National Institute for Health and Care Excellence

Draft for consultation

Type 2 diabetes in adults: management (medicines update)

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

NICE guideline GID-NG10336

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

August 2025

Draft for Consultation

This evidence review was developed by NICE



Disclaimer

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

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

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 All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

© NICE 2025. All rights reserved. Subject to Notice of Rights.

ISBN:

Contents

Appendices		5
	Forest plots	
Appendix F	GRADE tables	73
Appendix G	Economic evidence study selection	264
Appendix H	Economic evidence tables	265
Appendix I	Health economic model	271

Appendices

2 Appendix E Forest plots

- 3 E.1 Model 5: People with type 2 diabetes at high risk of
- 4 cardiovascular disease (no other comorbidities)
- 5 E.1.1 Biguanides

E.1.161 Metformin hydrochloride slow release compared to metformin hydrochloride standard release

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

	Metformi	n slow rele	ease	Metform	in standa	ard		Mean Difference			Mean Diff	erence		
Study or Subgroup	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV, Fixed, 95% CI [%]			IV, Fixed, 9	5% CI [%	6]	
Aggarwal 2018	-0.93	0.819	283	-0.96	0.823	285	80.2%	0.03 [-0.11, 0.17]						
Schwartz 2006	7.51	1.605	532	7.65	1.583	174	19.8%	-0.14 [-0.41, 0.13]			†			
Total (95% CI)			815			459	100.0%	-0.00 [-0.12, 0.12]						
Heterogeneity: Chi² =	1.20, df = 1 (F	P = 0.27); I	² = 17%						10		-		5	10
Test for overall effect:	Z = 0.06 (P =	0.95)							-10	-5 Favours	0 MET slow F	avours I	5 MET stand	10 dard

E.1.1122 Metformin compared to placebo

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

	Metfori	min	Place	bo		Risk Difference		Risk	Differe	nce	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	1	М-Н, І	ixed, 9	5% CI	
DeFronzo 1995	0	143	0	146	14.6%	0.00 [-0.01, 0.01]			•		
Goldstein 2007	0	364	1	176	24.1%	-0.01 [-0.02, 0.01]			•		
Haak 2012	1	291	0	72	11.7%	0.00 [-0.02, 0.02]			•		
Horton 2000	1	178	0	172	17.7%	0.01 [-0.01, 0.02]			•		
Ji 2016a	0	250	0	126	17.0%	0.00 [-0.01, 0.01]			•		
Pratley 2014	0	225	0	109	14.9%	0.00 [-0.01, 0.01]			1		
Total (95% CI)		1451		801	100.0%	0.00 [-0.01, 0.01]					
Total events	2		1								
Heterogeneity: Chi ² = ²	1.24, df =	5 (P = 0).94); I² =	0%			<u> </u>		$\overrightarrow{-}$	0.5	
Test for overall effect:	Z = 0.01 (P = 0.9	9)				-1	-0.5 Favours metform	0 in Fav	0.5 ours placebo	1

14 15

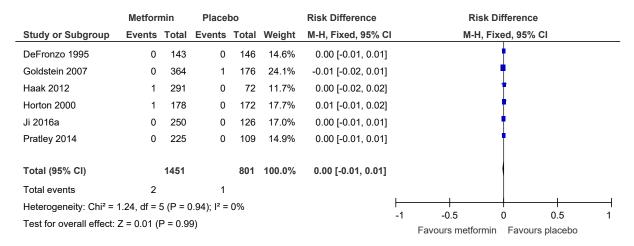
2

5 6

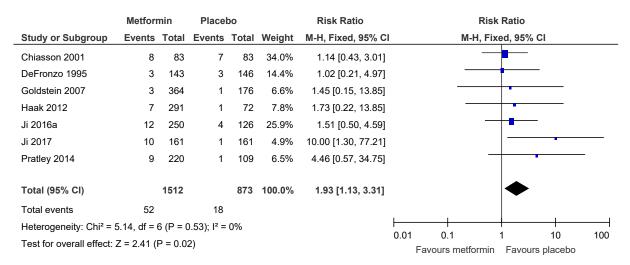
8 9

10

Figure 3: Cardiovascular mortality at end of follow-up



4 Figure 4: Hypoglycaemia episodes at end of follow-up



7 Figure 5: Severe hypoglycaemia at end of follow-up

	Metfori	nin	Place	bo		Risk Difference		Risk D	ifference		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fix	ed, 95% C	CI	
Haak 2012	1	291	0	72	19.1%	0.00 [-0.02, 0.02]			•		
Horton 2000	0	178	0	172	29.0%	0.00 [-0.01, 0.01]			•		
Ji 2016a	0	250	0	126	27.8%	0.00 [-0.01, 0.01]			•		
Pratley 2014	0	220	0	109	24.1%	0.00 [-0.01, 0.01]			•		
Total (95% CI)		939		479	100.0%	0.00 [-0.01, 0.01]					
Total events	1		0								
Heterogeneity: Chi ² = 0	0.10, df =	3 (P = 0).99); I² =	0%			<u> </u>	 	! 		$\overline{}$
Test for overall effect:	Z = 0.18 (P = 0.8	6)				-1	-0.5 Favours metformin	0 Favours	0.5 placebo	1

2

3 4

5

6

7

8

9

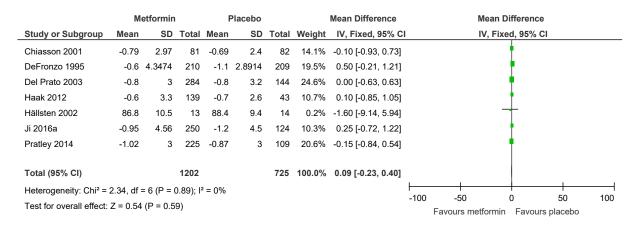
10

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

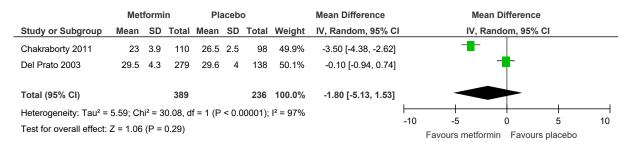
		N	/letformin	Placebo		Mean Difference		Mean	Difference		
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI		IV, Ran	dom, 95% C	ı	
Chakraborty 2011	-1.9	0.1675	110	98	8.0%	-1.90 [-2.23, -1.57]		-			
Chiasson 2001	-1.23	0.17	81	82	8.0%	-1.23 [-1.56, -0.90]		-			
DeFronzo 1995	-1.8	0.1414	143	146	8.3%	-1.80 [-2.08, -1.52]		•			
Del Prato 2003	-1.14	0.1855	250	127	7.8%	-1.14 [-1.50, -0.78]		•	•		
Goldstein 2007	-1.14	0.103	355	165	8.7%	-1.14 [-1.34, -0.94]					
Grant 1996	-1.66	0.2317	52	23	7.2%	-1.66 [-2.11, -1.21]		-			
Guo 2014	-1.9	0.1339	29	29	8.4%	-1.90 [-2.16, -1.64]		•			
Haak 2012	-0.95	0.1225	279	65	8.5%	-0.95 [-1.19, -0.71]		•	•		
Hällsten 2002	0.1	0.2216	13	14	7.4%	0.10 [-0.33, 0.53]			+		
Ji 2016a	-0.84	0.143	233	127	8.3%	-0.84 [-1.12, -0.56]		7	-		
Ji 2017	-1	0.2285	161	161	7.3%	-1.00 [-1.45, -0.55]		-	-		
Pratley 2014	-1.04	0.1105	211	102	8.6%	-1.04 [-1.26, -0.82]		•			
Wolever 2000	-1.2	0.6	62	45	3.3%	-1.20 [-2.38, -0.02]					
Total (95% CI)			1979	1184	100.0%	-1.22 [-1.48, -0.95]		♦			
Heterogeneity: Tau ² =	0.20; Chi ² = 114.38	, df = 12 (I	P < 0.0000	1); I² = 90%				- 	+		
Test for overall effect:	Z = 8.88 (P < 0.000	01)					-10	-5	0	5	10
	•	,						Favours metforming	Favours	piacebo	

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

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



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



E.1.113 Metformin compared to insulin

3

7 8

9

10

11 12

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

4 E.1.2 DPP-4 inhibitors

E.1.251 Alogliptin compared to metformin

6 Figure 9: Hypoglycaemia episodes at end of follow-up

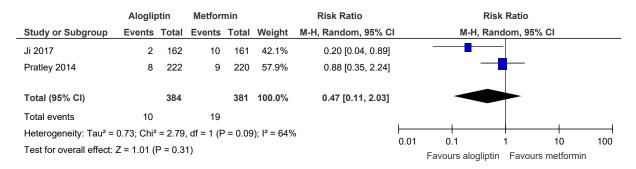
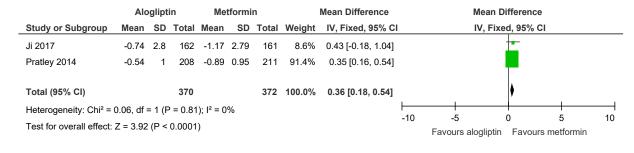
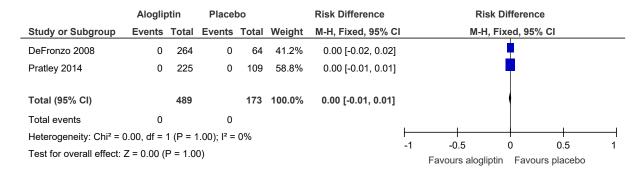


Figure 10: HbA1c change (%, lower values are better, change scores) at end of follow-up

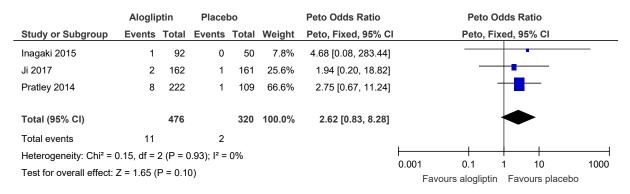


E.1.232 Alogliptin compared to placebo

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



1 Figure 12: Hypoglycaemia episodes at end of follow-up



3

2

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

	Alogli	otin	Placel	bo		Risk Difference		Ri	sk Differen	ce	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H	, Fixed, 95	% CI	
DeFronzo 2008	0	264	0	64	41.3%	0.00 [-0.02, 0.02]			•		
Pratley 2014	0	222	0	109	58.7%	0.00 [-0.01, 0.01]					
Total (95% CI)		486		173	100.0%	0.00 [-0.01, 0.01]					
Total events	0		0								
Heterogeneity: Chi ² =	0.00, df =	1 (P = 1	1.00); I ² =	0%			├	-0.5	 0	0.5	
Test for overall effect:	Z = 0.00 (P = 1.0	0)				•	-u.ɔ Favours alogl		urs placebo	1

6

7

8

5

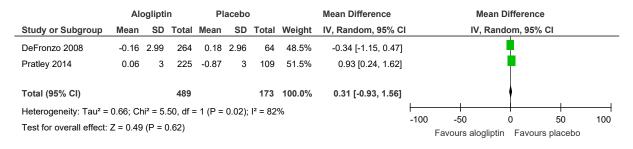
Figure 14: HbA1c change (%, lower values are better, change scores) at end of follow-up

	Ale	oglipti	n	PI	acebo	•		Mean Difference		Mear	Diffe	rence		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, F	ixed, 9	5% CI		
Inagaki 2015	-0.46	0.63	92	0.24	0.52	50	51.3%	-0.70 [-0.89, -0.51]						
Ji 2017	-0.74	2.8	162	-0.17	0.79	161	9.5%	-0.57 [-1.02, -0.12]			-			
Pratley 2014	-0.54	1	208	0.15	0.9	102	39.1%	-0.69 [-0.91, -0.47]			•			
Total (95% CI)			462			313	100.0%	-0.68 [-0.82, -0.55]			•			
Heterogeneity: Chi ² =	0.28, df	= 2 (P	= 0.87)	; I ² = 0%	6				10	<u> </u>	+	<u> </u>		
Test for overall effect:	Z = 9.68	B (P < 0	0.00001	1)					-10	-5 Favours aloglip	0 in Fa	5 avours place	ebo	10

2

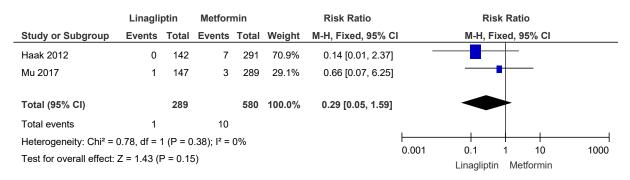
3 4

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



E.1.253 Linagliptin compared to metformin

6 Figure 16: Hypoglycaemia episodes at end of follow-up



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

	Linagli	ptin	Metfor	min		Risk Difference		Ris	k Differen	се	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, F	Random, 9	5% CI	
Haak 2012	0	142	1	291	40.7%	-0.00 [-0.02, 0.01]			•		
Mu 2017	0	147	0	289	59.3%	0.00 [-0.01, 0.01]			•		
Total (95% CI)		289		580	100.0%	-0.00 [-0.01, 0.01]					
Total events	0		1								
Heterogeneity: Tau ² =	0.00; Chi ²	= 0.17,	df = 1 (P	= 0.68); I ² = 0%		<u> </u>	 			
Test for overall effect:	Z = 0.34 (I	P = 0.7	3)				-1	-0.5 Linagli	0 otin Metfo	0.5 ormin	1

10 11

3 4

5

6

7 8

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

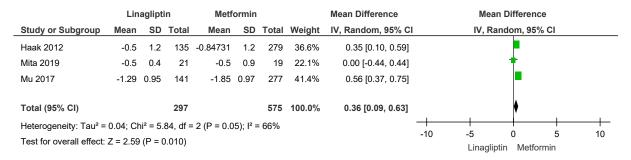


Figure 19: Weight change (kg, lower values are better, change scores) at end of follow-up

	SD Tota	l Mean	SD	Total	Woight	D/ Ei 050/ 01					
0.2					weignt	IV, Fixed, 95% CI		IV	, Fixed, 95%	6 CI	
0.2	3.2 112	-0.6	3.3	139	30.6%	0.80 [-0.01, 1.61]			•		
-0.2 2	.53 147	-0.89	3.01	289	69.4%	0.69 [0.15, 1.23]			•		
	259			428	100.0%	0.72 [0.28, 1.17]					
	•		%				-100	-50	0	50	100
5	-0.2 2.5, df = 1	-0.2 2.53 147 259 5, df = 1 (P = 0.82	-0.2 2.53 147 -0.89 259	-0.2 2.53 147 -0.89 3.01 259 5, df = 1 (P = 0.82); I ² = 0%	-0.2 2.53 147 -0.89 3.01 289 259 428 5, df = 1 (P = 0.82); l ² = 0%	-0.2 2.53 147 -0.89 3.01 289 69.4% 259 428 100.0% 5, df = 1 (P = 0.82); l ² = 0%	-0.2 2.53 147 -0.89 3.01 289 69.4% 0.69 [0.15, 1.23] 259 428 100.0% 0.72 [0.28, 1.17] 5, df = 1 (P = 0.82); I ² = 0%	-0.2 2.53 147 -0.89 3.01 289 69.4% 0.69 [0.15, 1.23] 259 428 100.0% 0.72 [0.28, 1.17] 5, df = 1 (P = 0.82); l ² = 0%	-0.2 2.53 147 -0.89 3.01 289 69.4% 0.69 [0.15, 1.23] 259 428 100.0% 0.72 [0.28, 1.17] 5, df = 1 (P = 0.82); I ² = 0% -100 -50	-0.2 2.53 147 -0.89 3.01 289 69.4% 0.69 [0.15, 1.23] 259 428 100.0% 0.72 [0.28, 1.17] 5, df = 1 (P = 0.82); l ² = 0% -100 -50 0	-0.2 2.53 147 -0.89 3.01 289 69.4% 0.69 [0.15, 1.23] 259 428 100.0% 0.72 [0.28, 1.17] 5, df = 1 (P = 0.82); I ² = 0% -100 -50 0 50

E.1.294 Linagliptin compared to placebo

10 Figure 20: Hypoglycaemia episodes at end of follow-up

	Linagli	ptin	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	l Peto, Fixed, 95% CI
Del Prato 2011	1	336	1	167	48.8%	0.47 [0.02, 8.91]	
Haak 2012	0	142	1	72	24.6%	0.05 [0.00, 3.24]	-
Wu 2015	1	34	0	23	26.5%	5.35 [0.10, 290.47]	
Total (95% CI)		512		262	100.0%	0.52 [0.07, 4.06]	
Total events	2		2				
Heterogeneity: Chi ² =	2.51, df =	2 (P = 0).28); I ² =	20%			
Test for overall effect:	Z = 0.63 (P = 0.53	3)				0.001 0.1 1 10 1000 Linagliptin Placebo

11

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

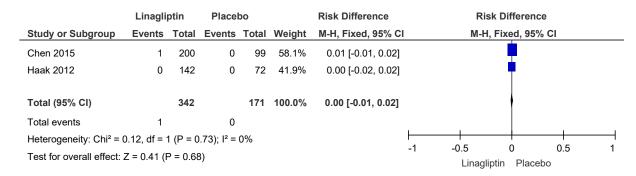


Figure 22: HbA1c change (%, lower values are better, change score) at end of follow-

	Lin	aglipti	in	PI	acebo	,		Mean Difference		Mea	n Differen	се	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C	l	IV, Ra	ndom, 95	% CI	
Chen 2015	-0.68	0.8	200	-0.18	0.8	99	23.7%	-0.50 [-0.69, -0.31]			•		
de Boer 2017	6	0.3	21	6.3	0.5	19	18.4%	-0.30 [-0.56, -0.04]			•		
Del Prato 2011	-0.44	0.9	333	0.25	0.9	163	25.9%	-0.69 [-0.86, -0.52]			•		
Haak 2012	-0.5	1.2	135	0.1	0.8	65	17.0%	-0.60 [-0.88, -0.32]			*		
Wu 2015	6.77	0.67	34	7.59	0.53	23	15.0%	-0.82 [-1.13, -0.51]			•		
Total (95% CI)			723			369	100.0%	-0.58 [-0.73, -0.42]			•		
Heterogeneity: Tau² =	0.02; Ch	ni² = 9.	07, df =	4 (P =	0.06);	I ² = 56	%		<u> </u>	<u> </u>		-	—
Test for overall effect:	Z = 7.19	(P < 0	0.00001)					-10	-5 Linaglip	0 tin Place	5 bo	10

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

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

	Lin	aglipt	in	Placebo Mean Difference				Me	an Differen	ce			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	l	IV.	Fixed, 95%	CI	
Chen 2015	-0.51	2.67	200	-0.99	2.67	99	68.4%	0.48 [-0.16, 1.12]					
de Boer 2017	97.9	17.6	22	94.4	14	21	0.3%	3.50 [-5.98, 12.98]			+		
Haak 2012	0.2	3.2	112	-0.7	2.6	43	29.6%	0.90 [-0.08, 1.88]			•		
Wu 2015	66.79	8.36	34	64.55	7.6	23	1.6%	2.24 [-1.95, 6.43]			+		
Total (95% CI)			368			186	100.0%	0.64 [0.11, 1.17]					
Heterogeneity: Chi ² =	1.42, df	= 3 (P	= 0.70)	; I ² = 09	6				-100	-5 0			100
Test for overall effect:	Fest for overall effect: Z = 2.37 (P = 0.02)										0 liptin Place	50 ebo	100

12 13

2

4

5

6 7

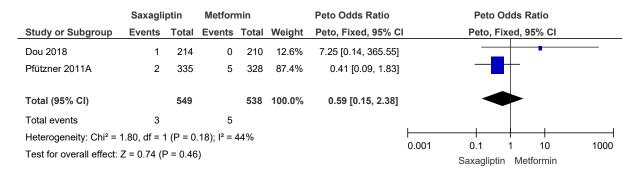
8

9

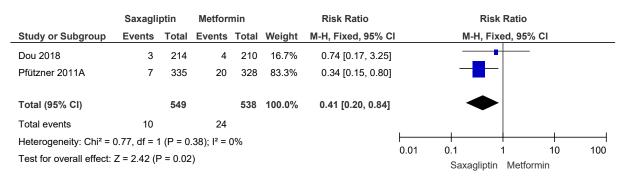
10

E.1.215 Saxagliptin compared to metformin

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



5 Figure 25: Hypoglycaemia episodes at end of follow-up



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

	Saxagli	ptin	Metfori	min		Risk Difference		Ris	sk Differen	ce	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H,	Random, 9	5% CI	
Dou 2018	0	214	0	210	55.4%	0.00 [-0.01, 0.01]			•		
Pfützner 2011A	0	335	2	328	44.6%	-0.01 [-0.02, 0.00]			Ť		
Total (95% CI)		549		538	100.0%	-0.00 [-0.01, 0.00]					
Total events	0		2								
Heterogeneity: Tau² =	0.00; Chi ²	= 0.84,	df = 1 (P	= 0.36); I ² = 0%				 		_
Test for overall effect:	Z = 0.78 (F	P = 0.44	1)				-1	-0.5 Saxagl	0 iptin Metfo	0.5 ormin	1

9 10

3 4

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

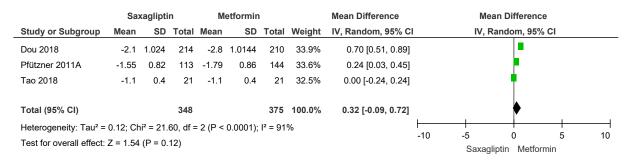


Figure 28: Weight change (kg, lower values are better, change scores) at end of follow-up

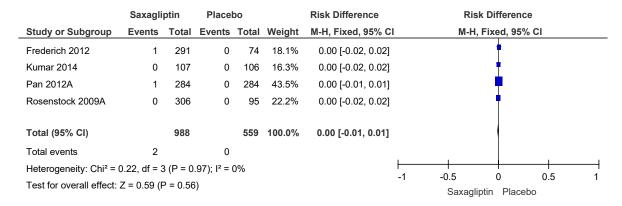
	Saxagliptin			М	etformin			Mean Difference		Me	ean Differen	ce	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% C		IV	, Fixed, 95%	CI	
Dou 2018	-0.14	2.9189	213	-1.56	2.8775	207	61.3%	1.42 [0.87, 1.97]			•		
Tao 2018	-1	0.82	21	-2.8	1.41	21	38.7%	1.80 [1.10, 2.50]			F		
Total (95% CI)			234			228	100.0%	1.57 [1.13, 2.00]					
0 ,	Heterogeneity: Chi² = 0.70, df = 1 (P = 0.40); l² = 0%											50	100
l est for overall effect:	est for overall effect: Z = 7.08 (P < 0.00001)										gliptin Metfo	ormin	

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

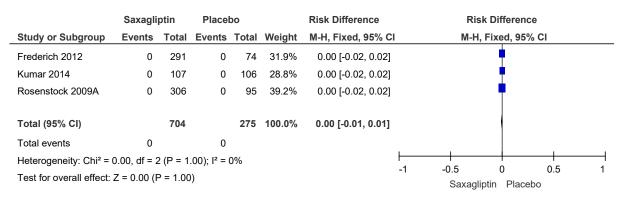
		Saxagliptin			Metformin			Mean Difference		Me	ean Differen	ce	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV,	Random, 95	% CI	
Dou 2018	-0.07	1.0216	213	-0.58	1.0071	207	51.2%	0.51 [0.32, 0.70]			•		
Tao 2018	-1.09	0.55225912	21	-0.52	0.70501164	21	48.8%	-0.57 [-0.95, -0.19]					
Total (95% CI)			234			228	100.0%	-0.02 [-1.07, 1.04]					
Heterogeneity: Tau ² =	0.56; Ch	ni² = 24.30, df	= 1 (P	< 0.000	01); I ² = 96%				-	+		+	
Test for overall effect:	Z = 0.03	3 (P = 0.98)							-100	-50 Sayar	0 ilintin Metfo	50 ormin	100

E.1.216 Saxagliptin compared to placebo

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



5 Figure 31: Cardiovascular mortality at end of follow-up



8 Figure 32: Hypoglycaemia episodes at end of follow-up

	Saxagli	ptin	Placel	bo	Risk Difference			Ris	sk Differen	ce	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	1	M-H,	Random, 9	5% CI	
Kumar 2014	0	107	0	106	28.9%	0.00 [-0.02, 0.02]			•		
Pan 2012A	5	284	2	284	29.1%	0.01 [-0.01, 0.03]			•		
Rosenstock 2009A	0	306	0	95	42.0%	0.00 [-0.02, 0.02]			•		
Total (95% CI)		697		485	100.0%	0.00 [-0.01, 0.01]					
Total events	5		2								
Heterogeneity: Tau ² =	0.00; Chi ²	= 1.18,	df = 2 (P	= 0.55)); I ² = 0%		<u> </u>				—
Test for overall effect:	Z = 0.62 (F	P = 0.54	!)				-1	-0.5 Saxagl	0 iptin Place	0.5 ebo	1

9 10

3 4

2

3 4

5

6

7 8

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

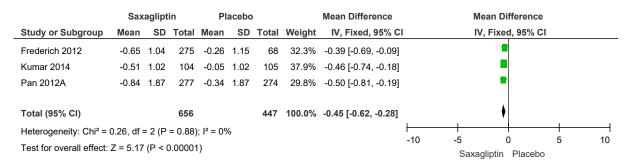
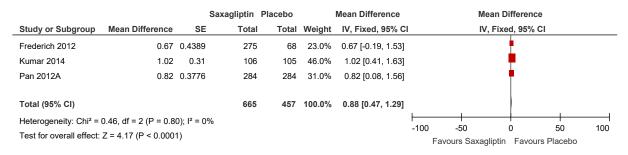


Figure 34: Weight change (kg, lower values are better, change scores) at end of followup



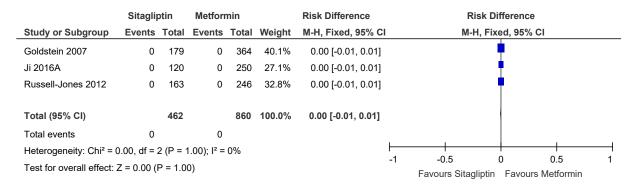
E.1.297 Sitagliptin compared to metformin

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

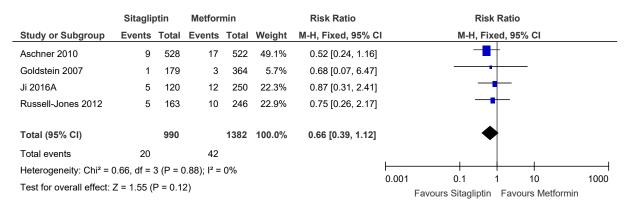
	Sitagli	ptin	Metfori	min		Risk Difference		Risk	Differen	ice	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H,	Fixed, 95	5% CI	
Aschner 2010	1	528	0	522	46.7%	0.00 [-0.00, 0.01]					
Goldstein 2007	0	179	0	364	21.4%	0.00 [-0.01, 0.01]			•		
Ji 2016A	0	120	0	250	14.4%	0.00 [-0.01, 0.01]			†		
Russell-Jones 2012	0	163	1	246	17.5%	-0.00 [-0.02, 0.01]			•		
Total (95% CI)		990		1382	100.0%	0.00 [-0.00, 0.00]					
Total events	1		1								
Heterogeneity: Chi ² = 0	0.83, df =	3 (P = 0	0.84); I ² =	0%			<u> </u>				
Test for overall effect:	Z = 0.08 (P = 0.9	4)				-1	-0.5 Favours Sitaglip	0 tin Favo	0.5 ours Metformin	1

2

Figure 36: Cardiovascular mortality at end of follow-up



4 Figure 37: Hypoglycaemia episodes at end of follow-up

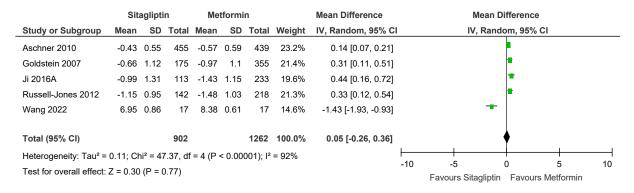


7 Figure 38: Severe hypoglycaemic episodes at end of follow-up

	Sitagli	ptin	Metfori	Metformin Risk Difference				Ris	k Differenc	e	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H,	Fixed, 95%	% CI	
Aschner 2010	2	528	0	522	76.4%	0.00 [-0.00, 0.01]					
Ji 2016A	0	120	0	250	23.6%	0.00 [-0.01, 0.01]			•		
Total (95% CI)		648		772	100.0%	0.00 [-0.00, 0.01]					
Total events	2		0								
Heterogeneity: Chi ² = 0	0.27, df =	1 (P = 0	0.60); I ² =	0%		ŀ	. 				-
Test for overall effect:	Z = 0.98 (P = 0.3	3)				-1	-0.5 Favours Sitagli	0 ptin Favoi	0.5 urs Metformin	1

8

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



4

5

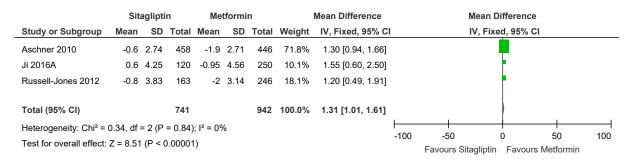
6

3

1

2

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



7 8

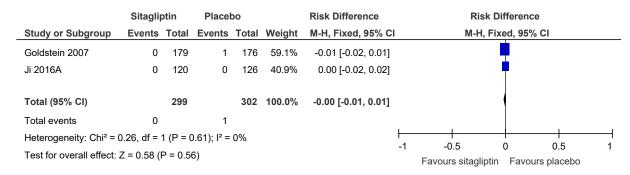
E.1.298 Sitagliptin compared to placebo

10

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

	Sitagli	otin	Place	bo		Risk Difference		Risk	Differen	ce	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H,	Fixed, 95	% CI	
Gantz 2017D	0	165	0	83	17.3%	0.00 [-0.02, 0.02]			•		
Goldstein 2007	0	179	1	176	27.9%	-0.01 [-0.02, 0.01]			•		
Ji 2016A	0	120	0	126	19.3%	0.00 [-0.02, 0.02]			•		
Roden 2015	1	223	1	229	35.5%	0.00 [-0.01, 0.01]			•		
Total (95% CI)		687		614	100.0%	-0.00 [-0.01, 0.01]					
Total events	1		2								
Heterogeneity: Chi ² =	3 (P = 0).94); I² =	<u> </u>								
Test for overall effect:	Z = 0.40 (P = 0.6	9)	-1	-0.5 Favours Sitaglin	0 itin Favo	0.5 urs Placebo				

1 Figure 42: Cardiovascular mortality at end of follow-up



3

2

4 Figure 43: Hypoglycaemia episodes at end of follow-up

	Sitagli	otin	Placebo Risk Difference				Risk D	ifference)		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fix	ed, 95%	CI	
Barzilai 2011	0	102	0	104	13.9%	0.00 [-0.02, 0.02]			•		
Gantz 2017D	1	165	0	83	14.9%	0.01 [-0.02, 0.03]			†		
Goldstein 2007	1	179	1	176	24.0%	-0.00 [-0.02, 0.02]			•		
Ji 2016A	5	120	4	126	16.6%	0.01 [-0.04, 0.06]			<u>†</u>		
Roden 2015	2	223	2	229	30.5%	0.00 [-0.02, 0.02]			•		
Total (95% CI)		789		718	100.0%	0.00 [-0.01, 0.01]			•		
Total events	9		7								
Heterogeneity: Chi ² = 0		<u></u>		+							
Test for overall effect:	Z = 0.46 (P = 0.6	4)	-1	-0.5 Favours sitagliptin	0 Favour	0.5 rs placebo	1			

5

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

	Sitagli	otin	Place	bo		Risk Difference	Risk Diff	erence	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixe	d, 95% CI	
Gantz 2017D	0	165	0	83	24.0%	0.00 [-0.02, 0.02]	•		
Ji 2016A	0	120	0	126	26.8%	0.00 [-0.02, 0.02]	•	I	
Roden 2015	0	223	0	229	49.2%	0.00 [-0.01, 0.01]			
Total (95% CI)		508		438	100.0%	0.00 [-0.01, 0.01]			
Total events	0		0						
Heterogeneity: Chi ² = 0	0.00, df = 2	2 (P = 1	1.00); I² =	0%		ł	1 05		
Test for overall effect:	Z = 0.00 (I	P = 1.0	0)			•	-1 -0.5 0 Favours sitagliptin	0.5 Favours placebo	1

8

3 4

5

6

7

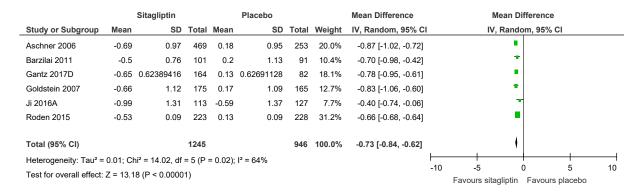
8

9

10

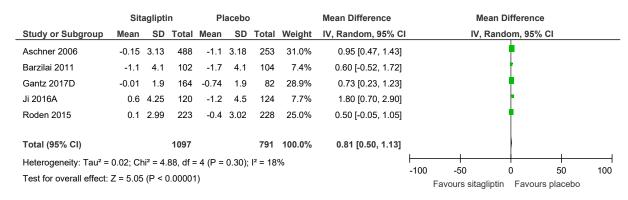
12

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



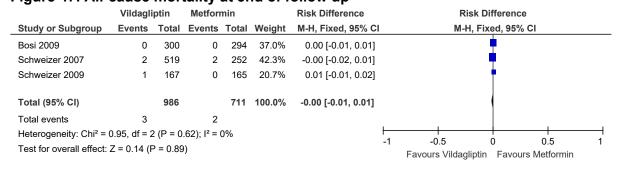
Note: Heterogeneity was not explained by sensitivity analysis, nor subgroup analysis by eGFR subgroups.

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



E.1.219 Vildagliptin compared to metformin

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



4

5 6

7

8

9

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

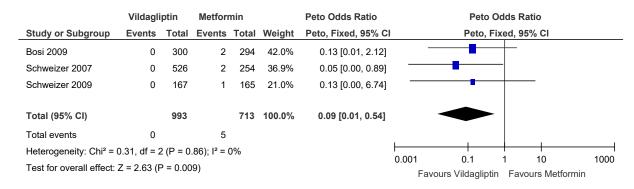


Figure 49: Hypoglycaemia episodes at end of follow-up

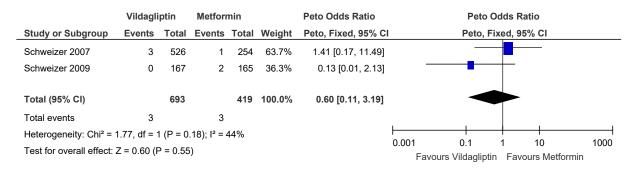
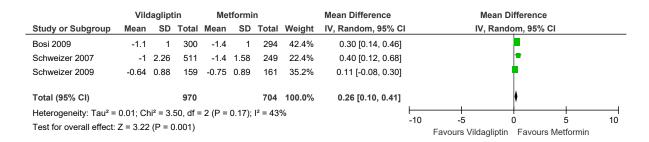


Figure 50: Severe hypoglycaemic episodes at end of follow up

	Vildagli	iptin	Metfor	min		Risk Difference	Risk Difference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
Bosi 2009	0	300	1	294	36.9%	-0.00 [-0.01, 0.01]	•	
Schweizer 2007	0	526	0	254	42.5%	0.00 [-0.01, 0.01]	•	
Schweizer 2009	0	167	0	165	20.6%	0.00 [-0.01, 0.01]	•	
Total (95% CI)		993		713	100.0%	-0.00 [-0.01, 0.00]		
Total events	0		1					
Heterogeneity: Chi ² =	0.41, df = 2	2 (P = 0	.81); I² =	0%		 	- 1 + 1	
Test for overall effect:	Z = 0.50 (F	P = 0.62	2)			-1	-0.5 0 0. Favours Vildagliptin Favours Meti	

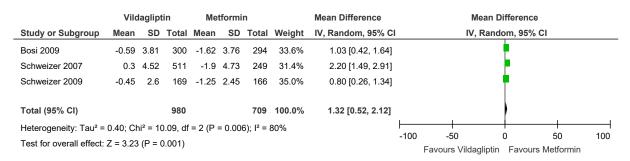
Figure 51: HbA1c change (%, lower values are better, change scores) at end of follow-up



2

3

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



4 5

E.1.2.60 Vildagliptin compared to placebo

7 8

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

	Vilo	Vildagliptin Metforn			tformi	n		Mean Difference		Mea	n Differenc	e	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl		IV, Ra	ndom, 95%	% CI	
Bosi 2009	-1.1	1	300	-1.4	1	294	42.4%	0.30 [0.14, 0.46]					
Schweizer 2007	-1	2.26	511	-1.4	1.58	249	22.4%	0.40 [0.12, 0.68]			-		
Schweizer 2009	-0.64	0.88	159	-0.75	0.89	161	35.2%	0.11 [-0.08, 0.30]			•		
Total (95% CI)			970			704	100.0%	0.26 [0.10, 0.41]			\		
Heterogeneity: Tau ² = Test for overall effect:			,	2 (P =		- 10	-5 Favours Vildaglig	0 otin Favou	5 Irs Metformin	10			

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

	Vilo	laglipt	in	PI	acebo)		Mean Difference		Mean I	ifferen	nce	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Rand	om, 95	5% CI	
Dejager 2007	-1	3.96	286	-1.4	3.88	94	32.4%	0.40 [-0.51, 1.31]			•		
Mari 2008	-0.5	3.52	138	-0.2	3.43	131	34.6%	-0.30 [-1.13, 0.53]			•		
Pi-Sunyer 2007	-0.27	3.35	252	-1.4	3.75	88	33.0%	1.13 [0.24, 2.02]			•		
Total (95% CI)			676			313	100.0%	0.40 [-0.43, 1.22]					
Heterogeneity: Tau ² = Test for overall effect:			,	= 2 (P =	0.07);	I ² = 62	%		-100 F	-50 avours Vildagliptin	0 Favo	50 burs Placebo	100

3 E.1.3 GLP-1 receptor agonist

E.1.341 Dulaglutide compared to placebo

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

6

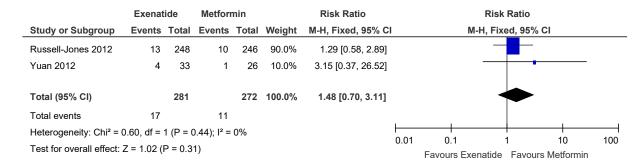
E.1.372 Dulaglutide compared to metformin

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

9

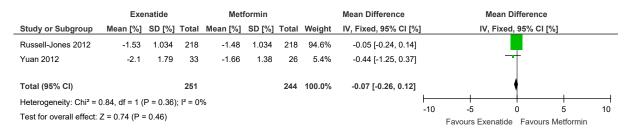
E.1.303 Exenatide compared to metformin

11 Figure 55: Hypoglycaemia episodes at end of follow-up



12

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



4

5

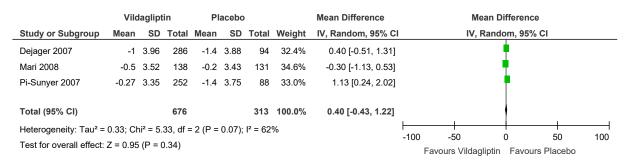
6

3

1

2

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



7 8

E.1.394 Exenatide compared to sitagliptin

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

11

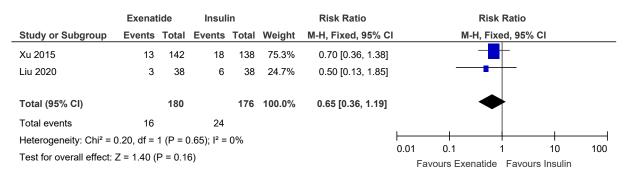
E.1.325 Exenatide compared to pioglitazone

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

14

E.1.356 Exenatide compared to insulin

16 Figure 58: Hypoglycaemia episodes at end of follow-up



17

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

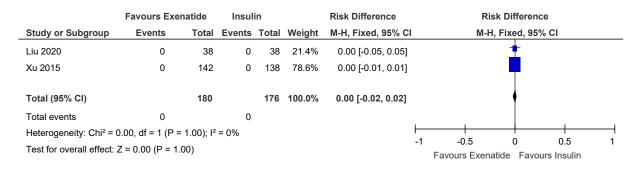


Figure 60: HbA1c change (%, lower values are better, change scores) at end of follow-up

		E	xenatide	Insulin		Mean Difference		IV	lean Differen	ce	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% C	l	IV,	Random, 95	% CI	
Liu 2020	-0.65	0.184	35	36	47.7%	-0.65 [-1.01, -0.29]					
Xu 2015	-0.1	0.1416	110	114	52.3%	-0.10 [-0.38, 0.18]			•		
Total (95% CI)			145	150	100.0%	-0.36 [-0.90, 0.18]			•		
Heterogeneity: Tau² =	0.12; Chi² = 5.61, di	f = 1 (P =	0.02); I ² = 8	2%			-10	-5	0	5	10
Test for overall effect:	Z = 1.32 (P = 0.19)							Favours Exe	-	urs Insulin	10

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

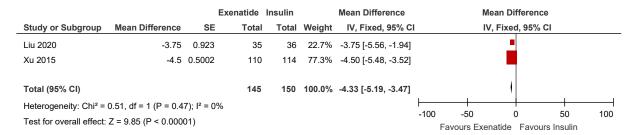
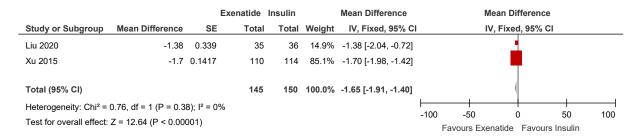


Figure 62: BMI change (kg/m2, lower values are better, change scores) at end of follow-up



E.1.317 Exenatide compared to placebo

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

3

5

E.1.348 Liraglutide compared to metformin

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

	Lira	glutide		Met	formin			Mean Difference		Mear	Differe	nce	
Study or Subgroup M	ean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV, Random, 95% CI [%]	IV, Rand	lom, 95%	6 CI [%]	
1.2.1 Final scores													
Lambadiari 2018	7	1.2	30	7.7	1	30	61.9%	-0.70 [-1.26, -0.14]			-		
Subtotal (95% CI)			30			30	61.9%	-0.70 [-1.26, -0.14]			lack		
Heterogeneity: Not applica	able												
Test for overall effect: Z =	2.45 (P =	0.01)											
1.2.2 Change from basel	ine												
Feng 2017	-3	2.19	30	-3.3	2.23	31	38.1%	0.30 [-0.81, 1.41]			+		
Subtotal (95% CI)			30			31	38.1%	0.30 [-0.81, 1.41]					
Heterogeneity: Not applica	able												
Test for overall effect: Z =	0.53 (P =	0.60)											
Total (95% CI)			60			61	100.0%	-0.32 [-1.27, 0.63]			♦		
Heterogeneity: Tau ² = 0.36	0; Chi² = 2	2.49, df =	1 (P =	0.11); I ² = 6	60%				<u></u>	<u> </u>	_		
Test for overall effect: Z =	0.66 (P =	0.51)							-10	-5	0	5	1
Test for subgroup differen	ces: Chi²	= 249 c	If = 1 /E	P = 0 11\ I ² :	= 50.8%					Favours Liraglution	ie Favo	ours Metformin	

6 7

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

	Lira	Liraglutide Mean [kg] SD [kg] Total			formin			Mean Difference		Mean D	ifference		
Study or Subgroup	Mean [kg]	SD [kg]	Total	Mean [kg]	SD [kg]	Total	Weight	IV, Random, 95% CI [kg]		IV, Randon	n, 95% CI	[kg]	
Feng 2017	75.5	10.77	29	71.2	13.73	29	52.0%	4.30 [-2.05, 10.65]			-		
Lambadiari 2018	92	16	30	77	14	30	48.0%	15.00 [7.39, 22.61]			-		
Total (95% CI)			59			59	100.0%	9.44 [-1.04, 19.91]			•		
Heterogeneity: Tau ² = Test for overall effect:			: 1 (P =	0.03); $I^2 = 78$	3%				-100	-50 Favours Liraglutide	0 Favours	50 Metformin	100

