National Institute for Health and Care Excellence

Draft for consultation

Type 2 diabetes in adults: management

[F4] Evidence reviews for subsequent pharmacological management of type 2 diabetes

NICE guideline GID-NG10336

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

August 2025

Draft for Consultation

This evidence review was developed by NICE



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ISBN:

Contents

Appendices		. 5
Appendix G	Forest plots – Model 2: Type 2 diabetes and cardiovascular disease	. 5
Appendix H	GRADE tables – Model 2: Type 2 diabetes and cardiovascular	
	disease	12

Appendices

2	Appendix G	Forest plots - Model 2: Type 2 diabetes an	d
3	cardiovascul	ar disease	

4 G.1 DPP-4 inhibitors

4	3.1 D 1	
5	G.1.1	Adding alogliptin compared to adding placebo
6	There are n	o forest plots for this comparison (all outcomes in a single study)
7	G.1.2	Adding linagliptin compared to adding glimepiride
8	There are n	o forest plots for this comparison (all outcomes in a single study)
9	G.1.3	Adding saxagliptin compared to adding placebo
10	There are n	o forest plots for this comparison (all outcomes in a single study)
11	G.1.4	Adding sitagliptin compared to adding placebo
12	There are n	o forest plots for this comparison (all outcomes in a single study)
13	G.1.5	Adding sitagliptin compared to adding insulin
14	There are n	o forest plots for this comparison (all outcomes in a single study)
15		
16	G.2	GLP-1 receptor agonist
17	G.2.1	Adding dulaglutide compared to adding placebo
18	There are n	o forest plots for this comparison (all outcomes in a single study)
19	G.2.2	Adding exenatide compared to adding insulin
20	There are n	o forest plots for this comparison (all outcomes included in a single study)
21	G.2.3	Adding liraglutide compared to adding sitagliptin
22	There are n	o forest plots for this comparison (all outcomes included in a single study)

23 G.2.4 Adding liraglutide compared to adding insulin

24 There are no forest plots for this comparison (all outcomes included in a single study)

25 G.2.5 Adding exenatide compared to adding placebo

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

1 G.2.6 Adding lixisenatide compared to adding placebo

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

4 G.3 Dual GIP/GLP-1 receptor co-agonists

5 G.3.1 Adding tirzepatide compared to adding insulin

6 There are no forest plots for this comparison (all outcomes included in a single study)

7 G.4 SGLT2 inhibitors

8 G.4.1 Adding canagliflozin compared to adding placebo

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

10 G.4.2 Adding dapagliflozin compared to adding placebo

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

	Dapagli	lozin	Place	Placebo		Placebo Risk Ratio		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	CI M-H, Fixed, 95% CI		
Cefalu 2015	7	460	2	462	0.6%	3.52 [0.73, 16.83]	<u> </u>		
Leiter 2014	5	482	4	483	1.2%	1.25 [0.34, 4.64]	<u></u>		
Wiviott 2019	299	3474	327	3500	98.2%	0.92 [0.79, 1.07]	1 -		
Total (95% CI)		4416		4445	100.0%	0.94 [0.81, 1.09]	•		
Total events	311		333						
Heterogeneity: Chi ² =	2.98, df = 2	P = 0.2	23); I ² = 3	3%					
Test for overall effect: Z = 0.81 (P = 0.42)							0.01 0.1 1 10 100 Favours Dapagliflozin Favours Placebo		

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Figure 2: Cardiovascular mortality at end of follow-up

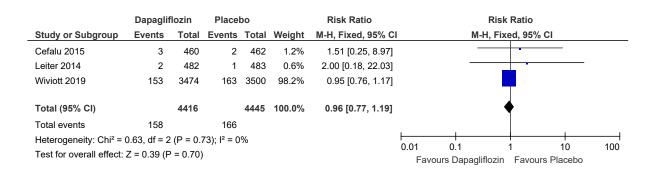


Figure 3: Non-fatal myocardial infarction at end of follow-up

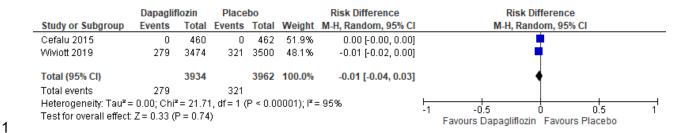


Figure 4: Hospitalisation for heart failure at end of follow-up

	Dapaglif	lozin	Placel	bo		Risk Ratio		Ris	k Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	l	M-H, Fix	ked, 95% CI		
Cefalu 2015	3	460	1	462	0.5%	3.01 [0.31, 28.86]					
Wiviott 2019	151	3474	192	3500	99.5%	0.79 [0.64, 0.98]					
Total (95% CI)		3934		3962	100.0%	0.80 [0.65, 0.99]		•			
Total events	154		193								
Heterogeneity: Chi ² =	1.33, df = 1	(P = 0.2	25); I² = 2	5%			0.04		+	+	400
Test for overall effect:	P = 0.04)					0.01 Favo	0.1 ours Dapagliflozin	Favours Pl	10 acebo	100	

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Figure 5: Persistent signs of worsening kidney disease at end of follow-up

	Dapaglif	lozin	Place	bo		Risk Ratio			Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	<u> </u>	M-H	I, Fixed, 95%	CI	
Cefalu 2015	21	460	11	462	68.7%	1.92 [0.94, 3.93]					
Leiter 2014	16	482	5	483	31.3%	3.21 [1.18, 8.68]			-		
Total (95% CI)		942		945	100.0%	2.32 [1.30, 4.14]			•		
Total events	37		16								
Heterogeneity: Chi ² =	0.68, df = 1	(P = 0.	41); I ² = 0	1%			0.01	0.1		10	100
Test for overall effect:	Z = 2.85 (F	P = 0.004	4)				0.01 Fav	0.1 ours Dapaglif	ı lozin Favour	10 s Placebo	100

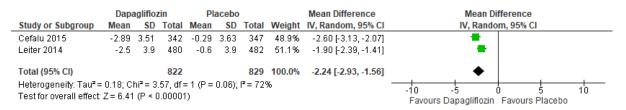
Figure 6: Hypoglycaemia episodes at end of follow-up

	Dapaglif	lozin	Placel	bo		Risk Ratio			Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		М-Н	, Fixed, 95%	6 CI	
Cefalu 2015	116	460	121	462	47.0%	0.96 [0.77, 1.20]			•		
Leiter 2014	122	483	136	482	53.0%	0.90 [0.73, 1.10]			-		
Total (95% CI)		943		944	100.0%	0.93 [0.80, 1.08]			•		
Total events	238		257								
Heterogeneity: Chi ² = 0	0.22, df = 1	(P = 0.0)	64); I ² = 0	%			0.01	0.1	1	10	100
Test for overall effect:	Z = 0.98 (F	9 = 0.33))					o. i ours Dapaglifle	ı ozin Favol		100

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

	Dapa	agliflo	zin	PI	acebo			Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
Cefalu 2015	-0.44	0.72	243	0.22	0.66	151	50.2%	-0.66 [-0.80, -0.52]		
Leiter 2014	-0.5	0.88	301	0	0.72	202	49.8%	-0.50 [-0.64, -0.36]	•	
Total (95% CI)			544			353	100.0%	-0.58 [-0.74, -0.42]	•	
Heterogeneity: Tau² : Test for overall effect				,	0.11);	I²= 60°	%		-10 -5 0 5 Favours Dapagliflozin Favours Placebo	10

Figure 8: Weight change (kg, lower values are better, change scores) at end of followup



G.4.3 Adding dapagliflozin compared to adding vildagliptin

4 There are no forest plots for this comparison (all outcomes included in a single study)

5 G.4.4 Adding empagliflozin compared to adding sitagliptin

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

G.4.5 Adding empagliflozin compared to adding placebo

Figure 9: All-cause mortality at end of follow-up

•	Empagli	flozin	Place	ebo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Gohari 2022	0	47	0	46	1.4%	0.00 [-0.04, 0.04]	+
Verma 2019	0	49	0	48	1.5%	0.00 [-0.04, 0.04]	
Zinman 2015	269	4687	194	2333	97.0%	-0.03 [-0.04, -0.01]	—
Total (95% CI)		4783		2427	100.0%	-0.02 [-0.04, -0.01]	•
Total events	269		194				
Heterogeneity: Chi2=	2.98, df=	2(P = 0)	$.22); I^2 =$	33%			1 15
Test for overall effect	Z = 3.87 (P = 0.00	01)				-1 -0.5 0 0.5 1 Favours Empagliflozin Favours Placebo

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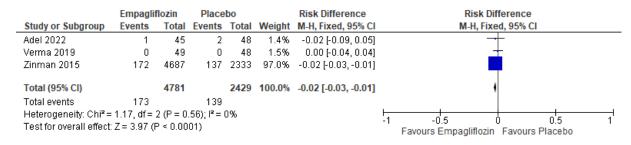
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1 Figure 10: Cardiovascular mortality at end of follow



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Figure 11: Non-fatal stroke at end of follow-up

	Empagli	flozin	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Verma 2019	0	49	0	48	1.5%	0.00 [-0.04, 0.04]	1 ±
Zinman 2015	150	4687	60	2333	98.5%	0.01 [-0.00, 0.01]	
Total (95% CI)		4736		2381	100.0%	0.01 [-0.00, 0.01]	1
Total events	150		60				Y 1000
Heterogeneity: Chi2=	0.10, df=	1 (P = 0)	.76); 2=	0%			1 05
Test for overall effect	Z = 1.50 (P = 0.13)				-1 -0.5 0 0.5 Favours Empagliflozin Favours Placebo

5

4

Figure 12: Non-fatal myocardial infarction at end of follow-up

•	Empagli	flozin	Place	bo		Risk Difference		F	Risk Difference	e	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M	-H, Fixed, 95%	CI	
Verma 2019	0	49	0	48	1.5%	0.00 [-0.04, 0.04]			+		
Zinman 2015	213	4687	121	2333	98.5%	-0.01 [-0.02, 0.00]					
Total (95% CI)		4736		2381	100.0%	-0.01 [-0.02, 0.00]					
Total events	213		121								
Heterogeneity: Chi2=	0.10, df=	1 (P = 0)	$.75$); $I^2 =$	0%			1	15	_ 	0.5	- 1
Test for overall effect	Z = 1.16 (P = 0.24)				F;	-0.5 avours Empag	liflozin Favou		

