National Institute for Health and Care Excellence

Draft for consultation

Type 2 diabetes in adults: management

[F5] 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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Appendices

Appendix I Forest plots – Model 3: Type 2 diabetes and chronic kidney disease

I.1 DPP-4 inhibitors

I.1.1 Adding linagliptin compared to adding placebo

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

	Linagli	ptin	Place	bo		Risk Ratio			Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C		M-H	I, Fixed, 95%	6 CI	
McGill 2013	3	68	3	65	75.2%	0.96 [0.20, 4.57]		_		_	
Groop 2017	2	182	1	178	24.8%	1.96 [0.18, 21.38]			-		
Total (95% CI)		250		243	100.0%	1.20 [0.33, 4.38]				-	
Total events	5		4								
Heterogeneity: Chi ² =	0.24, df =	1 (P = 0).62); I ² =	0%			0.01	0.1	-	10	100
Test for overall effect:	Z = 0.28 (I	P = 0.78	3)					ا . ا vours Linagl	ı iptin Favoı	ırs Placebo	

Figure 2: Non-fatal stroke at end of follow up

	Linagli	ptin	Place	bo		Risk Difference		Ris	k Differen	ce	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H,	Fixed, 95	% CI	
Groop 2017	0	182	0	178	73.0%	0.00 [-0.01, 0.01]					
McGill 2013	1	68	1	65	27.0%	-0.00 [-0.04, 0.04]			+		
Total (95% CI)		250		243	100.0%	-0.00 [-0.01, 0.01]			•		
Total events	1		1								
Heterogeneity: Chi ² =	0.00, df =	1 (P = 0).97); I ² =	0%			⊢ -1	-0.5	0	0.5	
Test for overall effect:	Z = 0.03 (I	P = 0.98	3)				-1	Favours Linagli	-	urs Placebo	'

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

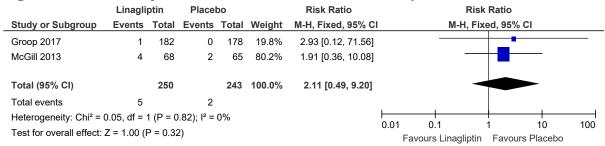


Figure 4: Hospitalisation for heart failure at end of follow up

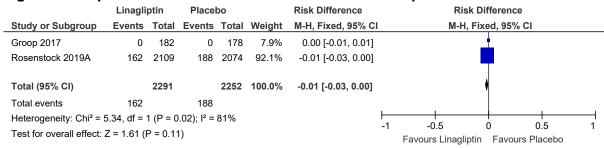


Figure 5: Hypoglycaemia episodes at end of follow up

	Linagli	ptin	Place	bo		Risk Ratio	Risk Ratio Risk Ratio								
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	l	M-H	, Fixed, 95%	ixed, 95% CI					
Groop 2017	24	182	10	178	23.6%	2.35 [1.16, 4.77]				-					
McGill 2013	43	68	32	65	76.4%	1.28 [0.95, 1.74]			-						
Total (95% CI)		250		243	100.0%	1.54 [1.14, 2.07]			•						
Total events	67		42												
Heterogeneity: Chi ² =	2.68, df =	1 (P = 0).10); I ² =	63%			0.01	0.1		10	100				
Test for overall effect:	Z = 2.82 (I	P = 0.00	05)				0.01 Fave	ours Linagli	ı ptin Favour	s Placebo					

Figure 6: Severe hypoglycaemic episodes at end of follow up

	Linagli	ptin	Place	bo		Risk Difference		Risk	Difference	e	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		М-Н,	Fixed, 95%	% CI	
Groop 2017	0	182	0	178	73.0%	0.00 [-0.01, 0.01]					
McGill 2013	3	68	3	65	27.0%	-0.00 [-0.07, 0.07]			+		
Total (95% CI)		250		243	100.0%	-0.00 [-0.02, 0.02]			•		
Total events	3		3								
Heterogeneity: Chi ² =	0.01, df =	1 (P = 0).91); I² =	0%			├─ -1	-0.5		0.5	-
Test for overall effect:	Z = 0.05 (I	P = 0.96	3)				-1	-0.5 Favours Linaglip	0 tin Favoi	urs Placebo	1

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

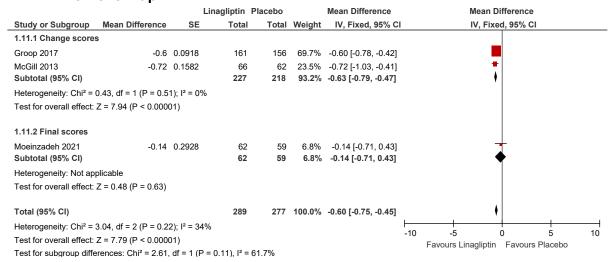


Figure 8: Weight change (kg, lower scores are better, change and final scores) at end of follow-up

			Linagliptin	Placebo		Mean Difference		Mean	Differen	ce	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Fixed, 95% C	1	IV, Fi	xed, 95%	CI	
1.12.1 Change score	s										
McGill 2013	-1.53	1.3164	66	62	78.1%	-1.53 [-4.11, 1.05]					
Subtotal (95% CI)			66	62	78.1%	-1.53 [-4.11, 1.05]			•		
Heterogeneity: Not ap	plicable										
Test for overall effect:	Z = 1.16 (P = 0.25)										
1.12.2 Final scores											
Moeinzadeh 2021	1.13	2.4865	62	59	21.9%	1.13 [-3.74, 6.00]			+		
Subtotal (95% CI)			62	59	21.9%	1.13 [-3.74, 6.00]			•		
Heterogeneity: Not ap	plicable										
Test for overall effect:	Z = 0.45 (P = 0.65)										
Total (95% CI)			128	121	100.0%	-0.95 [-3.23, 1.33]			•		
Heterogeneity: Chi ² =	0.89, df = 1 (P = 0.3	4); I ² = 0	1%				100				400
Test for overall effect:	Z = 0.81 (P = 0.42)						-100	-50 Favours Linaglipt	u in Favo	50 urs Placebo	100
Test for subgroup diffe	erences: Chi² = 0.89,	df = 1 (P = 0.34), I ² =	0%				i avours Emagnipo	iii ravo	uis i iacebo	

I.1.2 Adding linagliptin compared to adding liraglutide

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

I.1.3 Adding saxagliptin compared to adding placebo

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

I.1.4 Adding sitagliptin compared to adding linagliptin

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

I.1.5 Adding sitagliptin compared to adding liraglutide

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

I.1.6 Adding vildagliptin compared to adding sitagliptin

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

I.2 GLP-1 receptor agonist

I.2.1 Adding dulaglutide compared to adding insulin

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

I.2.2 Adding exenatide compared to adding insulin

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

I.2.3 Adding liraglutide compared to adding placebo

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

I.2.4 Adding semaglutide compared to adding placebo

Figure 9: All-cause mortality at follow-up, risk ratio

	Semagli	utide	Place	bo		Risk Ratio		Ris	k Ratio)	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, F	xed, 95	% CI	
Mosenzon 2019	1	163	2	161	0.7%	0.49 [0.05, 5.39]				_	
Perkovic 2024	227	1767	279	1766	99.3%	0.81 [0.69, 0.96]					
Total (95% CI)		1930		1927	100.0%	0.81 [0.69, 0.95]			•		
Total events	228		281								
Heterogeneity: Chi ² =	0.17, df = 1	(P = 0.	68); I² = ()%			0.01	0.1	+	10	100
Test for overall effect:	Z = 2.54 (F	P = 0.01)				0.01	Semaglutide	l Plac	10 ebo	100

Figure 10: Cardiovascular mortality at end of follow-up, risk ratio

	Semagl	utide	Place	bo		Risk Ratio			Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	l	M-l	H, Fixed, 95	% CI	
Mosenzon 2019	1	163	1	161	0.6%	0.99 [0.06, 15.66]					
Perkovic 2024	123	1767	169	1766	99.4%	0.73 [0.58, 0.91]					
Total (95% CI)		1930		1927	100.0%	0.73 [0.58, 0.91]			•		
Total events	124		170								
Heterogeneity: Chi² =	0.05, df = 1	(P = 0.	83); I ² = 0)%			0.04			10	
Test for overall effect:	Z = 2.79 (F	P = 0.00	5)				0.01	0.1 Semagli	1 utide Place	10 ebo	100

Figure 11: Acute kidney injury at end of follow-up, risk ratio

	Semagl	utide	Place	bo		Risk Ratio			Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H	l, Fixed, 95	% CI	
Mosenzon 2019	2	163	1	161	0.8%	1.98 [0.18, 21.57]		_			
Perkovic 2024	124	1767	123	1766	99.2%	1.01 [0.79, 1.28]			-		
Total (95% CI)		1930		1927	100.0%	1.02 [0.80, 1.29]			•		
Total events	126		124								
Heterogeneity: Chi² =	0.30, df = 1	(P = 0.	58); I² = 0)%			0.01	0.1	1	10	100
Test for overall effect:	Z = 0.13 (F	P = 0.90)				0.01	Semaglu	ıtide Place		100