8

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

	Lira	aglutide		Met	formin			Mean Difference		Me	an Differenc	e	
Study or Subgroup	Mean [kg/m2]	SD [kg/m2]	Total	Mean [kg/m2]	SD [kg/m2]	Total	Weight	IV, Random, 95% CI [kg/m2]		IV, Rand	lom, 95% CI	[kg/m2]	
Feng 2017	26.2	2.69	29	25.5	3.77	29	51.8%	0.70 [-0.99, 2.39]			+		
Lambadiari 2018	30.9	5	30	26.9	3	30	48.2%	4.00 [1.91, 6.09]			-		
Total (95% CI)			59			59	100.0%	2.29 [-0.94, 5.52]				-	
Heterogeneity: Tau ² =	4.51; Chi ² = 5.81	I, df = 1 (P = 0).02); l²	= 83%					<u></u>			<u> </u>	
Test for overall effect:	Z = 1.39 (P = 0.1	16)							-10	-5 Favoure Liragh	utide Eavou	te Metformin	10

9

E.1.319 Liraglutide compared to dulaglutide

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

3

E.1.3.40 Liraglutide compared to gliclazide

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

6

E.1.3.71 Liraglutide compared to glimepiride

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

9

E.1.3102 Liraglutide compared to placebo

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

	Liraglu	tide	Place	bo		Risk Difference		Risk D	ifferen	ice	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fix	red, 95	5% CI	
Yamada 2020	0	48	0	49	34.4%	0.00 [-0.04, 0.04]			•		
Miyagawa 2015	0	137	0	70	65.6%	0.00 [-0.02, 0.02]					
Total (95% CI)		185		119	100.0%	0.00 [-0.02, 0.02]			•		
Total events	0		0								
Heterogeneity: Chi ² =	0.00, df =	1 (P = 1	.00); I ² =	0%			<u> </u>	+	+		
Test for overall effect:	Z = 0.00 (I	⊃ = 1.00	0)				-1	-0.5 Favours Liraglutide	0 Favo	0.5 ours Placebo	1

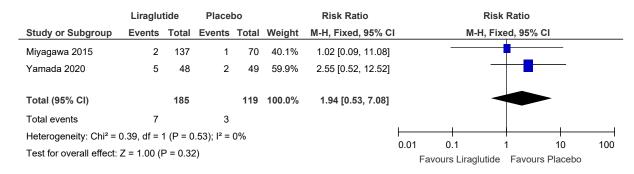
12 13

14 Figure 67: Cardiovascular mortality at end of follow-up

	Liraglu	tide	Placel	bo		Risk Difference		Ris	sk Differen	ce	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		М-Н	, Fixed, 95°	% CI	
Miyagawa 2015	0	137	0	70	65.6%	0.00 [-0.02, 0.02]					
Yamada 2020	0	48	0	49	34.4%	0.00 [-0.04, 0.04]			•		
Total (95% CI)		185		119	100.0%	0.00 [-0.02, 0.02]			•		
Total events	0		0								
Heterogeneity: Chi ² =	0.00, df =	1 (P = 1	.00); I² =	0%			<u> </u>			0.5	
Test for overall effect:	Z = 0.00 (I	P = 1.00	0)				-1	-0.5 Favours Liraglu	0 itide Favo	0.5 urs Placebo	1

15

1 Figure 68: Hypoglycaemia episodes at end of follow-up



3

2

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

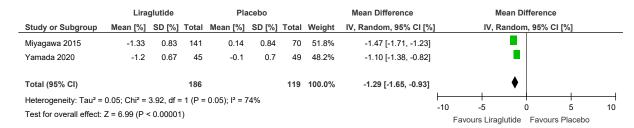
	Liraglu	tide	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Miyagawa 2015	0	137	0	70	65.6%	0.00 [-0.02, 0.02]	•
Yamada 2020	0	48	0	49	34.4%	0.00 [-0.04, 0.04]	•
Total (95% CI)		185		119	100.0%	0.00 [-0.02, 0.02]	
Total events	0		0				
Heterogeneity: Chi ² =	0.00, df =	1 (P = 1	.00); I ² =	⊢	 		
Test for overall effect:	Z = 0.00 (I	⊃ = 1.00	0)	-1	I -0.5 0 0.5 1 Favours Liraglutide Favours Placebo		

5 6

7

8

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



9 10

E.1.3113 Liraglutide compared to sitagliptin

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

13

E.1.3114 Semaglutide compared to liraglutide

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

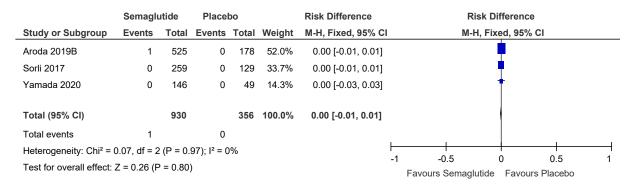
16

E.1.3175 Semaglutide compared to sitagliptin

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

E.1.3.86 Semaglutide compared to placebo

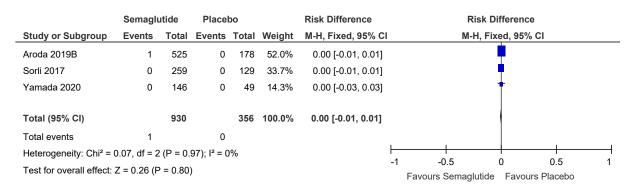
4 Figure 71: All-cause mortality at end of follow-up



6

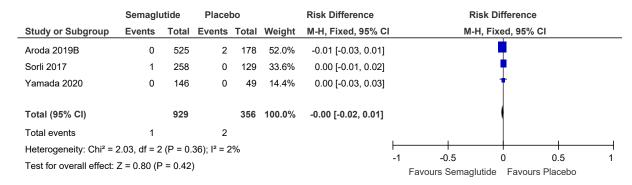
5

7 Figure 72: Cardiovascular mortality at end of follow-up



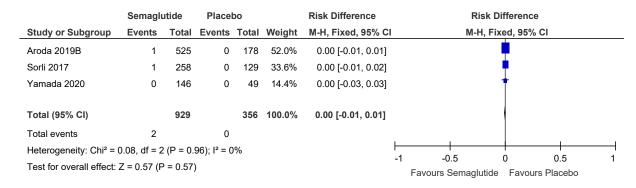
8

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

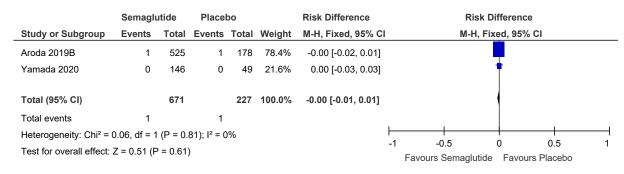


11

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



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



7 Figure 76: Hypoglycaemia episodes at end of follow-up

	Semagl	utide	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Aroda 2019B	7	525	1	178	52.0%	0.01 [-0.01, 0.02]	•
Sorli 2017	0	258	0	129	33.6%	0.00 [-0.01, 0.01]	•
Yamada 2020	6	146	2	49	14.4%	0.00 [-0.06, 0.06]	+
Total (95% CI)		929		356	100.0%	0.00 [-0.01, 0.02]	
Total events	13		3				
Heterogeneity: Chi ² =	0.70, df = 2	2 (P = 0.	71); I ² = (0%		⊢	+ + + +
Test for overall effect:	Z = 0.63 (F	P = 0.53)			-1	I -0.5 0 0.5 1 Favours Semaglutide Favours Placebo

8 9

2

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

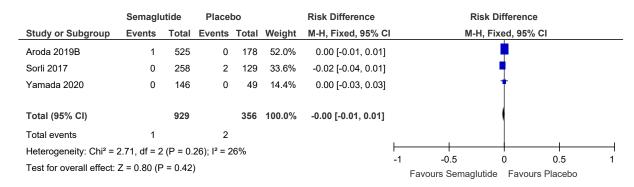


Figure 78: HbA1c change (%, lower values are better, change scores) at end of followup

			Semaglutide	Placebo		Mean Difference			N	lean Di	ifferen	ce		
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI			IV,	Rando	om, 95	% CI		
Aroda 2019B (1)	-0.6	0.102	175	60	15.6%	-0.60 [-0.80, -0.40]								
Aroda 2019B (2)	-1.1	0.102	175	59	15.6%	-1.10 [-1.30, -0.90]								
Aroda 2019B (3)	-0.9	0.102	175	59	15.6%	-0.90 [-1.10, -0.70]				•				
Sorli 2017	-1.48	0.127	258	129	14.8%	-1.48 [-1.73, -1.23]				•				
Yamada 2020 (4)	-0.8	0.1414	46	17	14.3%	-0.80 [-1.08, -0.52]				-				
Yamada 2020 (5)	-1.3	0.2016	49	16	12.0%	-1.30 [-1.70, -0.90]				-				
Yamada 2020 (6)	-1.4	0.2021	47	16	12.0%	-1.40 [-1.80, -1.00]				+				
Total (95% CI)			925	356	100.0%	-1.06 [-1.31, -0.82]				♦				
Heterogeneity: Tau ² =	0.09; Chi² = 39.71,	df = 6 (P	< 0.00001); l ²	= 85%			<u></u>		<u> </u>		-			
Test for overall effect:	Z = 8.46 (P < 0.000	01)					-10	Favour	-5 s Seman		0 Favo	5 urs Place	eho	10

Footnotes

2

4 5

6 7 (1) 3 mg semaglutide v placebo

(2) 14 mg semaglutide v placebo

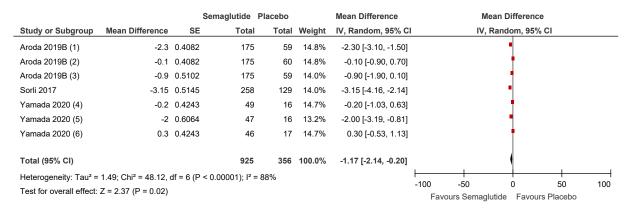
(3) 7 mg semaglutide v placebo

(4) 3 mg semagluitde v placebo

(5) 7 mg semaglutide v placebo

(6) 14 mg semaglutide v placebo

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



Footnotes

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

4

5

6

3

2

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

			Semaglutide 14 mg	Placebo		Mean Difference		Me	ean Differenc	e	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% Cl		IV,	Random, 95%	% CI	
Aroda 2019B (1)	-0.1	0.102	175	60	15.9%	-0.10 [-0.30, 0.10]			•		
Aroda 2019B (2)	-0.3	0.2041	175	59	13.7%	-0.30 [-0.70, 0.10]			•		
Aroda 2019B (3)	-0.9	0.1531	175	59	14.9%	-0.90 [-1.20, -0.60]			•		
Sorli 2017	-1.11	0.183	258	129	14.2%	-1.11 [-1.47, -0.75]			•		
Yamada 2020 (4)	-0.1	0.2041	49	16	13.7%	-0.10 [-0.50, 0.30]			†		
Yamada 2020 (5)	0.1	0.2041	49	17	13.7%	0.10 [-0.30, 0.50]			•		
Yamada 2020 (6)	-0.7	0.2041	48	16	13.7%	-0.70 [-1.10, -0.30]			†		
Total (95% CI)			929	356	100.0%	-0.45 [-0.79, -0.10]					
Heterogeneity: Tau ² =	0.18; Chi² = 44.93,	df = 6 (P	< 0.00001); I ² = 87%					+		+	
Test for overall effect:	Z = 2.53 (P = 0.01)						-100	-50	0	50	100
							Favours	Semaglutide 14	1 mg Favou	rs Placebo	

Footnotes

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

7

8

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

E.1.491 Tirzepatide compared to dulaglutide

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

1 E.1.5 SGLT2 inhibitors

E.1.521 Canagliflozin compared to metformin

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

E.1.552 Canagliflozin compared to placebo

4

7 8

6 Figure 81: Hypoglycaemia episodes at follow-up

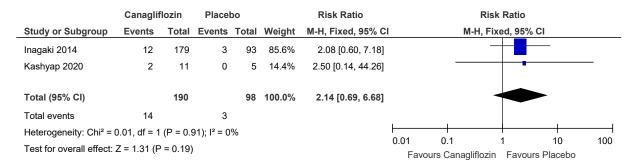


Figure 82: HbA1c change (%, lower values are better, change scores) at end of followup

Canagliflozin				F	Placebo			Mean Difference		Me	an Differen	ce	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, I	Random, 95	% CI	
Inagaki 2014	-0.75	0.81	178	0.29	0.68	93	43.7%	-1.04 [-1.22, -0.86]					
Kashyap 2020	-0.31	0.6103	11	0.11	0.6604	5	5.5%	-0.42 [-1.10, 0.26]			+		
Stenlöf 2013	-0.9	0.9	385	0.14	0.9	189	50.8%	-1.04 [-1.20, -0.88]					
Total (95% CI)			574			287	100.0%	-1.01 [-1.17, -0.84]			•		
0 ,	terogeneity: Tau ² = 0.01; Chi ² = 3.08, df = 2 (P = 0.21); l ² = 35% st for overall effect: Z = 11.99 (P < 0.00001)										0 lozin Favo	5 urs Placebo	10

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

	Canagliflozin			Р	lacebo		Mean Difference			Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV,	Random, 95°	% CI	
Inagaki 2014	-3.89	3.35	178	-0.76	3.37	93	42.9%	-3.13 [-3.97, -2.29]					
Kashyap 2020	-3.77	3.803	11	6.33	6.306	5	2.9%	-10.10 [-16.07, -4.13]			-		
Stenlöf 2013	-3.4	1.7	386	-0.6	2.8	190	54.2%	-2.80 [-3.23, -2.37]					
Total (95% CI)			575			288	100.0%	-3.15 [-4.19, -2.11]			•		
Heterogeneity: Tau ² = 0.47; Chi ² = 6.08, df = 2 (P = 0.05); l ² = 67%									400				
Test for overall effect: $Z = 5.95$ (P < 0.00001)								-100 Fa\	-50 ours Canagli	0 flozin Favou	50 irs Placebo	100	

12

9

E.1.513 Dapagliflozin compared to metformin

2

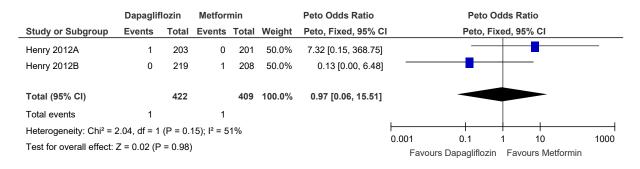
3 4

6 7

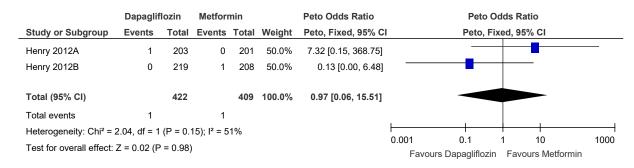
9

10

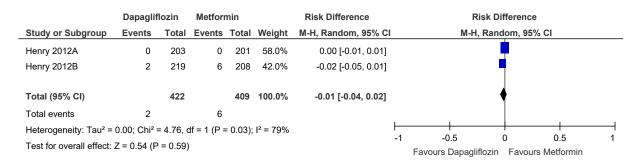
Figure 84: All-cause mortality at end of follow-up



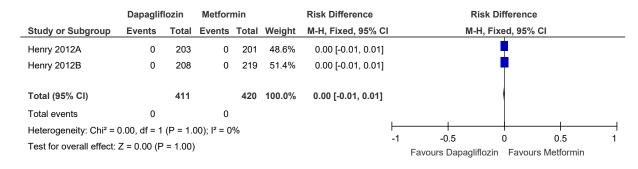
5 Figure 85: Cardiovascular mortality at end of follow-up



8 Figure 86: Hypoglycaemia episodes at end of follow-up



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



2

3

4 5

6

7

8 9

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

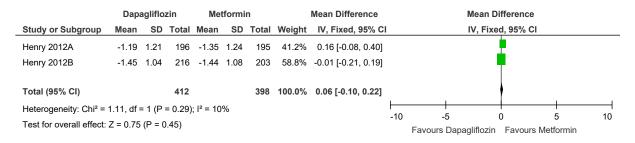
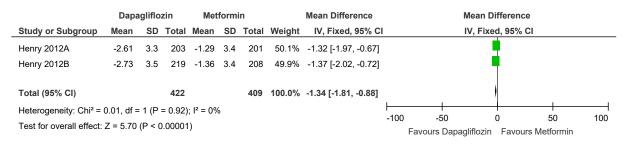


Figure 89: Weight change (kg, lower values are better, change scores) at end of follow-up



E.1.504 Dapagliflozin compared to placebo

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

	Dapagliflozin		Placebo			Risk Difference	Risk Difference			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	CI M-H, Fixed, 95% CI			
Bailey 2012	0	214	0	68	25.5%	0.00 [-0.02, 0.02]	•			
Ferrannini 2010	1	410	0	75	31.3%	0.00 [-0.02, 0.02]	•			
Ji 2014	0	261	0	132	43.3%	0.00 [-0.01, 0.01]	•			
Total (95% CI)		885		275	100.0%	0.00 [-0.01, 0.01]				
Total events	1		0							
Heterogeneity: Chi ² = 0	0.05, df = 2	(P = 0.9	97); I² = 0	%						
Test for overall effect:	Z = 0.16 (P	= 0.88)					-1 -0.5 0 0.5 1 Favours Dapagliflozin Favours Placebo			

5 6

7

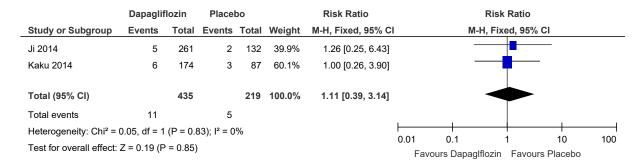
8

9 10

11

12

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



4 Figure 92: Hypoglycaemia episodes at end of follow-up

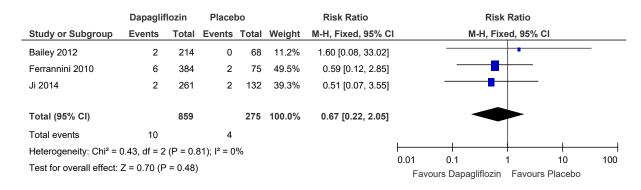
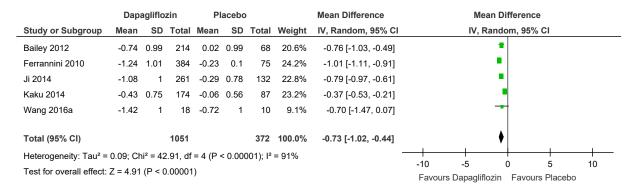
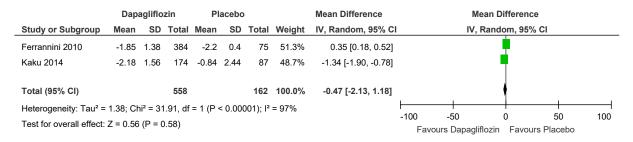


Figure 93: HbA1c change (%, lower values are better, change scores) at end of followup



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

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



3

1

2

•

E.1.555 Empagliflozin compared to metformin

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

7

E.1.536 Empagliflozin compared to linagliptin

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

10

E.1.517 Empagliflozin compared to sitagliptin

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

13

E.1.548 Empagliflozin compared to placebo

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

16

17 E.1.6 Sulfonylureas

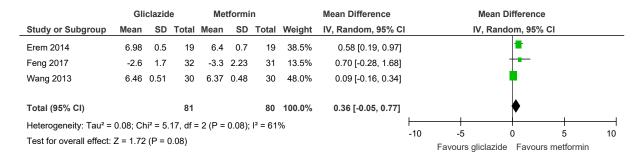
E.1.681 Gliclazide compared to metformin

19 Figure 95: Hypoglycaemia episodes at end of follow-up

	Gliclaz	ide	Metfori	min		Risk Difference		Risl	k Differend	e	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, R	andom, 9	5% CI	
Erem 2014	0	20	0	20	63.1%	0.00 [-0.09, 0.09]			-		
Feng 2017	2	32	2	31	36.9%	-0.00 [-0.12, 0.12]			+		
Total (95% CI)		52		51	100.0%	-0.00 [-0.07, 0.07]			•		
Total events	2		2								
Heterogeneity: Tau ² =				9 = 0.98	$B); I^2 = 0\%$		- 1	-0.5	0	0.5	
Test for overall effect:	Z = 0.02 (P = 0.9	8)					Favours gliclaz	ide Favoi	urs metformin	

20

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



4

5

3

1

2

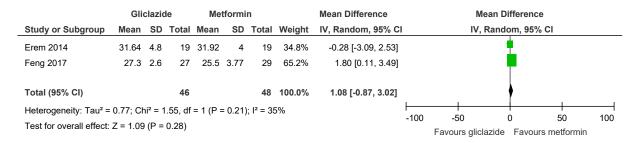
Figure 97: Weight change (kg, lower values are better, final values) at end of follow-up

	GI	iclazide	€	Me	etformii	า		Mean Difference		Me	an Differenc	e	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV,	Fixed, 95%	CI	
Erem 2014	91	26.2	19	83.4	13.3	19	10.5%	7.60 [-5.61, 20.81]			+-		
Feng 2017	77.54	13.35	27	71.2	13.73	29	36.4%	6.34 [-0.75, 13.43]					
Wang 2013	71.2	11	30	68.4	12.2	30	53.1%	2.80 [-3.08, 8.68]			+		
Total (95% CI)			76			78	100.0%	4.59 [0.31, 8.88]			♦		
Heterogeneity: Chi ² =	0.79, df	= 2 (P =	0.67);	I ² = 0%					-100	-50	0		100
Test for overall effect:	04)						-100	Favours glicla		rs metformir			

6 7

8

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



9

E.1.612 Gliclazide compared to vildagliptin

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

13

E.1.613 Glimepiride compared to metformin

2

3 4

5

6

7 8

9

10

11 12

15

Figure 99: Hypoglycaemia episodes at end of follow-up

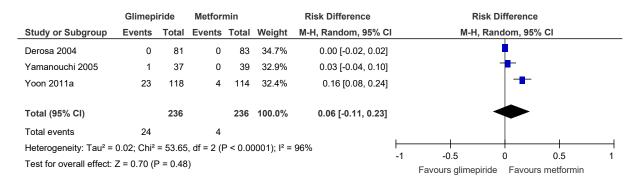


Figure 100: HbA1c change (%, lower values are better, change score and final value) at end of follow-up

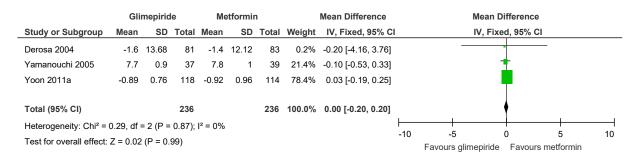
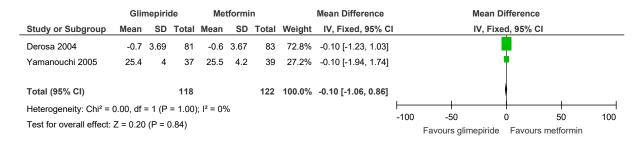


Figure 101: BMI change (kg/m2, lower values are better, change score and final value) at end of follow-up



E.1.634 Glimepiride compared to dulaglutide

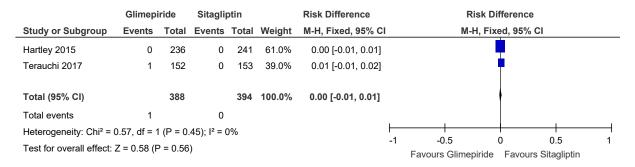
14 There are no forest plots reported for this comparison (all outcomes include a single study).

E.1.665 Glimepiride compared to saxagliptin

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

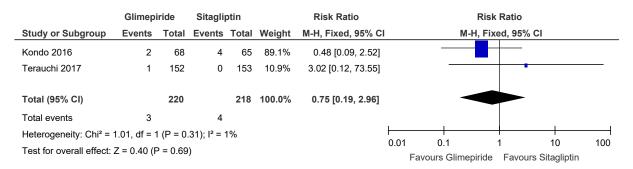
E.1.626 Glimepiride compared to sitagliptin

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



4 5

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



7

9 Figure 104: Hypoglycaemia episodes at end of follow-up

	Favours Glime	epiride	Sitagli	otin		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	CI Peto, Fixed, 95% CI
Hartley 2015	15	236	3	241	94.6%	4.07 [1.59, 10.44]	ı
Kondo 2016	1	68	0	65	5.4%	7.07 [0.14, 356.67]	•
Total (95% CI)		304		306	100.0%	4.20 [1.68, 10.48]	•
Total events	16		3				
Heterogeneity: Chi ² =	0.07, df = 1 (P = 0	0.79); I ² =	0%				
Test for overall effect:	Z = 3.07 (P = 0.0	02)					0.001 0.1 1 10 1000 Favours Glimepiride Favours Sitagliptin

10

4 5

6 7

8

9

10 11

14

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

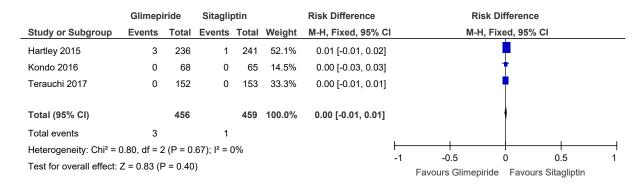


Figure 106: HbA1c change (%, lower values are better, change scores and final value) at end of follow up

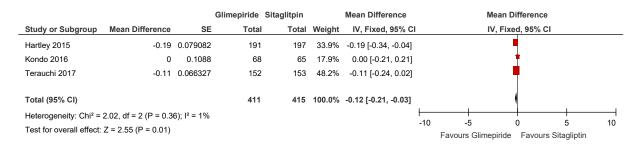
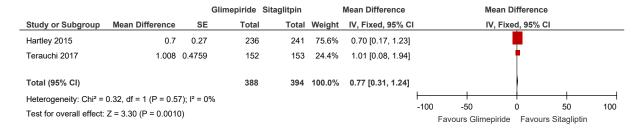


Figure 107: Weight change (kg, lower values are better, change scores) at end of follow-up



E.1.627 Glimepiride compared to canagliflozin

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

E.1.618 Glipizide compared to metformin

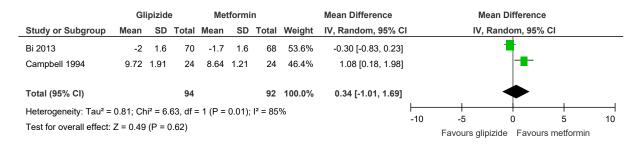
2

3

4 5

8 9

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



6 Figure 109: Weight change (kg, lower values are better, change score) at end of follow-7 up

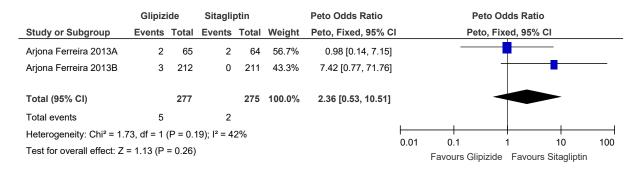
			Glipizide	Metformin		Mean Difference		Me	an Differen	се	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% Cl		IV, F	Random, 95	% CI	
Bi 2013	0.14	0.5	70	68	62.5%	0.14 [-0.84, 1.12]			p		
Campbell 1994	4.59	2.28	24	24	37.5%	4.59 [0.12, 9.06]			•		
Total (95% CI)			94	92	100.0%	1.81 [-2.41, 6.03]			•		
Heterogeneity: Tau ² =	7.18; Chi² = 3.63, d	f = 1 (F	P = 0.06); I	² = 72%			-100	-50	0	50	100
Test for overall effect:	Z = 0.84 (P = 0.40)							Favours glip		urs metform	

E.1.609 Glipizide compared to sitagliptin

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

	Glipiz	ide	Sitagli	ptin		Risk Ratio			Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	1	M-l	I, Fixed, 95%	% CI	
Arjona Ferreira 2013A	6	65	4	64	57.2%	1.48 [0.44, 4.99]					
Arjona Ferreira 2013B	7	212	3	210	42.8%	2.31 [0.61, 8.82]			+	<u> </u>	
Total (95% CI)		277		274	100.0%	1.83 [0.75, 4.50]				-	
Total events	13		7								
Heterogeneity: Chi ² = 0.	24, df = 1	(P = 0.6	33); I ² = 0	%			0.04		-	10	100
Test for overall effect: Z	= 1.33 (P	= 0.19)					0.01	0.1 Favours Glip	์ izide Favoเ	10 urs Sitagliptii	100 n

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



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

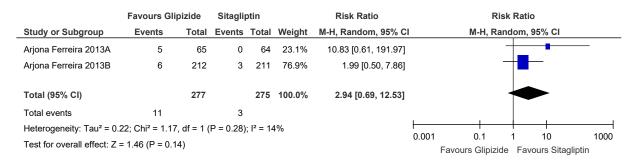


Figure 113: HbA1c change (%, lower values are better, change scores) at end of follow-up

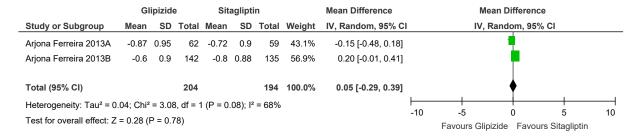
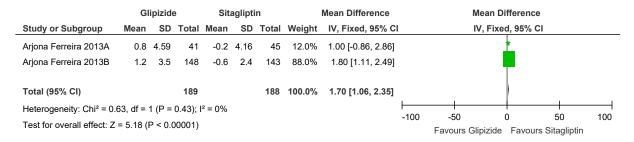


Figure 114: Weight change (kg, lower values are better, change scores) at end of follow-up



2

5 6

7

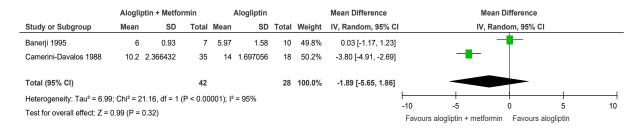
8

9 10

11

E.1.6.10 Glipizide compared to placebo

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



E.1.6. 1 Tolbutamide compared to insulin

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

E.1.6. 22 Tolbutamide compared to placebo

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

11 E.1.7 Thiazolidinediones

E.1.721 Pioglitazone compared to metformin

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

•				,		•				
	Pioglita	zone	Metfor	min		Risk Difference		Risk D	ifference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I	M-H, Fix	ed, 95% CI	
Erem 2014	0	20	0	20	2.6%	0.00 [-0.09, 0.09]		-	+	
Esposito 2011	0	55	0	55	7.2%	0.00 [-0.03, 0.03]			+	
Perez 2009	0	190	0	209	25.9%	0.00 [-0.01, 0.01]			•	
Russell-Jones 2012	0	163	1	246	25.6%	-0.00 [-0.02, 0.01]			•	
Schernthaner 2004	3	297	2	297	38.7%	0.00 [-0.01, 0.02]			•	
Total (95% CI)		725		827	100.0%	0.00 [-0.01, 0.01]				
Total events	3		3							
Heterogeneity: Chi ² =	0.61, df = 4	1 (P = 0.	96); I² = 0)%			<u></u>		 	
Test for overall effect:	Z = 0.07 (F	P = 0.95)				-1	-0.5 Favours Pioglitazone	0 0.5 Favours Metfor	nin

13

3

7

10

Figure 117: Cardiovascular mortality at end of follow up

	Pioglita	zone	Metfori	min		Risk Difference		Risk Difference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I	M-H, Fixed, 95% CI	
Erem 2014	0	20	0	20	4.3%	0.00 [-0.09, 0.09]		+	
Esposito 2011	0	55	0	55	11.7%	0.00 [-0.03, 0.03]		†	
Perez 2009	0	190	0	209	42.3%	0.00 [-0.01, 0.01]		•	
Russell-Jones 2012	0	163	1	246	41.7%	-0.00 [-0.02, 0.01]		•	
Total (95% CI)		428		530	100.0%	-0.00 [-0.01, 0.01]			
Total events	0		1						
Heterogeneity: Chi ² = 0	0.26, df = 3	B (P = 0.	97); I ² = 0)%			<u> </u>	 	\dashv
Test for overall effect:	Z = 0.37 (F	P = 0.71)				-1	-0.5 0 0.5 Favours Pioglitazone Favours Metformin	1

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

	Pioglita	zone	Metfor	min		Risk Difference		Risk D	iffere	nce	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fix	ced, 9	5% CI	
Erem 2014	0	20	0	20	9.1%	0.00 [-0.09, 0.09]		-	\pm		
Perez 2009	1	190	0	209	90.9%	0.01 [-0.01, 0.02]					
Total (95% CI)		210		229	100.0%	0.00 [-0.01, 0.02]			\		
Total events	1		0								
Heterogeneity: Chi ² =	0.01, df = 1	(P = 0.	90); I² = ()%			<u></u> -1	- 0.5	0	0.5	
Test for overall effect:	Test for overall effect: Z = 0.60 (P = 0.55)						-1	Favours Pioglitazone	-		

2

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

	Pioglita	zone	Metfor	min		Risk Difference		Risk	Diffe	rence	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, F	ixed,	95% CI	
Esposito 2011	0	55	0	55	73.3%	0.00 [-0.03, 0.03]					
Erem 2014	0	20	0	20	26.7%	0.00 [-0.09, 0.09]			+	-	
Total (95% CI)		75		75	100.0%	0.00 [-0.04, 0.04]			•		
Total events	0		0								
Heterogeneity: Chi ² =	0.00, df = 1	(P = 1.	00); I ² = 0)%			<u> </u>		$\overrightarrow{+}$	0.5	
Test for overall effect:	Z = 0.00 (F	P = 1.00)				-1	-0.5 Favours Pioglitazon	0 ne F	0.5 avours Metformin	

4

Figure 120: Hypoglycaemia episodes at end of follow up

	Pioglita	zone	Metfor	min		Risk Difference		Risk D	ifference		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	l	M-H, Fix	ed, 95% C	CI	
DeRosa 2009	0	69	0	67	13.0%	0.00 [-0.03, 0.03]			†		
Erem 2014	0	20	0	20	3.8%	0.00 [-0.09, 0.09]		_	+		
Perez 2009	1	190	3	209	38.2%	-0.01 [-0.03, 0.01]					
Russell-Jones 2012	6	163	10	246	37.6%	-0.00 [-0.04, 0.03]			•		
Yamanouchi 2005	0	38	0	39	7.4%	0.00 [-0.05, 0.05]		-	†		
Total (95% CI)		480		581	100.0%	-0.00 [-0.02, 0.01]			-		
Total events	7		13								
Heterogeneity: Chi ² =	0.35, df = 4	P = 0.	99); I² = 0)%			<u></u>		 	+	
Test for overall effect:	Z = 0.56 (F	P = 0.58)				-1	-0.5 Favours Pioglitazone	0 Favours	0.5 Metformin	1

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

		1	Pioglitazone Me	tformin		Mean Difference		Mean E	ifferer	ice	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI		IV, Rand	om, 95	5% CI	
Derosa 2009	0.3	0.1041	69	67	22.2%	0.30 [0.10, 0.50]			•		
Erem 2014	0.06	0.2057	19	19	10.7%	0.06 [-0.34, 0.46]			+		
Esposito 2011	0	0.0953	55	55	23.6%	0.00 [-0.19, 0.19]			•		
Pavo 2003	0.2	0.185	105	100	12.4%	0.20 [-0.16, 0.56]			+		
Russell-Jones 2012	-0.15	0.1063	137	218	21.8%	-0.15 [-0.36, 0.06]			•		
Yamanouchi 2005	0.1	0.2279	38	39	9.3%	0.10 [-0.35, 0.55]			+		
Total (95% CI)			423	498	100.0%	0.07 [-0.08, 0.23]			•		
Heterogeneity: Tau ² =	0.02; Chi² = 10.21,	df = 5 (P =	= 0.07); I ² = 51%					-	+	-	$\overline{}$
Test for overall effect:	Z = 0.92 (P = 0.36)	,	•				-10	-5 Favours Pioglitazone	0 Favo	5 ours Metformin	10

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

	Piog	litazone		Met	formin			Mean Difference		Mean	Difference	9	
Study or Subgroup	Mean [kg]	SD [kg]	Total	Mean [kg]	SD [kg]	Total	Weight	IV, Random, 95% CI [kg]		IV, Rando	om, 95% C	l [kg]	
Erem 2014	76.8	14.7	19	83.4	13.3	19	3.3%	-6.60 [-15.51, 2.31]		_	+		
Esposito 2011	1.4	0.9	55	-0.2	0.2	55	25.1%	1.60 [1.36, 1.84]			•		
Pavo 2003	0.7	4.099	105	-2.4	4	100	22.9%	3.10 [1.99, 4.21]			•		
Roden 2005	2.09	4.887	597	-2.64	4.887	597	24.6%	4.73 [4.18, 5.28]			•		
Russell-Jones 2012	1.5	3.83	163	-2	3.137	246	24.2%	3.50 [2.79, 4.21]			•		
Total (95% CI)			939			1017	100.0%	2.90 [1.16, 4.64]			♦		
Heterogeneity: Tau ² =	3.11: Chi ² = 1	122.27. df	= 4 (P	< 0.00001): I	² = 97%				-	-	+	-	
Test for overall effect:			`	,,					-100	-50 Favours Pioglitazor	0	50 s Metformin	100

8

1

2

3

4 5

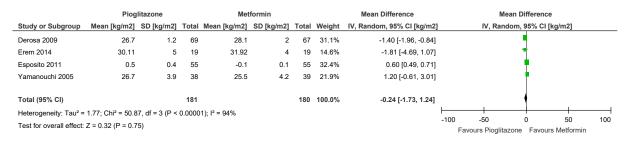
6

2

3 4

7

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



E.1.752 Pioglitazone compared to linagliptin

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

E.1.783 Pioglitazone compared to sitagliptin

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

	Pioglita	zone	Sitagli	ptin		Risk Difference		Risk Di	fference		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	l	M-H, Fixe	ed, 95% CI		
Henry 2014	1	565	1	186	63.2%	-0.00 [-0.01, 0.01]		_	-		
Russell-Jones 2012	0	163	0	163	36.8%	0.00 [-0.01, 0.01]		-	_		
Total (95% CI)		728		349	100.0%	-0.00 [-0.01, 0.01]		•			
Total events	1		1								
Heterogeneity: Chi ² =	0.20, df = 1	(P = 0.	66); I² = ()%			<u> </u>	-0.05) 0.	05	<u> </u>
Test for overall effect:	Z = 0.54 (F	P = 0.59)				-0.1	Favours Pioglitazone	Favours Sita	.05 gliptin	0.1

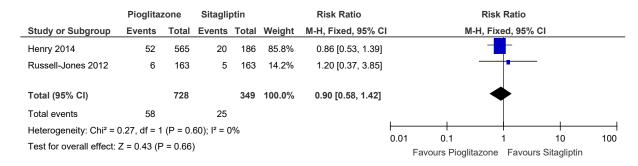
10 Figure 125: Cardiovascular mortality at end of follow-up

	Pioglita	zone	Sitagli	ptin		Risk Difference		Risk Di	fference		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fix	ed, 95% CI		
Henry 2014	0	565	0	186	63.2%	0.00 [-0.01, 0.01]			p		
Russell-Jones 2012	0	163	0	163	36.8%	0.00 [-0.01, 0.01]		I	Ť		
Total (95% CI)		728		349	100.0%	0.00 [-0.01, 0.01]					
Total events	0		0								
Heterogeneity: Chi ² =	0.00, df = 1	(P = 1.	00); I ² = ()%			<u> </u>	 	 	 	
Test for overall effect:	Z = 0.00 (F	P = 1.00)				-1	-0.5 Favours Pioglitazone	0 Favours S	0.5 itagliptin	1

11

9

1 Figure 126: Hypoglycaemia episodes at end of follow-up



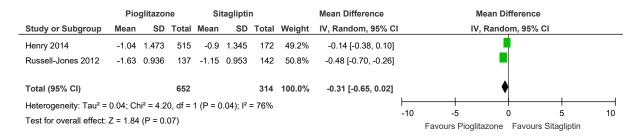
3

4

5

2

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

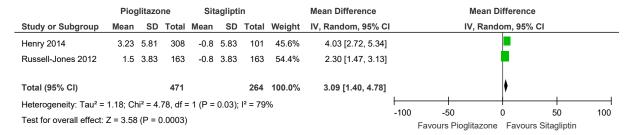


6 7

8

9

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



10 11

E.1.724 Pioglitazone compared to vildagliptin

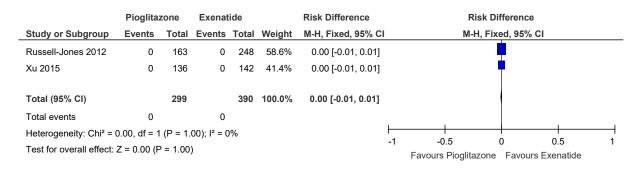
There are no forest plots reported for this comparison (all outcomes include a single study).