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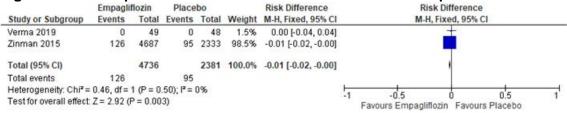
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Figure 13: Unstable angina at end of follow-up

_	Empagli	flozin	Place	bo		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	d, 95% CI	
Adel 2022	2	45	4	48	4.2%	0.53 [0.10, 2.77]		-		
Zinman 2015	133	4687	66	2333	95.8%	1.00 [0.75, 1.34]				
Total (95% CI)		4732		2381	100.0%	0.98 [0.74, 1.31]		•		
Total events	135		70						-	
Heterogeneity: Chi2=	0.55, df=	1 (P = 0)	.46); 2 = 1	0%			+	014	10	100
Test for overall effect	Z = 0.12 (P = 0.91)				0.01 Favour	s Empagliflozin	I 10 Favours Placebo	100

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Figure 14: Hospitalisation for heart failure at end of follow-up



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Figure 15: Persistent signs of worsening kidney disease at end of follow-up

	Empagli	flozin	Place	bo		Risk Ratio	Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fix	ed, 95% CI	
Verma 2019	1	49	0	48	0.1%	2.94 [0.12, 70.43]	-		_
Zinman 2015	459	4170	330	2102	99.9%	0.70 [0.61, 0.80]			
Total (95% CI)		4219		2150	100.0%	0.70 [0.62, 0.80]	•		
Total events	460		330						
Heterogeneity: Chi ² =	0.78, df=	1 (P = 0	.38); 2=	0%			501 01	1 10	100
Test for overall effect	Z = 5.25 (P < 0.00	001)				0.01 0.1 Favours Empagliflozin	Favours Placebo	100

3

Figure 16: Diabetic ketoacidosis at end of follow-up

	Empagliflozin Placebo					Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Verma 2019	0	49	0	48	1.5%	0.00 [-0.04, 0.04]	<u>+</u>
Zinman 2015	4	4687	1	2333	98.5%	0.00 [-0.00, 0.00]	
Total (95% CI)		4736		2381	100.0%	0.00 [-0.00, 0.00]	
Total events	4		1				20 00 00 00
Heterogeneity: Chi2=	0.00, df =	1 (P = 0	.98); 12=	0%			1 05 0 05 1
Test for overall effect	Z = 0.62 (P = 0.53)				-1 -0.5 0 0.5 1 Favours Empaoliflozin Favours Placebo

6

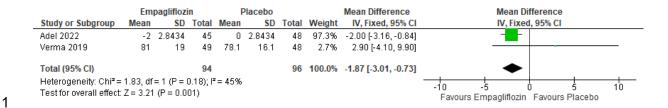
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Figure 17: HbA1c change (%, lower values are better, change scores and final values) at end of follow-up

	Empagliflozin			F	Placebo	-		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Adel 2022	7.1	3.4217	45	7.6	3.4217	48	9.3%	-0.50 [-1.89, 0.89]	-+-
Gohari 2022	-0.58	0.4153	43	0.07	0.4153	39	31.7%	-0.65 [-0.83, -0.47]	•
Verma 2019	-0.4	1	49	-0.3	0.9	48	27.9%	-0.10 [-0.48, 0.28]	+
Zinman 2015			4687	4687 -0.36 3.82 2			31.1%	0.12 [-0.10, 0.34]	†
Total (95% CI)			4824			2468	100.0%	-0.24 [-0.75, 0.26]	•
Heterogeneity: Tau ² =	eterogeneity: Tau² = 0.20; Chi² = 29.26, d				.00001);	$I^2 = 90^4$	%		-10 -5 0 5 10
Test for overall effect	est for overall effect: Z = 0.95 (P = 0.34)								Favours empagliflozin Favours placebo

8

Figure 18: Weight change (kg, lower values are better, change scores and final values) at end of follow-up



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G.4.6 Adding ertugliflozin compared to adding placebo

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

4 5

6 G.5 Sulfonylureas

7 G.5.1 Adding glimepiride compared to adding pioglitazone

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

9

10 G.6 Thiazolidinediones

11 G.6.1 Adding pioglitazone compared to adding placebo

Figure 19: All-cause mortality at end of follow-up

	Pioglita	zone	Place	ebo		Risk Ratio	Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixe	d, 95% CI	
Lee 2013B	0	60	1	61	0.8%	0.34 [0.01, 8.16]			
Wilcox 2008	177	2605	186	2633	99.2%	0.96 [0.79, 1.17]			
Total (95% CI)		2665		2694	100.0%	0.96 [0.78, 1.17]	•	•	
Total events	177		187						
Heterogeneity: Chi²=	0.41, df=	1 (P = 0)	0.52); l³ =	0%			0.01 0.1	10	100
Test for overall effect:	Z = 0.44 (P = 0.66	3)				Favours pioglitazone	Favours placebo	100

12

Figure 20: Non-fatal myocardial infarction at end of follow-up

	Pioglita	zone	Place	bo		Risk Ratio	Risk Ratio
Study or Subgro	oup Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Lee 2013B	2	60	1	61	0.7%	2.03 [0.19, 21.84]	
Wilcox 2008	119	2605	144	2633	99.3%	0.84 [0.66, 1.06]	<u> </u>
Total (95% CI)		2665		2694	100.0%	0.84 [0.67, 1.07]	◆
Total events	121		145				
Heterogeneity: C	hi² = 0.53, df =	1 (P = 0)	0.46); l ^z =	0%			0.01 0.1 1 10 100
Test for overall e	Heterogeneity: Chi² = 0.53, df = 1 (P = 0.46); l² = 04 Test for overall effect: Z = 1.42 (P = 0.16)						Favours pinglitazone Favours placebo

13

Appendix H GRADE

tables - Model 2: Type 2 diabetes and cardiovascular disease

H.1 DPP-4 inhibitors

H.1.1 Adding alogliptin compared to adding placebo

Table 1: clinical evidence profile: Adding alogliptin compared to adding placebo

Table 1. Chilical evidence profile. Adding a	. - 9 r	J 00	.pa.oa t	o aaaiii	g place						
No of studies	De sig n	Risk of bias	Indir ectne ss	Incons istenc y	Impre cision	Other considera tions	Interv ention N	Con trol N	Relative effect (95% CI)	Absolute effect	Cert aint y
all-cause mortality at end of follow-up – 18.0 months											
1 (white 2013) all-cause mortality at end of follow-up – 18.0 months	RC T	very seriou s ¹	not serio us	NA ²	seriou s³	NA	153/27 01	173/ 267 9	RR 0.88 (0.71, 1.08)	8 fewer per 1000 (19 fewer to 5 more)	very low
1 (white 2013) cardiovascular mortality at end of follow-up – 18.0 months	RC T	very seriou s ¹	not serio us	NA ²	seriou s³	NA	2701	267 9	HR 0.88 (0.71, 1.09)	Not estimable	very low

OTTABL tables Woder 2. Type 2 diabetes and care	alo vac	Joulal alo	0400								
1 (white 2013) cardiovascular mortality at end of follow-up	RC T	very seriou s ¹	not serio us	NA ²	seriou s³	NA	112/27 01	130/ 267 9	RR 0.85 (0.67, 1.09)	7 fewer per 1000 (16 fewer to 5 more)	very low
- 18.0 months 1 (white 2013)	RC T	very seriou s ¹	not serio us	NA ²	seriou s ³	NA	2701	267 9	HR 0.85 (0.66, 1.10)	Not estimable	very
4-point mace at end of follow-up – 18.0 months											
1 (white 2013) non-fatal stroke at end of follow-up – 18.0	RC T	very seriou s ¹	not serio us	NA ²	not seriou s	NA	344/27 01	359/ 267 9	RR 0.95 (0.83, 1.09)	7 fewer per 1000 (23 fewer to 12 more)	low
months 1 (white 2013)	RC T	very seriou s ¹	not serio us	NA ²	very seriou s ⁴	NA	29/270	32/2 679	RR 0.90 (0.55, 1.48)	1 fewer per 1000 (5 fewer to 6 more)	very
non-fatal stroke at end of follow-up – 18.0 months											
1 (white 2013)	RC T	very seriou s ¹	not serio us	NA ²	very seriou s ⁴	NA	2701	267 9	HR 0.91 (0.55, 1.51)	Not estimable	very low

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non-fatal myocardial infarction at end of follow-up – 18.0 months											
1 (white 2013) non-fatal myocardial infarction at end of follow-up – 18.0 months	RC T	very seriou s ¹	not serio us	NA ²	seriou s³	NA	187/27 01	173/ 267 9	RR 1.07 (0.88, 1.31)	5 more per 1000 (8 fewer to 20 more)	very low
1 (white 2013) unstable angina at end of follow-up – 18.0	RC T	very seriou s ¹	not serio us	NA ²	seriou s ³	NA	2701	267 9	HR 1.08 (0.88, 1.33)	Not estimable	very low
1 (white 2013)	RC T	very seriou s ¹	serio us ⁵	NA ²	very seriou s ⁴	NA	43/270	47/2 679	RR 0.91 (0.60, 1.37)	2 fewer per 1000 (7 fewer to 6 more)	very low
hospitalisation for heart failure at end of follow-up – 18.0 months											
1 (white 2013)	RC T	very seriou s ¹	not serio us	NA ²	seriou s³	NA	106/27 01	89/2 679	RR 1.18 (0.90, 1.56)	6 more per 1000 (3 fewer to 19 more)	very low
hospitalisation for heart failure at end of follow-up – 18.0 months											

OTTABL tables Woder 2. Type 2 diabetes and can	alo vac	Journal Glo	0000			1					
1 (white 2013)	RC T	very seriou s ¹	not serio us	NA ²	seriou s³	NA	2701	267 9	HR 1.19 (0.90, 1.57)	Not estimable	very low
development of end stage kidney disease at end of follow-up – 18.0 months											
		very	not		very				PETO OR 1.08	1 more per 1000	
1 (white 2013)	RC T	seriou s ¹	serio us	NA ²	seriou s ⁴	NA	24/270	22/2 679	(0.61, 1.93)	(4 fewer to 6 more)	very low
hypoglycaemia episodes at end of follow-up – 18.0 months										Í	
1 (white 2013)	RC T	very seriou s ¹	not serio us	NA ²	seriou s³	NA	181/27 01	173/ 267 9	RR 1.04 (0.85, 1.27)	2 more per 1000 (10 fewer to 17 more)	very low
severe hypoglycaemic episodes at end of follow-up – 18.0 months											
·		very	not		very				PETO OR 1.12	1 more per 1000	
1 (white 2013)	RC T	seriou s¹	serio	NA ²	seriou s ⁴	NA	18/270	16/2 679	(0.57, 2.19)	(4 fewer to 5 more)	very low
hba1c change (%, lower values are better, mean difference) at end of follow-up – 18.0 months	•				Ü		·	5.0			1044
	RC	very seriou	not serio		not seriou			267	MD -0.36 (-0.43, -	MD 0.36	
1 (white 2013)	Т	s ¹	us	NA ²	s	NA	2701	9	0.29)	lower	low