Figure 12: Severe hypoglycaemic episodes at end of follow-up, risk difference

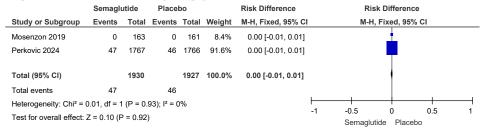


Figure 13: HbA1c change (%, lower values are better, change scores) at end of follow-up

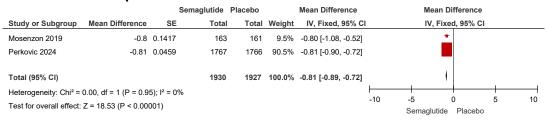
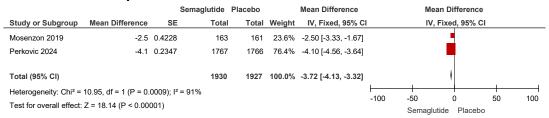


Figure 14: Weight change (kg, lower values are better, change scores) at end of follow-up



I.2.5 Adding semaglutide compared to adding dulaglutide

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

I.2.6 Switching to semaglutide compared to dulaglutide (switching from dulaglutide)

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

I.2.7 Switching to semaglutide compared to liraglutide (switching from liraglutide)

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

I.3 SGLT2 inhibitors

I.3.1 Adding canagliflozin compared to adding placebo

Figure 15: All-cause mortality at end of follow-up, risk ratio

	Canaglif	lozin	Place	bo		Risk Ratio			Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-l	H, Fixed, 95°	% CI	
Perkovic 2019	168	2022	201	2199	98.1%	0.91 [0.75, 1.11]					
Wada 2022	4	154	1	154	0.5%	4.00 [0.45, 35.38]			_	•	_
Yale 2013	4	179	2	90	1.4%	1.01 [0.19, 5.39]		_			
Total (95% CI)		2355		2443	100.0%	0.93 [0.76, 1.12]			•		
Total events	176		204								
Heterogeneity: Chi ² =	1.77, df = 2	(P = 0.	41); I ² = 0	%			0.01	0.1		10	100
Test for overall effect:	Z = 0.78 (F	9 = 0.44))					o. i ours canagli	ı flozin Favo	urs placebo	100

Figure 16: All-cause mortality at end of follow-up, hazard ratio

			Canagliflozin	Placebo		Hazard Ratio		н	azard	Ratio	
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Fixed, 95% C	l	IV,	Fixed	, 95% CI	
Perkovic 2019	-0.1863	0.1017	2202	2199	99.2%	0.83 [0.68, 1.01]					
Wada 2022	1.3271	1.1197	154	154	0.8%	3.77 [0.42, 33.84]				•	 _
Total (95% CI)			2356	2353	100.0%	0.84 [0.69, 1.02]			•		
Heterogeneity: Chi ² =	1.81, df = 1 (P = 0.18); I ² = 45 ⁶	%				0.04		+		 400
Test for overall effect:	Z = 1.72 (P = 0.09)						0.01 Fa	0.1 vours canaglifle	ozin	Favours place	100

Figure 17: Cardiovascular mortality at end of follow-up, risk ratio

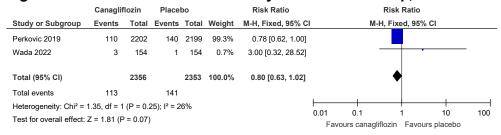


Figure 18: Cardiovascular mortality at end of follow-up, hazard ratio

			Canagliflozin	Placebo		Hazard Ratio		н	azard Ration	0	
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Fixed, 95% C	ı	IV,	Fixed, 95%	CI	
Perkovic 2019	-0.2485	0.1254	2202	2199	98.8%	0.78 [0.61, 1.00]					
Wada 2022	1.0152	1.1496	154	154	1.2%	2.76 [0.29, 26.27]		_	'		
Total (95% CI)			2356	2353	100.0%	0.79 [0.62, 1.01]			•		
Heterogeneity: Chi ² =	1.19, df = 1 (P = 0.27); I ² = 16 ⁹	%				<u></u>				
Test for overall effect:	Z = 1.87 (P = 0.06)						0.01 Far	0.1	1 ozin Favo	10 urs placebo	100

Figure 19: 5-point MACE at end of follow-up, risk ratio

	Canaglif	lozin	Place	bo		Risk Ratio			Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C		M-	H, Fixed, 95%	6 CI	
Perkovic 2019	273	2202	361	2199	98.1%	0.76 [0.65, 0.87]					
Wada 2022	10	154	7	154	1.9%	1.43 [0.56, 3.66]			-	-	
Total (95% CI)		2356		2353	100.0%	0.77 [0.67, 0.89]			•		
Total events	283		368								
Heterogeneity: Chi² =	1.73, df = 1	(P = 0.	19); I² = 4	2%			0.01	0.1		10	100
Test for overall effect:	Z = 3.60 (P	= 0.000	03)						ı iflozin Favoı		100

Figure 20: 5-point MACE at end of follow-up, hazard ratio

			Canagliflozin	Placebo		Hazard Ratio			Hazard Rati	0	
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Fixed, 95% C	l	IN	/, Fixed, 95%	6 CI	
Perkovic 2019	-0.3011	0.0821	2202	2199	97.3%	0.74 [0.63, 0.87]					
Wada 2022	0.3507	0.4933	154	154	2.7%	1.42 [0.54, 3.73]			 -	_	
Total (95% CI)			2356	2353	100.0%	0.75 [0.64, 0.88]			•		
Heterogeneity: Chi ² = Test for overall effect:		,-	%				0.01 Fa	0.1 vours Canagl	1 iflozin Favo	10 urs Placebo	100

Figure 21: Hospitalisation for heart failure at end of follow-up, risk ratio

	Canagli	lozin	Place	bo		Risk Ratio			Risk Ra	tio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	l	M-	H, Fixed,	95% CI	
Perkovic 2019	89	2202	141	2199	97.9%	0.63 [0.49, 0.82]					
Wada 2022	1	154	3	154	2.1%	0.33 [0.04, 3.17]	-		•		
Total (95% CI)		2356		2353	100.0%	0.62 [0.48, 0.81]			•		
Total events	90		144								
Heterogeneity: Chi ² =	0.30, df = 1	(P = 0.5	58); I² = 0	1%				 	- !	+	
Test for overall effect:	Z = 3.60 (F	9 = 0.000	03)				0.01 Fav	0.1 ours canagl	1 iflozin Fa	10 avours placebo	100

Figure 22: Hospitalisation for heart failure at end of follow-up, hazard ratio

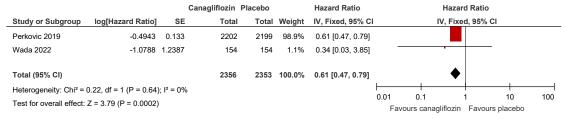


Figure 23: Diabetic ketoacidosis at end of follow-up

	Canaglif	lozin	Place	bo		Risk Ratio			Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	l	М-Н	, Random, 95	% CI	
Perkovic 2019	11	2200	1	2197	44.7%	10.98 [1.42, 85.01]					
Wada 2022	4	154	3	154	55.3%	1.33 [0.30, 5.86]				_	
Total (95% CI)		2354		2351	100.0%	3.42 [0.40, 29.37]					-
Total events	15		4								
Heterogeneity: Tau ² =	1.61; Chi ²	= 2.93, 0	df = 1 (P :	= 0.09);	I ² = 66%		0.04	0.1	- 	10	100
Test for overall effect:	Z = 1.12 (F	P = 0.26))				0.01 Fav	0.1 ours canagli	ı flozin Favoui	10 s placebo	100

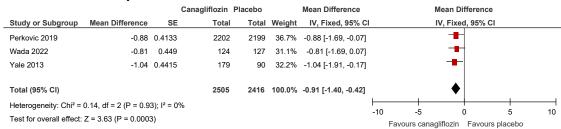
Figure 24: Hypoglycaemia episodes at end of follow-up

	Canaglif	lozin	Place	bo		Risk Ratio			Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-I	H, Fixed, 959	% CI	
Perkovic 2019	225	2200	240	2197	84.8%	0.94 [0.79, 1.11]					
Wada 2022	43	154	43	154	15.2%	1.00 [0.70, 1.43]			+		
Total (95% CI)		2354		2351	100.0%	0.95 [0.81, 1.11]			•		
Total events	268		283								
Heterogeneity: Chi² =	0.11, df = 1	(P = 0.7	74); I ² = 0	%					-	10	400
Test for overall effect:	Z = 0.70 (F	P = 0.48)	1				0.01 Fav	0.1 ours canagli	1 flozin Favo	10 urs placebo	100

