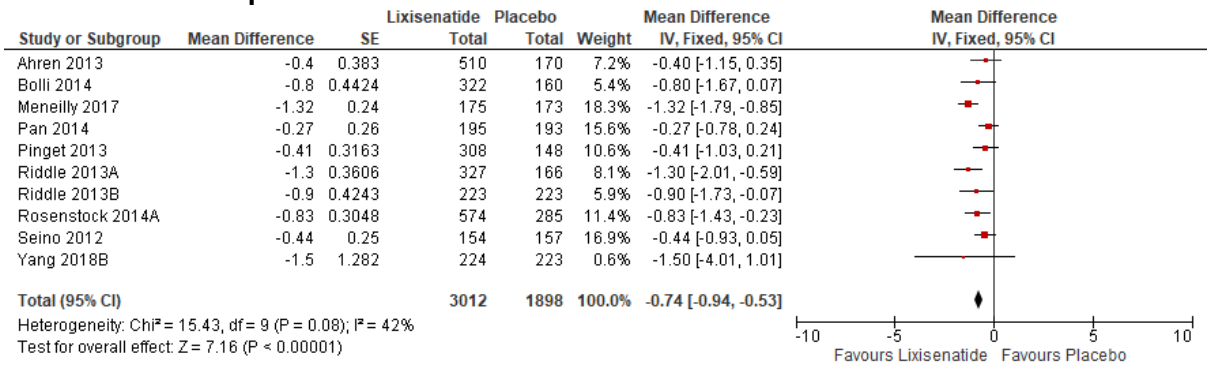


Figure 161: HbA1c change (%, lower values are better, mean difference) at end of follow up



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

Figure 162: Weight change (kg, lower values are better, mean difference) at end of follow up



K.1.3.16 Adding lixisenatide compared to adding insulin

Figure 163: All-cause mortality at end of follow up

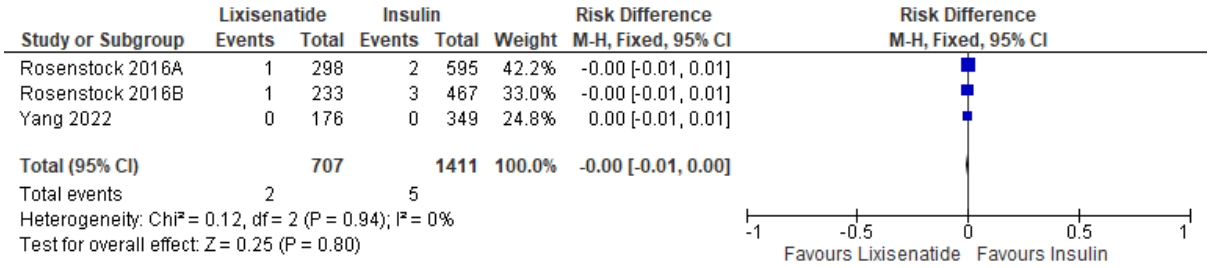


Figure 164: Cardiovascular mortality at end of follow up

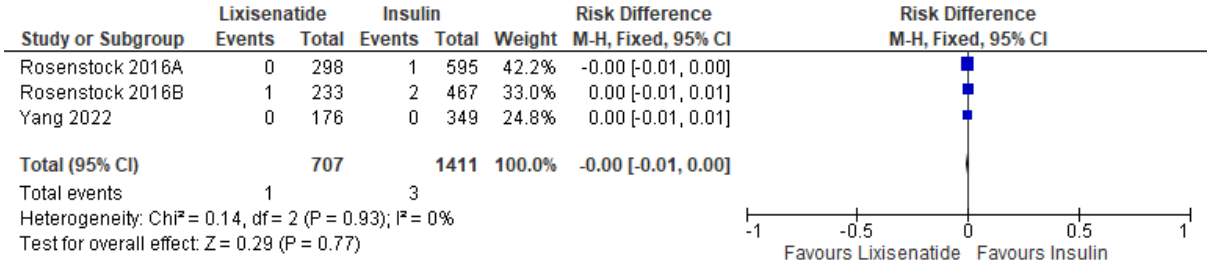


Figure 165: Hypoglycaemia episodes at end of follow up

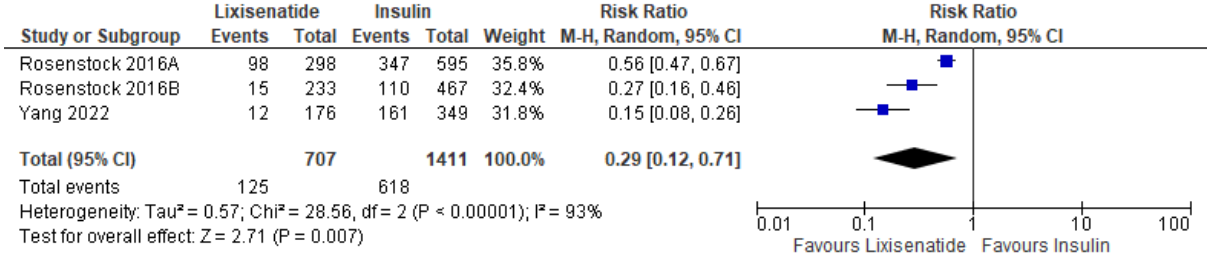


Figure 166: Severe hypoglycaemic episodes at end of follow up

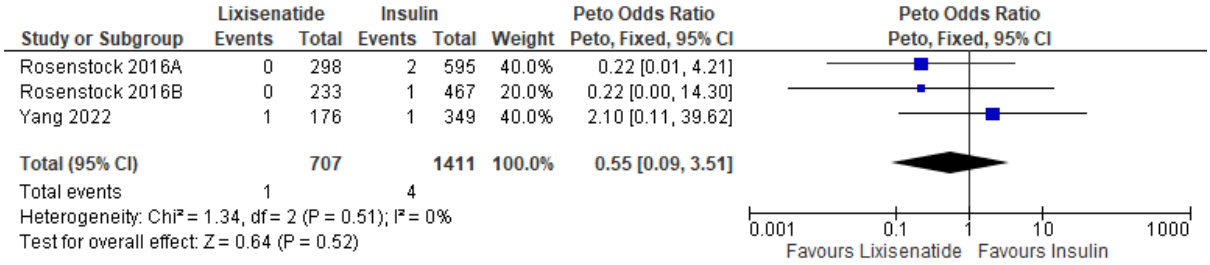


Figure 167: HbA1c change (%, lower values are better, change scores) at end of follow up

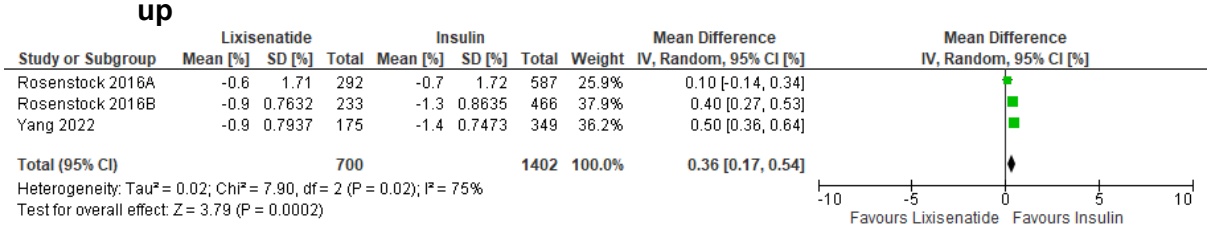
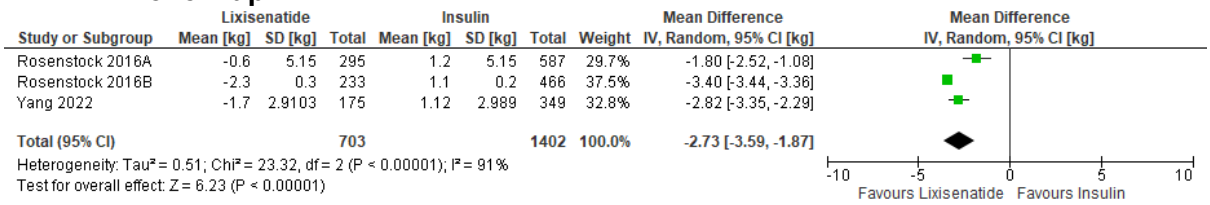


Figure 168: Weight change (kg, lower values are better, change scores) at end of follow up



K.1.3.17 Adding lixisenatide compared to adding exenatide

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

K.1.3.18 Adding lixisenatide compared to adding liraglutide

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

K.1.3.19 Adding lixisenatide compared to adding sitagliptin

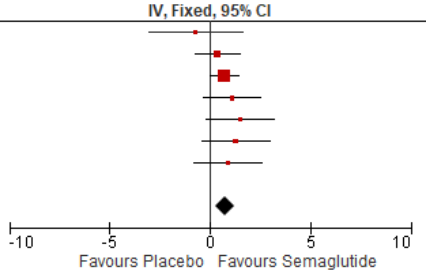
There are no forest plots for this comparison (all outcomes include a single study).

K.1.3.20 Adding semaglutide compared to adding placebo

Figure 169: Health-related quality of life - subscale mental component (SF-36, 0-100, higher values are better, change scores) at end of follow-up

Study or Subgroup	Mean Difference	SE	Semaglutide Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Davies 2017	-0.72	1.1876	559	71	4.1%	-0.72 [-3.05, 1.61]
Davies 2021	0.38	0.5714	381	374	17.6%	0.38 [-0.74, 1.50]
Marso 2016B	0.7	0.3605	1648	1649	44.1%	0.70 [-0.01, 1.41]
Zinman 2019A	1.1	0.7245	151	151	10.9%	1.10 [-0.32, 2.52]
Zinman 2019B (1)	1.5	0.8572	181	62	7.8%	1.50 [-0.18, 3.18]
Zinman 2019B (2)	1.27	0.8572	184	61	7.8%	1.27 [-0.41, 2.95]
Zinman 2019B (3)	0.88	0.86	182	61	7.8%	0.88 [-0.81, 2.57]
Total (95% CI)			**3286**	**2429**	**100.0%**	**0.75 [0.28, 1.22]**

Heterogeneity: Chi² = 3.36, df = 6 (P = 0.76); I² = 0%
Test for overall effect: Z = 3.14 (P = 0.002)

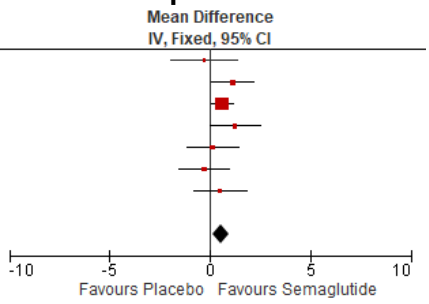


Footnotes
(1) 14 mg semaglutide v placebo
(2) 3 mg semaglutide v placebo
(3) 7 mg semaglutide v placebo

Figure 170: Health-related quality of life - subscale physical component (SF-36, 0-100, higher values are better, change scores) at end of follow-up

Study or Subgroup	Mean Difference	SE	Semaglutide Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Davies 2017	-0.29	0.8427	559	71	5.4%	-0.29 [-1.94, 1.36]
Davies 2021	1.14	0.5408	381	374	13.1%	1.14 [0.08, 2.20]
Marso 2016B	0.6	0.2884	1648	1649	45.9%	0.60 [0.03, 1.17]
Zinman 2019A	1.25	0.6378	151	151	9.4%	1.25 [-0.00, 2.50]
Zinman 2019B (1)	0.12	0.6582	184	61	8.8%	0.12 [-1.17, 1.41]
Zinman 2019B (2)	-0.3	0.6531	181	62	9.0%	-0.30 [-1.58, 0.98]
Zinman 2019B (3)	0.48	0.6735	182	61	8.4%	0.48 [-0.84, 1.80]
Total (95% CI)			**3286**	**2429**	**100.0%**	**0.55 [0.17, 0.93]**

Heterogeneity: Chi² = 5.55, df = 6 (P = 0.48); I² = 0%
Test for overall effect: Z = 2.82 (P = 0.005)



Footnotes
(1) 3 mg semagluitde v placebo
(2) 14 mg semaglutide v placebo
(3) 7 mg semaglutide v placebo

Figure 171: 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
Davies 2017	0	559	0	71	2.6%	0.00 [-0.02, 0.02]
Davies 2021	2	804	1	402	11.3%	0.00 [-0.01, 0.01]
Heise 2022	0	44	0	28	0.7%	0.00 [-0.06, 0.06]
Husain 2019	23	1591	45	1592	33.4%	-0.01 [-0.02, -0.00]
Marso 2016B	62	1648	60	1649	34.6%	0.00 [-0.01, 0.01]
Pratley 2019	3	285	1	142	4.0%	0.00 [-0.01, 0.02]
Rodbard 2018	0	263	0	133	3.7%	0.00 [-0.01, 0.01]
Sivalingam 2023	1	30	0	30	0.6%	0.03 [-0.05, 0.12]
Zinman 2019A	0	151	0	151	3.2%	0.00 [-0.01, 0.01]
Zinman 2019B	3	546	0	184	5.8%	0.01 [-0.00, 0.02]
Total (95% CI)		**5921**		**4382**	**100.0%**	**-0.00 [-0.01, 0.00]**
Total events	94		107			

Heterogeneity: Chi² = 11.05, df = 9 (P = 0.27); I² = 19%
Test for overall effect: Z = 1.19 (P = 0.23)

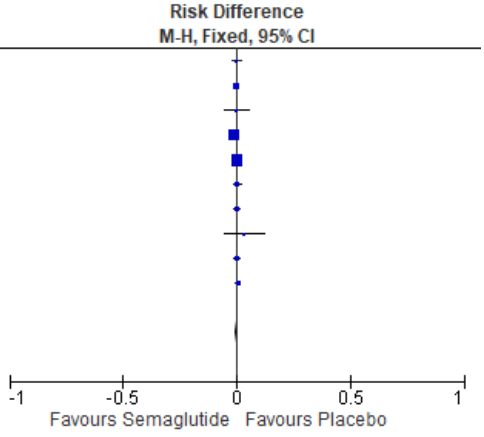


Figure 172: All-cause mortality at end of follow-up

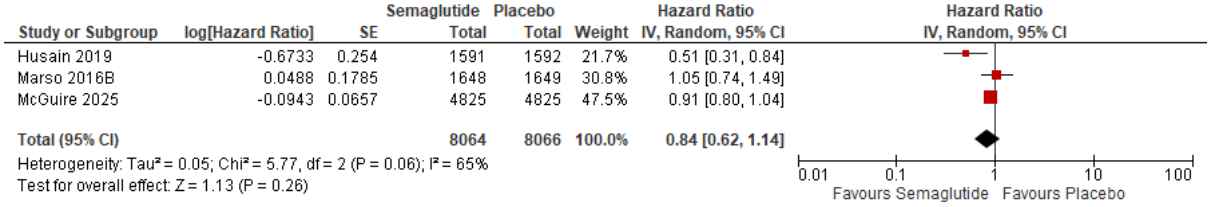


Figure 173: Cardiovascular mortality at end of follow-up

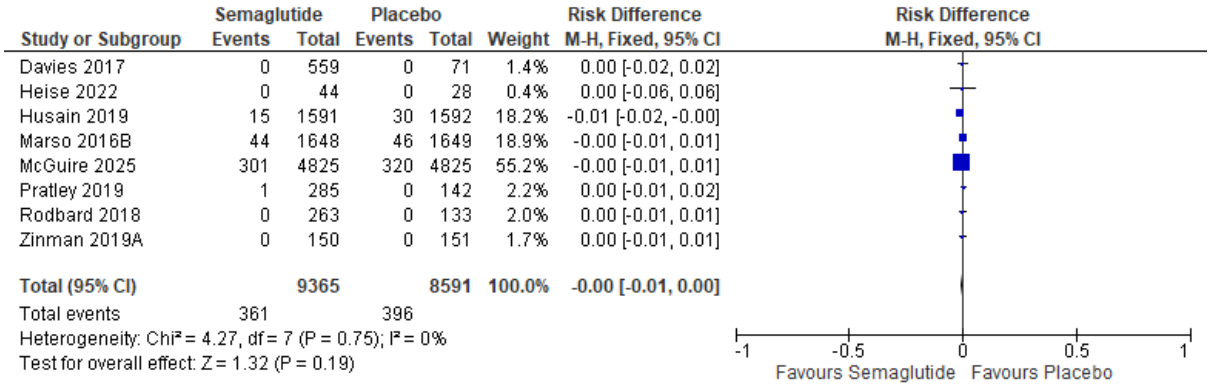


Figure 174: Cardiovascular mortality at end of follow-up

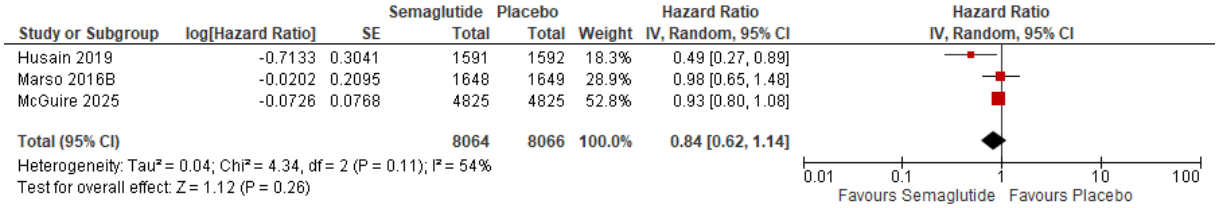


Figure 175: 3-point MACE at end of follow-up

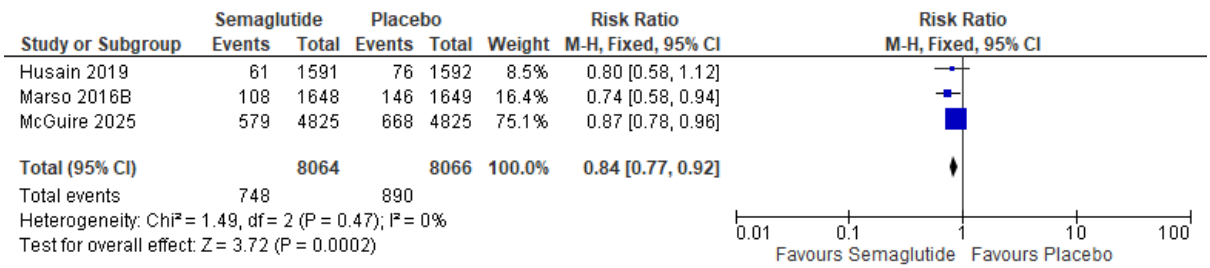


Figure 176: 3-point MACE at end of follow-up

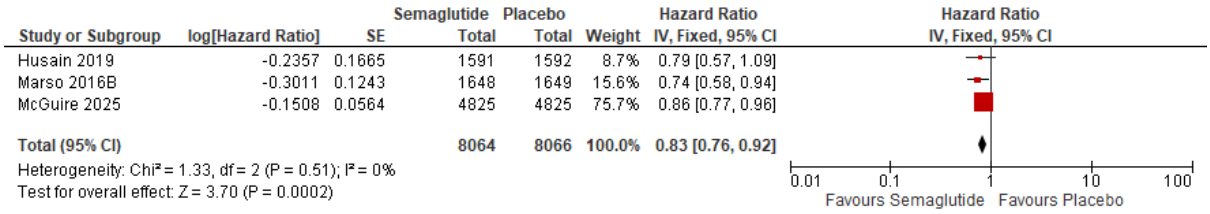


Figure 177: 5-point MACE at end of follow-up

Figure 178: 5-point MACE at end of follow-up

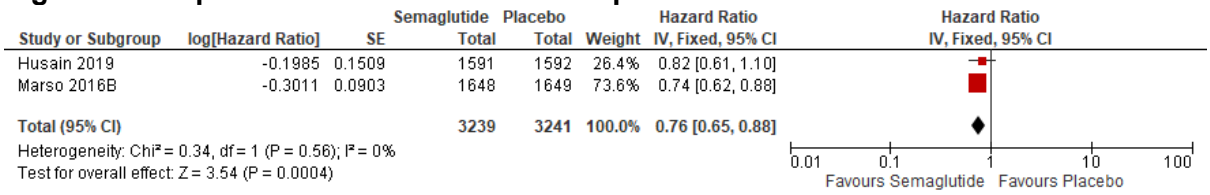


Figure 179: Non-fatal stroke at end of follow-up

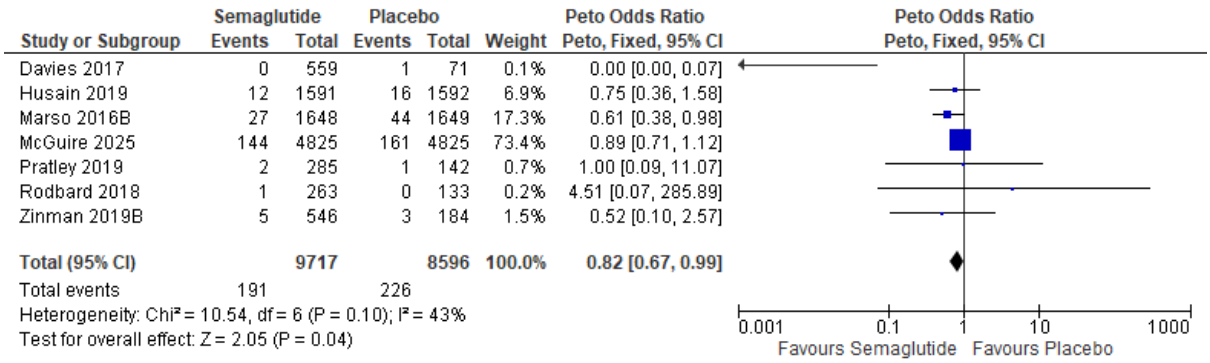


Figure 180: Non-fatal stroke at end of follow-up

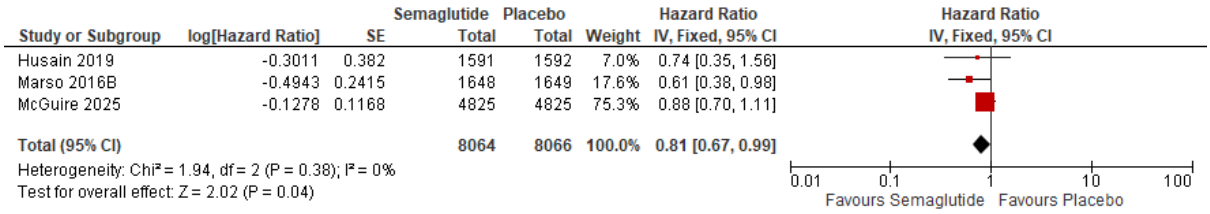


Figure 181: Non-fatal myocardial infarction at end of follow-up

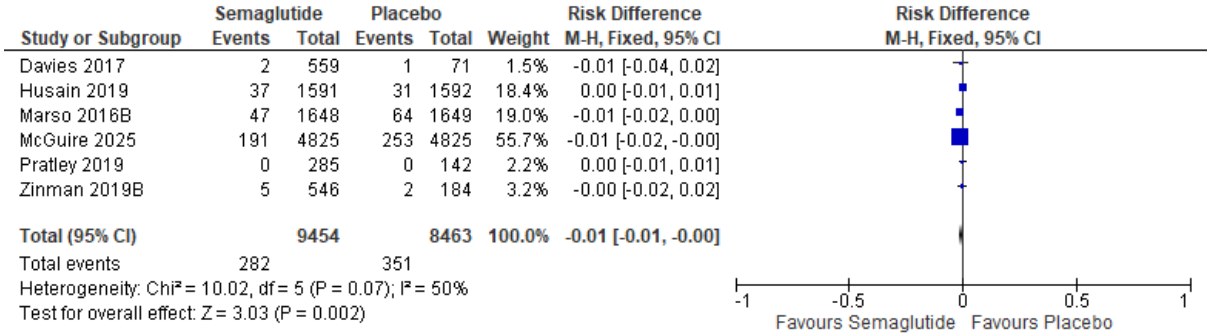


Figure 182: Non-fatal myocardial infarction at end of follow-up

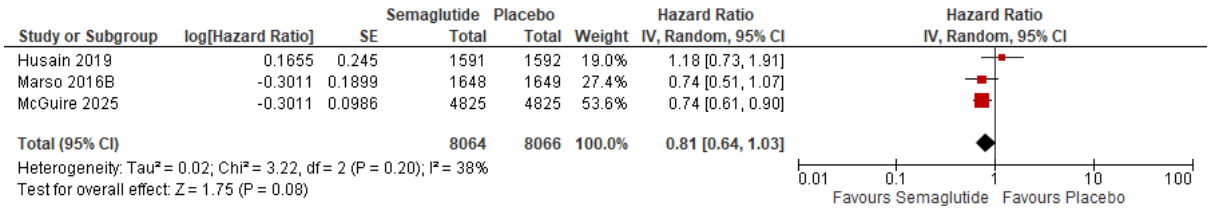


Figure 183: Unstable angina at end of follow-up

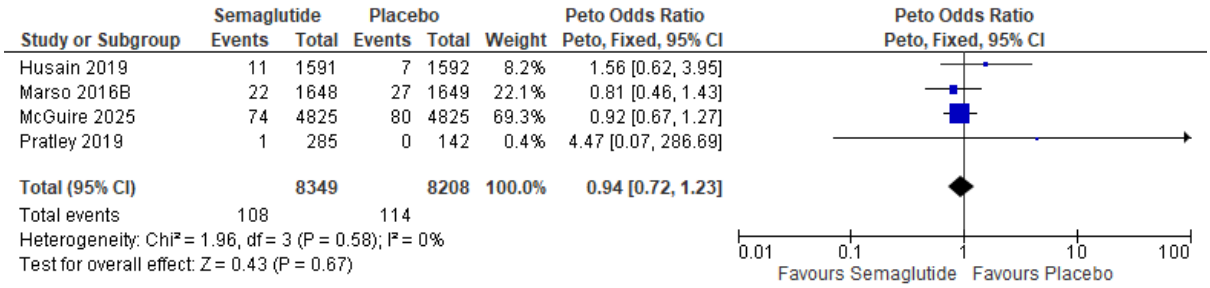


Figure 184: Unstable angina at end of follow-up

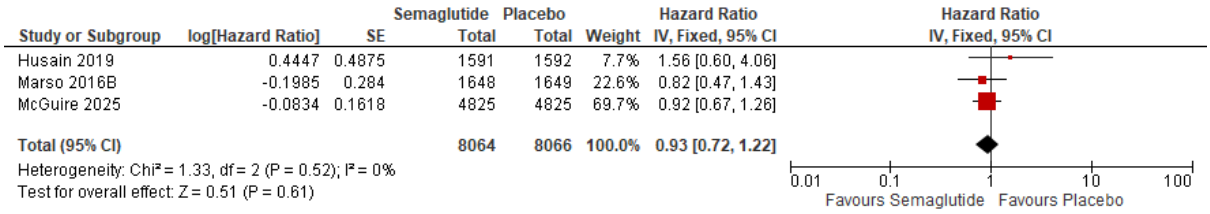


Figure 185: Hospitalisation for heart failure at end of follow-up

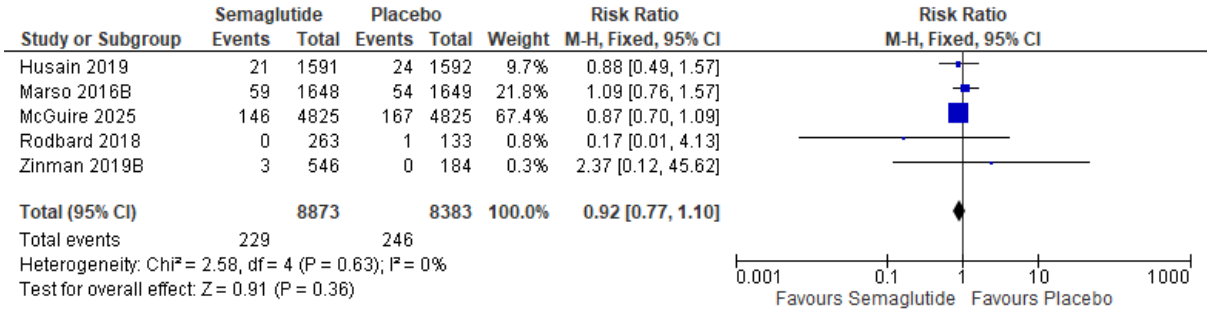


Figure 186: Hospitalisation for heart failure at end of follow-up

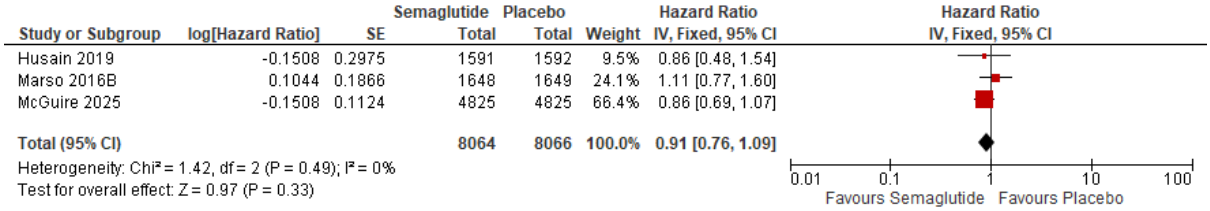


Figure 187: Acute kidney injury at end of follow-up

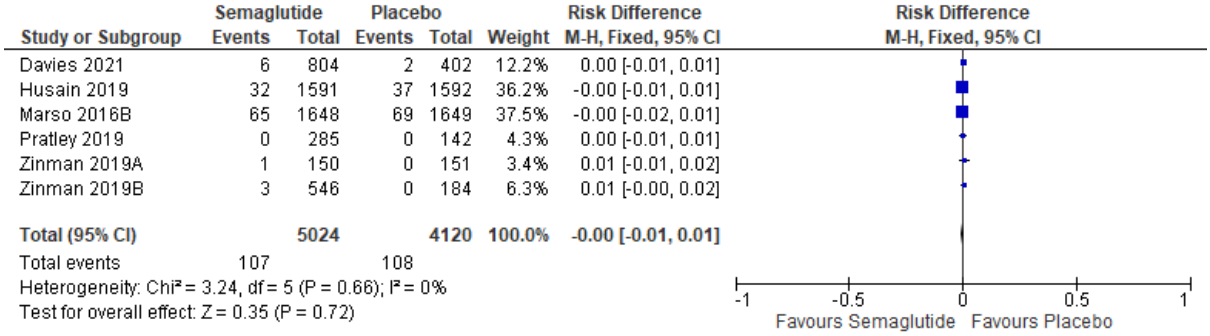
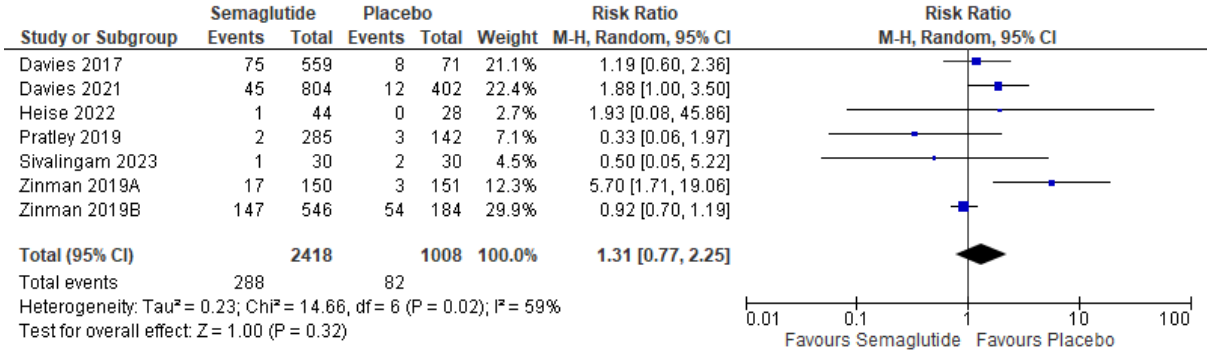


Figure 188: Hypoglycaemia episodes at end of follow-up



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

Figure 189: Severe hypoglycaemic episodes at end of follow-up

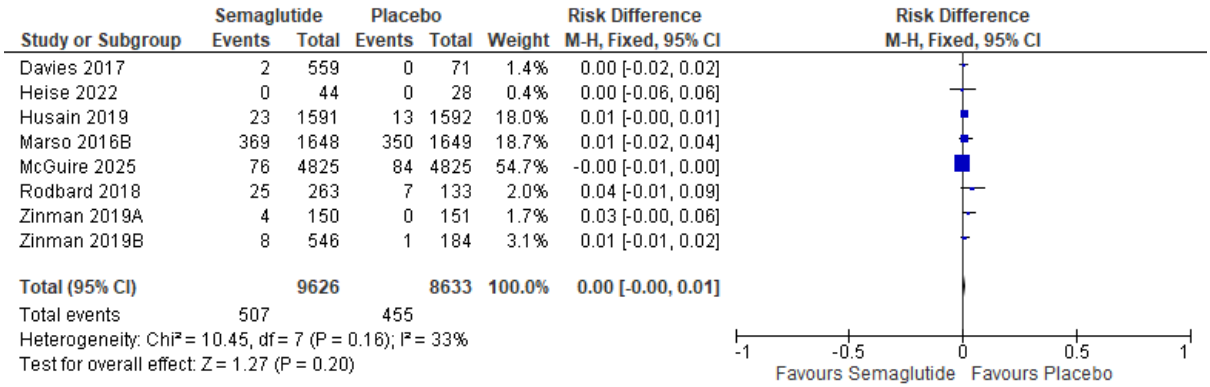
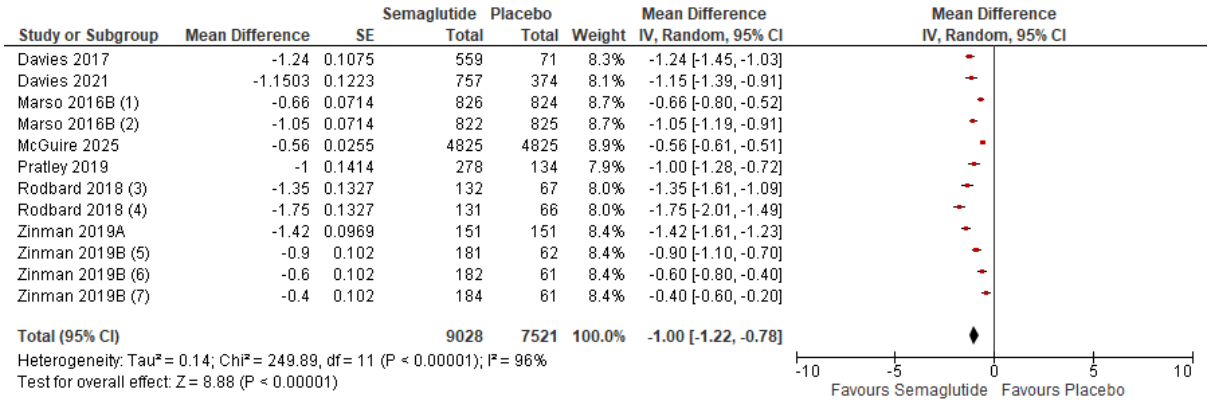


Figure 190: HbA1c change (%, lower values are better, change scores) at end of follow-up



Footnotes
(1) 0.5 mg semaglutide v placebo
(2) 1.0 mg semaglutide v placebo
(3) 0.5 mg semaglutide v placebo
(4) 1.0 mg semaglutide v placebo
(5) 14 mg semaglutide v placebo
(6) 7 mg semaglutide v placebo
(7) 3 mg semaglutide v placebo

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

Figure 191: HbA1c change (mmol/mol, lower values are better, change scores) at end of follow up

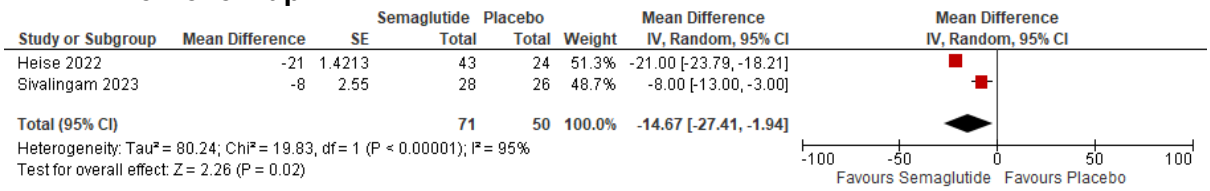
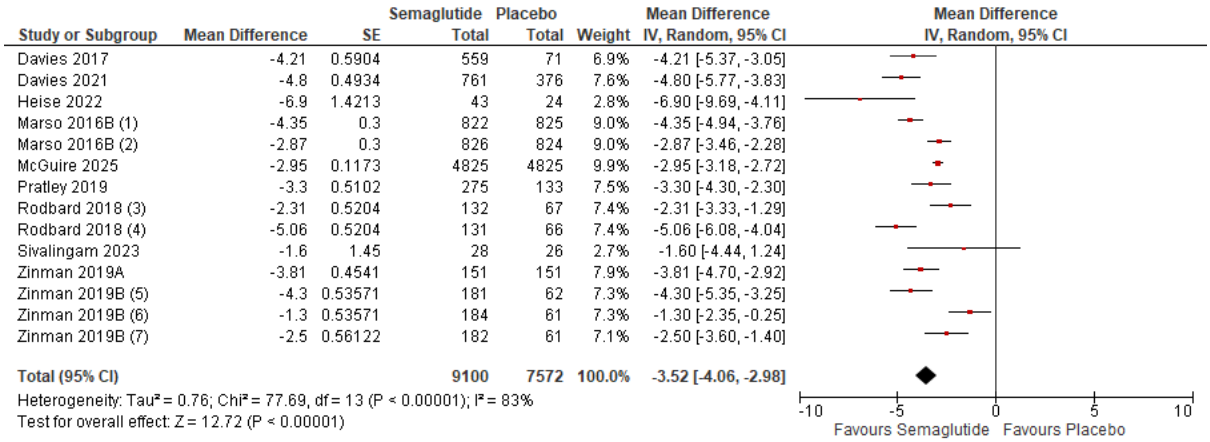


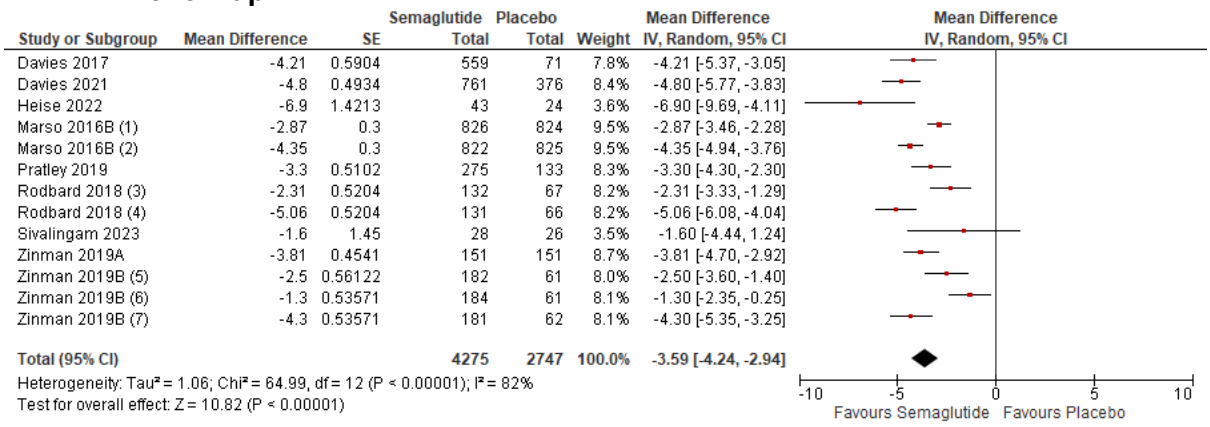
Figure 192: Weight change (kg, lower values are better, change scores) at end of follow-up