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GRADE tables - Model 2: Type 2 diabetes and cardiovascular disease

										(0.43 lower to 0.29 lower)	
weight change (kg, lower values are better, mean difference) at end of follow-up – 18.0 months											
1 (white 2013)	RC T	very seriou s ¹	not serio us	NA ²	not seriou	NA	2701	267 9	MD 0.06 (-0.25, 0.37)	MD 0.06 higher (0.25 lower to 0.37 higher)	low

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

H.1.2 Adding saxagliptin compared to adding placebo

Table 2: clinical evidence profile: Adding saxagliptin compared to adding placebo

						Other					
	Des	Risk of	Indirec	Inconsis	Imprec	consideratio	Interven	Contr	Relative effect	Absolute	Certa
No of studies	ign	bias	tness	tency	ision	ns	tion N	ol N	(95% CI)	effect	inty

3-point mace at end of follow-up – 25.2 months											
1 (scirica 2013) 3-point mace at end of follow-up – 25.2 months	RC T	very serious ¹	not serious	NA ²	not serious	NA	546/6494	550/6 465	RR 0.99 (0.88, 1.11)	1 fewer per 1000 (10 fewer to 9 more)	low
1 (scirica 2013)	RC T	very serious ¹	not serious	NA ²	not serious	NA	6494	6465	HR 0.97 (0.86, 1.09)	Not estimable	low

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

H.1.3 Adding sitagliptin compared to adding placebo

Table 2: clinical evidence profile: Adding sitagliptin compared to adding placebo

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
all-cause mortality at end of follow-up											
1 (green 2015)	RC T	not seriou s	not seriou s	NA ¹	not seriou s	NA	547/73 32	537/ 7339	RR 1.02 (0.91, 1.14)	1 more per 1000 (7 fewer to 10 more)	high
all-cause mortality at end of follow-up											

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1 (green 2015)	RC T	not seriou s	not seriou s	NA ¹	not seriou s	NA	7332	7339	HR 1.01 (0.90, 1.13)	Not estimable	high
cardiovascular mortality at end of follow-up											
1 (green 2015)	RC T	not seriou s	not seriou s	NA ¹	not seriou s	NA	380/73 32	366/ 7339	RR 1.04 (0.90, 1.20)	2 more per 1000 (5 fewer to 10 more)	high
cardiovascular mortality at end of follow-up											
1 (green 2015)	RC T	not seriou s	not seriou s	NA ¹	not seriou s	NA	7332	7339	HR 1.03 (0.89, 1.19)	Not estimable	high
4-point mace at end of follow-up											
1 (green 2015)	RC T	not seriou s	not seriou s	NA ¹	not seriou s	NA	839/73 32	851/ 7339	RR 0.99 (0.90, 1.08)	2 fewer per 1000 (11 fewer to 9 more)	high
4-point mace at end of follow-up											
1 (green 2015)	RC T	not seriou s	not seriou s	NA ¹	not seriou s	NA	7332	7339	HR 0.98 (0.89, 1.08)	Not estimable	high
non-fatal myocardial infarction at end of follow-up											

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1 (green 2015) unstable angina at end of follow-up	RC T	not seriou s	not seriou s	NA ¹	not seriou s	NA	289/73 32	302/ 7339	RR 0.96 (0.82, 1.12)	2 fewer per 1000 (7 fewer to 5 more)	high
1 (green 2015) unstable angina at end of follow-up	RC T	not seriou s	not seriou s	NA ¹	seriou s ²	NA	116/73 32	129/ 7339	RR 0.90 (0.70, 1.15)	2 fewer per 1000 (5 fewer to 3 more)	mod erat e
1 (green 2015) hospitalisation for heart failure at end of follow-up	RC T	not seriou s	not seriou s	NA ¹	seriou s²	NA	7332	7339	HR 0.90 (0.70, 1.16)	Not estimable	mod erat e
1 (green 2015) hospitalisation for heart failure at end of	RC T	not seriou s	not seriou s	NA ¹	not seriou s	NA	228/73 32	229/ 7339	RR 1.00 (0.83, 1.19)	0 fewer per 1000 (5 fewer to 6 more)	high
follow-up 1 (green 2015) persistent signs of worsening kidney disease at end of follow-up	RC T	not seriou s	not seriou s	NA ¹	not seriou s	NA	7332	7339	HR 1.00 (0.83, 1.20)	Not estimable	high

GRADE lables – Wodel 2. Type 2 diabetes and	a oarai	Ovasoaiai	alocasc	1		1				1	
1 (green 2015)	RC T	not seriou s	not seriou s	NA ¹	not seriou s	NA	552/73 32	553/ 7339	RR 1.00 (0.89, 1.12)	0 fewer per 1000 (8 fewer to 9 more)	high
development of end stage kidney disease at end of follow-up											
1 (green 2015)	RC T	not seriou s	not seriou s	NA ¹	seriou s²	NA	100/73 32	111/ 7339	RR 0.90 (0.69, 1.18)	1 fewer per 1000 (5 fewer to 3 more)	mod erat e
severe hypoglycaemic episodes at end of follow-up											
1 (green 2015)	RC T	not seriou s	not seriou s	NA ¹	seriou s²	NA	160/73 32	143/ 7339	RR 1.12 (0.90, 1.40)	2 more per 1000 (2 fewer to 8 more)	mod erat e
severe hypoglycaemic episodes at end of follow-up											
1 (green 2015)	RC T	not seriou s	not seriou s	NA ¹	seriou s ²	NA	7332	7339	HR 1.12 (0.89, 1.41)	Not estimable	mod erat e
hba1c change (%, lower value is better, mean difference) at end of follow-up											
1 (green 2015)	RC T	very seriou s ³	not seriou s	NA ¹	not seriou s	NA	1434	1386	MD -0.32 (-0.35, - 0.29)	MD 0.32 lower (0.35 lower to 0.29 lower)	low

1. Only one study so no inconsistency

- 2. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 3. >33.3% of the studies in the meta-analysis were at high risk of bias

H.1.4 Adding linagliptin compared to adding glimepiride

Table 3: clinical evidence profile: - Adding linagliptin compared to adding glimepiride

No of studies	Des ign	Risk of bias	Indirec tness	Inconsis tency	Imprec ision	Other consideratio ns	Interven tion N	Contr ol N	Relative effect (95% CI)	Absolute effect	Certa inty
3-point mace at end of											
follow-up – 75.6 months											
1 (rosenstock 2019b)	RC T	not serious	not serious	NA ¹	serious 2	NA	190/1051	199/1 038	RR 0.94 (0.79, 1.13)	11 fewer per 1000 (41 fewer to 25 more)	mode rate
3-point mace at end of follow-up – 75.6 months											
1 (rosenstock 2019b)	RC T	not serious	not serious	NA ¹	serious	NA	1962	1963	HR 0.94 (0.77, 1.15)	Not estimable	mode rate

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

compared to adding insulin

Table 4: clinical evidence profile: Adding sitagliptin compared to adding insulin

Table 4. cimical evidence prome. Adams	De sig	Risk of	Indir ectne	Incon sisten	Impr	Other considera	Interv ention	Con trol	Relative effect		Cert aint
No of studies	n	bias	SS	су	n	tions	N	N	(95% CI)	Absolute effect	У
hospitalisation for heart failure at the end of follow-up – 12 months											
1 (arturi 2017)	RC T	very serio us ¹	not serio us	NA ²	very serio us ³	NA	0/10	0/12	RD 0.00 (- 0.16, 0.16)	0 fewer per 1000 (161 fewer to 161 more)	very low
severe hypoglycaemic episodes at the end of follow-up – 12 months											
1 (arturi 2017)	RC T	very serio us ¹	not serio us	NA ²	very serio us ³	NA	0/10	0/12	RD 0.00 (- 0.16, 0.16)	0 fewer per 1000 (161 fewer to 161 more)	very low
hba1c change (%, lower values are better, final values) at the end of follow-up – 12 months											
1 (arturi 2017)	RC T	very serio us ¹	not serio us	NA ²	serio us ⁴	NA	10	12	MD 1.30 (0.11, 2.49)	MD 1.30 higher (0.11 higher to 2.49 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. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.

end of the defined MIDs (-0.50, 0.50)

H.2 GLP-1 receptor agonist

H.2.1 Adding dulaglutide compared to adding placebo

Table 3: clinical evidence profile: Adding dulaglutide compared to adding placebo

No of studies	Des ign	Risk of bias	Indirec tness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert ainty
3-point mace at the end of follow-up – 64.8 months											
1 (gerstein 2019a)	RC T	seriou s ¹	not seriou s	NA ²	seriou s³	NA	280/156 0	315/ 1554	RR 0.89 (0.77, 1.02)	23 fewer per 1000 (47 fewer to 5 more)	low
3-point mace at end of follow-up – 64.8 months											
1 (gerstein 2019a)	RC T	seriou s ¹	not seriou s	NA ²	seriou s³	NA	1560	1554	HR 0.87 (0.74, 1.02)	Not estimable	low

^{1. &}gt;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)

compared to adding insulin

Table 4: clinical evidence profile: Adding exenatide compared to adding insulin

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
all-cause mortality at end of follow-up											
1 (chen 2017)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	1/14	0/12	PETO OR 6.41 (0.13, 326.59)	72 more per 1000 (63 fewer to 206 more)	very
hba1c change (%, lower values are better, final values) at end of follow-up									,	,	
1 (chen 2017)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ⁴	NA	11	12	MD 0.30 (-0.89, 1.49)	MD 0.30 higher (0.89 lower to 1.49 higher)	very low
bmi change (kg/m2, lower values are better, final values) at end of follow-up											
1 (chen 2017)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s ⁵	NA	11	12	MD -2.40 (-5.14, 0.34)	MD 2.40 lower (5.14 lower to 0.34 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