14

13

E.1.715 Pioglitazone compared to exenatide

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



5 Figure 130: Cardiovascular mortality at end of follow-up

	Pioglita	zone	Exenat	tide		Risk Difference		Risk Di			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fix	ed, 95% CI		
Russell-Jones 2012	0	163	0	248	58.6%	0.00 [-0.01, 0.01]					
Xu 2015	0	136	0	142	41.4%	0.00 [-0.01, 0.01]			†		
Total (95% CI)		299		390	100.0%	0.00 [-0.01, 0.01]					
Total events	0		0								
Heterogeneity: Chi ² = 0	0.00, df = 1	(P = 1.	00); I ² = 0)%			<u> </u>	+	+	+	\rightarrow
Test for overall effect:	Z = 0.00 (F	P = 1.00)				-1	-0.5 Favours Pioglitazone	0 Favours Ex	0.5 xenatide	1

8 Figure 131: Hypoglycaemia episodes at end of follow-up

	Pioglita	zone	Exenat	ide		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Russell-Jones 2012	6	163	13	248	44.8%	0.70 [0.27, 1.81]	
Xu 2015	5	136	13	142	55.2%	0.40 [0.15, 1.10]	-
Total (95% CI)		299		390	100.0%	0.54 [0.27, 1.06]	•
Total events	11		26				
Heterogeneity: Chi ² = 0	0.63, df = 1	(P = 0.	43); I² = 0)%			0.01 0.1 1 10 100
Test for overall effect:	Z = 1.79 (F	P = 0.07)				Favours Pioglitazone Favours Exenatide

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

	Piog	litazone		Exe	natide		Mean Difference			Mean Di			ice	
Study or Subgroup	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV, Random, 95% CI [%]			IV, Rand	om, 95%	6 CI [%]	
Russell-Jones 2012	-1.63	0.936	137	-1.53	1.034	218	52.7%	-0.10 [-0.31, 0.11]						
Xu 2015	-1.5	1.086	118	-1.8	1.049	110	47.3%	0.30 [0.02, 0.58]						
Total (95% CI)			255			328	100.0%	0.09 [-0.30, 0.48]				•		
Heterogeneity: Tau ² Test for overall effect		-10			0	5	10							
Test for overall effect	t: Z = 0.45 (P :	= 0.66)								Favours	Pioglitazon	e Favo	urs Exena	ti

9

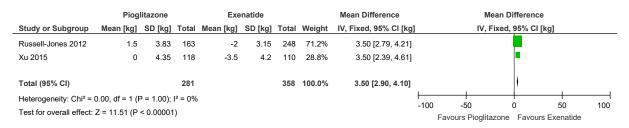
10

11

12

3 4

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



4 5

1

2

3

J

E.1.766 Pioglitazone compared to liraglutide

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

8

E.1.797 Pioglitazone compared to gliclazide

10 Figure 134: Hypoglycaemia episodes at end of follow-up

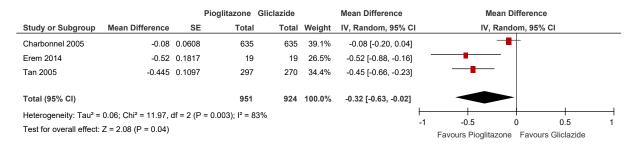
	Pioglita	zone	Gliclaz	zide		Risk Difference		Risk Difference		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI		
Charbonnel 2005	25	635	63	635	96.9%	-0.06 [-0.09, -0.03]				
Erem 2014	0	20	0	20	3.1%	0.00 [-0.09, 0.09]		_		
Total (95% CI)		655		655	100.0%	-0.06 [-0.09, -0.03]		•		
Total events	25		63							
Heterogeneity: Chi ² =	1.54, df = 1	(P = 0.	22); I² = 3	35%			<u> </u>	- 	+	<u> </u>
Test for overall effect:	Z = 4.20 (F	o.00	01)				-1	-0.5 0 Favours Pioglitazone Favours G	0.5 liclazide	1

11 12

13

14

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



15

2

3 4

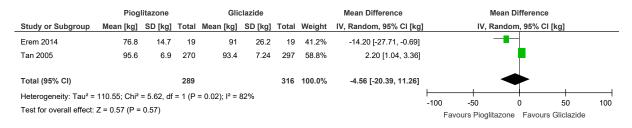
7 8

9

11 12

15

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



E.1.758 Pioglitazone compared to glimepiride

6 Figure 137: Hypoglycaemia episodes at follow-up

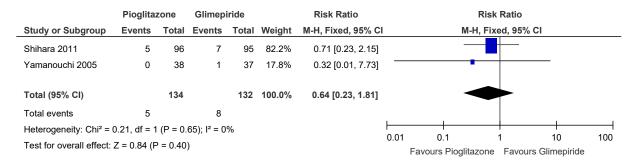
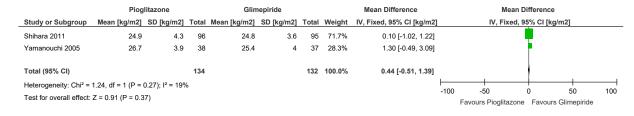


Figure 138: BMI change (kg/m2, lower values are better, final values) at end of follow-up

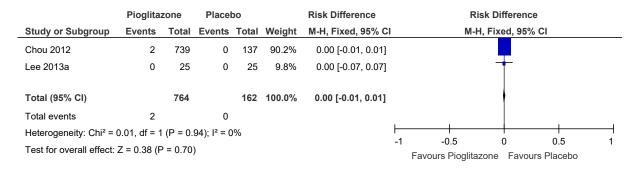


E.1.739 Pioglitazone compared to insulin

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

E.1.7.10 Pioglitazone compared to placebo

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



3

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

	Pioglitazon			bo	Risk Difference			Risk Difference			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fix	ked, 95% (CI	
Chou 2012	2	739	0	137	90.2%	0.00 [-0.01, 0.01]					
Lee 2013a	0	25	0	25	9.8%	0.00 [-0.07, 0.07]		-	+		
Total (95% CI)		764		162	100.0%	0.00 [-0.01, 0.01]					
Total events	2		0								
Heterogeneity: Chi ² =	0.01, df = 1	(P = 0.	94); I² = 0)%			<u> </u>	+	+		
Test for overall effect:	Z = 0.38 (F	P = 0.70)				-1	-0.5 Favours Pioglitazone	0 Favours	0.5 s Placebo	1

6 7

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

	Pioglita	zone	Place	bo		Risk Difference		Ri	sk Differend	ce	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H	I, Fixed, 95°	% CI	
Chou 2012	1	739	0	137	68.6%	0.00 [-0.01, 0.01]					
Kikuchi 2012	0	159	0	54	23.9%	0.00 [-0.03, 0.03]			•		
Lee 2013a	0	25	1	25	7.4%	-0.04 [-0.14, 0.06]			+		
Total (95% CI)		923		216	100.0%	-0.00 [-0.01, 0.01]			4		
Total events	1		1								
Heterogeneity: Chi ² =	0.93, df = 2	2 (P = 0.	63); I ² = 0)%			۲				
Test for overall effect:	Z = 0.32 (F	P = 0.75)				-1	-0.5 Favours Pioglita	0 zone Favo	0.5 urs Placebo	1

9

1 Figure 142: Hypoglycaemia episodes at end of follow-up

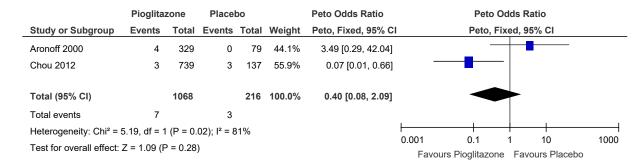


Figure 143: HbA1c change (%, lower values are better, change scores) at end of follow-up

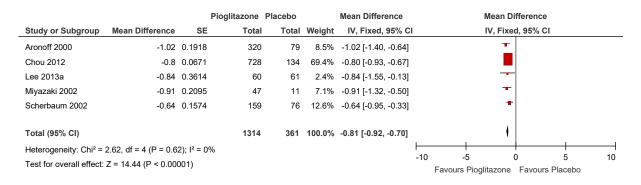


Figure 144: Weight change (kg, lower values are better, change scores and final values) at end of follow-up

	Piog	glitazon	e	Р	lacebo			Mean Difference		Me	an Differenc	e	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C	l	IV, F	Random, 95%	6 CI	
Aronoff 2000	91.434	14.8	326	90.4	13.07	79	10.9%	1.03 [-2.27, 4.33]			-		
Kikuchi 2012	2.8	2.1	159	-1	1.7	54	31.1%	3.80 [3.24, 4.36]				-	
Miyazaki 2002	2.367	1.771	47	-0.4	1.4	11	28.0%	2.77 [1.80, 3.74]			-	_	
Scherbaum 2002	0.5	2.7	159	-1.1	2.6	76	30.0%	1.60 [0.88, 2.32]			-		
Total (95% CI)			691			220	100.0%	2.55 [1.22, 3.88]			◀	>	
Heterogeneity: Tau² =	1.39; Chi	² = 23.8	0, df =	3 (P < 0	.0001);	I ² = 87	%		<u> </u>				
Test for overall effect:	Z = 3.76	(P = 0.0	002)						-10 F	-5 avours Pioglita	0 zone Favou	5 rs Placebo	10

10 11

2

4

5

6 7

8

1 E.1.8 Combinations

E.1.821 Alogliptin + metformin compared to metformin

3 Figure 145: Hypoglycaemia episodes at end of follow-up

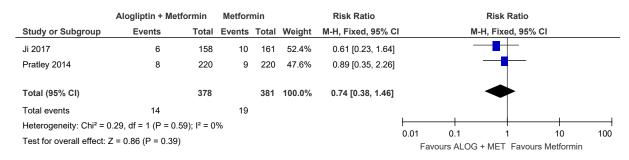


Figure 146: HbA1c change (%, lower values are better, change scores and final values) at end of follow-up

			Alogliptin + Metformin	Metformin		Mean Difference			Mean Di	fference		
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Fixed, 95% CI			IV, Fixed	i, 95% CI		
Ji 2017	-0.36	0.2209	158	161	15.0%	-0.36 [-0.79, 0.07]						
Pratley 2014	-0.5	0.0928	213	211	85.0%	-0.50 [-0.68, -0.32]						
Total (95% CI)			371	372	100.0%	-0.48 [-0.65, -0.31]			•			
Heterogeneity: Chi ² =	0.34, df = 1 (P = 0.5	6); I ² = 0	%				<u></u>					
Test for overall effect:	Z = 5.60 (P < 0.000	01)					-10	-5 Favours AL	.OG + MET		5 Metformin	10

E.1.802 Alogliptin + metformin compared to alogliptin

11 Figure 147: Hypoglycaemia episodes at end of follow-up

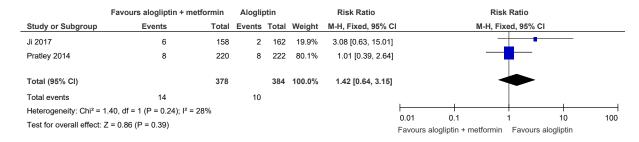


Figure 148: HbA1c change (%, lower values are better, change scores) at end of follow-up

			Alogliptin + Metformin	Alogliptin		Mean Difference	Mean Di	fference		
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Fixed, 95% CI	IV, Fixe	d, 95% CI		
Ji 2017	-0.74	0.22	158	162	15.9%	-0.74 [-1.17, -0.31]				
Pratley 2014	-0.85	0.0956	213	208	84.1%	-0.85 [-1.04, -0.66]				
Total (95% CI)			371	370	100.0%	-0.83 [-1.00, -0.66]	\			
Heterogeneity: Chi ² = Test for overall effect:		,.	%				5 otin + Metformin	-	5 ptin	10

12 13

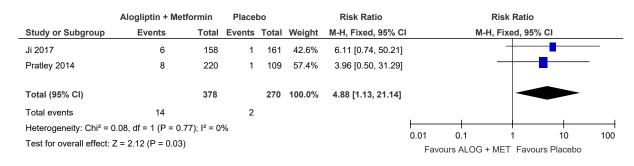
14

15

4 5

E.1.823 Alogliptin + metformin compared to placebo

3 Figure 149: Hypoglycaemia episodes at end of follow-up



4

5

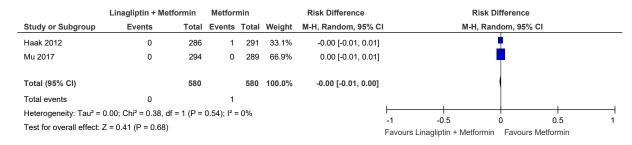
E.1.864 Linagliptin + metformin compared to metformin

7 Figure 150: Hypoglycaemia episodes at end follow-up

	Linagliptin + Met	ormin	Metfori	nin		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	I	M-H, Ran	dom, 95% CI	
Haak 2012	5	286	7	291	61.0%	0.73 [0.23, 2.26]			 	
Mu 2017	5	294	3	289	39.0%	1.64 [0.40, 6.79]				
Total (95% CI)		580		580	100.0%	1.00 [0.41, 2.42]		⋖		
Total events	10		10							
Heterogeneity: Tau ² =	0.00; Chi ² = 0.77, df	= 1 (P =	0.38); I² =	0%			0.04		1 10	100
Test for overall effect:	Z = 0.01 (P = 1.00)						0.01 Favours Li	0.1 nagliptin + Metformin	1 10 Favours Metformin	100

8 9

10 Figure 151: Severe hypoglycaemic episodes at end follow-up



11 12

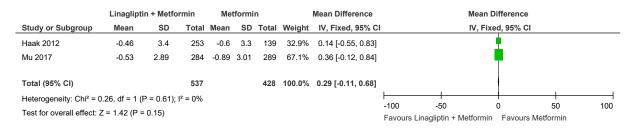
13

14

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

	Linagliptin + Metformin			Me	tformi	n		Mean Difference		Mean Di	fference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixe	d, 95% CI		
Haak 2012	-1.4	1.2	277	-0.85	1.2	279	44.6%	-0.55 [-0.75, -0.35]					
Mu 2017	-2.22	0.95	183	-1.85	0.97	277	55.4%	-0.37 [-0.55, -0.19]					
Total (95% CI) Heterogeneity: Chi² = 1	.73, df = 1 (F	P = 0.19);	460 I ² = 42%)		556	100.0%	-0.45 [-0.58, -0.32]	-10 -	5)	- 5	——————————————————————————————————————
Test for overall effect: Z				Favours Linaglip		Favours Metf	-	10					

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



E.1.865 Linagliptin + metformin compared to linagliptin

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

	Linagliptin + met	tformin	Linagli	ptin		Risk Difference		Ris	k Differen	се	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I	M-H,	Fixed, 95	% CI	
Haak 2012	0	286	0	142	54.6%	0.00 [-0.01, 0.01]			•		
Ross 2015	0	159	0	157	45.4%	0.00 [-0.01, 0.01]			Ť		
Total (95% CI)		445		299	100.0%	0.00 [-0.01, 0.01]					
Total events	0		0								
Heterogeneity: Chi² =	0.00, df = 1 (P = 1.0	0); I ² = 0%	, 0				-1	-0.5	0	0.5	
Test for overall effect:	Z = 0.00 (P = 1.00)						•	-0.5 iptin + metforr		gliptin	'

10 Figure 155: Cardiovascular mortality at end of follow-up

	Linagliptin + met	Linagliptin + metformin Li		ptin		Risk Difference		Risl	k Differen	ce	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	l	M-H,	Fixed, 95	% CI	
Haak 2012	0	286	0	142	54.6%	0.00 [-0.01, 0.01]					
Ross 2015	0	159	0	157	45.4%	0.00 [-0.01, 0.01]			•		
Total (95% CI)		445		299	100.0%	0.00 [-0.01, 0.01]					
Total events	0		0								
Heterogeneity: Chi ² =	0.00, df = 1 (P = 1.0	0); I ² = 0%	6				<u> </u>	+	 		
Test for overall effect:	Z = 0.00 (P = 1.00)						-1 Linag	-0.5 liptin + metforn	0 nin Linag	0.5 gliptin	1

11 12

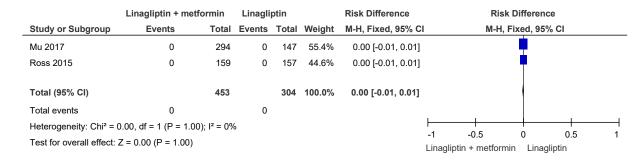
8 9

1

2

3

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



4 Figure 157: Hypoglycaemia episodes at end of follow-up

2 3

5 6

Linagliptin + metformin Linagliptin Risk Ratio Risk Ratio M-H, Fixed, 95% CI M-H, Fixed, 95% CI Study or Subgroup **Events** Total Events Total Weight Haak 2012 5 286 0 142 9.5% 5.48 [0.31, 98.43] Mu 2017 5 294 147 19.0% 2.50 [0.29, 21.20] Ross 2015 3 159 157 71.5% 0.59 [0.14, 2.44] Total (95% CI) 446 100.0% 1.42 [0.52, 3.87] Total events 13 6 Heterogeneity: Chi² = 2.57, df = 2 (P = 0.28); I² = 22% 0.001 0.1 1000 Test for overall effect: Z = 0.68 (P = 0.50)

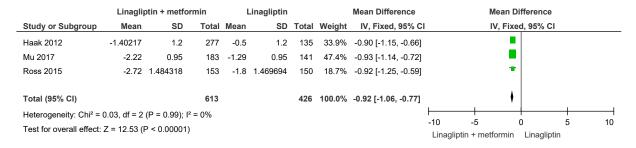
Linagliptin + metformin

Linagliptin

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

	Linagliptin + metf	ormin	Linagli	ptin		Risk Difference		Ris	k Differen	ce	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I	M-H,	Fixed, 95	% CI	
Haak 2012	0	286	0	142	34.9%	0.00 [-0.01, 0.01]			•		
Mu 2017	0	294	0	147	36.0%	0.00 [-0.01, 0.01]			•		
Ross 2015	0	159	0	157	29.1%	0.00 [-0.01, 0.01]			•		
Total (95% CI)		739		446	100.0%	0.00 [-0.01, 0.01]					
Total events	0		0								
Heterogeneity: Chi ² =	0.00, df = 2 (P = 1.00); I ² = 0%	6					+			
Test for overall effect:	Z = 0.00 (P = 1.00)						-1 Linag	-0.5 liptin + metforn	0 nin Linaç	0.5 gliptin	1

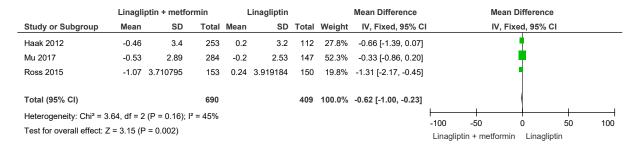
Figure 159: HbA1c change (%, lower values are better, change scores) at end of follow-up



8 9

10

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



4 5

1

2

3

E.1.86 Linagliptin + metfo

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

8

E.1.897 Saxagliptin + metformin compared to metformin

Linagliptin + metformin compared to placebo

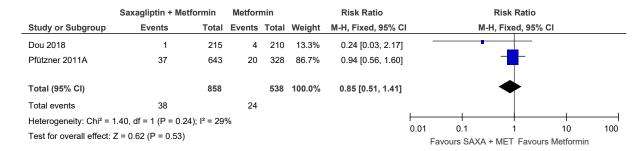
10

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

	Saxagliptin + Me	tformin	Metfori	min		Risk Difference		Ris	sk Differen	ce	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H,	Random, 9	5% CI	
Dou 2018	0	215	0	210	58.2%	0.00 [-0.01, 0.01]			-		
Pfützner 2011A	3	643	5	328	41.8%	-0.01 [-0.02, 0.00]		-	-		
Total (95% CI)		858		538	100.0%	-0.00 [-0.02, 0.01]			•		
Total events	3		5								
Heterogeneity: Tau ² =	0.00; Chi ² = 2.53, d	f = 1 (P = 0		-0.1	-0.05			+			
Test for overall effect:	est for overall effect: Z = 0.65 (P = 0.52)								MET Favo	0.05 ours Metformin	0.1 1

11

12 Figure 162: Hypoglycaemia episodes at end of follow-up



13

14

Figure 163: Severe hypoglycaemic episodes at end of follow up

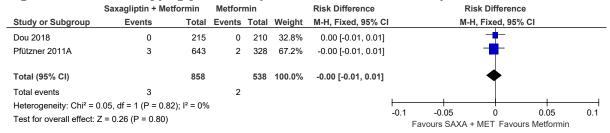


Figure 164: HbA1c change (%, lower values are better, change scores) at end of follow-up

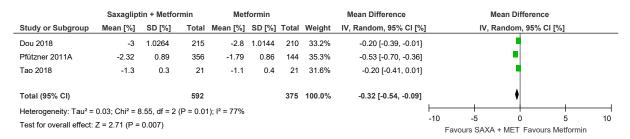


Figure 165: Weight change (kg, lower values are better, change scores) at end of follow-up

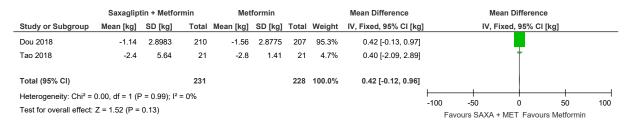
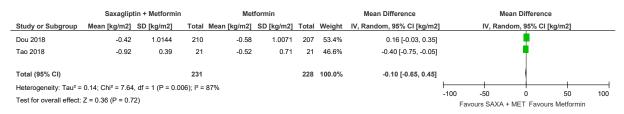
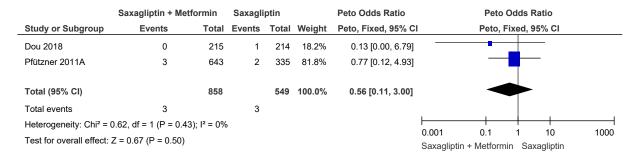


Figure 166: BMI change (kg/m2, lower values are better, change scores) at end of follow-up



E.1.818 Saxagliptin + metformin compared to saxagliptin

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



5 Figure 168: Hypoglycaemia episodes at end of follow-up

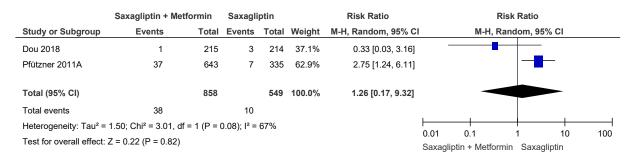


Figure 169: Severe hypoglycaemic episodes at end of follow up

			Metfor	min		Risk Difference		Ri	sk Differend	ce	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H	I, Fixed, 95°	% CI	
Dou 2018	0	215	0	210	32.8%	0.00 [-0.01, 0.01]			-		
Pfützner 2011A	3	643	2	328	67.2%	-0.00 [-0.01, 0.01]			-		
Total (95% CI)		858		538	100.0%	-0.00 [-0.01, 0.01]			•		
Total events	3		2								
Heterogeneity: Chi ² = 0	0.05, df = 1 (P = 0.82); I ² = 0%	,				-0.1	-0.05		0.05	0.1
Test for overall effect:						avours SAXA +	MET Favo		0.1		

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

	Saxagliptin + Metformin			Sa	xaglipti	in		Mean Difference		Me	an Differer	ice	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C		IV, I	Random, 95	5% CI	
Dou 2018	-3	1.0264	215	-2.1	1.024	214	33.4%	-0.90 [-1.09, -0.71]			•		
Pfützner 2011A	-2.32	0.89	356	-1.55	0.82	113	33.8%	-0.77 [-0.95, -0.59]			•		
Tao 2018	-1.3	0.3	21	-1.1	0.4	21	32.8%	-0.20 [-0.41, 0.01]					
Total (95% CI)			592			348	100.0%	-0.63 [-1.02, -0.23]			•		
Heterogeneity: Tau ² = Test for overall effect:		-10 Saxagi	-5 iptin + Metfo	0 ormin Saxa	5 agliptin	10							

11

8

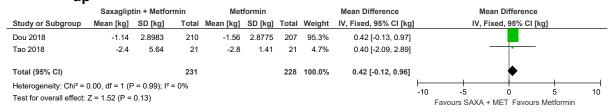
9

10

3 4

6 7

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



2

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

•													
	Saxaglip	tin + Metformi	n	Met	formin			Mean Difference		Mea	an Differenc	e	
Study or Subgroup	Mean [kg/m2]	SD [kg/m2]	Total	Mean [kg/m2]	SD [kg/m2]	Total	Weight	IV, Random, 95% CI [kg/m2]		IV, Rand	om, 95% CI	[kg/m2]	
Dou 2018	-0.42	1.0144	210	-0.58	1.0071	207	53.4%	0.16 [-0.03, 0.35]			+		
Tao 2018	-0.92	0.39	21	-0.52	0.71	21	46.6%	-0.40 [-0.75, -0.05]		-	-		
Total (95% CI)			231			228	100.0%	-0.10 [-0.65, 0.45]		~			
Heterogeneity: Tau ²	= 0.14; Chi ² = 7.64	I, df = 1 (P = 0.0	006); I ² =	87%					_				
Test for overall effect	: Z = 0.36 (P = 0.7	72)							-2	-1 Favours SAXA +	U MET Favor	1 Irs Metformin	2

3

E.1.849 Sitagliptin + metformin compared to metformin

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

	Sitagliptin + Metf	ormin	Metfori	min		Risk Difference		Ris	k Difference	9	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H	, Fixed, 95%	CI	
Goldstein 2007	0	372	0	364	59.7%	0.0000 [-0.0053, 0.0053]			•		
Ji 2016A	0	247	0	250	40.3%	0.0000 [-0.0078, 0.0078]			•		
Total (95% CI)		619		614	100.0%	0.0000 [-0.0045, 0.0045]					
Total events	0		0								
Heterogeneity: Chi ² =	0.00, df = 1 (P = 1.0	0); I ² = 0	%					+	+		
Test for overall effect:					-1 Favou	-0.5 rs Sitagliptin + Metfor	0 min Favou	0.5 rs Metformin	1		

5

Figure 174: Cardiovascular mortality at end of follow-up

	Sitagliptin + Met	formin	Metfori	min		Risk Difference		F	Risk Difference		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	l	M	-H, Fixed, 95%	CI	
Goldstein 2007	0	372	0	364	59.7%	0.0000 [-0.0053, 0.0053]			•		
Ji 2016A	0	247	0	250	40.3%	0.0000 [-0.0078, 0.0078]			•		
Total (95% CI)		619		614	100.0%	0.0000 [-0.0045, 0.0045]					
Total events	0		0								
Heterogeneity: Chi² =	0.00, df = 1 (P = 1.0	0); I ² = 0	%								
Test for overall effect:					-1 Favours S	-0.5 Sitagliptin + Met	0 formin Favours	0.5 Metformin	1		

Figure 175: Hypoglycaemia episodes at end of follow-up

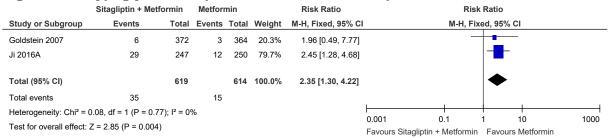
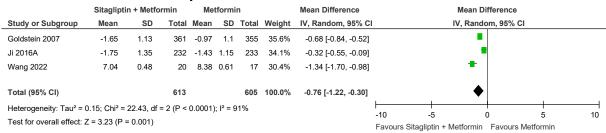


Figure 176: HbA1c change (%, lower values are better, change scores and final value) at end of follow-up



2

E.1.8.80 Sitagliptin + metformin compared to sitagliptin

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

	Sitagliptin + Met	formin	Sitagli	ptin		Risk Difference		R	isk Differenc	е	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-I	H, Fixed, 95%	CI	
Goldstein 2007	0	372	0	179	59.9%	0.00 [-0.01, 0.01]			•		
Ji 2016A	0	247	0	120	40.1%	0.00 [-0.01, 0.01]			•		
Total (95% CI)		619		299	100.0%	0.00 [-0.01, 0.01]					
Total events	0		0								
Heterogeneity: Chi ² =	0.00, df = 1 (P = 1.0	0); I ² = 0 ⁰	%				<u> </u>				
Test for overall effect:	Test for overall effect: Z = 0.00 (P = 1.00)						-1 Fav	-0.5 ours Sitagliptin	0 + Met Favou	0.5 rs Sitagliptin	1

4

Figure 178: Cardiovascular mortality at end of follow-up

	• .		Sitagli	ptin		Risk Difference		Risk Differenc	е	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I	M-H, Fixed, 95%	CI	
Goldstein 2007	0	372	0	179	59.9%	0.00 [-0.01, 0.01]		•		
Ji 2016A	0	247	0	120	40.1%	0.00 [-0.01, 0.01]		•		
Total (95% CI)		619		299	100.0%	0.00 [-0.01, 0.01]				
Total events	0		0							
Heterogeneity: Chi ² =	0.00, df = 1 (P = 1.0	00); I ² = 0 ⁶	%				1 05	 	0.5	
Test for overall effect:					-1 -0.5 Favours Sitag	0 liptin + Met Favou	0.5 rs Sitagliptin	1		

Figure 179: Hypoglycaemia episodes at end of follow-up

	Sitagliptin + Me	Sitagli	ptin		Risk Ratio	Risk Ratio					
Study or Subgroup	Events Total		Events	Total	Weight	M-H, Fixed, 95% C	1	M-I	H, Fixed, 95%	CI	
Goldstein 2007	6	372	1	179	16.7%	2.89 [0.35, 23.80]			<u> </u>		
Ji 2016A	29	247	5	120	83.3%	2.82 [1.12, 7.10]					
Total (95% CI)		619		299	100.0%	2.83 [1.21, 6.60]				>	
Total events	35		6								
Heterogeneity: Chi² =	0.00, df = 1 (P = 0	.98); I² = 0°	%				0.04		1	10	400
Test for overall effect:	Z = 2.41 (P = 0.02	2)					0.01 Favo	0.1 urs Sitagliptin ·	ı + Met Favour	10 s Sitagliptin	100

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

			-											
	Sitaglipti	n + Metfo	rmin	Sitagliptin				Mean Difference		Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C	l	IV	, Random, 95%	CI		
Goldstein 2007	-1.65	1.13	361	-0.66	1.12	175	36.2%	-0.99 [-1.19, -0.79]			•			
Ji 2016A	-1.75	1.35	232	-0.99	1.31	113	34.1%	-0.76 [-1.06, -0.46]			•			
Wang 2022	7.04	0.48	20	6.95	0.86	17	29.6%	0.09 [-0.37, 0.55]			<u>†</u>			
Total (95% CI)			613			305	100.0%	-0.59 [-1.12, -0.07]			•			
Heterogeneity: Tau ² =	0.19; Chi ² =	17.84, df	= 2 (P =	0.0001); I ² = 8	39%			\vdash	-		-		
			`	,	,,				-10	-5	0	5	10	
Test for overall effect:	Z = 2.21 (P =	= 0.03)							Favo	ırs Sitagliptir	+ Met Favou	rs Sitagliptin		

2

E.1.8.%1 Sitagliptin + metformin compared to glimepiride

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

5

E.1.8.62 Sitagliptin + metformin compared to pioglitazone

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

8

E.1.8.13 Sitagliptin + metformin compared to placebo

10

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

	Sitagliptin + Met	Placel	bo		Risk Difference		Risk Difference				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	l	% CI			
Goldstein 2007	0	372	1	176	58.9%	-0.01 [-0.02, 0.01]					
Ji 2016A	0	247	0	126	41.1%	0.00 [-0.01, 0.01]			+		
Total (95% CI)		619		302	100.0%	-0.00 [-0.01, 0.01]			•		
Total events	0		1								
Heterogeneity: Chi ² =	0.39, df = 1 (P = 0.5	3); I ² = 0 ⁹	%				+				+
Test for overall effect:	Z = 0.68 (P = 0.50)						-0.1 Fa	-0.05 vours SITA +	∪ ·MET Favo	0.05 urs Placebo	0.1

Figure 182: Cardiovascular mortality at end of follow up



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



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



E.1.8.94 Vildagliptin + metformin compared to metformin

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



12

1

3 4

5

6

7 8

10

2

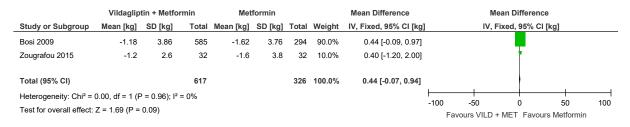
3 4

7

10

13

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



E.1.8.65 Vildagliptin + metformin compared to vildagliptin

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

E.1.8.66 Canagliflozin + metformin compared to canagliflozin

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

E.1.8117 Canagliflozin + metformin compared to metformin

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

E.1.8148 Dapagliflozin + metformin compared to dapagliflozin

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

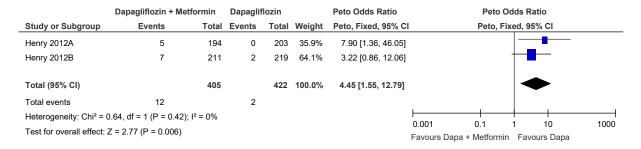
	Dapagliflozin + Met	formin	Dapagli	flozin		Risk Difference	Risk D	ifference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	CI M-H, Fix	ked, 95% CI	
Henry 2012A	0	194	1	203	48.0%	-0.00 [-0.02, 0.01]	I	•	
Henry 2012B	0	211	0	219	52.0%	0.00 [-0.01, 0.01]	1	T	
Total (95% CI)		405		422	100.0%	-0.00 [-0.01, 0.01]			
Total events	0		1						
Heterogeneity: Chi ² = 0	0.40, df = 1 (P = 0.53);	$I^2 = 0\%$					1 05	+ +	\dashv
Test for overall effect:	Z = 0.57 (P = 0.57)						-1 -0.5 Favours Dapa + Metformin	0 0.5 Favours Dapa	1

Figure 188: Cardiovascular mortality at end of follow-up

	Dapagliflozin + Me	tformin	Dapaglif	flozin		Risk Difference		Ri	sk Differenc	е	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	l	M-H	I, Fixed, 95%	6 CI	
Henry 2012A	0	194	1	203	48.0%	-0.00 [-0.02, 0.01]					
Henry 2012B	0	211	0	219	52.0%	0.00 [-0.01, 0.01]					
Total (95% CI)		405		422	100.0%	-0.00 [-0.01, 0.01]			•		
Total events	0		1								
Heterogeneity: Chi ² = 0	0.40, df = 1 (P = 0.53)	; I ² = 0%						- 	 		 !
Test for overall effect:	Z = 0.57 (P = 0.57)						-1 Favour	-0.5 s Dapa + Metfo	0 rmin Favou	0.5 Irs Dapa	1

16 17

Figure 189: Hypoglycaemia episodes at end of follow-up



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

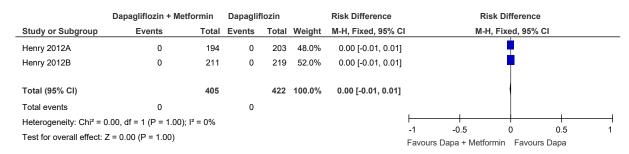


Figure 191: HbA1c change (%, lower values are better, change scores) at end of follow-up

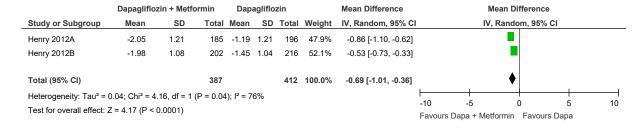
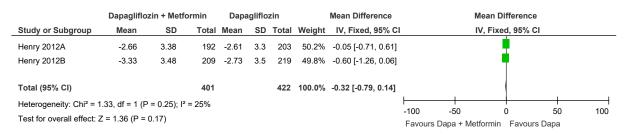
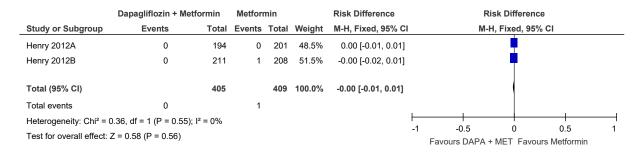


Figure 192: Weight change (kg, lower values are better, change scores) at end of follow-up

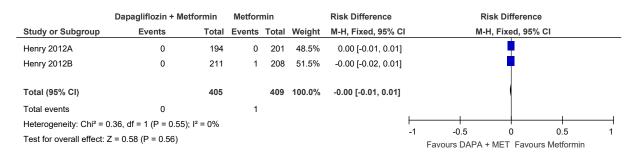


E.1.8.19 Dapagliflozin + metformin compared to metformin

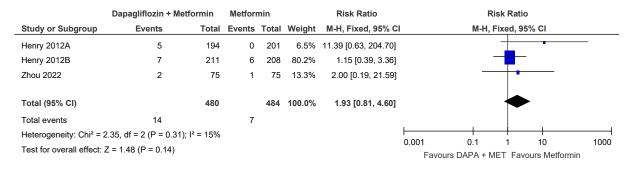
2 Figure 193: All-cause mortality at end of follow-up



5 Figure 194: Cardiovascular mortality at end of follow-up



8 Figure 195: Hypoglycaemia episodes at end of follow-up



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

	Dapagliflozin + Met	formin	Metfori	min		Risk Difference		Ri	sk Differend	:e	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H	l, Fixed, 95%	6 CI	
Henry 2012A	0	194	0	201	48.5%	0.00 [-0.01, 0.01]			•		
Henry 2012B	0	211	0	208	51.5%	0.00 [-0.01, 0.01]					
Total (95% CI)		405		409	100.0%	0.00 [-0.01, 0.01]					
Total events	0		0								
Heterogeneity: Chi ² =	0.00, df = 1 (P = 1.00);	$I^2 = 0\%$					<u> </u>		+		$\overline{}$
Test for overall effect:	Z = 0.00 (P = 1.00)						-1 F	-0.5 avours DAPA +	0 MET Favou	0.5 urs Metformin	1

9 10

3 4

2

3 4

5

6

7 8

11

14

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

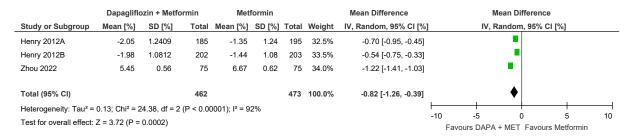
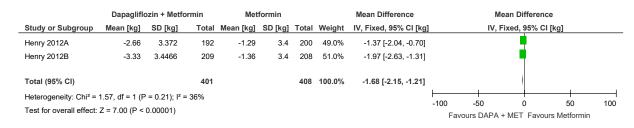


Figure 198: Weight change (kg, lower values are better, change scores and final values) at end of follow-up



E.1.8.20 Empagliflozin + metformin compared to metformin

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

E.1.8121 Empagliflozin + metformin compared to empagliflozin

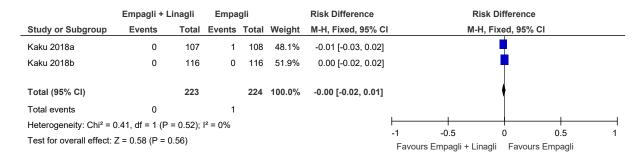
13 There are no forest plots reported for this comparison (all outcomes include a single study).

E.1.8122 Empagliflozin + linagliptin compared to empagliflozin

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

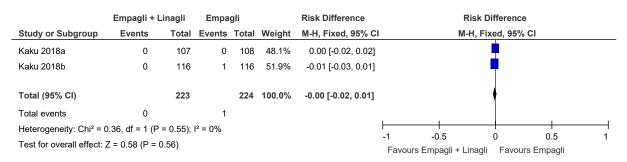
	Empagli + L	.inagli	Empa	gli		Risk Difference		Ri	sk Differenc	е	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-l	H, Fixed, 95%	6 CI	
Kaku 2018a	0	107	0	108	48.1%	0.00 [-0.02, 0.02]			•		
Kaku 2018b	0	116	0	116	51.9%	0.00 [-0.02, 0.02]			Ť		
Total (95% CI)		223		224	100.0%	0.00 [-0.01, 0.01]					
Total events	0		0								
Heterogeneity: Chi ² =	0.00, df = 1 (P	= 1.00);	$I^2 = 0\%$								
Test for overall effect:	Z = 0.00 (P = 1	1.00)					-1 Favoui	-0.5 rs Empagli + Lir	0 nagli Favou	0.5 ırs Empagli	1

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



2

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

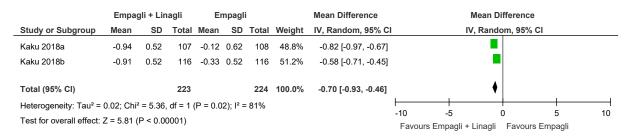


5 6

7

8

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



9 10

E.1.8123 Empagliflozin + linagliptin compared to linagliptin

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

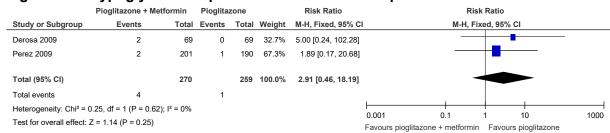
13

E.1.8124 Gliclazide + saxagliptin compared to saxagliptin + metformin

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

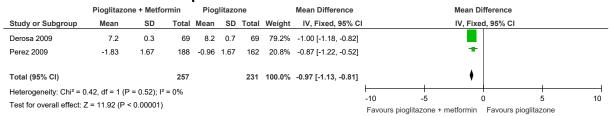
Pioglitazone + metformin compared to pioglitazone E.1.8.25

Figure 203: Hypoglycaemia episodes at end of follow-up



2 3

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



5

4

E.1.8.26 Glimepiride + metformin compared to canagliflozin + metformin

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

8

Glimepiride + metformin compared to metformin E.1.8.297

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

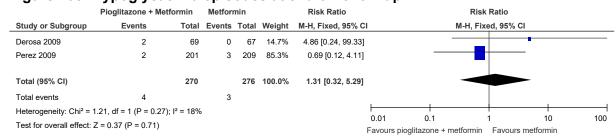
11

E.1.8128 Glimepiride + metformin compared to pioglitazone

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

E.1.8.29 Pioglitazone + metformin compared to metformin

Figure 205: Hypoglycaemia episodes at end of follow-up



2 3

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

	Pioglitazo	Pioglitazone + Metformin Metformin						Mean Difference	Mean Difference					
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C	CI .	IV,	Random, 95%	CI		
Derosa 2009	7.2	0.3	69	8.6	0.9	67	52.5%	-1.40 [-1.63, -1.17]						
Perez 2009	-1.83	1.67	188	-0.99	1.67	193	47.5%	-0.84 [-1.18, -0.50]	l		•			
Total (95% CI)			257			260	100.0%	-1.13 [-1.68, -0.59]			•			
Heterogeneity: Tau ² =	0.14; Chi ² = 7	'.35, df = 1	(P = 0.0	07); I² =	86%				10			<u> </u>		
Test for overall effect:	Z = 4.06 (P <	0.0001)							-10 Favours pi	-5 oglitazone + metf	0 ormin Favour	5 s metformin	10	

5

4

Pioglitazone + metformin compared to glimepiride + metformin E.1.8.360

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

8

Pioglitazone + alogliptin compared to alogliptin E.1.8.391

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

11

E.1.81322 Pioglitazone + alogliptin compared to pioglitazone

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

14

E.1.8133 Pioglitazone + linagliptin compared to linagliptin

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

17

E.1.81384 Pioglitazone + linagliptin compared to pioglitazone

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

E.1.8.25 Pioglitazone + sitagliptin compared to pioglitazone

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

4

E.1.8.56 Pioglitazone + vildagliptin compared to pioglitazone

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

7

E.1.8.37 Pioglitazone + vildagliptin compared to vildagliptin

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

Appendix F GRADE tables

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

F.1.1 Biguanides

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

Table 1: Clinical evidence profile: Metformin hydrochloride slow release compared to metformin hydrochloride standard release

						Other					
	Desi	Risk of	Indirect	Inconsist	Impreci	consideration	Intervent	Contr	Relative effect		Certai
No of studies	gn	bias	ness	ency	sion	S	ion N	ol N	(95% CI)	Absolute effect	nty
all-cause mortality Mean follow-up: 5.5 month(s)											
1 (aggarwal 2018)	RCT	serious	not serious	NA ²	very serious ³	NA	1/283	0/285	PETO OR 7.44 (0.15, 375.04)	4 more per 1000 (3 fewer to 10 more)	very low
hypoglycaemia episodes Mean follow-up: 5.5 month(s)											
1 (aggarwal 2018)	RCT	serious	not serious	NA ²	very serious ³	NA	0/283	3/285	PETO OR 0.14 (0.01, 1.31)	11 fewer per 1000 (22 fewer to 1 more)	very low
hba1c change Mean follow-up: 5.5 month(s)											
2	RCT	serious	not serious	serious ⁴	not serious	NA	815	459	MD -0.00 (-0.12, 0.12)	MD 0.00 lower (0.12 lower to 0.12 higher)	low

weight change Mean follow-up: 5.5 month(s)											
1 (aggarwal 2018)	RCT	serious	not serious	NA ²	not serious	NA	235	236	MD 0.15	MD 0.15 higher (0.53 lower to 0.83 higher)	moder ate

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. Downgraded by 1 or 2 increments due to heterogeneity, unexplained by subgroup analysis

F.1.1.2 Metformin compared to placebo

Table 2: Clinical evidence profile: Metformin compared to placebo

	De	Risk	Indire	Incons		Other	Interve	Cont	Relative		Cert
	sig	of	ctnes	istenc	Impre	considera	ntion	rol	effect (95%	Absolute	aint
No of studies	n	bias	S	у	cision	tions	N	N	CI)	effect	У
all-cause mortality at end of follow-up Mean follow-up: 5.9 month(s)											
6	RC T	very seriou s ¹	not seriou s	seriou s ²	very seriou s ³	NA	2/1451	1/80 1	RD 0.00 (-0.01, 0.01)	0 more per 1000 (6 fewer to 6 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 5.9 month(s)											
6	RC T	very seriou s ¹	not seriou s	seriou s ²	very seriou s ³	NA	2/1451	1/80	RD 0.00 (-0.01, 0.01)	0 more per 1000 (6 fewer to 6 more)	very low
non-fatal myocardial infarction at end of follow-up											

Mean follow-up: 6 month(s)											
1 (pratley 2014)	RC T	very seriou s ¹	not seriou s	NA ⁴	seriou s ⁵	NA	0/225	0/10 9	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	very low
hospitalisation for heart failure at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RC T	very seriou s ¹	not seriou s	NA ⁴	seriou s ⁵	NA	0/225	0/10 9	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	very low
diabetic ketoacidosis at end of follow-up Mean follow-up: 5.5 month(s)											
1 (goldstein 2007) hypoglycaemia episodes at end of follow-up	RC T	very seriou s ¹	not seriou s	NA ⁴	very seriou s ⁶	NA	0/364	1/17	PETO OR 0.05 (0.00, 3.04)	6 fewer per 1000 (17 fewer to 5 more)	very low
Mean follow-up: 6.2 month(s)											
7	RC T	very seriou s ¹	not seriou	not seriou s	seriou	NA	52/151 2	18/8 73	RR 1.93 (1.13, 3.31)	19 more per 1000 (3 more to 48 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.8 month(s)										,	
4	RC T	very seriou s ¹	not seriou s	seriou s ²	very seriou s ⁸	NA	1/939	0/47 9	RD 0.00 (-0.01, 0.01)	1 more per 1000 (6 fewer to 8 more)	very low
hba1c change (%, lower values are better, change scores and final values) at end of follow-up Mean follow-up: 6.3 month(s)									·		
13	RC T	very seriou s ¹	not seriou s	very seriou s ⁹	not seriou s	NA	1979	118 4	MD -1.22 (-1.48, - 0.95)	MD 1.22 lower	very low

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

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.03 (0.8-0.9 = serious, <0.8 = very serious).
- 4. Only one study so no inconsistency
- 5. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 6. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 7. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 8. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.23 (0.8-0.9 = serious, <0.8 = very serious).