Footnotes
(1) 1.0 mg semaglutide v placebo
(2) 0.5 mg semaglutide v placebo
(3) 0.5 mg semaglutide v placebo
(4) 1.0 mg semaglutide v placebo
(5) 14 mg semaglutide v placebo
(6) 3 mg semaglutide v placebo
(7) 7 mg semaglutide v placebo

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

Figure 193: BMI change (kg/m^2, lower values are better, change scores) at end of follow up



Footnotes
(1) 0.5 mg semaglutide v placebo
(2) 1.0 mg semaglutide v placebo
(3) 0.5 mg semaglutide v placebo
(4) 1.0 mg semaglutide v placebo
(5) 7 mg semaglutide v placebo
(6) 3 mg semaglutide v placebo
(7) 14 mg semaglutide v placebo

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

K.1.3.21 Adding semaglutide compared to adding insulin

Figure 194: All-cause mortality at end of follow up

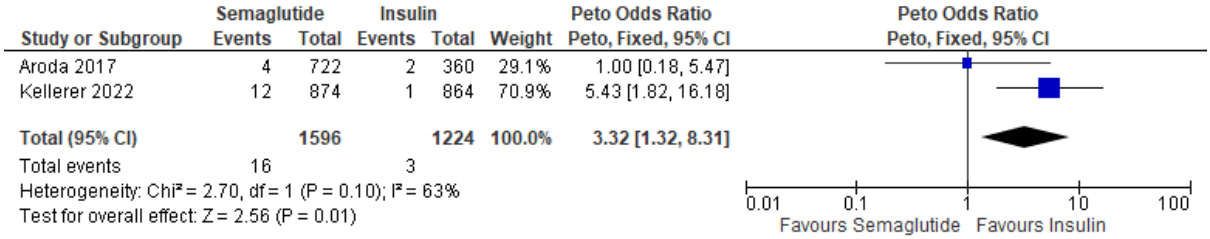


Figure 195: Severe hypoglycaemic episodes at end of follow up

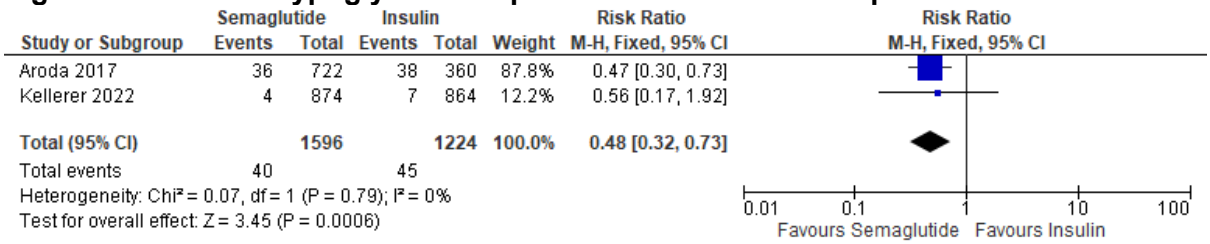
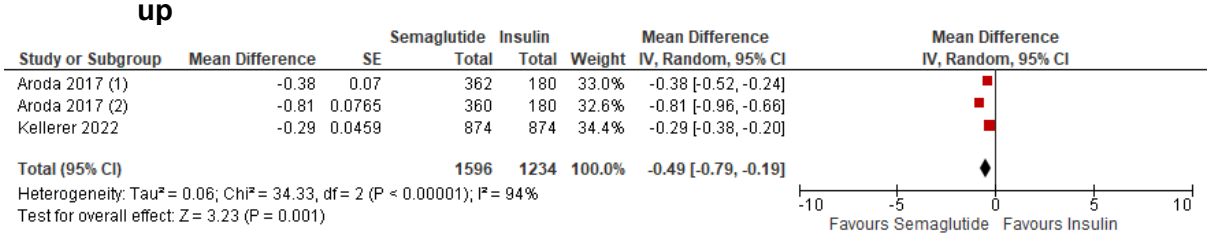
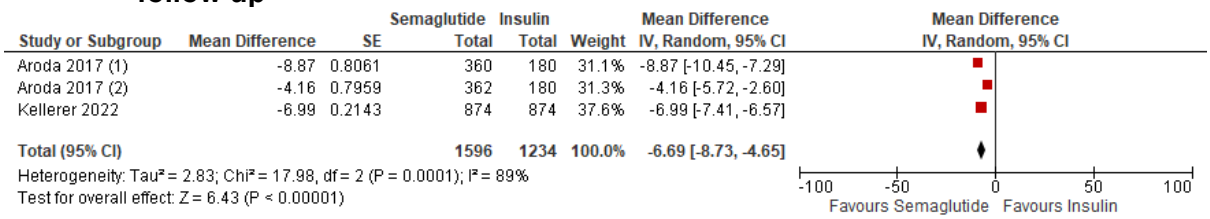


Figure 196: HbA1c change (%, lower values are better, change scores) at end of follow up



Footnotes
(1) 0.5 mg semaglutide v placebo
(2) 1.0 mg semaglutide v insulin

Figure 197: Weight change (kg, lower values are better, change scores) at end of follow up



Footnotes
(1) 1.0 mg semaglutide v insulin
(2) 0.5 mg semaglutide v insulin

K.1.3.22 Adding semaglutide compared to adding dulaglutide

Figure 198: All-cause mortality at end of follow up

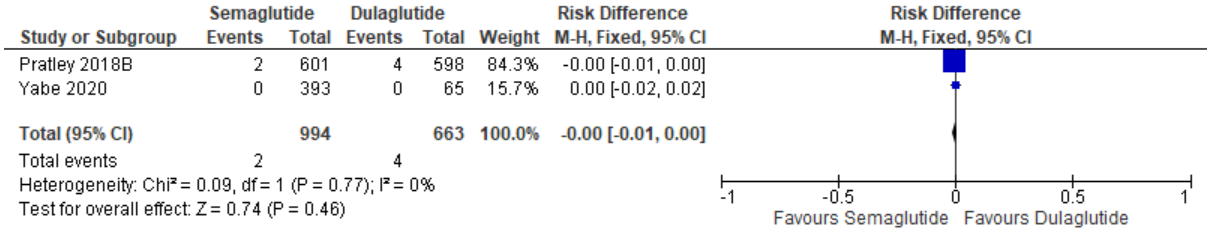


Figure 199: Cardiovascular mortality at end of follow up

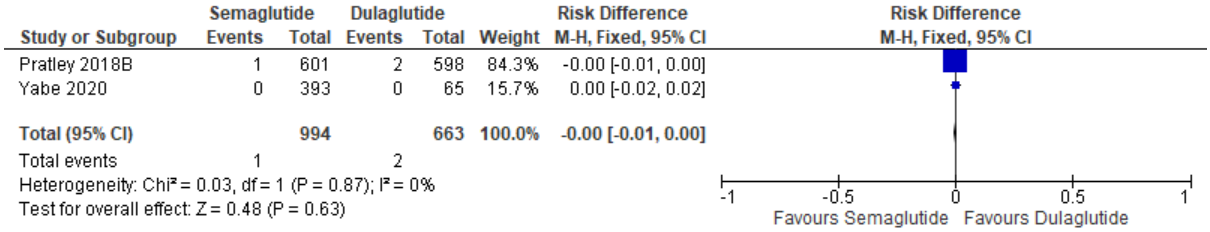


Figure 200: Hypoglycaemia episodes at end of follow up

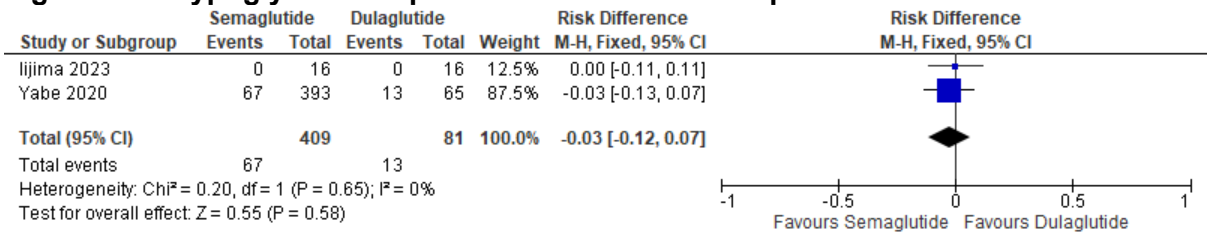


Figure 201: Severe hypoglycaemic episodes at end of follow up

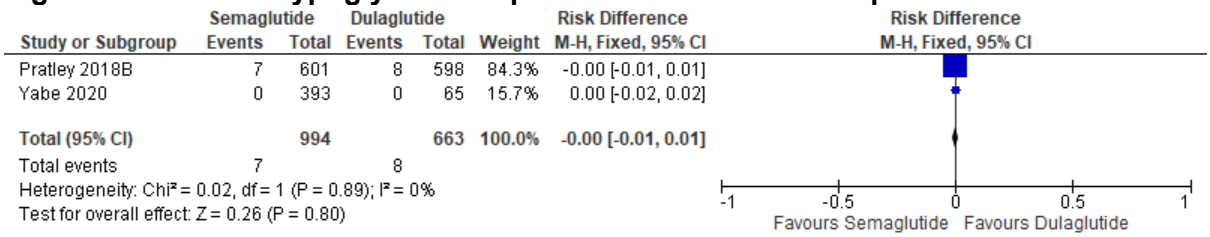


Figure 202: HbA1c change (%, lower values are better, change scores) at end of follow up

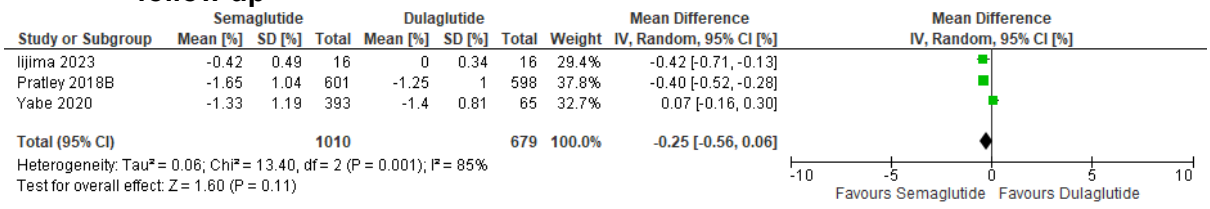


Figure 203: Weight change (kg, lower values are better, change scores) at end of follow up

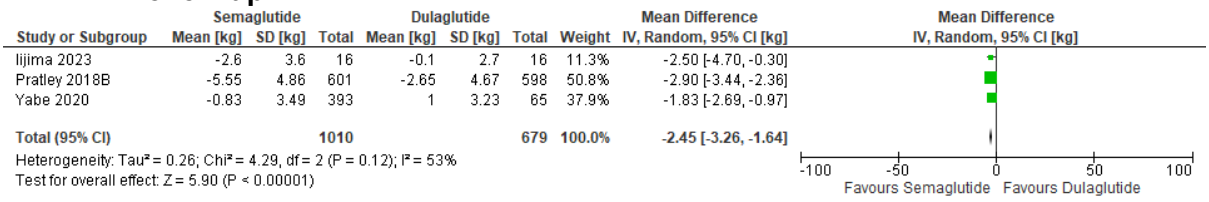
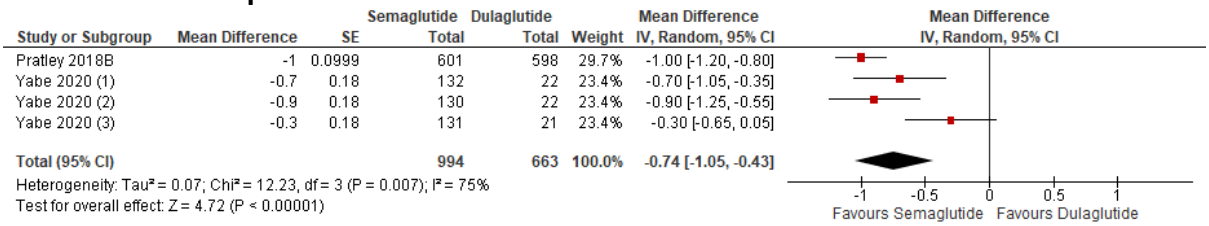


Figure 204: BMI change (kg/m^2, lower values are better, change scores) at end of follow up



Footnotes
(1) 7 mg semaglutide v dulaglutide
(2) 14 mg semaglutide v dulaglutide
(3) 3 mg semaglutide v dulaglutide

K.1.3.23 Adding semaglutide compared to adding exenatide

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

K.1.3.24 Adding semaglutide compared to adding liraglutide

Figure 205: All-cause mortality at end of follow up

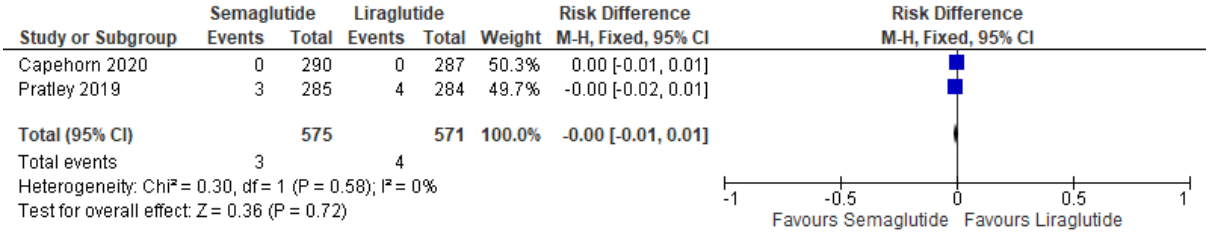


Figure 206: Cardiovascular mortality at end of follow up

Figure 207: Hypoglycaemia episodes at end of follow up

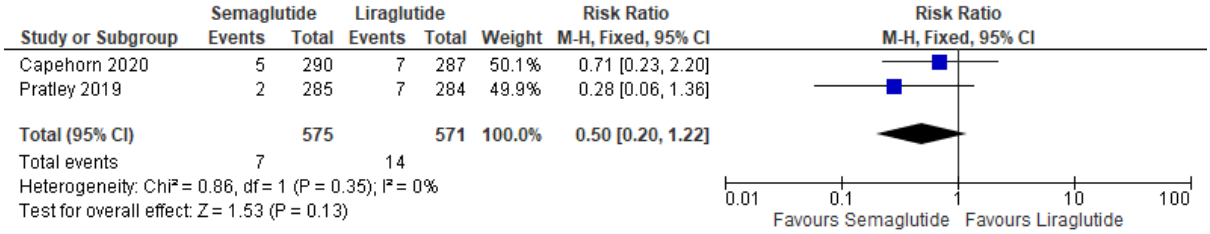


Figure 208: HbA1c change (%, lower values are better, change scores) at end of follow up

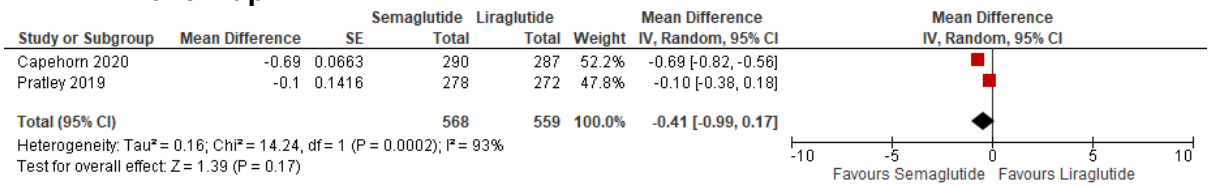


Figure 209: Weight change (kg, lower values are better, change scores) at end of follow up

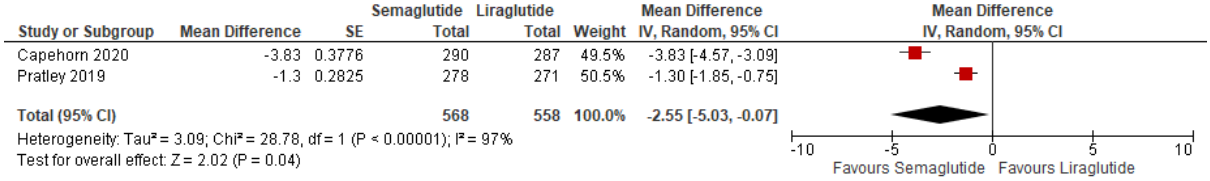
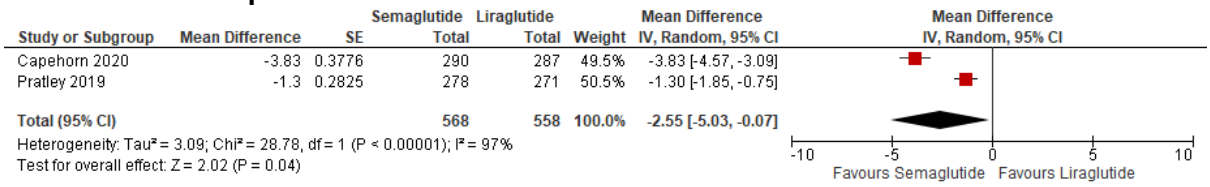
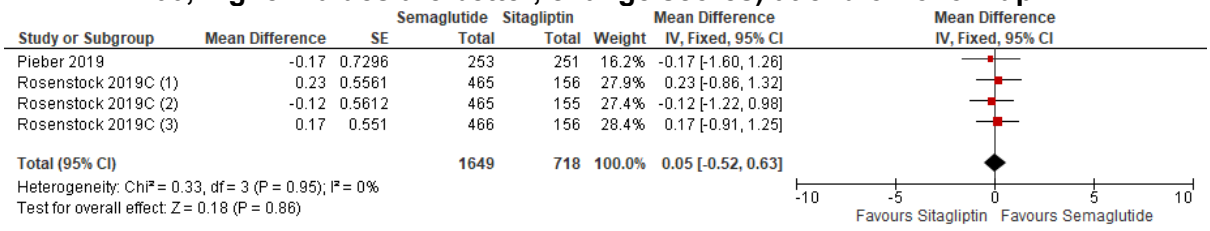


Figure 210: BMI change (kg/m^2, lower values are better, change scores) at end of follow up



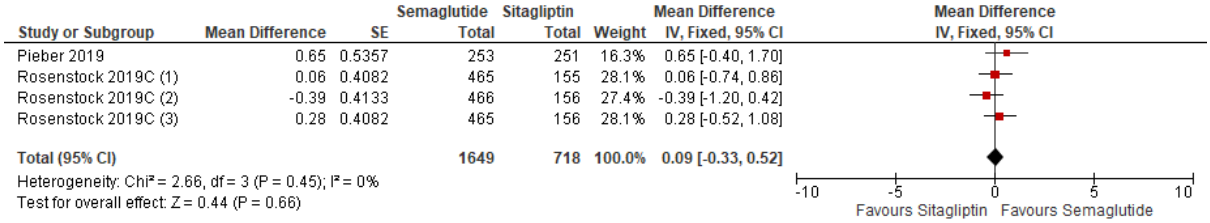
K.1.3.25 Adding semaglutide compared to adding sitagliptin

Figure 211: Health-related quality of life - subscale mental component (SF36 v2, 0-100, higher values are better, change scores) at end of follow-up



Footnotes
(1) 7 mg semaglutide v sitagliptin
(2) 14 mg semaglutide v sitagliptin
(3) 3 mg semaglutide v sitagliptin

Figure 212: Health-related quality of life - subscale physical component (SF36 v2, 0-100, higher values are better, change scores) at end of follow-up



Footnotes
(1) 14 mg semaglutide v sitagliptin
(2) 3 mg semaglutide v sitagliptin
(3) 7 mg semaglutide v sitagliptin

Figure 213: All-cause mortality at end of follow up

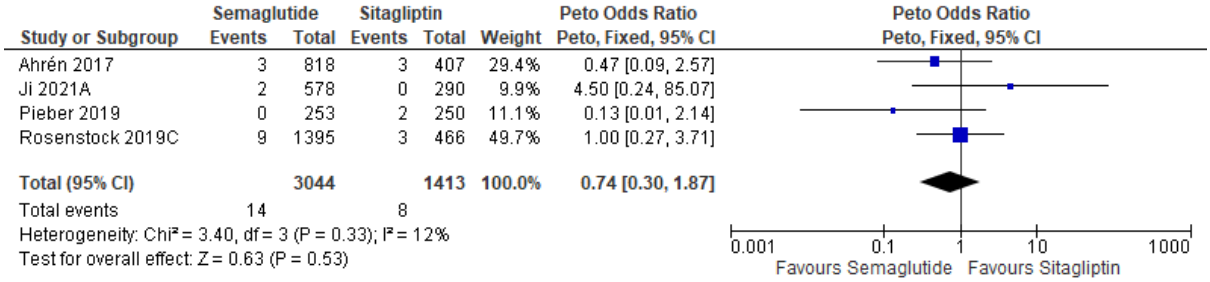


Figure 214: Cardiovascular mortality at end of follow up

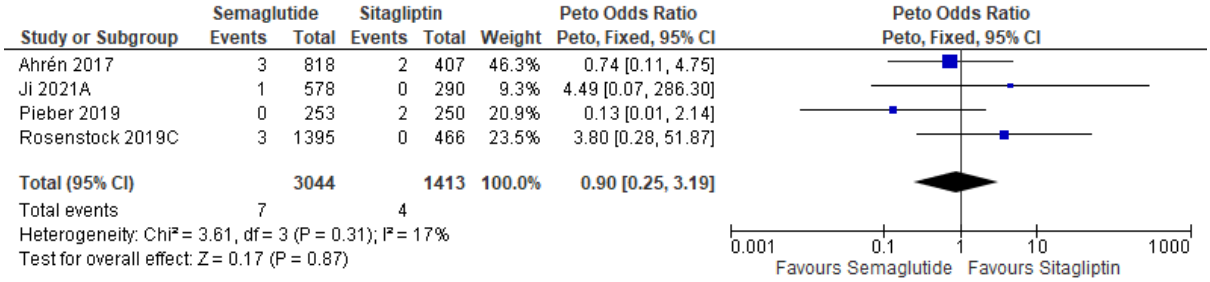


Figure 215: Hospitalisation for heart failure at end of follow up

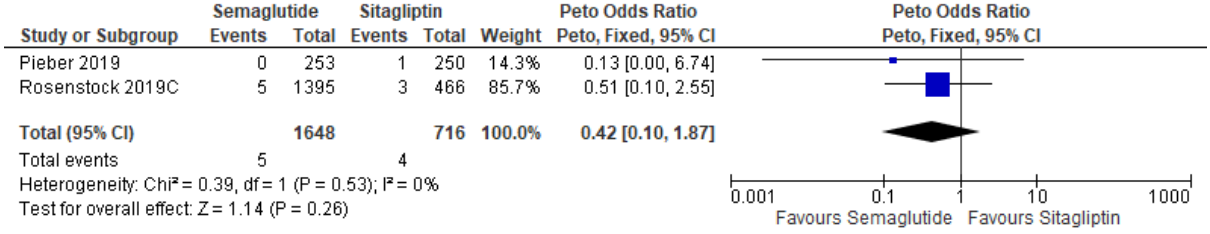


Figure 216: Acute kidney injury at end of follow up

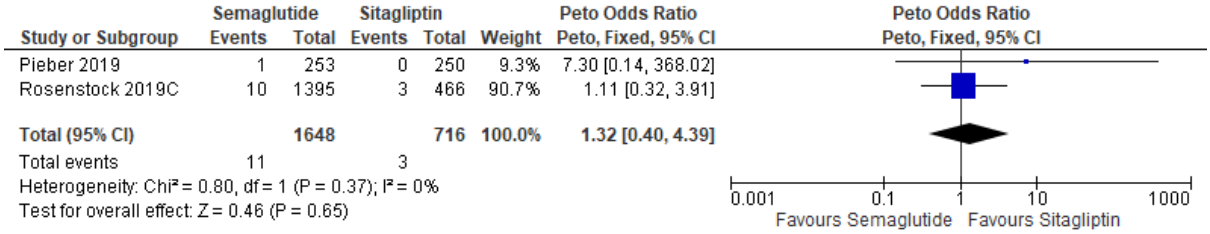


Figure 217: Hypoglycaemia episodes at end of follow up

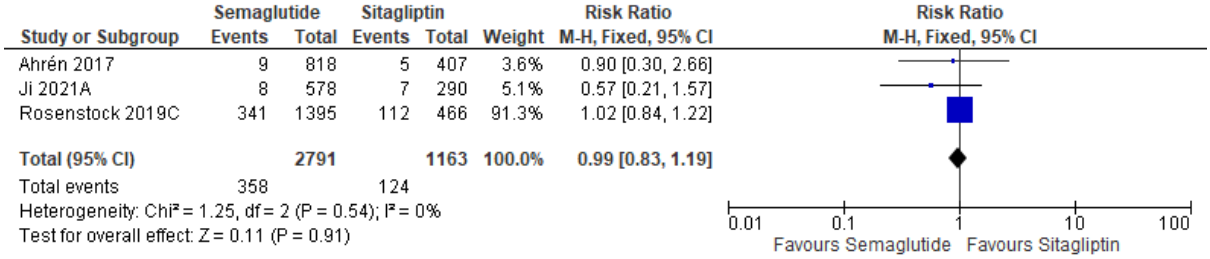


Figure 218: At night hypoglycaemic episodes at end of follow up

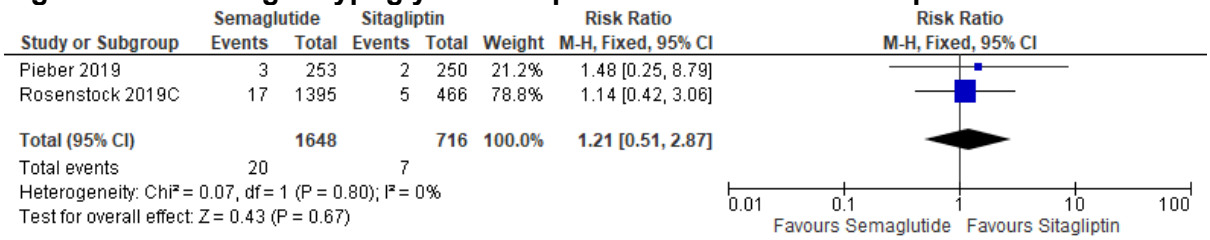


Figure 219: Severe hypoglycaemic episodes at end of follow up

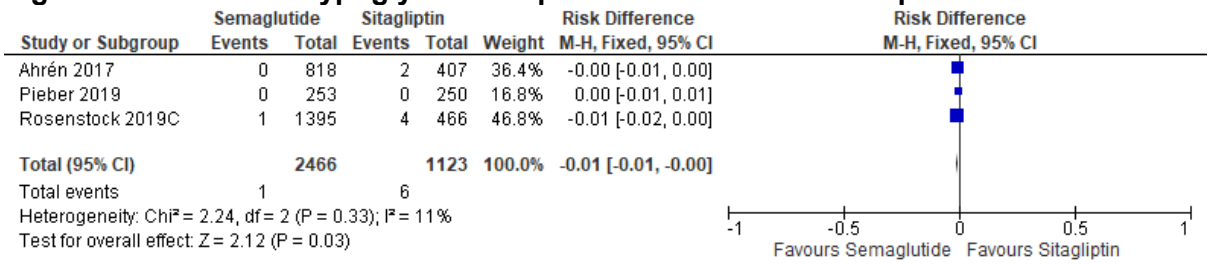
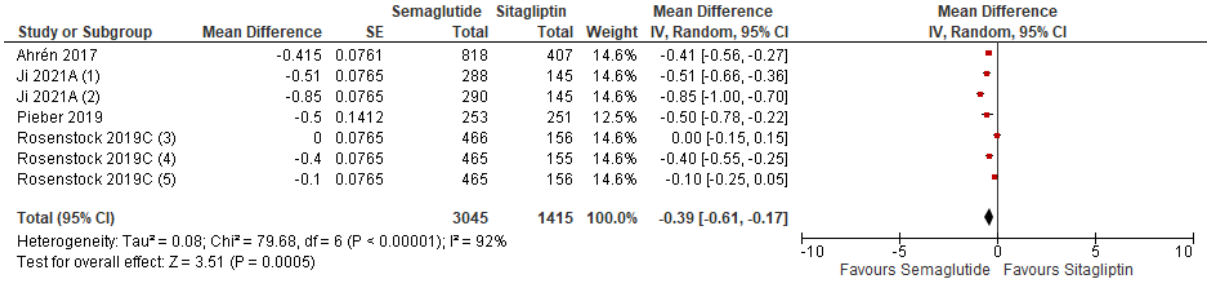


Figure 220: HbA1c change (%, lower values are better, change scores) at end of follow up



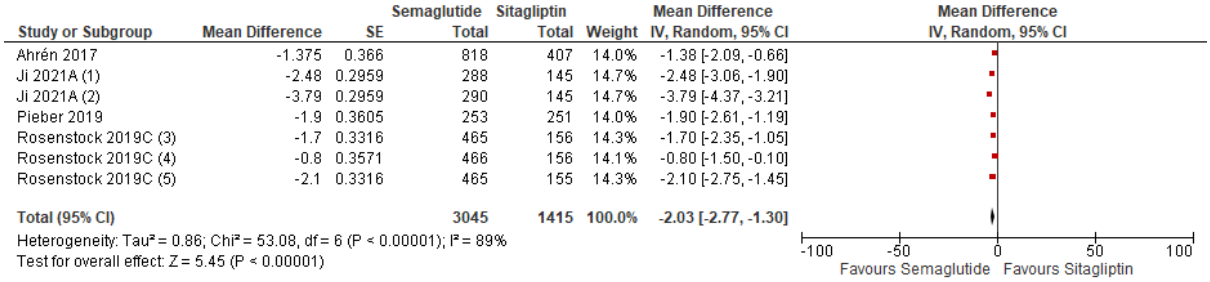
Study or Subgroup	Mean Difference	SE	Semaglutide Total	Sitagliptin Total	Weight	Mean Difference IV, Random, 95% CI
Ahrén 2017	-0.415	0.0761	818	407	14.6%	-0.41 [-0.56, -0.27]
Ji 2021A (1)	-0.51	0.0765	288	145	14.6%	-0.51 [-0.66, -0.36]
Ji 2021A (2)	-0.85	0.0765	290	145	14.6%	-0.85 [-1.00, -0.70]
Pieber 2019	-0.5	0.1412	253	251	12.5%	-0.50 [-0.78, -0.22]
Rosenstock 2019C (3)	0	0.0765	466	156	14.6%	0.00 [-0.15, 0.15]
Rosenstock 2019C (4)	-0.4	0.0765	465	155	14.6%	-0.40 [-0.55, -0.25]
Rosenstock 2019C (5)	-0.1	0.0765	465	156	14.6%	-0.10 [-0.25, 0.05]
Total (95% CI)			**3045**	**1415**	**100.0%**	**-0.39 [-0.61, -0.17]**

Heterogeneity: Tau² = 0.08; Chi² = 79.68, df = 6 (P < 0.00001); I² = 92%
Test for overall effect: Z = 3.51 (P = 0.0005)

Footnotes
(1) 0.5 mg semaglutide v sitagliptin
(2) 1.0 mg semaglutide v sitagliptin
(3) 3 mg semaglutide v sitagliptin
(4) 14 mg semaglutide v sitagliptin
(5) 7 mg semaglutide v sitagliptin

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

Figure 221: Weight change (kg, lower values are better, change scores) at end of follow up



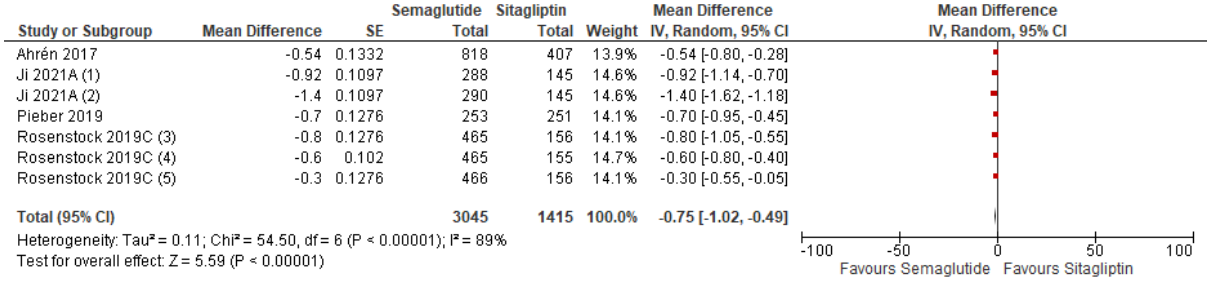
Study or Subgroup	Mean Difference	SE	Semaglutide Total	Sitagliptin Total	Weight	Mean Difference IV, Random, 95% CI
Ahrén 2017	-1.375	0.366	818	407	14.0%	-1.38 [-2.09, -0.66]
Ji 2021A (1)	-2.48	0.2959	288	145	14.7%	-2.48 [-3.06, -1.90]
Ji 2021A (2)	-3.79	0.2959	290	145	14.7%	-3.79 [-4.37, -3.21]
Pieber 2019	-1.9	0.3605	253	251	14.0%	-1.90 [-2.61, -1.19]
Rosenstock 2019C (3)	-1.7	0.3316	465	156	14.3%	-1.70 [-2.35, -1.05]
Rosenstock 2019C (4)	-0.8	0.3571	466	156	14.1%	-0.80 [-1.50, -0.10]
Rosenstock 2019C (5)	-2.1	0.3316	465	155	14.3%	-2.10 [-2.75, -1.45]
Total (95% CI)			**3045**	**1415**	**100.0%**	**-2.03 [-2.77, -1.30]**

Heterogeneity: Tau² = 0.86; Chi² = 53.08, df = 6 (P < 0.00001); I² = 89%
Test for overall effect: Z = 5.45 (P < 0.00001)

Footnotes
(1) 0.5 mg semaglutide v sitagliptin
(2) 1.0 mg semaglutide v sitagliptin
(3) 7 mg semaglutide v sitagliptin
(4) 3 mg semaglutide v sitagliptin
(5) 14 mg semaglutide v sitagliptin

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

Figure 222: BMI change (kg/m^2, lower values are better, change scores) at end of follow up



Study or Subgroup	Mean Difference	SE	Semaglutide Total	Sitagliptin Total	Weight	Mean Difference IV, Random, 95% CI
Ahrén 2017	-0.54	0.1332	818	407	13.9%	-0.54 [-0.80, -0.28]
Ji 2021A (1)	-0.92	0.1097	288	145	14.6%	-0.92 [-1.14, -0.70]
Ji 2021A (2)	-1.4	0.1097	290	145	14.6%	-1.40 [-1.62, -1.18]
Pieber 2019	-0.7	0.1276	253	251	14.1%	-0.70 [-0.95, -0.45]
Rosenstock 2019C (3)	-0.8	0.1276	465	156	14.1%	-0.80 [-1.05, -0.55]
Rosenstock 2019C (4)	-0.6	0.102	465	155	14.7%	-0.60 [-0.80, -0.40]
Rosenstock 2019C (5)	-0.3	0.1276	466	156	14.1%	-0.30 [-0.55, -0.05]
Total (95% CI)			**3045**	**1415**	**100.0%**	**-0.75 [-1.02, -0.49]**

Heterogeneity: Tau² = 0.11; Chi² = 54.50, df = 6 (P < 0.00001); I² = 89%
Test for overall effect: Z = 5.59 (P < 0.00001)

Footnotes
(1) 0.5 mg v sitagliptin
(2) 1.0 mg semaglutide v sitagliptin
(3) 14 mg semaglutide v sitagliptin
(4) 7 mg semaglutide v sitagliptin
(5) 3 mg semaglutide v sitagliptin

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

K.1.3.26 Adding subcutaneous semaglutide compared to adding oral semaglutide

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

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

K.1.4.1 Adding tirzepatide compared to adding placebo

Figure 223: All-cause mortality at end of follow up

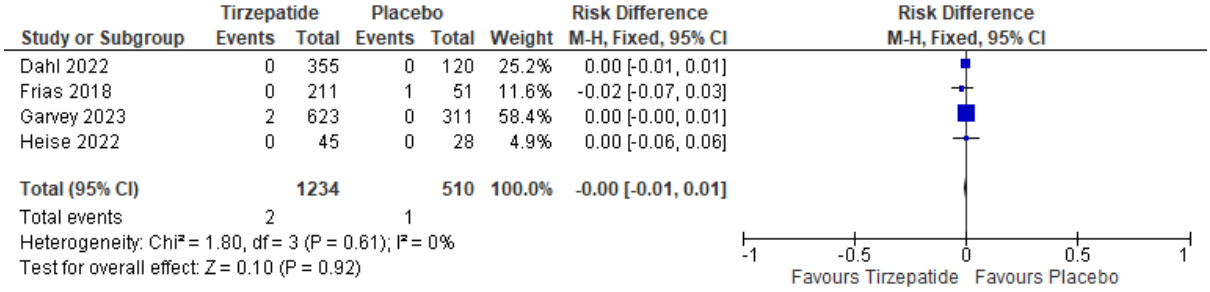


Figure 224: Cardiovascular mortality at end of follow up

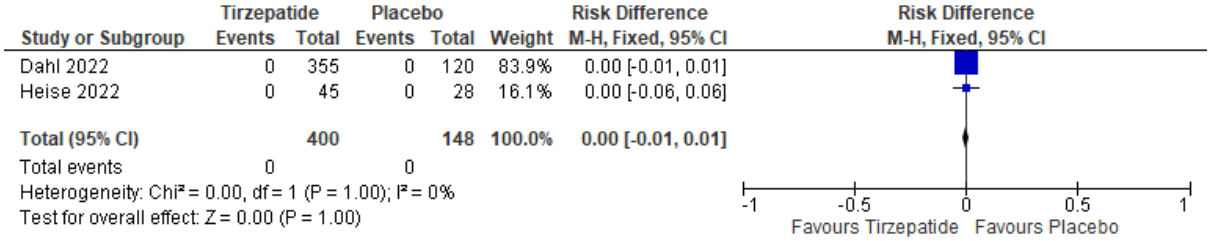
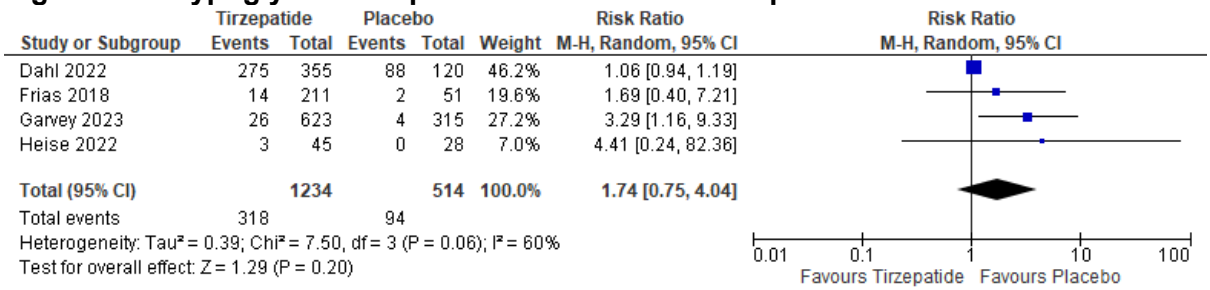


Figure 225: Hypoglycaemia episodes at end of follow up



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

Figure 226: Severe hypoglycaemia episodes at end of follow up

Study or Subgroup	Tirzepatide Events	Tirzepatide Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Dahl 2022	3	355	0	120	25.1%	0.01 [-0.01, 0.02]
Frias 2018	0	211	0	51	11.5%	0.00 [-0.03, 0.03]
Garvey 2023	0	623	0	315	58.6%	0.00 [-0.00, 0.00]
Heise 2022	0	45	0	28	4.8%	0.00 [-0.06, 0.06]
Total (95% CI)		**1234**		**514**	**100.0%**	**0.00 [-0.00, 0.01]**
Total events	3		0			

Heterogeneity: Chi² = 1.40, df = 3 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.65 (P = 0.52)

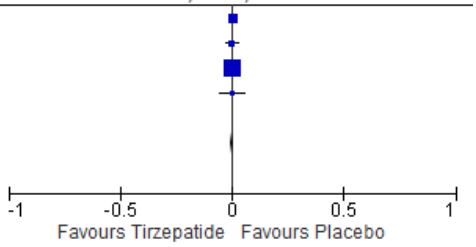


Figure 227: HbA1c change (%, lowr values are better, change scores) at end of follow up

Study or Subgroup	Tirzepatide Mean	Tirzepatide SD	Tirzepatide Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Dahl 2022	-2.29	0.94	355	-0.86	0.91	120	38.2%	-1.43 [-1.62, -1.24]
Frias 2018	-1.68	1.31	211	0.1	1.1426	51	10.6%	-1.78 [-2.14, -1.42]
Garvey 2023	-2.07	1.15	623	-0.51	1.24	315	51.2%	-1.56 [-1.72, -1.40]
Total (95% CI)			**1189**			**486**	**100.0%**	**-1.53 [-1.65, -1.42]**

Heterogeneity: Chi² = 3.04, df = 2 (P = 0.22); I² = 34%
Test for overall effect: Z = 25.61 (P < 0.00001)

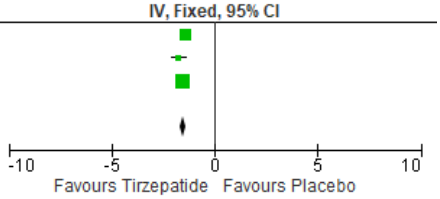
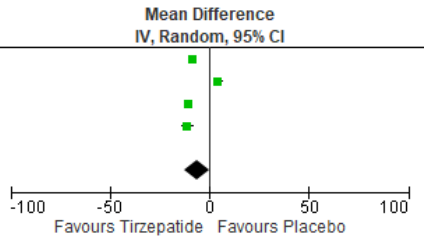


Figure 228: Weight change (kg, lower values are better, change scores) at end of follow up

Study or Subgroup	Tirzepatide Mean	Tirzepatide SD	Tirzepatide Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Dahl 2022	-7.25	6.45	355	1.6	6.36	120	25.3%	-8.85 [-10.17, -7.53]
Frias 2018	-0.4	5.7846	51	-4.77	8.28	211	25.0%	4.37 [2.43, 6.31]
Garvey 2023	-13.75	9.79	623	-3.2	8.87	315	25.3%	-10.55 [-11.80, -9.30]
Heise 2022	-11.2	5.3889	41	0	5.7628	24	24.4%	-11.20 [-14.03, -8.37]
Total (95% CI)			**1070**			**670**	**100.0%**	**-6.55 [-12.94, -0.16]**

Heterogeneity: Tau² = 41.55; Chi² = 177.22, df = 3 (P < 0.00001); I² = 98%
Test for overall effect: Z = 2.01 (P = 0.04)

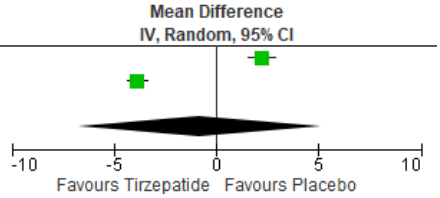


Note: Heterogeneity was not explained by sensitivity analysis nor subgroup analysis by eGFR, NAFLD, Obesity, and early onset subgroups.