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 one end of the defined MIDs (-0.80, 0.80)

H.2.3 Adding exenatide compared to adding placebo

Table 5: clinical evidence profile: -Adding exenatide compared to adding placebo

No of studies	Des ign	Risk of bias	Indirec tness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert ainty
3-point mace at the end of follow-up – 38.4 months											
1 (holman 2017)	RC T	not seriou s	not seriou s	NA ¹	not seriou s	NA	722/539 4	786/ 5388	RR 0.92 (0.84, 1.01)	12 fewer per 1000 (24 fewer to 1 more)	high
3-point mace at end of follow-up – 38.4 months											
1 (holman 2017)	RC T	not seriou s	not seriou s	NA ¹	not seriou s	NA	5394	5388	HR 0.90 (0.82, 0.99)	Not estimable	high

^{1.} Only one study so no inconsistency

H.2.4 Adding liraglutide compared to adding sitagliptin

Adding liraglutide compared to adding sitagliptin

No of studies	De sig n	Risk of bias	Indir ectne ss	Incon sisten cy	Impre cision	Other considera tions	Interv ention N	Con trol N	Relative effect (95% CI)	Absolute effect	Cert aint y
hospitalisation for heart failure at the end of follow-up – 12 months											
1 (arturi 2017)	RC T	very seriou s ¹	not serio us	NA ²	very seriou s ³	NA	0/10	0/10	RD 0.00 (- 0.17, 0.17)	0 fewer per 1000 (174 fewer to 174 more)	very low
severe hypoglycaemic episodes at the end of follow-up – 12 months											
1 (arturi 2017)	RC T	very seriou s ¹	not serio us	NA ²	very seriou s ³	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 values) at the end of follow-up – 12 months											
1 (arturi 2017)	RC T	very seriou s ¹	not serio us	NA ²	seriou s ⁴	NA	10	10	MD -1.10 (-1.98, - 0.22)	MD 1.10 lower (1.98 lower to 0.22 lower)	very low

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

compared to adding insulin

Table 7: Clinical evidence profile: Adding liraglutide compared to adding insulin

No of studies	De sig n	Risk of bias	Indire ctnes s	Incons istenc y	Impre cision	Other considerat ions	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
hospitalisation for heart failure at the end of follow-up – 12 months											
1 (arturi 2017)	RC T	very seriou s ¹	not seriou	NA ²	very seriou s ³	NA	0/10	0/12	RD 0.00 (-0.16, 0.16)	0 fewer per 1000 (161 fewer to 161 more)	very
severe hypoglycaemic episodes at the end of follow-up – 12 months		3	3		3	INA	0/10	0/12	0.10)	TOT More)	IOW
1 (arturi 2017)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	0/10	0/12	RD 0.00 (-0.16, 0.16)	0 fewer per 1000 (161 fewer to 161 more)	very low
hba1c change (%, lower values are better, final values) at the end of follow-up – 12 months											
1 (arturi 2017)	RC T	very seriou s ¹	not seriou	NA ²	very seriou s ⁴	NA	10	12	MD 0.20 (-0.99, 1.39)	MD 0.20 higher (0.99 lower to 1.39 higher)	very low

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 (-0.50, 0.50)

H.2.6 Adding lixisenatide compared to adding placebo

Table 8: Clinical evidence profile: Adding lixisenatide compared to adding placebo

No of studies	De sig n	Risk of bias	Indir ectne ss	Incons istenc y	Impre cision	Other considera tions	Interv ention N	Con trol N	Relative effect (95% CI)	Absolute effect	Certainty
all-cause mortality at end of follow-up - 25 months											
1 (pfeffer 2015) all-cause mortality at end of follow-up -	RC T	not serio us	not serio us	NA ¹	seriou s ²	NA	211/30 34	223/ 303 4	RR 0.95 (0.79, 1.13)	4 fewer per 1000 (15 fewer to 10 more)	moderate
25 months 1 (pfeffer 2015)	RC T	not serio us	not serio us	NA ¹	seriou s ²	NA	3034	303 4	HR 0.94 (0.78, 1.13)	Not estimable	moderate
cardiovascular mortality at end of follow-up - 25 months											

1 (pfeffer 2015) cardiovascular mortality at end of follow-up - 25 months	RC T	not serio us	not serio us	NA ¹	seriou s ²	NA	156/30 34	158/ 303 4	RR 0.99 (0.80, 1.22)	1 fewer per 1000 (11 fewer to 12 more)	moderate
1 (pfeffer 2015) 5-point mace at end of follow-up - 25 months	RC T	not serio us	not serio us	NA ¹	seriou s ²	NA	3034	303 4	HR 0.98 (0.78, 1.22)	Not estimable	moderate
1 (pfeffer 2015) 5-point mace at end of follow-up - 25	RC T	not serio us	not serio us	NA ¹	not seriou s	NA	456/30 34	469/ 303 4	RR 0.97 (0.86, 1.09)	4 fewer per 1000 (21 fewer to 15 more)	high
1 (pfeffer 2015) unstable angina at end of follow-up - 25	RC T	not serio us	not serio us	NA ¹	not seriou s	NA	3034	303 4	HR 0.97 (0.85, 1.10)	Not estimable	high
1 (pfeffer 2015) unstable angina at end of follow-up - 25 months	RC T	not serio us	not serio us	NA ¹	very seriou s ³	NA	11/303	10/3 034	PETO OR 1.10 (0.47, 2.59)	0 more per 1000 (3 fewer to 3 more)	low

Woder Z. Type 2 diabetes at	RC	not serio	not serio		very seriou			303	HR 1.11		
1 (pfeffer 2015)	Т	us	us	NA ¹	s ³	NA	3034	4	(0.47, 2.62)	Not estimable	low
hospitalisation for heart failure at end of follow-up - 25 months											
1 (pfeffer 2015)	RC T	not serio us	not serio us	NA ¹	seriou s ²	NA	122/30 34	127/ 303 4	RR 0.96 (0.75, 1.23)	2 fewer per 1000 (10 fewer to 9 more)	moderate
hospitalisation for heart failure at end of follow-up - 25 months											
1 (pfeffer 2015)	RC T	not serio us	not serio us	NA ¹	seriou s²	NA	3034	303 4	HR 0.96 (0.75, 1.23)	Not estimable	moderate
hypoglycaemia episodes at end of follow-up - 25 months											
1 (pfeffer 2015)	RC T	not serio us	not serio us	NA ¹	not seriou s	NA	504/30 34	462/ 303 4	RR 1.09 (0.97, 1.22)	14 more per 1000 (4 fewer to 34 more)	high
severe hypoglycaemic episodes at end of follow-up- 25 months											
1 (pfeffer 2015)	RC T	not serio us	not serio us	NA ¹	seriou s²	NA	14/303 4	24/3 034	PETO OR 0.59 (0.31, 1.11)	3 fewer per 1000 (7 fewer to 1 more)	moderate
hba1c change (%, lower values are better, change scores) at the end of follow-up - 25 months											

1 (pfeffer 2015)	RC T	not serio us	not serio us	NA¹	not seriou s	NA	3034	303	MD -0.27 (-0.31, -0.23)	MD 0.27 lower (0.31 lower to 0.23 lower)	high
weight change (kg, lower values are better, change scores) at the end of follow-up - 25 months											
1 (pfeffer 2015)	RC T	not serio us	not serio us	NA¹	not seriou s	NA	3034	303 4	MD -0.70 (-0.90, -0.50)	MD 0.70 lower (0.90 lower to 0.50 lower)	high

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

H.3 Dual GIP/GLP-1 receptor co-agonists

H.3.1 Adding tirzepatide compared to adding insulin

Table 9: Clinical evidence profile: Adding tirzepatide compared to adding insulin

No of studies	De sig n	Risk of bias	Indire ctnes s	Incons istenc y	Impre cision	Other considera tions	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
all-cause mortality at end of follow-up - 24 months											

1 (del prato 2021)	RC T	not serio us	not seriou s	NA ¹	seriou s ²	NA	25/991	35/1 000	RR 0.72 (0.43, 1.20)	10 fewer per 1000 (20 fewer to 7 more)	mod erat e
all-cause mortality at end of follow-up - 24 months											
1 (del prato 2021)	RC T	not serio us	not seriou	NA ¹	seriou s ²	NA	991	100	HR 0.70 (0.42, 1.17)	Not estimable	mod erat e
cardiovascular mortality at end of follow-up – 24 months		u.c					331		(0.12, 1.11)	THE COLUMN ASSESSMENT OF THE COLUMN ASSESSMENT	
1 (del prato 2021)	RC T	not serio us	not seriou s	NA ¹	very seriou s ³	NA	16/995	21/1 000	RR 0.77 (0.40, 1.46)	5 fewer per 1000 (13 fewer to 10 more)	low
4-point mace at end of follow-up - 24 months											
1 (del prato 2021)	RC T	not serio us	not seriou s	NA ¹	seriou s²	NA	47/995	62/1 000	RR 0.76 (0.53, 1.10)	15 fewer per 1000 (29 fewer to 6 more)	mod erat e
4-point mace at end of follow-up - 24 months											
1 (del prato 2021)	RC T	not serio us	not seriou s	NA ¹	seriou s²	NA	995	100 0	HR 0.74 (0.51, 1.07)	Not estimable	mod erat e
non-fatal stroke at end of follow-up - 24 months											

iou	NA ¹	very seriou s³ very seriou s³	NA NA	11/995	13/1 000 26/1 000	RR 0.85 (0.38, 1.89) RR 0.73 (0.41, 1.32)	2 fewer per 1000 (8 fewer to 12 more) 7 fewer per 1000 (15 fewer to 8 more)	low
iou		seriou s³ very seriou			26/1	(0.38, 1.89) RR 0.73	(8 fewer to 12 more) 7 fewer per 1000 (15 fewer to 8	
		very seriou			26/1	RR 0.73	7 fewer per 1000 (15 fewer to 8	
	NA ¹	seriou	NA	19/995			1000 (15 fewer to 8	low
	NA ¹	seriou	NA	19/995			1000 (15 fewer to 8	low
	NA ¹	seriou	NA	19/995			(15 fewer to 8	low
iou	NA ¹		NA	19/995		(0.41, 1.32)		low
		3		10/000	000	(0.11, 1.02)	merey	1011
						1		
							4 fewer per	
		very				RR 0.50	1000	
iou		seriou			8/10	KK 0.50	(7 fewer to 5	
	NA ¹	s ³	NA	4/995	00	(0.15, 1.66)	more)	low
							2 fewer per	
		very				RR 0.67		
iou	NA ¹		NA	4/995		(0.19.2.37)	,	low
	14/ (14/ (47000		(0.10, 2.01)	inore)	1000
		not		0.45/55	641/	RR 0.54	000 (
			NA		100	(0.49, 0.60)		high
i	iou	iou NA¹	NA1 seriou seriou sa serio	iou NA¹ seriou NA NA not seriou	iou NA¹ seriou NA 4/995 not seriou 346/99	iou NA1 seriou seriou NA 4/995 6/10 00 not seriou seriou 346/99 100	iou NA¹ seriou seriou solu NA¹ s³ NA 4/995 00 (0.19, 2.37) not seriou 346/99 641/ 100 RR 0.54	iou NA1 s3 NA 4/995 6/10 RR 0.67 (5 fewer to 8 more) not seriou seriou 346/99 641/ 100 RR 0.54 293 fewer per