9. 12 > 75%

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

F.1.1.3 Metformin compared to insulin

Table 3: Clinical evidence profile: Metformin compared to insulin

						Other			Relative		
	Des	Risk of	Indirec	Inconsi	Impre	considerati	Interven	Contr	effect (95%	Absolute	Cert
No of studies	ign	bias	tness	stency	cision	ons	tion N	ol N	CI)	effect	ainty
hypoglycaemia episodes at end of follow-up											
Mean follow-up: 8.4 month(s)										040 f	
1 (pistrosch 2013)	RC T	very serious	not serious	NA ²	seriou s³	NA	4/36	14/39	RR 0.31 (0.11, 0.85)	248 fewer per 1000 (319 fewer to 52 fewer)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 8.4 month(s)											
1 (pistrosch 2013)	RC T	very serious	not serious	NA ²	seriou s ⁴	NA	0/36	0/39	RD 0.00 (-0.05, 0.05)	0 fewer per 1000 (51 fewer to 51 more)	very low
hba1c change (%, lower values are better, change scores) Mean follow-up: 8.4 month(s)										,	
1 (pistrosch 2013)	RC T	very serious	not serious	NA ²	not seriou s	NA	36	39	MD 0.20 (-0.05, 0.45)	MD 0.20 higher (0.05 lower to 0.45 higher)	low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency

- 3. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 4. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.

F.1.2 DPP-4 inhibitors

F.1.2.1 Alogliptin compared to placebo

Table 4: Clinical evidence profile: Alogliptin v Placebo

Table in Chinical evidence promotiving	De					Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	У
all-cause mortality at end of follow-up Mean follow-up: 6 month(s)											
2	RC T	very seriou s ¹	not seriou s	not serious	not seriou s	NA	0/489	0/17 3	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	low
cardiovascular mortality at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s³	NA	0/225	0/10 9	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	very low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ⁴	NA	1/225	0/10 9	PETO OR 4.41 (0.07, 288.47)	4 more per 1000 (4 fewer to 13 more)	very low
hospitalisation for heart failure at end of follow-up											

Mean follow-up: 6 month(s)											
1 (pratley 2014)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s³	NA	0/225	0/10 9	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.8 month(s)											
3	RC T	very seriou s ¹	not seriou s	serious	seriou s ⁶	NA	11/476	2/32 0	PETO OR 2.62 (0.83, 8.28)	17 more per 1000 (1 more to 33 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 6 month(s)											
2	RC T	very seriou s ¹	not seriou s	not serious	not seriou s	NA	0/486	0/17	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.8 month(s)											
3	RC T	not seriou s	not seriou s	not serious	not seriou s	NA	462	313	MD -0.68 (-0.82, - 0.55)	MD 0.68 lower (0.82 lower to 0.55 lower)	high
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)											
2	RC T	very seriou s ¹	not seriou s	very serious	not seriou s	NA	489	173	MD 0.31 (-0.93, 1.56)	MD 0.31 higher (0.93 lower to 1.56 higher)	very low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 4. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 5. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 6. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 7.12 > 75%

F.1.2.2 Alogliptin compared to metformin

Table 5: Clinical evidence profile: Alogliptin compared to metformin

rable 3. Official evidence profile. Alogi	De					Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ions	ntion N	rol N	CI)	effect	У
all-cause mortality at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RC T	very seriou s ¹	not seriou	NA ²	not seriou s	NA	0/225	0/22	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	low
cardiovascular mortality at end of follow-up Mean follow-up: 6 month(s)	'	3	3	177	3	10.1	OIZZO	J	(0.01, 0.01)	morey	1000
1 (pratley 2014)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/225	0/22 5	RD 0.00 (-0.01, 0.01)	0 fewer per 1000	low

										(9 fewer to 9	
										more)	
non-fatal myocardial infarction at end of											
follow-up											
Mean follow-up: 6 month(s)									PETO OR	4 more per	
		very	not		very				7.39	1000	
	RC	seriou	seriou		seriou			0/22	(0.15,	(4 fewer to 13	very
1 (pratley 2014)	T	s ¹	s	NA ²	s ³	NA	1/225	5	372.38)	more)	low
hospitalisation for heart failure at end of									,	,	
follow-up											
Mean follow-up: 6 month(s)											
										0 fewer per	
		very	not		not			0/00	DD 0.00	1000	
1 (protley 2014)	RC	seriou s ¹	seriou	NA ²	seriou	NA	0/225	0/22 5	RD 0.00	(9 fewer to 9	love
1 (pratley 2014) hypoglycaemia episodes at end of	I	S	S	INA	S	INA	0/225	5	(-0.01, 0.01)	more)	low
follow-up											
Mean follow-up: 5.8 month(s)											
mount to not up to the mount (e)										26 fewer per	
		very	not		very					1000	
	RC	seriou	seriou	serious	seriou			19/3	RR 0.47	(44 fewer to	very
2	Т	s ¹	S	4	s ³	NA	10/384	81	(0.11, 2.03)	51 more)	low
severe hypoglycaemic episodes at end											
of follow-up											
Mean follow-up: 6 month(s)										0 f	
		vorv	not		not					0 fewer per 1000	
	RC	very seriou	seriou		seriou			0/22	RD 0.00	(9 fewer to 9	
1 (pratley 2014)	T	s ¹	S	NA ²	S	NA	0/222	0	(-0.01, 0.01)	more)	low
hba1c change (%, lower values are				, .		.5.	J,	Ť	(3.0 1, 0.0 1)		10.11
better, change score) at end of follow-up											
Mean follow-up: 5.8 month(s)											
										MD 0.36	
										higher	
	-	very	not _.						140.000	(0.18 higher	
2	RC	seriou	seriou	not	seriou	NA	270	272	MD 0.36	to 0.54	very
2	ı	s ¹	S	serious	s ⁵	INA	370	372	(0.18, 0.54)	higher)	low

weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)											
		very	not		not					MD 1.08 higher (0.53 higher	
	RC	seriou	seriou		seriou				MD 1.08	to 1.63	
1 (pratley 2014)	Τ	s ¹	S	NA ²	S	NA	225	225	(0.53, 1.63)	higher)	low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. I2 between 50% and 75%
- 5. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

F.1.2.3 Linagliptin compared to metformin

Table 6: Clinical evidence profile: linagliptin compared to metformin

	De	Risk	Indire	Incons		Other	Interve	Cont	Relative		Cert
	sig	of	ctnes	istenc	Impre	considerat	ntion	rol	effect (95%	Absolute	aint
No of studies	n	bias	S	у	cision	ions	N	N	CI)	effect	У
all-cause mortality at end of follow-up											
Mean follow-up: 6 month(s)											
									PETO OR	3 fewer per	
		very	not		very				0.23	1000	
	RC	seriou	seriou		seriou			1/29	(0.00,	(10 fewer to	very
1 (haak 2012)	Т	s ¹	S	NA^2	s ³	NA	0/142	1	14.69)	3 more)	low
cardiovascular mortality at end of follow-up											
Mean follow-up: 6 month(s)											

1 (haak 2012) 4-point mace at end of follow-up Mean follow-up: 5.5 month(s)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	0/142	1/29	PETO OR 0.23 (0.00, 14.69)	3 fewer per 1000 (10 fewer to 3 more)	very low
1 (mu 2017)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s³	NA	0/147	1/28	PETO OR 0.22 (0.00, 13.98)	3 fewer per 1000 (10 fewer to 3 more)	very low
hospitalisation for heart failure at end of follow-up Mean follow-up: 5.5 month(s)											
1 (mu 2017)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/147	0/28 9	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (10 fewer to 10 more)	low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.8 month(s)											
2	RC T	very seriou s ¹	not seriou s	not seriou s	very seriou s ³	NA	1/289	10/5 80	RR 0.29 (0.05, 1.59)	12 fewer per 1000 (16 fewer to 10 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.8 month(s)											
2	RC T	very seriou s ¹	not seriou s	seriou s ⁴	very seriou s ⁵	NA	0/289	1/58	RD -0.00 (-0.01, 0.01)	1 fewer per 1000 (9 fewer to 7 more)	very low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.7 month(s)											
3	RC T	very seriou s ¹	not seriou s	seriou s ⁶	seriou s ⁷	NA	297	575	MD 0.36 (0.09, 0.63)	MD 0.36 higher (0.09 higher to 0.63 higher)	very low

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

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 5. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.23 (0.8-0.9 = serious, <0.8 = very serious).
- 6. I2 between 50% and 75%
- 7. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 8. 95% confidence intervals cross both ends of the defined MIDs (-0.80, 0.80)

F.1.2.4 Linagliptin compared to placebo

Table 7: Clinical evidence profile: linagliptin v placebo

Table 7: Clinical evidence profile: linag	De	Piacei				Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n sig	bias	ctness	stency	cision	ions	ntion N	rol N	CI)	effect	
all-cause mortality at end of follow-up	- 11	Dias	cuiess	Stericy	CISIOII	10115	IIIIOII IN	TOLIN	Cij	enect	У
Mean follow-up: 6 month(s)											
1 (haak 2012)	RC T	very seriou s ¹	not seriou	NA ²	seriou s³	NA	0/142	0/72	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (21 fewer to 21 more)	very low
cardiovascular mortality at end of					_				(010=, 010=)		
follow-up Mean follow-up: 6 month(s)											
1 (haak 2012)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s³	NA	0/142	0/72	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (21 fewer to 21 more)	very low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 5.5 month(s)											
1 (chen 2015)	RC T	seriou s ⁴	not seriou s	NA ²	very seriou s ⁵	NA	0/200	1/99	PETO OR 0.05 (0.00, 3.14)	10 fewer per 1000 (30 fewer to 10 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.7 month(s)											
3	RC T	very seriou s ¹	not seriou s	serious	very seriou s ⁵	NA	2/512	2/26 2	PETO OR 0.52 (0.07, 4.06)	4 fewer per 1000 (16 fewer to 8 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.8 month(s)									,		

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

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 4. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 5. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 6. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 7. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.23 (0.8-0.9 = serious, <0.8 = very serious).
- 8. I2 between 50% and 75%
- 9. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

F.1.2.5 Saxagliptin compared to metformin

Table 8: Clinical evidence profile: Saxaglitpin compared to metformin

rable of official evidence profile. Oaxa	De	l			•	Other			Relative		Cert
	sig	Risk	Indire	Inconsi	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	of bias	ctness	stency	cision	ions	ntion N	rol N	CI)	effect	v
all-cause mortality at end of follow-up Mean follow-up: 11.8 month(s)				,					,		,
2	RC T	very seriou s ¹	not seriou s	serious	very seriou s ³	NA	3/549	5/53 8	PETO OR 0.59 (0.15, 2.38)	4 fewer per 1000 (14 fewer to 6 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 18 month(s)											
1 (pfützner 2011a)	RC T	very seriou s ¹	not seriou s	NA ⁴	very seriou s ³	NA	2/335	4/32 8	RR 0.49 (0.09, 2.65)	6 fewer per 1000 (11 fewer to 20 more)	very low
non-fatal stroke at end of follow-up Mean follow-up: 5.5 month(s)											
1 (dou 2018)	RC T	very seriou s ¹	not seriou s	NA ⁴	very seriou s ³	NA	1/214	1/21 0	RR 0.98 (0.06, 15.59)	0 fewer per 1000 (4 fewer to 69 more)	very low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 5.5 month(s)									,	Í	
1 (dou 2018)	RC T	very seriou s ¹	not seriou s	NA ⁴	very seriou s ³	NA	0/214	1/21 0	PETO OR 0.13 (0.00, 6.69)	5 fewer per 1000 (14 fewer to 5 more)	very low
persistent signs of worsening kidney disease at end of follow-up Mean follow-up: 5.5 month(s)											

1 (dou 2018)	RC T	very seriou s ¹	not seriou s	NA ⁴	very seriou s ³	NA	0/214	1/21	PETO OR 0.13 (0.00, 6.69)	5 fewer per 1000 (14 fewer to 5 more)	very low
progression of liver disease at end of follow-up Mean follow-up: 5.5 month(s)											
1 (dou 2018)	RC T	very seriou s ¹	not seriou s	NA ⁴	very seriou s ³	NA	1/214	0/21	PETO OR 7.25 (0.14, 365.55)	5 more per 1000 (4 fewer to 14 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 11.8 month(s)											
2	RC T	very seriou s ¹	not seriou s	not serious	seriou s ⁵	NA	10/549	24/5 38	RR 0.41 (0.20, 0.84)	26 fewer per 1000 (36 fewer to 7 fewer)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 11.8 month(s)											
2	RC T	very seriou s ¹	not seriou s	serious	very seriou s ⁶	NA	0/549	2/53 8	RD -0.00 (-0.01, 0.00)	3 fewer per 1000 (10 fewer to 4 more)	very low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
3	RC T	very seriou s ¹	not seriou s	very serious	seriou s ⁸	NA	348	375	MD 0.32 (-0.09, 0.72)	MD 0.32 higher (0.09 lower to 0.72 higher)	very low
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
2	RC T	very seriou s ¹	not seriou s	not serious	not seriou s	NA	234	228	MD 1.57 (1.13, 2.00)	MD 1.57 higher	low

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

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. Only one study so no inconsistency
- 5. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.52 (0.8-0.9 = serious, <0.8 = very serious).
- 7.12 > 75%
- $8.\ 95\%$ confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 9. 95% confidence intervals cross both ends of the defined MIDs (-0.80, 0.80)

F.1.2.6 Saxagliptin compared to placebo

Table 9: Clinical evidence profile: Saxagliptin compared to placebo

Ĭ	De	•			Other			Relative		Cert
	sig F	Risk Indir	Inconsi	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n of	f bias ctne	s stency	cision	ions	ntion N	rol N	CI)	effect	У

all-cause mortality at end of follow-up Mean follow-up: 5.5 month(s)											
4	RC T	very seriou s ¹	not seriou s	serious	very seriou s ³	NA	2/988	0/55 9	RD 0.00 (-0.01, 0.01)	2 more per 1000 (5 fewer to 9 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 5.5 month(s)											
3	RC T	very seriou s ¹	not seriou s	not serious	not seriou s	NA	0/704	0/27 5	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (10 fewer to 10 more)	low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)											
3	RC T	very seriou s ¹	not seriou s	serious	very seriou s ⁴	NA	5/697	2/48 5	RD 0.00 (-0.01, 0.01)	3 more per 1000 (7 fewer to 13 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)											
1 (pan 2012a)	RC T	very seriou s ¹	not seriou s	NA ⁵	not seriou s	NA	0/284	0/28 4	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
3	RC T	very seriou s ¹	not seriou s	not serious	seriou s ⁶	NA	656	447	MD -0.45 (-0.62, - 0.28)	MD 0.45 lower (0.62 lower to 0.28 lower)	very low
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											

3	RC T	very seriou s ¹	not seriou s	not serious	not seriou s	NA	665	457	MD 0.88 (0.47, 1.29)	MD 0.88 higher (0.47 higher to 1.29 higher)	low
bmi change (kg/m2, lower values are											
better, change score) at end of follow-up										145.0.40	
										MD 0.40	
										higher	
			not		not					(0.16 higher	mod
	RC	seriou	seriou		seriou				MD 0.40	to 0.64	erat
1 (kumar 2014)	Т	s ⁷	s	NA ⁵	s	NA	105	106	(0.16, 0.64)	higher)	е

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.42 (0.8-0.9 = serious, <0.8 = very serious).
- 4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.17 (0.8-0.9 = serious, <0.8 = very serious).
- 5. Only one study so no inconsistency
- 6. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 7. >33.3% of the studies in the meta-analysis were at moderate risk of bias

F.1.2.7 Sitagliptin compared to metformin

Table 10: Clinical evidence profile: Sitagliptin compared to metformin

	De	Risk	Indir	Incon		Other	Interv	Con	Relative		Cert
	sig	of	ectne	sisten	Impre	considera	ention	trol	effect	Absolute	aint
No of studies	n	bias	SS	су	cision	tions	N	N	(95% CI)	effect	У

health-related quality of life - overall (eq-5d, -0.11-1, higher values are better, change score) at end of											
follow-up Mean follow-up: 6 month(s)											
1 (russell-jones 2012) all-cause mortality at end of follow-up	R CT	not serio us	not serio us	NA ¹	seriou s ²	NA	149	227	MD -0.01 (-0.04, 0.02)	MD 0.01 lower (0.04 lower to 0.02 higher)	mod erat e
Mean follow-up: 5.6 month(s)										0	
4	R CT	serio us³	not serio us	seriou s ⁴	very seriou s ⁵	NA	1/990	1/13 82	RD 0.00 (-0.00, 0.00)	0 more per 1000 (4 fewer to 4 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 5.7 month(s)											
3	R CT	very serio us ⁶	not serio us	not seriou s	not seriou s	NA	0/462	0/86	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 5.5 month(s)											
1 (aschner 2010)	R CT	serio us³	not serio us	NA ¹	very seriou s ⁷	NA	0/528	1/52	PETO OR 0.13 (0.00, 6.74)	2 fewer per 1000 (6 fewer to 2 more)	very low
cardiac arrhythmia at end of follow-up Mean follow-up: 5.5 month(s)											
1 (aschner 2010)	R CT	serio us³	not serio us	NA¹	very seriou s ⁷	NA	0/528	1/52	PETO OR 0.13 (0.00, 6.74)	2 fewer per 1000 (6 fewer to 2 more)	very low
diabetic ketoacidosis at end of follow-up Mean follow-up: 5.5 month(s)											
1 (goldstein 2007)	R CT	serio us³	not serio us	NA ¹	not seriou s	NA	0/179	0/36 4	RD 0.00 (-0.01, 0.01)	0 fewer per 1000	mod erat e

										(9 fewer to 9 more)	
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.6 month(s)											
4	R CT	serio us³	not serio us	not seriou s	seriou s ⁸	NA	20/990	42/1 382	RR 0.66 (0.39, 1.12)	10 fewer per 1000 (18 fewer to 4 more)	low
severe hypoglycaemic episodes at end of follow- up Mean follow-up: 5.5 month(s)											
2	R CT	serio us³	not serio us	seriou s ⁴	very seriou s ⁹	NA	2/648	0/77	RD 0.00 (-0.00, 0.01)	3 more per 1000 (3 fewer to 9 more)	very low
hba1c change (%, lower values are better, change scores and final value) at end of follow-up Mean follow-up: 5.6 month(s)											
5	R CT	serio us ³	not serio us	very seriou s ¹⁰	not seriou s	NA	902	126 2	MD 0.05 (-0.26, 0.36)	MD 0.05 higher (0.26 lower to 0.36 higher)	very low
weight change (kg, higher values are better, change scores) at end of follow-up Mean follow-up: 5.7 month(s)											
3	R CT	serio us ³	not serio us	not seriou s	not seriou s	NA	741	942	MD 1.31 (1.01, 1.61)	MD 1.31 higher (1.01 higher to 1.61 higher)	mod erat e
bmi change (kg/m2, lower values are better, final value) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (wang 2022)	R CT	very serio us ⁶	not serio us	NA ¹	very seriou s ¹¹	NA	17	17	MD -1.36 (-3.58, 0.86)	MD 1.36 lower	very low

					(3.58 lower to 0.86	
					higher)	

- 1. Only one study so no inconsistency
- 2. 95% confidence intervals cross one end of the defined MIDs (-0.03, 0.03)
- 3. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 4. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 5. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.05 (0.8-0.9 = serious, <0.8 = very serious).
- 6. >33.3% of the studies in the meta-analysis were at high risk of bias
- 7. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 8. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 9. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.55 (0.8-0.9 = serious, <0.8 = very serious).
- 10. I2 > 75%
- 11. 95% confidence intervals cross both ends of the defined MIDs (-0.80, 0.80)

F.1.2.8 Sitagliptin compared to placebo

Table 11: Clinical evidence profile: Sitagliptin compared to placebo

•	De	Risk	lus altima			Other	ludam.	Count	Relative	Absolute	Cert
	sig	of	Indire	Inconsi	Imprec	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	ision	ions	ntion N	rol N	CI)	effect	У
all-cause mortality at end of follow-up Mean follow-up: 8.5 month(s)											

4	RC T	seriou s¹	not seriou s	serious	very serious	NA	1/687	2/61 4	RD -0.00 (-0.01, 0.01)	1 fewer per 1000 (9 fewer to 6 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 5.5 month(s)											
2	RC T	very seriou s ⁴	not seriou s	serious 2	very serious	NA	0/299	1/30	RD -0.00 (-0.01, 0.01)	3 fewer per 1000 (15 fewer to 8 more)	very low
diabetic ketoacidosis at end of follow-up Mean follow-up: 5.5 month(s)											
1 (goldstein 2007)	RC T	very seriou s ⁴	not seriou s	NA ⁶	very serious	NA	0/179	1/17	PETO OR 0.13 (0.00, 6.71)	6 fewer per 1000 (17 fewer to 5 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 7.9 month(s)											
5	RC T	very seriou s ⁴	not seriou	serious 2	very serious 8	NA	9/789	7/71	RD 0.00 (-0.01, 0.01)	3 more per 1000 (8 fewer to 14 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 9.5 month(s)											
3	RC T	seriou s ¹	not seriou s	not serious	not serious	NA	0/508	0/43	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	mod erat e
hba1c change (%, lower values are better, change scores) at end of follow- up Mean follow-up: 7.5 month(s)											
6	RC T	seriou s ¹	not seriou s	serious 9	not serious	NA	1245	946	MD -0.73 (-0.84, - 0.62)	MD 0.73 lower	low

										(0.84 lower to 0.62 lower)	
weight change (kg, lower values are											
better, change score) at end of follow-up Mean follow-up: 7.9 month(s)											
inicali follow-up: 1:3 month(s)										MD 0.81	
										higher	
			not							(0.50 higher	mod
	RC	seriou	seriou	not	not				MD 0.81	to 1.13	erat
5	Т	s ¹	s	serious	serious	NA	1097	791	(0.50, 1.13)	higher)	е

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.16 (0.8-0.9 = serious, <0.8 = very serious).
- 4. >33.3% of the studies in the meta-analysis were at high risk of bias
- 5. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.29 (0.8-0.9 = serious, <0.8 = very serious).
- 6. Only one study so no inconsistency
- 7. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 8. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.06 (0.8-0.9 = serious, <0.8 = very serious).
- 9. I2 between 50% and 75%

F.1.2.9 Vildagliptin compared to metformin

Table 12: Clinical evidence profile: Vildagliptin compared to metformin

	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ions	ntion N	rol N	CI)	effect	У
all-cause mortality at end of follow-up Mean follow-up: 7.8 month(s)											
3	RC T	seriou s ¹	not seriou s	serious	very seriou s ³	NA	3/986	2/71 1	RD -0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 5 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 5.5 month(s)											
1 (schweizer 2009)	RC T	seriou s ¹	not seriou s	NA ⁴	very seriou s ⁵	NA	1/167	0/16 5	PETO OR 7.30 (0.14, 367.98)	6 more per 1000 (6 fewer to 18 more)	very low
non-fatal myocardial infarction at end of follow up Mean follow-up: 7.8 month(s)											
3	RC T	seriou s ¹	not seriou s	not serious	not seriou s	NA	0/993	5/71 3	PETO OR 0.09 (0.01, 0.54)	7 fewer per 1000 (13 fewer to 1 fewer)	mod erat e
cardiac arrhythmia at end of follow-up Mean follow-up: 5.5 month(s)											
1 (schweizer 2009)	RC T	seriou s ¹	not seriou s	NA ⁴	very seriou s ⁵	NA	1/167	1/16 5	PETO OR 0.99 (0.06, 15.86)	0 fewer per 1000 (17 fewer to 17 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 8.8 month(s)											

2	RC T	very seriou s ⁶	not seriou s	serious 2	very seriou s ⁵	NA	3/693	3/41 9	PETO OR 0.60 (0.11, 3.19)	3 fewer per 1000 (12 fewer to 7 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 7.8 month(s)											
3	RC T	very seriou s ⁶	not seriou s	serious	very seriou s ⁷	NA	0/993	1/71	RD -0.00 (-0.01, 0.00)	1 fewer per 1000 (5 fewer to 4 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow- up Mean follow-up: 7.8 month(s)											
3	RC T	seriou s ¹	not seriou s	not serious	not seriou s	NA	970	704	MD 0.26 (0.10, 0.41)	MD 0.25 higher (0.14 higher to 0.37 higher)	mod erat e
weight change (kg, lower values are better, change scores) at end of follow- up Mean follow-up: 7.8 month(s)											
3	RC T	seriou s ¹	not seriou s	very serious	not seriou s	NA	980	709	MD 1.32 (0.52, 2.12)	MD 1.32 higher (0.52 higher to 2.12 higher)	very low

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.03 (0.8-0.9 = serious, <0.8 = very serious).
- 4. Only one study so no inconsistency

- 5. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 6. >33.3% of the studies in the meta-analysis were at high risk of bias
- 7. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.34 (0.8-0.9 = serious, <0.8 = very serious).
- 8. I2 > 75%

F.1.2.10 Vildagliptin compared to placebo

Table 13: Clinical evidence profile: Vildagliptin compared to placebo

Table 13. Official evidence profile. Vildag			l ca to p								_
	De	Risk		Incons		Other			Relative		Cert
	sig	of	Indire	istenc	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	у	cision	ions	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow-up Mean follow-up: 12 month(s)											
1 (mari 2008)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	0/156	1/15 0	PETO OR 0.13 (0.00, 6.56)	7 fewer per 1000 (20 fewer to 6 more)	very low
hypoglycaemia episodes at end follow-up Mean follow-up: 12 month(s)											
1 (mari 2008)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	0/153	1/14 9	PETO OR 0.13 (0.00, 6.64)	7 fewer per 1000 (20 fewer to 6 more)	very low
severe hypoglycaemic episodes at end follow-up Mean follow-up: 12 month(s)											
1 (mari 2008)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s ⁴	NA	0/149	0/15 3	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (13 fewer to 13 more)	very low

hba1c change (%, lower values are better, change scores) at the end of follow-up Mean follow-up: 8.8 month(s)											
4	RC T	very seriou s ¹	not seriou s	not seriou s	seriou s ⁵	NA	720	361	MD -0.48 (-0.67, - 0.29)	MD 0.48 lower (0.67 lower to 0.29 lower)	very low
weight change (kg, lower values are better, change scores) at the end of follow-up Mean follow-up: 8.8 month(s)											
3	RC T	very seriou s ¹	not seriou s	seriou s ⁶	not seriou s	NA	676	313	MD 0.40 (-0.43, 1.22)	MD 0.40 higher (0.43 lower to 1.22 higher)	very low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 5. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 6. I2 between 50% and 75%

F.1.3 GLP-1 receptor agonist

F.1.3.1 Dulaglutide compared to placebo

Table 14: Clinical evidence profile: dulaglutide v placebo

	De	Risk	Indir	Incon		Other	Interv	Con	Relative		Cer
	sig	of	ectn	sisten	Impre	consider	ention	trol	effect	Absolute	tain
No of studies	n	bias	ess	су	cision	ations	N	N	(95% CI)	effect	ty
hr-qol - subscale convenience/flexibility (pam-d21-j,											
0-100, higher values are better, final value) at end											
of follow-up											
Mean follow-up: 6 month(s)											
										MD 6.73	
		von	not						MD 6.73	higher (0.34 higher	
	R	very serio	serio		seriou				(0.34,	to 13.12	verv
1 (miyagawa 2015)	СТ	us ¹	us	NA ²	s ³	NA	280	70	13.12)	higher)	low
hr-qol - subscale perceived effectiveness (pam-									, , ,	,	
d21-j, 0-100, higher values are better, final value) at											
end of follow-up											
Mean follow-up: 6 month(s)											
										MD 50.79	
									MD 50 70	higher	
	R	very serio	not serio		seriou				MD 50.79 (20.80,	(20.80 higher to 80.78	Vorv
1 (miyagawa 2015)	СТ	us ¹	us	NA ²	senou s ⁴	NA	280	70	80.78)	higher)	low
hr-qol - subscale emotional effects (pam-d21-j, 0-	01	us	us	14/-1	3	INZ	200	70	00.70)	nigrici)	1044
100, higher values are better, final value) at end of											
follow-up											
Mean follow-up: 6 month(s)											
										MD 3.71	
										higher	
	_	very	not .						MD 3.71	(0.40 higher	
4 (mix a gave 2045)	R	serio	serio	NIA2	seriou	NIA	200	70	(0.40,	to 7.02	very
1 (miyagawa 2015)	CT	us ¹	us	NA ²	s ⁵	NA	280	70	7.02)	higher)	low

hr-qol - subscale physical effects (pam-d21-j, 0-100, higher values are better, final value) at end of follow-up											
Mean follow-up: 6 month(s)											
1 (miyagawa 2015) hr-qol - subscale satisfaction (idmq-j, 0-100, higher values are better, final value) at end of follow-up	R CT	very serio us ¹	not serio us	NA ²	not seriou s	NA	280	70	MD -0.95 (-2.71, 0.81)	MD 0.95 lower (2.71 lower to 0.81 higher)	low
Mean follow-up: 6 month(s)											
1 (miyagawa 2015)	R CT	very serio us ¹	not serio us	NA ²	seriou s ⁶	NA	280	70	MD 32.05 (13.12, 50.98)	MD 32.05 higher (13.12 higher to 50.98 higher)	very low
hr-qol - subscale ease of use (idmq-j, 0-100, higher values are better, final value) at end of follow-up Mean follow-up: 6 month(s)											
1 (miyagawa 2015)	R	very serio us ¹	not serio us	NA ²	seriou s ⁷	NA	280	70	MD 12.94 (5.30, 20.58)	MD 12.94 higher (5.30 higher to 20.58 higher)	very
hr-qol - subscale lifestyle impact (idmq-j, 0-100, higher values are better, final value) at end of follow-up Mean follow-up: 6 month(s)										<i>y</i> /	
1 (miyagawa 2015)	R	very serio us ¹	not serio us	NA ²	seriou s ⁸	NA	280	70	MD 10.12 (4.14, 16.10)	MD 10.12 higher (4.14 higher to 16.10 higher)	very
hr-qol - subscale blood glucose control (idmq-j, 0- 100, higher values are better, final value) at end of follow-up Mean follow-up: 6 month(s)	UI.	us'	us	IVA	5"	IVA	200	70	10.10)	riigriei)	low

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

Mean follow-up: 6 month(s)											
										MD 1.57	
			not		not				MD -1.57	lower (1.79 lower	mo
	R	serio	serio		seriou				(-1.79, -	to 1.35	der
1 (miyagawa 2015)	CT	us ¹⁰	us	NA ²	s	NA	281	70	1.35)	lower)	ate

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross one end of the defined MIDs (-12.20, 12.20)
- 4. 95% confidence intervals cross one end of the defined MIDs (-57.30, 57.30)
- 5. 95% confidence intervals cross one end of the defined MIDs (-6.30, 6.30)
- 6. 95% confidence intervals cross one end of the defined MIDs (-36.20, 36.20)
- 7. 95% confidence intervals cross one end of the defined MIDs (-14.60, 14.60)
- 8. 95% confidence intervals cross one end of the defined MIDs (-11.40, 11.40)
- 9. 95% confidence intervals cross one end of the defined MIDs (-38.80, 38.80)
- 10. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 11. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 12. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

F.1.3.2 **Dulaglutide v metformin**

	De sig	Risk of	Indire ctnes	Incons istenc	Impre	Other considera	Interve ntion	Cont rol	Relative effect (95%	Absolute	Cert aint
No of studies	n	bias	s	У	cision	tions	N	N	CI)	effect	у
all-cause mortality at end of follow up Mean follow-up: 12 month(s)											

1 (umpierrez 2014)	RC T	serio us ¹	not seriou s	NA ²	not seriou s	NA	0/539	0/26 8	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	mod erat e
cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)											
1 (umpierrez 2014)	RC T	serio us ¹	not seriou s	NA ²	not seriou s	NA	0/539	0/26 8	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	mod erat e
hypoglycaemia episodes at end of follow up Mean follow-up: 12 month(s)											
1 (umpierrez 2014) severe hypoglycaemic episodes at end of	RC T	serio us¹	not seriou s	NA ²	very seriou s ³	NA	63/539	34/2 68	RR 0.92 (0.62, 1.36)	10 fewer per 1000 (48 fewer to 46 more)	very low
follow up											
Mean follow-up: 12 month(s) 1 (umpierrez 2014)	RC T	serio us ¹	not seriou s	NA ²	not seriou s	NA	0/539	0/26	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	mod erat e
hba1c change (%, lower values are better, change scores and final values) at end of follow up Mean follow-up: 12 month(s)											
1 (umpierrez 2014)	RC T	serio us ¹	not seriou s	NA ²	not seriou s	NA	539	268	MD -0.18 (-0.33, - 0.04)	MD 0.18 lower (0.33 lower to 0.04 lower)	mod erat e
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (umpierrez 2014)	RC T	serio us ¹	not seriou s	NA ²	not seriou s	NA	539	268	MD 0.40 (-0.18, 0.97)	MD 0.40 higher	mod erat e

					(0.18 lower to 0.97	
					higher)	

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

F.1.3.3 Exenatide compared to metformin

Table 15: Clinical evidence profile: exenatide compared to metformin

	De	Risk	Indir	Incon	Impr	Other	Interv	Con	Relative		Cert
	sig	of	ectne	sisten	ecisio	considera	ention	trol	effect	Absolute	aint
No of studies	n	bias	SS	су	n	tions	N	N	(95% CI)	effect	У
health-related quality of life - overall (eq-5d, 0-100, higher values are better, change scores) at end of follow-up Mean follow-up: 6 month(s)											
1 (russell-jones 2012)	R CT	not serio us	not serio us	NA ¹	not serio us	NA	232	227	MD 0.00 (-0.03, 0.03)	MD 0.00 lower (0.03 lower to 0.03 higher)	high
all-cause mortality at end of follow-up Mean follow-up: 6 month(s)											
1 (russell-jones 2012)	R CT	not serio us	not serio us	NA¹	very serio us ²	NA	0/248	1/24	PETO OR 0.13 (0.00, 6.77)	4 fewer per 1000 (12 fewer to 4 more)	low
cardiovascular mortality at end of follow-up Mean follow-up: 6 month(s)								-	- /	3,	

1 (russell-jones 2012) hypoglycaemia episodes at end of follow-up	R CT	not serio us	not serio us	NA¹	not serio us	NA	0/248	0/24	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	high
Mean follow-up: 6 month(s)										19 more per	
2	R CT	not serio us	not serio us	not seriou s	very serio us ²	NA	17/281	11/2 72	RR 1.48 (0.70, 3.11)	1000 (12 fewer to 85 more)	low
severe hypoglycaemic episodes at end of follow- up Mean follow-up: 6 month(s)											
1 (yuan 2012)	R CT	very serio us ³	not serio us	NA ¹	very serio us ⁴	NA	0/33	0/26	RD 0.00 (-0.06, 0.06)	0 fewer per 1000 (65 fewer to 65 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow-up Mean follow-up: 6 month(s)											
2	R CT	not serio us	not serio us	not seriou s	not serio us	NA	251	244	MD -0.07 (-0.26, 0.12)	MD 0.07 lower (0.26 lower to 0.12 higher)	high
weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 6 month(s)									,	, , , , , , , , , , , , , , , , , , ,	
2	R CT	not serio us	not serio us	very seriou s ⁵	serio us ⁶	NA	281	272	MD -0.98 (-2.93, 0.97)	MD 0.98 lower (2.93 lower to 0.97 higher)	very low
bmi change (kg/m2, lower values are better, change scores) at end of follow-up Mean follow-up: 6 month(s)							-		- /	, ,	

										MD 1.41	
										lower	
		very	not		not				MD -1.41	(1.81 lower	
	R	serio	serio		serio				(-1.81, -	to 1.01	
1 (yuan 2012)	CT	us ³	us	NA ¹	us	NA	33	26	1.01)	lower)	low

- 1. Only one study so no inconsistency
- 2. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 3. >33.3% of the studies in the meta-analysis were at high risk of bias
- 4. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 5. 12 > 75%
- 6. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

F.1.3.4 Exenatide compared to sitagliptin

Table 16: Clinical evidence profile: exenatide compared to sitagliptin

rusio ro. emmour evidence preme. exemulade con	De sig	Risk of	Indir ectne	Incon sisten	Impr ecisio	Other considera	Interv ention	Con trol	Relative effect	Absolute	Cert aint
No of studies	n	bias	SS	су	n	tions	N	N	(95% CI)	effect	у
health-related quality of life - overall (eq-5d, 0-100, higher values are better, change scores) at end of follow-up Mean follow-up: 6 month(s)											
1 (russell-jones 2012)	R CT	not serio us	not serio us	NA ¹	serio us²	NA	232	149	MD 0.01 (-0.02, 0.04)	MD 0.01 higher (0.02 lower to 0.04 higher)	mod erat e
all-cause mortality at end of follow-up Mean follow-up: 6 month(s)											

1 (russell-jones 2012)	R CT	not serio us	not serio us	NA ¹	not serio us	NA	0/248	0/16	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (10 fewer to 10 more)	high
cardiovascular mortality at end of follow-up Mean follow-up: 6 month(s)											
1 (russell-jones 2012)	R CT	not serio us	not serio us	NA ¹	not serio us	NA	0/248	0/16	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (10 fewer to 10 more)	high
hypoglycaemia episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (russell-jones 2012) hba1c change (%, lower values are better, change scores) at end of follow-up	R CT	not serio us	not serio us	NA¹	very serio us ³	NA	13/248	5/16 3	RR 1.71 (0.62, 4.70)	22 more per 1000 (12 fewer to 114 more)	low
Mean follow-up: 6 month(s) 1 (russell-jones 2012) weight change (kg, lower values are better, change	R CT	not serio us	not serio us	NA ¹	serio us ⁴	NA	218	142	MD -0.38 (-0.59, - 0.17)	MD 0.38 lower (0.59 lower to 0.17 lower)	mod erat e
scores) at end of follow-up Mean follow-up: 6 month(s)											
1 (russell-jones 2012)	R CT	not serio us	not serio us	NA ¹	not serio us	NA	248	163	MD -1.20 (-1.91, - 0.49)	MD 1.20 lower (1.91 lower to 0.49 lower)	high

- 1. Only one study so no inconsistency
- 2. 95% confidence intervals cross one end of the defined MIDs (-0.03, 0.03)
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

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

F.1.3.5 Exenatide compared to pioglitazone

Table 17: Clinical evidence profile: exenatide compared to pioglitazone

	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
health-related quality of life - overall at end of follow-up Mean follow-up: 6 month(s)											
1 (russell-jones 2012)	RC T	not serio us	not seriou s	NA ¹	seriou s ²	NA	248	163	MD 0.04 (0.01, 0.07)	MD 0.04 higher (0.01 higher to 0.07 higher)	mod erat e
all-cause mortality at end of follow-up Mean follow-up: 6 month(s)											
1 (russell-jones 2012)	RC T	not serio us	not seriou s	NA ¹	not seriou s	NA	0/248	0/16 3	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (10 fewer to 10 more)	high
cardiovascular mortality at end of follow- up Mean follow-up: 6 month(s)											
1 (russell-jones 2012)	RC T	not serio us	not seriou s	NA ¹	not seriou s	NA	0/248	0/16 3	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (10 fewer to 10 more)	high
hypoglycaemia episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (russell-jones 2012)	RC T	not serio us	not seriou s	NA ¹	very seriou s ³	NA	13/248	6/16 3	RR 1.42 (0.55, 3.67)	16 more per 1000	low

										(16 fewer to 98 more)	
hba1c change (%, lower values are better, change scores) at end of follow-										·	
up ′											
Mean follow-up: 6 month(s)											
	RC	not serio	not seriou		not seriou				MD 0.10	MD 0.10 higher (0.09 lower to	
1 (russell-jones 2012)	Т	us	s	NA ¹	s	NA	248	163	(-0.09, 0.29)	0.29 higher)	high
weight change (kg, lower values are											
better, change scores) at end of follow-											
up Mean follow-up: 6 month(s)											
										MD 3.50	
		not	not		not				MD -3.50	lower	
	RC	serio	seriou		seriou				(-4.21, -	(4.21 lower to	
1 (russell-jones 2012)	Т	us	S	NA ¹	S	NA	248	163	2.79)	2.79 lower)	high

- 1. Only one study so no inconsistency
- 2. 95% confidence intervals cross one end of the defined MIDs (-0.03, 0.03)
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

F.1.3.6 Exenatide compared to insulin

Table 18: Clinical evidence profile: exenatide compared to insulin

	De sig	Risk of	Indire ctnes	Incons istenc	Impr ecisio	Other considera	Interv ention	Con trol	Relative effect (95%	Absolute	Cert aint
No of studies	n	bias	s	у	n	tions	N	N	CI)	effect	у
all-cause mortality at end of follow-up Mean follow-up: 11.1 month(s)											

1 (xu 2015) cardiovascular mortality at end of follow-up	RC T	very seriou s ¹	not serio us	NA ²	serio us ³	NA	0/142	0/13	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	very low
Mean follow-up: 11.1 month(s) 1 (xu 2015) hypoglycaemia episodes at end of follow-up	RC T	very seriou s ¹	not serio us	NA ²	serio us ³	NA	0/142	0/13	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	very low
Mean follow-up: 8.3 month(s)	RC T	very seriou s ¹	not serio us	not seriou s	serio us ⁴	NA	16/180	24/1 76	RR 0.65 (0.36, 1.19)	47 fewer per 1000 (87 fewer to 25 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 8.3 month(s)		very	not	not	not				RD 0.00	0 fewer per 1000	
hba1c change (%, lower values are better, change scores) at end of follow-up [%]	RC T	seriou s ¹	serio us	seriou s	serio us	NA	0/180	0/17 6	(-0.02, 0.02)	(16 fewer to 16 more)	low
Mean follow-up: 8.3 month(s)	RC T	very seriou s ¹	not serio us	very seriou s ⁵	serio us ⁶	NA	145	150	MD -0.36 (-0.90, 0.18)	MD 0.36 lower (0.90 lower to 0.18 higher)	very low
hba1c change (%, lower values are better, change scores and final values) at end of follow-up [%] Mean follow-up: 8.3 month(s)									MD C 22		
2	RC T	very seriou s ¹	not serio us	very seriou s ⁵	serio us ⁶	NA	145	150	MD -0.36 (-0.90, 0.18)	MD 0.36 lower	very low

										(0.90 lower to 0.18 higher)	
hba1c change (%, lower values are better, change scores and final values) at end of follow-up [%] Mean follow-up: 8.3 month(s)										Tilgrici)	
2	RC T	very seriou s ¹	not serio us	very seriou s ⁵	serio us ⁶	NA	145	150	MD -0.36 (-0.90, 0.18)	MD 0.36 lower (0.90 lower to 0.18 higher)	very low
weight change (kg, lower values are better, change scores) at end of follow-up [kg] Mean follow-up: 8.3 month(s)											
2	RC T	very seriou s ¹	not serio us	not seriou s	not serio us	NA	145	150	MD -4.33 (-5.19, - 3.47)	MD 4.33 lower (5.19 lower to 3.47 lower)	low
bmi change (kg/m2, lower values are better, change scores) at end of follow-up [kg/m2] Mean follow-up: 8.3 month(s)									,	,	
2	RC T	very seriou s ¹	not serio us	not seriou s	not serio us	NA	145	150	MD -1.65 (-1.91, - 1.40)	MD 1.65 lower (1.91 lower to 1.40 lower)	low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 4. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 5. I2 > 75%