Figure 229: BMI change (kg/m², lower values are better, change scores) at end of follow-up

Study or Subgroup	Tirzepatide Mean	Tirzepatide SD	Tirzepatide Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Frias 2018	-0.1	1.9996	51	-2.3	2.51	211	49.9%	2.20 [1.56, 2.84]
Garvey 2023	-5.05	3.54	623	-1.2	3.55	315	50.1%	-3.85 [-4.33, -3.37]
Total (95% CI)			**674**			**526**	**100.0%**	**-0.83 [-6.76, 5.10]**

Heterogeneity: Tau² = 18.22; Chi² = 217.38, df = 1 (P < 0.00001); I² = 100%
Test for overall effect: Z = 0.27 (P = 0.78)



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K.1.4.2 Adding tirzepatide compared to adding insulin

Figure 230: All-cause mortality at end of follow up

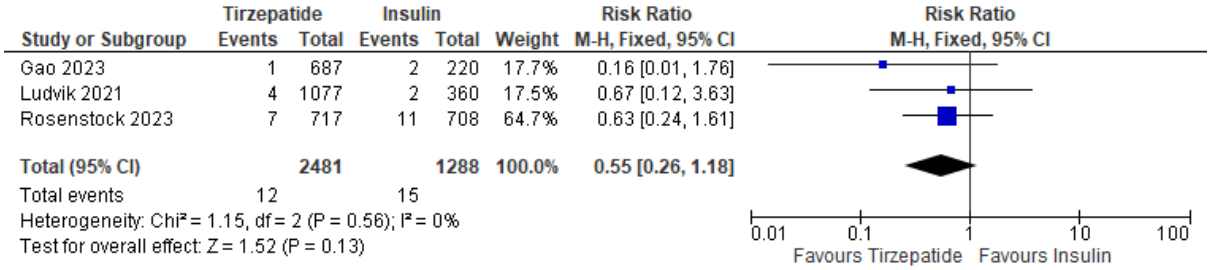


Figure 231: Cardiovascular mortality at end of follow up

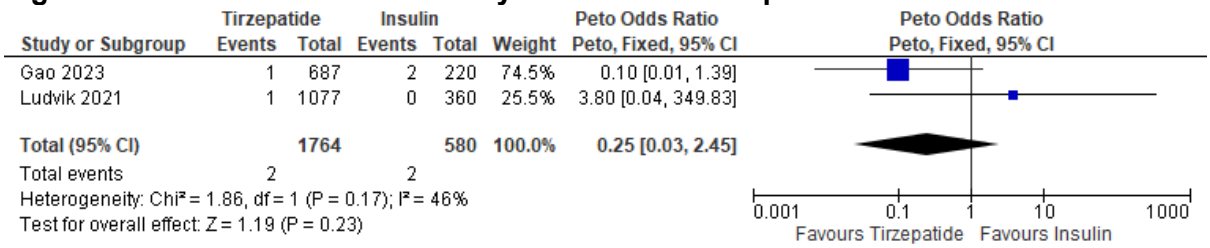


Figure 232: 4-point MACE at end of follow up

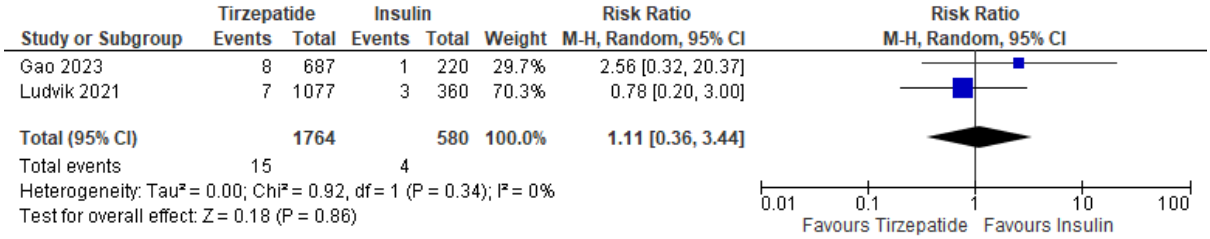


Figure 233: Hypoglycaemia episodes at end of follow up

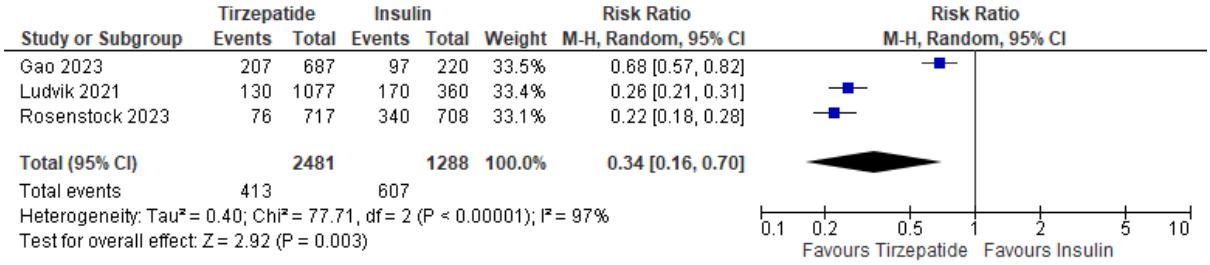


Figure 234: Severe hypoglycaemic episodes at end of follow up

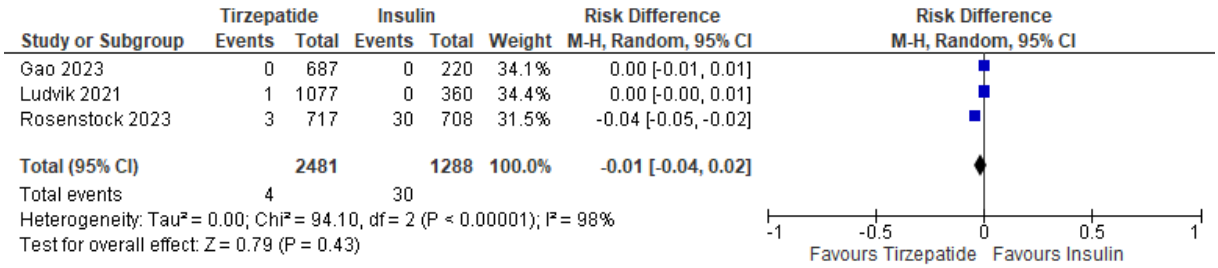


Figure 235: HbA1c change (%, lower values are better, change scores) at end of follow up

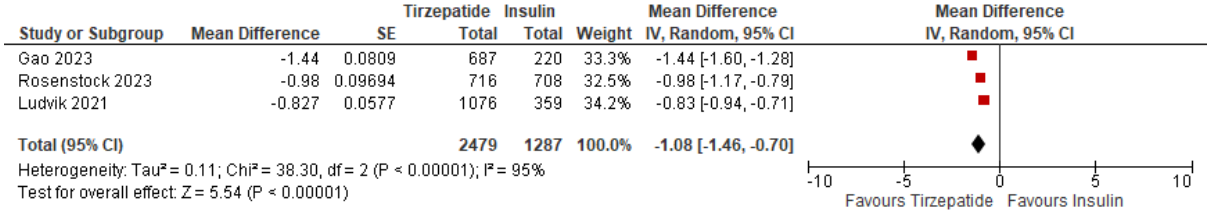
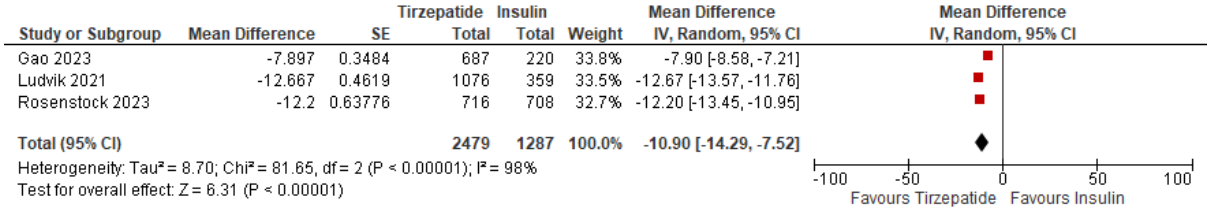


Figure 236: Weight change (kg, lower values are better, change scores) at end of follow up



K.1.4.3 Adding tirzepatide compared to adding dulaglutide

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

K.1.4.4 Adding tirzepatide compared to adding semaglutide

Figure 237: All-cause mortality at end of follow up

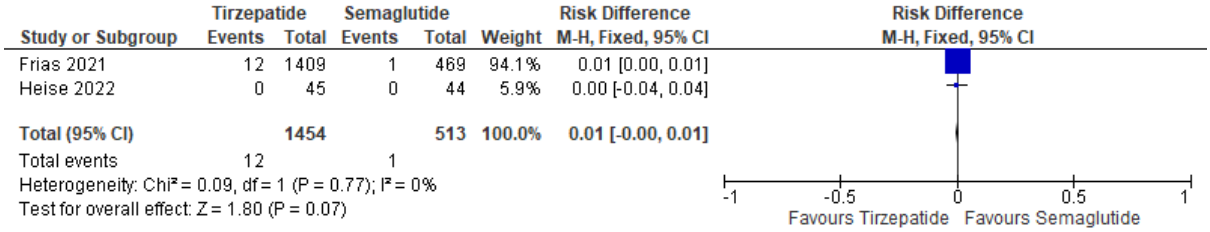


Figure 238: Cardiovascular mortality at end of follow up

Study or Subgroup	Tirzepatide Events	Tirzepatide Total	Semaglutide Events	Semaglutide Total	Weight	Risk Difference M-H, Fixed, 95% CI
Frias 2021	5	1410	0	469	94.1%	0.00 [-0.00, 0.01]
Heise 2022	0	45	0	44	5.9%	0.00 [-0.04, 0.04]
Total (95% CI)		**1455**		**513**	**100.0%**	**0.00 [-0.00, 0.01]**
Total events	5		0			

Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86); I² = 0%
Test for overall effect: Z = 1.34 (P = 0.18)

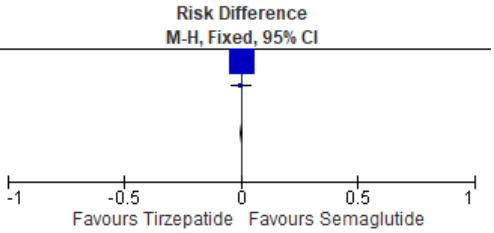


Figure 239: Hypoglycaemia episodes at end of follow up

Study or Subgroup	Tirzepatide Events	Tirzepatide Total	Semaglutide Events	Semaglutide Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Frias 2021	12	1409	2	469	73.0%	1.78 [0.53, 5.98]
Heise 2022	3	45	1	44	27.0%	2.75 [0.37, 20.22]
Total (95% CI)		**1454**		**513**	**100.0%**	**2.00 [0.71, 5.64]**
Total events	15		3			

Heterogeneity: Chi² = 0.14, df = 1 (P = 0.71); I² = 0%
Test for overall effect: Z = 1.31 (P = 0.19)

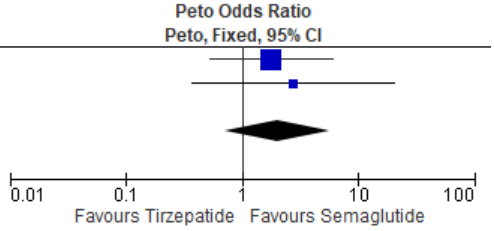


Figure 240: Severe hypoglycaemic episodes at end of follow up

Study or Subgroup	Tirzepatide Events	Tirzepatide Total	Semaglutide Events	Semaglutide Total	Weight	Risk Difference M-H, Fixed, 95% CI
Frias 2021	2	1409	0	469	94.1%	0.00 [-0.00, 0.01]
Heise 2022	0	45	0	44	5.9%	0.00 [-0.04, 0.04]
Total (95% CI)		**1454**		**513**	**100.0%**	**0.00 [-0.00, 0.01]**
Total events	2		0			

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.60 (P = 0.55)

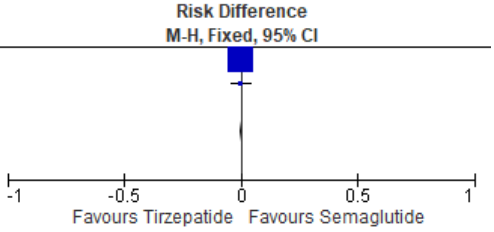
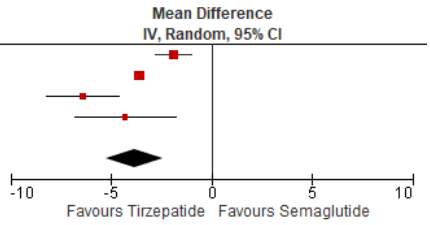


Figure 241: Weight change (kg, lower values are better, mean difference) at end of follow up

Study or Subgroup	Mean Difference	SE	Tirzepatide Total	Semaglutide Total	Weight	Mean Difference IV, Random, 95% CI
Frias 2021 (1)	-1.9	0.4592	470	156	29.2%	-1.90 [-2.80, -1.00]
Frias 2021 (2)	-3.6	0.0612	469	156	33.0%	-3.60 [-3.72, -3.48]
Frias 2021 (3)	-6.4	0.9184	469	156	21.5%	-6.40 [-8.20, -4.60]
Heise 2022	-4.3	1.2728	41	43	16.3%	-4.30 [-6.79, -1.81]
Total (95% CI)			**1449**	**511**	**100.0%**	**-3.82 [-5.24, -2.41]**

Heterogeneity: Tau² = 1.58; Chi² = 23.24, df = 3 (P < 0.0001); I² = 87%
Test for overall effect: Z = 5.29 (P < 0.00001)



Footnotes
(1) Tirzepatide 5 mg daily
(2) Tirzepatide 10 mg daily
(3) Tirzepatide 15 mg daily

Note: Heterogeneity for this outcome was not explored due to the small number of studies (2 studies, 3 different dose comparisons for 1 study).

K.1.5 SGLT2 inhibitors

K.1.5.1 Adding canagliflozin compared to adding placebo

Figure 242: All-cause mortality at end of follow up

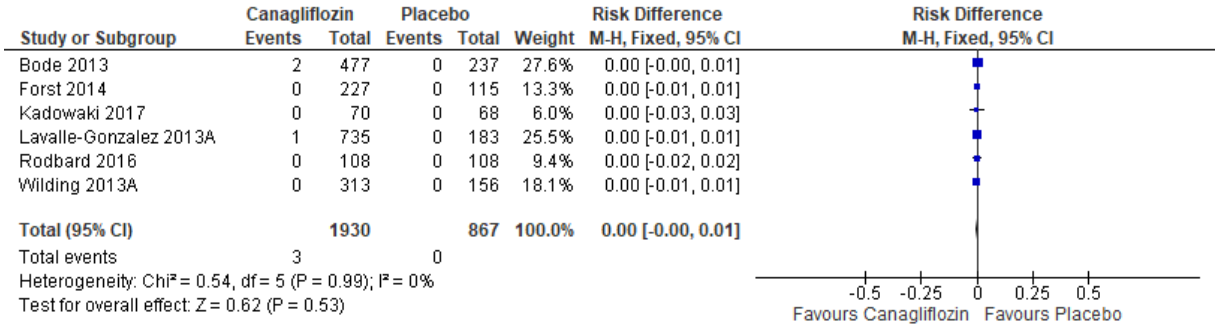


Figure 243: Cardiovascular mortality at end of follow up

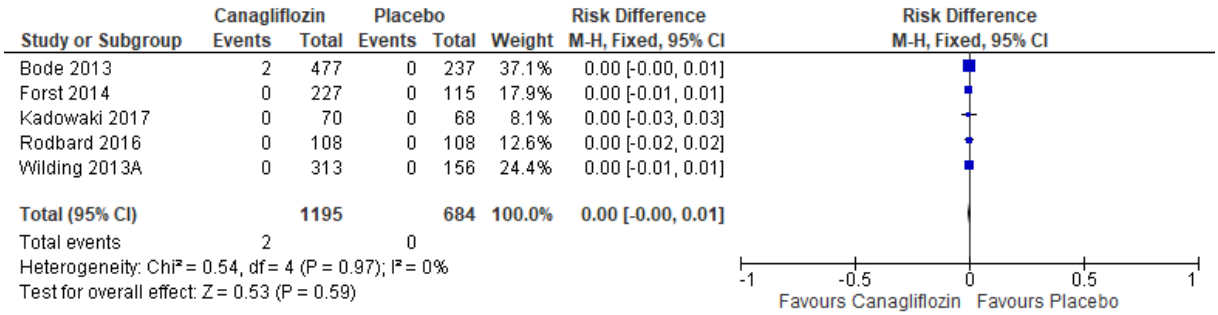


Figure 244: Diabetic ketoacidosis at end of follow up

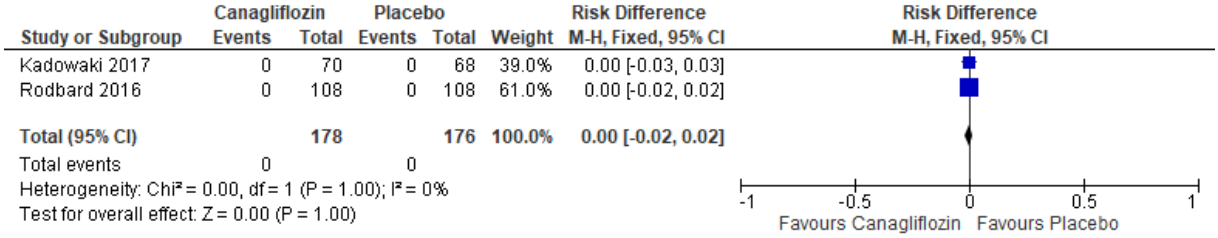
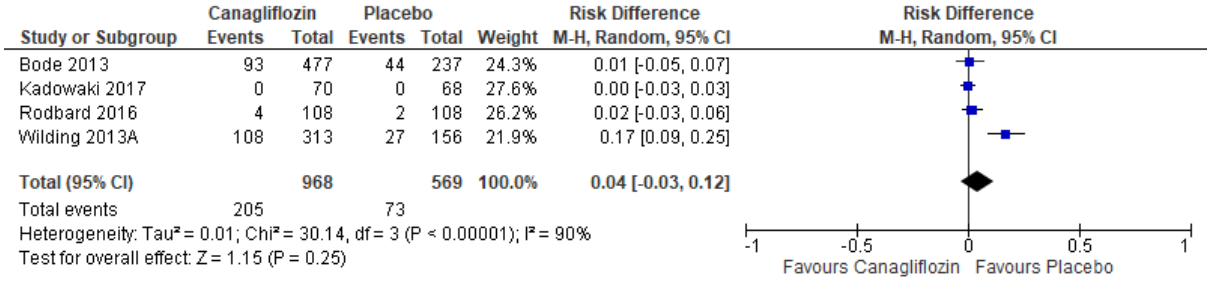


Figure 245: Hypoglycaemia episodes at end of follow up



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

Figure 246: Severe hypoglycaemia at end of follow up

Study or Subgroup	Canagliflozin Events	Canagliflozin Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Bode 2013	11	477	8	237	50.0%	-0.01 [-0.04, 0.02]
Rodbard 2016	0	108	0	108	17.1%	0.00 [-0.02, 0.02]
Wilding 2013A	2	313	1	156	32.9%	-0.00 [-0.02, 0.02]
Total (95% CI)		**898**		**501**	**100.0%**	**-0.01 [-0.02, 0.01]**
Total events	13		9			

Heterogeneity: Chi² = 0.96, df = 2 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.72 (P = 0.47)

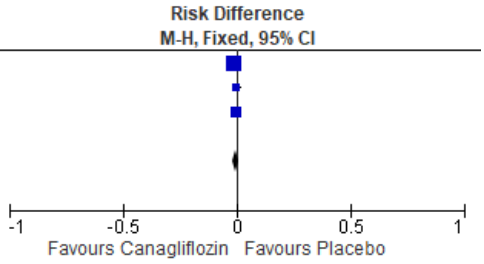
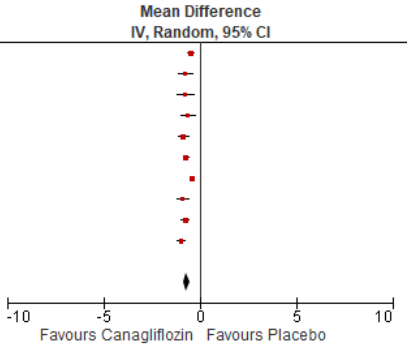


Figure 247: HbA1c change (%, lower values are better, change scores) at end of follow up

Study or Subgroup	Mean Difference	SE	Canagliflozin Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Bode 2013	-0.48	0.0981	425	170	11.2%	-0.48 [-0.67, -0.29]
Cusi 2019	-0.75	0.1895	24	27	7.9%	-0.75 [-1.12, -0.38]
Forst 2014 (1)	-0.76	0.23	114	57	6.7%	-0.76 [-1.21, -0.31]
Forst 2014 (2)	-0.62	0.19	113	58	7.9%	-0.62 [-0.99, -0.25]
Kadowaki 2017	-0.87	0.1414	70	68	9.6%	-0.87 [-1.15, -0.59]
Lavalle-Gonzalez 2013A	-0.7	0.0663	725	181	12.2%	-0.70 [-0.83, -0.57]
Mahaffey 2018	-0.39	0.0283	5795	4347	13.0%	-0.39 [-0.45, -0.33]
Rodbard 2016	-0.89	0.1531	99	94	9.2%	-0.89 [-1.19, -0.59]
Wilding 2013A (3)	-0.75	0.102	155	75	11.1%	-0.75 [-0.95, -0.55]
Wilding 2013A (4)	-0.97	0.102	152	75	11.1%	-0.97 [-1.17, -0.77]
Total (95% CI)			**7672**	**5152**	**100.0%**	**-0.71 [-0.87, -0.54]**

Heterogeneity: Tau² = 0.05; Chi² = 67.90, df = 9 (P < 0.00001); I² = 87%
Test for overall effect: Z = 8.36 (P < 0.00001)



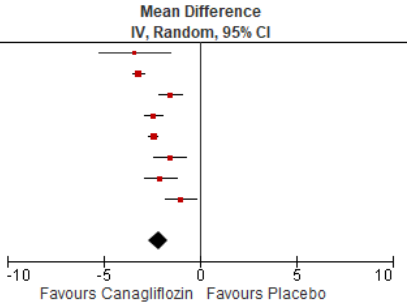
Footnotes
(1) 300 mg canagliflozin daily. Number of participants in placebo arm has been halved.
(2) 100mg canagliflozin daily. Number of participants in placebo arm has been halved.
(3) 100mg canagliflozin daily. Number of participants in placebo arm has been halved.
(4) 300mg canagliflozin daily. Number of participants in placebo arm has been halved.

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

Figure 248: Weight change (kg, lower values are better, change scores) at end of follow up

Study or Subgroup	Mean Difference	SE	Canagliflozin Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Cusi 2019	-3.4	0.9431	24	27	5.2%	-3.40 [-5.25, -1.55]
Forst 2014	-3.2	0.1533	227	115	15.8%	-3.20 [-3.50, -2.90]
Kadowaki 2017	-1.51	0.3183	69	67	13.4%	-1.51 [-2.13, -0.89]
Lavalle-Gonzalez 2013A	-2.4	0.245	725	181	14.6%	-2.40 [-2.88, -1.92]
Mahaffey 2018	-2.4	0.1204	5795	4347	16.2%	-2.40 [-2.64, -2.16]
Rodbard 2016	-1.55	0.4337	103	104	11.4%	-1.55 [-2.40, -0.70]
Wilding 2013A (1)	-2.05	0.4337	154	75	11.4%	-2.05 [-2.90, -1.20]
Wilding 2013A (2)	-1	0.4082	156	75	11.9%	-1.00 [-1.80, -0.20]
Total (95% CI)			**7253**	**4991**	**100.0%**	**-2.16 [-2.67, -1.65]**

Heterogeneity: Tau² = 0.40; Chi² = 51.57, df = 7 (P < 0.00001); I² = 86%
Test for overall effect: Z = 8.30 (P < 0.00001)



Footnotes
(1) 300 mg canagliflozin daily. Number of participants in placebo arm has been halved.
(2) 100mg canagliflozin daily. Number of participants in placebo arm has been halved.

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

K.1.5.2 Adding canagliflozin compared to adding semaglutide

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

K.1.5.3 Adding canagliflozin compared to adding sitagliptin

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

K.1.5.4 Adding dapagliflozin compared to adding placebo

Figure 249: Health-related quality of life - overall (EQ-5D, -0.59-1.0, higher values are better, change scores) at end of follow up

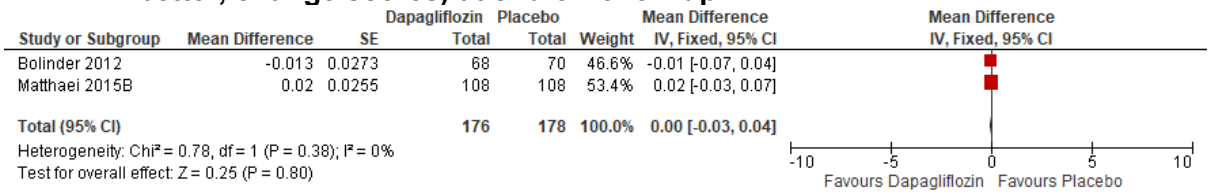


Figure 250: All-cause mortality at end of follow up

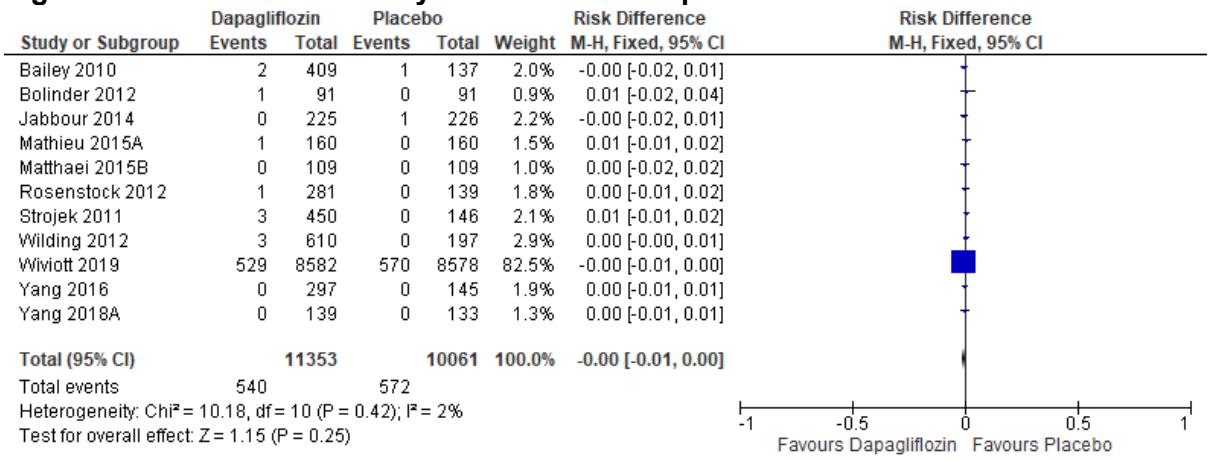


Figure 251: Cardiovascular mortality at end of follow up

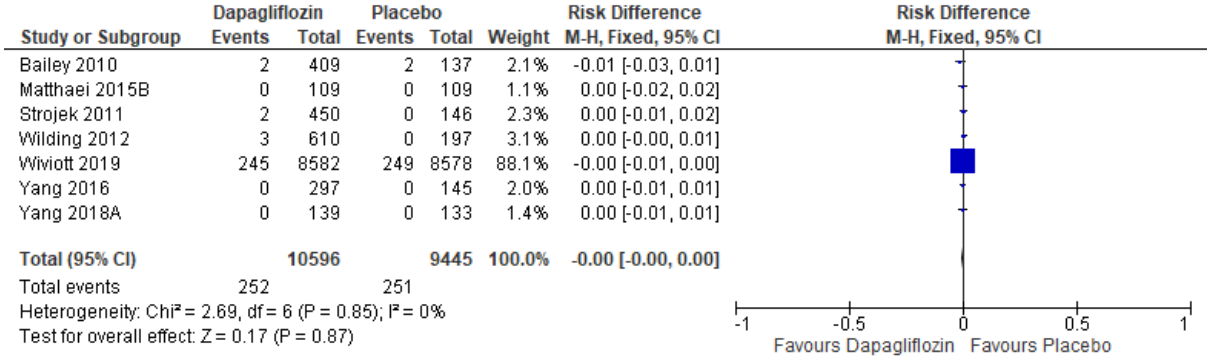


Figure 252: Non-fatal stroke at end of follow up

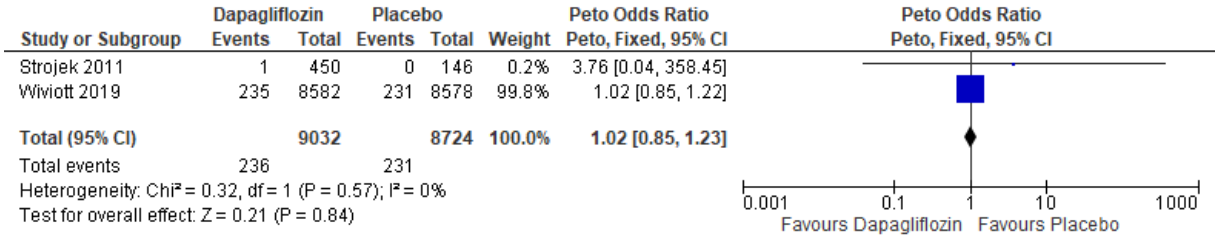


Figure 253: Persistent signs of worsening kidney disease at end of follow up

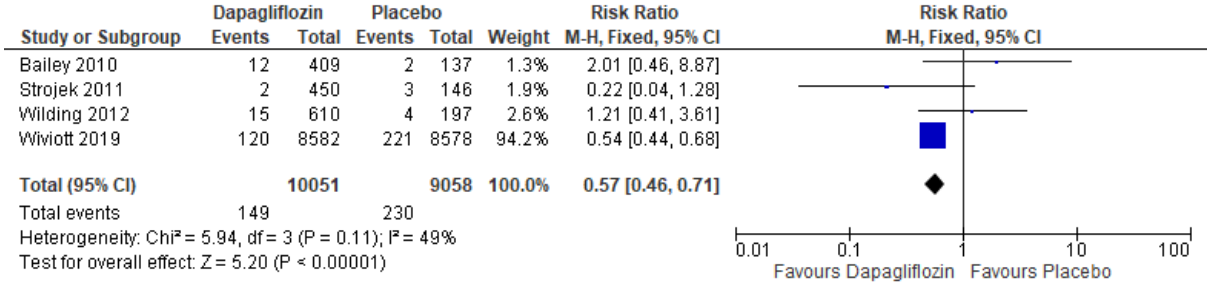


Figure 254: Development of end stage kidney disease at end of follow up

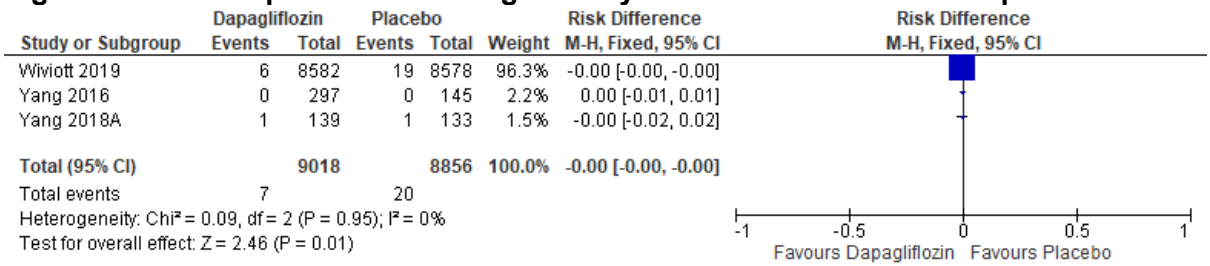


Figure 255: Diabetic ketoacidosis at end of follow up

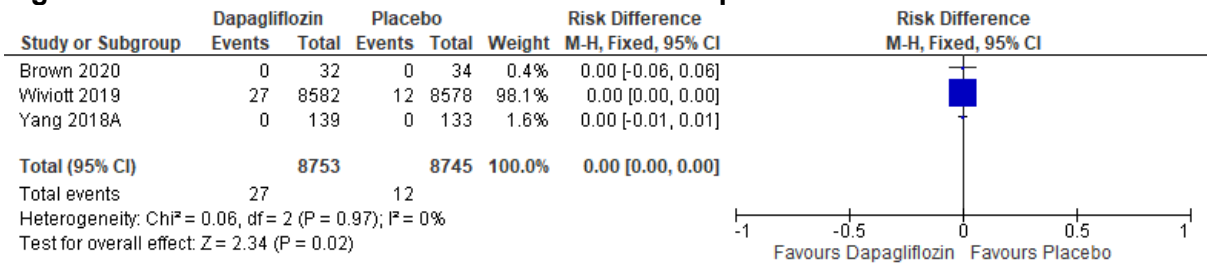
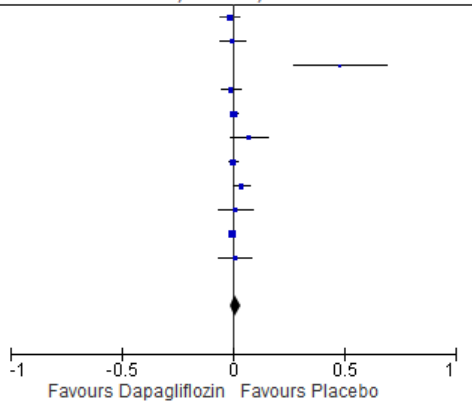


Figure 256: Hypoglycaemia episodes at end of follow up

Study or Subgroup	Dapagliflozin Events	Dapagliflozin Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
Bailey 2010	19	409	8	137	9.6%	-0.01 [-0.06, 0.03]
Bolinder 2012	4	91	4	91	7.2%	0.00 [-0.06, 0.06]
Brown 2020	22	32	7	34	0.9%	0.48 [0.27, 0.69]
Jabbour 2014	12	225	14	226	9.9%	-0.01 [-0.05, 0.03]
Mathieu 2015A	1	160	0	160	15.2%	0.01 [-0.01, 0.02]
Matthaei 2015B	17	109	9	109	4.4%	0.07 [-0.01, 0.16]
Rosenstock 2012	3	281	1	139	14.9%	0.00 [-0.02, 0.02]
Strojek 2011	30	450	4	146	11.5%	0.04 [0.00, 0.07]
Wilding 2012	376	610	119	197	5.0%	0.01 [-0.07, 0.09]
Yang 2016	0	297	0	145	16.2%	0.00 [-0.01, 0.01]
Yang 2018A	17	139	15	133	5.2%	0.01 [-0.07, 0.09]
Total (95% CI)		**2803**		**1517**	**100.0%**	**0.01 [-0.01, 0.03]**
Total events	501		181			

Heterogeneity: Tau² = 0.00; Chi² = 42.03, df = 10 (P < 0.00001); I² = 76%
Test for overall effect: Z = 1.20 (P = 0.23)



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

Figure 257: Severe hypoglycaemic episodes at end of follow up

Study or Subgroup	Dapagliflozin Events	Dapagliflozin Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Bailey 2010	0	409	0	137	2.0%	0.00 [-0.01, 0.01]
Bolinder 2012	0	91	0	91	0.9%	0.00 [-0.02, 0.02]
Jabbour 2014	1	225	1	226	2.2%	0.00 [-0.01, 0.01]
Mathieu 2015A	0	160	0	160	1.5%	0.00 [-0.01, 0.01]
Matthaei 2015B	0	109	0	109	1.0%	0.00 [-0.02, 0.02]
Rosenstock 2012	0	281	0	139	1.8%	0.00 [-0.01, 0.01]
Strojek 2011	1	450	0	146	2.1%	0.00 [-0.01, 0.01]
Wilding 2012	2	610	0	197	2.9%	0.00 [-0.01, 0.01]
Wiviott 2019	58	8582	83	8578	82.5%	-0.00 [-0.01, -0.00]
Yang 2016	0	297	0	145	1.9%	0.00 [-0.01, 0.01]
Yang 2018A	0	139	0	133	1.3%	0.00 [-0.01, 0.01]
Total (95% CI)		**11353**		**10061**	**100.0%**	**-0.00 [-0.00, 0.00]**
Total events	62		84			