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

			Canagliflozin	Placebo		Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Perkovic 2019	-0.11	0.0867	2202	2199	47.9%	-0.11 [-0.28, 0.06]	
Wada 2022	-0.23	0.1173	124	127	26.1%	-0.23 [-0.46, -0.00]	•
Yale 2013	-0.33	0.1176	179	90	26.0%	-0.33 [-0.56, -0.10]	•
Total (95% CI)			2505	2416	100.0%	-0.20 [-0.32, -0.08]	•
Heterogeneity: Chi² = Test for overall effect	, ,		5%				-10 -5 0 5 10 Favours canagliflozin Favours placebo

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



I.3.2 Adding dapagliflozin compared to adding placebo

Figure 27: All-cause mortality at end of follow up

	Dapagli	flozin	Place	bo		Risk Difference		F	Risk Differen	ce	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H	, Random, 9	5% CI	
Fioretto 2018	0	160	0	161	31.3%	0.00 [-0.01, 0.01]			•		
Kohan 2014	5	168	5	84	11.0%	-0.03 [-0.09, 0.03]			+		
Pollock 2019	1	145	0	148	27.8%	0.01 [-0.01, 0.03]			•		
Wiviott 2019 CKD	254	2944	315	2940	29.9%	-0.02 [-0.04, -0.01]			•		
Total (95% CI)		3417		3333	100.0%	-0.01 [-0.03, 0.02]			♦		
Total events	260		320								
Heterogeneity: Tau ² =	0.00; Chi ²	= 16.86,	df = 3 (P	= 0.00	08); I ² = 82	2%	\vdash		 	 	
Test for overall effect:	Z = 0.65 (F	P = 0.51)					-1	-0.5 Favours Dapagl	0 iflozin Favo	0.5 urs Placebo	1

Figure 28: Cardiovascular mortality at end of follow up

_	Dapaglif	lozin	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Fioretto 2018	0	160	0	161	5.0%	0.00 [-0.01, 0.01]	†
Kohan 2014	4	168	3	84	3.5%	-0.01 [-0.06, 0.03]	土
Wiviott 2019 CKD	126	2944	138	2940	91.5%	-0.00 [-0.01, 0.01]	•
Total (95% CI)		3272		3185	100.0%	-0.00 [-0.01, 0.01]	•
Total events	130		141				
Heterogeneity: Chi ² =	0.57, df = 2	(P = 0.	75); I ² = 0	1%			1 05 0 05 1
Test for overall effect:	Z = 0.84 (F	P = 0.40))				-1 -0.5 0 0.5 1 Favours Dapagliflozin Favours Placebo

Figure 29: Persistent signs of worsening kidney disease at end of follow up

	Dapaglif	flozin	Place	bo		Peto Odds Ratio		Peto	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% C		Peto,	Fixed, 95% C	H
Kohan 2014	5	168	3	84	87.4%	0.82 [0.19, 3.66]		_		
Pollock 2019	0	145	1	148	12.6%	0.14 [0.00, 6.96]		•		
Total (95% CI)		313		232	100.0%	0.66 [0.16, 2.65]		⋖		
Total events	5		4							
Heterogeneity: Chi ² =	0.70, df = 1	(P = 0.	40); I ² = 0	%			0.004	0.4	1 1	
Test for overall effect:	Z = 0.59 (F	P = 0.56))				0.001 Favou	0.1 rs Dapaglifloz	1 10 in Favours	

Figure 30: Diabetic ketoacidosis at end of follow up

	Dapaglif	lozin	Place	bo		Risk Difference		Risk D	ifference		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	l	M-H, Fix	ced, 95% CI		
Fioretto 2018	0	160	0	161	4.9%	0.00 [-0.01, 0.01]			†		
Pollock 2019	1	145	0	148	4.5%	0.01 [-0.01, 0.03]			<u>†</u>		
Wiviott 2019 CKD	6	2944	6	2940	90.6%	-0.00 [-0.00, 0.00]			-		
Total (95% CI)		3249		3249	100.0%	0.00 [-0.00, 0.00]					
Total events	7		6								
Heterogeneity: Chi ² =	0.54, df = 2	(P = 0.	76); I ² = 0	%			<u>⊢</u>	-0.5	0	0.5	
Test for overall effect:	Z = 0.26 (F	P = 0.80))				-1	Favours Dapagliflozin	-		'

Figure 31: Hypoglycaemia episodes 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	l	M-H	I, Fixed, 95%	CI	
Fioretto 2018	17	160	18	161	17.3%	0.95 [0.51, 1.78]			_		
Kohan 2014	71	168	43	84	55.1%	0.83 [0.63, 1.09]			-		
Pollock 2019	35	145	29	148	27.6%	1.23 [0.80, 1.90]			+		
Total (95% CI)		473		393	100.0%	0.96 [0.77, 1.20]			•		
Total events	123		90								
Heterogeneity: Chi ² =	,	`	,,	7%			0.01	0.1	1	 10	100
Test for overall effect:	Z = 0.37 (P	P = 0.71)				Favo	ours Dapaglif	lozin Favou	rs Placebo	

Figure 32: Severe hypoglycaemic episodes at end of follow up

	Dapaglif	lozin	Place	bo	Risk Difference			Risk Di	fference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	1	M-H, Fix	ed, 95% CI	
Fioretto 2018	0	160	0	161	4.8%	0.00 [-0.01, 0.01]			1	
Kohan 2014	2	168	4	84	3.3%	-0.04 [-0.08, 0.01]		_	†	
Pollock 2019	0	145	1	148	4.4%	-0.01 [-0.03, 0.01]		_	<u>t</u>	
Wiviott 2019 CKD	25	2944	43	2940	87.5%	-0.01 [-0.01, -0.00]				
Total (95% CI)		3417		3333	100.0%	-0.01 [-0.01, -0.00]				
Total events	27		48							
Heterogeneity: Chi ² = 2	2.66, df = 3	(P = 0.4	45); I ² = 0	%			<u> </u>	 	 	+
Test for overall effect: Z = 2.61 (P = 0.009)							-1	-0.5 Favours Dapagliflozin	0 0 Favours Pla	cebo

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

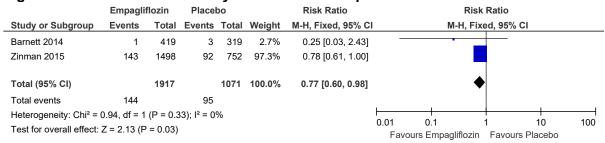
			Dapagliflozin	Placebo		Mean Difference		Mean	Differe	ence	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Fixed, 95% CI		IV, Fi	ced, 95	5% CI	
Fioretto 2018	-0.34	0.1361	159	161	39.1%	-0.34 [-0.61, -0.07]					
Kohan 2014	-0.28	0.4632	18	4	3.4%	-0.28 [-1.19, 0.63]			+		
Pollock 2019	-0.16	0.1122	140	145	57.5%	-0.16 [-0.38, 0.06]					
Total (95% CI)			317	310	100.0%	-0.23 [-0.40, -0.07]			•		
Heterogeneity: Chi² = Test for overall effect:		,.	6				-10	-5 Favours Dapaglifloz	0 n Fa	5 vours Placebo	10

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

	Dap	agliflo	zin	PI	acebo			Mean Difference		M	e:e		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	l	IV,	Random, 95%	6 CI	
Fioretto 2018	-3.17	3.78	159	-1.92	3.75	161	58.0%	-1.25 [-2.08, -0.42]			-		
Kohan 2014					42	42.0%	-3.39 [-5.26, -1.52]			_			
Total (95% CI)			251			203	100.0%	-2.15 [-4.22, -0.08]		⋖			
Heterogeneity: $Tau^2 = 1.75$; $Chi^2 = 4.23$, $df = 1$ ($P = 0.04$); $I^2 = 76\%$ Test for overall effect: $Z = 2.04$ ($P = 0.04$)										-5 ours Dapagli	0 flozin Favou	5 Irs Placebo	10

I.3.3 Adding empagliflozin compared to adding placebo

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



I.3.4 Adding empagliflozin compared to adding linagliptin

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

I.3.5 Adding ertugliflozin compared to adding placebo

Figure 36: HbA1c change (%, lower values are better, change scores) at end of follow-

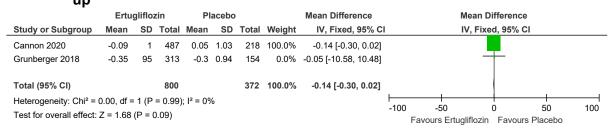
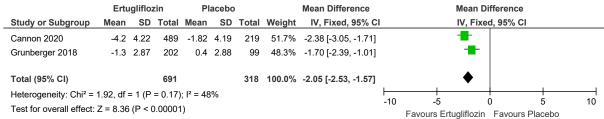


Figure 37: Weight change (kg, lower values are better, change scores) at end of follow-up



I.4 Sulphonylureas

I.4.1 Adding glimepiride compared to adding insulin

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

I.5 Thiazolidinediones

I.5.1 Adding pioglitazone compared to adding placebo

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

I.6 Combinations

I.6.1 Adding dapagliflozin + saxagliptin compared to adding placebo

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

I.6.2 Adding dapagliflozin + saxagliptin compared to adding dapagliflozin

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

Appendix J GRADE tables – Model 3: Type 2 diabetes and chronic kidney disease

J.1 DPP-4 inhibitors

J.1.1 Adding linagliptin compared to adding placebo

Table 1: Clinical evidence profile: Adding linagliptin compared to adding placebo