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7.											
										(325 fewer to 258 fewer)	
severe hypoglycaemia episodes at end of follow-up - 24 months											
1 (del prato 2021)	RC T	not serio us	not seriou s	NA ¹	seriou s ²	NA	4/995	11/1 000	RR 0.37 (0.12, 1.14)	7 fewer per 1000 (10 fewer to 2 more)	mod erat e
hba1c change (%, lower values are better, change scores) at end of follow-up - 24 months											
1 (del prato 2021)	RC T	not serio us	not seriou s	NA ¹	not seriou s	NA	981	978	MD -0.98 (-1.06, - 0.90)	MD 0.98 lower (1.06 lower to 0.90 lower)	high
weight change (kg, change scores, lower values are better) at end of follow-up - 24 months											
1 (del prato 2021)	RC T	not serio us	not seriou s	NA¹	not seriou s	NA	981	978	MD -11.35 (-11.90, - 10.80)	MD 11.35 lower (11.90 lower to 10.80 lower)	high

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

H.4 SGLT2 inhibitors

H.4.1 Adding canagliflozin compared to adding placebo

Table 8: Clinical evidence profile: Adding canagliflozin compared to adding placebo

Table 8: Clinical evidence profile: A	uum	j carray	IIIIOZIII	Compare	u to auu	ing placebo					
No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Imprec ision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolut e effect	Certainty
all-cause mortality at end of follow- up - 43 months											
1 (mahaffey 2018)	RC T	not serio us	not seriou s	NA ¹	serious 2	NA	2900	3756	HR 0.90 (0.75, 1.07)	Not estimab le	moderate
cardiovascular mortality at the end of follow-up - 43 months											
1 (mahaffey 2018)	RC T	not serio us	not seriou s	NA ¹	serious 2	NA	2900	3756	HR 0.86 (0.70, 1.06)	Not estimab le	moderate
3-point mace at the end of follow-up - 43 months											
1 (mahaffey 2018)	RC T	not serio us	not seriou s	NA ¹	serious	NA	2900	3756	HR 0.83 (0.72, 0.95)	Not estimab le	moderate
non-fatal stroke at the end of - 43 months											
1 (mahaffey 2018)	RC T	not serio us	not seriou s	NA¹	serious	NA	2900	3756	HR 0.88 (0.67, 1.16)	Not estimab le	moderate

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Woder 2. Type 2 diabete	o arra	our dio va	o o a i a i a i a i a i a i a i a i a i								
non-fatal myocardial infarction at the end of follow-up - 43 months											
1 (mahaffey 2018)	RC T	not serio us	not seriou s	NA ¹	serious	NA	2900	3756	HR 0.79 (0.63, 0.99)	Not estimab le	moderate
hospitalisation for heart failure at the end of follow-up - 43 months											
1 (mahaffey 2018)	RC T	not serio us	not seriou s	NA ¹	serious	NA	2900	3756	HR 0.68 (0.51, 0.90)	Not estimab le	moderate
persistent signs of worsening kidney disease at the end of follow- up - 43 months											
1 (mahaffey 2018)	RC T	not serio us	not seriou s	NA ¹	serious 2	NA	2900	3756	HR 0.74 (0.67, 0.82)	Not estimab le	moderate
development of end stage kidney disease at the end of follow-up - 43 months											
1 (mahaffey 2018)	RC T	not serio us	not seriou s	NA ¹	very serious	NA	2900	3756	HR 0.69 (0.18, 2.64)	Not estimab le	low
diabetic ketoacidosis at the end of follow-up - 43 months											
1 (mahaffey 2018)	RC T	not serio us	not seriou s	NA ¹	very serious	NA	2900	3756	HR 4.62 (0.56, 38.04)	Not estimab	low

GRADE tables - Model 2: Type 2 diabetes and cardiovascular disease

hypoglycaemia episodes at the end of follow-up - 43 months											
1 (mahaffey 2018)	RC T	not serio us	not seriou s	NA ¹	serious	NA	2900	3756	HR 1.19 (0.94, 1.50)	Not estimab le	moderate

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

H.4.2 Adding dapagliflozin compared to adding placebo

Table 9: clinical evidence profile: Adding dapagliflozin compared to adding placebo

No of studies	De sig n	Risk of bias	Indire ctnes s	Incons istenc y	Impre cision	Other considerat ions	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
all-cause mortality at end of follow-up – 24.7 months											
3 all-cause mortality at end of follow-up – 50.4	RC T	seriou s ¹	not seriou s	not seriou s	not seriou s	NA	311/44 16	333/ 444 5	RR 0.94 (0.81, 1.09)	4 fewer per 1000 (14 fewer to 7 more)	mod erat e
months											

1 (wiviott 2019)	RC T	seriou s¹	not seriou s	NA ³	seriou s²	NA	3474	350 0	HR 0.92 (0.79, 1.07)	Not estimable	low
cardiovascular mortality at end of follow-up – 24.7 months											
3	RC T	seriou s ¹	not seriou s	not seriou s	seriou s²	NA	158/44 16	166/ 444 5	RR 0.96 (0.77, 1.19)	2 fewer per 1000 (8 fewer to 7 more)	low
cardiovascular mortality at end of follow-up – 50.4 months											
1 (wiviott 2019) 3-point mace at end of follow-up – 50.4 months	RC T	seriou s ¹	not seriou s	NA ³	seriou s ²	NA	3474	350 0	HR 0.94 (0.76, 1.16)	Not estimable	low
1 (wiviott 2019)	RC T	seriou s ¹	not seriou s	NA ³	not seriou s	NA	483/34 74	537/ 350 0	RR 0.91 (0.81, 1.02)	14 fewer per 1000 (29 fewer to 2 more)	mod erat e
3-point mace at end of follow-up – 50.4 months											
1 (wiviott 2019)	RC T	seriou s ¹	not seriou s	NA ³	seriou s²	NA	3474	350 0	HR 0.90 (0.79, 1.03)	Not estimable	low
non-fatal stroke at end of follow-up – 50.4 months											

Woder Z. Type Z diabetes and early											
										1 fewer per	
			not					142/	RR 0.97	1000	
	RC	seriou	seriou		seriou		137/34	350	100.97	(9 fewer to 9	
1 (wiviott 2019)	Т	s ¹	S	NA ³	s ²	NA	74	0	(0.77, 1.22)	more)	low
non-fatal stroke at end of follow-up – 50.4 months											
			not						HR 0.97		
1 (wiviott 2019)	RC T	seriou s ¹	seriou s	NA ³	seriou s ²	NA	3474	350 0	(0.76, 1.24)	Not estimable	low
non-fatal myocardial infarction at end of follow-up – 31.2 months											
									RD -0.01	10 fewer per 1000	
			not		very			321/			
2	RC T	seriou s ¹	seriou s	seriou s ⁴	seriou s ⁵	NA	279/39 34	396 2	(-0.02, 0.00)	(22 fewer to 2 more)	very low
	1	3	3	3	3	INA	34		0.00)	2 more)	IOW
non-fatal myocardial infarction at end of follow-up – 50.4 months											
			not _.					0.50	HR 0.87		
1 (wiviott 2019)	RC T	seriou s ¹	seriou s	NA ³	seriou s ²	NA	3474	350 0	(0.74, 1.02)	Not estimable	low
unstable angina at end of follow-up – 12 months											
										9 fewer per	
		Verv	not		very				PETO OR	1000	
	RC	very seriou	seriou		seriou			7/46	0.45	(22 fewer to	very
1 (cefalu 2015)	Т	s ⁶	s	NA ³	s ⁷	NA	3/460	2	(0.13, 1.56)	5 more)	low

hospitalisation for heart failure at end of follow-up – 31.2 months											
2	RC T	seriou s ¹	not seriou s	not seriou s	seriou s ²	NA	154/39 34	193/ 396 2	RR 0.80 (0.65, 0.99)	10 fewer per 1000 (17 fewer to 1 fewer)	low
hospitalisation for heart failure at end of follow-up – 50.4 months											
1 (wiviott 2019)	RC T	seriou s¹	not seriou s	NA ³	seriou s ²	NA	3474	350 0	HR 0.78 (0.63, 0.97)	Not estimable	low
acute kidney injury at end of follow-up – 12 months											
1 (cefalu 2015)	RC	very seriou s ⁶	not seriou	NA ³	very seriou s ⁷	NA	3/460	0/46	PETO OR 7.45 (0.77, 71.83)	7 more per 1000 (1 fewer to 14 more)	very
persistent signs of worsening kidney disease at end of follow-up - 12 months	ı	<u> </u>	S	INA	5'	INA	3/400	2	71.03)	14 more)	low
2	RC T	very seriou s ⁶	not seriou s	not seriou s	not seriou s	NA	37/942	16/9 45	RR 2.32 (1.30, 4.14)	22 more per 1000 (5 more to 53 more)	low
development of end stage kidney disease at end of follow-up – 12 months											