Heterogeneity: Chi² = 3.45, df = 10 (P = 0.97); I² = 0%
Test for overall effect: Z = 1.91 (P = 0.06)

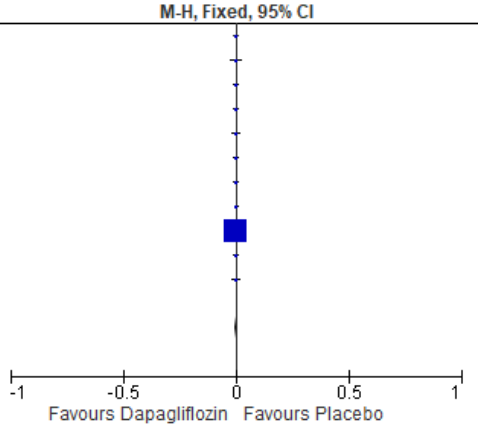
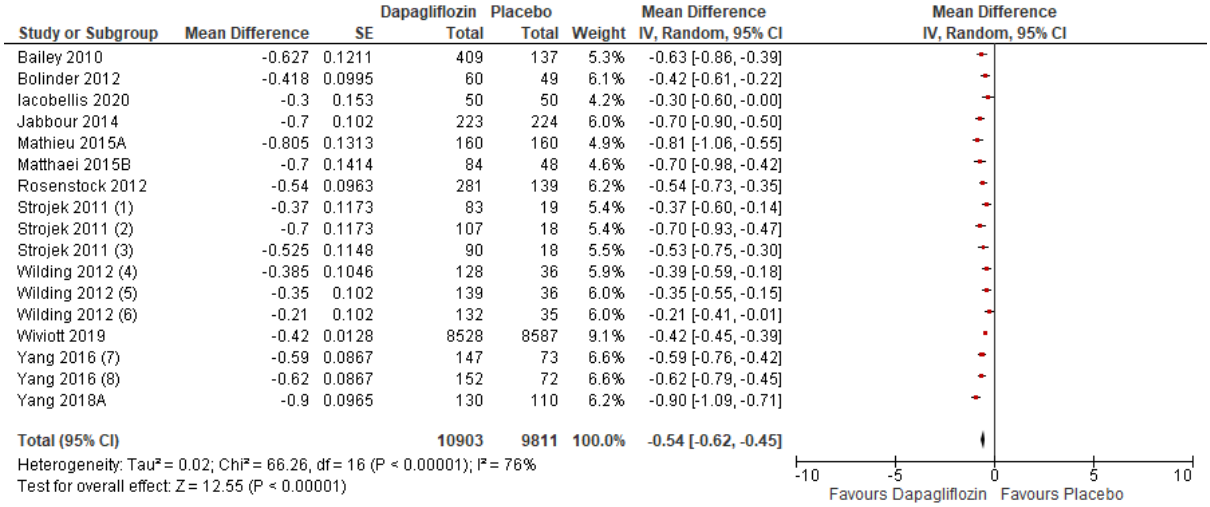


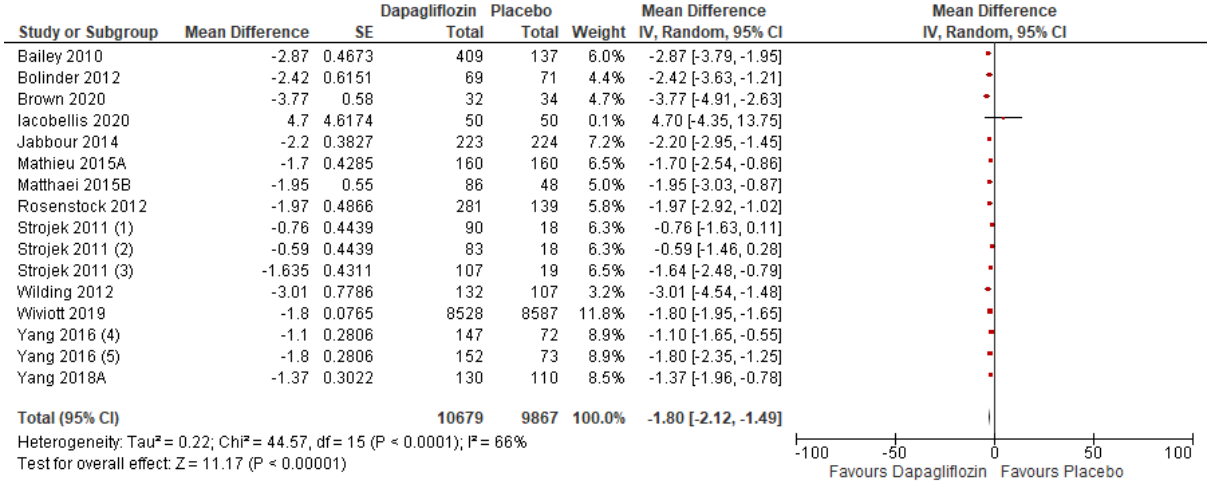
Figure 258: HbA1c change (%, lower values are better, change scores) at end of follow up



Footnotes
(1) 2.5 mg dapagliflozin daily. Number of participants for placebo arm has been divided by 3.
(2) 10 mg dapagliflozin daily. See above.
(3) 5 mg dapagliflozin daily. See above.
(4) 5/10 mg dapagliflozin daily. Number of participants for placebo arm has been divided by 3.
(5) 10 mg dapagliflozin daily. Number of participants for placebo arm has been divided by 3
(6) 2.5 mg dapagliflozin daily. Number of participants for placebo arm has been divided by 3.
(7) 5 mg dapagliflozin daily. See above.
(8) 10 mg dapagliflozin daily. Number of participants for placebo arm is halved.

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

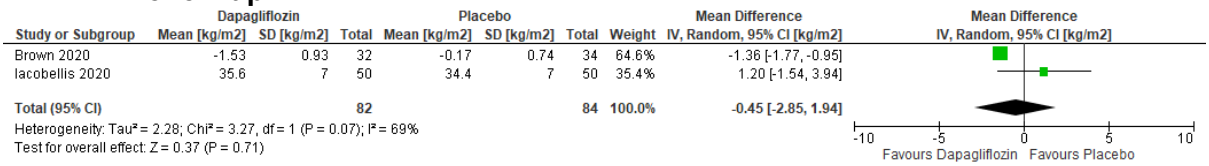
Figure 259: Weight change (kg, lower values are better, change scores) at end of follow up



Footnotes
(1) 5 mg dapagliflozin daily. See above.
(2) 2.5 mg dapagliflozin daily. See above.
(3) 10mg dapagliflozin daily. Number of participants for placebo arm has been divided by 3.
(4) 5mg dapagliflozin daily. Number of participants for placebo arm is halved.
(5) 10mg dapagliflozin daily. Number of participants for placebo arm is halved.

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

Figure 260: BMI change (kg/m^2, lower values are better, change scores) at end of follow up



K.1.5.5 Adding dapagliflozin compared to adding exenatide

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

K.1.5.6 Adding dapagliflozin compared to adding liraglutide

Figure 261: Severe hypoglycaemic episodes at end of follow up

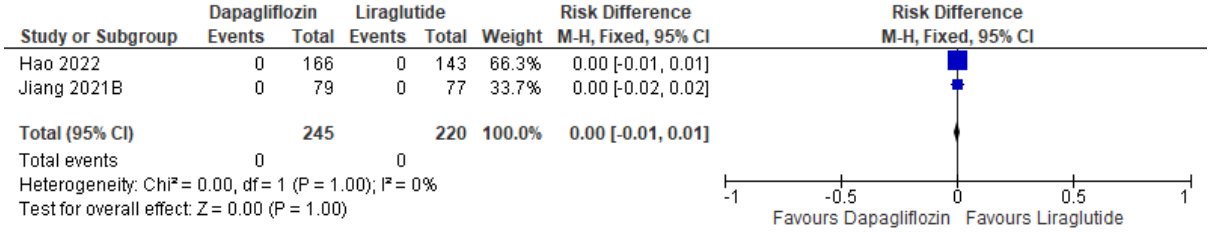
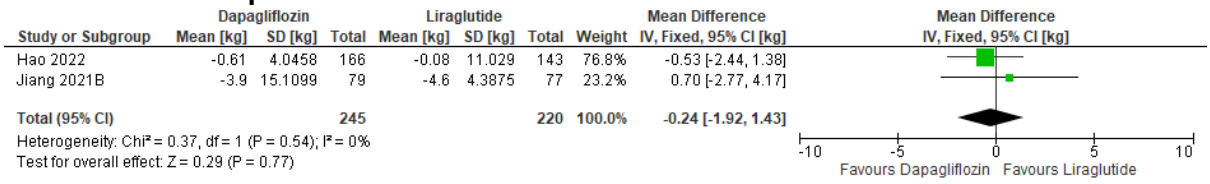


Figure 262: Weight change (kg, lower values are better, change scores) at end of follow up



K.1.5.7 Adding dapagliflozin compared to adding saxagliptin

Figure 263: All-cause mortality at end of follow up

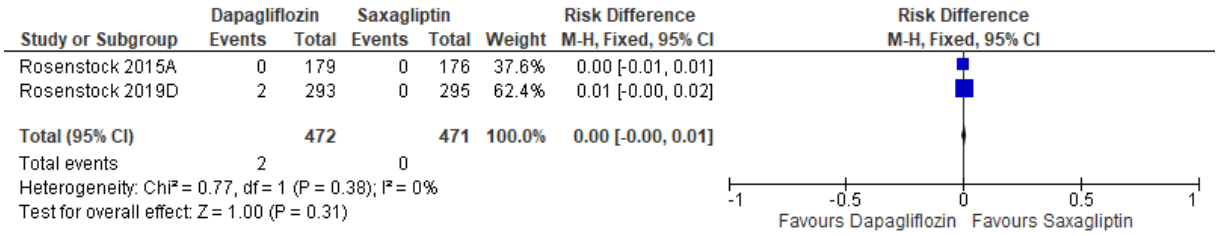


Figure 264: Cardiovascular mortality at end of follow up

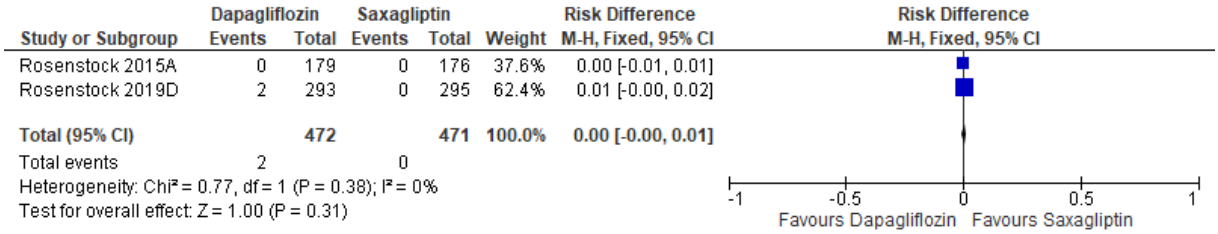


Figure 265: Hypoglycaemia episodes at end of follow up

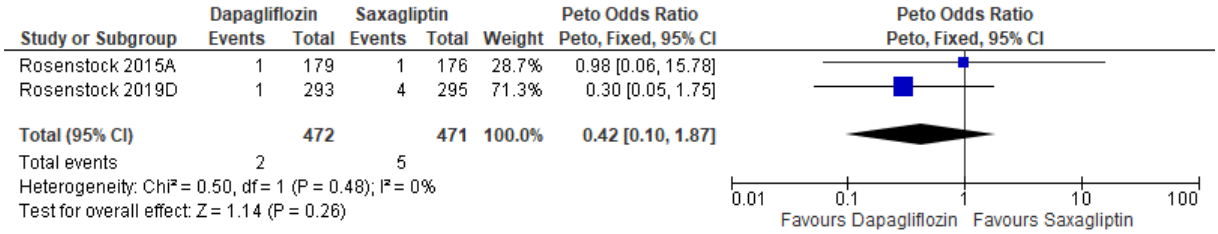


Figure 266: Severe hypoglycaemic episodes at end of follow up

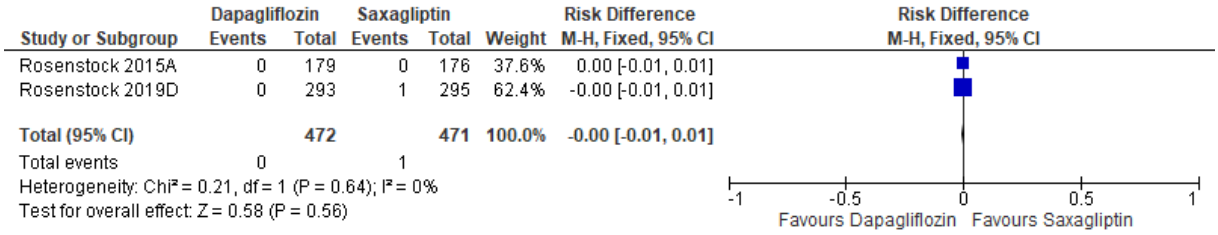
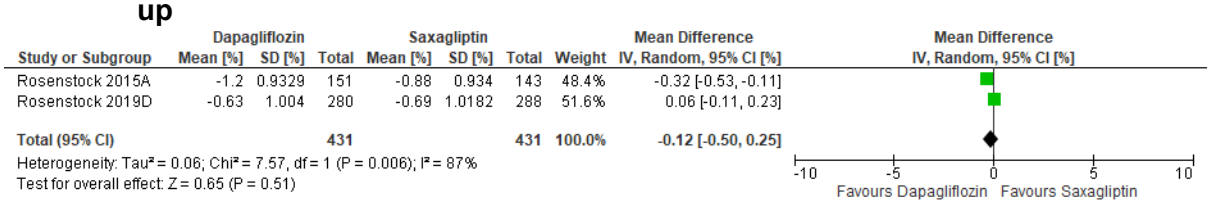


Figure 267: HbA1c change (%, lower values are better, change scores) at end of follow up



K.1.5.8 Adding dapagliflozin compared to adding sitagliptin

Figure 268: Hypoglycaemia episodes at end of follow up

Figure 269: Severe hypoglycaemic episodes at end of follow up

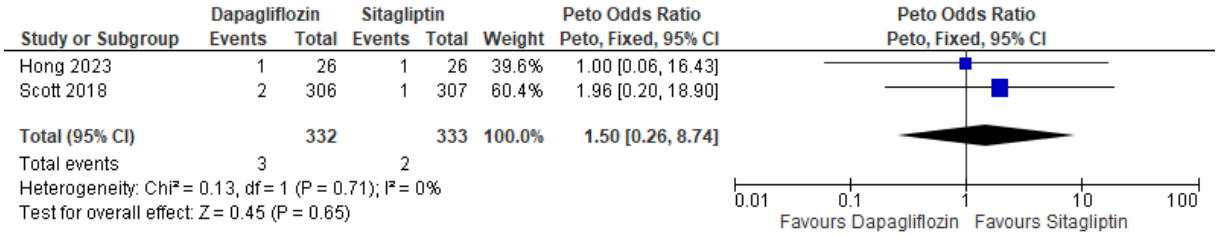
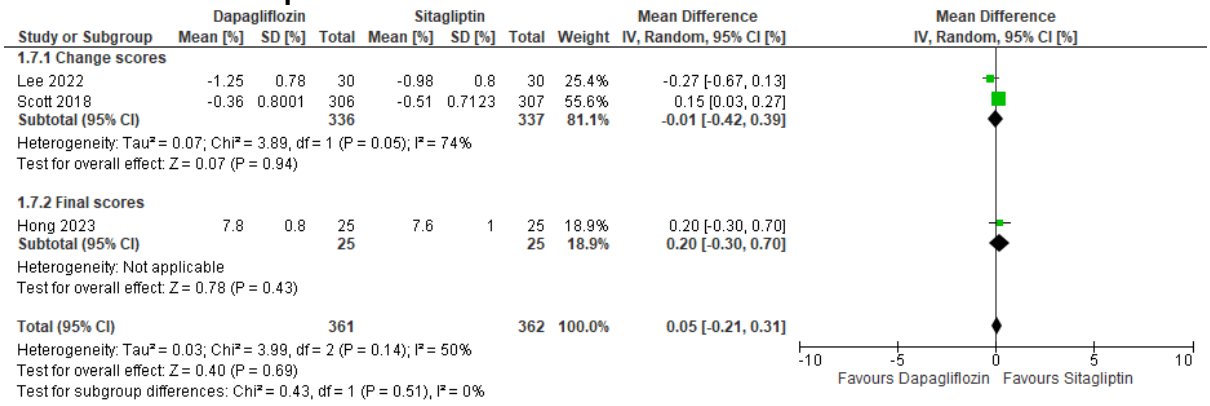


Figure 270: HbA1c change (%, lower values are better, change and final scores) at end of follow up



K.1.5.9 Adding empagliflozin compared to adding placebo

Figure 271: All-cause mortality at end of follow up

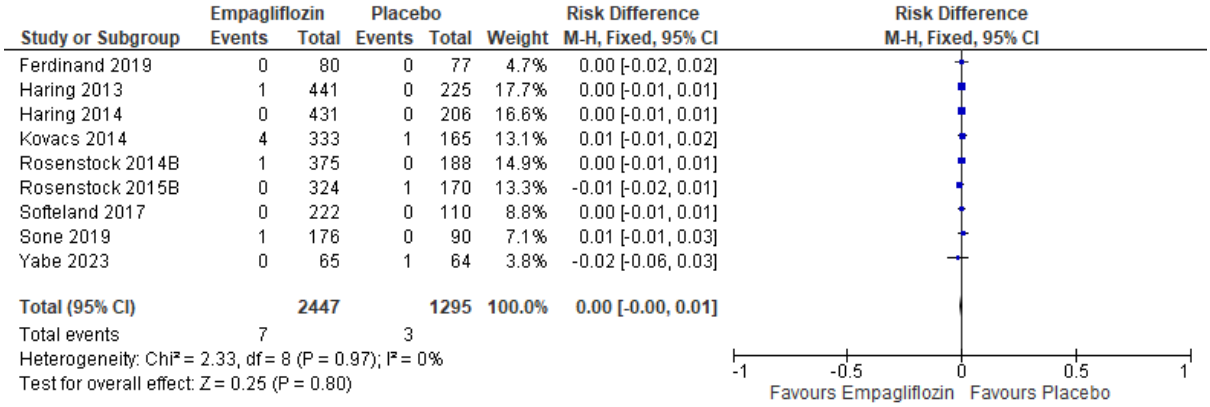


Figure 272: Cardiovascular mortality at end of follow up

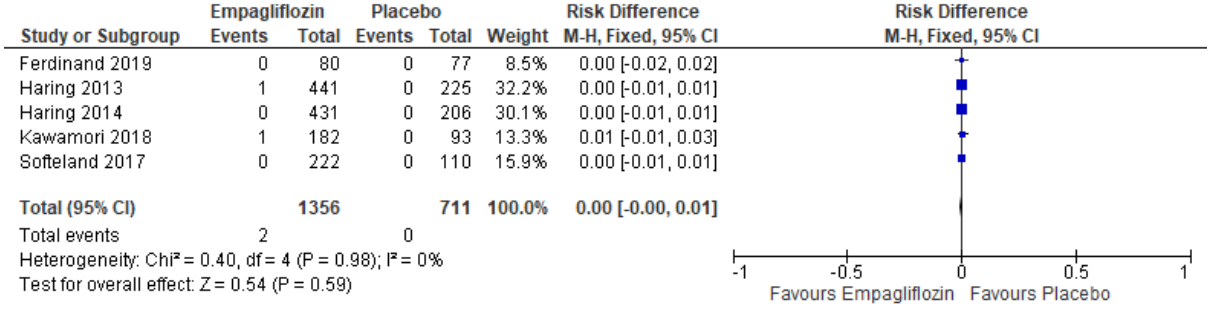


Figure 273: Acute kidney injury at end of follow up

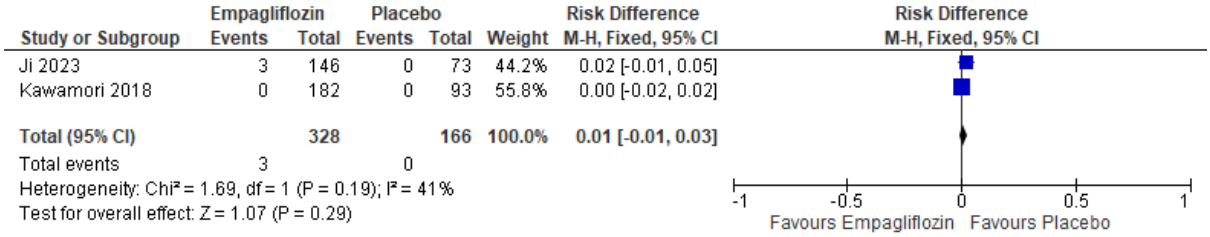


Figure 274: Persistent signs of worsening kidney disease at end of follow up

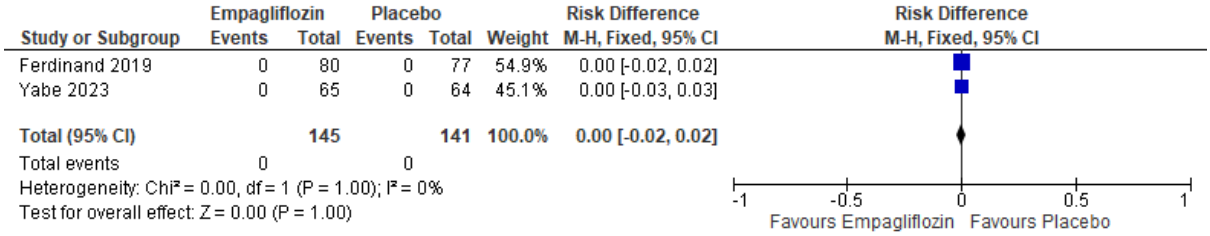


Figure 275: Diabetic ketoacidosis at end of follow up

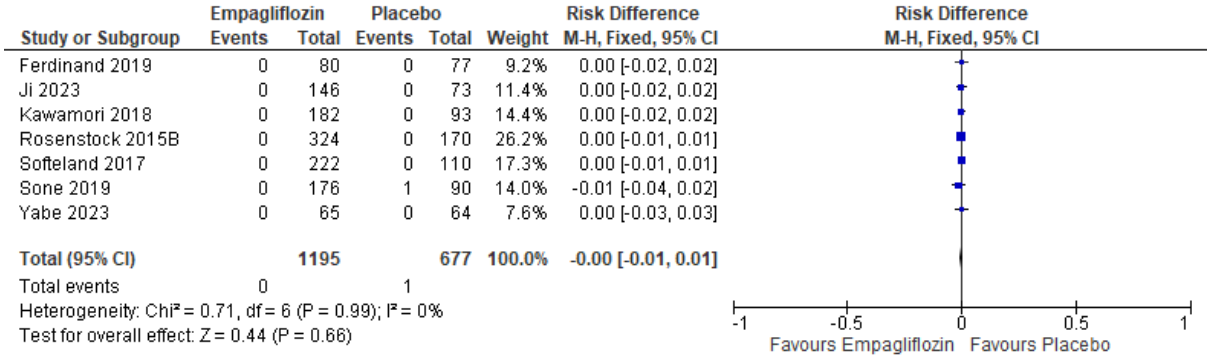


Figure 276: Hypoglycaemia episodes at end of follow up

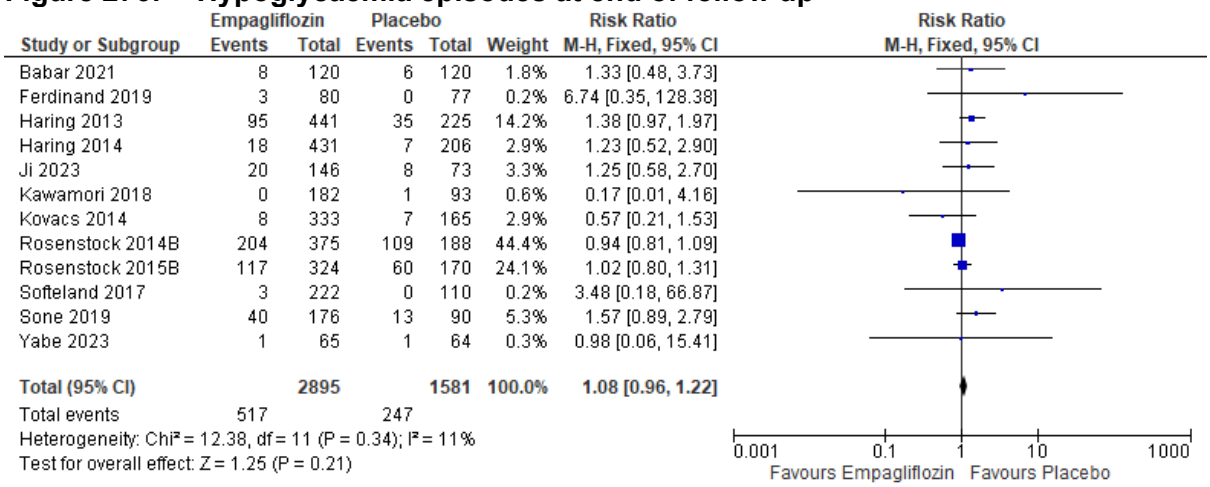


Figure 277: Severe hypoglycaemic episodes at end of follow up

Study or Subgroup	Empagliflozin Events	Empagliflozin Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Ferdinand 2019	0	80	0	77	5.0%	0.00 [-0.02, 0.02]
Haring 2013	1	441	1	225	19.1%	-0.00 [-0.01, 0.01]
Haring 2014	1	431	0	206	17.9%	0.00 [-0.01, 0.01]
Ji 2023	0	146	0	73	6.3%	0.00 [-0.02, 0.02]
Rosenstock 2014B	4	375	3	188	16.1%	-0.01 [-0.03, 0.02]
Rosenstock 2015B	2	324	0	170	14.3%	0.01 [-0.01, 0.02]
Softeland 2017	1	222	0	110	9.5%	0.00 [-0.01, 0.02]
Sone 2019	0	176	0	90	7.7%	0.00 [-0.02, 0.02]
Yabe 2023	0	65	0	64	4.1%	0.00 [-0.03, 0.03]
Total (95% CI)		**2260**		**1203**	**100.0%**	**0.00 [-0.00, 0.01]**
Total events	9		4			

Heterogeneity: Chi² = 1.80, df = 8 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.17 (P = 0.87)

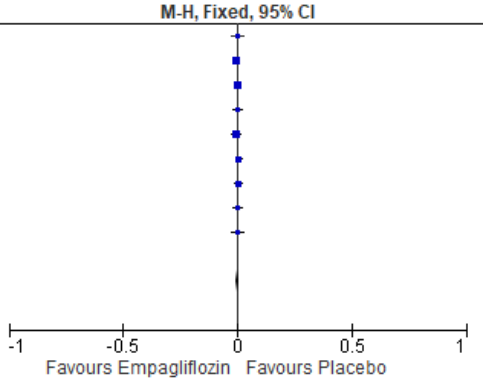
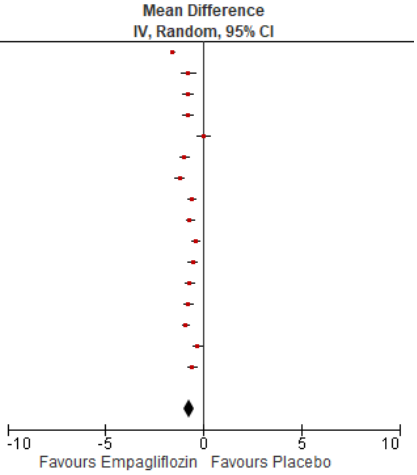


Figure 278: HbA1c change (%, lower values are better, change scores and final values) at end of follow up

Study or Subgroup	Mean Difference	SE	Empagliflozin Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Babar 2021	-1.58	0.0414	120	120	6.6%	-1.58 [-1.66, -1.50]
Ferdinand 2019	-0.78	0.198	78	72	5.7%	-0.78 [-1.17, -0.39]
Haring 2013	-0.8	0.1224	213	76	6.2%	-0.80 [-1.04, -0.56]
Haring 2014	-0.8	0.1227	248	70	6.2%	-0.80 [-1.04, -0.56]
Hattori 2018	0.02	0.1715	51	51	5.9%	0.02 [-0.32, 0.36]
Ji 2023	-0.99	0.1196	145	73	6.3%	-0.99 [-1.22, -0.76]
Kawamori 2018	-1.22	0.1173	182	93	6.3%	-1.22 [-1.45, -0.99]
Kovacs 2014 (1)	-0.59	0.09949	165	83	6.4%	-0.59 [-0.78, -0.40]
Kovacs 2014 (2)	-0.69	0.096939	168	82	6.4%	-0.69 [-0.88, -0.50]
Rosenstock 2014B	-0.41	0.0943	375	188	6.4%	-0.41 [-0.59, -0.23]
Rosenstock 2015B	-0.55	0.1227	237	112	6.2%	-0.55 [-0.79, -0.31]
Softeland 2017 (3)	-0.7	0.119879	100	44	6.3%	-0.70 [-0.93, -0.47]
Softeland 2017 (4)	-0.79	0.119879	100	44	6.3%	-0.79 [-1.02, -0.56]
Sone 2019	-0.93	0.0851	176	90	6.4%	-0.93 [-1.10, -0.76]
Tanaka 2019	-0.32	0.1212	48	52	6.2%	-0.32 [-0.56, -0.08]
Yabe 2023	-0.57	0.11	65	64	6.3%	-0.57 [-0.79, -0.35]
Total (95% CI)			**2471**	**1314**	**100.0%**	**-0.74 [-0.99, -0.49]**

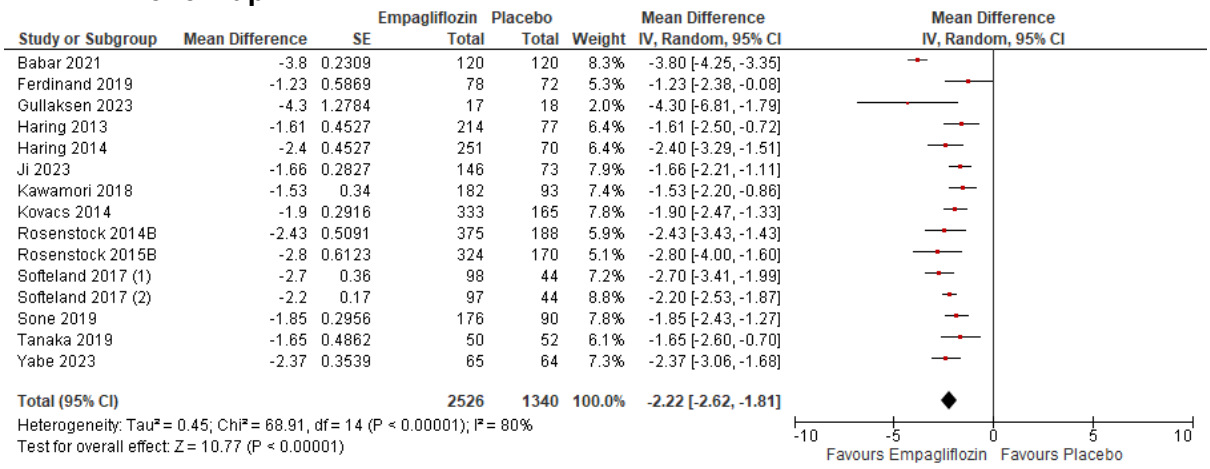
Heterogeneity: Tau² = 0.25; Chi² = 378.23, df = 15 (P < 0.00001); I² = 96%
Test for overall effect: Z = 5.77 (P < 0.00001)



Footnotes
(1) 10 mg Empagliflozin v Placebo
(2) 25 mg Empagliflozin v Placebo
(3) 25 mg Empagliflozin v Placebo
(4) 10 mg Empagliflozin v Placebo

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

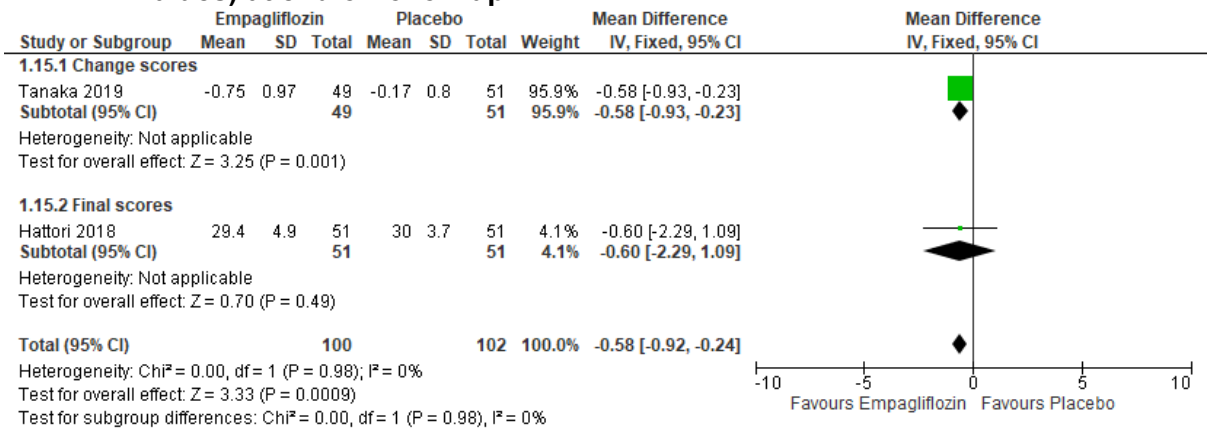
Figure 279: Weight change (kg, lower values are better, change scores) at end of follow up



Footnotes
(1) 10 mg Empagliflozin v Placebo
(2) 25 mg Empagliflozin v Placebo

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

Figure 280: BMI change (kg/m^2, lower values are better, change scores and final values) at end of follow up



K.1.5.10 Adding empagliflozin compared to adding insulin

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

K.1.5.11 Adding empagliflozin compared to adding linagliptin

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

K.1.5.12 Adding empagliflozin compared to adding liraglutide

Figure 281: HbA1c change (%, lower scores are better, change scores and final values) at end of follow up

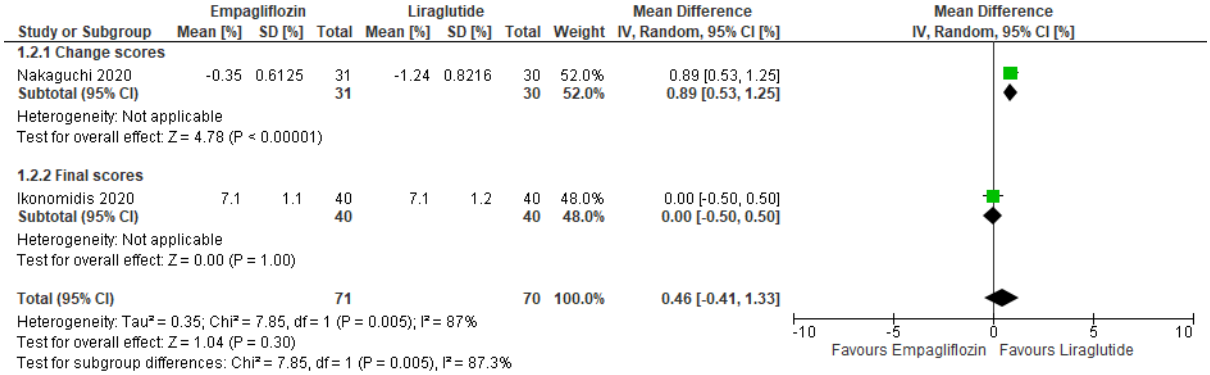


Figure 282: Weight change (kg, lower scores are better, change scores and final values) at end of follow up

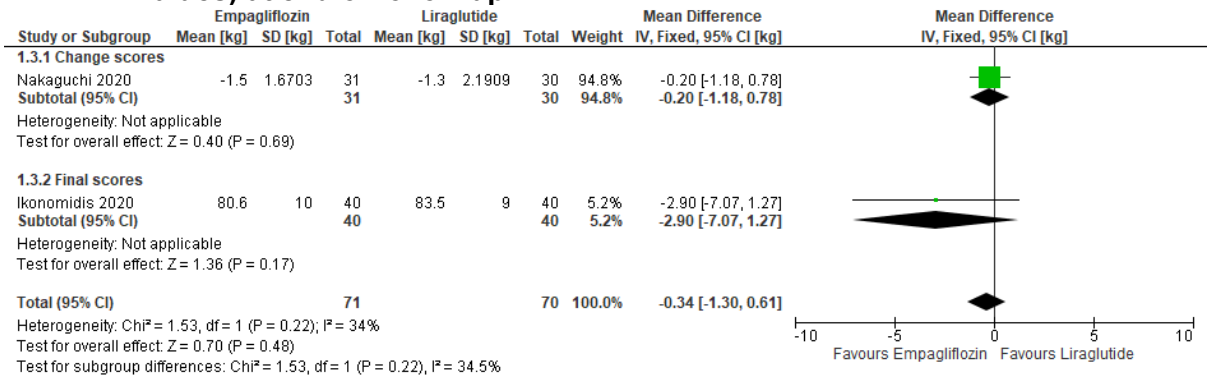
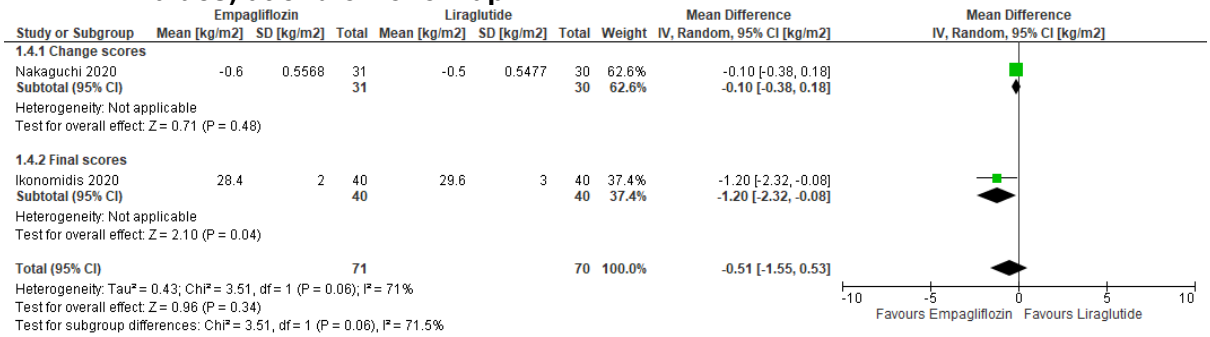


Figure 283: BMI change (kg/m^2, lower scores are better, change scores and final values) at end of follow up