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

F.1.3.7 Exenatide compared to placebo

Table 19: Clinical evidence profile: exenatide compared to placebo

Table 10. Chillion evidence preme. exem	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow-up Mean follow-up: 5.5 month(s)											
1 (moretto 2008)	RC T	seriou s¹	not seriou s	NA ²	seriou s³	NA	0/155	0/77	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	low
cardiovascular mortality at end of follow- up Mean follow-up: 5.5 month(s)											
1 (moretto 2008)	RC T	seriou s ¹	not seriou s	NA ²	seriou s³	NA	0/155	0/77	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	low
hypoglycaemia episodes at end of follow- up Mean follow-up: 5.5 month(s)											
1 (moretto 2008)	RC T	seriou s ¹	not seriou s	NA ²	very seriou s ⁴	NA	7/155	1/77	RR 3.48 (0.44, 27.76)	32 more per 1000 (7 fewer to 348 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)											
1 (moretto 2008)	RC T	seriou s ¹	not seriou s	NA ²	seriou s³	NA	0/155	0/77	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	low

hba1c change (%, lower values are better, change scores) at end of follow- up Mean follow-up: 5.5 month(s)											
1 (moretto 2008) weight change (kg, lower values are better, change scores) at end of follow-up	RC T	seriou s ¹	not seriou s	NA ²	seriou s ⁵	NA	155	77	MD -0.60 (-0.84, - 0.36)	MD 0.60 lower (0.84 lower to 0.36 lower)	low
Mean follow-up: 5.5 month(s)										MD 1.55	
1 (moretto 2008)	RC T	seriou s ¹	not seriou s	NA ²	not seriou s	NA	155	77	MD -1.55 (-2.27, - 0.83)	lower (2.27 lower to 0.83 lower)	mod erat e

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. Only one study so no inconsistency
- 3. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 4. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 5. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

F.1.3.8 Liraglutide compared to metformin

Table 20: Clinical evidence profile: liraglutide compared to metformin

	De	Risk	Indire	Incons		Other	Interve	Cont	Relative		Cert
	sig	of	ctnes	istenc	Impre	considera	ntion	rol	effect (95%	Absolute	aint
No of studies	n	bias	S	у	cision	tions	N	N	CI)	effect	у

hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)											
1 (feng 2017)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	0/30	2/31	RR 0.21 (0.01, 4.13)	51 fewer per 1000 (64 fewer to 202 more)	very low
hba1c change (%, lower values are better, change scores and final values) at end of follow-up Mean follow-up: 5.8 month(s)											
2	RC T	very seriou s ¹	not seriou s	seriou s ⁴	very seriou s ⁵	NA	60	61	MD -0.32 (-1.27, 0.63)	MD -0.32 lower (-1.27 lower to 0.63 higher)	very low
weight change (kg, lower values are better, final values) at end of follow-up Mean follow-up: 5.8 month(s)											
2	RC T	very seriou s ¹	not seriou s	very seriou s ⁶	seriou s ⁸	NA	59	59	MD 9.44 (-1.04, 19.91)	MD 9.44 higher (-1.04 lower to 19.91 higher)	very low
bmi change (kg/m2, lower values are better, final values) at end of follow-up Mean follow-up: 5.8 month(s)											
2	RC T	very seriou s ¹	not seriou s	very seriou s ⁶	very seriou s ⁷	NA	59	59	MD 2.29 (-0.94, 5.52)	MD 2.29 higher (-0.94 lower to 5.52 higher)	very low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. I2 between 50% and 75%

- 5. 95% confidence intervals cross both ends of the defined MIDs (-0.50, 0.50)
- 6. I2 > 75%
- 7. 95% confidence intervals cross both ends of the defined MIDs (-0.80, 0.80)
- 8. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

F.1.3.9 Liraglutide compared to dulaglutide

Table 21: Clinical evidence profile: Liraglutide compared to dulaglutide

Table 21. Offical evidence profile. Linagiande compare											
	De	Risk	Indir	Incon	Impr	Other	Interv	Con	Relative		Cer
	sig	of	ectn	siste	ecisi	consider	entio	trol	effect	Absolute	tai
No of studies	n	bias	ess	ncy	on	ations	n N	N	(95% CI)	effect	nty
health-related quality of life - subscale convenience/flexibility (pam-d21-j, 0-100, higher values are better, change scores) at end of follow-up Mean follow-up: 6 month(s)											
1 (miyagawa 2015)	R C T	very serio us ¹	not serio us	NA ²	not serio us	NA	137	280	MD -5.64 (-10.58, - 0.70)	MD 5.64 lower (10.58 lower to 0.70 lower)	low
health-related quality of life - subscale perceived effectiveness (pam-d21-j, 0-100, higher values are better, change scores) at end of follow-up Mean follow-up: 6 month(s)											
1 (miyagawa 2015)	R C T	very serio us ¹	not serio us	NA ²	not serio us	NA	137	280	MD -0.43 (-5.74, 4.88)	MD 0.43 lower (5.74 lower to 4.88 higher)	low

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

health-related quality of life - subscale lifestyle impact (idmq-j, 0-100, higher values are better, change scores) at end of follow-up											
Mean follow-up: 6 month(s)											
1 (miyagawa 2015) health-related quality of life - subscale blood glucose control (idmq-j, 0-100, higher values are better, change scores) at end of follow-up Mean follow-up: 6 month(s)	R C T	very serio us ¹	not serio us	NA ²	not serio us	NA	137	280	MD 4.21 (-0.04, 8.46)	MD 4.21 higher (0.04 lower to 8.46 higher)	low
mount on the manufe,										MD 2.04	
1 (miyagawa 2015)	R C T	very serio us ¹	not serio us	NA ²	not serio us	NA	137	280	MD -2.04 (-5.90, 1.82)	lower (5.90 lower to 1.82 higher)	low
all-cause mortality at end of follow-up Mean follow-up: 12 month(s)									,	,	
1 (miyagawa 2015)	R C T	serio us³	not serio us	NA ²	not serio us	NA	0/137	0/2 80	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (11 fewer to 11 more)	mo der ate
cardiovascular mortality at end of follow-up Mean follow-up: 12 month(s)											
1 (miyagawa 2015)	R C T	serio us³	not serio us	NA ²	not serio us	NA	0/137	0/2 80	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (11 fewer to 11 more)	mo der ate
hypoglycaemia episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (miyagawa 2015)	R C T	serio us ³	not serio us	NA ²	very serio us ⁴	NA	4/137	8/2 80	RR 1.02 (0.31, 3.33)	1 more per 1000	ver y low

										(20 fewer to 67 more)	
at night hypoglycaemic episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (miyagawa 2015)	R C T	serio us³	not serio us	NA ²	very serio us ⁴	NA	1/137	2/2 80	RR 1.02 (0.09, 11.17)	0 more per 1000 (6 fewer to 73 more)	ver y low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (miyagawa 2015)	R C T	serio us³	not serio us	NA ²	not serio us	NA	0/137	0/2 80	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (11 fewer to 11 more)	mo der ate
hba1c change (%, lower values are better, change scores) at end of follow-up Mean follow-up: 6 month(s)											
	R	very	not		not				MD 0.20	MD 0.20 higher (0.00 higher to	
1 (miyagawa 2015)	C T	serio us ¹	serio us	NA ²	serio us	NA	137	280	(0.00, 0.40)	0.40 higher)	low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 4. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

F.1.3.10 Liraglutide compared to gliclazide

Table 22: Clinical evidence profile: liraglutide compared to gliclazide

	De					Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	У
hypoglycaemia episodes at end of											
follow-up Mean follow-up: 5.5 month(s)											
	RC T	very seriou s ¹	not seriou	NIA2	very seriou s ³	NIA	0/20	0/20	PETO OR 0.14	63 fewer per 1000 (146 fewer to	very
1 (feng 2017) hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)		5'	S	NA ²	5	NA	0/30	2/32	(0.01, 2.29)	21 more)	low
1 (feng 2017)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ⁴	NA	30	32	MD -0.40 (-1.38, 0.58)	MD 0.40 lower (1.38 lower to 0.58 higher)	very low
weight change (kg, lower values are better, final value) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (feng 2017)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ⁵	NA	29	27	MD -2.04 (-8.42, 4.34)	MD 2.04 lower (8.42 lower to 4.34 higher)	very low
bmi change (kg/m2, lower values are better, final value) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (feng 2017)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s ⁶	NA	29	27	MD -1.10 (-2.49, 0.29)	MD 1.10 lower (2.49 lower to 0.29 higher)	very low

^{1. &}gt;33.3% of the studies in the meta-analysis were at high risk of bias

- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. 95% confidence intervals cross both ends of the defined MIDs (-0.50, 0.50)
- 5. 95% confidence intervals cross both ends of the defined MIDs (-2.40, 2.40)
- 6. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

F.1.3.11 Liraglutide compared to glimepiride

Table 23: Clinical evidence profile: liraglutide compared to glimepiride

	De					Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
hba1c change (%, lower values are better, change score) at end of follow-up											
Mean follow-up: 12 month(s)											
										MD 0.51	
		very	not						MD -0.51	lower	
	RC	seriou	seriou		seriou				(-0.84, -	(0.84 lower to	very
1 (garber 2009)	T	s ¹	S	NA ²	s^3	NA	178	94	0.18)	0.18 lower)	low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

F.1.3.12 Liraglutide compared to placebo

Table 24: Clinical evidence profile: Liraglutide compared to placebo

rable 24: Clinical evidence profile: Lira	7	e compa	i eu to p	Jiacebo		Oth			Dalation		Card
	De					Other			Relative		Cert
	sig	Risk	Indire	Inconsi	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	of bias	ctness	stency	cision	ions	ntion N	rol N	CI)	effect	У
all-cause mortality at end of follow-up Mean follow-up: 12 month(s)											
2	RC T	very seriou s ¹	not seriou s	not serious	seriou s ²	NA	0/185	0/11	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	very low
cardiovascular mortality at end of follow- up Mean follow-up: 12 month(s)											
2	RC T	seriou s³	not seriou s	not serious	seriou s ²	NA	0/185	0/11 9	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	low
non-fatal stroke at end of follow-up Mean follow-up: 12 month(s)											
1 (yamada 2020)	RC T	very seriou s ¹	not seriou s	NA ⁴	seriou s ²	NA	0/48	0/49	RD 0.00 (-0.04, 0.04)	0 fewer per 1000 (39 fewer to 39 more)	very low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 12 month(s)											
1 (yamada 2020)	RC T	very seriou s ¹	not seriou s	NA ⁴	seriou s²	NA	0/48	0/49	RD 0.00 (-0.04, 0.04)	0 fewer per 1000 (39 fewer to 39 more)	very low
unstable angina at end of follow-up Mean follow-up: 12 month(s)											
44 1 2000)	RC	very seriou	not seriou		seriou		0440	0/40	RD 0.00	0 fewer per	very
1 (yamada 2020)	Т	s ¹	S	NA ⁴	s ²	NA	0/48	0/49	(-0.04, 0.04)	1000	low

										(39 fewer to	
acute kidney injury at end of follow-up										39 more)	
Mean follow-up: 12 month(s)											
1 (yamada 2020)	RC T	very seriou s ¹	not seriou s	NA ⁴	seriou s²	NA	0/48	0/49	RD 0.00 (-0.04, 0.04)	0 fewer per 1000 (39 fewer to 39 more)	very low
cardiac arrhythmia at end of follow-up Mean follow-up: 12 month(s)											
1 (yamada 2020)	RC T	very seriou s ¹	not seriou s	NA ⁴	seriou s²	NA	0/48	0/49	RD 0.00 (-0.04, 0.04)	0 fewer per 1000 (39 fewer to 39 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 9 month(s)											
2	RC T	very seriou s ¹	not seriou s	not serious	very seriou s ⁵	NA	7/185	3/11 9	RR 1.94 (0.53, 7.08)	24 more per 1000 (12 fewer to 153 more)	very low
at night hypoglycaemic episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (miyagawa 2015)	RC T	seriou s³	not seriou	NA ⁴	seriou s ²	NA	0/137	0/70	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (22 fewer to 22 more)	low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 9 month(s)									(11,111)	,	
2	RC T	seriou s³	not seriou s	not serious	seriou s ²	NA	0/185	0/11	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	low
hba1c change (%, lower values are better, change scores) at end of follow- up											

Mean follow-up: 9 month(s)											
2	RC T	seriou s³	not seriou s	serious	not seriou s	NA	186	119	MD -1.29 (-1.65, - 0.93)	MD 1.29 lower (1.65 lower to 0.93 lower)	low
weight change (kg, lower values are better, change scores) at end of follow- up Mean follow-up: 12 month(s)											
1 (yamada 2020)	RC T	very seriou s ¹	not seriou s	NA ⁴	not seriou s	NA	45	49	MD 0.60 (-0.25, 1.45)	MD 0.60 higher (0.25 lower to 1.45 higher)	low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 3. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 4. Only one study so no inconsistency
- 5. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 6. I2 between 50% and 75%

F.1.3.13 Liraglutide compared to sitagliptin

	De sig	Risk of	Indire	Inconsi	Impre	Other considerati	Interve	Cont	Relative effect (95%	Absolute	Cert aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
hba1c change (%, lower values are better, final values) at end of follow up Mean follow-up: 6 month(s)											
1 (suzuki 2014)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s³	NA	24	16	MD -0.60 (-1.57, 0.37)	MD 0.60 lower (1.57 lower to 0.37 higher)	very low

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

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 4. 95% confidence intervals cross both ends of the defined MIDs (-2.40, 2.40)

F.1.3.14 Semaglutide compared to liraglutide

Table 25: Clinical evidence profile: Semaglutide compared to liraglutide

-	De	Risk	Indir	Incon	Impr	Other	Interv	Con	Relative		Cer
	sig	of	ectn	siste	ecisi	consider	entio	trol	effect	Absolute	tai
No of studies	n	bias	ess	ncy	on	ations	n N	N	(95% CI)	effect	nty
health-related quality of life - subscale physical component (sf-36v2 acute, 0-100, higher values are better, change scores) at end of follow-up Mean follow-up: 12 month(s)											
i	R C	very serio	not serio		serio				MD -1.02 (-2.02, -	MD 1.02 lower (2.02 lower to 0.01	ver y
1 (yamada 2020,yamada 2020,yamada 2020)	Т	us ¹	us	NA ²	us ³	NA	142	49	0.01)	lower)	low
health-related quality of life - subscale mental component (sf-36v2 acute, 0-100, higher values are better, change scores) at end of follow-up											
Mean follow-up: 12 month(s)											

1 (yamada 2020,yamada 2020,yamada 2020) all-cause mortality at end of follow-up	R C T	very serio us ¹	not serio us	NA ²	not serio us	NA	140	49	MD -0.57 (-2.07, 0.93)	MD 0.57 lower (2.07 lower to 0.93 higher)	low
Mean follow-up: 12 month(s)											
1 (yamada 2020)	R C T	very serio us ¹	not serio us	NA ²	serio us ⁴	NA	0/146	0/4	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (30 fewer to 30 more)	ver y low
cardiovascular mortality at end of follow-up Mean follow-up: 12 month(s)											
1 (yamada 2020)	R C T	very serio us ¹	not serio us	NA ²	serio us ⁴	NA	0/146	0/4	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (30 fewer to 30 more)	ver y low
non-fatal stroke at end of follow-up Mean follow-up: 12 month(s)											
1 (yamada 2020) non-fatal myocardial infarction at end of follow-up	R C T	very serio us ¹	not serio us	NA ²	serio us ⁴	NA	0/146	0/4	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (30 fewer to 30 more)	ver y low
Mean follow-up: 12 month(s)											
1 (yamada 2020)	R C T	very serio us ¹	not serio us	NA ²	serio us ⁴	NA	0/146	0/4 8	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (30 fewer to 30 more)	ver y low
unstable angina at end of follow-up Mean follow-up: 12 month(s)											

1 (yamada 2020)	R C T	very serio us ¹	not serio us	NA ²	serio us ⁴	NA	0/146	0/4	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (30 fewer to 30 more)	ver y low
acute kidney injury at end of follow-up Mean follow-up: 12 month(s)											
1 (yamada 2020)	R C T	very serio us ¹	not serio us	NA ²	serio us ⁴	NA	0/146	0/4	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (30 fewer to 30 more)	ver y low
cardiac arrhythmia at end of follow-up Mean follow-up: 12 month(s)											
1 (yamada 2020)	R C T	very serio us ¹	not serio us	NA ²	serio us ⁴	NA	0/146	0/4	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (30 fewer to 30 more)	ver y low
hypoglycaemia episodes at end of follow-up Mean follow-up: 12 month(s)											
1 (yamada 2020)	R C T	very serio us ¹	not serio us	NA ²	serio us ⁵	NA	6/146	5/4 8	RR 0.39 (0.13, 1.23)	63 fewer per 1000 (91 fewer to 24 more)	ver y low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 12 month(s)											
1 (yamada 2020)	R C T	very serio us ¹	not serio us	NA ²	serio us ⁴	NA	0/146	0/4	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (30 fewer to 30 more)	ver y low
hba1c change (%, lower values are better, change scores) at end of follow-up Mean follow-up: 12 month(s)											

1 (yamada 2020)	R C T	very serio us ¹	not serio us	NA ²	not serio us	NA	142	45	MD -0.07 (-0.30, 0.16)	MD 0.07 lower (0.30 lower to 0.16 higher)	low
weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 12 month(s)									Í	, , , , , , , , , , , , , , , , , , ,	
1 (yamada 2020)	R	very serio us ¹	not serio us	NA ²	not serio us	NA	142	45	MD -1.22 (-1.94, - 0.50)	MD 1.22 lower (1.94 lower to 0.50 lower)	low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross one end of the defined MIDs (-2.00, 2.00)
- 4. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 5. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

F.1.3.15 Semaglutide compared to sitagliptin

	De	Risk	Indir	Incon	Impr	Other	Interv	Con	Relative		Cer
	sig	of	ectn	sisten	ecisi	consider	ention	trol	effect		tain
No of studies	n	bias	ess	су	on	ations	N	N	(95% CI)	Absolute effect	ty
hba1c change (%, lower values are better,											
change scores) at end of follow up ~ Mean											
follow-up: 7 month(s)											
		not	not		not				MD -1.35	MD 1.35 lower	
	R	serio	serio		serio				(-1.63, -	(1.63 lower to	
1 (seino 2018)	CT	us	us	NA^1	us	NA	305	103	1.07)	1.07 lower)	high

weight change (kg, lower values are better, change score) at end of follow up ~ Mean follow-up: 7 month(s)											
		not	not						MD -3.05	MD 3.05 lower	mo
	R	serio	serio		Serio				(-3.88, -	(3.88 lower to	der
1 (seino 2018)	CT	us	us	NA^1	us ²	NA	305	103	2.22)	2.22 lower)	ate
bmi change (kg/m2, lower values are better, change score) at end of follow up ~ Mean follow-up: 7 month(s)											
		not	not		not				MD -1.10	MD 1.10 lower	
	R	serio	serio		serio				(-1.38, -	(1.38 lower to	
1 (seino 2018)	CT	us	us	NA^1	us	NA	305	103	0.82)	0.82 lower)	high
severe hypoglycaemic episodes at end of follow up ~ Mean follow-up: 8 month(s)											
		not	not		not				RD 0.00 (-	0 fewer per 1000	
	R	serio	serio		serio			0/10	0.01,	(14 fewer to 14	
1 (seino 2018)	CT	us	us	NA^1	us	NA	0/305	3	0.01)	more)	high

- 1. Only one study so no inconsistency
- 2. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

F.1.3.16 Semaglutide compared to placebo

Table 26: Clinical evidence profile: Semaglutide compared to placebo

	De sig	Risk of	Indir ectn	Incon siste	Impr ecisi	Other consider	Interv entio	Con trol	Relative effect	Absolute	Cer tai
No of studies	n	bias	ess	ncy	on	ations	n N	N	(95% CI)	effect	nty
health-related quality of life - subscale physical component (sf-36v2 acute, 0-100, higher values are better, change scores) at end of follow-up Mean follow-up: 12 month(s)											
1 (yamada 2020,yamada 2020)	R C T	very serio us ¹	not serio us	NA ²	not serio us	NA	142	49	MD -0.76 (-1.72, 0.21)	MD 0.76 lower	low

										(1.72 lower to 0.21	
health-related quality of life - subscale mental component										higher)	
(sf-36v2 acute, 0-100, higher values are better, change											
scores) at end of follow-up											
Mean follow-up: 12 month(s)										MD 1.73	
										higher	
	R	Verv	not						MD 1.73	(0.31 higher to	ver
	C	very serio	serio		serio				(0.31,	3.15	У
1 (yamada 2020,yamada 2020)	Т	us ¹	us	NA ²	us ³	NA	142	49	3.15)	higher)	low
all-cause mortality at end of follow-up Mean follow-up: 8.1 month(s)											
mean renew up. e.r menan(s)										1 more per	
	R	not _.	not _.		very			0.40	RD 0.00	1000	ver
3	C	serio us	serio us	serio us ⁵	serio us ⁶	NA	1/930	0/3 56	(-0.01, 0.01)	(7 fewer to 8 more)	y low
cardiovascular mortality at end of follow-up	-	5.5	5.5	3.5	<u></u>		.,,,,,		0.0.7	<u> </u>	
Mean follow-up: 8.1 month(s)										1 mara nar	
	R	not	not		very				RD 0.00	1 more per 1000	ver
	С	serio	serio	serio	serio			0/3	(-0.01,	(7 fewer to	у
non-fatal stroke at end of follow-up	Т	us	us	us ⁵	us ⁶	NA	1/930	56	0.01)	8 more)	low
Mean follow-up: 8.1 month(s)											
, , ,										5 fewer	
	R	not serio	not serio	serio	very serio			2/3	RD -0.00 (-0.02,	per 1000 (16 fewer	ver y
3	T	us	us	us ⁵	us ⁷	NA	1/929	56	0.01)	to 7 more)	low
non-fatal myocardial infarction at end of follow-up									,		
Mean follow-up: 8.1 month(s)										2 more per	
	R	not			very				RD 0.00	1000	ver
	С	serio	serio	serio	serio		0/633	0/3	(-0.01,	(6 fewer to	у
3	Т	us	us ⁸	us ⁵	us ⁹	NA	2/929	56	0.01)	10 more)	low
unstable angina at end of follow-up											

Mean follow-up: 12 month(s)											
1 (yamada 2020)	R C T	very serio us ¹	not serio us	NA ²	serio us ¹⁰	NA	0/146	0/4	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (29 fewer to 29 more)	ver y low
hospitalisation for heart failure at end of follow-up Mean follow-up: 5.5 month(s)											
1 (aroda 2019b)	R C T	not serio us	not serio us	NA ²	not serio us	NA	0/525	0/1 78	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	hig h
acute kidney injury at end of follow-up Mean follow-up: 8.8 month(s)											
2	R C T	not serio us	not serio us	serio us ⁵	very serio us ¹¹	NA	1/671	1/2 27	RD -0.00 (-0.01, 0.01)	3 fewer per 1000 (14 fewer to 8 more)	ver y low
cardiac arrhythmia at end of follow-up Mean follow-up: 12 month(s)											
1 (yamada 2020)	R C T	very serio us ¹	not serio us	NA ²	serio us ¹⁰	NA	0/146	0/4 9	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (29 fewer to 29 more)	ver y low
hypoglycaemia episodes at end of follow-up Mean follow-up: 8.1 month(s)											
3	R C T	not serio us	not serio us	serio us ⁵	very serio us ¹²	NA	13/92 9	3/3 56	RD 0.00 (-0.01, 0.02)	4 more per 1000 (9 fewer to 17 more)	ver y low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 8.1 month(s)											
3	R C T	not serio us	not serio us	serio us ⁵	very serio us ⁷	NA	1/929	2/3 56	RD -0.00 (-0.01, 0.01)	4 fewer per 1000 (15 fewer to 6 more)	ver y low

hba1c change (%, lower values are better, change scores) at end of follow-up Mean follow-up: 9.1 month(s)											
3	R C T	very serio us ¹	not serio us	very serio us ¹³	not serio us	NA	927	356	MD -1.07 (-1.31, - 0.83)	MD 1.07 lower (1.31 lower to 0.83 lower)	ver y low
weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 9.1 month(s)											
3	R C T	very serio us ¹	not serio us	very serio us ¹³	not serio us	NA	925	356	MD -1.17 (-2.14, - 0.20)	MD 1.17 lower (2.14 lower to 0.20 lower)	ver y low
bmi change (kg/m2, lower values are better, change scores) at end of follow-up Mean follow-up: 9.1 month(s)											
	R C	very serio	not serio	very serio	not serio				MD -0.45 (-0.79, -	MD 0.45 lower (0.79 lower to 0.10	ver y
3	Т	us ¹	us	us ¹³	us	NA	929	356	0.10)	lower)	low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross one end of the defined MIDs (-3.00, 3.00)
- 4. 95% confidence intervals cross one end of the defined MIDs (-4.53, 4.53)
- 5. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.22 (0.8-0.9 = serious, <0.8 = very serious).

- 7. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.51 (0.8-0.9 = serious, <0.8 = very serious).
- 8. Largest proportion of studies in the meta-analysis came from partially direct studies
- 9. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.38 (0.8-0.9 = serious, <0.8 = very serious).
- 10. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 11. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.21 (0.8-0.9 = serious, <0.8 = very serious).
- 12. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.27 (0.8-0.9 = serious, <0.8 = very serious).

13. I2 > 75%

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

F.1.4.1 Tirzepatide compared to dulaglutide

Table 27: Clinical evidence profile: Tirzepatide compared to dulaglutide

	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	У
all-cause mortality at end of follow-up Mean follow-up: 12 month(s)											
1 (inagaki 2022)	RC T	seriou s ¹	not seriou	NA ²	not seriou s	NA	0/477	0/15 9	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	mod erat e
cardiovascular mortality at end of follow- up Mean follow-up: 12 month(s)									(= =) = = = = = = = = = = = = = = = =		

1 (inagaki 2022)	RC T	seriou s ¹	not seriou	NA ²	not seriou	NA	0/477	0/15	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	mod erat e
3-point mace at end of follow-up	1	5	5	INA	3	INA	0/4//	9	(-0.01, 0.01)	more)	6
Mean follow-up: 12 month(s) 1 (inagaki 2022)	RC T	seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	4/477	2/15 9	RR 0.67 (0.12, 3.61)	4 fewer per 1000 (11 fewer to 33 more)	very low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 12 month(s)											
1 (inagaki 2022)	RC T	seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	1/477	0/15 9	PETO OR 3.79 (0.04, 350.61)	2 more per 1000 (2 fewer to 6 more)	very low
unstable angina at end of follow-up Mean follow-up: 12 month(s)											
1 (inagaki 2022)	RC T	seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	1/477	1/15 9	RR 0.33 (0.02, 5.30)	4 fewer per 1000 (6 fewer to 27 more)	very low
cardiac arrhythmia at end of follow-up Mean follow-up: 12 month(s)											
1 (inagaki 2022)	RC T	seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	1/477	1/15	RR 0.33 (0.02, 5.30)	4 fewer per 1000 (6 fewer to 27 more)	very low
hypoglycaemia episodes at end of follow- up Mean follow-up: 12 month(s)											
1 (inagaki 2022)	RC T	seriou s ¹	not seriou s	NA ²	not seriou s	NA	1/477	11/1 59	RR 0.03 (0.00, 0.23)	67 fewer per 1000 (69 fewer to 53 fewer)	mod erat e
severe hypoglycaemic episodes at end of follow-up											

1 (inagaki 2022)	RC T	seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/477	0/15 9	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	mod erat e
hba1c change (%, lower values are better, change scores) at end of follow-											
up											
Mean follow-up: 12 month(s)											
1 (inagaki 2022)	RC T	seriou s ¹	not seriou s	NA ²	not seriou s	NA	477	159	MD -1.30 (-1.53, - 1.07)	MD 1.30 lower (1.53 lower to 1.07 lower)	mod erat e
weight change (kg, lower values are better, change scores) at end of follow-											
up											
Mean follow-up: 12 month(s)										145 7 04	
			not		not				MD -7.84	MD 7.84 lower (8.76 lower	mod
	RC	seriou	seriou		seriou				(-8.76, -	to 6.92	erat
1 (inagaki 2022)	T	s ¹	S	NA ²	S	NA	477	159	6.92)	lower)	е

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

F.1.5 SGLT2 inhibitors

F.1.5.1 Canagliflozin compared to metformin

Table 28: Clinical evidence profile: Canagliflozin v metformin

Tubic 20. Official evidence profile. Gain	De					Other			Relative		Cert
	sig	Risk	Indire	Inconsi	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	of bias	ctness	stency	cision	ions	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow-up											
Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RC T	very seriou s ¹	not seriou	NA ²	very seriou s ³	NA	0/475	1/23 7	PETO OR 0.05 (0.00, 3.17)	4 fewer per 1000 (12 fewer to 4 more)	very low
cardiovascular mortality at end of follow-									,	,	
up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	0/475	1/23 7	PETO OR 0.05 (0.00, 3.17)	4 fewer per 1000 (12 fewer to 4 more)	very low
non-fatal stroke at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	1/475	0/23 7	PETO OR 4.48 (0.07, 286.61)	2 more per 1000 (2 fewer to 6 more)	very low
unstable angina at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/475	0/23 7	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	low
cardiac arrhythmia at end of follow-up Mean follow-up: 5.5 month(s)									, , , , , , , , ,	,	

1 (rosenstock 2016) diabetic ketoacidosis at end of follow-up	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	1/475	0/23	PETO OR 4.48 (0.07, 286.61)	2 more per 1000 (2 fewer to 6 more)	very low
Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	1/475	0/23 7	PETO OR 4.48 (0.07, 286.61)	2 more per 1000 (2 fewer to 6 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	16/475	11/2 37	RR 0.73 (0.34, 1.54)	13 fewer per 1000 (31 fewer to 25 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	0/475	1/23 7	PETO OR 0.05 (0.00, 3.17)	4 fewer per 1000 (12 fewer to 4 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow- up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	464	230	MD -0.10 (-0.27, 0.07)	MD 0.10 lower (0.27 lower to 0.07 higher)	low
weight change (kg, lower values are better, change scores) at end of follow- up Mean follow-up: 5.5 month(s)									, , ,	y /	

										MD 1.35	
		very	not		not				MD -1.35	lower	
	RC	seriou	seriou		seriou				(-2.07, -	(2.07 lower to	
1 (rosenstock 2016)	T	s ¹	S	NA^2	S	NA	472	237	0.63)	0.63 lower)	low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

F.1.5.2 Canagliflozin compared to placebo

Table 29: Clinical evidence profile: canadliflozin compared to placebo

·	De			•		Other			Relative		Cert
	sig	Risk	Indire	Inconsi	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	of bias	ctness	stency	cision	ions	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow-up Mean follow-up: 6 month(s)											
1 (stenlöf 2013)	RC T	not seriou s	not seriou s	NA ¹	very seriou s ²	NA	1/392	1/19	RR 0.49 (0.03, 7.79)	3 fewer per 1000 (5 fewer to 35 more)	low
cardiovascular mortality at end of follow- up Mean follow-up: 6 month(s)											
1 (stenlöf 2013)	RC T	not seriou s	not seriou s	NA ¹	very seriou s ²	NA	0/392	1/19 2	PETO OR 0.05 (0.00, 3.10)	5 fewer per 1000 (15 fewer to 5 more)	low
hypoglycaemia episodes at end of follow- up Mean follow-up: 5.8 month(s)											

2	RC T	very seriou s ³	not seriou s	not serious	very seriou s ²	NA	14/190	3/98	RR 2.14 (0.69, 6.68)	35 more per 1000 (10 fewer to 174 more)	very low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.8 month(s)											
3	RC T	seriou s ⁴	not seriou s	not serious	not seriou s	NA	574	287	MD -1.01 (-1.17, - 0.84)	MD 1.01 lower (1.17 lower to 0.84 lower)	mod erat e
weight change (kg, lower values are better, change scores) at end of follow- up Mean follow-up: 5.8 month(s)											
3	RC T	seriou s ⁴	not seriou	serious	seriou s ⁶	NA	575	288	MD -3.15 (-4.19, - 2.11)	MD 3.15 lower (4.19 lower to 2.11 lower)	very low
bmi change (kg/m2, lower values are better, change scores) at end of follow- up Mean follow-up: 6 month(s)											
1 (kashyap 2020)	RC T	very seriou s ³	not seriou s	NA ¹	not seriou s	NA	11	5	MD -2.89 (-4.54, - 1.24)	MD 2.89 lower (4.54 lower to 1.24 lower)	low

- 1. Only one study so no inconsistency
- 2. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 3. >33.3% of the studies in the meta-analysis were at high risk of bias
- 4. >33.3% of the studies in the meta-analysis were at moderate risk of bias

- 5. I2 between 50% and 75%
- 6. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

F.1.5.3 Dapagliflozin compared to metformin

Table 30: Clinical evidence profile: dapagliflozin compared to metformin

	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow-up Mean follow-up: 5.5 month(s)											
2	RC T	not seriou s	not seriou s	serious	very seriou s ²	NA	1/422	1/40 9	PETO OR 0.97 (0.06, 15.51)	0 fewer per 1000 (7 fewer to 7 more)	very low
cardiovascular mortality at end of follow- up Mean follow-up: 5.5 month(s)											
2	RC T	not seriou s	not seriou s	serious	very seriou s ²	NA	1/422	1/40	PETO OR 0.97 (0.06, 15.51)	0 fewer per 1000 (7 fewer to 7 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)											
2	RC T	not seriou s	not seriou s	serious	very seriou s ³	NA	2/422	6/40 9	RD -0.01 (-0.04, 0.02)	8 fewer per 1000 (38 fewer to 22 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)											

2	RC T	not seriou s	not seriou s	not serious	not seriou s	NA	0/411	0/42	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	high
hba1c change (%, lower values are better, change scores) at end of follow- up Mean follow-up: 5.5 month(s)											
2	RC T	not seriou s	not seriou s	not serious	not seriou s	NA	412	398	MD 0.06 (-0.10, 0.22)	MD 0.06 higher (0.10 lower to 0.22 higher)	high
weight change (kg, lower values are better, change scores) at end of follow- up Mean follow-up: 5.5 month(s)											
2	RC T	not seriou s	not seriou s	not serious	not seriou s	NA	422	409	MD -1.34 (-1.81, - 0.88)	MD 1.34 lower (1.81 lower to 0.88 lower)	high

- 1. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 2. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.54 (0.8-0.9 = serious, <0.8 = very serious).

F.1.5.4 Dapagliflozin compared to placebo

Table 31: Clinical evidence profile: dapagliflozin compared to placebo

	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	У
all-cause mortality at end of follow-up											

Mean follow-up: 5.7 month(s)											
3	RC T	seriou s ¹	not seriou s	serious	very seriou s ³	NA	1/885	0/27 5	RD 0.00 (-0.01, 0.01)	1 more per 1000 (9 fewer to 10 more)	very low
persistent signs of worsening kidney disease at end of follow-up Mean follow-up: 5.5 month(s)											
2	RC T	not seriou s	not seriou s	not serious	very seriou s ⁴	NA	11/435	5/21 9	RR 1.11 (0.39, 3.14)	2 more per 1000 (14 fewer to 49 more)	low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.7 month(s)											
3	RC T	seriou s ¹	not seriou s	not serious	very seriou s ⁴	NA	10/859	4/27 5	RR 0.67 (0.22, 2.05)	5 fewer per 1000 (11 fewer to 15 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow- up Mean follow-up: 5.6 month(s)											
5	RC T	seriou s ¹	not seriou s	very serious	seriou s ⁶	NA	1051	372	MD -0.73 (-1.02, - 0.44)	MD 0.73 lower (1.02 lower to 0.44 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow- up Mean follow-up: 5.5 month(s)											
2	RC T	seriou s ¹	not seriou s	very serious	not seriou s	NA	558	162	MD -0.47 (-2.13, 1.18)	MD 0.47 lower (2.13 lower to 1.18 higher)	very low

^{1. &}gt;33.3% of the studies in the meta-analysis were at moderate risk of bias

- 2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.21 (0.8-0.9 = serious, <0.8 = very serious).
- 4. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 5. I2 > 75%
- 6. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

F.1.5.5 Empagliflozin compared to metformin

Table 32: Clinical evidence profile: empagliflozin compared to metformin

Tubic 02: Omnour evidence prome: om	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow-up Mean follow-up: 5.5 month(s)											
1 (hadjadj 2016)	RC T	not seriou s	not seriou s	NA ¹	not seriou s	NA	0/339	0/34	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	high
cardiovascular mortality at end of follow-up Mean follow-up: 5.5 month(s)											
1 (hadjadj 2016)	RC T	not seriou s	not seriou s	NA ¹	not seriou s	NA	0/339	0/34	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	high
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)											J

1 (hadjadj 2016)	RC T	not seriou s	not seriou s	NA ¹	very seriou s ²	NA	2/339	2/34 1	RR 1.01 (0.14, 7.10)	0 more per 1000 (5 fewer to 36 more)	low
hba1c change (%, lower values are better, change score) at end of follow-up											
Mean follow-up: 5.5 month(s)											
										MD 0.15	
		not	not		not					higher	
	RC	seriou	seriou		seriou				MD 0.15	(0.02 lower to	
1 (hadjadj 2016)	Т	S	S	NA ¹	S	NA	285	269	(-0.02, 0.32)	0.32 higher)	high

- 1. Only one study so no inconsistency
- 2. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

F.1.5.6 Empagliflozin compared to linagliptin

Table 33: Clinical evidence profile: empagliflozin v linagliptin

	De		- J - P -			Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	У
all-cause mortality at end of follow-up Mean follow-up: 12 month(s)											
1 (lewin 2015)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	3/270	0/13 5	PETO OR 4.52 (0.41, 50.09)	11 more per 1000 (1 fewer to 24 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 12 month(s)											
1 (lewin 2015)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	1/270	0/13 5	PETO OR 4.48 (0.07, 286.49)	4 more per 1000 (4 fewer to 11 more)	very low

hypoglycaemia episodes at end of follow-up											
Mean follow-up: 12 month(s)											
1 (lewin 2015)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	5/270	1/13 5	RR 2.50 (0.30, 21.19)	11 more per 1000 (5 fewer to 150 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 12 month(s)											
1 (lewin 2015)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/270	0/13 5	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (11 fewer to 11 more)	low
hba1c change (%, lower values are better, change scores) at end of follow- up Mean follow-up: 5.5 month(s)											
1 (lewin 2015)	RC T	seriou s ⁴	not seriou s	NA ²	not seriou s	NA	265	133	MD -0.23 (-0.39, - 0.07)	MD 0.23 lower (0.39 lower to 0.07 lower)	mod erat e
weight change (kg, lower values are better) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (lewin 2015)	RC T	not seriou s	not seriou s	NA ²	seriou s ⁵	NA	266	133	MD -1.40 (-4.82, 2.02)	MD 1.40 lower (4.82 lower to 2.02 higher)	mod erat e

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 5. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

F.1.5.7 Empagliflozin compared to sitagliptin

Table 34: Clinical evidence profile: empagliflozin compared to sitagliptin

Table 34. Officer evidence profile.	<u> </u>	Risk				Other			Relative		
	Des	of	Indirec	Inconsi	Imprec	considerati	Interve	Cont	effect (95%	Absolute	Cert
No of studies	ign	bias	tness	stency	ision	ons	ntion N	rol N	CI)	effect	ainty
all-cause mortality at end of follow- up Mean follow-up: 17.5 month(s)				,							-
1 (roden 2015)	RC T	seriou s ¹	not seriou s	NA ²	very serious	NA	1/447	1/223	RR 0.50 (0.03, 7.94)	2 fewer per 1000 (4 fewer to 31 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 17.5 month(s)											
1 (roden 2015)	RC T	seriou s ¹	not seriou s	NA ²	very serious	NA	4/447	2/223	RR 1.00 (0.18, 5.41)	0 fewer per 1000 (7 fewer to 40 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 17.5 month(s)											
1 (roden 2015)	RC T	seriou s ¹	not seriou s	NA ²	very serious	NA	1/447	0/223	PETO OR 4.48 (0.07, 286.62)	2 more per 1000 (2 fewer to 7 more)	very low
hba1c change (%, lower values are better) at end of follow-up Mean follow-up: 17.5 month(s)											
1 (roden 2015)	RC T	seriou s ¹	not seriou s	NA ²	not serious	NA	448	223	MD -0.18 (-0.20, -0.16)	MD 0.18 lower (0.20 lower to 0.16 lower)	mod erate
weight change (kg, lower values are better) at end of follow-up											

Mean follow-up: 17.5 month(s)											
			not							MD 2.45 lower	
	RC	seriou	seriou		serious				MD -2.45	(2.93 lower to	
1 (roden 2015)	T	s ¹	S	NA ²	4	NA	448	223	(-2.93, -1.97)	1.97 lower)	low

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

F.1.5.8 Empagliflozin compared to placebo

Table 35: Clinical evidence profile: empagliflozin compared to placebo

	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow-up Mean follow-up: 17.5 month(s)											
1 (roden 2015)	RC T	seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	1/447	1/22	RR 0.51 (0.03, 8.15)	2 fewer per 1000 (4 fewer to 31 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 17.5 month(s)	•	3	3	10/1	3	10/1	1/		(0.00, 0.10)	more	low
1 (roden 2015)	RC T	seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	4/447	2/22 9	RR 1.02 (0.19, 5.55)	0 more per 1000 (7 fewer to 40 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 17.5 month(s)											

1 (roden 2015)	RC T	seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	1/447	0/22 9	PETO OR 4.54 (0.07, 285.28)	2 more per 1000 (2 fewer to 7 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow- up Mean follow-up: 11.5 month(s)											
2	RC T	seriou s ¹	not seriou s	very serious	seriou s ⁵	NA	490	270	MD -0.52 (-1.16, 0.11)	MD 0.52 lower (1.16 lower to 0.11 higher)	very low
weight change (kg, lower values are better, change scores) at end of follow- up Mean follow-up: 11.5 month(s)											
2	RC T	seriou s ¹	not seriou s	not serious	seriou s ⁶	NA	490	270	MD -2.04 (-2.49, - 1.60)	MD 2.04 lower (2.49 lower to 1.60 lower)	low

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. I2 > 75%
- 5. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 6. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

F.1.6 Sulfonylureas

F.1.6.1 Gliclazide compared to metformin

Table 36: Clinical evidence profile: gliclazide compared to metformin

rable 30. Chilical evidence prome. gliciazidi	De	Risk	Indire	Incons		Other	Interve	Cont	Relative		Cert
	sig	of	ctnes	istenc	Impre	considera	ntion	rol	effect (95%	Absolute	aint
No of studies	n	bias	S	у	cision	tions	N	N	CI)	effect	у
cardiovascular mortality at end of follow-up											-
Mean follow-up: 12 month(s)		verv	not		very				RD 0.00	0 fewer per 1000	
1 (erem 2014)	RC T	seriou s ¹	seriou s	NA ²	seriou s ³	NA	0/20	0/20	(-0.09, 0.09)	(92 fewer to 92 more)	very low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 12 month(s)											
1 (erem 2014)	RC T	very seriou s ¹	not seriou	NA ²	very seriou s ³	NA	0/20	0/20	RD 0.00 (-0.09, 0.09)	0 fewer per 1000 (92 fewer to 92 more)	very low
hospitalisation for heart failure at end of follow-up Mean follow-up: 12 month(s)	_	3	3	10.1	3	14/1	UI ZU	0/20	0.00)	oz more)	1011
1 (erem 2014)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	0/20	0/20	RD 0.00 (-0.09, 0.09)	0 fewer per 1000 (92 fewer to 92 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 8.8 month(s)										·	
2	RC T	very seriou s ¹	not seriou s	seriou s ⁴	very seriou s ⁵	NA	2/52	2/51	RD -0.00 (-0.07, 0.07)	1 fewer per 1000 (74 fewer to 72 more)	very low
severe hypoglycaemic episodes at end of follow-up											