1 (cefalu 2015) cardiac arrhythmia at end of follow-up – 50.4	RC T	very seriou s ⁶	not seriou s	NA ³	very seriou s ⁷	NA	6/460	3/46 2	PETO OR 1.97 (0.53, 7.31)	7 more per 1000 (6 fewer to 19 more)	very low
months 1 (wiviott 2019)	RC T	seriou s ¹	not seriou s	NA ³	seriou s ²	NA	141/34 74	170/ 350 0	RR 0.84 (0.67, 1.04)	8 fewer per 1000 (16 fewer to 2 more)	low
cardiac arrhythmia at end of follow-up – 50.4 months											
1 (wiviott 2019) progression of liver disease at end of follow-	RC T	seriou s ¹	not seriou s	NA ³	seriou s ²	NA	3474	350 0	HR 0.83 (0.66, 1.04)	Not estimable	low
up – 12 months 1 (cefalu 2015)	RC T	very seriou s ⁶	not seriou s	NA ³	very seriou s ⁷	NA	9/460	9/46	RR 1.00 (0.40, 2.51)	0 more per 1000 (12 fewer to 29 more)	very
hypoglycaemia episodes at end of follow-up – 12 months											
2	RC T	seriou s ¹	not seriou s	not seriou s	seriou s ²	NA	238/94	257/ 944	RR 0.93 (0.80, 1.08)	20 fewer per 1000 (55 fewer to 21 more)	low

severe hypoglycaemic episodes at end of follow-up – 12 months											
	RC	very seriou	not seriou		not seriou			0/46	RD 0.00 (-0.00,	0 fewer per 1000 (4 fewer to 4	
1 (cefalu 2015)	Т	s ⁶	S	NA ³	S	NA	0/460	2	0.00)	more)	low
hba1c change (%, lower values are better, change scores) at end of follow-up – 12 months											
2	RC T	very seriou s ⁶	not seriou s	seriou s ⁸	seriou s ⁹	NA	544	353	MD -0.58 (-0.74, - 0.42)	MD 0.58 lower (0.74 lower to 0.42 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow-up – 12 months											
2	RC T	not seriou s	not seriou s	seriou s ⁸	seriou s ¹⁰	NA	822	829	MD -2.24 (-2.93, - 1.56)	MD 2.24 lower (2.93 lower to 1.56 lower)	low

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 3. 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)

Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.67 (0.8-0.9 = serious, <0.8 = very serious).

- 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. I2 between 50% and 75%
- 9. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 10. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

H.4.3 Adding dapagliflozin compared to adding vildagliptin

Table 10: Clinical evidence profile: Adding dapagliflozin compared to adding vildagliptin

		Risk of		Inconsi	Impr ecisi	Other consider	Interv ention	Control	Relative effect	Absolute	
No of studies	Design	bias	Indirectness	stency	on	ations	N	N	(95% CI)	effect	Certainty
all-cause mortality at end of follow-up- 6 months											
1 (phrommintikul 2019)	RCT	not serio us	not serious	NA ¹	very serio us ²	NA	0/25	0/24	RD 0.00 (-0.08, 0.08)	0 fewer per 1000 (76 fewer to 76 more)	low
cardiovascular mortality at end of follow-up – 6 months											
		not serio			very serio				RD 0.00 (-0.08,	0 fewer per 1000 (76 fewer to	
1 (phrommintikul 2019)	RCT	us	not serious	NA ¹	us ²	NA	0/25	0/24	0.08)	76 more)	low

GRADE tables – Wodel Z. Type Z	diabetes	and oar	alovascalai alse	,430							
non-fatal stroke at end of follow-up – 6months											
4 (11 has respected that 1 0040)	DOT	not serio		NIA 1	very serio	NA	0/05	0/04	RD 0.00 (-0.08,	0 fewer per 1000 (76 fewer to	I
1 (phrommintikul 2019)	RCT	us	not serious	NA ¹	us ²	NA	0/25	0/24	0.08)	76 more)	low
non-fatal myocardial infarction at end of follow-up – 6 months											
		not serio			very serio				PETO OR 7.10 (0.14,	40 more per 1000 (37 fewer to	
1 (phrommintikul 2019)	RCT	us	not serious	NA ¹	us ³	NA	1/25	0/24	358.08)	117 more)	low
hospitalisation for heart failure – 6 months									,	,	
		not serio			very serio				RD 0.00 (-0.07,	0 fewer per 1000 (75 fewer to	
1 (phrommintikul 2019)	RCT	us	not serious	NA ¹	us ²	NA	0/25	0/25	0.07)	75 more)	low
hba1c change (%, lower values are better, change values) at end of follow-up – 6 months											
1 (phrommintikul 2019)	RCT	serio us 4	not serious	NA¹	very serio us ⁵	NA	21	22	MD 0.21 (-0.53, 0.95)	MD 0.21 higher (0.53 lower to 0.95 higher)	very low

weight change (kg, lower values are better, change scores) at end of follow-up – 6 months											
1 (phrommintikul 2019) bmi change (kg/m2, lower scores are better, change scores) at end of follow-up – 6 months	RCT	serio us ⁴	not serious	NA ¹	serio us ⁶	NA	21	22	MD -2.99 (-4.16, - 1.82)	MD 2.99 lower (4.16 lower to 1.82 lower)	low
1 (phrommintikul 2019)	RCT	serio us ⁴	not serious	NA ¹	serio us ⁷	NA	21	22	MD -1.20 (-1.68, - 0.72)	MD 1.20 lower (1.68 lower to 0.72 lower)	low

- 1. Only one study so no inconsistency
- 2. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 5. 95% confidence intervals cross both ends of the defined MIDs (-0.50, 0.50)
- 6. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)
- 7. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

compared to adding placebo

Table 10 Clinical evidence profile: Adding empagliflozin compared to adding placebo

No of studies all-cause mortality at end of follow-up Mean follow-up: 16.4 month(s)	De sig n	Risk of bias	Indire ctnes s	Incons istenc y	Impre cision	Other considera tions	Interv ention N	Con trol N	Relative effect (95% CI)	Absolute effect	Cert aint y
all-cause mortality at end of follow-up	RC T	not seriou s	not seriou s	seriou s ¹	not seriou s	NA	269/47 83	194/ 242 7	RD -0.02 (-0.04, - 0.01)	25 fewer per 1000 (38 fewer to 12 fewer)	mod erat e
Mean follow-up: 37.2 month(s) 1 (zinman 2015)	RC T	not seriou s	not seriou s	NA ²	seriou s³	NA	4687	233	HR 0.68 (0.57, 0.81)	Not estimable	mod erat e
cardiovascular mortality at end of follow-up Mean follow-up: 16.4 month(s)										20 fautor par	
cardiovascular mortality at end of follow-up	RC T	not seriou s	not seriou s	seriou s ¹	not seriou s	NA	173/47 81	139/ 242 9	RD -0.02 (-0.03, - 0.01)	20 fewer per 1000 (31 fewer to 10 fewer)	mod erat e

Mean follow-up: 37.2 month(s)											
1 (zinman 2015)	RC T	not seriou s	not seriou s	NA ²	not seriou s	NA	4687	233	HR 0.62 (0.49, 0.78)	Not estimable	high
3-point mace at end of follow-up Mean follow-up: 6 month(s)											
1 (verma 2019) 4-point mace at end of follow-up	RC T	not seriou s	not seriou s	NA ²	seriou s ⁴	NA	0/49	0/48	RD 0.00 (-0.04, 0.04)	0 fewer per 1000 (39 fewer to 39 more)	mod erat e
Mean follow-up: 37.2 month(s) 1 (zinman 2015) 4-point mace at end of follow-up	RC T	not seriou s	not seriou s	NA ²	seriou s ³	NA	599/46 87	333/ 233 3	RR 0.90 (0.79, 1.01)	15 fewer per 1000 (30 fewer to 2 more)	mod erat e
Mean follow-up: 37.2 month(s)	RC	not seriou	not seriou	NA2	seriou	NA.	4007	233	HR 0.89	Not	mod erat
1 (zinman 2015) non-fatal stroke at end of follow-up Mean follow-up: 21.6 month(s)		S	S	NA ²	s ³	NA	4687	3	(0.80, 0.99)	estimable	е

2	RC T	not seriou s	not seriou s	seriou s ¹	very seriou s ⁵	NA	150/47 36	60/2 381	RD 0.01 (-0.00, 0.01)	6 more per 1000 (2 fewer to 14 more)	very low
non-fatal stroke at end of follow-up Mean follow-up: 37.2 month(s)											
1 (zinman 2015)	RC T	not seriou s	not seriou s	NA ²	seriou s³	NA	4687	233	HR 1.24 (0.92, 1.67)	Not estimable	mod erat e
non-fatal myocardial infarction at end of follow-up Mean follow-up: 21.6 month(s)											
2	RC T	not seriou s	not seriou s	seriou s ¹	very seriou s ⁶	NA	213/47 36	121/ 238 1	RD -0.01 (-0.02, 0.00)	6 fewer per 1000 (17 fewer to 4 more)	very low
non-fatal myocardial infaRCTion at end of follow-up Mean follow-up: 37.2 month(s)											
1 (zinman 2015)	RC T	not seriou s	not seriou s	NA ²	seriou s³	NA	4687	233	HR 0.87 (0.70, 1.08)	Not estimable	mod erat e
unstable angina at end of follow-up Mean follow-up: 21.6 month(s)											

2	RC T	not seriou s	not seriou s	not seriou s	very seriou s ⁷	NA	135/47 32	70/2 381	RR 0.98 (0.74, 1.31)	0 fewer per 1000 (8 fewer to 9 more)	low
unstable angina at end of follow-up Mean follow-up: 37.2 month(s)											
1 (zinman 2015)	RC T	not seriou s	not seriou s	NA ²	very seriou s ⁷	NA	4687	233	HR 0.99 (0.74, 1.32)	Not estimable	low
hospitalisation for heart failure at end of follow-up Mean follow-up: 21.6 month(s)											
2	RC T	not seriou s	not seriou s	seriou s ¹	not seriou s	NA	126/47 36	95/2 381	RD -0.01 (-0.02, - 0.00)	14 fewer per 1000 (23 fewer to 4 fewer)	mod erat e
hospitalisation for heart failure at end of follow-up Mean follow-up: 37.2 month(s)											
1 (zinman 2015)	RC T	not seriou s	not seriou s	NA ²	seriou s³	NA	4687	233	HR 0.65 (0.50, 0.85)	Not estimable	mod erat e
acute kidney injury at end of follow-up Mean follow-up: 37.2 month(s)											