K.1.5.13 Adding empagliflozin compared to adding semaglutide

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

K.1.5.14 Adding empagliflozin compared to adding sitagliptin

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

K.1.5.15 Adding empagliflozin compared to adding vildagliptin

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

K.1.5.16 Adding ertugliflozin compared to adding placebo

Figure 284: All-cause mortality at end of follow up

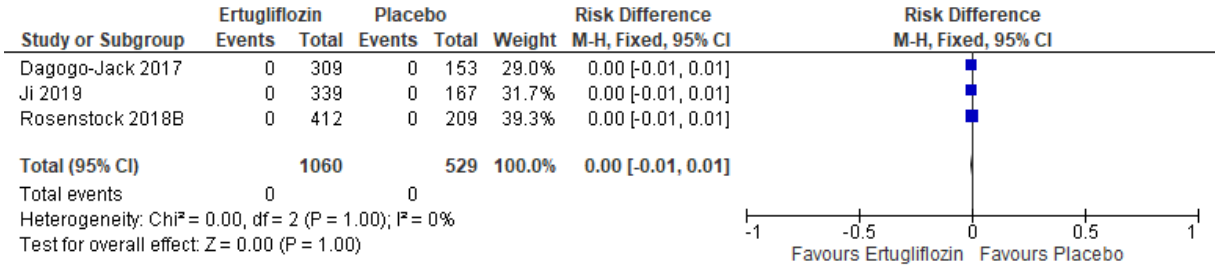


Figure 285: Cardiovascular mortality at end of follow up

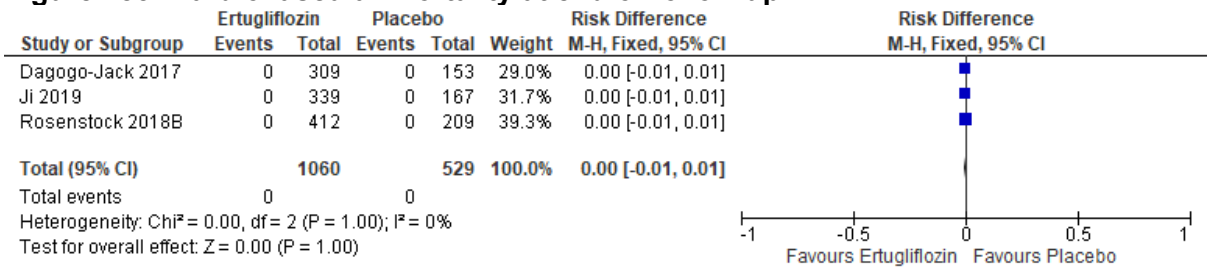


Figure 286: Hypoglycaemia episodes at end of follow up

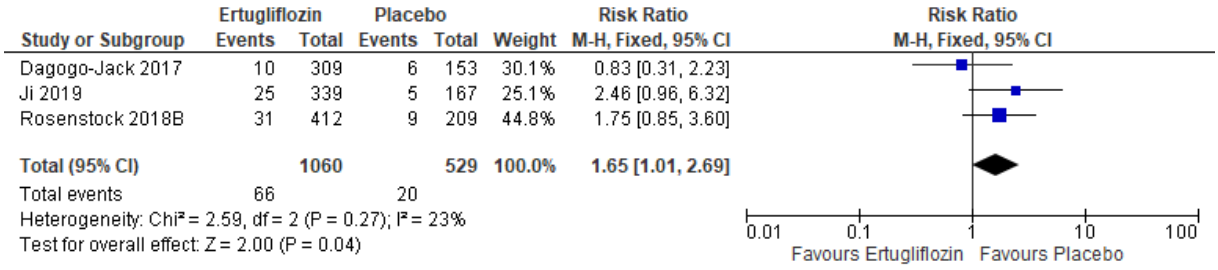


Figure 287: HbA1c change (%, lower scores are better, change scores) at end of follow up

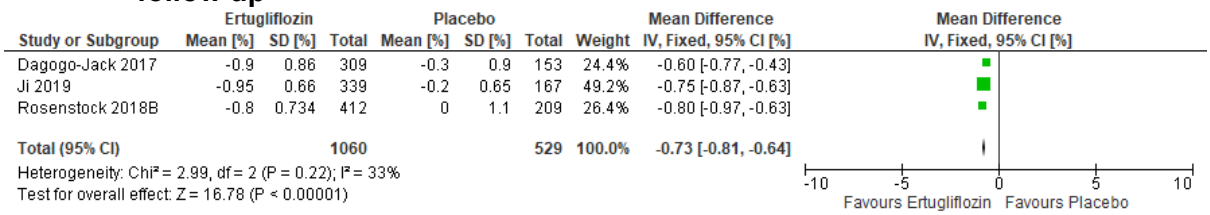
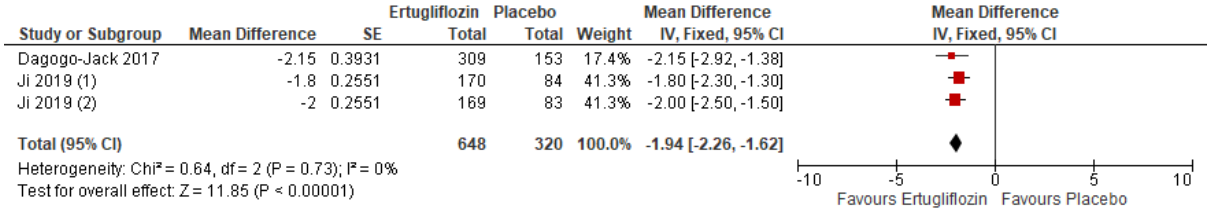


Figure 288: Weight change (kg, lower scores are better, change scores) at end of follow up



Footnotes
(1) 5mg ertugliflozin daily. Number of participants for placebo arm has been halved.
(2) 15mg ertugliflozin daily. Number of participants for placebo arm has been halved

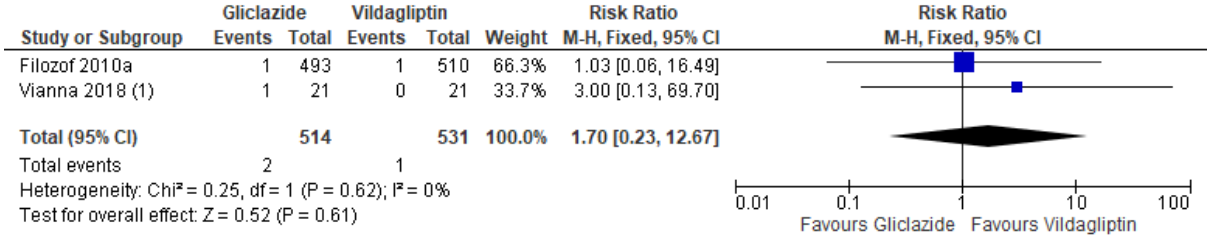
K.1.5.17 Adding ertugliflozin compared to adding sitagliptin

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

K.1.6 Sulfonylureas

K.1.6.1 Adding gliclazide compared to adding vildagliptin

Figure 289: All-cause mortality at end of follow up



Footnotes
(1) Modified release formulation

Figure 290: HbA1c change (%, lower values are better, change scores) at end of follow up

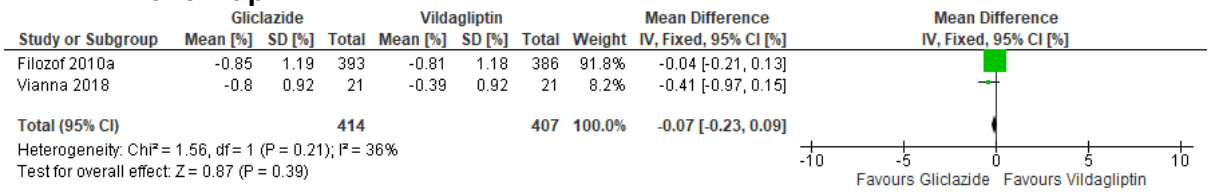
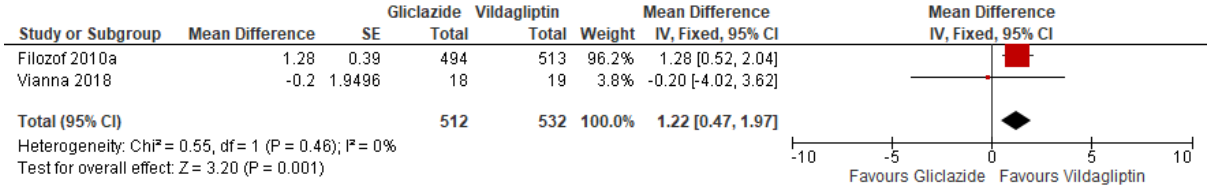


Figure 291: Weight change (kg, lower values are better, change scores) at end of follow up



K.1.6.2 Adding glimepiride compared to adding placebo

Figure 292: All-cause mortality

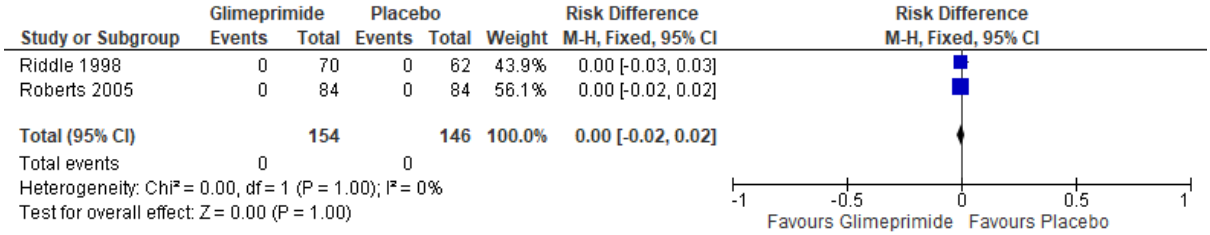


Figure 293: Cardiovascular mortality

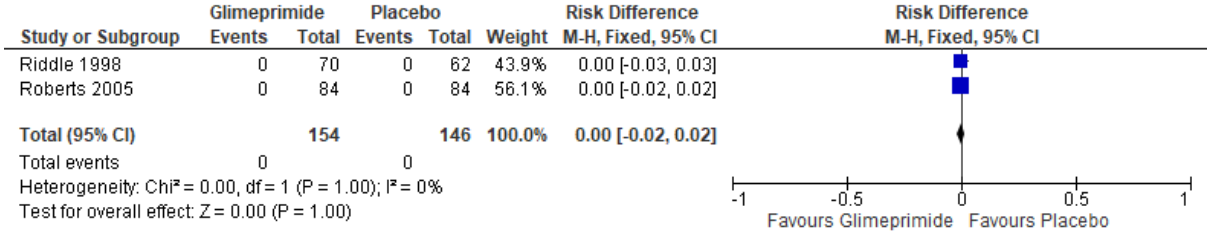


Figure 294: Non-fatal myocardial infarction

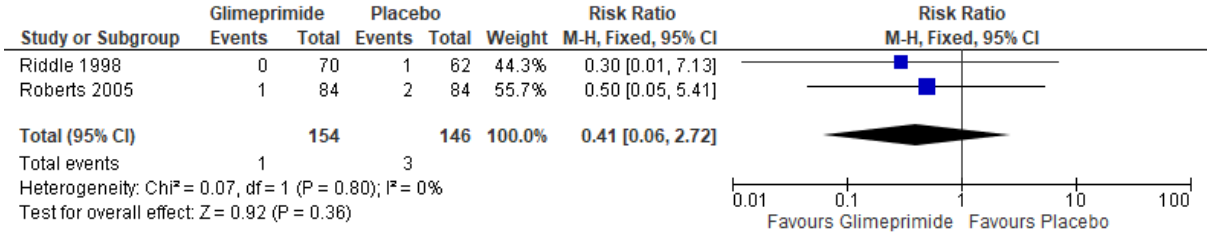
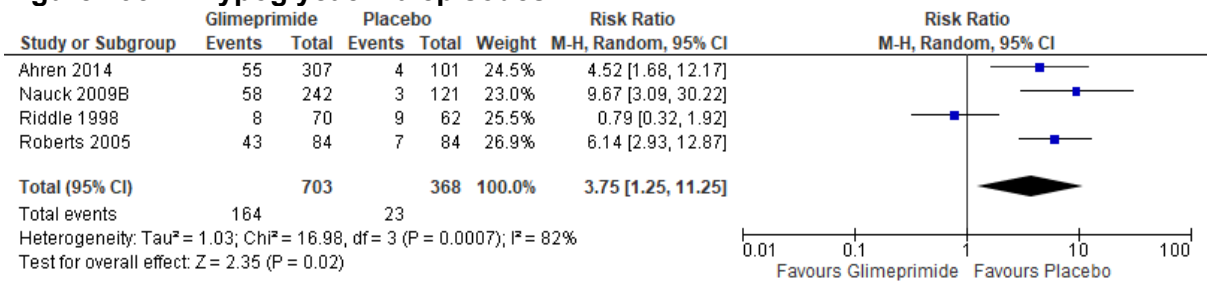


Figure 295: Hypoglycaemia episodes



Note: Heterogeneity for this outcome could not be explored due to low number of studies for each subgroup so random effects model has been chosen.

Figure 296: Severe hypoglycaemic episodes

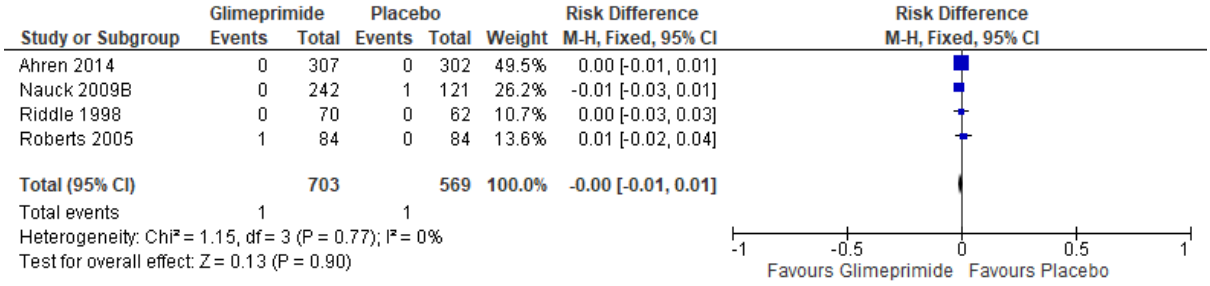
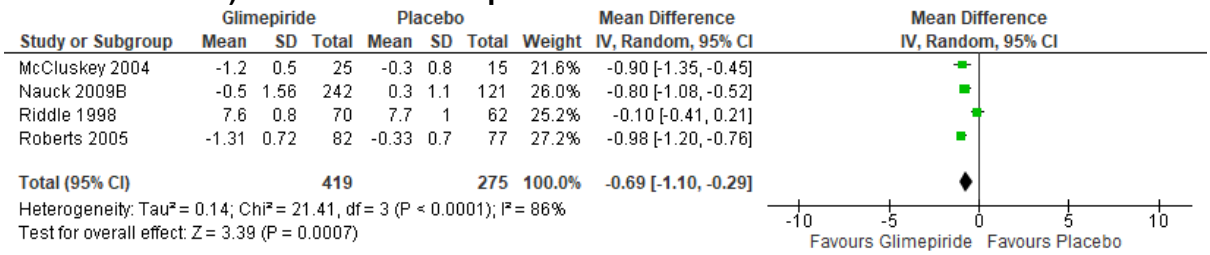
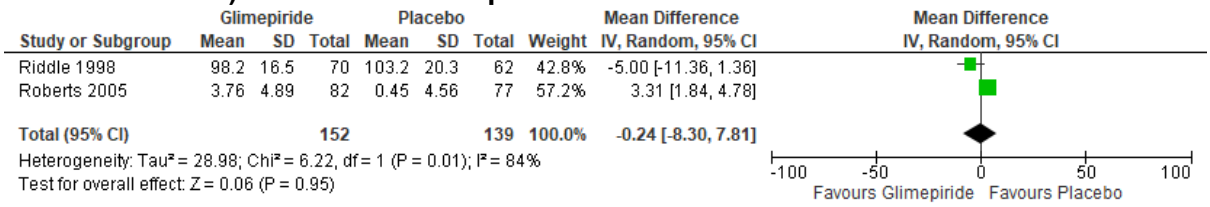


Figure 297: HbA1c change (%, lower values are better, change scores and final values) at end of follow up



Note: Heterogeneity for this outcome could not be explored due to low number of studies for each subgroup so a random effects model has been chosen.

Figure 298: Weight change (kg, lower values are better, change scores and final values) at end of follow up



K.1.6.3 Adding glimepiride compared to adding metformin

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

K.1.6.4 Adding glimepiride compared to adding insulin

Figure 299: Hypoglycaemia episodes at end of follow up

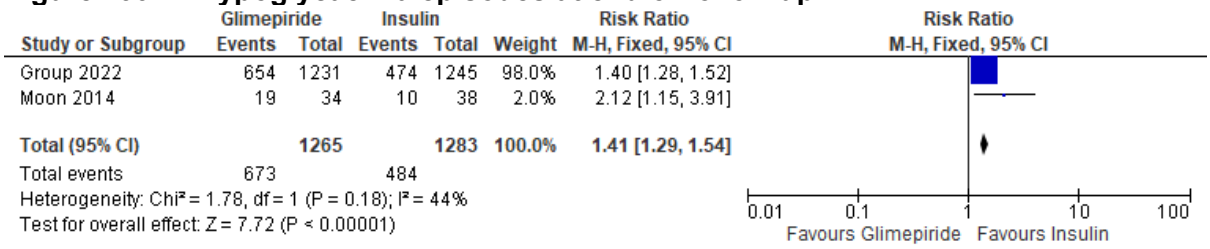


Figure 300: Severe hypoglycaemic episodes at end of follow up

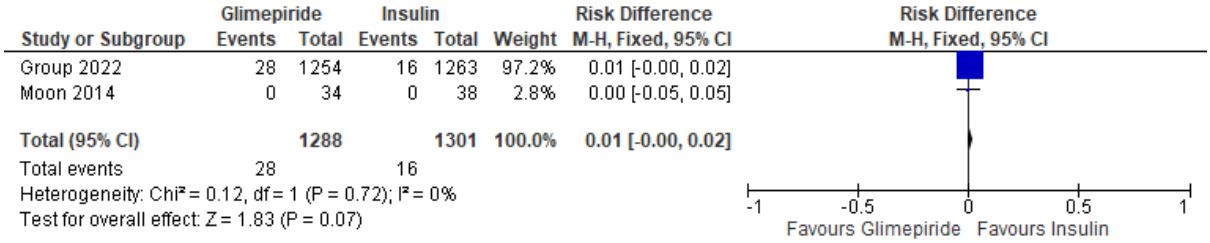
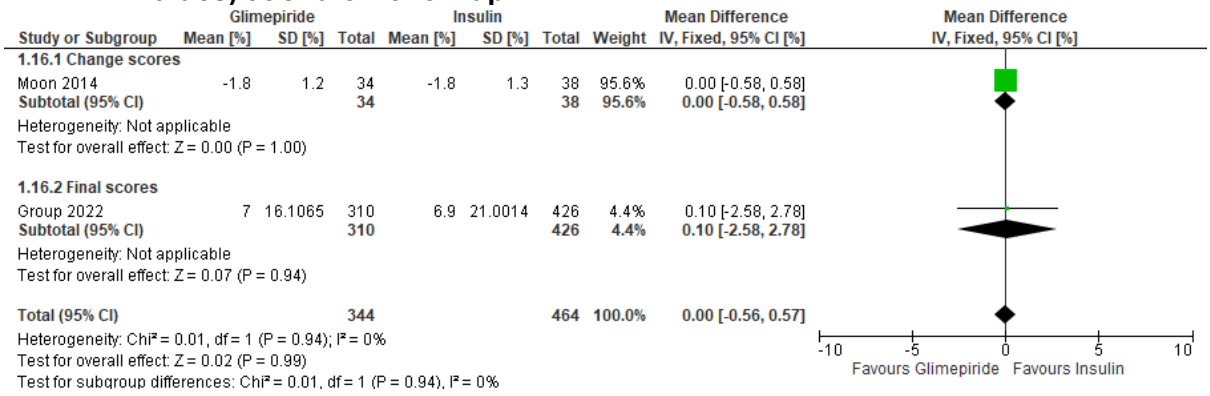


Figure 301: HbA1c change (%, lower values are better, change scores and final values) at end of follow up



K.1.6.5 Adding glimepiride compared to adding canagliflozin

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

K.1.6.6 Adding glimepiride compared to adding dapagliflozin

Figure 302: Hypoglycaemia episodes at end of follow up

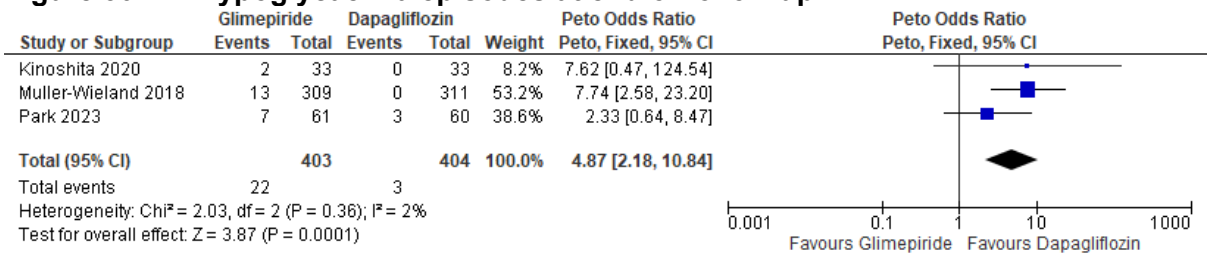


Figure 303: HbA1c change (%, lower values are better, change scores) at end of follow up

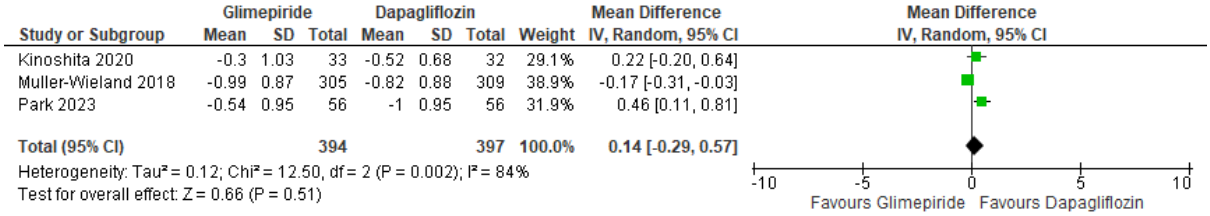
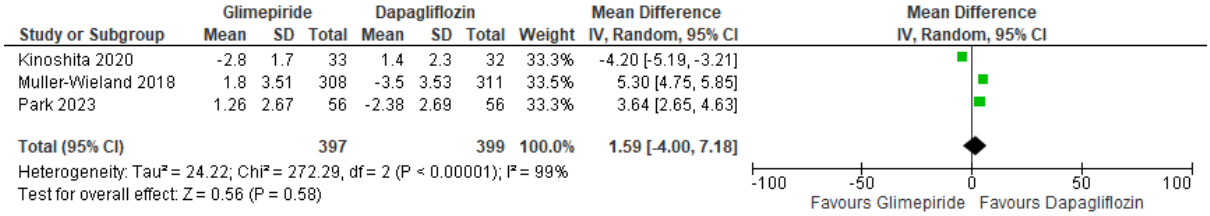


Figure 304: Weight change (kg, lower values are better, change score) at end of follow up



K.1.6.7 Adding glimepiride compared to adding empagliflozin

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

K.1.6.8 Adding glimepiride compared to adding ertugliflozin

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

K.1.6.9 Adding glimepiride compared to adding exenatide

Figure 305: Hypoglycaemia episodes at end of follow up

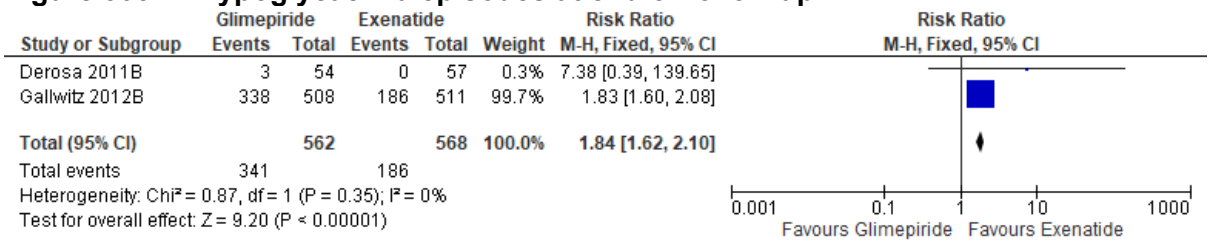


Figure 306: HbA1c change (%, lower values are better, change scores and final values) at end of follow up

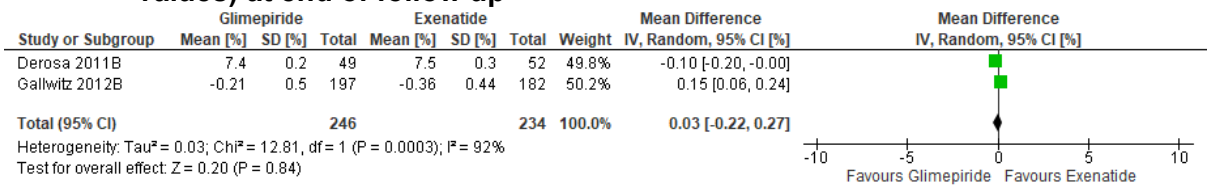


Figure 307: Weight change (kg, lower values are better, change scores and final values) at end of follow up

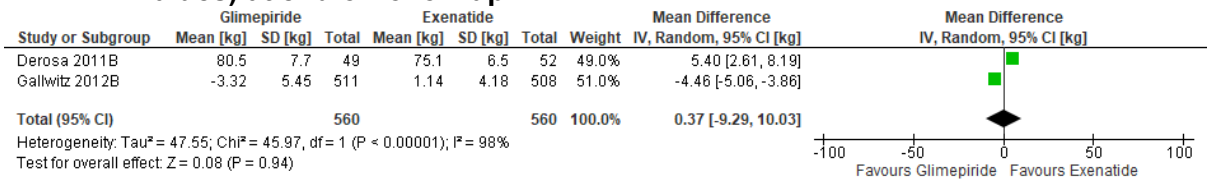
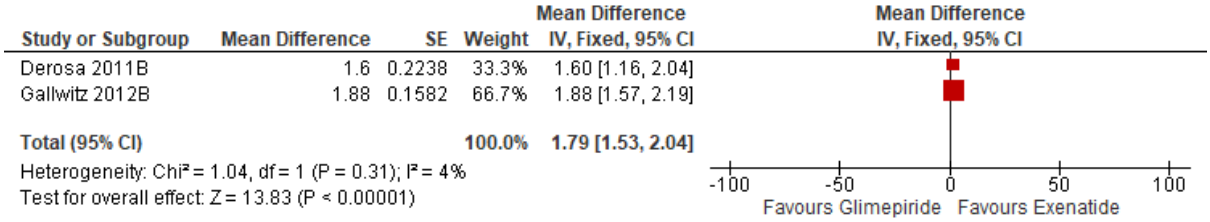


Figure 308: BMI change (kg/m^2, lower values are better, change scores and final values) at end of follow up



K.1.6.10 Adding glimepiride compared to adding gliclazide

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

K.1.6.11 Adding glimepiride compared to adding linagliptin

Figure 309: All-cause mortality at end of follow up

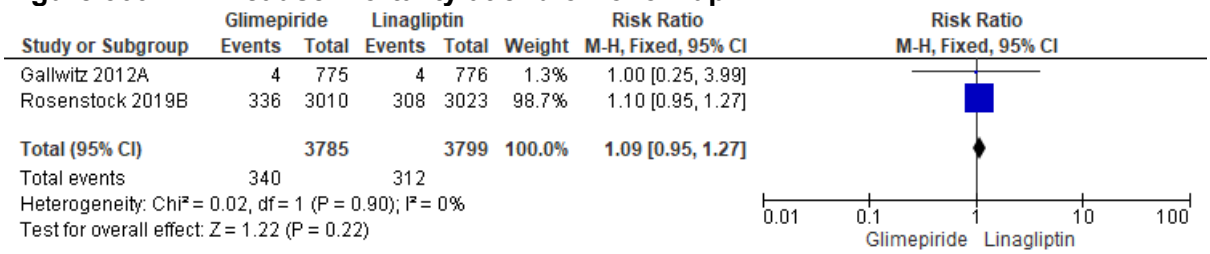


Figure 310: Cardiovascular mortality at end of follow up

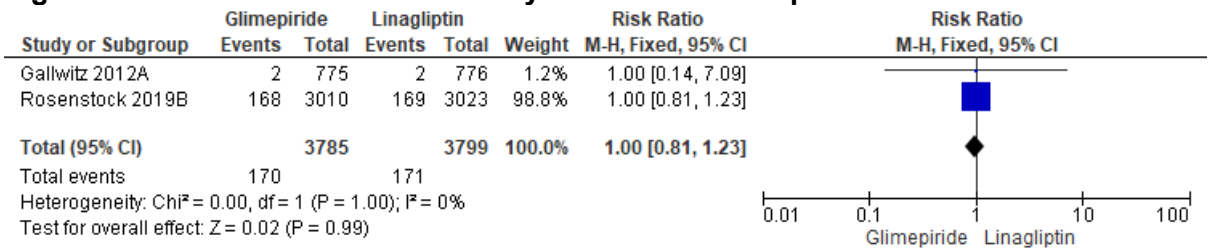


Figure 311: Non-fatal stroke at end of follow up

Study or Subgroup	Glimepiride Events	Glimepiride Total	Linagliptin Events	Linagliptin Total	Weight	Risk Ratio M-H, Random, 95% CI
Gallwitz 2012A	11	775	3	776	35.2%	3.67 [1.03, 13.11]
Rosenstock 2019B	104	3010	91	3023	64.8%	1.15 [0.87, 1.51]
Total (95% CI)		**3785**		**3799**	**100.0%**	**1.73 [0.58, 5.14]**
Total events	115		94			

Heterogeneity: Tau² = 0.46; Chi² = 3.07, df = 1 (P = 0.08); I² = 67%
Test for overall effect: Z = 0.98 (P = 0.33)

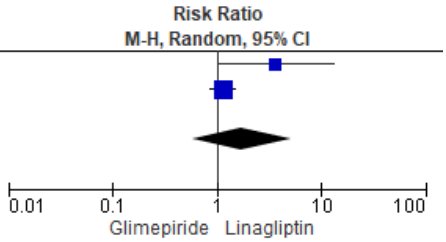


Figure 312: Unstable angina at end of follow up

Study or Subgroup	Glimepiride Events	Glimepiride Total	Linagliptin Events	Linagliptin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gallwitz 2012A	3	775	3	776	4.8%	1.00 [0.20, 4.95]
Rosenstock 2019B	56	3010	60	3023	95.2%	0.94 [0.65, 1.34]
Total (95% CI)		**3785**		**3799**	**100.0%**	**0.94 [0.66, 1.34]**
Total events	59		63			

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.34 (P = 0.73)

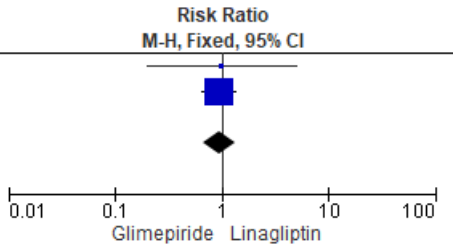


Figure 313: Hospitalisation for heart failure at follow up

Study or Subgroup	Glimepiride Events	Glimepiride Total	Linagliptin Events	Linagliptin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gallwitz 2012A	2	775	3	776	2.6%	0.67 [0.11, 3.98]
Rosenstock 2019B	92	3010	112	3023	97.4%	0.82 [0.63, 1.08]
Total (95% CI)		**3785**		**3799**	**100.0%**	**0.82 [0.63, 1.07]**
Total events	94		115			

Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² = 0%
Test for overall effect: Z = 1.44 (P = 0.15)

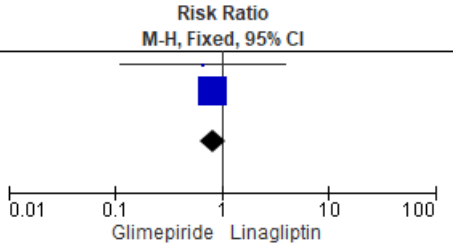


Figure 314: Hypoglycaemia episodes at end of follow up

Study or Subgroup	Glimepiride Events	Glimepiride Total	Linagliptin Events	Linagliptin Total	Weight	Risk Ratio M-H, Random, 95% CI
Gallwitz 2012A	280	775	58	776	42.2%	4.83 [3.71, 6.30]
Rosenstock 2019B	1132	3010	320	3023	57.8%	3.55 [3.17, 3.98]
Total (95% CI)		**3785**		**3799**	**100.0%**	**4.05 [3.00, 5.45]**
Total events	1412		378			

Heterogeneity: Tau² = 0.04; Chi² = 4.41, df = 1 (P = 0.04); I² = 77%
Test for overall effect: Z = 9.18 (P < 0.00001)

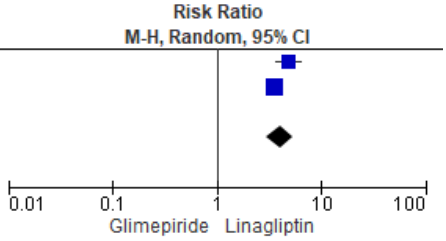


Figure 315: Severe hypoglycaemic episodes at end of follow up

Study or Subgroup	Glimepiride Events	Glimepiride Total	Linagliptin Events	Linagliptin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gallwitz 2012A	12	775	1	776	9.1%	12.02 [1.57, 92.18]
Rosenstock 2019B	65	3010	10	3023	90.9%	6.53 [3.36, 12.68]
Total (95% CI)		**3785**		**3799**	**100.0%**	**7.03 [3.74, 13.20]**
Total events	77		11			

Heterogeneity: Chi² = 0.31, df = 1 (P = 0.58); I² = 0%
Test for overall effect: Z = 6.06 (P < 0.00001)

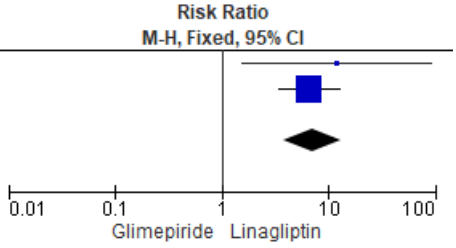


Figure 316: HbA1c change (%, lower values are better, change scores) at end of follow up

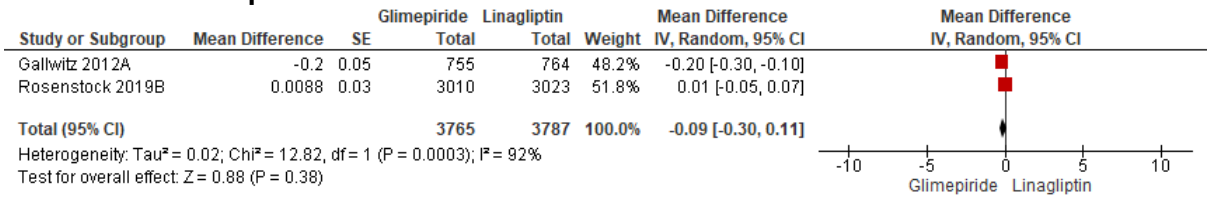
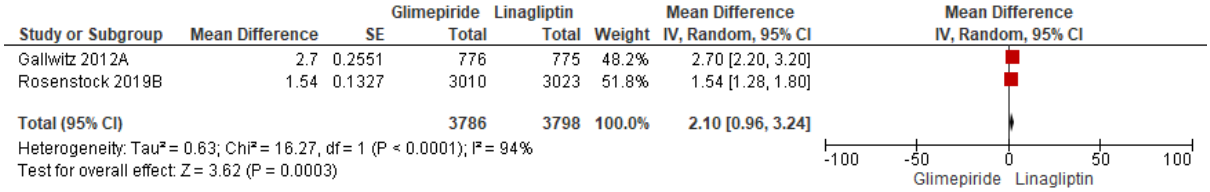


Figure 317: Weight change (kg, lower values are better, change scores) at end of follow up



K.1.6.12 Adding glimepiride compared to adding liraglutide

Figure 318: Hypoglycaemia episodes at end of follow up

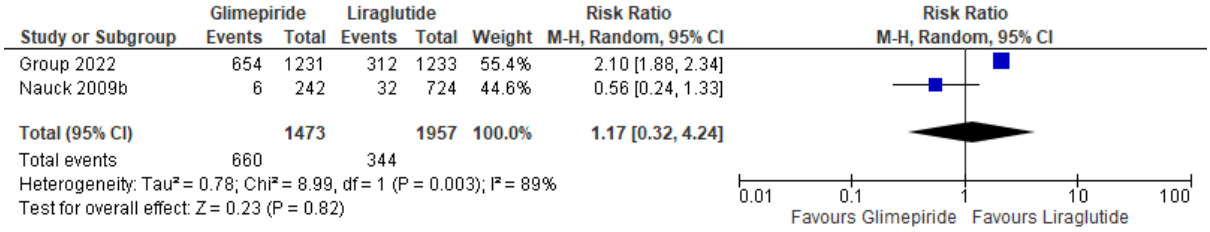
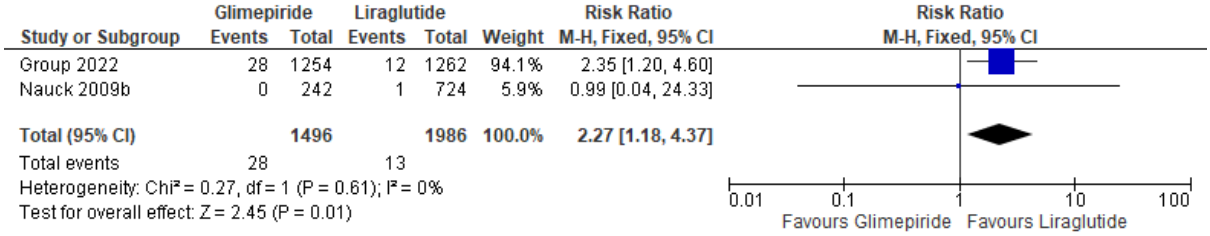


Figure 319: Severe hypoglycaemic episodes at end of follow up



K.1.6.13 Adding glimepiride compared to adding saxagliptin

Figure 320: Hypoglycaemia episodes at end of follow up

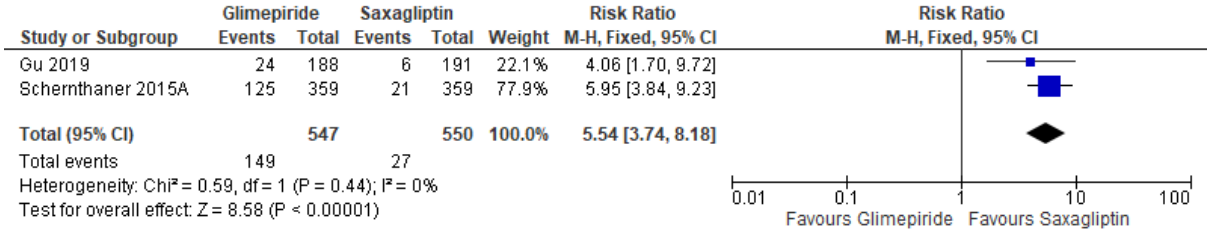
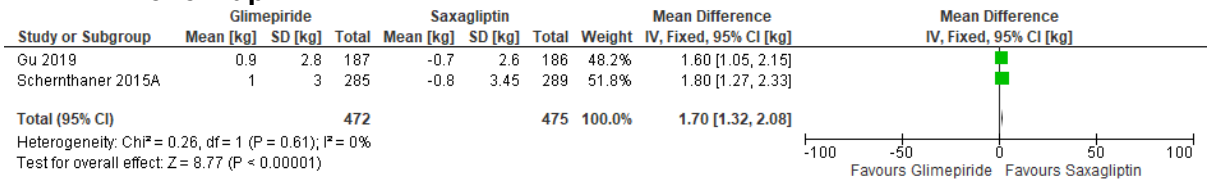