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

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 4. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

- 5. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.03 (0.8-0.9 = serious, <0.8 = very serious).
- 6. I2 between 50% and 75%
- 7. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 8. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)
- 9. 95% confidence intervals cross both ends of the defined MIDs (-0.80, 0.80)

F.1.6.2 Gliclazide compared to vildagliptin

Table 37: Clinical evidence profile: glizlacide compared to vildagliptin

3	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ions	ntion N	rol N	CI)	effect	у
all-cause mortality end of follow-up Mean follow-up: 24 month(s)											
1 (foley 2009)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	9/546	6/54 6	RR 1.50 (0.54, 4.19)	5 more per 1000 (5 fewer to 35 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow- up Mean follow-up: 24 month(s)											
1 (foley 2009)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	546	546	MD 0.13 (-0.07, 0.33)	MD 0.13 higher (0.07 lower to 0.33 higher)	low
weight change (kg, lower values are better, change scores) at end of follow- up Mean follow-up: 24 month(s)											

										MD 0.80	
										higher	
		very	not		not					(0.25 higher	
	RC	seriou	seriou		seriou				MD 0.80	to 1.35	
1 (foley 2009)	Т	s ¹	S	NA^2	s	NA	546	546	(0.25, 1.35)	higher)	low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

F.1.6.3 Glimepiride compared to metformin

Table 38: Clinical evidence profile: glimepiride compared to metformin

	De	Risk	Indire	Incons		Other	Interve	Cont	Relative		Cert
	sig	of	ctnes	istenc	Impre	considera	ntion	rol	effect (95%	Absolute	aint
No of studies	n	bias	S	У	cision	tions	N	N	CI)	effect	у
hypoglycaemia episodes at end of follow-up Mean follow-up: 11.7 month(s)											
3	RC T	very seriou s ¹	not seriou s	seriou s ²	not seriou s	NA	24/236	4/23 6	RD 0.06 (-0.11, 0.23)	61 more per 1000 (109 fewer to 230 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 12 month(s)											
1 (derosa 2004)	RC T	very seriou s ¹	not seriou s	NA ³	seriou s ⁴	NA	0/81	0/83	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (24 fewer to 24 more)	very low
hba1c change (%, lower values are better, change score and final value) at end of follow-up Mean follow-up: 11.7 month(s)											

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

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 3. Only one study so no inconsistency
- 4. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 5. 95% confidence intervals cross both ends of the defined MIDs (-0.80, 0.80)

F.1.6.4 Glimepiride compared to dulaglutide

Table 39: Clinical evidence profile: glimepiride compared to dulaglutide

	De					Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ions	ntion N	rol N	CI)	effect	У
all-cause mortality at end of follow-up Mean follow-up: 6 month(s)											

1 (chen 2018b)	RC T	very serious	not seriou s	NA ²	very seriou s ³	NA	0/243	1/49	PETO OR 0.22 (0.00, 14.47)	2 fewer per 1000 (6 fewer to 2 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 6 month(s)									,	ŕ	
1 (chen 2018b)	RC T	very serious	not seriou s	NA ²	not seriou s	NA	0/243	0/49	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	low
non-fatal stroke at end of follow-up Mean follow-up: 6 month(s)											
1 (chen 2018b)	RC T	very serious	not seriou s	NA ²	very seriou s ³	NA	0/243	1/49	PETO OR 0.22 (0.00, 14.47)	2 fewer per 1000 (6 fewer to 2 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (chen 2018b)	RC T	very serious	not seriou	NA ²	not seriou s	NA	38/243	23/4 92	RR 3.35 (2.04, 5.48)	110 more per 1000 (49 more to 210 more)	low
at night hypoglycaemic episodes at end of follow-up Mean follow-up: 6 month(s)										,	
1 (chen 2018b)	RC T	very serious	not seriou s	NA ²	not seriou s	NA	9/243	2/49 2	RR 9.11 (1.98, 41.84)	33 more per 1000 (4 more to 166 more)	low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 6 month(s)											
	RC	very serious	not seriou		not seriou			0/49	RD 0.00	0 fewer per 1000 (6 fewer to 6	
1 (chen 2018b)	T	1	S	NA ²	S	NA	0/243	2	(-0.01, 0.01)	more)	low

hba1c change (%, lower values are better, change scores) at end of follow- up Mean follow-up: 6 month(s)											
1 (chen 2018b) weight change (kg, lower values are better, change scores) at end of follow-	RC T	very serious	not seriou s	NA ²	seriou s ⁴	NA	242	478	MD 0.45 (0.28, 0.62)	MD 0.45 higher (0.28 higher to 0.62 higher)	very low
up											
Mean follow-up: 6 month(s) 1 (chen 2018b)	RC T	very serious	not seriou s	NA ²	seriou s ⁵	NA	242	478	MD 2.01 (1.55, 2.47)	MD 2.01 higher (1.55 higher to 2.47 higher)	very low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 5. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

F.1.6.5 Glimepiride compared to saxagliptin

Table 40: Clinical evidence profile: glimepiride compared to saxagliptin

	De					Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у

hba1c change (%, lower values are better, final value) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (li 2019a) bmi change (kg/m2, lower values are better, final value) at end of follow-up Mean follow-up: 5.5 month(s)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	33	30	MD 0.01 (-0.25, 0.27)	MD 0.01 higher (0.25 lower to 0.27 higher)	low
1 (li 2019a)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s³	NA	33	30	MD -1.04 (-2.85, 0.77)	MD 1.04 lower (2.85 lower to 0.77 higher)	very low

- 1. Largest proportion of studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

F.1.6.6 Glimepiride compared to sitagliptin

Table 41: Clinical evidence profile: glimepiride compared to sitagliptin

	De sig	Risk of	Indire ctnes	Incons	Impre	Other considera	Interve ntion	Cont rol	Relative effect (95%	Absolute	Cert aint
No of studies	n	bias	s	у	cision	tions	N	N	CI)	effect	у
all-cause mortality at end of follow up Mean follow-up: 15.5 month(s)											
2	RC T	not seriou s	not seriou s	seriou s ¹	very seriou s ²	NA	1/388	0/39 4	RD 0.00 (-0.01, 0.01)	3 more per 1000 (6 fewer to 11 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 7 month(s)									·	,	

1 (hartley 2015) persistent signs of worsening kidney disease at end of follow-up Mean follow-up: 12 month(s)	RC T	not seriou s	not seriou s	NA ³	not seriou s	NA	0/236	0/24	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	high
1 (kondo 2016) progression of liver disease at end of follow-	RC T	very seriou s ⁴	not seriou s	NA ³	seriou s ⁵	NA	0/68	3/65	PETO OR 0.13 (0.01, 1.23)	46 fewer per 1000 (97 fewer to 5 more)	very low
up Mean follow-up: 18 month(s)										5 fewer per	
2	RC T	very seriou s ⁴	not seriou s	not seriou s	very seriou s ⁶	NA	3/220	4/21 8	RR 0.75 (0.19, 2.96)	1000 (15 fewer to 36 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 9.5 month(s)											
2	RC T	not seriou s	not seriou s	seriou s ¹	not seriou s	NA	16/304	3/30	PETO OR 4.20 (1.68, 10.48)	43 more per 1000 (15 more to 70 more)	mod erat e
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 14.3 month(s)											
3	RC T	not seriou s	not seriou s	seriou s ¹	very seriou s ⁷	NA	3/456	1/45 9	RD 0.00 (-0.01, 0.01)	4 more per 1000 (6 fewer to 15 more)	very low
hba1c change (%, lower values are better, change scores and final value) at end of follow-up Mean follow-up: 10.3 month(s)											
3	RC T	very seriou s ⁴	not seriou s	not seriou s	not seriou s	NA	411	415	MD -0.12 (-0.21, - 0.03)	MD 0.12 lower	low

										(0.21 lower to 0.03 lower)	
weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 15.5 month(s)											
2	RC T	not seriou s	not seriou s	not seriou s	not seriou s	NA	388	394	MD 0.77 (0.31, 1.24)	MD 0.77 higher (0.31 higher to 1.24 higher)	high
bmi change (kg/m2, lower values are better, final value) at end of follow-up Mean follow-up: 12 month(s)											
	RC	very seriou	not seriou		not seriou				MD 0.00 (-0.36,	MD 0.00 lower (0.36 lower to 0.36	
1 (kondo 2016)	T	s ⁴	S	NA ³	S	NA	68	65	0.36)	higher)	low

- 1. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 2. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.29 (0.8-0.9 = serious, <0.8 = very serious).
- 3. Only one study so no inconsistency
- 4. >33.3% of the studies in the meta-analysis were at high risk of bias
- 5. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 6. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 7. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.3 (0.8-0.9 = serious, <0.8 = very serious).

F.1.6.7 Glipizide compared to metformin

Table 42: Clinical evidence profile: glipizide compared to metformin

	De	Risk	Indire	Incons		Other	Interve	Cont	Relative		Cert
	sig	of	ctnes	istenc	Impre	considera	ntion	rol	effect (95%	Absolute	aint
No of studies	n	bias	S	у	cision	tions	N	N	CI)	effect	у
hypoglycaemia episodes at end of follow-up Mean follow-up: 12 month(s)											
1 (campbell 1994)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	0/24	0/24	RD 0.00 (-0.08, 0.08)	0 fewer per 1000 (78 fewer to 78 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 12 month(s)											
1 (campbell 1994)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	0/24	0/24	RD 0.00 (-0.08, 0.08)	0 fewer per 1000 (78 fewer to 78 more)	very low
hba1c change (%, lower values are better, change score and final value) at end of follow-up Mean follow-up: 8.8 month(s)											
2	RC T	very seriou s ¹	not seriou s	very seriou s ⁴	very seriou s ⁵	NA	94	92	MD 0.34 (-1.01, 1.69)	MD 0.34 higher (1.01 lower to 1.69 higher)	very low
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
2	RC T	very seriou s ¹	not seriou s	seriou s ⁶	very seriou s ⁷	NA	94	92	MD 1.81 (-2.41, 6.03)	MD 1.81 higher (2.41 lower to 6.03 higher)	very low

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

F.1.6.8 Glipizide compared to sitagliptin

Table 43: Clinical evidence profile: glipizide compared to sitagliptin

	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow-up Mean follow-up: 12.4 month(s)											
2	RC T	serio us¹	not seriou s	not serious	very seriou s ²	NA	13/277	7/27 4	RR 1.83 (0.75, 4.50)	21 more per 1000 (6 fewer to 89 more)	very low
cardiovascular mortality at end of follow- up Mean follow-up: 12.4 month(s)											
1 (arjona ferreira 2013b)	RC T	serio us¹	not seriou s	NA ³	very seriou s ²	NA	3/212	2/21 0	RR 1.49 (0.25, 8.80)	5 more per 1000 (7 fewer to 74 more)	very low
non-fatal stroke at end of follow-up Mean follow-up: 12.4 month(s)											

1 (arjona ferreira 2013b)	RC T	serio us¹	not seriou	NA ³	very seriou s ²	NA	1/212	2/21	RR 0.50 (0.05, 5.42)	5 fewer per 1000 (9 fewer to 42 more)	very
hospitalisation for heart failure at end of follow-up Mean follow-up: 12.4 month(s)									(2.2.2, 2.7, 2.7,		
2	RC T	serio us ¹	not seriou s	serious	very seriou s ²	NA	5/277	2/27 5	PETO OR 2.36 (0.53, 10.51)	11 more per 1000 (8 fewer to 29 more)	very low
development of end stage kidney disease at end of follow-up Mean follow-up: 12.4 month(s)											
1 (arjona ferreira 2013b)	RC T	serio us¹	not seriou s	NA ³	very seriou s ²	NA	1/210	2/21 2	RR 0.50 (0.05, 5.52)	5 fewer per 1000 (9 fewer to 43 more)	very low
diabetic ketoacidosis at end of follow-up Mean follow-up: 12.4 month(s)											
1 (arjona ferreira 2013b)	RC T	serio us ¹	not seriou s	NA ³	very seriou s ²	NA	0/212	1/21	PETO OR 0.13 (0.00, 6.76)	5 fewer per 1000 (14 fewer to 5 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 12.4 month(s)											
2	RC T	serio us ¹	not seriou s	not serious	very seriou s ²	NA	11/277	3/27 5	RR 2.94 (0.69, 12.53)	21 more per 1000 (3 fewer to 126 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow- up Mean follow-up: 12.4 month(s)											
2	RC T	serio us ¹	not seriou s	serious 5	not seriou s	NA	204	194	MD 0.05 (-0.29, 0.39)	MD 0.05 higher	low

										(0.29 lower to 0.39 higher)	
weight change (kg, lower values are better, change scores) at end of follow-											
up											
Mean follow-up: 12.4 month(s)											
										MD 1.70	
										higher	
			not		not					(1.06 higher	mod
	RC	serio	seriou	not	seriou				MD 1.70	to 2.35	erat
2	T	us ¹	S	serious	S	NA	189	188	(1.06, 2.35)	higher)	е

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 3. Only one study so no inconsistency
- 4. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 5. I2 between 50% and 75%

F.1.6.9 Glipizide compared to placebo

Table 44: Clinical evidence profile: glipizide compared to placebo

Table 44. Chillean Cylachica promot gil			- с с р								
	De					Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Imprec	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	ision	ons	ntion N	rol N	CI)	effect	у
remission at end of follow-up											
Mean follow-up: 22 month(s)											
										0 fewer per	
					very					1000	
	RC	seriou	seriou		serious				RR 1.00	(263 fewer to	very
1 (banerji 1995)	T	s ¹	s ²	NA^3	4	NA	4/10	4/10	(0.34, 2.93)	770 more)	low

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

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. Largest proportion of studies in the meta-analysis came from partially direct studies
- 3. Only one study so no inconsistency
- 4. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 5. >33.3% of the studies in the meta-analysis were at high risk of bias

- 6. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 7. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 8. I2 > 75%
- 9. 95% confidence intervals cross both ends of the defined MIDs (-0.50, 0.50)
- 10. 95% confidence intervals cross both ends of the defined MIDs (-0.80, 0.80)

F.1.6.10 Tolbutamide compared to insulin

Table 45: Clinical evidence profile: Tolbutamide compared to insulin

									1		
						Other			Relative		
	Des	Risk of	Indirec	Inconsi	Imprec	considerati	Interve	Cont	effect (95%	Absolute	Cert
No of studies	ign	bias	tness	stency	ision	ons	ntion N	rol N	CI)	effect	ainty
all-cause mortality at end of follow-											
up											
Mean follow-up: 60 month(s)											
1 (goldner 1971)	RC T	very serious	not seriou s	NA ²	serious	NA	30/204	38/4 14	RR 1.60 (1.02, 2.51)	55 more per 1000 (2 more to 138 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 60 month(s)											
1 (goldner 1971)	RC T	very serious	not seriou s	NA ²	not serious	NA	26/204	25/4 14	RR 2.11 (1.25, 3.56)	67 more per 1000 (15 more to 155 more)	low
persistent signs of worsening kidney disease at end of follow-up Mean follow-up: 60 month(s)											

1 (goldner 1971)	RC T	very serious	not seriou s	NA ²	very serious	NA	11/188	18/3 78	RR 1.23 (0.59, 2.55)	11 more per 1000 (19 fewer to 74 more)	very low
cardiac arrhythmia at end of follow-											
up											
Mean follow-up: 60 month(s)											
										4 more per	
		very	not		very					1000	
	RC	serious	seriou		serious			31/3	RR 1.05	(33 fewer to	very
1 (goldner 1971)	Т	1	S	NA ²	4	NA	16/193	92	(0.59, 1.87)	69 more)	low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 4. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

F.1.6.11 Tolbutamide compared to placebo

Table 46: Clinical evidence profile: Tolbutamide compared to placebo

						Other			Relative		
	Des	Risk of	Indirec	Inconsi	Imprec	considerati	Interve	Cont	effect (95%	Absolute	Cert
No of studies	ign	bias	tness	stency	ision	ons	ntion N	rol N	CI)	effect	ainty
all-cause mortality at end of follow-											
up											
Mean follow-up: 60 month(s)											
										45 more per	
		very	not							1000	
	RC	serious	seriou		serious			21/2	RR 1.44	(15 fewer to	very
1 (goldner 1971)	Т	1	S	NA ²	3	NA	30/204	05	(0.85, 2.42)	146 more)	low
cardiovascular mortality at end of follow-up											

Mean follow-up: 60 month(s)											
1 (goldner 1971)	RC T	very serious	not seriou s	NA ²	not serious	NA	26/204	10/2 05	RR 2.61 (1.29, 5.28)	79 more per 1000 (14 more to 209 more)	low
persistent signs of worsening kidney disease at end of follow-up Mean follow-up: 60 month(s)											
1 (goldner 1971)	RC T	very serious	not seriou s	NA ²	very serious	NA	11/188	12/1 84	RR 0.90 (0.41, 1.98)	7 fewer per 1000 (39 fewer to 64 more)	very low
cardiac arrhythmia at end of follow- up Mean follow-up: 60 month(s)									, ,	,	
1 (goldner 1971)	RC T	very serious	not seriou s	NA ²	serious	NA	16/193	27/1 93	RR 0.59 (0.33, 1.06)	57 fewer per 1000 (94 fewer to 9 more)	very low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 4. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

F.1.7 Thiazolidinedione

F.1.7.1 Pioglitazone compared to metformin

Figure 207: Clinical evidence profile: Pioglitazone compared to metformin

I igure 207. Omnicui evider						Other			Relative		
	Des	Risk of	Indirec	Inconsis	Impreci	consideratio	Interven	Contr	effect (95%		Certa
No of studies	ign	bias	tness	tency	sion	ns	tion N	ol N	CI)	Absolute effect	inty
health-related quality of life - overall - eq5d Mean follow-up: 6 month(s)											
1 (russell-jones 2012)	RC T	not serious	not serious	NA ¹	serious ²	NA	146	227	MD -0.04 (-0.07, -0.01)	MD 0.04 lower (0.07 lower to 0.01 lower)	mode rate
all-cause mortality Mean follow-up: 8.2 month(s)											
5	RC T	not serious	not serious	serious ³	very serious ⁴	NA	3/725	3/827	RD -0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 6 more)	very low
cardiovascular mortality Mean follow-up: 7.2 month(s)											
4	RC T	very serious	not serious	serious ³	very serious ⁶	NA	0/428	1/530	RD -0.00 (-0.01, 0.01)	1 fewer per 1000 (9 fewer to 6 more)	very low
non-fatal myocardial infarction Mean follow-up: 8.8 month(s)											
2	RC T	very serious	not serious	serious ³	very serious ⁷	NA	1/210	0/229	RD 0.01 (-0.01, 0.02)	5 more per 1000 (9 fewer to 19 more)	very low

hospitalisation for heart failure Mean follow-up: 8.8 month(s)											
2	RC T	not serious	not serious	not serious	serious ⁸	NA	0/75	0/75	RD 0.00 (-0.04, 0.04)	0 fewer per 1000 (37 fewer to 37 more)	mode rate
hypoglycaemia episodes Mean follow-up: 10.1 month(s)											
5	RC T	very serious	not serious	serious ³	very serious ⁶	NA	7/480	13/58 1	RD -0.01 (-0.02, 0.01)	5 fewer per 1000 (19 fewer to 9 more)	very low
severe hypoglycaemic episodes Mean follow-up: 12 month(s)											
1 (erem 2014)	RC T	very serious	not serious	NA ¹	very serious ⁸	NA	0/20	0/20	RD 0.00 (-0.09, 0.09)	0 fewer per 1000 (92 fewer to 92 more)	very low
hba1c change Mean follow-up: 9.7 month(s)											
6	RC T	not serious	not serious	serious ⁹	not serious	NA	423	498	MD 0.07 (-0.08, 0.23)	MD 0.07 higher (0.08 lower to 0.23 higher)	mode rate
weight change Mean follow-up: 8.6 month(s)											
5	RC T	not serious	not serious	very serious ¹	serious ¹	NA	939	1017	MD 2.90 (1.16, 4.64)	MD 2.90 higher (1.16 higher to 4.64 higher)	very low
bmi change Mean follow-up: 11.1 month(s)											

				very	very					MD 0.24 lower	
	RC	not	not	serious1	serious1				MD -0.24	(1.73 lower to	very
4	Т	serious	serious	0	2	NA	181	180	(-1.73, 1.24)	1.24 higher)	low

- 1. Only one study so no inconsistency
- 2. 95% confidence intervals cross one end of the defined MIDs (-0.03, 0.03)
- 3. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.04 (0.8-0.9 = serious, <0.8 = very serious).
- 5. >33.3% of the studies in the meta-analysis were at high risk of bias
- 6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.27 (0.8-0.9 = serious, <0.8 = very serious).
- 7. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.3 (0.8-0.9 = serious, <0.8 = very serious).
- 8. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 9. I2 between 50% and 75%
- 10. I2 > 75%
- 11. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)
- 12. 95% confidence intervals cross both ends of the defined MIDs (-0.80, 0.80)

F.1.7.2 Pioglitazone compared to linagliptin

Figure 208: Clinical evidence profile: Pioglitazone compared to linagliptin

i igare 200. Omnear evidence p						Other			Relative		
	Des	Risk of	Indirec	Inconsis	Impreci	consideratio	Interven	Contr	effect (95%	Absolute	Certa
Alan Calladia					_				•		
No of studies	ign	bias	tness	tency	sion	ns	tion N	ol N	CI)	effect	inty
4-point mace at end of follow-											
up											
Mean follow-up: 6.9 month(s)											
										10 fewer per	
					very				PETO OR	1000	
	RC	seriou	not		serious				0.26	(31 fewer to	very
1 (nauck 2016)	Т	s ¹	serious	NA ²	3	NA	2/409	2/135	(0.03, 2.50)	12 more)	low
hypoglycaemia episodes at											
end of follow-up											
Mean follow-up: 6.9 month(s)											
										12 more per	
					very				PETO OR	1000	
	RC	seriou	not		serious				3.82	(2 more to	very
1 (nauck 2016)	Т	s ¹	serious	NA ²	3	NA	5/409	0/135	(0.50, 29.27)	23 more)	low
severe hypoglycaemic											
episodes at end of follow-up											
Mean follow-up: 6.9 month(s)											
										0 fewer per	
										1000	
	RC	seriou	not		not				RD 0.00	(11 fewer to	mode
1 (nauck 2016)	Т	s ¹	serious	NA ²	serious	NA	0/409	0/135	(-0.01, 0.01)	11 more)	rate

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

F.1.7.3 Pioglitazone compared to sitagliptin

Table 47: Clinical evidence profile: Pioglitazone compared to sitagliptin

Table 47. Chilical evidence prome					9	Other			Relative		
	Des	Risk of	Indire	Inconsi	Imprec	considerati	Interve	Cont	effect (95%	Absolute	Cert
No of studies	ign	bias	ctness	stency	ision	ons	ntion N	rol N	CI)	effect	ainty
health-related quality of life - overall - eq-5d at end of follow-up Mean follow-up: 6 month(s)											
1 (russell-jones 2012)	RC T	not serious	not seriou s	NA ¹	serious 2	NA	146	149	MD -0.03 (-0.06, -0.00)	MD 0.03 lower (0.06 lower to 0.00 lower)	mod erate
all-cause mortality at end of follow- up Mean follow-up: 9 month(s)											
2	RC T	very serious	not seriou s	serious	very serious	NA	1/728	1/34 9	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (10 fewer to 6 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 9 month(s)											
2	RC T	very serious	not seriou s	not serious	not serious	NA	0/728	0/34 9	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	low
non-fatal stroke at end of follow-up Mean follow-up: 12 month(s)											
1 (henry 2014)	RC T	very serious	not seriou s	NA ¹	very serious	NA	2/568	1/18 6	RR 0.65 (0.06, 7.18)	2 fewer per 1000 (5 fewer to 33 more)	very low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 12 month(s)											

1 (henry 2014)	RC T	very serious	not seriou s	NA ¹	not serious	NA	0/568	2/18 6	PETO OR 0.02 (0.00, 0.43)	11 fewer per 1000 (26 fewer to 4 more)	low
hypoglycaemia episodes at end of follow-up Mean follow-up: 9 month(s)											
2	RC T	very serious	not seriou s	not serious	very serious	NA	58/728	25/3 49	RR 0.90 (0.58, 1.42)	7 fewer per 1000 (30 fewer to 30 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 12 month(s)											
1 (henry 2014)	RC T	very serious	not seriou s	NA¹	very serious	NA	0/565	1/18	PETO OR 0.02 (0.00, 1.65)	5 fewer per 1000 (16 fewer to 5 more)	very low
hba1c change (%, change score, lower values better) Mean follow-up: 9 month(s)										,	
2	RC T	not serious	not seriou s	very serious	serious 8	NA	652	314	MD -0.31 (-0.65, 0.02)	MD 0.31 lower (0.65 lower to 0.02 higher)	very low
weight change (kg, change score, lower values better) Mean follow-up: 9 month(s)											
2	RC T	not serious	not seriou s	very serious	serious	NA	471	264	MD 3.09 (1.40, 4.78)	MD 3.09 higher (1.40 higher to 4.78 higher)	very low

- 1. Only one study so no inconsistency
- 2. 95% confidence intervals cross one end of the defined MIDs (-0.03, 0.03)
- 3. > 33.3% of the studies in the meta-analysis were at high risk of bias

- 4. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 5. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.11 (0.8-0.9 = serious, <0.8 = very serious).
- 6. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 7.12 > 75%
- 8. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 9. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

F.1.7.4 Pioglitazone compared to vildagliptin

Table 48: Clinical evidence profile: Pioglitazone compared to vildagliptin

Tuble 40. Officer evidence prome. 1 is	De				•	Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
hypoglycaemia episodes at end of											
follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2007a)	RC T	very seriou s ¹	not seriou	NA ²	very seriou s ³	NA	0/161	1/15 3	PETO OR 0.13 (0.00, 6.48)	7 fewer per 1000 (19 fewer to 6 more)	very low
hba1c change (%, change score, lower scores better) at end of follow-up Mean follow-up: 5.5 month(s)	٠						9, 10 1		(6:66, 6:16)		
1 (rosenstock 2007a)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s ⁴	NA	157	150	MD -0.30 (-0.58, - 0.02)	MD 0.30 lower (0.58 lower to 0.02 lower)	very low
weight change (kg, change score, lower scores better) Mean follow-up: 5.5 month(s)									·		

										MD 1.30	
		very	not		not					higher	
	RC	seriou	seriou		seriou				MD 1.30	(0.47 higher to	
1 (rosenstock 2007a)	Т	s ¹	S	NA^2	S	NA	157	150	(0.47, 2.13)	2.13 higher)	low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

F.1.7.5 Pioglitazone compared to exenatide

Table 49: Clinical evidence profile: Pioglitazone compared to exenatide

		J				Other			Relative		
	Doo	Diele of	Indirec	Inconsic	Imamuaa	consideratio	Intonion	Contr			Conto
	Des	Risk of	indirec	Inconsis	Imprec	consideratio	Interven	Contr	effect (95%		Certa
No of studies	ign	bias	tness	tency	ision	ns	tion N	ol N	CI)	Absolute effect	inty
health-related quality of											
life - overall - eq-5d											
Mean follow-up: 6											
month(s)											
- 1										MD 0.04 lower	
	RC	not	not		serious				MD -0.04	(0.07 lower to	mode
1 (russell-jones 2012)	Т	serious	serious	NA^1	2	NA	146	232	(-0.07, -0.01)	0.01 lower)	rate
all-cause mortality											
Mean follow-up: 8.6											
month(s)											
										0 fewer per	
										1000	
	RC	not	not	not	not				RD 0.00	(8 fewer to 8	
2	Т	serious	serious	serious	serious	NA	0/299	0/390	(-0.01, 0.01)	more)	high
cardiovascular mortality											

Mean follow-up: 8.6 month(s)											
2 hypoglycaemia episodes	RC T	not serious	not serious	not serious	not serious	NA	0/299	0/390	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	high
Mean follow-up: 8.6 month(s)											
2	RC T	very serious	not serious	not serious	serious	NA	11/299	26/39 0	RR 0.54 (0.27, 1.06)	31 fewer per 1000 (49 fewer to 4 more)	very low
severe hypoglycaemic episodes Mean follow-up: 11.1 month(s)											
1 (xu 2015)	RC T	very serious	not serious	NA¹	serious 5	NA	0/136	0/142	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	very low
hba1c change Mean follow-up: 8.6 month(s)											
2	RC T	not serious	not serious	very serious ⁶	not serious	NA	255	328	MD 0.09 (-0.30, 0.48)	MD 0.09 higher (0.30 lower to 0.48 higher)	low
weight change Mean follow-up: 8.6 month(s)											
2	RC T	not serious	not serious	not serious	not serious	NA	281	358	MD 3.50 (2.90, 4.10)	MD 3.50 higher (2.90 higher to 4.10 higher)	high
bmi change Mean follow-up: 11.1 month(s)											

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

- 1. Only one study so no inconsistency
- 2. 95% confidence intervals cross one end of the defined MIDs (-0.03, 0.03)
- 3. >33.3% of the studies in the meta-analysis were at high risk of bias
- 4. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 5. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 6. I2 > 75%

F.1.7.6 Pioglitazone compared to liraglutide

Table 50: Clinical evidence profile: Pioglitazone compared to liraglutide

Table 50. Cillical evid	401100	promo. i	rogiitazo	ne compa	ioa to ilia	giatiae					
						Other					
	Desi	Risk of	Indirect	Inconsis	Impreci	consideratio	Intervent	Contr	Relative effect		Certai
No of studies	gn	bias	ness	tency	sion	ns	ion N	ol N	(95% CI)	Absolute effect	nty
hypoglycaemia episodes Mean follow-up: 5.5 month(s)											
1 (zhang 2020a)	RC T	very serious ¹	not serious	NA ²	very serious ³	NA	2/30	1/30	RR 2.00 (0.19, 20.90)	33 more per 1000 (27 fewer to 663 more)	very low
severe hypoglycaemic episodes Mean follow-up: 5.5 month(s)											
1 (zhang 2020a)	RC T	very serious ¹	not serious	NA ²	very serious ⁴	NA	0/30	0/30	RD 0.00 (-0.06, 0.06)	0 fewer per 1000	very low

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

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 5. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

F.1.7.7 Pioglitazone compared to gliclazide

Table 51: Clinical evidence profile: Pioglitazone compared to glicazide

	 <u> </u>		
cardiovascular mortality			

Mean follow-up: 12											
month(s)											
	RC	very	not		very	Ν			RD 0.00	0 fewer per 1000	very
1 (erem 2014)	Т	serious ¹	serious	NA ²	serious ³	Α	0/20	0/20	(-0.09, 0.09)	(92 fewer to 92 more)	low
non-fatal myocardial											
infarction											
Mean follow-up: 12 month(s)											
month(s)	RC	very	not		very	N			RD 0.00	0 fewer per 1000	very
1 (erem 2014)	T	serious ¹	serious	NA ²	serious ³	A	0/20	0/20	(-0.09, 0.09)	(92 fewer to 92 more)	low
hospitalisation for heart							515		(0100, 0100)	(
failure											
Mean follow-up: 12											
month(s)											
	RC	very	not .		very	N	0.400	0.400	RD 0.00	0 fewer per 1000	very
1 (erem 2014)	Т	serious ¹	serious	NA ²	serious ³	Α	0/20	0/20	(-0.09, 0.09)	(92 fewer to 92 more)	low
hypoglycaemia episodes											
Mean follow-up: 12 month(s)											
month(3)									RD -0.06		
	RC	very	not		not	N	25/65	63/65	(-0.09, -	58 fewer per 1000	very
2	T	serious ¹	serious	serious4	serious	Α	5	5	0.03)	(85 fewer to 31 fewer)	low
severe hypoglycaemic									,		
episodes											
Mean follow-up: 12											
month(s)									55.000	1000	
1 (27272 2014)	RC T	very	not	NA ²	very	N	0/00	0/20	RD 0.00	0 fewer per 1000	very
1 (erem 2014) hba1c change	I	serious ¹	serious	INA	serious ³	Α	0/20	0/20	(-0.09, 0.09)	(92 fewer to 92 more)	low
Mean follow-up: 12											
month(s)											
(5)									MD -0.32	MD 0.32 lower	
	RC	very	not	very		Ν			(-0.63, -	(0.63 lower to 0.02	very
3	Т	serious ¹	serious	serious ⁵	serious ⁶	Α	951	924	0.02)	lower)	low
weight change											
Mean follow-up: 12											
month(s)											

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

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 4. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 5. I2 > 75%
- 6. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 7. 95% confidence intervals cross both ends of the defined MIDs (-2.40, 2.40)
- 8. 95% confidence intervals cross both ends of the defined MIDs (-0.80, 0.80)

F.1.7.8 Pioglitazone compared to glimepiride

Table 52: Clinical evidence profile: Pioglitazone compared to glimepiride

						Other					
	Desi	Risk of	Indirect	Inconsist	Impreci	consideration	Intervent	Contr	Relative effect		Certai
No of studies	gn	bias	ness	ency	sion	S	ion N	ol N	(95% CI)	Absolute effect	nty
hypoglycaemia episodes Mean follow-up: 9 month(s)											

2	RC T	serious ¹	not serious	not serious	very serious ²	NA	5/134	8/132	RR 0.64 (0.23, 1.81)	22 fewer per 1000 (47 fewer to 49 more)	very low
hba1c change Mean follow-up: 12 month(s)											
1 (yamanouchi 2005)	RC T	very serious ³	not serious	NA ⁴	serious ⁵	NA	38	37	MD 0.20 (-0.23, 0.63)	MD 0.20 higher (0.23 lower to 0.63 higher)	very low
weight change Mean follow-up: 6 month(s)											
1 (shihara 2011)	RC T	very serious ³	not serious	NA ⁴	very serious ⁶	NA	96	95	MD -0.20 (-3.92, 3.52)	MD 0.20 lower (3.92 lower to 3.52 higher)	very low
bmi change Mean follow-up: 9 month(s)										-	
2	RC T	very serious ³	not serious	not serious	serious ⁷	NA	134	132	MD 0.44 (-0.51, 1.39)	MD 0.44 higher (0.51 lower to 1.39 higher)	very low

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 3. >33.3% of the studies in the meta-analysis were at high risk of bias
- 4. Only one study so no inconsistency
- 5. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 6. 95% confidence intervals cross both ends of the defined MIDs (-2.40, 2.40)
- 7. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

F.1.7.9 Pioglitazone compared to insulin

Figure 209: Clinical evidence profile: Pioglitazone v insulin

	5	D'al af	1 12			Other			Balait a effect		
No of studies	Desi gn	Risk of bias	Indirect ness	Inconsist ency	Impreci sion	consideration s	Intervent ion N	Contr ol N	Relative effect (95% CI)	Absolute effect	Certai nty
all-cause mortality Mean follow-up: 11.1 month(s)	g			Siloy	o.c			- Critic	(concern)		,
1 (xu 2015)	RC T	very serious ¹	not serious	NA ²	serious 3	NA	0/136	0/138	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	very low
mortality Mean follow-up: 11.1 month(s)											
1 (xu 2015)	RC T	very serious ¹	not serious	NA ²	serious 3	NA	0/136	0/142	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	very low
hypoglycaemia episodes Mean follow-up: 11.1 month(s)											
1 (xu 2015)	RC T	very serious ¹	not serious	NA ²	not serious	NA	5/136	18/13 8	RR 0.28 (0.11, 0.74)	94 fewer per 1000 (116 fewer to 34 fewer)	low
severe hypoglycaemic episodes Mean follow-up: 11.1 month(s)											
1 (xu 2015)	RC T	very serious ¹	not serious	NA ²	serious 3	NA	0/136	0/138	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	very low
hba1c change											

Mean follow-up: 11.1 month(s)											
1 (xu 2015)	RC T	very serious ¹	not serious	NA ²	not serious	NA	118	114	MD 0.20 (-0.08, 0.48)	MD 0.20 higher (0.08 lower to 0.48 higher)	low
weight change Mean follow-up: 11.1 month(s)											
1 (xu 2015)	RC T	very serious ¹	not serious	NA ²	not serious	NA	118	114	MD -1.00 (-1.98, -0.02)	MD 1.00 lower (1.98 lower to 0.02 lower)	low
bmi change Mean follow-up: 11.1 month(s)											
1 (xu 2015)	RC T	very serious ¹	not serious	NA ²	not serious	NA	118	114	MD -0.40 (-0.68, -0.12)	MD 0.40 lower (0.68 lower to 0.12 lower)	low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.

F.1.7.10 Pioglitazone compared to placebo

Table 53: Clinical evidence profile: Pioglitazone compared to placebo

						Other					
	Desi	Risk of	Indirect	Inconsist	Impreci	consideration	Intervent	Contr	Relative effect		Certai
No of studies	gn	bias	ness	ency	sion	S	ion N	ol N	(95% CI)	Absolute effect	nty
all-cause mortality Mean follow-up: 6 month(s)											
	RC	oorious1	not	oorious ²	very	NIA	0/764	0/160	RD 0.00	2 mars per 1000	very
4	ı	serious ¹	serious	serious ²	serious ³	NA	2/764	0/162	(-0.01, 0.01)	2 more per 1000	low

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

Mean follow-up: 6 month(s)											
5	RC T	serious ¹	not serious	not serious	not serious	NA	1314	361	MD -0.81 (-0.92, -0.70)	MD 0.81 lower (0.92 lower to 0.70 lower)	mode rate
weight change Mean follow-up: 6.1 month(s)											
4	RC T	very serious ⁷	not serious	very serious ⁸	serious ⁹	NA	691	220	MD 2.55 (1.22, 3.88)	MD 2.55 higher (1.22 higher to 3.88 higher)	very low
bmi change Mean follow-up: 6 month(s)											
1 (miyazaki 2002)	RC T	very serious ⁷	not serious	NA ⁴	serious ¹	NA	47	11	MD 0.77 (0.45, 1.10)	MD 0.77 higher (0.45 higher to 1.10 higher)	very low

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.34 (0.8-0.9 = serious, <0.8 = very serious).
- 4. Only one study so no inconsistency
- 5. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.35 (0.8-0.9 = serious, <0.8 = very serious).
- 7. >33.3% of the studies in the meta-analysis were at high risk of bias
- 8. I2 > 75%
- 9. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)
- 10. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

F.1.8 Combinations

F.1.8.1 Alogliptin + metformin compared to metformin

Table 54: Clinical evidence profile: Alogliptin + metformin compared to metformin

Table 34. Chilical evidence prome. Alogipun	. 1117	GUOIIIIII	Compa	ica to ii	ictioiiii	111					
	De		Indire	Incons		Other	Interv	Con	Relative		Cert
	sig	Risk of	ctnes	istenc	Impre	considera	ention	trol	effect (95%	Absolute	aint
No of studies	n	bias	S	у	cision	tions	N	N	CI)	effect	У
all-cause mortality at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/225	0/22 5	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	low
cardiovascular mortality at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014) non-fatal myocardial infarction at end of	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/225	0/22	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	low
follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/225	0/22	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	low
hospitalisation for heart failure at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/225	0/22	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	low

hypoglycaemia episodes at end of follow-up Mean follow-up: 5.8 month(s)											
2	RC T	very seriou s ¹	not seriou s	not seriou s	very seriou s ³	NA	14/378	19/3 81	RR 0.74 (0.38, 1.46)	13 fewer per 1000 (31 fewer to 23 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RC T	very seriou s 1	not seriou s	NA ²	not seriou s	NA	0/220	0/22	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	low
hba1c change (%, lower values are better, change scores) at end of follow-up Mean follow-up: 5.8 month(s)										,	
2	RC T	very seriou s ¹	not seriou s	not seriou s	seriou s ⁴	NA	371	372	MD -0.48 (-0.65, - 0.31)	MD 0.48 lower (0.65 lower to 0.31 lower)	very low
weight change (kg, lower values are better, change scores and final values) at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	225	225	MD 0.15 (-0.40, 0.69)	MD 0.15 higher (0.40 lower to 0.69 higher)	low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

F.1.8.2 Alogliptin + metformin compared to alogliptin

Table 55: Clinical evidence profile: alogliptin + metformin compared to alogliptin

rable 55. Chilical evidence profile. alog	De			paroa	to alogn	Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
all-cause mortality Mean follow-up: 6 month(s)									-		-
1 (pratley 2014)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/225	0/22 5	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	low
cardiovascular mortality at end of follow- up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/225	0/22 5	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	0/225	1/22 5	PETO OR 0.14 (0.00, 6.82)	4 fewer per 1000 (13 fewer to 4 more)	very low
hospitalisation for heart failure at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/225	0/22 5	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	low
hypoglycaemia episodes at end of follow-up											

Mean follow-up: 5.8 month(s)											
2	RC T	very seriou s ¹	not seriou s	not serious	very seriou s³	NA	14/378	10/3 84	RR 1.42 (0.64, 3.15)	11 more per 1000 (9 fewer to 56 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/220	0/22	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.8 month(s)										,	
2	RC T	very seriou s ¹	not seriou s	not serious	not seriou s	NA	371	370	MD -0.83 (-1.00, - 0.66)	MD 0.83 lower (1.00 lower to 0.66 lower)	low
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	225	225	MD -0.93 (-1.48, - 0.38)	MD 0.93 lower (1.48 lower to 0.38 lower)	low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

F.1.8.3 Alogliptin + metformin compared to placebo

Table 56: Clinical evidence profile: alogliptin + metformin v placebo

rable 56. Chilical evidence prome. alognpun	De	Risk	Indire	Incons	Impr	Other	Interve	Cont	Relative		Cert
	sig	of	ctnes	istenc	ecisio	considera	ntion	rol	effect (95%	Absolute	aint
No of studies	n	bias	s	у	n	tions	N	N	CI)	effect	у
all-cause mortality at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RC T	very seriou s ¹	not seriou s	NA ²	serio us³	NA	0/225	0/10 9	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RC T	very seriou s ¹	not seriou s	NA ²	serio us³	NA	0/225	0/10 9	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	very low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RC T	very seriou s ¹	not seriou s	NA ²	serio us ³	NA	0/225	0/10 9	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	very low
hospitalisation for heart failure at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RC T	very seriou s ¹	not seriou s	NA ²	serio us³	NA	0/225	0/10 9	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.8 month(s)											
2	RC T	very seriou s ¹	not seriou s	not seriou s	serio us ⁴	NA	14/378	2/27 0	RR 4.88 (1.13, 21.14)	29 more per 1000	very low

										(1 more to 149 more)	
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (pratley 2014)	RC T	very seriou s ¹	not seriou s	NA ²	serio us³	NA	0/220	0/10 9	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	very low
hba1c change (%, lower values are better, change scores and final values) at end of follow-up Mean follow-up: 6 month(s)									Í		
1 (pratley 2014)	RC T	very seriou s ¹	not seriou	NA ²	not serio us	NA	213	102	MD -1.26 (-1.48, - 1.04)	MD 1.26 lower (1.48 lower to 1.04 lower)	low
weight change* Mean follow-up: 6 month(s)				147.	uo	14/1	2.10	102	1.0 1)	lowery	
	RC	very seriou	not seriou		not serio				MD -0.00 (-0.68,	MD 0.00 lower (0.68 lower to 0.68	
1 (pratley 2014)	Т	s ¹	S	NA ²	us	NA	225	109	0.68)	higher)	low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 4. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