No of studies	Desig n	Risk of bias	Indirectn ess	Inconsiste	Imprecisi on	Other considerati ons	Interventi on N	Control	Relativ e effect (95% CI)	Absolute effect	Certain ty
all-cause mortality at end of follow up – 8.8 months		Dias	E33	ncy	Oil	OHS	OII IV	IN	Cij	enect	ty
2	RCT	very seriou s ¹	not serious	not serious	very serious ²	NA	5/250	4/243	RR 1.20 (0.33, 4.38)	3 more per 1000 (11 fewer to 56 more)	very low
cardiovascular mortality at end of follow up – 5.5 months									,		
1 (groop 2017)	RCT	not seriou s	not serious	NA ³	very serious ²	NA	2/182	0/178	PETO OR 7.27 (0.45, 116.68)	11 more per 1000 (4 fewer to 26 more)	low
non-fatal stroke at end of follow up – 8.8 months									·		
2	RCT	not seriou	not serious	serious ⁴	very serious ⁵	NA	1/250	1/243	RD - 0.00 (- 0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	very low

GRADE tables – Model 3: Type 2 diabetes and chronic kidney disease

non-fatal myocardial											
infarction at end of follow up – 8.8 months											
2	RCT	very seriou s ¹	not serious	serious ⁴	very serious ²	NA	5/250	2/243	RR 2.11 (0.49, 9.20)	9 more per 1000 (4 fewer to 68 more)	very low
hospitalisation for heart failure at end of follow up – 16 months											
2	RCT	not seriou s	not serious	serious ⁴	very serious ⁶	NA	162/2291	188/22 52	RD - 0.01 (- 0.03, 0.00)	13 fewer per 1000 (28 fewer to 3 more)	very low
hospitalisation for heart failure at end of follow up – 26.4 months											
1 (rosenstock 2019a)	RCT	not seriou	not serious	NA ³	serious ⁷	NA NA	2109	2074	HR 0.84 (0.68, 1.04)	Not estimable	modera te
acute kidney injury at end of follow up – 12 months											
1 (mcgill 2013)	RCT	very seriou s ¹	not serious	NA ³	very serious ²	NA	5/68	4/65	RR 1.19 (0.34, 4.25)	12 more per 1000 (41 fewer to 200 more)	very low
development of end stage kidney disease at end of follow up – 5.5 months									ŕ		
1 (groop 2017)	RCT	not seriou	not serious	NA ³	not serious	NA NA	0/182	0/178	RD 0.00 (- 0.01, 0.01)	0 fewer per 1000 (11 fewer to 11 more)	high
hypoglycaemia episodes at end of follow up – 8.8 months	IXOI	3	3611003	IVA	SCHOUS	IVA	0/102	0/1/0	0.01)	illore)	riigii

GRADE tables - Model 3: Type 2 diabetes and chronic kidney disease

2 severe hypoglycaemic episodes at end of follow up – 8.8 months	RCT	very seriou s ¹	not serious	serious ⁸	serious ⁷	NA	67/250	42/243	RR 1.54 (1.14, 2.07)	93 more per 1000 (24 more to 184 more)	very low
2 hba1c change (%, lower scores are better, change and final scores) at end of	RCT	not seriou s	not serious	serious ⁴	very serious ⁵	NA	3/250	3/243	RD - 0.00 (- 0.02, 0.02)	0 fewer per 1000 (21 fewer to 20 more)	very low
follow up – 7.8 months	RCT	not seriou s	not serious	not serious	serious ⁹	NA	289	277	MD - 0.60 (- 0.75, - 0.45)	MD 0.60 lower (0.75 lower to 0.45 lower)	modera te
weight change (kg, lower scores are better, change and final scores) at end of follow up – 9 months										MD 0.95	
2	RCT	very seriou s ¹	not serious	not serious	serious ¹⁰	NA	128	121	MD - 0.95 (- 3.23, 1.33)	lower (3.23 lower to 1.33 higher)	very low

- 1. >33.3% of the studies in the meta-analysis were at high 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. 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. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.63 (0.8-0.9 = serious, <0.8 = very serious).
- 7. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 8. I2 between 50% and 75%
- 9. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 10. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

J.1.2 Switching from or adding to linagliptin compared to switching from or adding to linaglutide

Table 2: Clinical evidence profile: Linagliptin compared to liraglutide (switching from, or adding to, other glucose-lowering drugs)

No of studies	Desig n	Risk of bias	Indirectne ss	Inconsisten cy	Imprecisi on	Other consideratio ns	Interventi on N	Contr ol N	Relativ e effect (95% CI)	Absolute effect	Certaint y
all-cause mortality at end of follow up - 48 months											
1 (hiramatsu 2018)	RCT	very seriou s ¹	not serious	NA ²	very serious ³	NA	2/45	2/45	RR 1.00 (0.15, 6.79)	0 fewer per 1000 (38 fewer to 257 more)	very low
non-fatal myocardial infarction at end of follow up - 48 months											
1 (hiramatsu 2018)	RCT	very seriou s ¹	not serious	NA ²	very serious ³	NA	2/45	1/45	RR 2.00 (0.19, 21.28)	22 more per 1000	very low

GRADE tables – Model 3: Type 2 diabetes and chronic kidney disease

OTTABL tables Woder 5. 1	ypo z aic	abotoo ant	a officiallo ittali	ey alcoace							
										(18 fewer	
										to 451	
										more)	
hospitalisation for heart										1110107	
failure at end of follow											
up - 48 months											
										0 fewer	
									RR	per 1000	
		very							1.00	(52 fewer	
		seriou	not		very				(0.21,	to 246	
1 (hiramatsu 2018)	RCT	s ¹	serious	NA ²	serious ³	NA	3/45	3/45	4.69)	more)	very low
development of end	1.01		CONCUC	147 (Concac	100	0/10	0/10	1.00)	1110107	very lev
stage kidney disease at											
end of follow up - 48											
months											
										0 fewer	
									RR	per 1000	
		very							1.00	(52 fewer	
		seriou	not		very				(0.21,	to 246	
1 (hiramatsu 2018)	RCT	s ¹	serious	NA ²	serious ³	NA	3/45	3/45	4.69)	more)	very low
	INCT	3	Serious	INA	Serious	INA	3/43	3/43	4.09)	illore)	very low
cardiac arrhythmia at											
end of follow up - 48											
months											
										22 more	
									RR	per 1000	
		very							2.00	(18 fewer	
		seriou	not		very				(0.19,	to 451	
1 (hiramatsu 2018)	RCT	s ¹	serious	NA ²	serious ³	NA	2/45	1/45	21.28)	more)	very low
	INCT	3	3611003	INA	Serious	INA	2/43	1/43	21.20)	more)	very low
hba1c change (%, lower											
values are better, final											
scores) at end of follow											
up - 48 months											
										MD 0.05	
									MD -	lower	
		very							0.05	(0.34 lower	
		seriou	not		not				(-0.34,	to 0.24	
1 (hiramatsu 2018)	RCT	seriou s ¹	serious	NA ²	serious	NA	32	32	0.24)	higher)	low
i (iliiailiaisu 2010)	ICI	٥.	Sellous	INA-	Sellous	INA	JZ	JZ	0.24)	nigher)	IUW

GRADE tables - Model 3: Type 2 diabetes and chronic kidney disease

bmi change (kg/m2, lower values are better, final scores) at end of follow up - 48 months											
		very seriou	not		Verv				MD 0.10 (-1.84,	MD 0.10 higher (1.84 lower to 2.04	
1 (hiramatsu 2018)	RCT	s ¹	serious	NA ²	very serious ⁴	NA	32	32	2.04)	higher)	very low

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

J.1.3 Adding saxagliptin compared to adding placebo

Table 3: Clinical evidence profile: Adding saxagliptin compared to adding placebo

No of studies	Desig n	Risk of bias	Indirectn ess	Inconsiste ncy	Imprecisi on	Other considerati ons	Interventi on N	Contr ol N	Relativ e effect (95% CI)	Absolute effect	Certain ty
all-cause mortality at end of follow up – 12 months											
1 (nowicki 2011a)	RCT	very seriou s ¹	not serious	NA ²	very serious ³	NA	3/85	4/85	RR 0.75 (0.17, 3.25)	12 fewer per 1000 (39 fewer to 106 more)	very low
hypoglycaemia episodes at end of follow up – 12 months	NOT	3	Serious	INC	Serious	INA	0,00	4/00	3.23)	more)	IOVV