Figure 321: Weight change (kg, lower values are better, change scores) at end of follow up



K.1.6.14 Adding glimepiride compared to adding sitagliptin

Figure 322: All-cause mortality at end of follow up

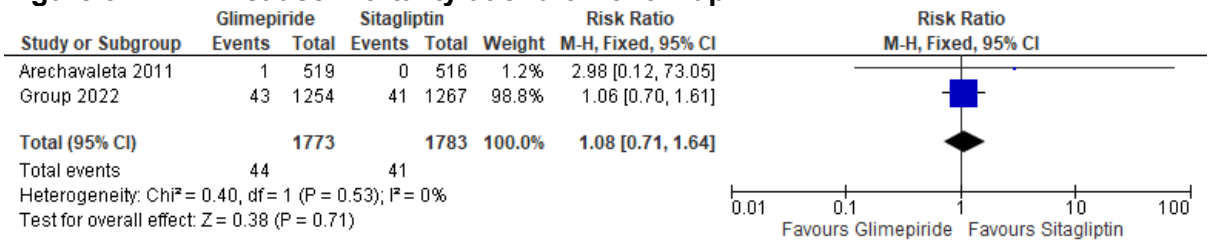


Figure 323: Cardiovascular mortality at end of follow up

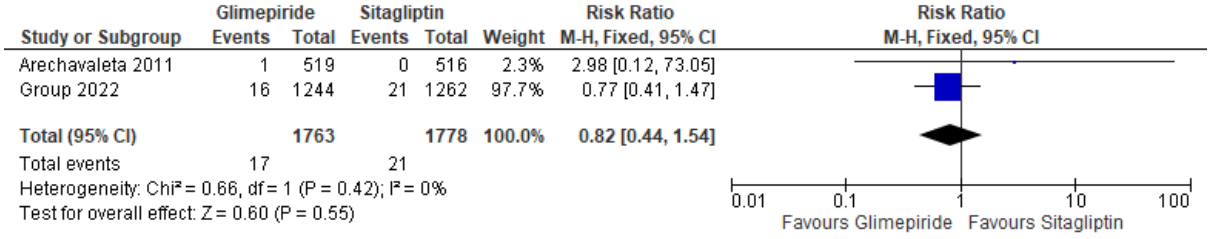


Figure 324: Hospitalisation for heart failure at end of follow up

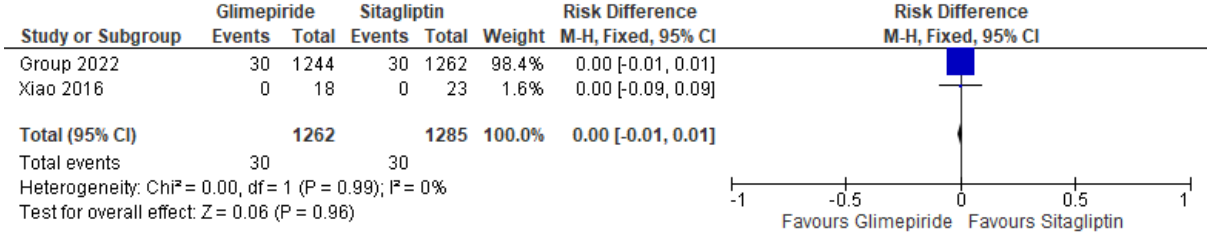
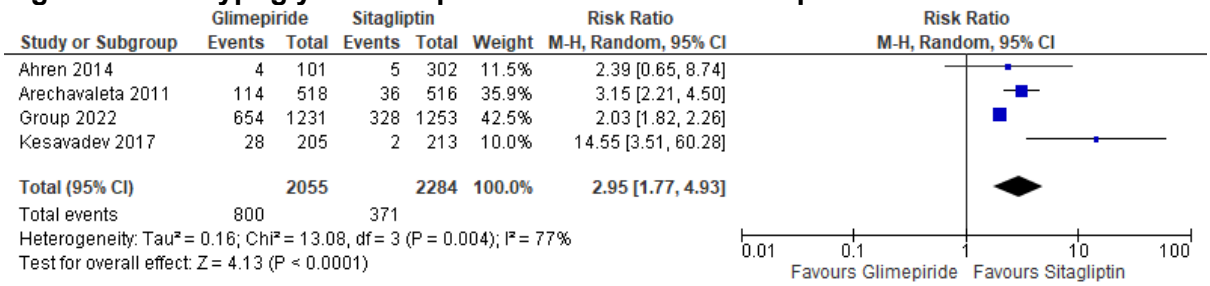
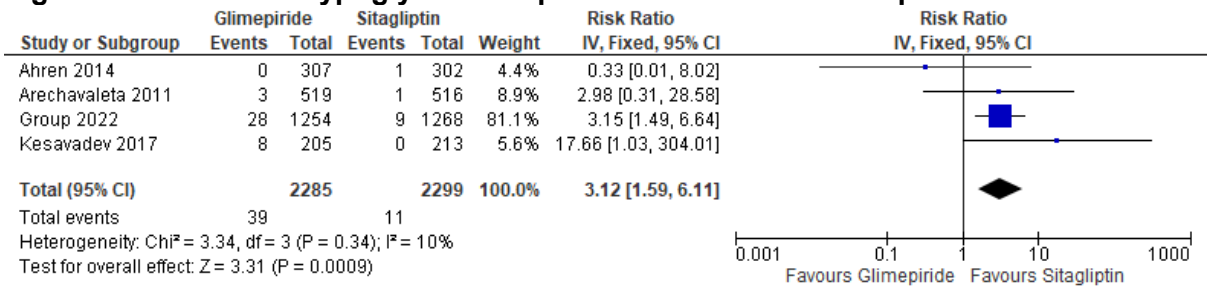


Figure 325: Hypoglycaemia episodes at end of follow up



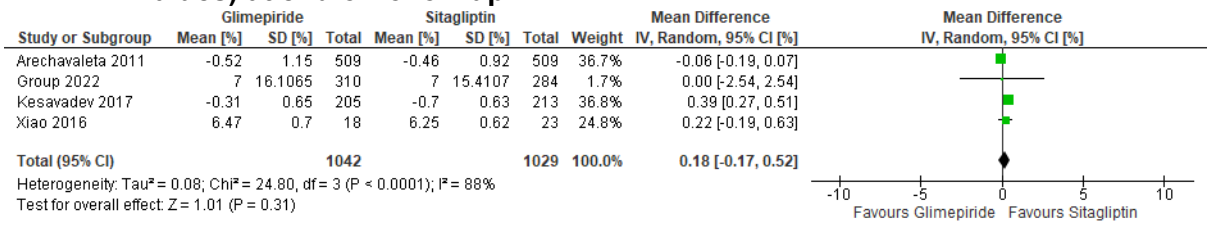
Note: Heterogeneity for this outcome could not be explored due to low number of studies for each subgroup so random effects model has been chosen.

Figure 326: Severe hypoglycaemic episodes at end of follow up



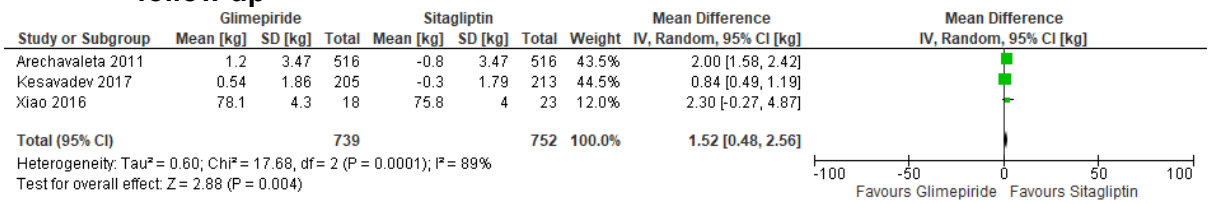
Note: Heterogeneity for this outcome could not be explored due to low number of studies for each subgroup so random effects model has been chosen.

Figure 327: HbA1c change (%, lower values are better, change scores and final values) at end of follow up



Note: Heterogeneity for this outcome could not be explored due to low number of studies for each subgroup so random effects model has been chosen.

Figure 328: Weight change (kg, lower values are better, change scores) at end of follow up



K.1.6.15 Adding glimepiride compared to adding vildagliptin

Figure 329: All-cause mortality at end of follow up

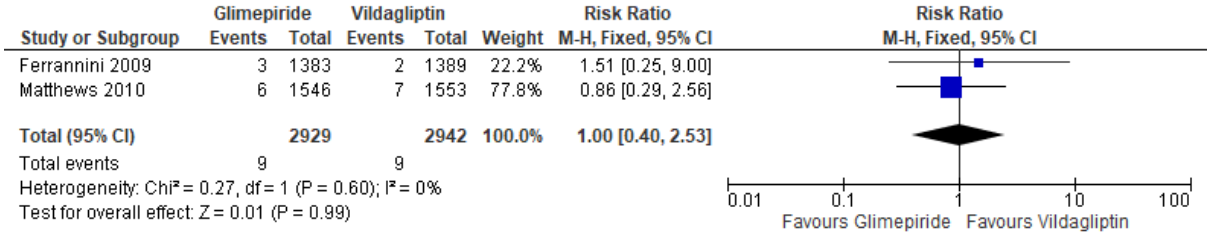


Figure 330: Hypoglycaemia episodes at end of follow up

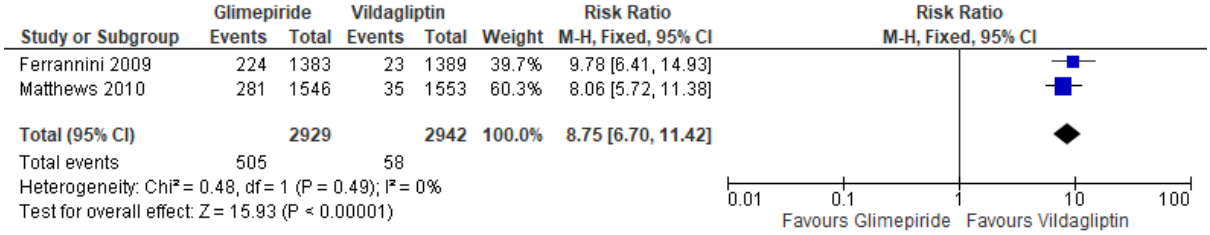


Figure 331: Severe hypoglycaemic episodes at end of follow up

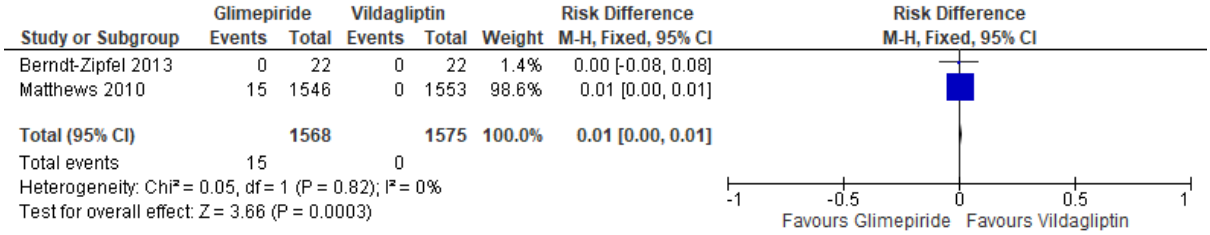


Figure 332: HbA1c change (%, lower values are better, change scores and final values) at end of follow up

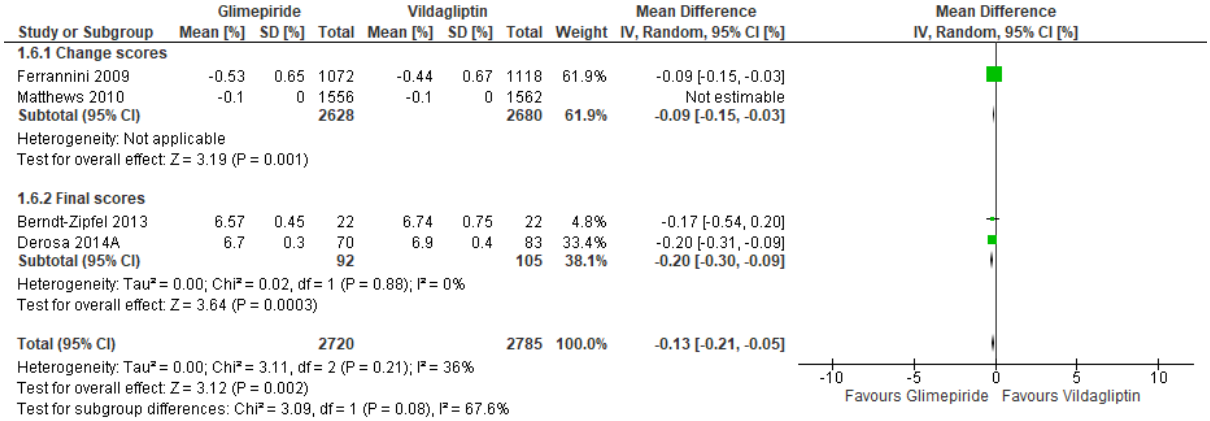
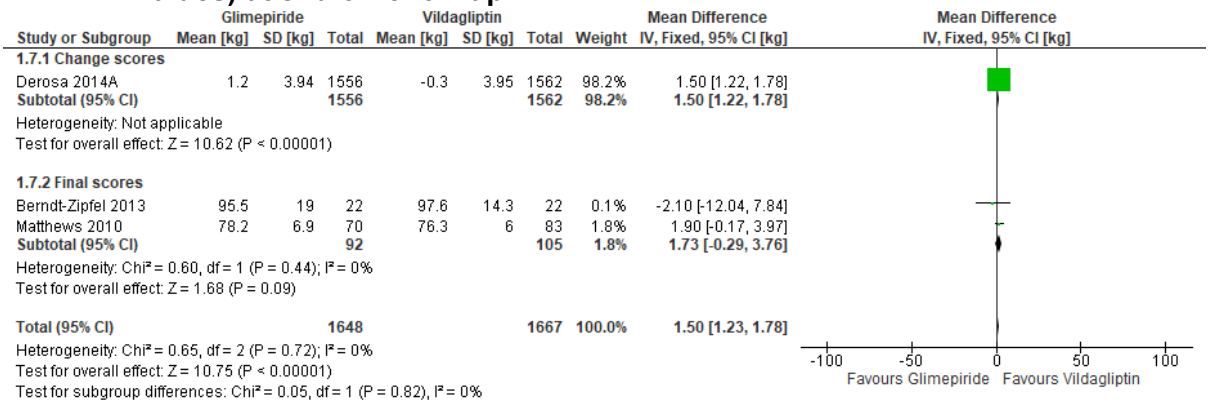


Figure 333: Weight change (kg, lower values are better, change scores and final values) at end of follow up



K.1.6.16 Adding glipizide compared to adding placebo

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

K.1.6.17 Adding glipizide compared to adding metformin

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

K.1.6.18 Adding glipizide compared to adding alogliptin

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

K.1.6.19 Adding glipizide compared to adding dapagliflozin

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

K.1.6.20 Adding glipizide compared to adding saxagliptin

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

K.1.6.21 Adding glipizide compared to adding sitagliptin

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

K.1.7 Thiazolidinediones

K.1.7.1 Adding pioglitazone compared to adding placebo

Figure 334: All-cause mortality at end of follow up

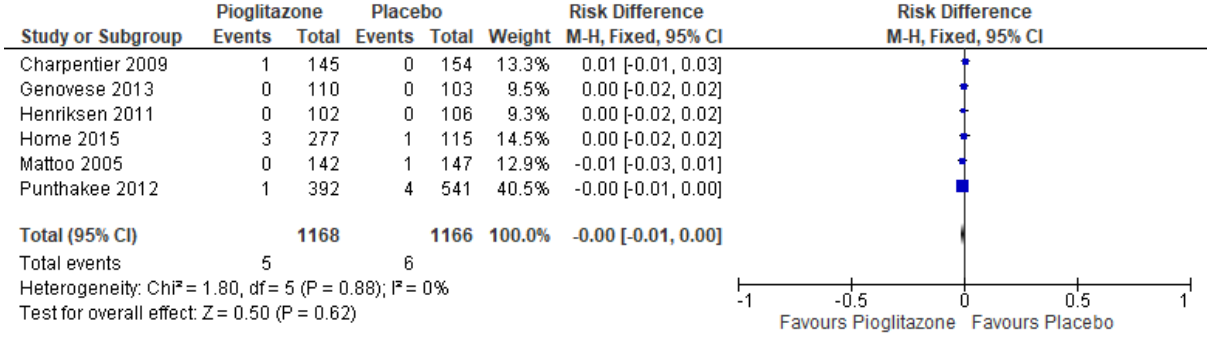


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Figure 335: Cardiovascular mortality at end of follow up

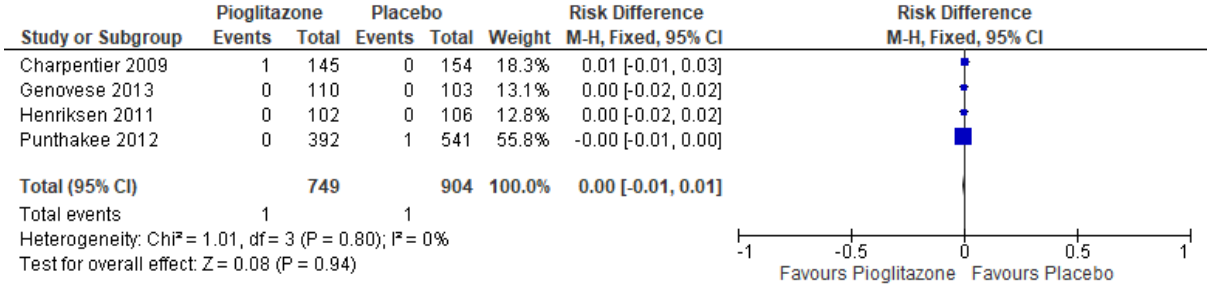


Figure 336: 3-point MACE at end of follow up

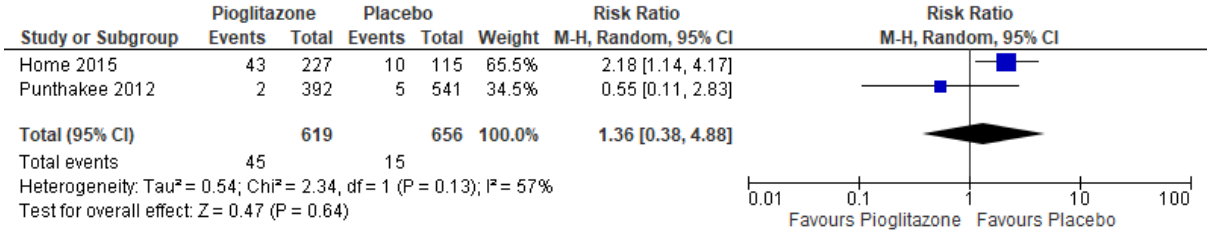


Figure 337: Non-fatal myocardial infarction at follow up

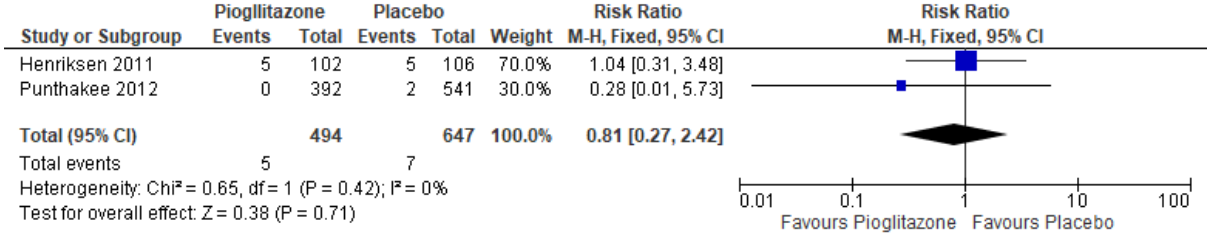


Figure 338: Hospitalisation for heart failure at end of follow up

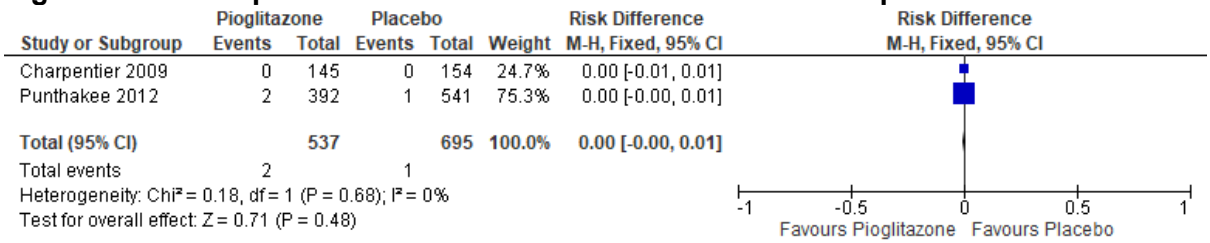
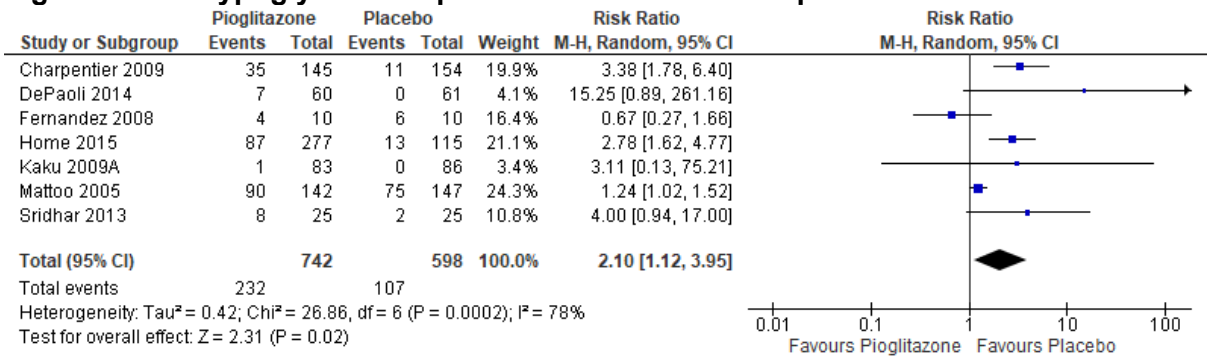


Figure 339: Hypoglycaemia episodes at end of follow up



Note: Heterogeneity for this outcome could not be explored due to low number of studies for each subgroup so random effects model has been chosen

Figure 340: Severe hypoglycaemic episodes at end of follow up

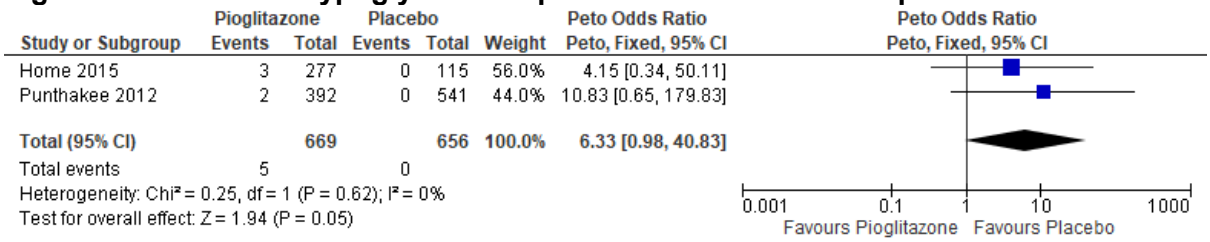
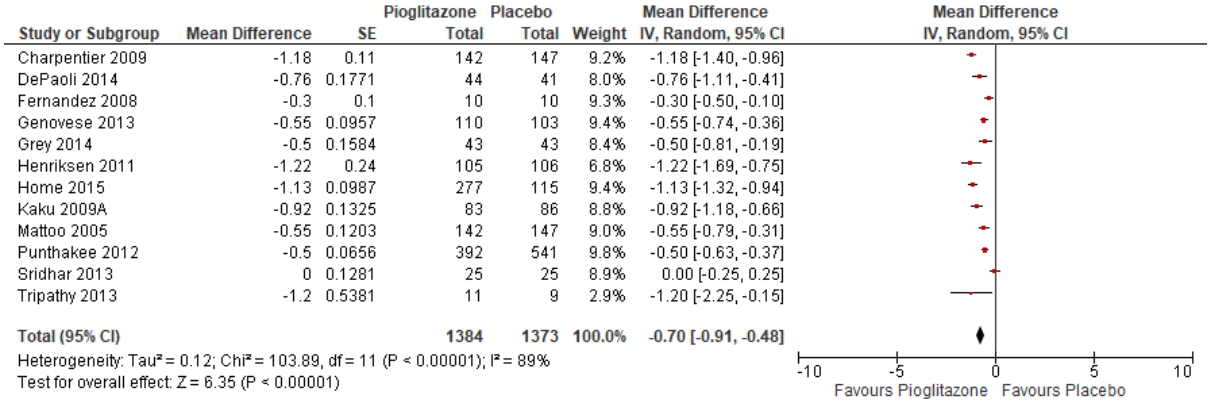
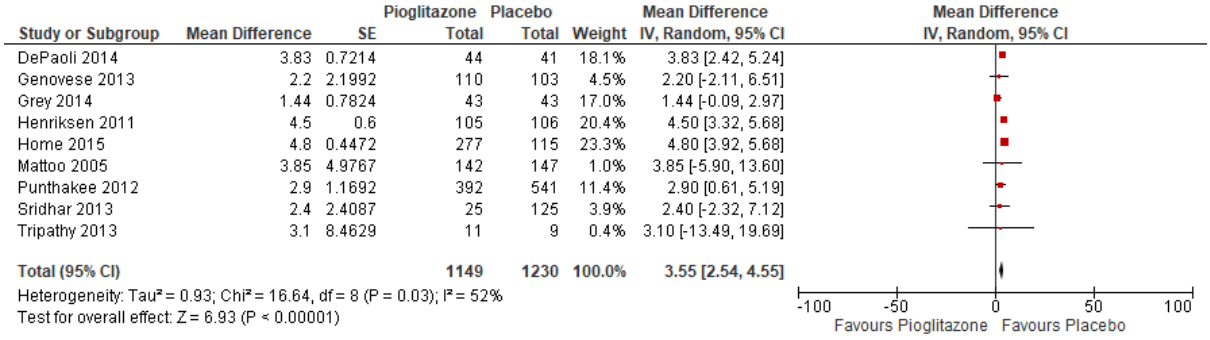


Figure 341: HbA1c change (%, lower values are better, change scores and final values) at end of follow up



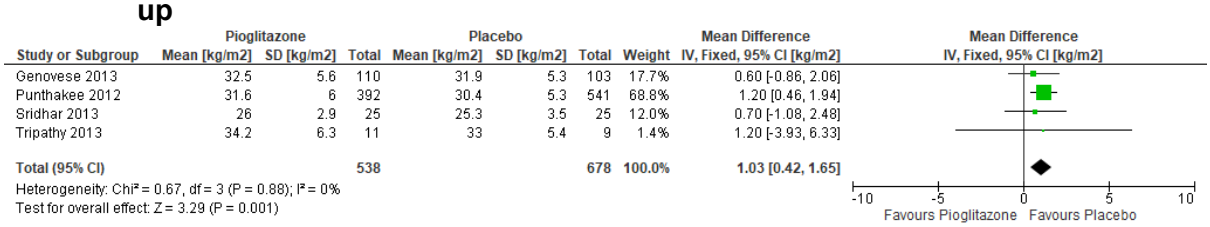
Note: Heterogeneity was not explained by sensitivity analysis nor subgroup analysis.

Figure 342: Weight change (kg, 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.

Figure 343: BMI change (kg/m^2, lower values are better, final values) at end of follow up



K.1.7.2 Adding pioglitazone compared to adding metformin

Figure 344: All-cause mortality at end of follow up

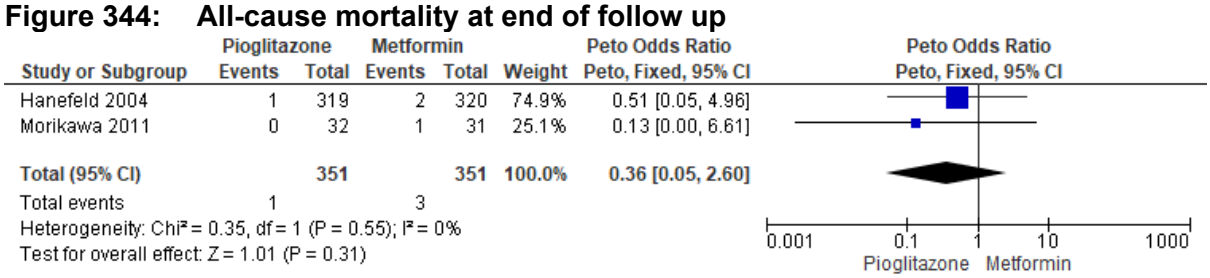


Figure 345: Hypoglycaemia episodes at end of follow up

Study or Subgroup	Pioglitazone Events	Pioglitazone Total	Metformin Events	Metformin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hanefeld 2004	36	319	50	320	85.0%	0.72 [0.48, 1.08]
Hanefeld 2011	8	40	9	42	15.0%	0.93 [0.40, 2.18]
Total (95% CI)		**359**		**362**	**100.0%**	**0.75 [0.53, 1.08]**
Total events	44		59			

Heterogeneity: Chi² = 0.29, df = 1 (P = 0.59); I² = 0%
Test for overall effect: Z = 1.53 (P = 0.13)

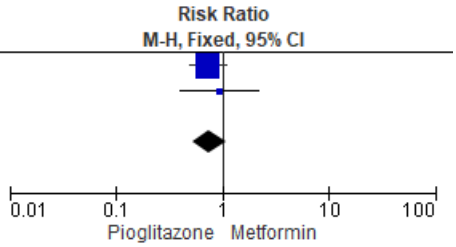


Figure 346: HbA1c change (%, lower values are better, change scores and final values) at end of follow up

Study or Subgroup	Mean Difference	SE	Pioglitazone Total	Metformin Total	Weight	Mean Difference IV, Fixed, 95% CI
Hanefeld 2004	0.13	0.09	315	313	45.5%	0.13 [-0.05, 0.31]
Hanefeld 2011	-0.04	0.9841	37	39	0.4%	-0.04 [-1.97, 1.89]
Kanazawa 2010	0	0.3436	22	23	3.1%	0.00 [-0.67, 0.67]
Morikawa 2011	-0.32	0.234	32	31	6.7%	-0.32 [-0.78, 0.14]
Park 2011	0.1	0.1242	34	33	23.9%	0.10 [-0.14, 0.34]
van der Meer 2009	0.2	0.1404	39	39	18.7%	0.20 [-0.08, 0.48]
Wu 2014	0.1	0.4669	46	47	1.7%	0.10 [-0.82, 1.02]
Total (95% CI)			**525**	**525**	**100.0%**	**0.10 [-0.02, 0.22]**

Heterogeneity: Chi² = 3.94, df = 6 (P = 0.68); I² = 0%
Test for overall effect: Z = 1.65 (P = 0.10)

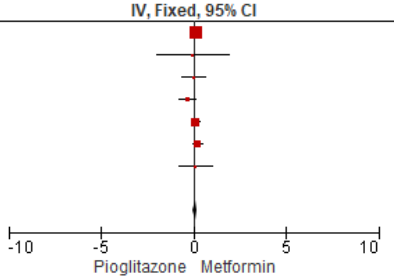


Figure 347: Weight change (kg, lower values are better, change scores and final values) at end of follow up

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]
Kanazawa 2010	61.2	8.8	22	62.7	10.8	23	22.6%	-1.50 [-7.24, 4.24]
Roden 2005 1.2	3.06	4.09	316	-1.02	4.11	320	60.4%	4.08 [3.44, 4.72]
van der Meer 2009	94	12.49	39	92	18.73	39	17.0%	2.00 [-5.07, 9.07]
Total (95% CI)			**377**			**382**	**100.0%**	**2.47 [-0.96, 5.89]**

Heterogeneity: Tau² = 4.96; Chi² = 3.89, df = 2 (P = 0.14); I² = 49%
Test for overall effect: Z = 1.41 (P = 0.16)

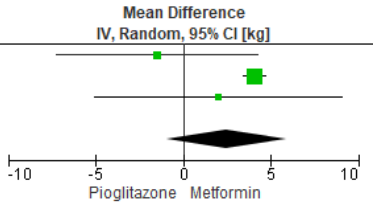
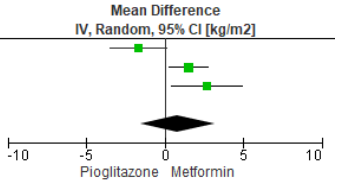


Figure 348: BMI change (kg/m², lower values are better, final values) at end of follow up

Study or Subgroup	Pioglitazone Mean [kg/m2]	Pioglitazone SD [kg/m2]	Pioglitazone Total	Metformin Mean [kg/m2]	Metformin SD [kg/m2]	Metformin Total	Weight	Mean Difference IV, Random, 95% CI [kg/m2]
Kanazawa 2010	23.4	2.6	22	25.1	3.6	23	33.0%	-1.70 [-3.53, 0.13]
Park 2011	26.3	3.2	82	24.8	2.9	33	37.1%	1.50 [0.29, 2.71]
Wu 2014	24.8	5.6	46	22.1	5.5	47	29.9%	2.70 [0.44, 4.96]
Total (95% CI)			**150**			**103**	**100.0%**	**0.80 [-1.56, 3.17]**

Heterogeneity: Tau² = 3.53; Chi² = 11.16, df = 2 (P = 0.004); I² = 82%
Test for overall effect: Z = 0.67 (P = 0.51)



K.1.7.3 Adding pioglitazone compared to adding insulin

Figure 349: Hypoglycaemia episodes at end of follow up

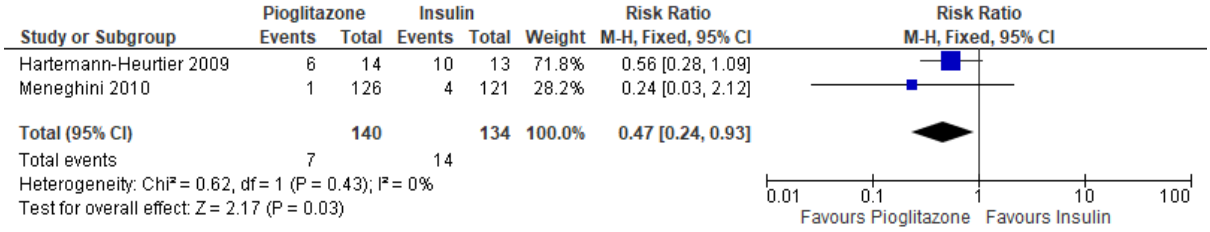


Figure 350: Severe hypoglycaemic episodes at end of follow up

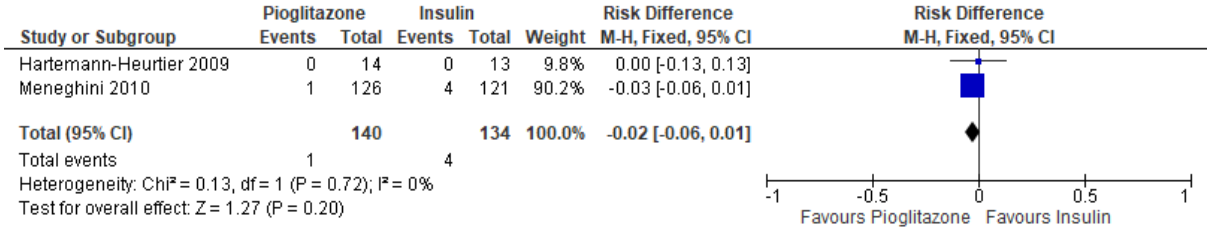
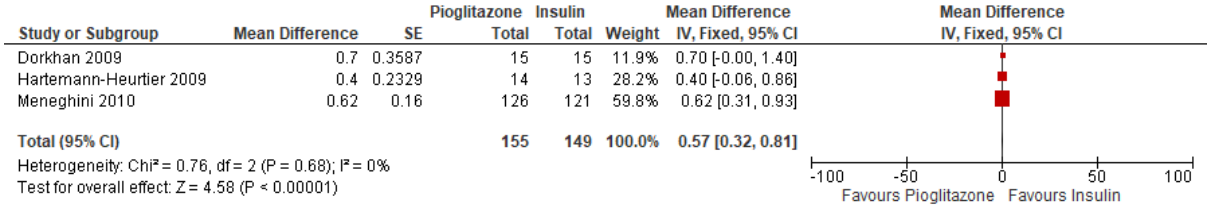


Figure 351: HbA1c change (%, lower values are better, change scores and final values) at end of follow up



K.1.7.4 Adding pioglitazone compared to adding dapagliflozin

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

K.1.7.5 Adding pioglitazone compared to adding empagliflozin

Figure 352: Hypoglycaemia episodes at end of follow up

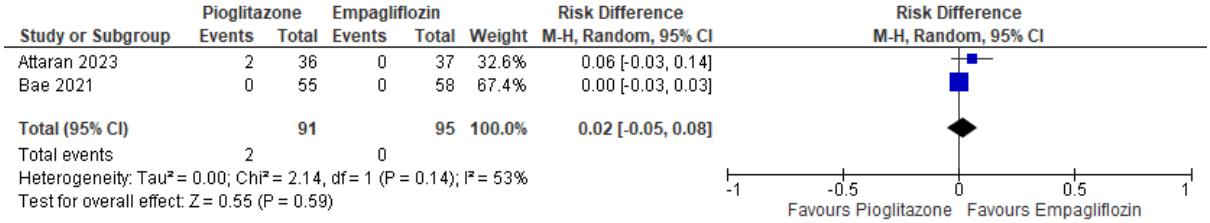


Figure 353: Severe hypoglycaemic episodes at end of follow up

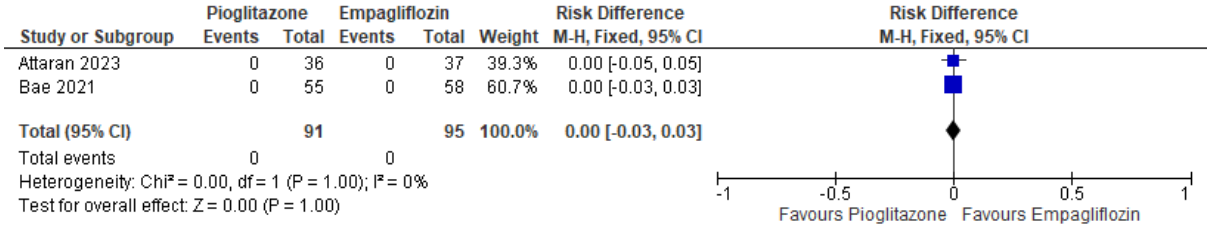


Figure 354: HbA1c change (%, lower values are better, change scores and final values) at end of follow up