F.1.8.4 Linagliptin + metformin v placebo

Table 57: Clinical evidence profile: linagliptin + metformin v placebo

Tubic of Formous evidence promot midgipus	De	Risk	Indire	Incons		Other	Interve	Cont	Relative		Cert
	sig	of	ctnes	istenc	Impre	considera	ntion	rol	effect (95%	Absolute	aint
No of studies	n	bias	S	У	cision	tions	N	N	CI)	effect	у
all-cause mortality at end of follow-up Mean follow-up: 6 month(s)				-							
1 (haak 2012) cardiovascular mortality at end of follow-up	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/286	0/72	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	low
Mean follow-up: 6 month(s)											
1 (haak 2012)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/286	0/72	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	low
hypoglycaemia episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (haak 2012)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	5/286	1/72	RR 1.26 (0.15, 10.61)	4 more per 1000 (12 fewer to 133 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (haak 2012)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/286	0/72	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	low
hba1c change (%, lower values are better, change scores and final values) at end of follow-up Mean follow-up: 6 month(s)									,	,	

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

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

F.1.8.5 Linagliptin + metformin compared to metformin

Table 58: Clinical evidence profile: Linagliptin + metformin compared to metformin

	De					Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow-up Mean follow-up: 6 month(s)											
	RC	very seriou	not seriou		very seriou			1/29	PETO OR 0.14	3 fewer per 1000 (10 fewer to 3	very
1 (haak 2012)	Т	s ¹	S	NA ²	s ³	NA	0/286	1	(0.00, 6.94)	more)	low
cardiovascular mortality at end of follow-up											

Mean follow-up: 6 month(s)											
1 (haak 2012)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	0/286	1/29	PETO OR 0.14 (0.00, 6.94)	3 fewer per 1000 (10 fewer to 3 more)	very low
4-point mace at end of follow-up Mean follow-up: 5.5 month(s)											
1 (mu 2017)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	0/294	1/28 9	PETO OR 0.13 (0.00, 6.70)	3 fewer per 1000 (10 fewer to 3 more)	very low
hospitalisation for heart failure at end of follow-up Mean follow-up: 5.5 month(s)											
1 (mu 2017)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/294	0/28 9	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	low
hypoglycaemia episodes at end follow- up Mean follow-up: 5.8 month(s)											
2	RC T	very seriou s ¹	not seriou s	serious	very seriou s ³	NA	10/580	10/5 80	RR 1.00 (0.41, 2.42)	0 fewer per 1000 (10 fewer to 25 more)	very low
severe hypoglycaemic episodes at end follow-up Mean follow-up: 5.8 month(s)											
2	RC T	very seriou s ¹	not seriou s	serious 5	very seriou s ⁶	NA	0/580	1/58 0	RD -0.00 (-0.01, 0.00)	1 fewer per 1000 (7 fewer to 4 more)	very low
hba1c change (%, lower vales are better, change scores) at end of follow-up Mean follow-up: 5.8 month(s)											
2	RC T	very seriou s ¹	not seriou s	not serious	seriou s ⁷	NA	460	556	MD -0.45 (-0.58, - 0.32)	MD 0.45 lower	very low

										(0.58 lower to 0.32 lower)	
weight change (kg, lower vales are better, change scores) at end of follow-											
up											
Mean follow-up: 5.8 month(s)											
										MD 0.29	
		very	not		not					higher	
	RC	seriou	seriou	not	seriou				MD 0.29	(0.11 lower to	
2	Т	s ¹	s	serious	S	NA	537	428	(-0.11, 0.68)	0.68 higher)	low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. Downgraded by 1 or 2 increments because of heterogeneity, unexplained by subgroup analysis
- 5. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.29 (0.8-0.9 = serious, <0.8 = very serious).
- 7. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

F.1.8.6 Linagliptin + metformin compared to linagliptin

Table 59: Clinical evidence profile: linagliptin + metformin v linagliptin

rable 66: Chimean evidence prome: mag			<u> </u>	agpt.	<u> </u>						
	De					Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow-up											
Mean follow-up: 5.8 month(s)											

2	RC T	very seriou s ¹	not seriou s	not serious	not seriou s	NA	0/445	0/29 9	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	low
cardiovascular mortality at end of follow- up Mean follow-up: 5.8 month(s)											
2	RC T	very seriou s ¹	not seriou s	not serious	not seriou s	NA	0/445	0/29 9	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	low
4-point mace at end of follow-up Mean follow-up: 5.5 month(s)											
1 (mu 2017)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/294	0/14 7	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (10 fewer to 10 more)	low
hospitalisation for heart failure at end of follow-up Mean follow-up: 5.5 month(s)											
2	RC T	very seriou s ¹	not seriou s	not serious	not seriou s	NA	0/453	0/30	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.7 month(s)										,	
3	RC T	not seriou s	not seriou s	not serious	very seriou s ³	NA	13/739	6/44 6	RR 1.42 (0.52, 3.87)	6 more per 1000 (6 fewer to 39 more)	low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.7 month(s)		_	_						,		
	RC	very seriou	not seriou	not	not seriou			0/44	RD 0.00	0 fewer per 1000 (6 fewer to 6	
3	T	s ¹	S	serious	S	NA	0/739	6	(-0.01, 0.01)	more)	low

hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.7 month(s)											
3 weight change (kg, lower values are better, change score) at end of follow-up	RC T	very seriou s ¹	not seriou s	not serious	not seriou s	NA	613	426	MD -0.92 (-1.06, - 0.77)	MD 0.92 lower (1.06 lower to 0.77 lower)	low
Mean follow-up: 5.7 month(s)											
2	RC	very seriou	not seriou	not	not seriou	NA	600	400	MD -0.62 (-1.00, -	MD 0.62 lower (1.00 lower to 0.23	low
3	Т	s ¹	s	serious	s	NA	690	409	0.23)	lower)	lo

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

F.1.8.7 Saxagliptin + metformin compared to metformin

Table 60: Clinical evidence profile: Saxagliptin + metformin compared to metformin

	De					Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow-up											
Mean follow-up: 11.8 month(s)											
										4 fewer per	
		very	not		very					1000	
	RC	seriou	seriou	serious	seriou			5/53	RD -0.00	(18 fewer to 9	very
2	T	s ¹	S	2	s ³	NA	3/858	8	(-0.02, 0.01)	more)	low

cardiovascular mortality at end of follow-											
up											
Mean follow-up: 18 month(s)											
1 (pfützner 2011a)	RC T	very seriou s ¹	not seriou s	NA ⁴	very seriou s ⁵	NA	2/643	4/32 8	RR 0.26 (0.05, 1.39)	9 fewer per 1000 (12 fewer to 5 more)	very low
non-fatal stroke at end of follow-up Mean follow-up: 5.5 month(s)											
1 (dou 2018)	RC T	very seriou s ¹	not seriou s	NA ⁴	very seriou s ⁵	NA	0/215	1/21	PETO OR 0.13 (0.00, 6.66)	5 fewer per 1000 (14 fewer to 5 more)	very low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 5.5 month(s)											
1 (dou 2018)	RC T	very seriou s ¹	not seriou s	NA ⁴	very seriou s ⁵	NA	0/215	1/21	PETO OR 0.13 (0.00, 6.66)	5 fewer per 1000 (14 fewer to 5 more)	very low
persistent signs of worsening kidney disease at end of follow-up Mean follow-up: 5.5 month(s)											
1 (dou 2018)	RC T	very seriou s ¹	not seriou s	NA ⁴	very seriou s ⁵	NA	0/215	1/21	PETO OR 0.13 (0.00, 6.66)	5 fewer per 1000 (14 fewer to 5 more)	very low
progression of liver disease at end of follow-up Mean follow-up: 5.5 month(s)									, , , ,	,	
1 (dou 2018)	RC T	very seriou s ¹	not seriou s	NA ⁴	not seriou s	NA	0/215	0/21	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	low
hypoglycaemia episodes at end of follow-up Mean follow-up: 11.8 month(s)											

2	RC T	very seriou s ¹	not seriou s	not serious	very seriou s ⁵	NA	38/858	24/5 38	RR 0.85 (0.51, 1.41)	7 fewer per 1000 (22 fewer to 18 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 11.8 month(s)											
2	RC T	very seriou s ¹	not seriou s	serious	very seriou s ⁶	NA	3/858	2/53 8	RD -0.00 (-0.01, 0.01)	1 fewer per 1000 (7 fewer to 6 more)	very low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
3	RC T	very seriou s ¹	not seriou s	very serious	seriou s ⁸	NA	592	375	MD -0.32 (-0.54, - 0.09)	MD 0.32 lower (0.54 lower to 0.09 lower)	very low
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
2	RC T	very seriou s ¹	not seriou s	not serious	not seriou s	NA	231	228	MD 0.42 (-0.12, 0.96)	MD 0.42 higher (0.12 lower to 0.96 higher)	low
bmi change (kg/m2, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
2	RC T	very seriou s ¹	not seriou s	very serious	not seriou s	NA	231	228	MD -0.10 (-0.65, 0.45)	MD 0.10 lower (0.65 lower to 0.45 higher)	very low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

- 3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.48 (0.8-0.9 = serious, <0.8 = very serious).
- 4. Only one study so no inconsistency
- 5. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.03 (0.8-0.9 = serious, <0.8 = very serious).
- 7.12 > 75%
- 8. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

F.1.8.8 Saxagliptin + metformin compared to saxagliptin

Table 61: Clinical evidence profile: Saxagliptin + metformin compared to saxagliptin

Tubic of Chimour evidence promor eax	De			•		Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow-up											
Mean follow-up: 11.8 month(s)											
2	RC T	very seriou s ¹	not seriou	serious	very seriou s ³	NA	3/858	3/54 9	PETO OR 0.56 (0.11, 3.00)	2 fewer per 1000 (9 fewer to 5 more)	very low
cardiovascular mortality at end of follow-	-						0,000	_	(01111, 01100)		
up											
Mean follow-up: 18 month(s)											
1 (pfützner 2011a)	RC T	very seriou s ¹	not seriou s	NA ⁴	very seriou s ³	NA	2/643	2/33 5	RR 0.52 (0.07, 3.68)	3 fewer per 1000 (6 fewer to 16 more)	very low
non-fatal stroke at end of follow-up Mean follow-up: 5.5 month(s)									,	ŕ	

1 (dou 2018) non-fatal myocardial infarction at end of	RC T	very seriou s ¹	not seriou s	NA ⁴	very seriou s ³	NA	0/215	1/21	PETO OR 0.13 (0.00, 6.79)	5 fewer per 1000 (14 fewer to 4 more)	very low
follow-up Mean follow-up: 5.5 month(s)											
1 (dou 2018)	RC T	very seriou s ¹	not seriou s	NA ⁴	not seriou s	NA	0/215	0/21 4	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	low
persistent signs of worsening kidney disease at end of follow-up Mean follow-up: 5.5 month(s)											
1 (dou 2018)	RC T	very seriou s ¹	not seriou s	NA ⁴	not seriou s	NA	0/215	0/21	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	low
progression of liver disease at end of follow-up Mean follow-up: 5.5 month(s)											
1 (dou 2018)	RC T	very seriou s ¹	not seriou s	NA ⁴	very seriou s ³	NA	0/215	1/21	PETO OR 0.13 (0.00, 6.79)	5 fewer per 1000 (14 fewer to 4 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 11.8 month(s)											
2	RC T	very seriou s ¹	not seriou s	serious 5	very seriou s ³	NA	38/858	10/5 49	RR 1.26 (0.17, 9.32)	5 more per 1000 (15 fewer to 152 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 11.8 month(s)										,	
2	RC T	very seriou s ¹	not seriou s	serious 2	very seriou s ⁶	NA	3/858	0/54 9	RD 0.00 (-0.00, 0.01)	3 more per 1000	very low

										(3 fewer to 8 more)	
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
3	RC T	very seriou s ¹	not seriou s	very serious	seriou s ⁸	NA	592	348	MD -0.63 (-1.02, - 0.23)	MD 0.63 lower (1.02 lower to 0.23 lower)	very low
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
2	RC T	very seriou s ¹	not seriou s	serious	not seriou s	NA	231	234	MD -0.54 (-2.06, 0.98)	MD 0.54 lower (2.06 lower to 0.98 higher)	very low
bmi change (kg/m2, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
2	RC T	very seriou s ¹	not seriou	very serious	not seriou	NA	231	234	MD -0.10 (-0.61, 0.41)	MD 0.10 lower (0.61 lower to 0.41 higher)	very low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. Only one study so no inconsistency
- 5. I2 between 50% and 75%
- 6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.6 (0.8-0.9 = serious, <0.8 = very serious).
- 7.12 > 75%

- 8. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 9. Downgraded by 1 or 2 increments because of heterogeneity, unexplained by subgroup analysis

F.1.8.9 Sitagliptin + metformin compared to metformin

Table 62: Clinical evidence profile: Sitagliptin + metformin compared to metformin

	De	Risk	Indire	Incons		Other	Interve	Cont	Relative		Cert
	sig	of	ctnes	istenc	Impre	considera	ntion	rol	effect (95%	Absolute	aint
No of studies	n	bias	S	У	cision	tions	N	N	CI)	effect	у
all-cause mortality at end follow-up Mean follow-up: 5.5 month(s)											
2	RC T	very seriou s ¹	not seriou s	not seriou s	not seriou s	NA	0/619	0/61	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (4 fewer to 4 more)	low
cardiovascular mortality at end follow-up Mean follow-up: 5.5 month(s)											
2	RC T	very seriou s ¹	not seriou s	not seriou s	not seriou s	NA	0/619	0/61	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (4 fewer to 4 more)	low
diabetic ketoacidosis at end follow-up Mean follow-up: 5.5 month(s)											
1 (goldstein 2007)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/372	0/36	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (5 fewer to 5 more)	low
hypoglycaemia episodes at end follow-up Mean follow-up: 5.5 month(s)											
2	RC T	seriou s³	not seriou	not seriou s	not seriou	NA	35/619	15/6 14	RR 2.35 (1.30, 4.22)	33 more per 1000 (7 more to 79 more)	mod erat e

severe hypoglycaemic episodes at end follow-up Mean follow-up: 5.5 month(s)											
1 (ji 2016a)	RC T	seriou s³	not seriou s	NA ²	not seriou s	NA	0/247	0/25 0	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	mod erat e
hba1c change (%, lower values are better, change scores and final values) at end follow-up Mean follow-up: 5.5 month(s)											
3	RC T	very seriou s ¹	not seriou s	very seriou s ⁴	seriou s ⁵	NA	613	605	MD -0.76 (-1.22, - 0.30)	MD 0.76 lower (1.22 lower to 0.30 lower)	very low
weight change (kg, lower values are better, change scores) at end follow-up Mean follow-up: 5.5 month(s)											
1 (ji 2016a)	RC T	seriou s³	not seriou s	NA ²	not seriou s	NA	247	250	MD 1.15 (0.40, 1.90)	MD 1.15 higher (0.40 higher to 1.90 higher)	mod erat e
bmi change (kg/m2, lower values are better, final values) at end follow-up Mean follow-up: 5.5 month(s)											
1 (wang 2022)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ⁶	NA	20	17	MD -0.22 (-2.36, 1.92)	MD 0.22 lower (2.36 lower to 1.92 higher)	very low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. >33.3% of the studies in the meta-analysis were at moderate risk of bias

- 4. I2 > 75%
- 5. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 6. 95% confidence intervals cross both ends of the defined MIDs (-0.80, 0.80)

F.1.8.10 Sitagliptin + metformin compared to sitagliptin

Table 63: Clinical evidence profile: Sitagliptin + metformin compared to sitagliptin

3.4											
	De	Risk	Indire	Incons		Other	Interve	Cont	Relative		Cert
	sig	of	ctnes	istenc	Impre	considera	ntion	rol	effect (95%	Absolute	aint
No of studies	n	bias	s	у	cision	tions	N	N	CI)	effect	у
all-cause mortality at end of follow-up				-					-		-
Mean follow-up: 5.5 month(s)											
										0 fewer per	
			not	not	not				RD 0.00	1000	mod
	RC	seriou	seriou	seriou	seriou			0/29	(-0.01,	(7 fewer to 7	erat
2	Т	s ¹	S	S	S	NA	0/619	9	0.01)	more)	е
cardiovascular mortality at end of follow-up											
Mean follow-up: 5.5 month(s)											
										0 fewer per	
			not	not	not				RD 0.00	1000	mod
	RC	seriou	seriou	seriou	seriou			0/29	(-0.01,	(7 fewer to 7	erat
2	Т	s ¹	S	S	S	NA	0/619	9	0.01)	more)	е
diabetic ketoacidosis at end of follow-up											
Mean follow-up: 5.5 month(s)											
										0 fewer per	
			not		not				RD 0.00	1000	mod
	RC	seriou	seriou		seriou			0/17	(-0.01,	(9 fewer to 9	erat
1 (goldstein 2007)	Т	s ¹	S	NA ²	S	NA	0/372	9	0.01)	more)	е
hypoglycaemia episodes at end of follow-up											
Mean follow-up: 5.5 month(s)											
			not	not							
	RC	seriou	seriou	seriou	seriou			6/29	RR 2.83	37 more per	
2	Τ	s ¹	S	S	s ³	NA	35/619	9	(1.21, 6.60)	1000	low

										(4 more to 112 more)	
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)										112 more)	
1 (ji 2016a)	RC T	seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/247	0/12 0	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (13 fewer to 13 more)	mod erat e
hba1c change (%, lower values are better, change scores and final value) at end of follow-up Mean follow-up: 5.5 month(s)											
3	RC T	seriou s ¹	not seriou s	very seriou s ⁴	seriou s ⁵	NA	613	305	MD -0.59 (-1.12, - 0.07)	MD 0.59 lower (1.12 lower to 0.07 lower)	very low
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (ji 2016a)	RC T	seriou s ¹	not seriou s	NA ²	not seriou s	NA	247	120	MD -0.40 (-1.31, 0.51)	MD 0.40 lower (1.31 lower to 0.51 higher)	mod erat e
bmi change (kg/m2, lower values are better, final value) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (wang 2022)	RC T	very seriou s ⁶	not seriou s	NA ²	very seriou s ⁷	NA	20	17	MD 1.14 (-0.81, 3.09)	MD 1.14 higher (0.81 lower to 3.09 higher)	very low

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. Only one study so no inconsistency

- 3. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 4. I2 > 75%
- 5. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 6. >33.3% of the studies in the meta-analysis were at high risk of bias
- 7. 95% confidence intervals cross both ends of the defined MIDs (-0.80, 0.80)

F.1.8.11 Sitagliptin + metformin compared to glimepiride

Table 64: Clinical evidence profile: Sitagliptin + metformin compared to glimepiride

	De					Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow-up Mean follow-up: 7 month(s)											
1 (kim 2017)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s³	NA	0/146	0/14 4	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (13 fewer to 13 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 7 month(s)											
1 (kim 2017)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	8/146	29/1 44	RR 0.27 (0.13, 0.57)	147 fewer per 1000 (175 fewer to 86 fewer)	low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 7 month(s)											
4 (live 2047)	RC	very seriou	not seriou	NIA?	very seriou	NIA.	0/4.40	1/14	PETO OR 0.13	7 fewer per	very
1 (kim 2017)	I	s ¹	S	NA ²	s ⁴	NA	0/146	4	(0.00, 6.73)	1000	low

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

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 4. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 5. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

F.1.8.12 Sitagliptin + metformin compared to pioglitazone

Table 65: Clinical evidence profile: Sitagliptin + metformin compared to pioglitazone

rabie con chinear criacites promot citag			• • • • • • • • • • • • • • • • • • • •								
	De					Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у

hypoglycaemia episodes at end of follow-up Mean follow-up: 7.4 month(s)											
1 (wainstein 2012)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s ³	NA	22/261	11/2 56	RR 1.96 (0.97, 3.96)	41 more per 1000 (1 fewer to 127 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 7.4 month(s)											
1 (wainstein 2012)	RC T	very seriou s ¹	not seriou	NA ²	not seriou	NA	0/261	0/26	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 7.4 month(s)	1	3	3	10.1	3	TV.	0/201		(0.01, 0.01)	morey	1000
1 (wainstein 2012)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s ⁴	NA	253	246	MD -0.50 (-0.68, - 0.32)	MD 0.50 lower (0.68 lower to 0.32 lower)	very low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 4. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

F.1.8.13 Sitagliptin + metformin compared to placebo

Table 66: Clinical evidence profile: Sitagliptin + metformin compared to placebo

Table 66. Chilical evidence profile. Sita	De				, , , , , , , , , , , , , , , , , , ,	Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ions	ntion N	rol N	CI)	effect	У
all-cause mortality at end of follow-up Mean follow-up: 5.5 month(s)											
2	RC T	seriou s¹	not seriou s	serious	very seriou s ³	NA	0/619	1/30	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (12 fewer to 7 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 5.5 month(s)											
2	RC T	seriou s¹	not seriou s	serious	very seriou s ³	NA	0/619	1/30	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (12 fewer to 7 more)	very low
diabetic ketoacidosis at end of follow-up Mean follow-up: 5.5 month(s)											
1 (goldstein 2007)	RC T	very seriou s ⁴	not seriou s	NA ⁵	very seriou s ⁶	NA	0/372	1/17 6	PETO OR 0.04 (0.00, 2.96)	6 fewer per 1000 (17 fewer to 5 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)											
2	RC T	seriou s ¹	not seriou s	not serious	not seriou s	NA	35/619	5/30 2	RR 3.52 (1.40, 8.84)	42 more per 1000 (7 more to 130 more)	mod erat e
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)											

1 (ji 2016a)	RC T	seriou s¹	not seriou s	NA ⁵	not seriou s	NA	0/247	0/12	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	mod erat e
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)	RC T	very seriou s ⁴	not seriou s	serious 7	not seriou s	NA	562	292	MD -0.97 (-1.31, - 0.64)	MD 0.97 lower (1.31 lower to 0.64 lower)	very low
1 (ji 2016a)	RC T	seriou s ¹	not seriou s	NA ⁵	not seriou s	NA	247	124	MD 1.40 (0.46, 2.34)	MD 1.40 higher (0.46 higher to 2.34 higher)	mod erat e

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.42 (0.8-0.9 = serious, <0.8 = very serious).
- 4. >33.3% of the studies in the meta-analysis were at high risk of bias
- 5. Only one study so no inconsistency
- 6. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 7. I2 between 50% and 75%

F.1.8.14 Vildagliptin + metformin compared to metformin

Table 67: Clinical evidence profile: Vildagliptin + metformin compared to metformin

Table 67: Clinical evidence profile: Vilda		III + IIIet	1011111111	compare	u to met						
	De					Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	У
all-cause mortality at end of follow-up Mean follow-up: 6 month(s)											
1 (bosi 2009)	RC T	seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	1/585	0/29	PETO OR 4.49 (0.07, 286.22)	2 more per 1000 (2 fewer to 5 more)	very low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 6 month(s)									,	,	
1 (bosi 2009)	RC T	seriou s ¹	not seriou s	NA ²	seriou s ⁴	NA	0/585	2/29 4	PETO OR 0.05 (0.00, 0.95)	7 fewer per 1000 (16 fewer to 3 more)	low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (bosi 2009)	RC T	seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	0/585	1/29 4	PETO OR 0.05 (0.00, 3.20)	3 fewer per 1000 (10 fewer to 3 more)	very low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)											
2	RC T	seriou s¹	not seriou s	not serious	not seriou s	NA	617	326	MD -0.32 (-0.45, - 0.18)	MD 0.32 lower (0.45 lower to 0.18 lower)	mod erat e
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)											

2	RC T	seriou s ¹	not seriou s	not serious	not seriou s	NA	617	326	MD 0.44 (-0.07, 0.94)	MD 0.44 higher (0.07 lower to 0.94 higher)	mod erat e
bmi change (kg/m2, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)											
1 (zougrafou 2015)	RC T	very seriou s ⁵	not seriou s	NA ²	not seriou s	NA	32	32	MD 0.20 (-0.35, 0.75)	MD 0.20 higher (0.35 lower to 0.75 higher)	low

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 5. >33.3% of the studies in the meta-analysis were at high risk of bias

F.1.8.15 Vildagliptin + metformin compared to vildagliptin

Table 68: Clinical evidence profile: Vildagliptin + metformin compared to vildagliptin

·	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
all-cause mortality at end follow-up											
Mean follow-up: 6 month(s)											
									PETO OR	2 more per	
			not		very				4.54	1000	
	RC	seriou	seriou		seriou			0/30	(0.07,	(2 fewer to 5	very
1 (bosi 2009)	Т	s ¹	s	NA ²	s^3	NA	1/585	0	285.24)	more)	low

non-fatal myocardial infarction at end follow-up Mean follow-up: 6 month(s)											
1 (bosi 2009)	RC T	seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/585	0/30	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (5 fewer to 5 more)	mod erat e
severe hypoglycaemic episodes at end follow-up Mean follow-up: 6 month(s)											
1 (bosi 2009) hba1c change (%, lower values are	RC T	seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/585	0/30	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (5 fewer to 5 more)	mod erat e
better, change scores) at end follow-up Mean follow-up: 6 month(s)											
1 (bosi 2009)	RC T	seriou s ¹	not seriou s	NA ²	seriou s ⁴	NA	585	300	MD -0.60 (-0.74, - 0.46)	MD 0.60 lower (0.74 lower to 0.46 lower)	low
weight change (kg, lower values are better, change scores) at end follow-up Mean follow-up: 6 month(s)											
1 (bosi 2009)	RC T	seriou s ¹	not seriou s	NA ²	not seriou s	NA	585	300	MD -0.59 (-1.12, - 0.06)	MD 0.59 lower (1.12 lower to 0.06 lower)	mod erat e

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

F.1.8.16 Canagliflozin + metformin compared to metformin

Table 69: Clinical evidence profile: Canagliflozin + metformin compared to metformin

	De	Risk	Indire	Incons		Other	Interve	Cont	Relative		Cert
	sig	of	ctnes	istenc	Impre	considera	ntion	rol	effect (95%	Absolute	aint
No of studies	n	bias	S	у	cision	tions	N	N	CI)	effect	у
all-cause mortality at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	0/474	1/23 7	PETO OR 0.05 (0.00, 3.18)	4 fewer per 1000 (12 fewer to 4 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	0/474	1/23 7	PETO OR 0.05 (0.00, 3.18)	4 fewer per 1000 (12 fewer to 4 more)	very low
non-fatal stroke at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	1/474	0/23 7	PETO OR 4.48 (0.07, 286.49)	2 more per 1000 (2 fewer to 6 more)	very low
unstable angina at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	1/474	0/23 7	PETO OR 4.48 (0.07, 286.49)	2 more per 1000 (2 fewer to 6 more)	very low
persistent signs of worsening kidney disease at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	4/474	0/23 7	PETO OR 4.51 (0.56, 36.22)	8 more per 1000 (0 more to 17 more)	very low

cardiac arrhythmia at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/474	0/23 7	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	low
diabetic ketoacidosis at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/474	0/23 7	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	23/474	11/2 37	RR 1.05 (0.52, 2.11)	2 more per 1000 (22 fewer to 51 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RC T	very seriou s ¹	not seriou	NA ²	very seriou s ³	NA	0/474	1/23	PETO OR 0.05 (0.00, 3.18)	4 fewer per 1000 (12 fewer to 4 more)	very low
hba1c change (%, lower values are better, change scores and final values) at end of follow-up Mean follow-up: 5.5 month(s)									(3.2.2)	,	
1 (rosenstock 2016)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s ⁴	NA	471	230	MD -0.47 (-0.64, -	MD 0.47 lower (0.64 lower to 0.30 lower)	very low
weight change (kg, lower values are better, change scores and final values) at end of follow-up Mean follow-up: 5.5 month(s)									,	,	

										MD 1.75	
										lower	
		very	not						MD -1.75	(2.47 lower	
	RC	seriou	seriou		seriou				(-2.47, -	to 1.03	very
1 (rosenstock 2016)	Т	s ¹	S	NA^2	s ⁵	NA	473	237	1.03)	lower)	low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 5. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

F.1.8.17 Canagliflozin + metformin compared to canagliflozin

Table 70: Clinical evidence profile: Canagliflozin + metformin v canagliflozin

premer early	De					Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/474	0/47 5	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (4 fewer to 4 more)	low
cardiovascular mortality at end of follow-up Mean follow-up: 5.5 month(s)									,	,	
1 (rosenstock 2016)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/474	0/47 5	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (4 fewer to 4 more)	low

non-fatal stroke at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	1/474	1/47 5	RR 1.00 (0.06, 15.97)	0 more per 1000 (2 fewer to 32 more)	very low
unstable angina at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	1/474	0/47 5	PETO OR 7.40 (0.15, 373.17)	2 more per 1000 (2 fewer to 6 more)	very low
cardiac arrhythmia at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	0/474	1/47 5	PETO OR 0.14 (0.00, 6.83)	2 fewer per 1000 (6 fewer to 2 more)	very low
diabetic ketoacidosis at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	0/474	1/47 5	PETO OR 0.14 (0.00, 6.83)	2 fewer per 1000 (6 fewer to 2 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	23/474	16/4 75	RR 1.44 (0.77, 2.69)	15 more per 1000 (8 fewer to 57 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)											
	RC	very seriou	not seriou		not seriou			0/47	RD 0.00	0 fewer per 1000 (4 fewer to 4	
1 (rosenstock 2016)	T	s ¹	S	NA ²	S	NA	0/474	5	(-0.00, 0.00)	more)	low

hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2016)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s ⁴	NA	471	464	MD -0.37 (-0.51, - 0.23)	MD 0.37 lower (0.51 lower to 0.23 lower)	very low
weight change (kg, lower values are											
better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
mean rene n apr ere meninge,										MD 0.40	
		very	not _.		not _.					lower	
4 (RC	seriou	seriou	N1A2	seriou		470	470	MD -0.40	(0.99 lower to	
1 (rosenstock 2016)	I	S ¹	S	NA^2	S	NA	473	472	(-0.99, 0.19)	0.19 higher)	low

- 1. Largest proportion of studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

F.1.8.18 Dapagliflozin + metformin compared to dapagliflozin

Table 71: Clinical evidence profile: dapagliflozin + metformin compared to dapagliflozin

	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow-up Mean follow-up: 5.5 month(s)											

2	RC T	not seriou s	not seriou s	serious	very seriou s ²	NA	0/405	1/42	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (10 fewer to 6 more)	very low
cardiovascular mortality at end of follow- up Mean follow-up: 5.5 month(s)											
2	RC T	not seriou s	not seriou s	serious	very seriou s ²	NA	0/405	1/42 2	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (10 fewer to 6 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)											
2	RC T	not seriou s	not seriou s	not serious	not seriou s	NA	12/405	2/42 2	RR 5.20 (1.35, 20.07)	20 more per 1000 (2 more to 90 more)	high
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)											
2	RC T	not seriou s	not seriou s	not serious	not seriou s	NA	0/405	0/42	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	high
hba1c change (%, lower values are better, change scores) at end of follow- up Mean follow-up: 5.5 month(s)											
2	RC T	not seriou s	not seriou s	very serious	seriou s ⁴	NA	387	412	MD -0.69 (-1.01, - 0.36)	MD 0.69 lower (1.01 lower to 0.36 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow- up Mean follow-up: 5.5 month(s)											

										MD 0.32	
		not	not		not					lower	
	RC	seriou	seriou	not	seriou				MD -0.32	(0.79 lower to	
2	Τ	S	S	serious	S	NA	401	422	(-0.79, 0.14)	0.14 higher)	high

- 1. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 2. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.29 (0.8-0.9 = serious, <0.8 = very serious).
- 3.12 > 75%

F.1.8.19

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

Dapagliflozin + metformin compared to metformin

Table 72: Clinical evidence profile: dapagliflozin + metformin compared to metformin

	De	Risk	Indire	Incons		Other	Interve	Cont	Relative		Cert
	sig	of	ctnes	istenc	Impre	considera	ntion	rol	effect (95%	Absolute	aint
No of studies	n	bias	S	у	cision	tions	N	N	CI)	effect	У
all-cause mortality at end of follow-up Mean follow-up: 5.5 month(s)											
2	RC T	not seriou s	not seriou s	seriou s ¹	very seriou s ²	NA	0/405	1/40 9	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (11 fewer to 6 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 5.5 month(s)											
2	RC T	not seriou s	not seriou s	seriou s ¹	very seriou s ²	NA	0/405	1/40 9	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (11 fewer to 6 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)											

3	RC T	not seriou s	not seriou s	not seriou s	seriou s³	NA	14/480	7/48 4	RR 1.93 (0.81, 4.60)	13 more per 1000 (3 fewer to 52 more)	mod erat e
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)											
2	RC T	not seriou s	not seriou s	not seriou s	not seriou s	NA	0/405	0/40	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	high
hba1c change (%, lower values are better, change scores and final values) at end of follow-up Mean follow-up: 5.5 month(s)											
3	RC T	not seriou s	not seriou s	very seriou s ⁴	seriou s ⁵	NA	462	473	MD -0.82 (-1.26, - 0.39)	MD 0.82 lower (1.26 lower to 0.39 lower)	very low
weight change (kg, lower values are better, change scores and final values) at end of follow-up Mean follow-up: 5.5 month(s)									,		
2	RC T	not seriou s	not seriou s	not seriou s	not seriou s	NA	401	408	MD -1.68 (-2.15, - 1.21)	MD 1.68 lower (2.15 lower to 1.21 lower)	high
bmi change (kg/m2, lower values are better, change scores and final values) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (zhou 2022)	RC T	very seriou s ⁶	not seriou s	NA 7	seriou s ⁸	NA	75	75	MD -0.91 (-1.27, - 0.55)	MD 0.91 lower (1.27 lower to 0.55 lower)	very low

- 1. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 2. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.29 (0.8-0.9 = serious, <0.8 = very serious).
- 3. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 4. 12 > 75%
- 5. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 6. >33.3% of the studies in the meta-analysis were at high risk of bias
- 7. Only one study so no inconsistency
- 8. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

F.1.8.20 Empagliflozin + metformin compared to metformin

Table 73: Clinical evidence profile: empagliflozin + metformin compared to metformin

promote on	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	У
all-cause mortality end at of follow-up Mean follow-up: 5.5 month(s)											
1 (hadjadj 2016)	RC T	not seriou s	not seriou	NA ¹	not seriou s	NA	0/680	0/34	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (5 fewer to 5 more)	high
cardiovascular mortality at end follow- up Mean follow-up: 5.5 month(s)									(, , , , , , , , , , , , , , , , , , ,	,	
1 (hadjadj 2016)	RC T	not seriou s	not seriou s	NA ¹	not seriou s	NA	0/680	0/34	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (5 fewer to 5 more)	high

hypoglycaemia episodes at end follow- up											
Mean follow-up: 5.5 month(s)											
1 (hadjadj 2016) hba1c change (%, lower vales are better, change scores) at end of follow-up Mean follow-up: 5.5 month(s)	RC T	not seriou s	not seriou s	NA ¹	very seriou s ²	NA	7/680	2/34	RR 1.76 (0.37, 8.40)	4 more per 1000 (4 fewer to 43 more)	low
1 (hadjadj 2016)	RC T	not seriou s	not seriou s	NA ¹	seriou s³	NA	569	269	MD -0.54 (-0.69, - 0.39)	MD 0.54 lower (0.69 lower to 0.39 lower)	mod erat e

- 1. Only one study so no inconsistency
- 2. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 3. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

F.1.8.21 Empagliflozin + metformin compared to empagliflozin

Table 74: Clinical evidence profile: empagliflozin + metformin compared to empagliflozin

	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	У
all-cause mortality at end of follow-up Mean follow-up: 5.5 month(s)											
	RC	not seriou	not seriou		not seriou			0/33	RD 0.00	0 fewer per 1000 (5 fewer to 5	
1 (hadjadj 2016)	Т	S	S	NA ¹	S	NA	0/680	9	(-0.00, 0.00)	more)	high
cardiovascular mortality at end of follow- up											

Mean follow-up: 5.5 month(s)											
1 (hadjadj 2016)	RC T	not seriou s	not seriou s	NA ¹	not seriou s	NA	0/680	0/33 9	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (5 fewer to 5 more)	high
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)											
1 (hadjadj 2016)	RC T	not seriou	not seriou	NA ¹	very seriou s ²	NA	7/680	2/33 9	RR 1.74 (0.36, 8.35)	4 more per 1000 (4 fewer to 43 more)	low
hba1c change (%, lower values are better, change scores) at end of follow-up Mean follow-up: 5.5 month(s)										,	
1 (hadjadj 2016)	RC T	not seriou	not seriou	NA ¹	not seriou	NA	569	285	MD -0.69 (-0.83, -	MD 0.69 lower (0.83 lower to 0.55 lower)	high

- 1. Only one study so no inconsistency
- 2. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

F.1.8.22 Gliclazide + saxagliptin compared to saxagliptin + metformin

Table 75: Clinical evidence profile: Gliclazide + saxagliptin compared to saxagliptin + metformin

	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow-up											
Mean follow-up: 5.5 month(s)											

1 (chen 2022)	RC T	not serio us	not seriou s	NA ¹	not seriou s	NA	0/216	0/21 6	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	high
cardiovascular mortality at end of follow- up Mean follow-up: 5.5 month(s)											
1 (chen 2022)	RC T	not serio us	not seriou s	NA ¹	not seriou s	NA	0/216	0/21	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	high
hypoglycaemia episodes at end of follow- up Mean follow-up: 5.5 month(s)											
1 (chen 2022)	RC T	serio us ²	not seriou s	NA ¹	seriou s ³	NA	23/216	11/2 16	RR 2.09 (1.05, 4.18)	56 more per 1000 (2 more to 162 more)	low
hba1c change (%, lower values are better, change scores) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (chen 2022)	RC T	not serio us	not seriou s	NA ¹	not seriou s	NA	216	216	MD 0.10 (-0.11, 0.31)	MD 0.10 higher (0.11 lower to 0.31 higher)	high
bmi change (kg/m2, lower values are better, change scores) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (chen 2022)	RC T	not serio us	not seriou s	NA ¹	very seriou s ⁴	NA	216	216	MD 1.00 (-0.92, 2.92)	MD 1.00 higher (0.92 lower to 2.92 higher)	low

- 1. Only one study so no inconsistency
- 2. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 3. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

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

F.1.8.23 Glimepiride + metformin compared to canagliflozin + metformin

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

	De					Other			Relative		Cert
	sig	Risk	Indire	Inconsi	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	of bias	ctness	stency	cision	ions	ntion N	rol N	CI)	effect	у
weight change (kg, lower values are better, change scores) at end of follow- up Mean follow-up: 5.5 month(s)											
1 (zhou 2021)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	13	12	MD 1.57 (0.80, 2.34)	MD 1.57 higher (0.80 higher to 2.34 higher)	low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency

F.1.8.24 Empagliflozin + linagliptin compared to empagliflozin

Table 77: Clinical evidence profile: empagliflozin + linagliptin compared to empagliflozin

	De					Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	У
all-cause mortality at end of follow-up											
		very	not		not						
	RC	seriou	seriou	not	seriou			0/22	RD 0.00	0 fewer per	
2	Т	s ¹	S	serious	s	NA	0/223	4	(-0.01, 0.01)	1000	low

										(12 fewer to 12 more)	
non-fatal myocardial infarction at end of follow-up										,	
2	RC T	very seriou s ¹	not seriou s	serious	very seriou s ³	NA	0/223	1/22 4	RD -0.00 (-0.02, 0.01)	4 fewer per 1000 (20 fewer to 11 more)	very low
severe hypoglycaemic episodes at end of follow-up											
2	RC T	very seriou s ¹	not seriou s	serious	very seriou s ³	NA	0/223	1/22	RD -0.00 (-0.02, 0.01)	4 fewer per 1000 (20 fewer to 11 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow- up Mean follow-up: 8.8 month(s)											
2	RC T	very seriou s ¹	not seriou s	very serious	seriou s ⁵	NA	223	224	MD -0.70 (-0.93, - 0.46)	MD 0.70 lower (0.93 lower to 0.46 lower)	very low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.29 (0.8-0.9 = serious, <0.8 = very serious).
- 4.12 > 75%
- 5. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

F.1.8.25 Empagliflozin + linagliptin compared to linagliptin

Empagimoziii - imagiiptiii compared to	De					Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow up Mean follow-up: 12 month(s)											
1 (lewin 2015)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	1/272	0/13 5	PETO OR 4.47 (0.07, 286.91)	4 more per 1000 (4 fewer to 11 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)									,	,	
1 (lewin 2015)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	1/272	0/13 5	PETO OR 4.47 (0.07, 286.91)	4 more per 1000 (4 fewer to 11 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 12 month(s)											
1 (lewin 2015)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	0/272	1/13 5	RR 0.17 (0.01, 4.05)	6 fewer per 1000 (7 fewer to 23 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											
1 (lewin 2015)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/272	0/13 5	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (11 fewer to 11 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											

										MD 0.48	
										lower	
		very	not						MD -0.48	(0.64 lower	
	RC	seriou	seriou		seriou				(-0.64, -	to 0.31	very
1 (lewin 2015)	T	s ¹	S	NA ²	s ⁴	NA	245	112	0.31)	lower)	low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

F.1.8.26 Glimepiride + metformin compared to metformin

Table 78: Clinical evidence profile: glimepiride + metformin compared to metformin

Table 161 Chillian Straches promot gin	De	Risk		•		Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
hypoglycaemia episodes at end of follow-up Mean follow-up: 15 month(s)											
1 (derosa 2009)	RC T	not seriou s	seriou s ¹	NA ²	very seriou s ³	NA	3/66	0/67	PETO OR 7.74 (0.79, 75.70)	46 more per 1000 (5 fewer to 96 more)	very low
hba1c change (%, lower values are better, final value) at end of follow-up Mean follow-up: 15 month(s)											
1 (derosa 2009)	RC T	not seriou s	not seriou s	NA ²	not seriou s	NA	66	67	MD -0.80 (-1.04, - 0.56)	MD 0.80 lower (1.04 lower to 0.56 lower)	high

bmi change (kg/m2, lower values are better, final value) at end of follow-up Mean follow-up: 15 month(s)											
										MD 0.30	
		not	not							higher	
	RC	seriou	seriou		seriou				MD 0.30	(0.41 lower to	mod
1 (derosa 2009)	Т	S	S	NA ²	s ⁴	NA	66	67	(-0.41, 1.01)	1.01 higher)	erate

- 1. Largest proportion of studies in the meta-analysis came from partially direct studies
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

F.1.8.27 Glimepiride + metformin compared to pioglitazone

Table 79: Clinical evidence profile: glimepiride + metformin compared to pioglitazone

	De	Risk		_		Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ions	ntion N	rol N	CI)	effect	y
hypoglycaemia episodes at follow-up											
Mean follow-up: 15 month(s)											
1 (derosa 2009)	RC T	not serio us	seriou	NA ²	seriou s³	NA	3/66	0/69	PETO OR 7.98 (0.82, 78.04)	46 more per 1000 (5 fewer to 96 more)	low
hba1c change final value at follow-up (%, lower values are better, change scores) Mean follow-up: 15 month(s)							5,55	3,00	,		
1 (derosa 2009)	RC T	not serio us	not seriou s	NA ²	seriou s ⁴	NA	66	69	MD -0.40 (-0.59, - 0.21)	MD 0.40 lower (0.59 lower to 0.21 lower)	mod erat e

bmi change (kg/m2, final values) at end of follow-up Mean follow-up: 15 month(s)											
	RC	not serio	not seriou		not seriou				MD 1.70	MD 1.70 higher (1.10 higher to 2.30	
1 (derosa 2009)	Т	us	S	NA ²	S	NA	66	69	(1.10, 2.30)	higher)	high

- 1. Largest proportion of studies in the meta-analysis came from partially direct studies
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 4. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

F.1.8.28 Pioglitazone + metformin compared to metformin

Table 80: Clinical evidence profile: Pioglitazone + metformin compared to metformin