GRADE tables - Model 3: Type 2 diabetes and chronic kidney disease

1 (nowicki 2011a)	RCT	very seriou s ¹	not serious	NA ²	very serious ³	NA	8/85	4/85	RR 2.00 (0.63, 6.39)	47 more per 1000 (18 fewer to 254 more)	very low
development of end stage kidney disease at end of follow up – 12 months											
1 (nowicki 2011a)	RCT	very seriou s ¹	not serious	NA ²	very serious ³	NA	0/85	2/85	PETO OR 0.13 (0.01, 2.16)	24 fewer per 1000 (56 fewer to 9 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up – 12 months									,		
1 (nowicki 2011a)	RCT	very seriou s ¹	not serious	NA ²	serious ⁴	NA	26	34	MD - 0.63 (- 1.24, - 0.02)	MD 0.63 lower (1.24 lower to 0.02 lower)	very low

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

J.1.4 Sitagliptin compared to linagliptin

Table 4: Clinical evidence profile: Sitagliptin compared to linagliptin (switching from, or adding to, other glucose-lowering drugs)

						Other			Relative		
	Desig	Risk of	Indirectne	Inconsisten	Imprecisio	consideratio	Interventio	Contr	effect	Absolute	Certaint
No of studies	n	bias	SS	су	n	ns	n N	ol N	(95% CI)	effect	у

GRADE tables – Model 3: Type 2 diabetes and chronic kidney disease

all acres montality at	.) 0 = 0	1		noy alocaec							
all-cause mortality at end of follow up - 48											
months 1 (hiramatsu 2018)	RCT	very serious	not serious	NA ²	very serious ³	NA	2/49	2/45	RR 0.92 (0.13, 6.25)	4 fewer per 1000 (38 fewer to 233 more)	very low
non-fatal myocardial infarction at end of follow up - 48 months											
1 (hiramatsu 2018)	RCT	very serious	not serious	NA ²	very serious ³	NA	3/49	2/45	RR 1.38 (0.24, 7.87)	17 more per 1000 (34 fewer to 305 more)	very low
hospitalisation for heart failure at end of follow up - 48 months											
1 (hiramatsu 2018)	RCT	very serious	not serious	NA ²	very serious ³	NA	3/49	3/45	RR 0.92 (0.20, 4.32)	5 fewer per 1000 (54 fewer to 221 more)	very low
development of end stage kidney disease at end of follow up - 48 months									,		
1 (hiramatsu 2018)	RCT	very serious	not serious	NA ²	very serious ³	NA	5/49	3/45	RR 1.53 (0.39, 6.04)	35 more per 1000 (41 fewer to 336 more)	very low
cardiac arrhythmia at end of follow up - 48 months											

GRADE tables - Model 3: Type 2 diabetes and chronic kidney disease

1 (hiramatsu 2018) hba1c change (%, lower values are	RCT	very serious	not serious	NA ²	very serious ³	NA	2/49	2/45	RR 0.92 (0.13, 6.25)	4 fewer per 1000 (38 fewer to 233 more)	very low
better, final scores) a											
end of follow up - 48 months											
1 (hiramatsu 2018)	RCT	very serious	not serious	NA ²	serious ⁴	NA	34	32	MD 0.34 (-0.02, 0.70)	MD 0.34 higher (0.02 lower to 0.70 higher)	very low
bmi change (kg/m2, lower values are better, final scores) a end of follow up - 48 months											
1 (hiramatsu 2018)	RCT	very serious	not serious	NA ²	very serious ⁵	NA	34	32	MD 1.10 (-1.05, 3.25)	MD 1.10 higher (1.05 lower to 3.25 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 both ends of the defined MIDs (-0.80, 0.80)

liraglutide

Table 5: Clinical evidence profile: Sitagliptin compared to liraglutide (switching from, or adding to, other glucose-lowering drugs)

No of studies	Desig n	Risk of bias	Indirectne ss	Inconsisten cy	Imprecision	Other consideratio	Interventio n N	Contr	Relativ e effect (95% CI)	Absolute effect	Certaint v
all-cause mortality at end of follow up - 48 months		3.03	33			,,,		0.11	C.,		
1 (hiramatsu 2018)	RCT	very serious	not serious	NA ²	very serious ³	NA	2/49	2/45	RR 0.92 (0.13, 6.25)	4 fewer per 1000 (38 fewer to 233 more)	very low
non-fatal myocardial infarction at end of follow up - 48 months											
1 (hiramatsu 2018)	RCT	very serious	not serious	NA ²	very serious ³	NA	3/49	1/45	RR 2.76 (0.30, 25.54)	39 more per 1000 (16 fewer to 545 more)	very low
hospitalisation for heart failure at end of follow up - 48 months											
1 (hiramatsu 2018)	RCT	very serious	not serious	NA ²	very serious ³	NA	3/49	3/45	RR 0.92 (0.20, 4.32)	5 fewer per 1000 (54 fewer to 221 more)	very low
development of end stage kidney						-		.,	/	/	

GRADE tables – Model 3: Type 2 diabetes and chronic kidney disease

disease at end of				,							
follow up - 48 months											
1 (hiramatsu 2018)	RCT	very serious	not serious	NA ²	very serious ³	NA	5/49	3/45	RR 1.53 (0.39, 6.04)	35 more per 1000 (41 fewer to 336 more)	very low
cardiac arrhythmia at end of follow up - 48 months											
1 (hiramatsu 2018)	RCT	very serious	not serious	NA ²	very serious ³	NA	2/49	1/45	RR 1.84 (0.17, 19.57)	19 more per 1000 (18 fewer to 413 more)	very low
hba1c change (%, lower values are better, final scores) at end of follow up - 48 months											·
1 (hiramatsu 2018)	RCT	very serious	not serious	NA ²	serious ⁴	NA	34	32	MD 0.29 (-0.11, 0.69)	MD 0.29 higher (0.11 lower to 0.69 higher)	very low
bmi change (kg/m2, lower values are better, final scores) at end of follow up – 48 months											
1 (hiramatsu 2018)	RCT	very serious	not serious	NA ²	serious ⁵	NA	34	32	MD 1.20~(- 0.62, 3.02)	MD 1.20 higher~(0.6 2 lower to	very low

GRADE tables - Model 3: Type 2 diabetes and chronic kidney disease

					3.02	
					higher)	

- 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 (-0.80, 0.80)

J.1.6 Adding vildagliptin compared to adding sitagliptin

Table 6: Clinical evidence profile: Adding vildagliptin compared to adding sitagliptin

	De sig	Risk of bias	Indire ctnes s	Incon	Impr ecisi on	Other consider ations	Interv ention N	Con trol N	Relative effect (95% CI)	Absolute effect	Cert
all-cause mortality at end of follow up – 5.5 months	n	Dias	3	су	OII	ations	N	N	(93 % C1)		У
1 (kothny 2015) cardiovascular mortality at end of follow	RC T	not serio us	not seriou s	NA ¹	very serio us ²	NA	2/83	2/65	RR 0.78 (0.11, 5.41)	7 fewer per 1000 (27 fewer to 136 more)	low
up – 5.5 months											
1 (kothny 2015)	RC T	very serio us ³	not seriou	NA ¹	very serio us ²	NA	1/83	0/65	PETO OR 5.95 (0.11, 308.70)	12 more per 1000 (11 fewer to 36 more)	very low

GRADE tables - Model 3: Type 2 diabetes and chronic kidney disease

- 71											
hypoglyaemia episodes at end of follow up – 5.5 months											
1 (kothny 2015)	RC T	not serio us	not seriou s	NA ¹	very serio us ²	NA	13/83	10/6 5	RR 1.02 (0.48, 2.17)	3 more per 1000 (80 fewer to 180 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up – 5.5 months											
1 (kothny 2015)	RC T	serio us ⁴	not seriou s	NA ¹	not serio us	NA	78	62	MD 0.02 (-0.33, 0.37)	MD 0.02 higher (0.33 lower to 0.37 higher)	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. >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

J.2 GLP-1 receptor agonists

J.2.1 Switching to dulaglutide compared to insulin

Table 7: Clinical evidence profile: Switching to dulaglutide compared to switching to insulin

No of studies	Desig n Risk of bias	Indirectne ss	Inconsisten cy	Imprecisi on	Other considerati ons	Interventi on N	Contr ol N	Relati ve effect	Absolu te effect	Certain ty
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GRADE tables - Model 3: Type 2 diabetes and chronic kidney disease

or the Education in the Education Type Education			Thailey dies						(95%		
									CI)		
all-cause mortality at end of follow up - 12 months											
1 (tuttle 2018)	RCT	very seriou s ¹	not serious	NA ²	very serious ³	NA	8/382	4/194	RR 1.02 (0.31, 3.33)	0 more per 1000 (14 fewer to 48 more)	very low
cardiovascular mortality at end of follow up - 12 months											
1 (tuttle 2018)	RCT	very seriou s ¹	not serious	NA ²	very serious ³	NA	8/382	4/194	RR 1.02 (0.31, 3.33)	0 more per 1000 (14 fewer to 48 more)	very low
persistent signs of worsening kidney disease at end of follow up - 12 months											
1 (tuttle 2018)	RCT	very seriou s ¹	not serious	NA ²	serious ⁴	NA	152/382	91/19 4	RR 0.85 (0.70, 1.03)	71 fewer per 1000 (141 fewer to 14 more)	very low
development of end stage kidney disease at end of follow up - 12 months										ŕ	
1 (tuttle 2018)	RCT	very seriou s ¹	not serious	NA ²	very serious ³	NA	22/382	16/19 4	RR 0.70	25 fewer	very low