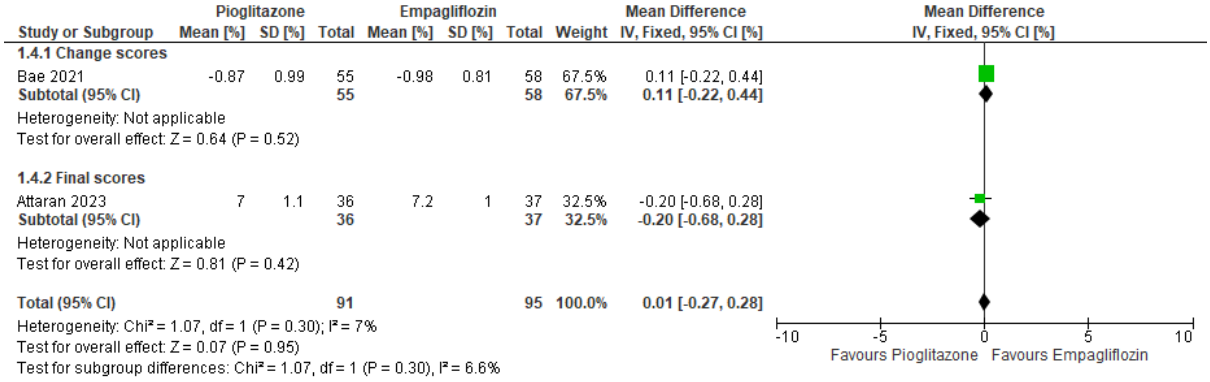
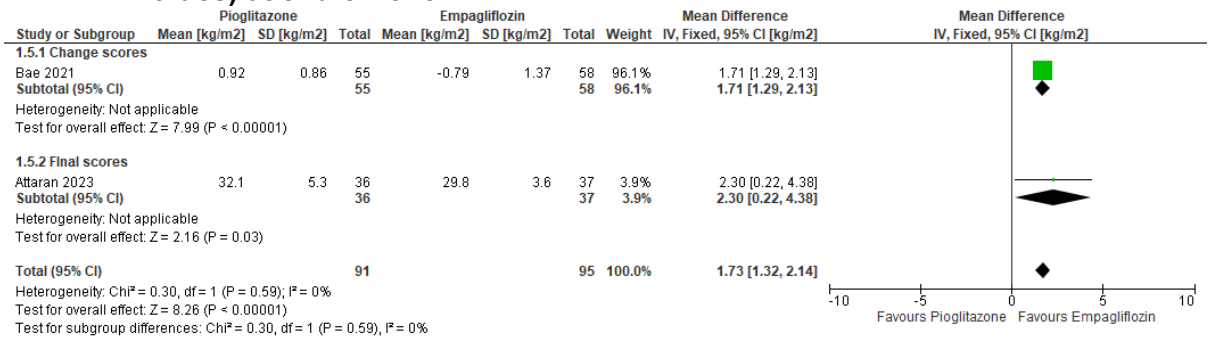


Figure 355: BMI change (kg/m^2, lower values are better, change scores and final values) at end of follow



K.1.7.6 Adding pioglitazone compared to adding exenatide

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

K.1.7.7 Adding pioglitazone compared to adding gliclazide

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

K.1.7.8 Adding pioglitazone compared to adding glimepiride

Figure 356: Non-fatal stroke at end of follow up

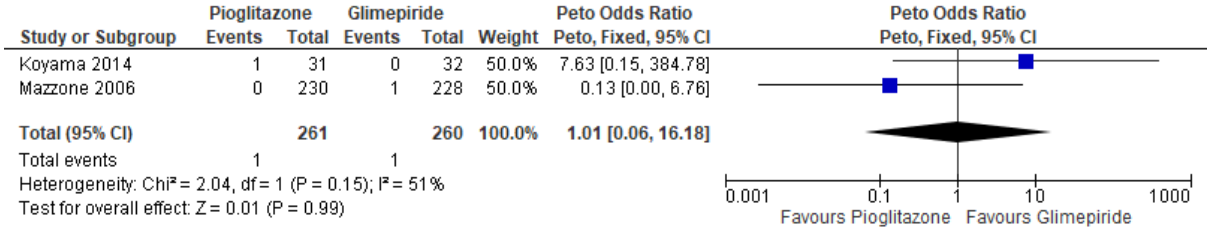


Figure 357: Non-fatal myocardial infarction at end of follow up

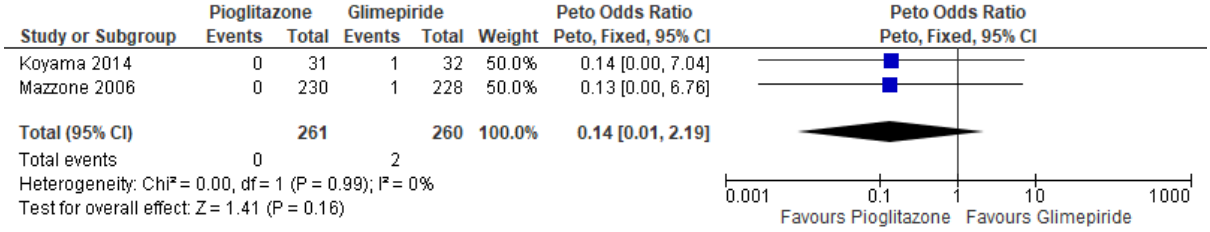


Figure 358: Hospitalisation for heart failure at end of follow up

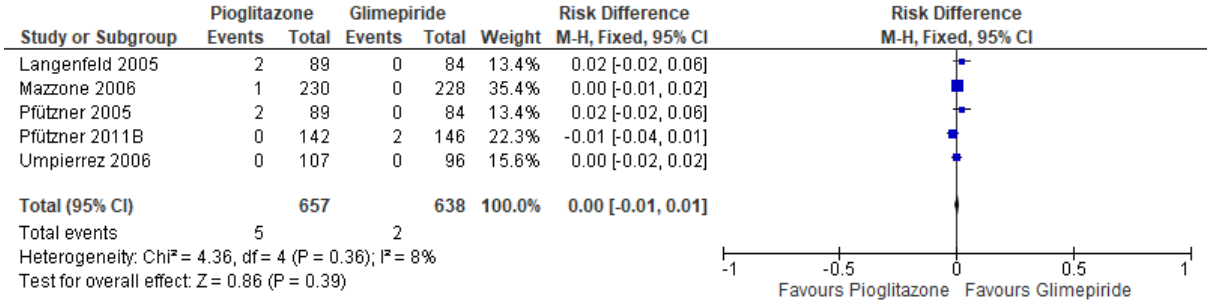
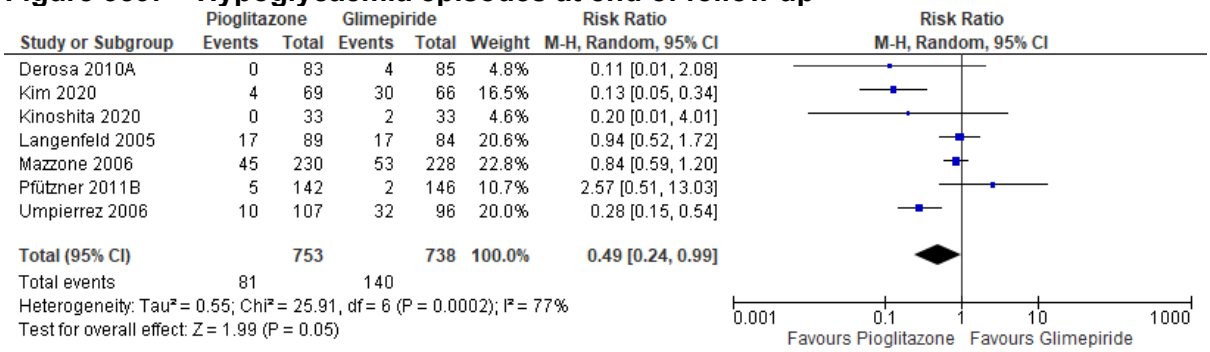


Figure 359: Hypoglycaemia episodes at end of follow up



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

Figure 360: Severe hypoglycaemic episodes at end of follow up

Study or Subgroup	Pioglitazone Events	Pioglitazone Total	Glimepiride Events	Glimepiride Total	Weight	Risk Difference M-H, Fixed, 95% CI
Langenfeld 2005	0	89	0	84	31.5%	0.00 [-0.02, 0.02]
Pfützner 2005	0	89	0	84	31.5%	0.00 [-0.02, 0.02]
Umpierrez 2006	0	107	0	96	36.9%	0.00 [-0.02, 0.02]
Total (95% CI)		**285**		**264**	**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)

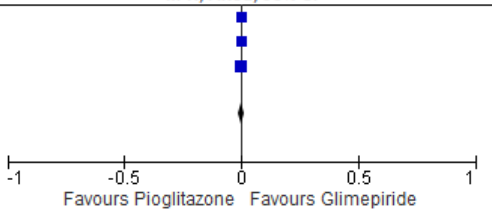


Figure 361: HbA1c change (%, lower values are better, change scores and final values) at end of follow up

Study or Subgroup	Pioglitazone Mean [%]	Pioglitazone SD [%]	Pioglitazone Total	Glimepiride Mean [%]	Glimepiride SD [%]	Glimepiride Total	Weight	Mean Difference IV, Random, 95% CI [%]
1.12.1 Change scores								
Kim 2020	-0.81	1.1	69	-1.05	0.87	66	7.4%	0.24 [-0.09, 0.57]
Kinoshita 2020	-0.48	1.03	33	-0.3	1.03	33	4.4%	-0.18 [-0.68, 0.32]
Koyama 2014	-0.28	0.78	27	0.1	0.77	30	5.9%	-0.38 [-0.78, 0.02]
Ohira 2014A	-0.82	1.07	30	-0.44	1.23	30	3.4%	-0.38 [-0.96, 0.20]
Pfützner 2005	-0.8	0.9	89	-0.6	0.8	84	9.9%	-0.20 [-0.45, 0.05]
Pfützner 2011B	-1	0.9	142	-0.8	0.9	146	11.5%	-0.20 [-0.41, 0.01]
Umpierrez 2006	-1.23	0.76	107	-1.3	0.75	96	11.5%	0.07 [-0.14, 0.28]
Subtotal (95% CI)			**497**			**485**	**54.0%**	**-0.11 [-0.27, 0.05]**

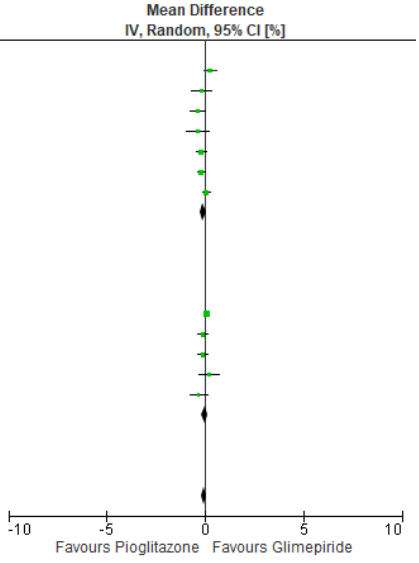
Heterogeneity: Tau² = 0.02; Chi² = 10.87, df = 6 (P = 0.09); I² = 45%
Test for overall effect: Z = 1.36 (P = 0.17)

1.12.2 Final scores								
Derosa 2010A	6.9	0.2	78	6.8	0.1	77	17.2%	0.10 [0.05, 0.15]
Forst 2005	6.71	0.89	89	6.83	0.85	84	9.7%	-0.12 [-0.38, 0.14]
Langenfeld 2005	6.71	0.89	89	6.83	0.85	84	9.7%	-0.12 [-0.38, 0.14]
Papathanassiou 2009	7.1	0.8	14	6.9	0.5	14	4.4%	0.20 [-0.29, 0.69]
Petrica 2011	6.85	0.73	34	7.19	1.12	34	5.1%	-0.34 [-0.79, 0.11]
Subtotal (95% CI)			**304**			**293**	**46.0%**	**-0.03 [-0.19, 0.14]**

Heterogeneity: Tau² = 0.02; Chi² = 8.77, df = 4 (P = 0.07); I² = 54%
Test for overall effect: Z = 0.31 (P = 0.76)

Total (95% CI)			**801**			**778**	**100.0%**	**-0.07 [-0.19, 0.05]**

Heterogeneity: Tau² = 0.02; Chi² = 28.28, df = 11 (P = 0.003); I² = 61%
Test for overall effect: Z = 1.22 (P = 0.22)
Test for subgroup differences: Chi² = 0.52, df = 1 (P = 0.47), I² = 0%



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

Figure 362: Weight change (kg, lower values are better, change scores and final values) at end of follow up

Study or Subgroup	Pioglitazone Mean [kg]	Pioglitazone SD [kg]	Pioglitazone Total	Glimepiride Mean [kg]	Glimepiride SD [kg]	Glimepiride Total	Weight	Mean Difference IV, Random, 95% CI [kg]
1.13.1 Change scores								
Kinoshita 2020	2.5	2.3	33	1.4	2.3	33	16.6%	1.10 [-0.01, 2.21]
Koyama 2014	1.49	1.61	27	0.21	2.9	30	15.8%	1.28 [0.08, 2.48]
Mazzone 2006	3.2	5.4	232	1	3.7	230	18.8%	2.20 [1.36, 3.04]
Ohira 2014A	1.98	2.34	30	0.37	1.86	30	16.9%	1.61 [0.54, 2.68]
Umpierrez 2006	1.85	3.93	107	1.74	4.02	96	16.7%	0.11 [-0.99, 1.21]
Subtotal (95% CI)			**429**			**419**	**84.9%**	**1.30 [0.59, 2.02]**

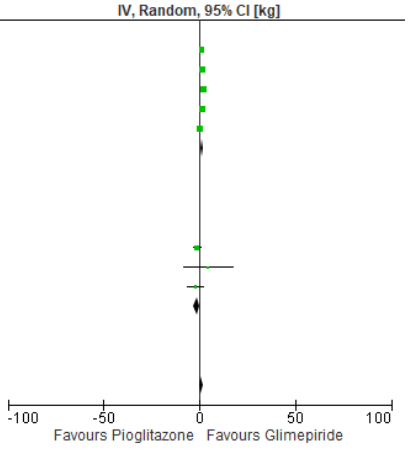
Heterogeneity: Tau² = 0.38; Chi² = 9.24, df = 4 (P = 0.06); I² = 57%
Test for overall effect: Z = 3.56 (P = 0.0004)

1.13.2 Final scores								
Derosa 2010A	77.2	5.4	78	78.6	6.4	77	11.0%	-1.40 [-3.27, 0.47]
Papathanassiou 2009	86.4	19.2	14	82	15.4	14	0.4%	4.40 [-8.49, 17.29]
Pfützner 2011B	94.8	18.2	142	96.9	17.8	146	3.6%	-2.10 [-6.26, 2.06]
Subtotal (95% CI)			**234**			**237**	**15.1%**	**-1.42 [-3.10, 0.27]**

Heterogeneity: Tau² = 0.00; Chi² = 0.89, df = 2 (P = 0.64); I² = 0%
Test for overall effect: Z = 1.64 (P = 0.10)

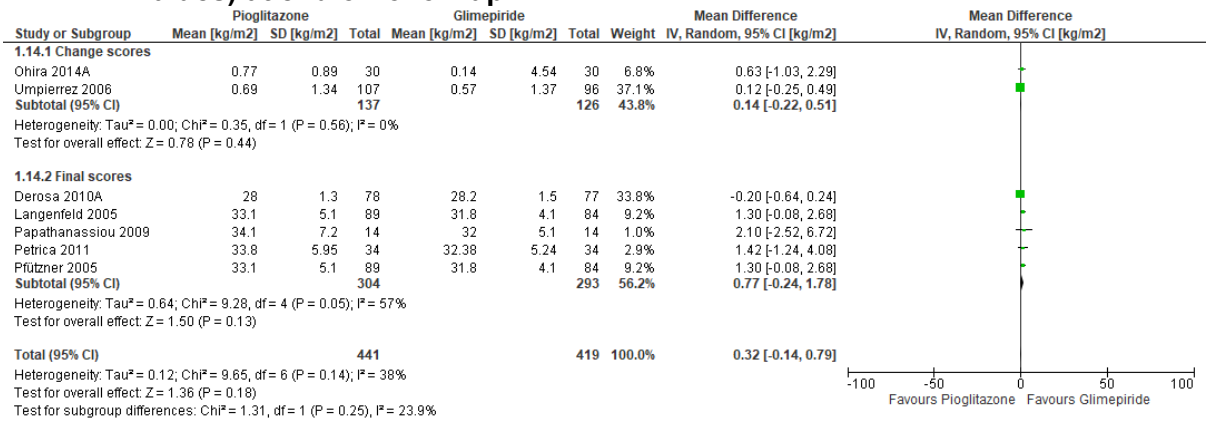
Total (95% CI)			**663**			**656**	**100.0%**	**0.88 [0.02, 1.74]**

Heterogeneity: Tau² = 0.83; Chi² = 19.92, df = 7 (P = 0.006); I² = 65%
Test for overall effect: Z = 2.01 (P = 0.04)
Test for subgroup differences: Chi² = 8.45, df = 1 (P = 0.004), I² = 88.2%



Note: Heterogeneity for this outcome could not be explored due to low number of studies for each subgroup so random effects model has been chosen

Figure 363: BMI change (kg/m^2, lower values are better, change scores and final values) at end of follow up



Note: Heterogeneity for this outcome could not be explored due to low number of studies for each subgroup so random effects model has been chosen

K.1.7.9 Adding pioglitazone compared to adding glipizide

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

K.1.7.10 Adding pioglitazone compared to adding sitagliptin

Figure 364: Hypoglycaemia episodes at end of follow up

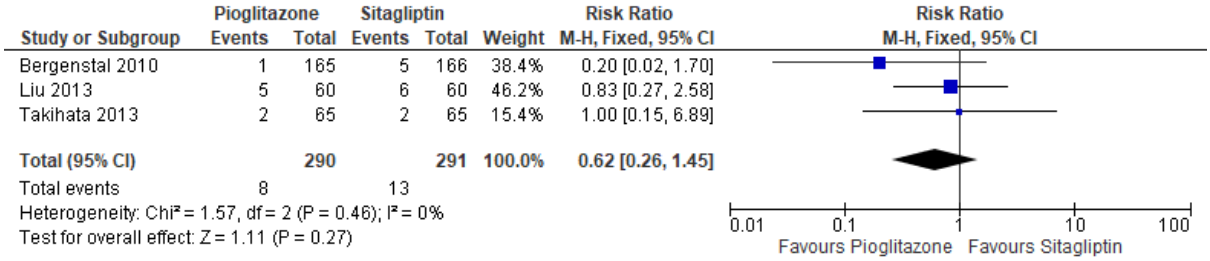


Figure 365: Severe hypoglycaemic episodes at end of follow up

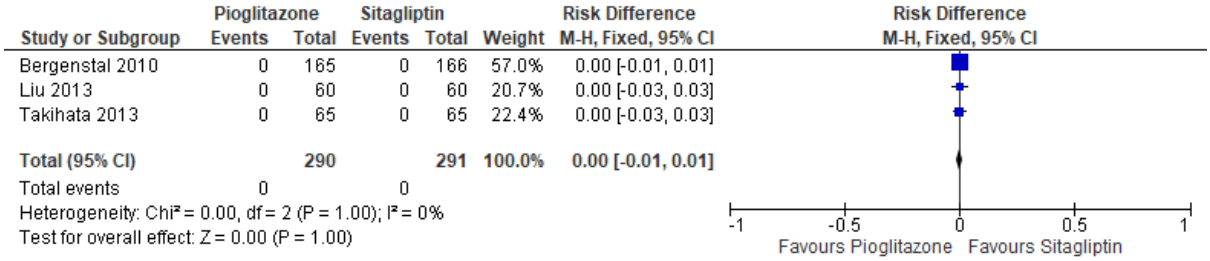
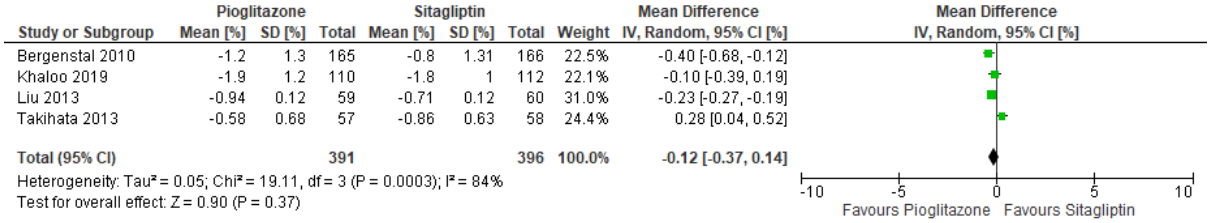
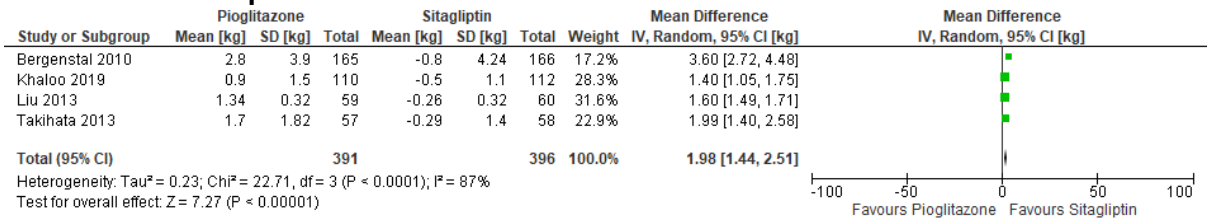


Figure 366: HbA1c change (%, lower values are better, change scores) at end of follow up



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

Figure 367: Weight change (kg, lower values are better, change scores) at end of follow up



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

K.1.7.11 Adding pioglitazone compared to adding vildagliptin

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

K.1.8 Insulin combinations

K.1.8.1 Adding insulin degludec/Liraglutide compared to adding placebo

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

K.1.8.2 Adding insulin degludec/Liraglutide compared to adding insulin

Figure 368: Health-related quality of life - subscale mental component (SF-36 v2, 0-100, higher scores are better, change scores and final values) at end of follow up

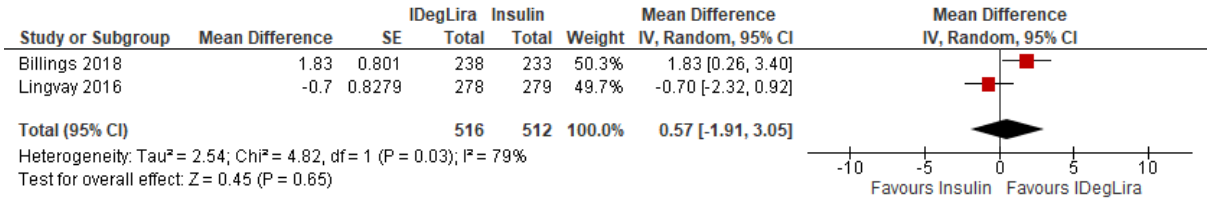


Figure 369: Health-related quality of life - subscale physical component (SF-36 v2, 0-100, higher scores are better, change scores and final values) at end of follow up

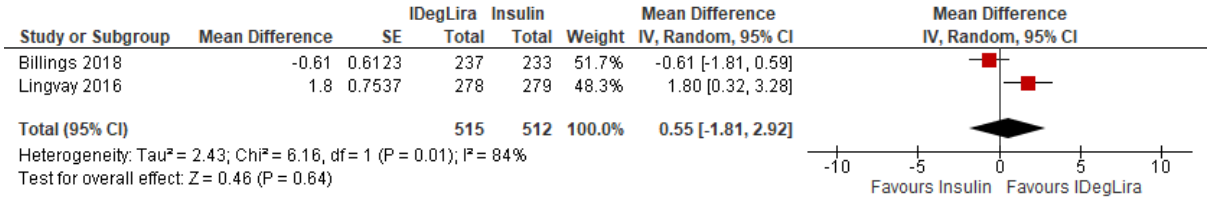


Figure 370: All-cause mortality at end of follow up

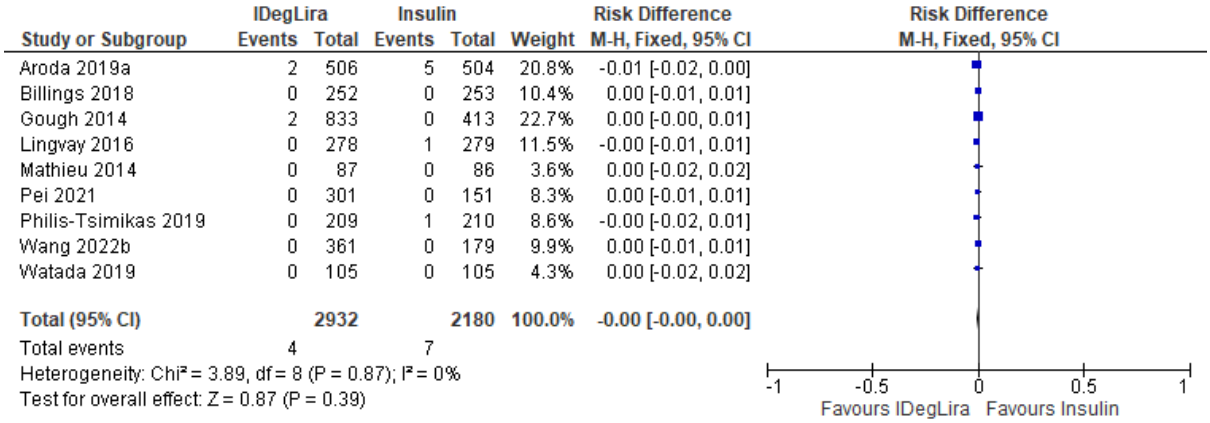


Figure 371: Cardiovascular mortality at end of follow up

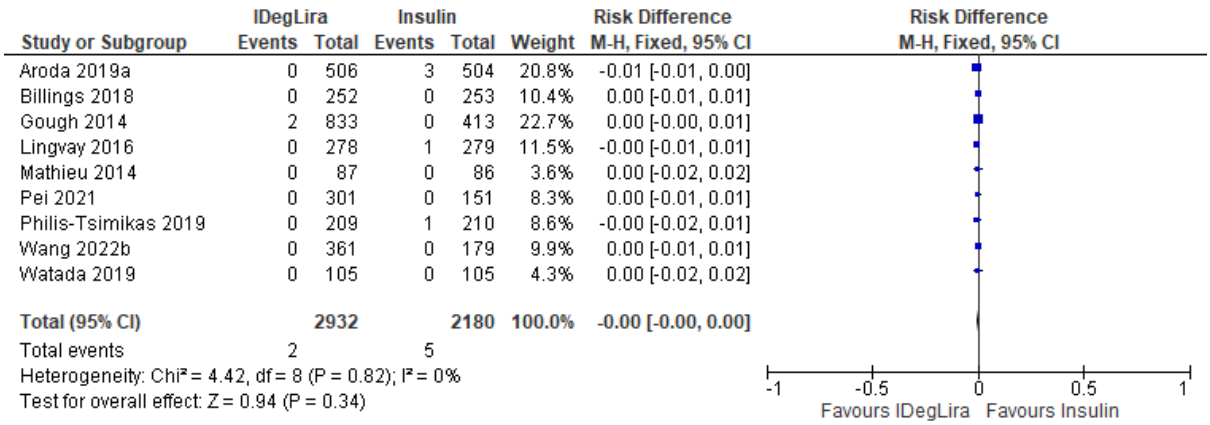


Figure 372: 3-point MACE at end of follow up

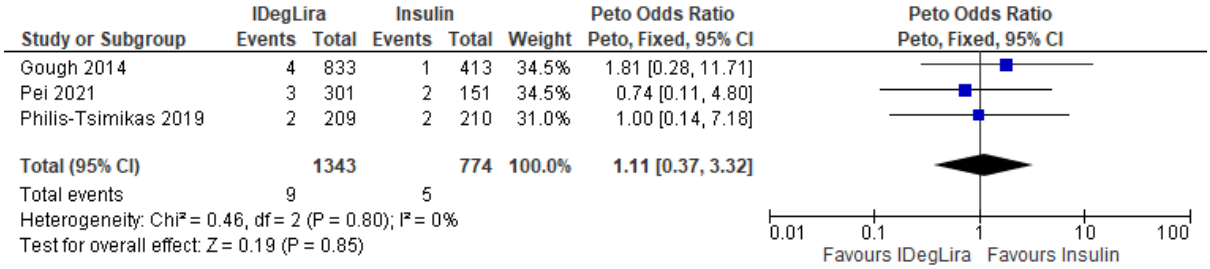


Figure 373: Non-fatal stroke at end of follow up

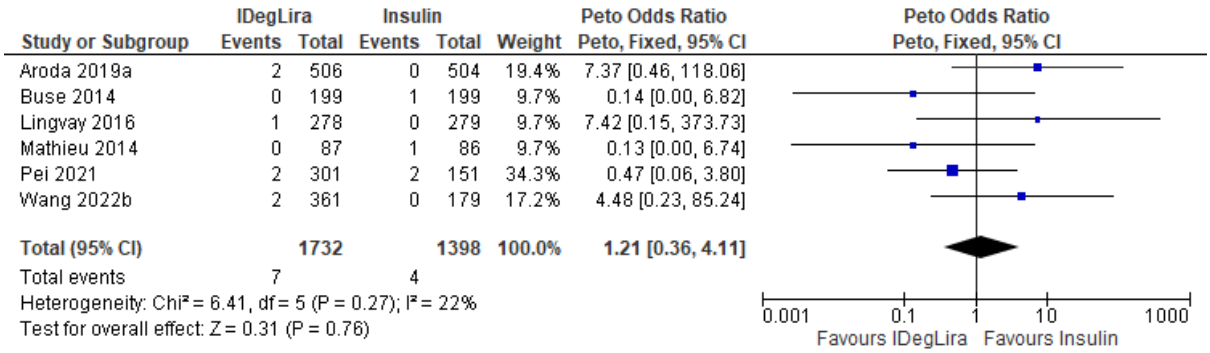


Figure 374: Non-fatal myocardial infarction at end of follow up

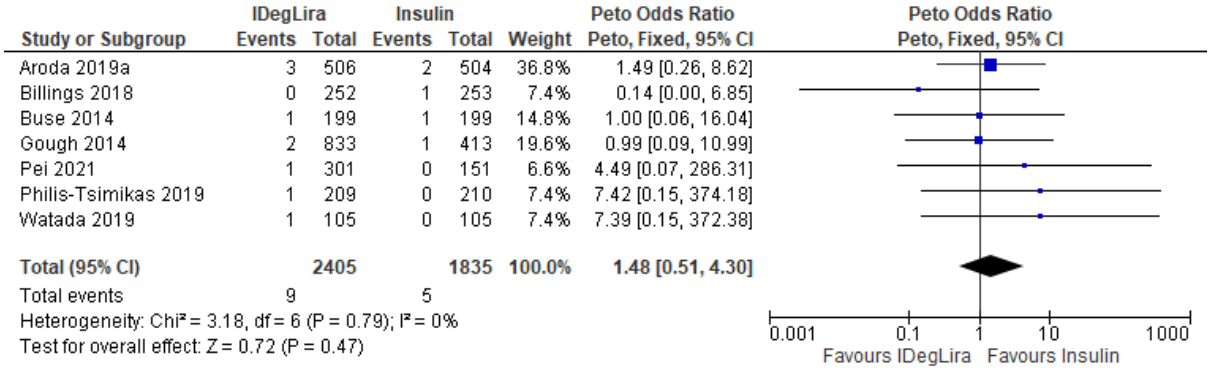


Figure 375: Unstable angina at end of follow up

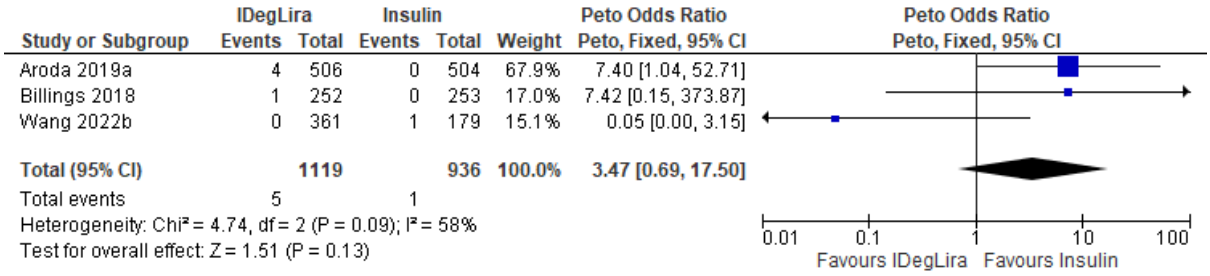


Figure 376: Hospitalisation for heart failure at end of follow up

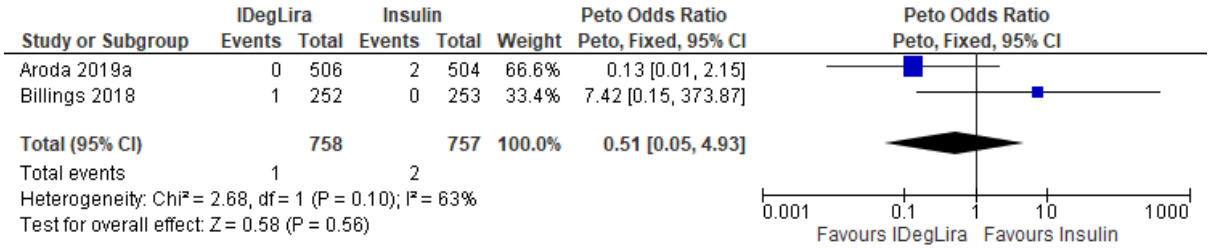


Figure 377: Cardiac arrhythmia at end of follow up

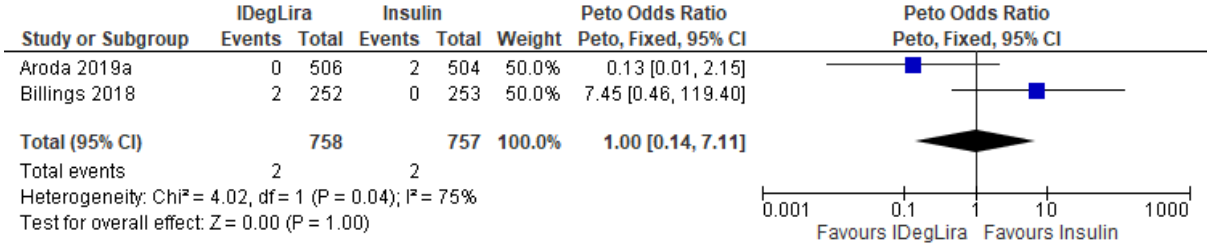


Figure 378: Hypoglycaemia episodes at end of follow up

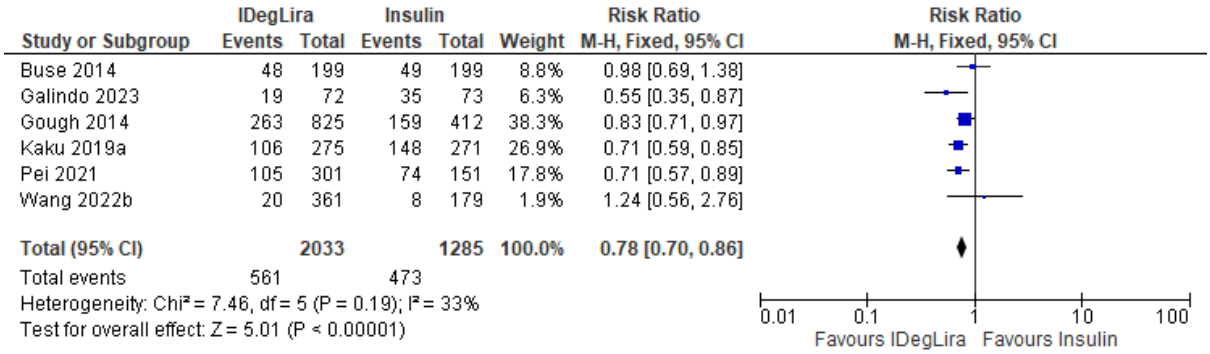


Figure 379: At night hypoglycaemic episodes

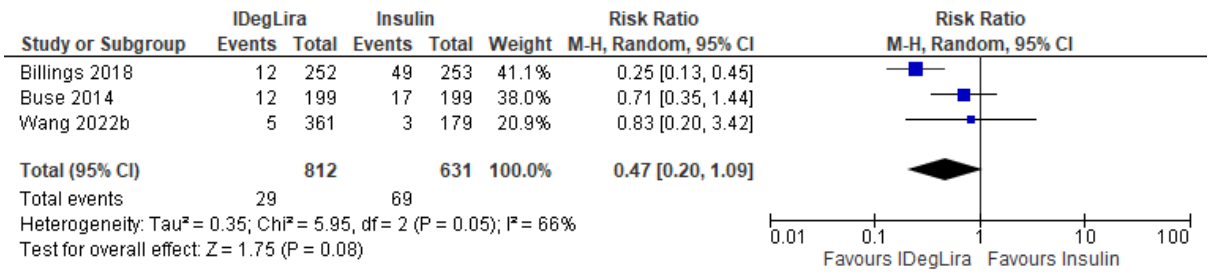


Figure 380: Severe hypoglycaemic episodes

Study or Subgroup	IDegLira Events	IDegLira Total	Insulin Events	Insulin Total	Weight	Risk Difference M-H, Fixed, 95% CI
Billings 2018	3	252	4	254	24.5%	-0.00 [-0.02, 0.02]
Buse 2014	1	199	0	199	19.3%	0.01 [-0.01, 0.02]
Galindo 2023	7	72	14	73	7.0%	-0.09 [-0.21, 0.02]
Gough 2014	3	151	2	413	21.4%	0.02 [-0.01, 0.04]
Mathieu 2014	0	87	0	86	8.4%	0.00 [-0.02, 0.02]
Pei 2021	2	301	0	151	19.5%	0.01 [-0.01, 0.02]
Total (95% CI)		**1062**		**1176**	**100.0%**	**-0.00 [-0.01, 0.01]**
Total events	16		20			

Heterogeneity: Chi² = 7.29, df = 5 (P = 0.20); I² = 31%
Test for overall effect: Z = 0.36 (P = 0.72)

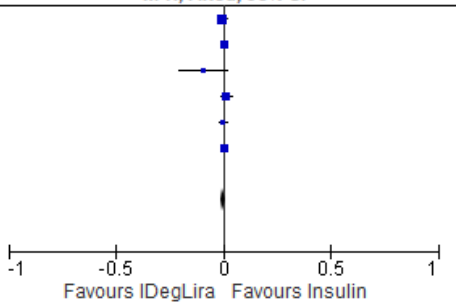
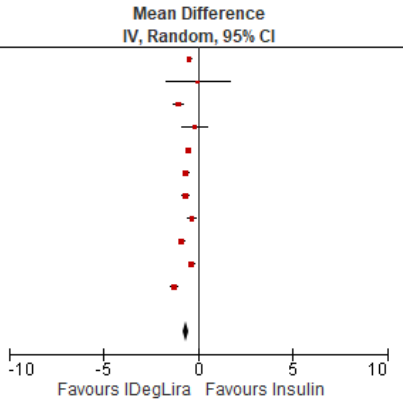


Figure 381: HbA1c change (%, lower values are better, change scores) at end of follow up

Study or Subgroup	Mean Difference	SE	IDegLira Total	Insulin Total	Weight	Mean Difference IV, Random, 95% CI
Aroda 2019a	-0.47	0.0561	506	506	11.3%	-0.47 [-0.58, -0.36]
Billings 2018	-0.02	0.8572	252	254	0.9%	-0.02 [-1.70, 1.66]
Buse 2014	-1.05	0.1276	199	199	9.4%	-1.05 [-1.30, -0.80]
Galindo 2023	-0.18	0.3417	72	73	4.1%	-0.18 [-0.85, 0.49]
Gough 2014	-0.5	0.0622	834	414	11.2%	-0.50 [-0.62, -0.38]
Kaku 2019a	-0.63	0.0612	275	271	11.2%	-0.63 [-0.75, -0.51]
Lingvay 2016	-0.68	0.0874	278	279	10.5%	-0.68 [-0.85, -0.51]
Mathieu 2014	-0.32	0.1071	88	89	10.0%	-0.32 [-0.53, -0.11]
Pei 2021	-0.9	0.0765	302	151	10.8%	-0.90 [-1.05, -0.75]
Philis-Tsimikas 2019	-0.36	0.0765	210	210	10.8%	-0.36 [-0.51, -0.21]
Watada 2019	-1.28	0.1122	105	105	9.8%	-1.28 [-1.50, -1.06]
Total (95% CI)			**3121**	**2551**	**100.0%**	**-0.65 [-0.82, -0.48]**

Heterogeneity: Tau² = 0.06; Chi² = 92.09, df = 10 (P < 0.00001); I² = 89%
Test for overall effect: Z = 7.64 (P < 0.00001)

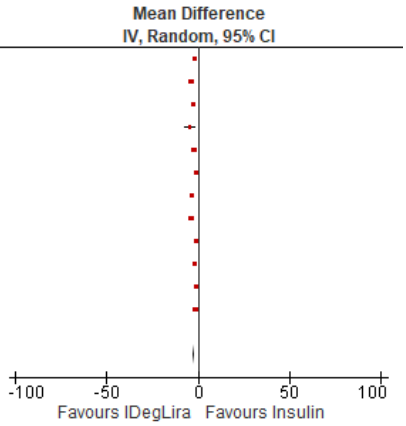


Note: Heterogeneity was not explained by sensitivity analysis, nor subgroup analysis by eGFR and NAFLD subgroups.