	De sig	Risk of	Indir ectne	Incon sisten	Impre	Other considera	Interv ention	Con trol	Relative effect	Absolute	Cert aint
No of studies	n	bias	SS	су	cision	tions	N	N	(95% CI)	effect	У
all-cause mortality at end of follow-up Mean follow-up: 5.5 month(s)											
1 (perez 2009)	RC T	very seriou s ¹	not serio us	NA ²	not seriou s	NA	0/201	0/20 9	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (10 fewer to 10 more)	low
cardiovascular mortality at end of follow-up Mean follow-up: 5.5 month(s)									,		
1 (perez 2009)	RC T	very seriou s ¹	not serio us	NA ²	not seriou s	NA	0/201	0/20 9	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (10 fewer to 10 more)	low

non-fatal myocardial infarction at end of follow- up											
Mean follow-up: 5.5 month(s) 1 (perez 2009) hypoglycaemia episodes at end of follow-up	RC T	very seriou s ¹	not serio us	NA ²	not seriou s	NA	0/201	0/20	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (10 fewer to 10 more)	low
Mean follow-up: 10.2 month(s)											
2	RC T	very seriou s ¹	serio us ³	not seriou s	very seriou s ⁴	NA	4/270	3/27 6	RR 1.31 (0.32, 5.29)	3 more per 1000 (7 fewer to 47 more)	very low
hba1c change and final (%, lower values are better, change scores and final values) at end of follow-up Mean follow-up: 10.2 month(s)											
2	RC T	not seriou s	not serio us	very seriou s ⁵	not seriou s	NA	257	260	MD -1.13 (-1.68, - 0.59)	MD 1.13 lower (1.68 lower to 0.59 lower)	low
bmi change final value (kg/m2, lower values are better, change scores) at end of follow-up Mean follow-up: 15 month(s)										,	
1 (derosa 2009)	RC T	not seriou s	not serio us	NA ²	seriou s ⁶	NA	69	67	MD -1.20 (-1.77, - 0.63)	MD 1.20 lower (1.77 lower to 0.63 lower)	mod erat e

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 4. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

5. I2 > 75%

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

F.1.8.29 Pioglitazone + metformin compared to pioglitazone

Table 81: Clinical evidence profile: Pioglitazone + metformin compared to pioglitazone

Table 01. Officer evidence profile. I logitaze	De	Risk	Indire	Incons	Piogn	Other	Interve	Cont	Relative		Cert
	sig	of	ctnes	istenc	Impre	considera	ntion	rol	effect (95%	Absolute	aint
No of studies	n	bias	S	y	cision	tions	N	N	CI)	effect	y
all-cause mortality at end of follow-up Mean follow-up: 5.5 month(s)				,					,		,
1 (perez 2009)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/201	0/19	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (10 fewer to 10 more)	low
cardiovascular mortality at end of follow-up Mean follow-up: 5.5 month(s)											
1 (perez 2009)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/201	0/19	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (10 fewer to 10 more)	low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 5.5 month(s)											
1 (perez 2009)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	0/201	1/19	PETO OR 0.13 (0.00, 6.45)	5 fewer per 1000 (16 fewer to 5 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 10.2 month(s)											
2	RC T	very seriou s ¹	not seriou s	not seriou s	very seriou s ³	NA	4/270	1/25 9	RR 2.91 (0.46, 18.19)	7 more per 1000 (2 fewer to 66 more)	very low

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

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

F.1.8.30 Pioglitazone + metformin compared to glimepiride + metformin

Table 82: Clinical evidence profile: Pioglitazone + metformin compared to glimepiride + metformin

	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	У
hypoglycaemia episodes at end of											
follow-up											
Mean follow-up: 15 month(s)											
1 (derosa 2009)	RC T	not seriou s	seriou s¹	NA ²	very seriou s ³	NA	2/69	3/66	RR 0.64 (0.11, 3.70)	16 fewer per 1000 (40 fewer to 123 more)	very low
hba1c change final value (%, lower values are better) at end of follow-up Mean follow-up: 15 month(s)											
		not	not						MD -0.60		
	RC	seriou	seriou		seriou				(-0.72, -	MD 0.60	mod
1 (derosa 2009)	T	S	S	NA ²	s ⁴	NA	69	66	0.48)	lower	erate

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

- 1. Largest proportion of studies in the meta-analysis came from partially direct studies
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

F.1.8.31 Pioglitazone + alogliptin compared to alogliptin

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

	De	Risk	gp	gp		Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	У
hba1c change (%, lower values are better, final values) at the end of follow-											
up											
Mean follow-up: 6 month(s)											
	RC	seriou	not seriou		seriou				MD -0.68 (-0.88, -	MD 0.68 lower (0.88 lower to	
1 (rosenstock 2010)	Т	s ¹	S	NA^2	s^3	NA	327	164	0.48)	0.48 lower)	low
weight change (kg, lower values are better, final values) at the end of follow- up											

Mean follow-up: 6 month(s)											
										MD 3.12 higher	
			not		not					(2.42 higher	mod
	RC	seriou	seriou		seriou				MD 3.12	to 3.82	erat
1 (rosenstock 2010)	T	s ¹	S	NA ²	S	NA	327	164	(2.42, 3.82)	higher)	e

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

F.1.8.32 Pioglitazone + alogliptin compared to pioglitazone

Table 84: Clinical evidence profile: Pioglitazone + alogliptin compared to pioglitazone

	De	Risk			•	Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
hba1c change (%, lower values are better, final values) at the end of follow-up											
Mean follow-up: 6 month(s)											
1 (rosenstock 2010) weight change (kg, lower values are	RC T	seriou s ¹	not seriou s	NA ²	seriou s³	NA	327	163	MD -0.49 (-0.69, - 0.29)	MD 0.49 lower (0.69 lower to 0.29 lower)	low
better, final values) at the end of follow-											
up Mean follow-up: 6 month(s)											
1 (rosenstock 2010)	RC	seriou s ¹	not seriou s	NA ²	not seriou	NA	327	163	MD 0.64 (-0.08, 1.36)	MD 0.64 higher (0.08 lower to 1.36 higher)	mod erat e
1 (1036113100K ZU10)	ı	3	3	11/7	3	INA	321	103	(-0.00, 1.30 <i>)</i>	1.50 higher)	C

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

F.1.8.33 Pioglitazone + linagliptin compared to linagliptin

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

No of studies 4-point MACE at end of follow up Mean follow-up: 6.9 month(s)	Des ign		Indirec tness	Inconsis tency	Impreci sion	Other consideratio ns	Interven tion N	Contr ol N	Relative effect (95% CI)	Absolute effect	Certa inty
	RC T	serious 1	not serious		very serious ³	NA	2/392		RR 0.34	10 fewer per 1000 (14 fewer to 21 more)	very low
	RC T	serious	not serious		very serious³	NA	4/392		PETO OR 3.87	10 more per 1000 (0 more to 20 more)	very low

Mean follow-up: 6.9 month(s)										
1 (nauck 2016)	RC T	serious	not serious	NA ²	very serious ³	NA	1/392	3.84	, .	very low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 6.9 month(s)										
1 (nauck 2016)	RC T	serious	not serious	NA ²	serious ⁴	NA	371		MD 0.67 lower (0.86 lower to 0.48 lower)	low
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 6.9 month(s)										
1 (nauck 2016)	RC T	serious	not serious	NA ²	serious ⁵	NA	272	MD 1.63 (0.10, 3.16)	MD 1.63 higher (0.10 higher to 3.16 higher)	low

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 5. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

F.1.8.34 Pioglitazone + linagliptin compared with pioglitazone

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

-	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
4-point mace at end of follow up Mean follow-up: 6.9 month(s)											
1 (nauck 2016)	RC T	seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	2/392	2/40 9	RR 1.04 (0.15, 7.37)	0 more per 1000 (4 fewer to 31 more)	very low
hypoglycaemia episodes at end of follow- up Mean follow-up: 6.9 month(s)											
1 (nauck 2016)	RC T	seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	4/392	5/40 9	RR 0.83 (0.23, 3.09)	2 fewer per 1000 (9 fewer to 25 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 6.9 month(s)											
1 (nauck 2016)	RC T	seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	1/392	0/40	PETO OR 7.72 (0.15, 389.23)	3 more per 1000 (2 fewer to 8 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow- up Mean follow-up: 6.9 month(s)											
1 (nauck 2016)	RC T	seriou s ¹	not seriou s	NA ²	not seriou s	NA	392	409	MD -0.32 (-0.45, - 0.19)	MD 0.32 lower (0.45 lower to 0.19 lower)	mod erat e

weight change (kg, lower values are better, change scores) at end of follow- up											
Mean follow-up: 6.9 month(s)											
										MD 1.21	
										lower	
			not		not				MD -1.21	(2.26 lower	mod
	RC	seriou	seriou		seriou				(-2.26, -	to 0.16	erat
1 (nauck 2016)	Т	s ¹	S	NA^2	S	NA	272	258	0.16)	lower)	е

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

F.1.8.35 Pioglitazone + sitagliptin compared to pioglitazone

Table 87: Clinical evidence profile: Pioglitazone + sitagliptin compared to pioglitazone

	De					Other			Relative		Cert
	sig	Risk	Indire	Inconsi	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	of bias	ctness	stency	cision	ions	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow-up Mean follow-up: 12.5 month(s)											
		very	not		very			0/45	PETO OR 6.91	6 more per 1000	
4 (RC	seriou	seriou	NIA?	seriou	NIA	4/404	0/15	(0.14,	(6 fewer to 18	very
1 (yoon 2012)	ı	S ¹	S	NA ²	s ³	NA	1/164	3	349.05)	more)	low
cardiovascular mortality at end of follow-											
up											
Mean follow-up: 12.5 month(s)											
		very	not		very				PETO OR 6.91	6 more per 1000	
	RC	seriou	seriou		seriou			0/15	(0.14,	(6 fewer to 18	very
1 (yoon 2012)	T	s ¹	s	NA ²	s^3	NA	1/164	3	349.05)	more)	low

hypoglycaemia episodes at end of follow-up											
Mean follow-up: 12.5 month(s) 1 (yoon 2012)	RC	very seriou s ¹	not seriou	NA ²	seriou s ⁴	NA	4/164	0/15	PETO OR 7.04 (0.98, 50.50)	24 more per 1000 (1 more to 48 more)	very
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 12.5 month(s)	,	3	3	IVA	3	INA	4/104	3	30.30)	more)	IOW
1 (yoon 2012)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s ⁵	NA	0/164	0/15	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	very low
hba1c change (%, lower values are better) at end of follow-up Mean follow-up: 12.5 month(s)											
1 (yoon 2012)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s ⁶	NA	161	149	MD -0.50 (-0.71, - 0.29)	MD 0.50 lower (0.71 lower to 0.29 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow- up Mean follow-up: 12.5 month(s)											
1 (yoon 2012)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	164	153	MD 0.70 (-0.74, 2.14)	MD 0.70 higher (0.74 lower to 2.14 higher)	low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 5. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.

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

F.1.8.36 Pioglitazone + vildagliptin compared to pioglitazone

Table 88: Clinical evidence profile: Pioglitazone + sitagliptin compared to pioglitazone

	De	Risk			,	Other			Relative		Cert
	sig	of	Indire	Incons	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	istency	cision	ions	ntion N	rol N	CI)	effect	у
hypoglycaemia episodes at the end of											
follow-up											
Mean follow-up: 5.5 month(s)										_	
									PETO OR	3 more per	
		very	not		very				4.72	1000	
	RC	seriou	seriou		seriou			0/16	(0.08,	(3 fewer to	very
1 (rosenstock 2007a)	Т	S ¹	S	NA ²	s ³	NA	1/292	1	283.23)	10 more)	low
hba1c change (%, lower values are better,											
change values) at the end of follow-up											
Mean follow-up: 5.5 month(s)											
										MD 0.40	
		very	not						MD -0.40	lower	
	RC	seriou	seriou		seriou				(-0.64, -	(0.64 lower to	very
1 (rosenstock 2007a)	T	s ¹	s	NA^2	s ⁴	NA	285	157	0.16)	0.16 lower)	low
weight change (%, lower values are									•	,	
better, change values) at the end of											
follow-up											
Mean follow-up: 5.5 month(s)											
•										MD 0.26	
		very	not		not					higher	
	RC	seriou	seriou		seriou				MD 0.26	(0.46 lower to	
1 (rosenstock 2007a)	Т	s ¹	s	NA ²	S	NA	285	157	(-0.46, 0.98)	0.98 higher)	low

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

2. Only one study so no inconsistency

- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

F.1.8.37 Pioglitazone + vildagliptin compared to vildagliptin

Table 89: Clinical evidence profile: Pioglitazone + vildagliptin compared to vildagliptin

Table 65. Gillical evidence prome. 1 16	De	00 1.	i dagiipti			Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	v
	••	Dias	Ctiless	Stericy	CISIOII	Olis	TICIOTI IN	10114	Cij	enect	y
hypoglycaemia episodes at end follow-											
up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2007a)	RC T	very seriou s ¹	not seriou	NA ²	very seriou s ³	NA	1/292	1/15 3	PETO OR 0.50 (0.03, 9.27)	3 fewer per 1000 (18 fewer to 11 more)	very low
hba1c change (%, lower values are	•	3	3	INA	3	INA	1/232	3	(0.00, 9.21)	TT more)	IOW
better, change scores) at end follow-up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2007a)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s ⁴	NA	285	150	MD -0.70 (-0.94, - 0.46)	MD 0.70 lower (0.94 lower to 0.46 lower)	very low
weight change (kg, lower values are better, change scores) at end follow-up Mean follow-up: 5.5 month(s)									,	,	
1 (rosenstock 2007a)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	285	150	MD 1.56 (0.84, 2.28)	MD 1.56 higher (0.84 higher to 2.28 higher)	low

^{1. &}gt;33.3% of the studies in the meta-analysis were at high risk of bias

- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

F.1.8.38 Saxagliptin + metformin compared to metformin

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

persistent signs of worsening kidney disease at end of follow-up Mean follow-up: 5.5 month(s)											
1 (dou 2018)	R C T	very serious ¹	not seriou s	NA ⁴	very serious ⁵	N A	0/21	1/21 0	PETO OR 0.13 (0.00, 6.66)	5 fewer per 1000 (14 fewer to 5 more)	very low
progression of liver disease at end of follow-up Mean follow-up: 5.5 month(s)											
1 (dou 2018)	R C T	very serious ¹	not seriou s	NA ⁴	not serious	N A	0/21 5	0/21 0	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	low
hypoglycaemia episodes at end of follow-up Mean follow-up: 11.8 month(s)									·		
2	R C T	very serious ¹	not seriou s	not serious	very serious ⁵	N A	38/8 58	24/5 38	RR 0.85 (0.51, 1.41)	7 fewer per 1000 (22 fewer to 18 more)	very low
severe hypoglycaemic episodes at end of follow- up Mean follow-up: 11.8 month(s)									,	,	
2	R C T	very serious ¹	not seriou s	serious ²	very serious ⁶	N A	3/85 8	2/53 8	RD -0.00 (-0.01, 0.01)	1 fewer per 1000 (7 fewer to 6 more)	very low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)									,	,	

3	R C T	very serious ¹	not seriou s	very serious ⁷	serious ⁸	N A	592	375	MD -0.32 (-0.54, - 0.09)	MD 0.32 lower (0.54 lower to 0.09 lower)	very low
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
2	R C T	very serious ¹	not seriou s	not serious	not serious	N A	231	228	MD 0.42 (-0.12, 0.96)	MD 0.42 higher (0.12 lower to 0.96 higher)	low
bmi change (kg/m2, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
2	R C T	very serious ¹	not seriou s	very serious ⁷	not serious	N A	231	228	MD -0.10 (-0.65, 0.45)	MD 0.10 lower (0.65 lower to 0.45 higher)	very low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.48 (0.8-0.9 = serious, <0.8 = very serious).
- 4. Only one study so no inconsistency
- 5. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.03 (0.8-0.9 = serious, <0.8 = very serious).
- 7.12 > 75%
- 8. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

F.1.9 Saxagliptin + metformin compared to saxagliptin

Table 91: Clinical evidence profile: Saxagliptin + metformin compared to saxagliptin

Table 31. Officer evidence profile. Caxe	De					Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	У
all-cause mortality at end of follow-up Mean follow-up: 11.8 month(s)											
2	RC T	very seriou s ¹	not seriou s	serious	very seriou s ³	NA	3/858	3/54 9	PETO OR 0.56 (0.11, 3.00)	2 fewer per 1000 (9 fewer to 5 more)	very low
cardiovascular mortality at end of follow- up Mean follow-up: 18 month(s)											
1 (pfützner 2011a)	RC T	very seriou s ¹	not seriou s	NA ⁴	very seriou s ³	NA	2/643	2/33 5	RR 0.52 (0.07, 3.68)	3 fewer per 1000 (6 fewer to 16 more)	very low
non-fatal stroke at end of follow-up Mean follow-up: 5.5 month(s)											
1 (dou 2018)	RC T	very seriou s ¹	not seriou s	NA ⁴	very seriou s ³	NA	0/215	1/21 4	PETO OR 0.13 (0.00, 6.79)	5 fewer per 1000 (14 fewer to 4 more)	very low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 5.5 month(s)										,	
1 (dou 2018)	RC T	very seriou s ¹	not seriou s	NA ⁴	not seriou s	NA	0/215	0/21 4	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	low
persistent signs of worsening kidney disease at end of follow-up Mean follow-up: 5.5 month(s)									,	,	

1 (dou 2018)	RC T	very seriou s ¹	not seriou s	NA ⁴	not seriou s	NA	0/215	0/21	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	low
progression of liver disease at end of follow-up Mean follow-up: 5.5 month(s)											
1 (dou 2018)	RC T	very seriou s ¹	not seriou s	NA ⁴	very seriou s ³	NA	0/215	1/21	PETO OR 0.13 (0.00, 6.79)	5 fewer per 1000 (14 fewer to 4 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 11.8 month(s)											
2	RC T	very seriou s ¹	not seriou s	serious 5	very seriou s ³	NA	38/858	10/5 49	RR 1.26 (0.17, 9.32)	5 more per 1000 (15 fewer to 152 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 11.8 month(s)											
2	RC T	very seriou s ¹	not seriou s	serious	very seriou s ⁶	NA	3/858	0/54 9	RD 0.00 (-0.00, 0.01)	3 more per 1000 (3 fewer to 8 more)	very low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
3	RC T	very seriou s ¹	not seriou s	very serious	seriou s ⁸	NA	592	348	MD -0.63 (-1.02, - 0.23)	MD 0.63 lower (1.02 lower to 0.23 lower)	very low
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
2	RC T	very seriou s ¹	not seriou s	not serious	not seriou s	NA	231	234	MD -0.54 (-2.06, 0.98)	MD 0.54 lower	low

										(2.06 lower to 0.98 higher)	
bmi change (kg/m2, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
mean follow-up. 0.0 month(3)		verv	not	very	not					MD 0.10 lower	
2	RC T	seriou s ¹	seriou s	serious	seriou s	NA	231	234	MD -0.10 (-0.61, 0.41)	(0.61 lower to 0.41 higher)	very low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. Only one study so no inconsistency
- 5. I2 between 50% and 75%
- 6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.6 (0.8-0.9 = serious, <0.8 = very serious).
- 7.12 > 75%
- 8. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

F.1.10 Sitagliptin + metformin compared to metformin

Table 92: Clinical evidence profile: Sitagliptin + metformin compared to metformin

	De sig	Risk of	Indire ctnes	Incons istenc	Impre	Other considera	Interve ntion	Cont rol	Relative effect (95%	Absolute	Cert aint
No of studies	n	bias	s	у	cision	tions	N	N	CI)	effect	у
all-cause mortality at end follow-up Mean follow-up: 5.5 month(s)											

2 cardiovascular mortality at end follow-up Mean follow-up: 5.5 month(s)	RC T	very seriou s ¹	not seriou s	not seriou s	not seriou s	NA	0/619	0/61	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (4 fewer to 4 more)	low
2 diabetic ketoacidosis at end follow-up	RC T	very seriou s ¹	not seriou s	not seriou s	not seriou s	NA	0/619	0/61	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (4 fewer to 4 more)	low
Mean follow-up: 5.5 month(s) 1 (goldstein 2007)	RC T	very seriou s ¹	not seriou	NA ²	not seriou s	NA	0/372	0/36	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (5 fewer to 5 more)	low
hypoglycaemia episodes at end follow-up Mean follow-up: 5.5 month(s)	RC T	seriou s³	not seriou	not seriou	not seriou	NA	35/619	15/6 14	RR 2.35 (1.30, 4.22)	33 more per 1000 (7 more to 79 more)	mod erat e
severe hypoglycaemic episodes at end follow-up Mean follow-up: 5.5 month(s)	1	3	3	3	3	TV.	00/010		(1.00, 4.22)	0 fewer per	
1 (ji 2016a) hba1c change (%, lower values are better,	RC T	seriou s³	not seriou s	NA ²	not seriou s	NA	0/247	0/25	RD 0.00 (-0.01, 0.01)	1000 (8 fewer to 8 more)	mod erat e
change scores and final values) at end follow-up Mean follow-up: 5.5 month(s)										MD 0.76	
3	RC T	very seriou s ¹	not seriou s	very seriou s ⁴	seriou s ⁵	NA	613	605	MD -0.76 (-1.22, - 0.30)	lower (1.22 lower to 0.30 lower)	very low

weight change (kg, lower values are better, change scores) at end follow-up Mean follow-up: 5.5 month(s)											
1 (ji 2016a) bmi change (kg/m2, lower values are better,	RC T	seriou s³	not seriou s	NA ²	not seriou s	NA	247	250	MD 1.15 (0.40, 1.90)	MD 1.15 higher (0.40 higher to 1.90 higher)	mod erat e
final values) at end follow-up Mean follow-up: 5.5 month(s)											
	RC	very seriou	not seriou		very seriou				MD -0.22 (-2.36,	MD 0.22 lower (2.36 lower to 1.92	very
1 (wang 2022)	T	s ¹	S	NA ²	s ⁶	NA	20	17	1.92)	higher)	low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 4.12 > 75%
- 5. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 6. 95% confidence intervals cross both ends of the defined MIDs (-0.80, 0.80)

F.1.11 Sitagliptin + metformin compared to sitagliptin

Table 93: Clinical evidence profile: Sitaglipttin + metformin compared to sitagliptin

	De	Risk	Indire	Incons		Other	Interve	Cont	Relative		Cert
	sig	of	ctnes	istenc	Impre	considera	ntion	rol	effect (95%	Absolute	aint
No of studies	n	bias	S	у	cision	tions	N	N	CI)	effect	У

all-cause mortality at end of follow-up											
Mean follow-up: 5.5 month(s)											
2	RC T	seriou s ¹	not seriou s	not seriou s	not seriou s	NA	0/619	0/29 9	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	mod erat e
cardiovascular mortality at end of follow-up Mean follow-up: 5.5 month(s)											
2	RC T	seriou s ¹	not seriou s	not seriou s	not seriou s	NA	0/619	0/29 9	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	mod erat e
diabetic ketoacidosis at end of follow-up Mean follow-up: 5.5 month(s)											
1 (goldstein 2007)	RC T	seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/372	0/17	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	mod erat e
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)											
2	RC T	seriou s ¹	not seriou	not seriou s	seriou s³	NA	35/619	6/29 9	RR 2.83 (1.21, 6.60)	37 more per 1000 (4 more to 112 more)	low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)											
1 (ji 2016a)	RC T	seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/247	0/12	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (13 fewer to 13 more)	mod erat e
hba1c change (%, lower values are better, change scores and final value) at end of follow-up Mean follow-up: 5.5 month(s)											
3	RC T	seriou s¹	not seriou s	very seriou s ⁴	seriou s ⁵	NA	613	305	MD -0.59 (-1.12, - 0.07)	MD 0.59 lower	very low

										(1.12 lower to 0.07 lower)	
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (ji 2016a)	RC T	seriou s ¹	not seriou s	NA ²	not seriou s	NA	247	120	MD -0.40 (-1.31, 0.51)	MD 0.40 lower (1.31 lower to 0.51 higher)	mod erat e
bmi change (kg/m2, lower values are better, final value) at end of follow-up Mean follow-up: 5.5 month(s)											
	RC	very seriou	not seriou		very seriou				MD 1.14 (-0.81,	MD 1.14 higher (0.81 lower to 3.09	very
1 (wang 2022)	Т	s ⁶	s	NA ²	s ⁷	NA	20	17	3.09)	higher)	low

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 4. I2 > 75%
- 5. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 6. > 33.3% of the studies in the meta-analysis were at high risk of bias
- 7. 95% confidence intervals cross both ends of the defined MIDs (-0.80, 0.80)

F.1.12 Sitagliptin + metformin compared to placebo

Table 94: Clinical evidence profile: Sitagliptin + metformin compared to placebo

rable 34. Offfical evidence profile. Offa	De					Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ions	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow-up Mean follow-up: 5.5 month(s)											
2	RC	seriou s ¹	not seriou	serious	very seriou s ³	NA	0/619	1/30	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (12 fewer to 7 more)	very low
cardiovascular mortality at end of follow-up Mean follow-up: 5.5 month(s)	'	5	3		3	INA	0/019	2	(-0.01, 0.01)	more)	IOW
2	RC T	seriou s¹	not seriou s	serious	very seriou s ³	NA	0/619	1/30 2	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (12 fewer to 7 more)	very low
diabetic ketoacidosis at end of follow-up Mean follow-up: 5.5 month(s)											
1 (goldstein 2007)	RC T	very seriou s ⁴	not seriou s	NA ⁵	very seriou s ⁶	NA	0/372	1/17 6	PETO OR 0.04 (0.00, 2.96)	6 fewer per 1000 (17 fewer to 5 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)											
2	RC T	seriou s ¹	not seriou s	not serious	not seriou s	NA	35/619	5/30 2	RR 3.52 (1.40, 8.84)	42 more per 1000 (7 more to 130 more)	mod erat e
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)											

1 (ji 2016a)	RC T	seriou s¹	not seriou s	NA ⁵	not seriou s	NA	0/247	0/12	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	mod erat e
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
2	RC T	very seriou s ⁴	not seriou s	serious	not seriou s	NA	562	292	MD -0.97 (-1.31, - 0.64)	MD 0.97 lower (1.31 lower to 0.64 lower)	very low
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (ji 2016a)	RC T	seriou s ¹	not seriou s	NA ⁵	not seriou s	NA	247	124	MD 1.40 (0.46, 2.34)	MD 1.40 higher (0.46 higher to 2.34 higher)	mod erat e

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.42 (0.8-0.9 = serious, <0.8 = very serious).
- 4. >33.3% of the studies in the meta-analysis were at high risk of bias
- 5. Only one study so no inconsistency
- 6. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 7. I2 between 50% and 75%

F.1.1 Sitagliptin + metformin compared to metformin

Table 95: Clinical evidence profile: Sitagliptin + metformin compared to metformin

Table 33. Official evidence profile. Offagript	De	Risk	Indire	Incons		Other	Interve	Cont	Relative		Cert
	sig	of	ctnes	istenc	Impre	considera	ntion	rol	effect (95%	Absolute	aint
No of studies	n	bias	S	v	cision	tions	N	N	CI)	effect	V
all-cause mortality at end follow-up	•••	Dias		У	CISIOII	tions	14	13	Cij	Circu	y
Mean follow-up: 5.5 month(s)											
2	RC T	very seriou s ¹	not seriou s	not seriou s	not seriou s	NA	0/619	0/61	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (4 fewer to 4 more)	low
cardiovascular mortality at end follow-up Mean follow-up: 5.5 month(s)											
2	RC T	very seriou s ¹	not seriou s	not seriou s	not seriou s	NA	0/619	0/61 4	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (4 fewer to 4 more)	low
diabetic ketoacidosis at end follow-up Mean follow-up: 5.5 month(s)											
1 (goldstein 2007)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/372	0/36	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (5 fewer to 5 more)	low
hypoglycaemia episodes at end follow-up Mean follow-up: 5.5 month(s)											
2 severe hypoglycaemic episodes at end	RC T	seriou s³	not seriou s	not seriou s	not seriou s	NA	35/619	15/6 14	RR 2.35 (1.30, 4.22)	33 more per 1000 (7 more to 79 more)	mod erat e
follow-up Mean follow-up: 5.5 month(s)											
1 (ji 2016a)	RC T	seriou s³	not seriou	NA ²	not seriou	NA	0/247	0/25 0	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	mod erat e

hba1c change (%, lower values are better, change scores and final values) at end follow-up Mean follow-up: 5.5 month(s)											
3	RC T	very seriou s ¹	not seriou s	very seriou s ⁴	seriou s ⁵	NA	613	605	MD -0.76 (-1.22, - 0.30)	MD 0.76 lower (1.22 lower to 0.30 lower)	very low
weight change (kg, lower values are better, change scores) at end follow-up Mean follow-up: 5.5 month(s)											
1 (ji 2016a)	RC T	seriou s³	not seriou s	NA ²	not seriou s	NA	247	250	MD 1.15 (0.40, 1.90)	MD 1.15 higher (0.40 higher to 1.90 higher)	mod erat e
bmi change (kg/m2, lower values are better, final values) at end follow-up Mean follow-up: 5.5 month(s)											
1 (wang 2022)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ⁶	NA	20	17	MD -0.22 (-2.36, 1.92)	MD 0.22 lower (2.36 lower to 1.92 higher)	very low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 4. I2 > 75%
- 5. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 6. 95% confidence intervals cross both ends of the defined MIDs (-0.80, 0.80)

F.1.2 Sitagliptin + metformin compared to glimepiride

Table 96: Clinical evidence profile: Sitagliptin + metformin compared to glimepiride

Table 30. Chinical evidence prome. Otta	De					Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	У
all-cause mortality at end of follow-up Mean follow-up: 7 month(s)											
1 (kim 2017)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s ³	NA	0/146	0/14	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (13 fewer to 13 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 7 month(s)											
1 (kim 2017)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	8/146	29/1 44	RR 0.27 (0.13, 0.57)	147 fewer per 1000 (175 fewer to 86 fewer)	low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 7 month(s)											
1 (kim 2017)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ⁴	NA	0/146	1/14	PETO OR 0.13 (0.00, 6.73)	7 fewer per 1000 (21 fewer to 7 more)	very low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 7 month(s)											
1 (kim 2017)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	146	144	MD -0.78 (-0.96, - 0.60)	MD 0.78 lower (0.96 lower to 0.60 lower)	low
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 7 month(s)		3	J	14/3	3	TVA	140	1 7 7	0.00)	iowei)	1044

										MD 1.72	
										lower	
		very	not						MD -1.72	(2.74 lower	
	RC	seriou	seriou		seriou				(-2.74, -	to 0.70	very
1 (kim 2017)	T	s ¹	S	NA ²	s ⁵	NA	146	144	0.70)	lower)	low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 4. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 5. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

F.1.3 Sitagliptin + metformin compared to pioglitazone

Table 97: Clinical evidence profile: Sitagliptin + metformin compared to pioglitazone

	De					Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	У
hypoglycaemia episodes at end of											
follow-up											
Mean follow-up: 7.4 month(s)											
1 (wainstein 2012)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s³	NA	22/261	11/2 56	RR 1.96 (0.97, 3.96)	41 more per 1000 (1 fewer to 127 more)	very low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 7.4 month(s)											
1 (wainstein 2012)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/261	0/26 1	RD 0.00 (-0.01, 0.01)	0 fewer per 1000	low

										(7 fewer to 7 more)	
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 7.4 month(s)											
4 (RC	very seriou	not seriou	N14.2	seriou		050	0.40	MD -0.50 (-0.68, -	MD 0.50 lower (0.68 lower to	very
1 (wainstein 2012)	Τ	S ¹	S	NA^2	S ⁴	NA	253	246	0.32)	0.32 lower)	low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 4. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

F.1.4 Vilagliptin + metformin compared to metformin

Table 98: Clinical evidence profile: Vildagliptin + metformin compared to metformin

	De					Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow-up Mean follow-up: 6 month(s)											
	RC	seriou	not seriou		very seriou			0/29	PETO OR 4.49 (0.07,	2 more per 1000 (2 fewer to 5	very
1 (bosi 2009)	Т	s ¹	S	NA ²	s^3	NA	1/585	4	286.22)	more)	low
non-fatal myocardial infarction at end of follow-up											
Mean follow-up: 6 month(s)											

1 (bosi 2009)	RC T	seriou s ¹	not seriou s	NA ²	seriou s ⁴	NA	0/585	2/29 4	PETO OR 0.05 (0.00, 0.95)	7 fewer per 1000 (16 fewer to 3 more)	low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (bosi 2009)	RC T	seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	0/585	1/29	PETO OR 0.05 (0.00, 3.20)	3 fewer per 1000 (10 fewer to 3 more)	very low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)											
2	RC T	seriou s ¹	not seriou s	not serious	not seriou s	NA	617	326	MD -0.32 (-0.45, - 0.18)	MD 0.32 lower (0.45 lower to 0.18 lower)	mod erat e
weight change (kg, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)											
2	RC T	seriou s ¹	not seriou s	not serious	not seriou s	NA	617	326	MD 0.44 (-0.07, 0.94)	MD 0.44 higher (0.07 lower to 0.94 higher)	mod erat e
bmi change (kg/m2, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)											
1 (zougrafou 2015)	RC T	very seriou s ⁵	not seriou s	NA ²	not seriou s	NA	32	32	MD 0.20 (-0.35, 0.75)	MD 0.20 higher (0.35 lower to 0.75 higher)	low

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

- 4. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 5. >33.3% of the studies in the meta-analysis were at high risk of bias

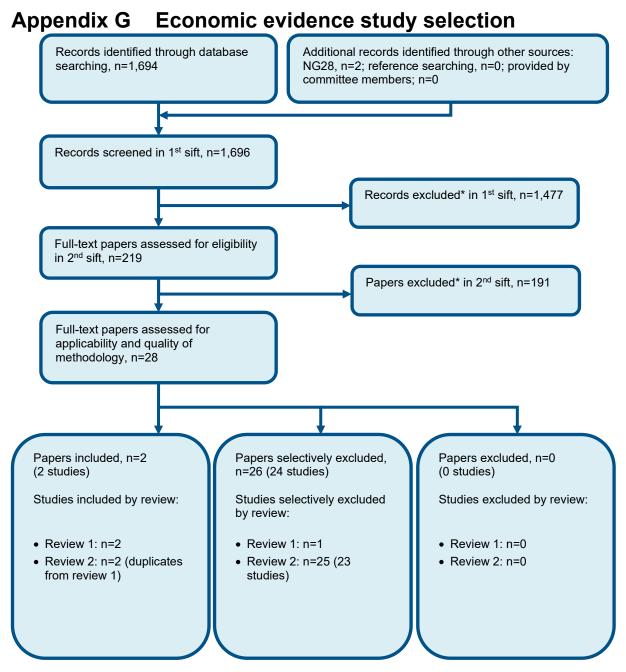
F.1.5 Vildagliptin + metformin compared to vildagliptin

Table 99: Clinical evidence profile: Vildagliptin + metformin compared to vildagliptin

•	De	Risk		•		Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
all-cause mortality at end follow-up Mean follow-up: 6 month(s)											
1 (bosi 2009)	RC T	seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	1/585	0/30	PETO OR 4.54 (0.07, 285.24)	2 more per 1000 (2 fewer to 5 more)	very low
non-fatal myocardial infarction at end follow-up Mean follow-up: 6 month(s)											
1 (bosi 2009)	RC T	seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/585	0/30	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (5 fewer to 5 more)	mod erat e
severe hypoglycaemic episodes at end follow-up Mean follow-up: 6 month(s)											
1 (bosi 2009)	RC T	seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/585	0/30	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (5 fewer to 5 more)	mod erat e
hba1c change (%, lower values are better, change scores) at end follow-up Mean follow-up: 6 month(s)											

1 (bosi 2009)	RC T	seriou s ¹	not seriou s	NA ²	seriou s ⁴	NA	585	300	MD -0.60 (-0.74, - 0.46)	MD 0.60 lower (0.74 lower to 0.46 lower)	low
weight change (kg, lower values are better, change scores) at end follow-up Mean follow-up: 6 month(s)											
4.44	RC	seriou	not seriou		not seriou				MD -0.59 (-1.12, -	MD 0.59 lower (1.12 lower to	mod erat
1 (bosi 2009)	T	S ¹	S	NA ²	S	NA	585	300	0.06)	0.06 lower)	е

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)



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

Appendix H Economic evidence tables

Study	National Institute for Health and Care Excellence (NG28) 2015										
Study details	Population & interventions	Cost effectiveness (pa)									
Economic analysis: CUA (health outcome: QALY) Study design: Individual patient simulation model. Patient	Population: Initial therapy in adults aged 18 years and over with type 2 diabetes.	Intervention in order of cost	Cost ^(c)	QALYs	Inc. costs versus metformin	Inc. QALYs versus metformin	Cost per QALY gained versus metformin				
population based on real-world	Cohort settings: Start age (years): 59.8	Metformin	£19,250	9.033							
UK cohort. Treatment effects	Male: 57.1%	Repaglinide	£19,298	8.974	£48	-0.059	Dominated				
based on systematic literature review and network meta-	HbA1c: 66mmol/mol	Pioglitazone	£19,412	8.973	£163	-0.060	Dominated				
analysis of guideline clinical		Sulfonylurea	£19,580	8.950	£330	-0.082	Dominated				
review results.	Interventions: Various drug interventions and no treatment were compared to each other – see table to right.	No treatment (placebo)	£20,043	8.912	£794	-0.121	Dominated				
Approach to analysis: The		Sitagliptin	£20,457	8.990	£1,207	-0.043	Dominated				
UKPDS OM1 was used to conduct modelling analysis.	other – see table to right.	Vildagliptin	£20,627	8.954	£1,377	-0.074	Dominated				
Outcomes of interest included: 1. Ischaemic heart disease 2. Myocardial infarction 3. Heart failure 4. Stroke 5. Amputation 6. Severe vision loss 7. Renal failure Perspective: UK NHS Time horizon: lifetime/ 40 years Treatment effect duration: Treatment effects to HbA1c	Treatment intensification following failure to control HbA1c levels with initial treatment were based on results for metformin-sulfonylurea. Further intensification was based on results for metformin-NPH insulin.	Currency & cost 2012/13 UK poun Cost component Drug costs, drug of (needles, self-monglucose strips and bins), staff time for initiation, diabetes complications cost	ds ^(b) s incorpora consumables nitoring bloo d lancets, sh or GLP-1 and s-related	s d arps	versus all oth threshold): 88 For people w repaglinide w initial therapy ICER of £20k followed by p Analysis of u remained the		ake metformin, ost-effective m acceptable rations, 5%). Metformin ective				

Type 2 diabetes in adults: management (medicines update): evidence reviews for Initial pharmacological management DRAFT FOR CONSULTATION [Aug 2025]

were modelled at 1 year and were taken from the NMA. Treatment-related weight gain was assumed to last indefinitely and weight loss to last for one year with an immediate gain within the following year. Hypoglycaemic episode rates remained constant over time.	effects data for HbA1c and weight change were applied.
Discounting: Costs: 3.5%; Outcomes: 3.5%	

Data sources

Health outcomes: Baseline data for demographic factors (age, sex, ethnicity, duration of diabetes, height, weight), clinical risk factors (HbA1c, SBP, total cholesterol, HDL, smoking status and presence of atrial fibrillation and PAD) and history of diabetes-related complications were taken from The Health Improvement Network (THIN) 2014. Treatment effectiveness data were all taken from NMAs conducted as part of the guideline clinical review and were four: HbA1c, weight change, hypoglycaemic events and treatment discontinuation. Changes in HbA1c were used to predict diabetes related complications. Quality-of-life weights: EQ-5D UK tariff valuations taken from the UKPDS RCT. Cost sources: Drug unit costs were taken from the NHS June Drug Tariff 2014. Drug consumable costs were based on weighted averages of prescribed usage from the Health and Social Care Information Centre (HSCIC) 2014. Staff costs were taken from the Personal Social Services Research Unit (PSSRU) 2014. Diabetes-related complications costs (except for renal failure costs) were sourced from the UKPDS RCT and inflated to 2012/13 costs. Renal failure costs were taken from a UK study (Lamping 2000).

Comments

Source of funding: UK Department of Health and Social Care (DHSC). **Limitations:** Newer GLP-1 agonists and SGLT-2 inhibitors are missing from the analysis. Tirzepatide is also missing from the analysis. The validity of HbA1c as a surrogate marker used to predict cardiovascular outcomes and mortality has been questioned. Sources of costs are dated and do not accurately reflect current NHS conditions. The proportion of hypoglycaemic episodes that are severe (2%) and (therefore incur costs to the NHS) was assumed to be the same across all treatments. **Other:**

Overall applicability:(c) Directly applicable Overall quality:(d) Potentially serious limitations

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

- (a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.
- (b) Directly applicable / Partially applicable / Not applicable
- (c) Minor limitations / Potentially serious limitations / Very serious limitations

Study	National Institute for Health and Care Excellence (NG28) 2022										
Study details	Population & interventions	Cost effectiveness (da)									
Economic analysis: CUA (health outcome: QALY)	Population: Adults aged 18 years and over with type 2 diabetes	CVOTs as additions (compared to metformin alone)									
simulation to predict diabetes-	Cohort settings: Start age (years): 58.79 Male: 57%	Intervention in order of cost	Cost ^(c)	QALYs	Inc. costs versus metformin	Inc. QALYs versus metformin	Cost per QALY gained versus metformin				
states were assigned according	HbA1c: 66mmol/mol	Metformin	£17,565	9.47							
to complications. CVD treatment effects were applied		Pioglitazone + metformin	£19,212	9.373	£1,647	-0.097	Dominated				
Patient population based on real-world UK cohort. Treatment effects based on systematic literature review and network meta-analysis of CVOT combin metfor to met to met (standard).	Interventions: Various CVOT drugs in	Alogliptin + metformin	£22,061	9.408	£4,496	-0.062	Dominated				
	combination with metformin were compared to metformin alone (standard care) – see table to right.	Ertugliflozin + metformin	£22,316	9.668	£4,751	0.198	£24,004				
		Linagliptin + metformin	£22,813	9.491	£5,248	0.021	£248,971				
guideline clinical review results.		Sitagliptin + metformin	£23,387	9.503	£5,822	0.033	£177,546				
part model was constructed in R. In the first part, the UKPDS risk equations were used to also conducted for also conducted for also conducted for the part model was constructed in also conducted for als	Subgroup analyses were also conducted for those:	Dapagliflozin + metformin	£23,399	9.837	£5,834	0.367	£15,899				
	 with a BMI of greater than or equal to 30kg/m2 at high risk of a 	Empagliflozin + metformin	£23,785	9.714	£6,220	0.244	£25,526				
simulate outcomes for the standard care arm. Treatment		Saxagliptin + metformin	£23,806	9.2	£6,241	-0.27	Dominated				
the second part of the model. Outcomes of interest included: 1. Ischaemic heart disease (IHD) 2. Myocardial infarction have no prior events in the second part of the model. 3. Who have no prior events in the second part of the model. 4. combination of the second part of the model. 3. Who have not prior events in the second part of the model. 4. combination part of the model. 2. Myocardial infarction	CV event who have not had a	Canagliflozin + metformin	£24,485	9.696	£6,920	0.226	£30,664				
	prior event 3. who have had a	Lixisenatide + metformin	£26,543	9.179	£8,977	-0.291	Dominated				
	prior CV event 4. combination of numbers 2 and 3	Semaglutide (injection) + metformin Dulaglutide +	£30,130	9.943	£12,565	0.473	£26,552				
3. Heart failure (HF)	(MI) above			9.631	£12,589	0.161	£78,166				

4. Stroke

5. Amputation

6. Ulceration

7. Severe vision loss

8. Renal complications

Perspective: UK NHS

Time horizon: lifetime/ 40

years

Treatment effect duration:(a)

Discounting: Costs: 3.5%;

Outcomes: 3.5%

These have been presented here – see table to right.

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

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

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

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

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

Currency & cost year:

2020/21 UK pounds(b)

Cost components incorporated:

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

Analysis of uncertainty:

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

Data sources

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

Comments

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

Overall applicability:(c) Directly applicable Overall quality:(d) Potentially serious limitations

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

- (a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.
- (b) Directly applicable / Partially applicable / Not applicable

Minor limitations / Potentially serious limitations / Very serious limitations

Appendix I Health economic model

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