GRADE tables – Model 3: Type 2 diabetes and chronic kidney disease

									(0.38, 1.30)	per 1000 (52 fewer to 25 more)	
death from renal causes at end of follow up - 12 months											
1 (tuttle 2018)	RCT	very seriou s ¹	not serious	NA ²	not serious	NA	0/382	0/194	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	low
hypoglycaemia episodes at end of follow up - 12 months											
1 (tuttle 2018)	RCT	very seriou s ¹	not serious	NA ²	not serious	NA	12/382	16/19 4	RR 0.38 (0.18, 0.79)	51 fewer per 1000 (67 fewer to 17 fewer)	low
at night hypoglycaemic episodes at end of follow up - 12 months											
1 (tuttle 2018)	RCT	very seriou s ¹	not serious	NA²	not serious	NA	84/382	93/19 4	RR 0.46 (0.36, 0.58)	fewer per 1000 (306 fewer to 200 fewer)	low

GRADE tables - Model 3: Type 2 diabetes and chronic kidney disease

severe hypoglycaemic episodes at end of follow up - 12 months											
1 (tuttle 2018)	RCT	very seriou s ¹	not serious	NA²	not serious	NA	5/382	13/19 4	RR 0.20 (0.07, 0.54)	fewer per 1000 (62 fewer to 31 fewer)	low
hba1c change (%, lower values are better, change scores) at end of follow-up - 12 months											
1 (tuttle 2018)	RCT	very seriou s ¹	not serious	NA ²	not serious	NA	363	186	MD - 0.10 (-0.34, 0.14)	MD 0.10 lower (0.34 lower to 0.14 higher)	low
weight change (kg, lower values are better, change scores) at end of follow-up - 12 months											
1 (tuttle 2018)	RCT	very seriou s ¹	not serious	NA ²	not serious	NA	382	194	MD - 3.80 (-4.81, -2.79)	MD 3.80 lower (4.81 lower to 2.79 lower)	low

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

cross one end of the defined MIDs (0.80, 1.25)

J.2.2 Switching to exenatide compared to switching to insulin

Table 8: Clinical evidence profile: Switching to exenatide compared to switching to insulin

	Desig	Risk of	Indirectne	Inconsisten	Imprecisi	Other consideratio	Interventi	Contr	Relativ e effect (95%	Absolute	Certain
No of studies	n	bias	SS	су	on	ns	on N	ol N	CI)	effect	ty
hypoglycaemia episodes at end of follow-up - 5.5 months											
1 (wang 2020b)	RCT	very seriou s ¹	not serious	NA ²	serious ³	NA	10/46	20/46	RR 0.50 (0.26, 0.95)	217 fewer per 1000 (320 fewer to 23 fewer)	very low
severe hypoglycaemic episodes at end of follow-up - 5.5 months											
1 (wang 2020b)	RCT	very seriou s ¹	not serious	NA ²	very serious ⁴	NA	0/46	2/46	Peto OR 0.13 (0.01, 2.15)	44 fewer per 1000 (102 fewer to 15 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow-up - 5.5 months											
1 (wang 2020b)	RCT	very seriou s ¹	not serious	NA ²	serious ⁵	NA	43	38	MD 0.22 (-0.43, 0.87)	MD 0.22 higher (0.43 lower to 0.87 higher)	very low

GRADE tables - Model 3: Type 2 diabetes and chronic kidney disease

weight change (kg, lower values are better, change scores) at end of follow-up - 5.5 months											
1 (wang 2020b)	RCT	very seriou s ¹	not serious	NA ²	serious ⁶	NA	43	38	MD - 2.68 (-4.47, - 0.89)	MD 2.68 lower (4.47 lower to 0.89 lower)	very low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 4. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 5. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 6. 95% confidence intervals cross one end of the defined MIDs (-3.00, 3.00)

J.2.3 Adding Liraglutide compared to adding placebo

Table 9: Clinical evidence profile: Adding liraglutide compared to adding placebo

	Desig	Risk of	Indirectnes	Inconsistenc	Imprecisio	Other consideration	Interventio	Contro	Relative effect	Absolute	Certaint
No of studies	n	bias	s	у	n	s	n N	ΙN	(95% CI)	effect	у
all-cause mortality at end of follow up – 6 months											

GRADE tables - Model 3: Type 2 diabetes and chronic kidney disease

1 (davies 2016)	RCT	serious	not serious	NA ²	very serious ³	NA	4/140	1/137	PETO OR 3.31 (0.57, 19.33)	21 more per 1000 (10 fewer to 52 more)	very low
cardiovascular mortality at end of follow up – 6 months											
1 (davies 2016)	RCT	serious	not serious	NA ²	very serious ³	NA	2/140	1/137	PETO OR 1.92 (0.20, 18.57)	7 more per 1000 (17 fewer to 31 more)	very low
diabetic ketoacidosis at end of follow up – 6 months											
1 (davies 2016)	RCT	serious	not serious	NA ²	very serious ³	NA	1/140	0/137	PETO OR 7.23 (0.14, 364.57)	7 more per 1000 (7 fewer to 21 more)	very low
hypoglycaemia episodes at end of follow up – 6 months											
1 (davies 2016)	RCT	serious	not serious	NA ²	serious ⁴	NA	29/140	36/137	RR 0.79 (0.51, 1.21)	56 fewer per 1000 (128 fewer to 55 more)	low
severe hypoglycaemic episodes at end of follow up – 6 months											

GRADE tables - Model 3: Type 2 diabetes and chronic kidney disease

1 (davies 2016)	RCT	serious	not serious	NA ²	very serious ³	NA	1/140	0/137	PETO OR 7.23 (0.14, 364.57)	7 more per 1000 (7 fewer to 21 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up – 6 months											
1 (davies 2016)	RCT	serious	not serious	NA ²	serious ⁵	NA	140	137	MD -0.66 (-0.90, - 0.42)	MD 0.66 lower (0.90 lower to 0.42 lower)	low
weight change (kg, lower values are better, change scores) at end of follow up – 6 months											
1 (davies 2016)	RCT	serious	not serious	NA ²	not serious	NA	140	137	MD -1.32 (-2.24, - 0.40)	MD 1.32 lower (2.24 lower to 0.40 lower)	moderat e
bmi change (kg/m2, lower values are better, change scores) at end of follow up – 6 months											
1 (davies 2016)	RCT	serious	not serious	NA ²	serious ⁶	NA	140	137	MD -0.50	MD 0.50 lower	low

GRADE tables - Model 3: Type 2 diabetes and chronic kidney disease

				(-0.83, -	(0.83	
				0.17)	lower to	
				,	0.17	
					lower)	

- 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. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 6. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

J.2.4 Adding semaglutide compared to adding placebo

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

		Risk of	Indirect	Inconsis	Impreci	Other conside	Interven	Control	Relative effect (95%	Absolute	
No of studies	Design	bias	ness	tency	sion	rations	tion N	N	CI)	effect	Certainty
health-related quality of life - subscale physical component (sf-36 version 2 [acute version], 0-100, higher values are better, change score) at end of follow up ~ Mean followup: 6 month(s)											
1 (mosenzon 2019)	RCT	not serious	not serious	NA ¹	serious ²	NA	163	161	MD 1.98~(0.57, 3.39)	MD 1.98 higher~(0. 57 higher to 3.39 higher)	moderate

health-related quality of life - subscale mental component (sf-36 version 2 [acute version], 0-100, higher values are better, change score) at end of											
follow up ~ Mean follow- up: 6 month(s)											
1 (mosenzon 2019)	RCT	not serious	not serious	NA ¹	not serious	NA	163	161	MD 0.68~(- 1.23, 2.59)	MD 0.68 higher~(1. 23 lower to 2.59 higher)	high
all-cause mortality at end of follow up ~ Mean follow-up: 40.8 month(s)											
1 (perkovic 2024)	RCT	not serious	not serious	NA ¹	serious ³	NA	1767	1766	HR 0.80~(0.67, 0.96)	Not estimable	moderate
all-cause mortality at end of follow up ~ Mean follow-up: 23.4 month(s)											
2	RCT	not serious	not serious	not serious	serious ³	NA	228/193 0	281/192 7	RR 0.81~(0.69, 0.95)	28 fewer per 1000~(45 fewer to 7 fewer)	moderate
cardiovascular mortality at end of follow up ~ Mean follow-up: 40.8 month(s)											
1 (perkovic 2024)	RCT	not serious	not serious	NA ¹	serious ³	NA	1767	1766	HR 0.71~(0.56, 0.90)	Not estimable	moderate
cardiovascular mortality at end of follow up ~											