Figure 382: Weight change (kg, lower values are better, change scores) at end of follow up

Study or Subgroup	Mean Difference	SE	IDegLira Total	Insulin Total	Weight	Mean Difference IV, Random, 95% CI
Aroda 2019a	-1.7	0.4243	506	506	8.2%	-1.70 [-2.53, -0.87]
Billings 2018	-3.6	0.3061	506	506	9.0%	-3.60 [-4.20, -3.00]
Buse 2014	-2.5	0.3571	199	199	8.7%	-2.50 [-3.20, -1.80]
Galindo 2023	-4.6	1.2194	72	73	3.7%	-4.60 [-6.99, -2.21]
Gough 2014	-2.1	0.2309	834	414	9.4%	-2.10 [-2.55, -1.65]
Kaku 2019a	-1.19	0.3112	275	271	8.9%	-1.19 [-1.80, -0.58]
Lingvay 2016	-3.2	0.2877	278	279	9.1%	-3.20 [-3.76, -2.64]
Mathieu 2014	-3.7	0.4841	88	89	7.8%	-3.70 [-4.65, -2.75]
Pei 2021	-1.05	0.2806	302	151	9.1%	-1.05 [-1.60, -0.50]
Philis-Tsimikas 2019	-1.92	0.3674	210	210	8.6%	-1.92 [-2.64, -1.20]
Wang 2022b	-1.08	0.2398	361	179	9.3%	-1.08 [-1.55, -0.61]
Watada 2019	-1.41	0.4337	105	105	8.2%	-1.41 [-2.26, -0.56]
Total (95% CI)			**3736**	**2982**	**100.0%**	**-2.21 [-2.79, -1.63]**

Heterogeneity: Tau² = 0.87; Chi² = 98.92, df = 11 (P < 0.00001); I² = 89%
Test for overall effect: Z = 7.50 (P < 0.00001)



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

K.1.8.3 Adding insulin degludec/Liraglutide compared to adding liraglutide

Figure 383: All-cause mortality at end of follow up

Study or Subgroup	IDegLira Events	IDegLira Total	Liraglutide Events	Liraglutide Total	Weight	Risk Difference M-H, Fixed, 95% CI
Gough 2014	2	833	0	414	69.7%	0.00 [-0.00, 0.01]
Wang 2022B	0	361	0	180	30.3%	0.00 [-0.01, 0.01]
Total (95% CI)		**1194**		**594**	**100.0%**	**0.00 [-0.00, 0.01]**
Total events	2		0			

Heterogeneity: Chi² = 0.23, df = 1 (P = 0.63); I² = 0%
Test for overall effect: Z = 0.75 (P = 0.45)

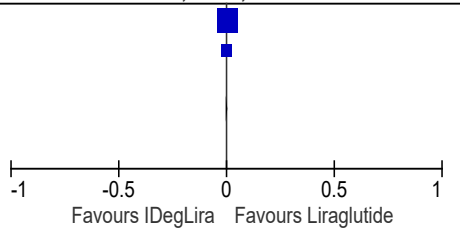


Figure 384: Hypoglycaemia episodes at end of follow up

Study or Subgroup	IDegLira Events	IDegLira Total	Liraglutide Events	Liraglutide Total	Weight	Risk Ratio M-H, Random, 95% CI
Gough 2014	263	825	28	412	44.9%	4.69 [3.24, 6.80]
Kaku 2019A	106	275	6	273	37.4%	17.54 [7.84, 39.24]
Wang 2022B	20	361	1	180	17.7%	9.97 [1.35, 73.71]
Total (95% CI)		**1461**		**865**	**100.0%**	**8.77 [3.03, 25.43]**
Total events	389		35			

Heterogeneity: Tau² = 0.62; Chi² = 9.05, df = 2 (P = 0.01); I² = 78%
Test for overall effect: Z = 4.00 (P < 0.0001)

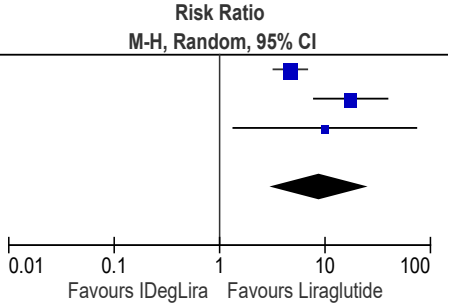


Figure 385: HbA1c change (%, lower values are better, mean difference) at end of follow up

Study or Subgroup	Mean Difference	SE	IDegLira Total	Liraglutide Total	Weight	Mean Difference IV, Fixed, 95% CI
Gough 2014	-0.6	0.0661	834	415	46.2%	-0.60 [-0.73, -0.47]
Kaku 2019A	-0.48	0.0612	361	273	53.8%	-0.48 [-0.60, -0.36]
Total (95% CI)			**1195**	**688**	**100.0%**	**-0.54 [-0.62, -0.45]**

Heterogeneity: Chi² = 1.77, df = 1 (P = 0.18); I² = 44%
Test for overall effect: Z = 11.92 (P < 0.00001)

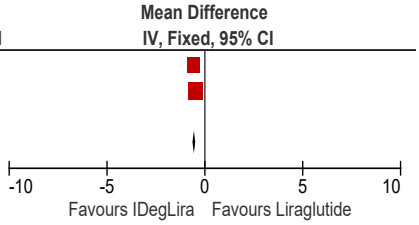
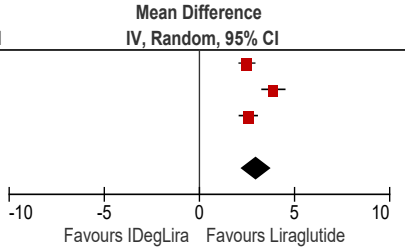


Figure 386: Weight change (kg, lower values are better, mean difference) at end of follow up

Study or Subgroup	Mean Difference	SE	IDegLira Total	Liraglutide Total	Weight	Mean Difference IV, Random, 95% CI
Gough 2014	2.5	0.2104	834	414	34.8%	2.50 [2.09, 2.91]
Kaku 2019A	3.89	0.3061	275	273	31.4%	3.89 [3.29, 4.49]
Wang 2022B	2.57	0.2398	361	180	33.8%	2.57 [2.10, 3.04]
Total (95% CI)			**1470**	**867**	**100.0%**	**2.96 [2.17, 3.75]**

Heterogeneity: Tau² = 0.42; Chi² = 15.62, df = 2 (P = 0.0004); I² = 87%
Test for overall effect: Z = 7.36 (P < 0.00001)



K.1.8.4 Adding insulin glargine/Lixisenatide compared to adding insulin

Figure 387: All-cause mortality at end of follow up

Study or Subgroup	Insulin glargine/Lixisenatide Events	Total	Insulin Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Aroda 2016B	1	366	2	365	17.6%	-0.00 [-0.01, 0.01]
Kaneto 2020	0	255	0	257	12.4%	0.00 [-0.01, 0.01]
Rosenstock 2016B	2	469	3	467	22.6%	-0.00 [-0.01, 0.01]
Rosenstock 2016C	0	161	0	162	7.8%	0.00 [-0.01, 0.01]
Terauchi 2020	1	260	0	261	12.6%	0.00 [-0.01, 0.01]
Yang 2022	0	348	0	349	16.8%	0.00 [-0.01, 0.01]
Yuan 2022	0	211	0	212	10.2%	0.00 [-0.01, 0.01]
Total (95% CI)		**2070**		**2073**	**100.0%**	**-0.00 [-0.00, 0.00]**
Total events	4		5			

Heterogeneity: Chi² = 1.06, df = 6 (P = 0.98); I² = 0%
Test for overall effect: Z = 0.27 (P = 0.79)

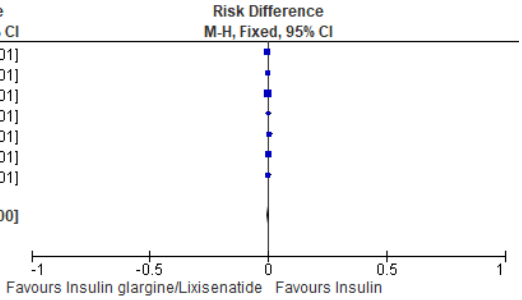


Figure 388: Cardiovascular mortality at end of follow up

Study or Subgroup	Insulin glargine/Lixisenatide Events	Total	Insulin Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Aroda 2016B	0	366	1	365	17.6%	-0.00 [-0.01, 0.00]
Kaneto 2020	48	255	43	257	12.4%	0.02 [-0.05, 0.09]
Rosenstock 2016B	1	469	2	467	22.6%	-0.00 [-0.01, 0.01]
Rosenstock 2016C	0	161	0	162	7.8%	0.00 [-0.01, 0.01]
Terauchi 2020	1	260	0	261	12.6%	0.00 [-0.01, 0.01]
Yang 2022	0	348	0	349	16.8%	0.00 [-0.01, 0.01]
Yuan 2022	0	211	0	212	10.2%	0.00 [-0.01, 0.01]
Total (95% CI)		**2070**		**2073**	**100.0%**	**0.00 [-0.01, 0.01]**
Total events	50		46			

Heterogeneity: Chi² = 4.17, df = 6 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.47 (P = 0.64)

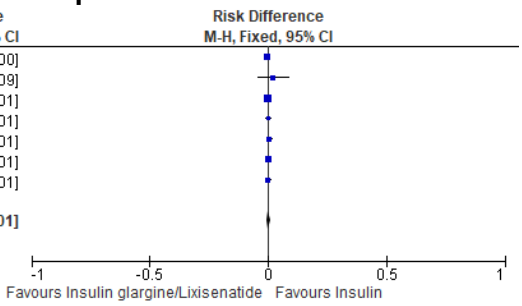


Figure 389: Hypoglycaemia episodes at end of follow up

Study or Subgroup	Insulin glargine/Lixisenatide Events	Total	Insulin Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Aroda 2016B	146	365	155	365	17.6%	-0.02 [-0.10, 0.05]
Kaneto 2020	0	255	0	257	12.4%	0.00 [-0.01, 0.01]
Rosenstock 2016B	120	469	110	467	22.6%	0.02 [-0.03, 0.08]
Rosenstock 2016C	35	161	37	162	7.8%	-0.01 [-0.10, 0.08]
Terauchi 2020	1	260	0	261	12.6%	0.00 [-0.01, 0.01]
Yang 2022	0	348	0	349	16.8%	0.00 [-0.01, 0.01]
Yuan 2022	97	211	95	212	10.2%	0.01 [-0.08, 0.11]
Total (95% CI)		**2069**		**2073**	**100.0%**	**0.00 [-0.02, 0.02]**
Total events	399		397			

Heterogeneity: Chi² = 1.56, df = 6 (P = 0.96); I² = 0%
Test for overall effect: Z = 0.10 (P = 0.92)

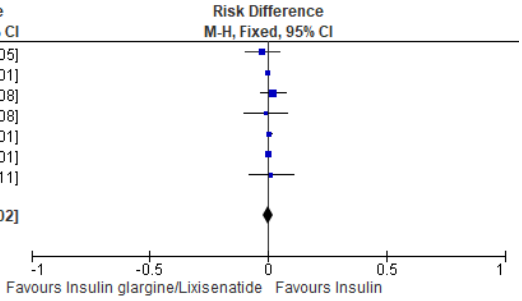


Figure 390: Severe hypoglycaemic episodes at end of follow up

Study or Subgroup	Insulin glargine/Lixisenatide Events	Total	Insulin Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Aroda 2016B	4	365	1	365	17.6%	0.01 [-0.00, 0.02]
Kaneto 2020	0	255	1	257	12.4%	-0.00 [-0.01, 0.01]
Rosenstock 2016B	0	469	1	467	22.6%	-0.00 [-0.01, 0.00]
Rosenstock 2016C	0	161	0	162	7.8%	0.00 [-0.01, 0.01]
Terauchi 2020	0	260	0	261	12.6%	0.00 [-0.01, 0.01]
Yang 2022	1	348	1	349	16.8%	0.00 [-0.01, 0.01]
Yuan 2022	2	211	2	212	10.2%	0.00 [-0.02, 0.02]
Total (95% CI)		**2069**		**2073**	**100.0%**	**0.00 [-0.00, 0.00]**
Total events	7		6			

Heterogeneity: Chi² = 3.05, df = 6 (P = 0.80); I² = 0%
Test for overall effect: Z = 0.25 (P = 0.81)

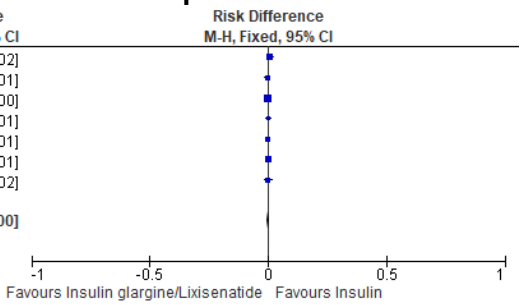
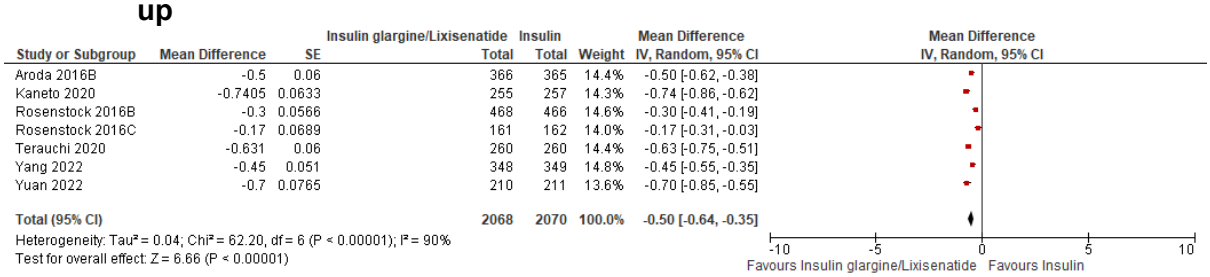
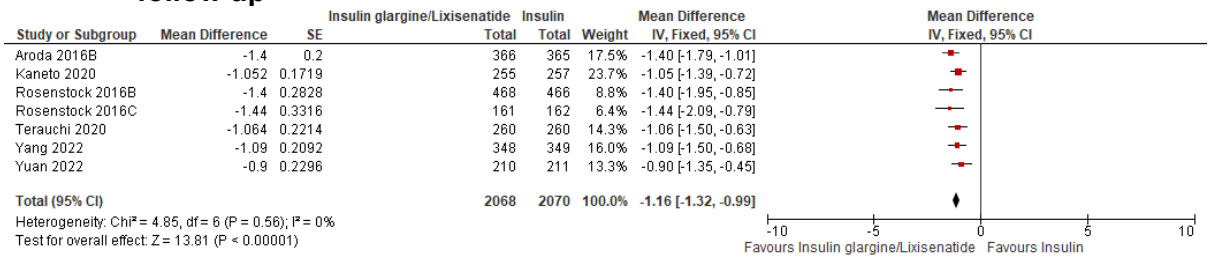


Figure 391: HbA1c change (%, lower values are better, change scores) at end of follow up



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

Figure 392: Weight change (kg, lower values are better, change scores) at end of follow up



K.1.8.5 Adding insulin glargine/Lixisenatide compared to adding lixisenatide

Figure 393: All-cause mortality at end of follow up

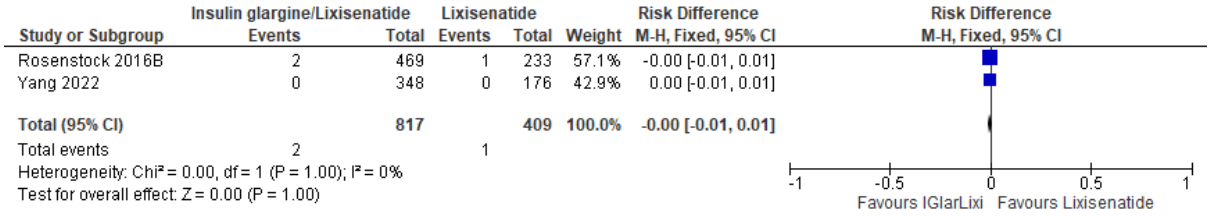


Figure 394: Cardiovascular mortality at end of follow up

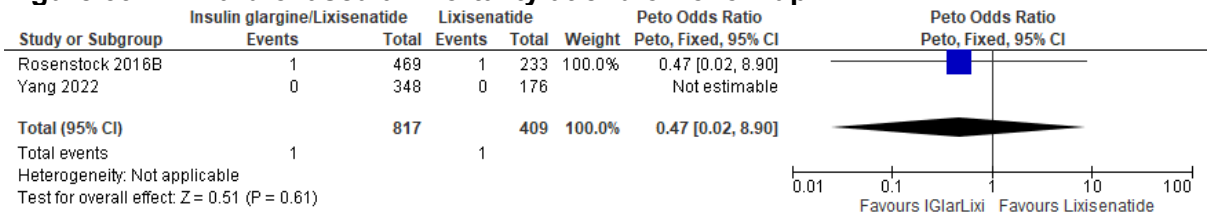


Figure 395: Hypoglycaemia episodes at end of follow up

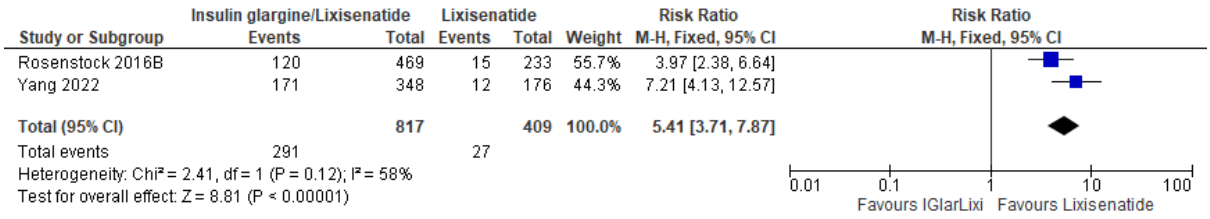


Figure 396: Severe hypoglycaemic episodes at end of follow up

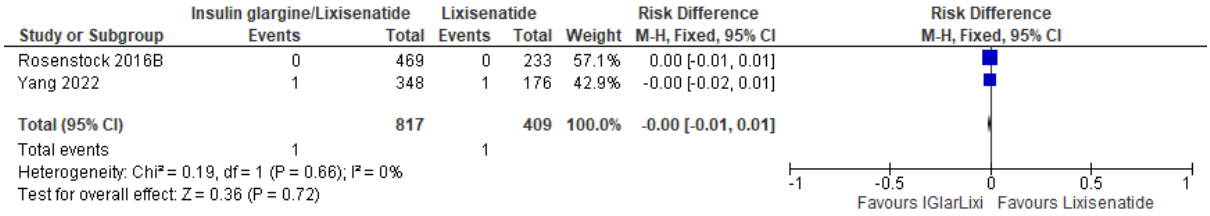


Figure 397: HbA1c change (%, lower values are better, change scores) at end of follow up

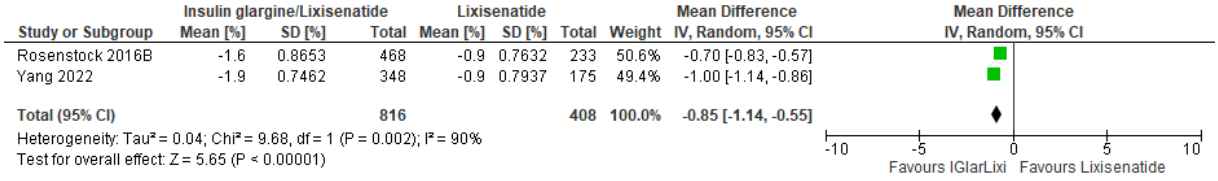
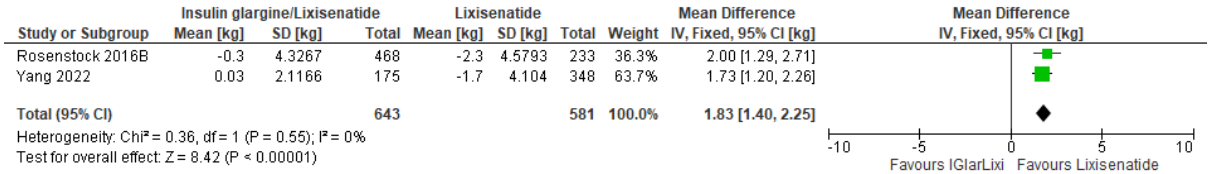


Figure 398: Weight change (kg, lower values are better, change scores) at end of follow up



K.1.9 Combinations

K.1.9.1 Adding dapagliflozin + exenatide compared to adding dapagliflozin

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

K.1.9.2 Adding dapagliflozin + exenatide compared to adding exenatide

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

K.1.9.3 Adding dapagliflozin + saxagliptin compared to adding dapagliflozin

Figure 399: All-cause mortality at end of follow up

Study or Subgroup	Dapagliflozin + Saxagliptin Events	Total	Dapagliflozin Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Rosenstock 2015A	0	179	0	179	37.9%	0.00 [-0.01, 0.01]
Rosenstock 2019D	1	293	2	293	62.1%	-0.00 [-0.01, 0.01]
Total (95% CI)		**472**		**472**	**100.0%**	**-0.00 [-0.01, 0.01]**
Total events	1		2			

Heterogeneity: Chi² = 0.19, df = 1 (P = 0.66); I² = 0%
Test for overall effect: Z = 0.50 (P = 0.62)

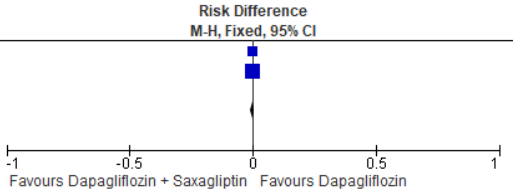


Figure 400: Cardiovascular mortality at end of follow up

Study or Subgroup	Dapagliflozin + Saxagliptin Events	Total	Dapagliflozin Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Rosenstock 2015A	0	179	0	179	37.9%	0.00 [-0.01, 0.01]
Rosenstock 2019D	0	293	2	293	62.1%	-0.01 [-0.02, 0.00]
Total (95% CI)		**472**		**472**	**100.0%**	**-0.00 [-0.01, 0.00]**
Total events	0		2			

Heterogeneity: Chi² = 0.78, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 1.00 (P = 0.32)

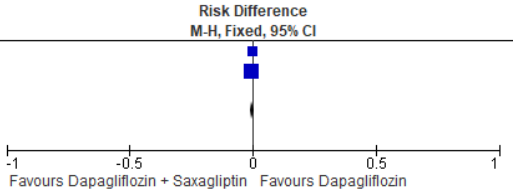


Figure 401: Hypoglycaemia episodes at end of follow up

Study or Subgroup	Dapagliflozin + Saxagliptin Events	Total	Dapagliflozin Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Muller-Wieland 2018	1	312	0	311	8.4%	7.37 [0.15, 371.20]
Rosenstock 2015A	2	179	2	179	33.3%	1.00 [0.14, 7.16]
Rosenstock 2019D	6	293	1	293	58.2%	4.23 [0.96, 18.78]
Total (95% CI)		**784**		**783**	**100.0%**	**2.74 [0.88, 8.54]**
Total events	9		3			

Heterogeneity: Chi² = 1.58, df = 2 (P = 0.45); I² = 0%
Test for overall effect: Z = 1.74 (P = 0.08)

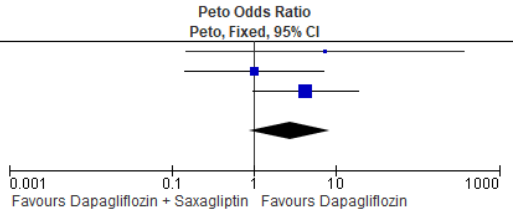


Figure 402: Severe hypoglycaemic episodes at end of follow up

Study or Subgroup	Dapagliflozin + Saxagliptin Events	Total	Dapagliflozin Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Muller-Wieland 2018	0	312	0	311	39.8%	0.00 [-0.01, 0.01]
Rosenstock 2015A	0	179	0	179	22.8%	0.00 [-0.01, 0.01]
Rosenstock 2019D	1	293	1	293	37.4%	0.00 [-0.01, 0.01]
Total (95% CI)		**784**		**783**	**100.0%**	**0.00 [-0.00, 0.00]**
Total events	1		1			

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

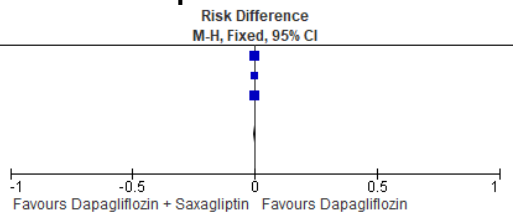


Figure 403: HbA1c change (%, lower values are better, change scores) at end of follow up

Study or Subgroup	Dapagliflozin + Saxagliptin Mean [%]	SD [%]	Total	Dapagliflozin Mean [%]	SD [%]	Total	Weight	Mean Difference IV, Fixed, 95% CI [%]
Muller-Wieland 2018	-1.2	0.88	311	-0.82	0.88	309	47.7%	-0.38 [-0.52, -0.24]
Rosenstock 2015A	-1.465	0.9864	158	-1.197	0.9764	151	19.1%	-0.27 [-0.49, -0.05]
Rosenstock 2019D	-1.03	1.0111	284	-0.63	1.004	280	33.1%	-0.40 [-0.57, -0.23]
Total (95% CI)			**753**			**740**	**100.0%**	**-0.37 [-0.46, -0.27]**

Heterogeneity: Chi² = 0.97, df = 2 (P = 0.62); I² = 0%
Test for overall effect: Z = 7.48 (P < 0.00001)

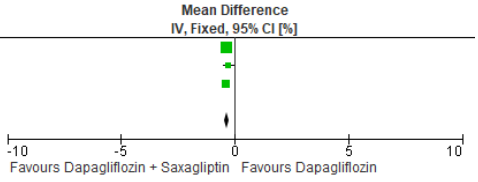
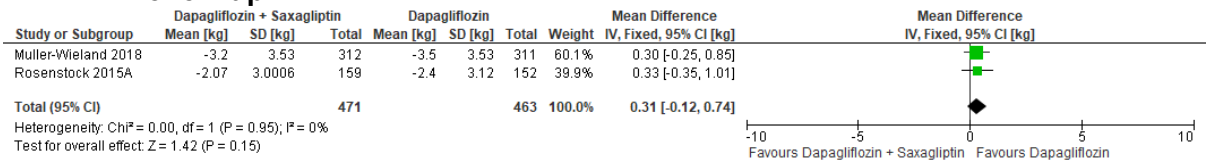


Figure 404: Weight change (kg, lower values are better, change scores) at end of follow up



K.1.9.4 Adding dapagliflozin + saxagliptin compared to adding glimepiride

Figure 405: Hospitalisation for heart failure at end of follow up

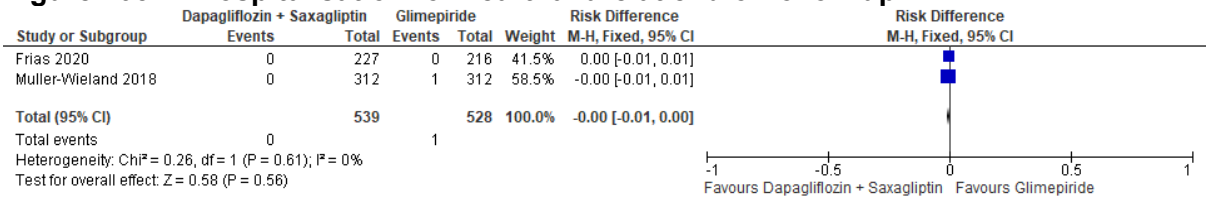


Figure 406: Hypoglycaemia episodes at end of follow up

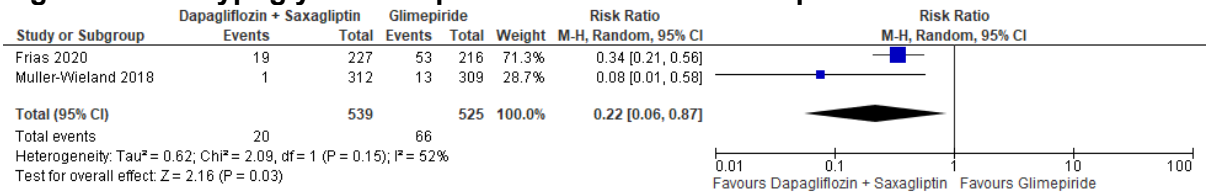


Figure 407: Severe hypoglycaemic episodes at end of follow up

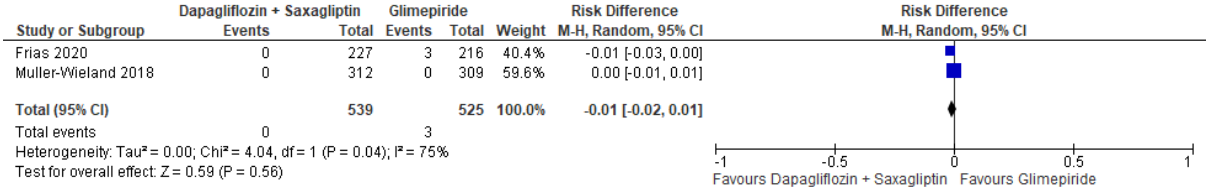


Figure 408: HbA1c change (%, lower values are better, change scores) at end of follow up

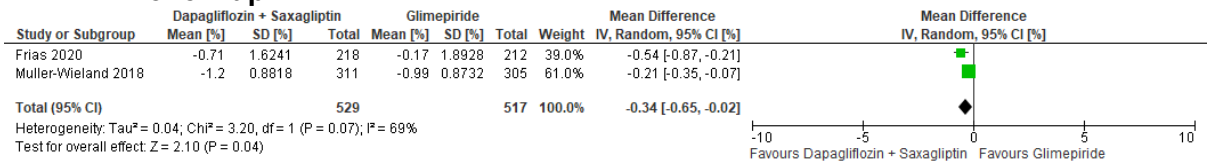
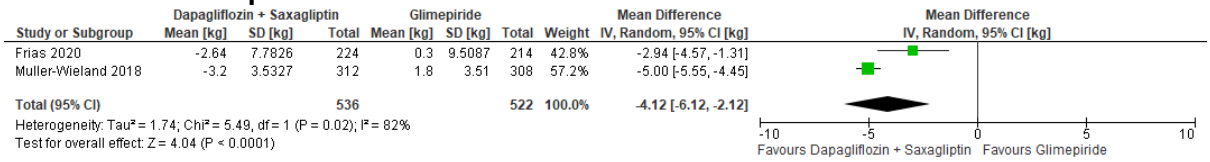


Figure 409: Weight change (kg, lower values are better, change scores) at end of follow up



K.1.9.5 Adding dapagliflozin + saxagliptin compared to adding insulin

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

K.1.9.6 Adding dapagliflozin + saxagliptin compared to adding saxagliptin

Figure 410: All-cause mortality at end of follow up

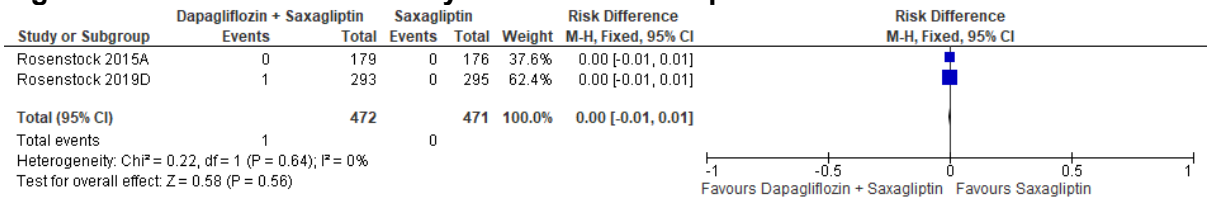


Figure 411: Cardiovascular mortality at end of follow up

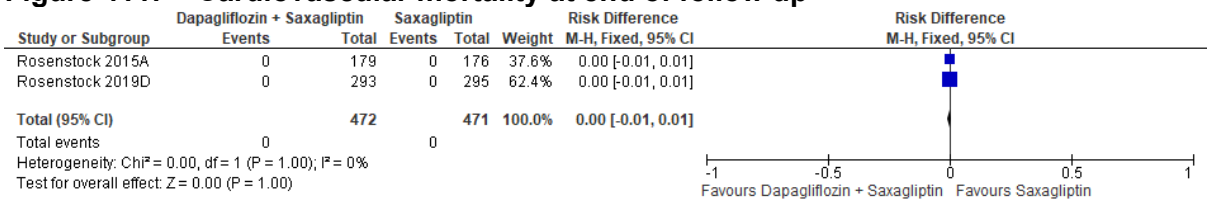


Figure 412: Hypoglycaemia episodes at end of follow up

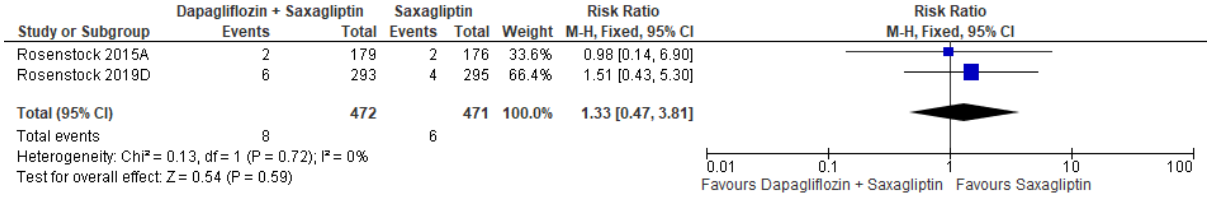


Figure 413: Severe hypoglycaemic episodes at end of follow up

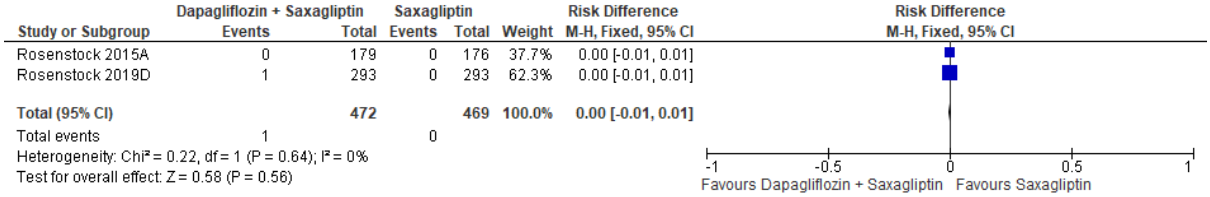


Figure 414: HbA1c change (%, lower values are better, change scores) at end of follow up

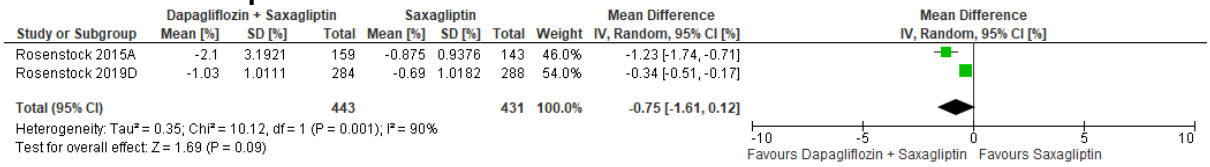
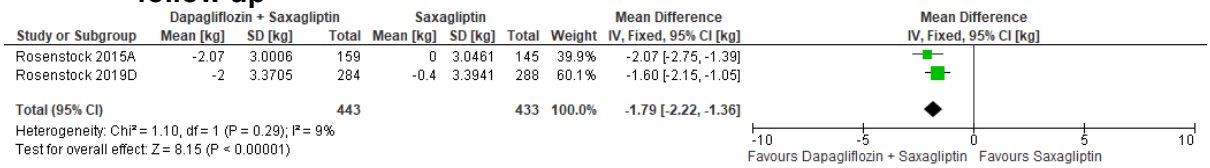


Figure 415: Weight change (kg, lower values are better, change scores) at end of follow up



K.1.9.7 Adding dapagliflozin + saxagliptin compared to adding sitagliptin

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

K.1.9.8 Adding empagliflozin + liraglutide compared to adding empagliflozin

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

K.1.9.9 Adding empagliflozin + liraglutide compared to adding insulin

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

K.1.9.10 Adding empagliflozin + liraglutide compared to adding liraglutide

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

K.1.9.11 Adding ertugliflozin + sitagliptin compared to adding ertugliflozin

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

K.1.9.12 Adding ertugliflozin + sitagliptin compared to adding sitagliptin

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

K.1.9.13 Adding glimepiride + metformin compared to adding glimepiride

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

K.1.9.14 Adding glimepiride + metformin compared to adding metformin

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

K.1.9.15 Adding glimepiride + metformin slow release compared to adding glimepiride + metformin standard release

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

K.1.9.16 Adding liraglutide + metformin compared to adding metformin

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

K.1.9.17 Adding pioglitazone + alogliptin compared to adding pioglitazone

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

K.1.9.18 Adding pioglitazone + exenatide compared to adding insulin

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

K.1.9.19 Adding pioglitazone + exenatide compared to adding pioglitazone

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

K.1.9.20 Adding pioglitazone + metformin compared to adding metformin

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

K.1.9.21 Adding pioglitazone + metformin compared to adding pioglitazone

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

K.2 Switching

K.2.1 Metformin

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

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

K.2.2 DPP-4 inhibitors

K.2.2.1 Switching to sitagliptin compared to switching to placebo

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

K.2.2.2 Switching to vildagliptin compared to switching to alogliptin

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

K.2.3 GLP-1 receptor agonist

K.2.3.1 Switching to liraglutide compared to staying on sitagliptin

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

K.2.3.2 Switching to semaglutide compared to switching to dulaglutide

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

K.2.3.3 Switching to semaglutide compared to staying on sitagliptin

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

K.2.4 SGLT2 inhibitors

K.2.4.1 Switching to glimepiride compared to switching to liraglutide

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

K.2.4.2 Switching to canagliflozin compared to switching to liraglutide

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

K.2.1 Thiazolidinediones

K.2.1.1 Staying on pioglitazone compared to switching to dapagliflozin

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

K.2.1.2 Switching to pioglitazone compared to switching to glimepiride

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

K.2.2 Combinations

K.2.2.1 Switching to fixed-dose combination glimepiride/metformin slow release compared to staying on fixed-dose combination glimepiride/metformin standard release

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