1 (zinman 2015) persistent signs of worsening kidney disease at end of follow-up Mean follow-up: 21.6 month(s)	RC T	not seriou s	not seriou s	NA ²	seriou s³	NA	45/468 7	37/2 333	RR 0.61 (0.39, 0.93)	6 fewer per 1000 (10 fewer to 1 fewer)	mod erat e
persistent signs of worsening kidney disease at end of follow-up	RC T	not seriou s	not seriou s	seriou s ¹	seriou s³	NA	460/42 19	330/ 215 0	RR 0.70 (0.62, 0.80)	45 fewer per 1000 (59 fewer to 30 fewer)	mod erat e
Mean follow-up: 37.2 month(s) 1 (zinman 2015) development of end stage kidney disease at	RC T	not seriou s	not seriou s	NA ²	not seriou s	NA	4170	210	HR 0.62 (0.54, 0.71)	Not estimable	high
end of follow-up Mean follow-up: 37.2 month(s)									PETO OR	0 fewer per	
1 (zinman 2015) cardiac arrhythmia at end of follow-up Mean follow-up: 6 month(s)	RC T	not seriou s	not seriou s	NA ²	very seriou s ⁷	NA	6/4687	3/23 33	1.00 (0.25, 3.99)	(2 fewer to 2 more)	low

1 (verma 2019) diabetic ketoacidosis at end of follow-up Mean follow-up: 21.6 month(s)	RC T	not seriou s	not seriou s	NA ²	very seriou s ⁷	NA	1/49	0/48	PETO OR 7.24 (0.14, 364.94)	20 more per 1000 (19 fewer to 60 more)	low
2	RC T	not seriou s	not seriou s	seriou s ¹	very seriou s ⁸	NA	4/4736	1/23 81	RD 0.00 (-0.00, 0.00)	0 more per 1000 (1 fewer to 2 more)	very low
progression of liver disease at end of follow- up Mean follow-up: 6 month(s)											
1 (verma 2019)	RC T	not seriou s	not seriou s	NA ²	seriou s ⁴	NA	0/49	0/48	RD 0.00 (-0.04, 0.04)	0 fewer per 1000 (39 fewer to 39 more)	mod erat e
hypoglycaemia episodes at end of follow-up Mean follow-up: 37.2 month(s)											
1 (zinman 2015)	RC T	not seriou s	not seriou s	NA ²	not seriou s	NA	1303/4 687	650/ 233 3	RR 1.00 (0.92, 1.08)	1 fewer per 1000 (22 fewer to 23 more)	high
severe hypoglycaemia episodes at end of follow-up											

Mean follow-up: 37.2 month(s)											
1 (zinman 2015)	RC T	not seriou s	not seriou s	NA ²	very seriou s ⁷	NA	63/468 7	36/2 333	RR 0.87 (0.58, 1.31)	2 fewer per 1000 (6 fewer to 5 more)	low
hba1c change (%, lower values are better, change scores and final values) at end of follow-up Mean follow-up: 16.4 month(s)											
weight change (kg, lower values are better,	RC T	not seriou s	not seriou s	very seriou s ⁹	seriou s ¹⁰	NA	4824	246 8	MD -0.24 (-0.75, 0.26)	MD 0.24 lower (0.75 lower to 0.26 higher)	very low
change scores and final values) at end of follow-up Mean follow-up: 6 month(s)											
2	RC T	very seriou s ¹¹	seriou s ¹²	not seriou s	seriou s ¹³	NA	94	96	MD -1.87 (-3.01, - 0.73)	MD 1.87 lower (3.01 lower to 0.73 lower)	very low
bmi change (kg/m2, lower values are better, final values) at end of follow-up Mean follow-up: 6 month(s)											

	RC	not seriou	not seriou		very seriou				MD 0.90 (-1.28,	MD 0.90 higher (1.28 lower to 3.08	
1 (verma 2019)	Т	S	S	NA^2	s ¹⁴	NA	49	48	3.08)	higher)	low

- 1. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 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.
- 5. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.64 (0.8-0.9 = serious, <0.8 = very serious).
- 6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.37 (0.8-0.9 = serious, <0.8 = very serious).
- 7. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 8. 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).
- 9. 12 > 75%
- 10. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 11. >33.3% of the studies in the meta-analysis were at high risk of bias
- 12. Largest proportion of studies in the meta-analysis came from partially direct studies
- 13. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)
- 14. 95% confidence intervals cross both ends of the defined MIDs (-0.80, 0.80)

compared to adding sitagliptin

Table 12: Clinical evidence profile: Adding empagliflozin compared to adding sitagliptin

No of studies	De sig n	Risk of bias	Indire ctnes s	Incons istenc y	Impre cision	Other considerat ions	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
hba1c change (%, lower values are better, final values) at the end of follow-up - 6 months											
1 (oh 2021) weight change (kg, lower values are better, final values) at the end of follow-up - 6 months	RC T	serio us ¹	not seriou s	NA ²	not seriou s	NA	48	49	MD 0.10 (-0.14, 0.34)	MD 0.10 higher (0.14 lower to 0.34 higher)	mod erat e
1 (oh 2021)	RC T	serio us ¹	not seriou s	NA ²	very seriou s ³	NA	48	49	MD 0.20 (-4.16, 4.56)	MD 0.20 higher (4.16 lower to 4.56 higher)	very low

^{1. &}gt;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 (-2.40, 2.40)

compared to adding placebo

Table 13: clinical evidence profile: Adding ertugliflozin compared to adding placebo

Table 13. Chilleat evidence	<u>, , </u>	Adding	, crtagiiio	ziii compai	ca to aaa	ing placebe					
No of studies	Desi gn	Risk of bias	Indirectn ess	Inconsiste ncy	Imprecis ion	Other considerati ons	Intervent ion N	Contro I N	Relative effect (95% CI)	Absolute effect	Certai nty
all-cause mortality at end of follow-up – 36 months											
1 (cannon 2020)	RCT	not serio us	not serious	NA ¹	not serious	NA	473/5499	254/27 47	RR 0.93 (0.80, 1.08)	6 fewer per 1000 (18 fewer to 7 more)	high
all-cause mortality at end of follow-up – 36 months											
1 (cannon 2020)	RCT	not serio us	not serious	NA ¹	not serious	NA	5499	2747	HR 0.93 (0.80, 1.08)	Not estimable	high
cardiovascular mortality at end of follow-up – 36 months											
1 (cannon 2020)	RCT	not serio us	not serious	NA ¹	serious ²	NA	341/5499	184/27 47	RR 0.93 (0.78, 1.10)	5 fewer per 1000 (15 fewer to 7 more)	moder ate
cardiovascular mortality at end of follow-up – 36 months											

1 (cannon 2020)	RCT	not serio us	not serious	NA ¹	serious ²	NA	5499	2747	HR 0.92	Not estimable	moder ate
4-point mace at end of follow-up – 36 months									1.10)		
1 (cannon 2020)	RCT	not serio us	not serious	NA ¹	not serious	NA	823/5499	439/27 47	RR 0.94 (0.84, 1.04)	10 fewer per 1000 (25 fewer to 7 more)	high
4-point mace at end of follow-up – 36 months											
1 (cannon 2020)	RCT	not serio us	not serious	NA ¹	not serious	NA	5499	2747	HR 0.92 (0.82, 1.03)	Not estimable	high
non-fatal stroke at end of follow-up – 36 months											
1 (cannon 2020)	RCT	not serio us	not serious	NA ¹	very serious ³	NA	157/5499	78/274 7	RR 1.01 (0.77, 1.31)	0 more per 1000 (7 fewer to 9 more)	low
non-fatal stroke at end of follow-up – 36 months											
1 (cannon 2020)	RCT	not serio us	not serious	NA ¹	very serious ³	NA	5499	2747	HR 1.00 (0.76, 1.32)	Not estimable	low

non-fatal myocardial infarction at end of follow-up – 36 months											
1 (cannon 2020)	RCT	not serio us	not serious	NA ¹	serious ²	NA	310/5499	148/27 47	RR 1.05 (0.86, 1.27)	2 more per 1000 (7 fewer to 14 more)	moder ate
non-fatal myocardial infarction at end of follow-up – 36 months											
1 (cannon 2020)	RCT	not serio us	not serious	NA ¹	serious ²	NA	5499	2747	HR 1.04 (0.86, 1.26)	Not estimable	moder ate
unstable angina at the end of follow-up – 36 months											
1 (cannon 2020)	RCT	not serio us	not serious	NA ¹	serious ²	NA	145/5493	89/274 5	RR 0.81 (0.63, 1.06)	6 fewer per 1000 (12 fewer to 2 more)	moder ate
hospitalisation for heart failure at the end of follow- up – 36 months											
1 (cannon 2020)	RCT	not serio us	not serious	NA ¹	serious ²	NA	139/5499	99/274 7	RR 0.70 (0.54, 0.90)	11 fewer per 1000 (16 fewer to 3 fewer)	moder ate

hospitalisation for heart failure at the end of follow- up – 36 months			i diovasculai								
1 (cannon 2020)	RCT	not serio us	not serious	NA ¹	serious ²	NA	5499	2747	HR 0.70 (0.54, 0.91)	Not estimable	moder ate
acute kidney injury at the end of follow-up – 36 months											
1 (cannon 2020)	RCT	not serio us	not serious	NA ¹	serious ²	NA	101/5493	60/274 5	RR 0.84 (0.61, 1.15)	3 fewer per 1000 (8 fewer to 3 more)	moder ate
persistent signs of worsening kidney disease at the end of follow-up – 36 months											
1 (cannon 2020)	RCT	not serio us	not serious	NA ¹	serious ²	NA	168/5499	105/27 47	RR 0.80 (0.63, 1.02)	8 fewer per 1000 (14 fewer to 1 more)	moder ate
development of end stage kidney disease at end of follow-up – 36 months											
1 (cannon 2020)	RCT	very serio us ⁴	not serious	NA ¹	very serious ³	NA	7/5499	3/2747	PETO OR 1.16 (0.31, 4.33)	0 more per 1000 (1 fewer to 2 more)	very low