Mean follow-up: 23.4 month(s)											
2	RCT	not serious	not serious	not serious	serious ³	NA	124/193 0	170/192 7	RR 0.73~(0.58, 0.91)	24 fewer per 1000~(37 fewer to 8 fewer)	moderate
3-point mace at end of follow-up ~ Mean follow- up: 40.8 month(s)											
1 (perkovic 2024)	RCT	not serious	not serious	NA ¹	serious ³	NA	1767	1766	HR 0.82~(0.58, 0.99)	Not estimable	moderate
3-point mace at end of follow-up ~ Mean follow-up: 40.8 month(s)											
1 (perkovic 2024)	RCT	not serious	not serious	NA¹	serious ³	NA	212/176 7	254/176 6	RR 0.83~(0.70, 0.99)	24 fewer per 1000~(43 fewer to 2 fewer)	moderate
non-fatal stroke at end of follow-up ~ Mean follow- up: 40.8 month(s)									,	,	
1 (perkovic 2024)	RCT	not serious	not serious	NA ¹	serious ³	NA	1767	1766	HR 1.22~(0.84, 1.77)	Not estimable	moderate
non-fatal stroke at end of follow-up ~ Mean follow- up: 40.8 month(s)											
1 (perkovic 2024)	RCT	not serious	not serious	NA ¹	serious ³	NA	63/1767	51/1766	RR 1.23~(0.86, 1.78)	7 more per 1000~(4 fewer to 22 more)	moderate
non-fatal myocardial infarction at end of									Í	,	

follow-up ~ Mean follow-											
up: 40.8 month(s)											
1 (perkovic 2024) non-fatal myocardial infarction at end of follow-up ~ Mean follow- up: 40.8 month(s)	RCT	not serious	not serious	NA ¹	serious ³	NA	1767	1766	HR 0.80~(0.55, 1.16)	Not estimable	moderate
1 (perkovic 2024) unstable angina at end of follow-up ~ Mean follow-	RCT	not serious	not serious	NA¹	serious ³	NA	52/1767	64/1766	RR 0.81~(0.57, 1.16)	7 fewer per 1000~(16 fewer to 6 more)	moderate
up: 40.8 month(s)											
1 (perkovic 2024)	RCT	not serious	not serious	NA ¹	serious ³	NA	12/1767	22/1766	PETO OR 0.55~(0.28, 1.08)	6 fewer per 1000~(12 fewer to 1 more)	moderate
hospitalisation for heart failure at end of follow up ~ Mean follow-up: 6 month(s)											
1 (mosenzon 2019)	RCT	not serious	not serious	NA ¹	very serious ⁴	NA	0/163	1/161	PETO OR 0.13~(0.00, 6.74)	6 fewer per 1000~(18 fewer to 6 more)	low
acute kidney injury at end of follow up ~ Mean follow-up: 23.4 month(s)											
2	RCT	not serious	not serious	not serious	very serious ⁴	NA	126/193 0	124/192 7	RR 1.02~(0.80, 1.29)	1 more per 1000~(13	low

OTABL tables Woder of Typ			,							fewer to	
										19 more)	
persistent signs of worsening kidney disease at end of follow- up ~ Mean follow-up: 40.8 month(s)										,	
1 (perkovic 2024)	RCT	not serious	not serious	NA¹	serious ³	NA	1767	1766	HR 0.73~(0.59, 0.89)	Not estimable	moderate
persistent signs of worsening kidney disease at end of follow- up ~ Mean follow-up: 40.8 month(s)											
1 (perkovic 2024)	RCT	not serious	not serious	NA ¹	serious ³	NA	165/176 7	213/176 6	RR 0.77~(0.64, 0.94)	27 fewer per 1000~(44 fewer to 7 fewer)	moderate
development of end stage kidney disease at end of follow-up ~ Mean follow- up: 40.8 month(s)											
1 (perkovic 2024)	RCT	not serious	not serious	NA ¹	serious ³	NA	1767	1766	HR 0.84~(0.63, 1.12)	Not estimable	moderate
development of end stage kidney disease at end of follow-up ~ Mean follow- up: 40.8 month(s)											
1 (perkovic 2024)	RCT	not serious	not serious	NA ¹	serious ³	NA	87/1767	100/176 6	RR 0.87~(0.66, 1.15)	7 fewer per 1000~(19 fewer to 8 more)	moderate

death from renal causes											
at end of follow-up ~											
Mean follow-up: 40.8 month(s)											
(0)									HR		
4 (БОТ	not .	not .		very		4707	4700	0.97~(0.27,	Not	
1 (perkovic 2024) death from renal causes	RCT	serious	serious	NA ¹	serious ⁴	NA	1767	1766	3.48)	estimable	low
at end of follow-up ~											
Mean follow-up: 40.8 month(s)											
. ,										0 fewer	
									PETO OR	per 1000~(4	
		not	not		very				1.00~(0.29,	fewer to 4	
1 (perkovic 2024)	RCT	serious	serious	NA ¹	serious4	NA	5/1767	5/1766	3.46)	more)	low
hypoglycaemia episodes											
at end of follow up ~ Mean follow-up: 6											
month(s)											
										37 more	
									RR	per 1000~(3	
		not	not						2.96~(0.82,	fewer to	
1 (mosenzon 2019)	RCT	serious	serious	NA ¹	serious ³	NA	9/163	3/161	10.75)	182 more)	moderate
cardiac arrhythmia at end											
of follow-up ~ Mean follow-up: 40.8 month(s)											
										5 more	
									RR	per	
		not	not						1.41~(0.82,	1000~(2 fewer to	
1 (perkovic 2024)	RCT	serious	serious	NA ¹	serious ³	NA	31/1767	22/1766	2.42)	18 more)	moderate
diabetic ketoacidosis at											
end of follow-up ~ Mean follow-up: 40.8 month(s)											
ionow-up. 40.6 monun(s)											

1 (perkovic 2024) severe hypoglycaemic episodes at end of follow up ~ Mean follow-up: 40.8 month(s)	RCT	very serious ⁵	not serious	NA ¹	very serious ⁴	NA	10/1767	7/1766	PETO OR 1.42~(0.55, 3.69)	2 more per 1000~(3 fewer to 6 more)	very low
1 (perkovic 2024) severe hypoglycaemic episodes at end of follow up ~ Mean follow-up: 23.4 month(s)	RCT	not serious	not serious	NA ¹	very serious ⁴	NA	1767	1766	HR 1.02~(0.62, 1.68)	Not estimable	low
hba1c change (%, lower values are better, change scores) at end of follow up ~ Mean follow-up: 23.4	RCT	not serious	not serious	serious ⁶	very serious ⁷	NA	47/1930	46/1927	RD 0.00~(- 0.01, 0.01)	1 more per 1000~(9 fewer to 10 more)	very low
month(s)	RCT	not serious	not serious	not serious	not serious	NA	1930	1927	MD - 0.81~(- 0.89, -0.72)	MD 0.81 lower~(0. 89 lower to 0.72 lower)	high
weight change (kg, lower values are better, change scores) at end of follow up ~ Mean follow-up: 14.9 month(s)									. ,		V

bmi change (kg/m2, lower values are better, change scores) at end of follow up ~ Mean follow-up: 6 month(s)	RCT	very serious ⁵	not serious	very serious ⁸	not serious	NA	1930	1927	MD - 3.72~(- 4.13, -3.32)	MD 3.72 lower~(4. 13 lower to 3.32 lower)	very low
1 (mosenzon 2019)	RCT	not serious	not serious	NA ¹	serious ⁹	NA	163	161	MD - 0.90~(- 1.20, -0.60)	MD 0.90 lower~(1. 20 lower to 0.60 lower)	moderate

- 1. Only one study so no inconsistency
- 2. 95% confidence intervals cross one end of the defined MIDs (-2.00, 2.00)
- 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. >33.3% of the studies in the meta-analysis were at high risk of bias
- 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 = 0.03 (0.8-0.9 = serious, <0.8 = very serious).
- 8. I2 > 75%
- $9.\,95\%$ confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

compared to adding dulaglutide

Table 11: Clinical evidence profile: Adding semaglutide compared to adding dulaglutide

No of studies health-related quality of life - overall (dtr-qol, 0-100, higher values are better, final score) at end of follow up – Mean follow-up: 5.5 month(s)	Desig n	Risk of bias	Indirectne ss	Inconsistenc y	Imprecisio n	Other consideratio ns	Interventio n N	Contr ol N	Relativ e effect (95% CI)	Absolut e effect	Certaint Y
1 (kimura 2023) hospitalisation for heart failure at end of follow up – Mean	RCT	very serious	not serious	NA ²	not serious	NA	54	53	MD 0.90 (-4.35, 6.15)	MD 0.90 higher (4.35 lower to 6.15 higher)	low
1 (kimura 2023) diabetic ketoacidosis at end of follow up –	RCT	serious 3	not serious	NA ²	very serious ⁴	NA	1/54	0/53	PETO OR 7.25 (0.14, 365.61)	19 more per 1000 (17 fewer to 54 more)	very low