Ortibe tables moder 2. Type 2		1			1						
death from renal causes at the end of follow-up – 36 months											
1 (cannon 2020)	RCT	very serio us ⁴	not serious	NA ¹	not serious	NA	0/5499	0/2747	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (1 fewer to 1 more)	low
cardiac arrhythmia at the end of follow-up – 36 months											
1 (cannon 2020)	RCT	not serio us	not serious	NA ¹	serious ²	NA	61/5493	37/274 5	RR 0.82 (0.55, 1.24)	2 fewer per 1000 (6 fewer to 3 more)	moder ate
diabetic ketoacidosis at the end of follow-up – 36 months											
1 (cannon 2020)	RCT	very serio us ⁴	not serious	NA ¹	serious ²	NA	19/5493	2/2745	PETO OR 2.93 (1.18, 7.26)	3 more per 1000 (1 more to 5 more)	very low
hypoglycaemia episodes at the end of follow-up – 36 months											
1 (cannon 2020)	RCT	not serio us	not serious	NA ¹	not serious	NA	1496/549 3	790/27 45	RR 0.95 (0.88, 1.02)	15 fewer per 1000 (35 fewer to 5 more)	high

71											
severe hypoglycaemic episodes at the end of follow-up – 36 months											
1 (cannon 2020)	RCT	not serio us	not serious	NA ¹	serious ²	NA	284/5493	162/27 45	RR 0.88 (0.73, 1.06)	7 fewer per 1000 (16 fewer to 3 more)	moder ate
hba1c change (%, lower value is better, mead difference) end of follow-up – 36 months											
1 (cannon 2020)	RCT	very serio us ⁴	not serious	NA ¹	not serious	NA	5499	2747	MD -0.17 (-0.26, - 0.08)	MD 0.17 lower (0.26 lower to 0.08 lower)	low
weight change (kg, lower value is better, change difference) at end of follow- up – 36 months											
1 (cannon 2020)	RCT	very serio us ⁴	not serious	NA ¹	serious ⁵	NA	5499	2747	MD -2.60 (-3.05, - 2.15)	MD 2.60 lower (3.05 lower to 2.15 lower)	very low

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

H.5.1 Adding glimepiride compared to adding pioglitazone

Table 14: Clinical evidence profile: Adding glimepiride compared to adding pioglitazone

No of studies	De sig n	Risk of bias	Indir ectne ss	Incons istenc y	Impre cision	Other considera tions	Interv ention N	Con trol N	Relative effect (95% CI)	Absolute effect	Cert aint y
all-cause mortality at end of follow- up - 18 months											
1 (nissen 2008)	RC T	serio us¹	not serio us	NA ²	very seriou s ³	NA	2/273	3/27 0	PETO OR 0.66 (0.11, 3.84)	4 fewer per 1000 (20 fewer to 12 more)	very low
cardiovascular mortality at end of follow-up - 18 months											
1 (nissen 2008)	RC T	serio us¹	not serio us	NA ²	very seriou s³	NA	1/273	3/27 0	PETO OR 0.36 (0.05, 2.58)	7 fewer per 1000 (22 fewer to 7 more)	very low
5-point mace at end of follow-up - 18 months											
1 (nissen 2008)	RC T	serio us ¹	not serio us	NA ²	very seriou s ³	NA	13/273	11/2 70	RR 1.17 (0.53, 2.56)	7 more per 1000 (19 fewer to 64 more)	very low
non-fatal stroke at end of follow-up - 18 months											

1 (nissen 2008) non-fatal myocardial infarction at end of follow-up - 18 months	RC T	serio us¹	not serio us	NA ²	very seriou s ³	NA	1/273	0/27	PETO OR 7.31 (0.15, 368.34)	4 more per 1000 (3 fewer to 11 more)	very low
1 (nissen 2008) unstable angina at end of follow-up -	RC T	serio us ¹	not serio us	NA ²	very seriou s ³	NA	4/273	2/27	RR 1.98 (0.37, 10.71)	7 more per 1000 (5 fewer to 72 more)	very low
1 (nissen 2008) hospitalisation for heart failure at end of follow-up - 18 months	RC T	serio us ¹	not serio us	NA ²	very seriou s ³	NA	2/273	4/27	RR 0.49 (0.09, 2.68)	7 fewer per 1000 (13 fewer to 25 more)	very low
1 (nissen 2008) hypoglycaemia episodes at end of follow-up - 18 months	RC T	serio us ¹	not serio us	NA ²	very seriou s ³	NA	5/273	4/27	RR 1.24 (0.34, 4.55)	4 more per 1000 (10 fewer to 53 more)	very low
1 (nissen 2008) hba1c change (%, lower values are better, change scores) at end of follow-up - 18 months	RC T	serio us ¹	not serio us	NA ²	not seriou s	NA	101/27	41/2 70	RR 2.44 (1.77, 3.36)	218 more per 1000 (116 more to 358 more)	mod erat e

1 (nissen 2008) weight change (kg, lower values are better, final values) at end of follow-	RC T	serio us ¹	not serio us	NA ²	not seriou s	NA	181	179	MD 0.19 (0.01, 0.37)	MD 0.19 higher (0.01 higher to 0.37 higher)	mod erat e
up - 18 months	D 0		not						MD -2.90	MD 2.90 lower	
1 (nissen 2008)	RC T	serio us¹	serio us	NA ²	seriou s ⁴	NA	181	179	(-7.06, 1.26)	(7.06 lower to 1.26 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 (2.40, -2.40)

H.5.2 Adding glimepiride compared to adding insulin

Table 11: Clinical evidence profile: Adding glimepiride compared to adding insulin

No of studies hypoglycaemia episodes at end of follow-up – 5.5 months	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
1 (li 2014c)	RC T	not seriou s	not seriou s	NA ¹	not seriou s	NA	7/29	19/2 9	RR 0.37 (0.18, 0.74)	414 fewer per 1000 (535 fewer to 170 fewer)	high

GRADE tables - Model 2: Type 2 diabetes and cardiovascular disease

hba1c change (%, lower values are better) at end of follow-up – 5.5 months											
1 (li 2014c) weight change (kg, lower values are better) at end of follow-up – 5.5. months	RC T	not seriou s	not seriou s	NA ¹	seriou s²	NA	29	26	MD -0.60 (-1.29, 0.09)	MD 0.60 lower (1.29 lower to 0.09 higher)	mod erat e
1 (li 2014c)	RC T	not seriou s	not seriou s	NA ¹	very seriou s ³	NA	29	26	MD -2.90 (-11.66, 5.86)	MD 2.90 lower (11.66 lower to 5.86 higher)	low

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

H.6 Thiazolidinedione

H.6.1 Adding pioglitazone compared to adding placebo

Table 12 Clinical evidence profile: Adding pioglitazone compared to adding placebo

	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
all-cause mortality at end of follow-up											

GRADE tables – Model 2. Type 2 diabetes and		very	not						RR 0.96	3 fewer per 1000	
2	RC T	seriou s ¹	seriou s	serious 2	seriou s ³	NA	177/26 65	187/ 2694	(0.78, 1.17)	(15 fewer to 12 more)	very low
all-cause mortality at end of follow-up	-								(0.1.0, 1.1.1)	,	
1 (wilcox 2008)	RC T	very seriou s ¹	not seriou s	NA ⁴	seriou s ³	NA	2605	2633	HR 0.96 (0.78, 1.18)	Not estimable	very low
cardiovascular mortality at end of follow- up	•	3	3	10.	3		2000	2000	(0.70, 1.10)	Communic	1011
1 (wilcox 2008)	RC T	very seriou s ¹	not seriou s	NA ⁴	seriou s³	NA	127/26 05	136/ 2633	RR 0.94 (0.75, 1.19)	3 fewer per 1000 (13 fewer to 10 more)	very low
cardiovascular mortality at end of follow- up											
1 (wilcox 2008)	RC T	very seriou s ¹	not seriou s	NA ⁴	seriou s ³	NA	2605	2633	HR 0.94 (0.74, 1.19)	Not estimable	very low
3-point mace at end of follow-up											
1 (wilcox 2008)	RC T	very seriou s ¹	not seriou s	NA ⁴	seriou s³	NA	257/26 05	313/ 2633	RR 0.83 (0.71, 0.97)	20 fewer per 1000 (34 fewer to 4 fewer)	very low
3-point mace at end of follow-up											

1 (wilcox 2008)	RC T	very seriou s ¹	not seriou s	NA ⁴	seriou s³	NA	2605	2633	HR 0.82 (0.70, 0.96)	Not estimable	very low
non-fatal stroke at end of follow-up									, ,		
1 (wilcox 2008) non-fatal stroke at end of follow-up	RC T	very seriou s ¹	not seriou s	NA ⁴	seriou s³	NA	86/260 5	107/2633	RR 0.81 (0.61, 1.07)	8 fewer per 1000 (16 fewer to 3 more)	very low
non-iatai stroke at end of follow-up			4								
1 (wilcox 2008)	RC T	very seriou s ¹	not seriou s	NA ⁴	seriou s ³	NA	2605	2633	HR 0.81 (0.61, 1.08)	Not estimable	very low
non-fatal myocardial infarction at end of follow-up											
2	RC T	very seriou s ¹	not seriou s	not serious	seriou s³	NA	121/26 65	145/ 2694	RR 0.84 (0.67, 1.07)	8 fewer per 1000 (18 fewer to 4 more)	very low
non-fatal myocardial infarction at end of follow-up											
1 (wilcox 2008)	RC T	very seriou s ¹	not seriou s	NA ⁴	seriou s³	NA	2605	2633	HR 0.83 (0.65, 1.06)	Not estimable	very low
hospitalisation for heart failure at end of follow-up											

1 (wilcox 2008)	RC T	very seriou s ¹	not seriou s	NA ⁴	seriou s³	NA	149/26 05	108/ 2633	RR 1.39 (1.10, 1.78)	16 more per 1000 (4 more to 32 more)	very low
cardiac arrhythmia at end of follow-up 1 (wilcox 2008)	RC T	very seriou s ¹	not seriou s	NA ⁴	seriou s ³	NA	42/260 5	51/2 633	RR 0.83 (0.56, 1.25)	3 fewer per 1000 (9 fewer to 5 more)	very low
hypoglycaemia episodes at end of follow-up											
1 (wilcox 2008)	RC T	very seriou s ¹	not seriou s	NA ⁴	not seriou s	NA	726/26 05	528/ 2633	RR 1.39 (1.26, 1.53)	78 more per 1000 (52 more to 107 more)	low
hba1c change (%, lower values are better, change scores) at end of follow-up											
1 (lee 2013b)	RC T	very seriou s ¹	not seriou s	NA ⁴	seriou s ⁵	NA	60	61	MD -0.84 (-1.55, - 0.13)	MD 0.84 lower (1.55 lower to 0.13 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. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

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