Moon follow up: 5.5) P = 2 GIV	I and a second		,							
Mean follow-up: 5.5 month(s)											
1 (kimura 2023)	RCT	serious	not serious	NA ²	serious ⁵	NA	0/54	0/53	RD 0.00 (-0.04, 0.04)	0 fewer per 1000 (36 fewer to 36 more)	low
progression of liver disease at end of follow up – Mean follow-up: 5.5 month(s)											
1 (kimura 2023)	RCT	serious 3	not serious	NA ²	very serious ⁴	NA	18/54	13/53	RR 1.36 (0.74, 2.49)	88 more per 1000 (63 fewer to 365 more)	very low
severe hypoglycaemic episodes at end of follow up – Mean follow-up: 5.5 month(s)									·		
1 (kimura 2023)	RCT	serious	not serious	NA ²	serious ⁵	NA	0/54	0/53	RD 0.00 (-0.04, 0.04)	0 fewer per 1000 (36 fewer to 36 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up – Mean follow-up: 5.5 month(s)											

	J 1			,							
1 (kimura 2023)	RCT	serious	not serious	NA ²	serious ⁶	NA	54	53	MD - 0.40 (-0.63, -0.17)	MD 0.40 lower (0.63 lower to 0.17 lower)	low
weight change (kg, lower values are better, change scores) at end of follow up – Mean follow-up: 5.5 month(s)											
1 (kimura 2023)	RCT	serious	not serious	NA ²	serious ⁷	NA	54	53	MD - 2.50 (-3.36, -1.64)	MD 2.50 lower (3.36 lower to 1.64 lower)	low
bmi change (kg/m2, lower values are better, change scores) at end of follow up – Mean follow-up: 5.5 month(s)											
1 (kimura 2023)	RCT	serious	not serious	NA ²	serious ⁸	NA	54	53	MD - 1.00 (-1.33, -0.67)	MD 1.00 lower (1.33 lower to 0.67 lower)	low

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

5. 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)
- 7. 95% confidence intervals cross one end of the defined MIDs (-3.00, 3.00)
- 8. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

Table 12: Clinical evidence profile: Switching to semaglutide compared to dulaglutide (switching from dulaglutide)

Table 12: Chinear evide	1	1			I	January (1		
No of studies	Desig n	Risk of bias	Indirectne ss	Inconsisten cy	Imprecisio n	Other consideratio ns	Interventio n N	Contr ol N	Relative effect (95% CI)	Absolut e effect	Certaint y
hypoglycaemia episodes at end of follow up – Mean follow-up: 5.5 month(s)											
1 (takahashi 2023)	RCT	seriou s ¹	not serious	NA ²	very serious³	NA	2/35	1/35	RR 2.00 (0.19, 21.06)	29 more per 1000 (23 fewer to 573 more)	very low
severe hypoglycaemic episodes at end of follow up – Mean follow-up: 5.5 month(s)											
1 (takahashi 2023)	RCT	seriou s ¹	not serious	NA ²	very serious ⁴	NA	0/35	0/35	RD 0.00 (-0.05, 0.05)	0 fewer per 1000 (54 fewer to 54 more)	very low
hba1c change (%, lower values are better, change scores) at end											

-	STURBE RABIOS TVICACIO. I	<i>)</i>			-)							
	of follow up – Mean follow-up: 5.5 month(s)											
	1 (takahashi 2023)	RCT	seriou s ¹	not serious	NA ²	serious ⁵	NA	31	32	MD - 0.60 (-0.91, - 0.29)	MD 0.60 lower (0.91 lower to 0.29 lower)	low
	weight change (kg, lower values are better, change scores) at end of follow up – Mean follow-up: 5.5 month(s)											
	1 (takahashi 2023)	RCT	seriou s ¹	not serious	NA ²	serious ⁶	NA	31	32	MD - 2.70 (-3.55, - 1.85)	MD 2.70 lower (3.55 lower to 1.85 lower)	low
	bmi change (kg/m2, lower values are better, change scores) at end of follow up – Mean follow-up: 5.5 month(s)											
	1 (takahashi 2023)	RCT	seriou s ¹	not serious	NA ²	serious ⁷	NA	31	32	MD - 1.00 (-1.34, - 0.66)	MD 1.00 lower (1.34 lower to 0.66 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)

determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.

- 5. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 6. 95% confidence intervals cross one end of the defined MIDs (-3.00, 3.00)
- 7. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

J.2.6 Switching to semaglutide compared to liraglutide

Table 13: Clinical evidence profile: Switching to semaglutide compared to liraglutide (switching from liraglutide)

	Desig	Risk of	Indirectne	Inconsisten	Imprecisi	Other consideratio	Interventi	Contr	Relativ e effect (95%	Absolute	Certain
No of studies	n	bias	SS	су	on	ns	on N	ol N	CI)	effect	ty
hypoglycaemia episodes at end of follow up – Mean follow-up: 5.5 month(s)											
1 (takahashi 2023) severe hypoglycaemic	RCT	seriou s¹	not serious	NA ²	very serious ³	NA	1/20	3/20	RR 0.33 (0.04, 2.94)	fewer per 1000 (144 fewer to 291 more)	very low
episodes at end of follow up – Mean follow-up: 5.5 month(s)											
4 (Askah sahi 2022)	DOT	seriou	not	NIA2	very	NA	0/20	0/20	RD 0.00 (-0.09,	0 fewer per 1000 (92 fewer to 92	very
1 (takahashi 2023)	RCT	s ¹	serious	NA ²	serious ⁴	NA	0/20	0/20	0.09)	more)	low

hba1c change (%, lower scores are better, change scores) at end of follow up – Mean follow-up: 5.5			·								
month(s) 1 (takahashi 2023)	RCT	seriou s ¹	not serious	NA ²	serious ⁵	NA	19	18	MD - 0.50 (-0.86, -0.14)	MD 0.50 lower (0.86 lower to 0.14 lower)	low
weight change (kg, lower scores are better, change scores) at end of follow up - Mean follow-up: 5.5 month(s)											
1 (takahashi 2023)	RCT	seriou	not serious	NA ²	not serious	NA	19	18	MD - 0.20 (-1.87, 1.47)	MD 0.20 lower (1.87 lower to 1.47 higher)	modera te
bmi change (kg/m2, lower scores are better, change scores) at end of follow up – Mean follow-up: 5.5 month(s)									,		
1 (takahashi 2023)	RCT	seriou s ¹	not serious	NA ²	not serious	NA	19	18	MD 0.00 (-0.65, 0.65)	MD 0.00 lower (0.65 lower to 0.65 higher)	modera te

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

3. 95% confidence intervals

cross both ends of the defined MIDs (0.80, 1.25)

- 4. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 5. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

J.3 SGLT2 inhibitors

J.3.1 Adding canagliflozin compared to adding placebo

Table 14: Clinical evidence profile: Adding canagliflozin compared to adding placebo

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 - 22.8 months											
3	RCT	not serio us	not serious	not serious	serious ¹	NA	176/2355	204/24 43	RR 0.93 (0.76, 1.12)	6 fewer per 1000 (20 fewer to 10 more)	moder ate
all-cause mortality at end of follow-up – 28.2 months											
2	RCT	not serio us	not serious	not serious	serious ¹	NA	2356	2353	HR 0.84 (0.69, 1.02)	Not estimable	moder ate
cardiovascular mortality at end of follow-up – 28.2 months											

OT UTBE TOPICS THOUGH OF TYPO E				y aleedee							
2	RCT	not serio us	not serious	not serious	serious ¹	NA	113/2356	141/23 53	RR 0.80 (0.63, 1.02)	12 fewer per 1000 (22 fewer to 1 more)	moder ate
cardiovascular mortality at end of follow-up – 28.2 months											
2	RCT	not serio us	not serious	not serious	serious ¹	NA	2356	2353	HR 0.79 (0.62, 1.01)	Not estimable	moder ate
5-point mace at end of follow-up – 28.2 months											
2	RCT	not serio us	not serious	not serious	serious ¹	NA	283/2356	368/23 53	RR 0.77 (0.67, 0.89)	36 fewer per 1000 (52 fewer to 18 fewer)	moder ate
5-point mace at end of follow-up – 28.2 months											
2	RCT	not serio us	not serious	not serious	serious ¹	NA	2356	2353	HR 0.75 (0.64, 0.88)	Not estimable	moder ate
hospitalisation for heart failure at end of follow-up – 28.2 months											
2	RCT	not serio us	not serious	not serious	serious ¹	NA	90/2356	144/23 53	RR 0.62	23 fewer per 1000	moder ate

CIVIDE tables Wooder 6. Type 2									(0.40	(20 favoranta	
									(0.48, 0.81)	(32 fewer to 12 fewer)	
hospitalisation for heart failure at end of follow-up – 28.2 months											
2	RCT	not serio us	not serious	not serious	not serious	NA	2356	2353	HR 0.61 (0.47, 0.79)	Not estimable	high
acute kidney injury at end of follow-up – 31.4 months											
1 (perkovic 2019)	RCT	not serio us	not serious	NA ²	serious ¹	NA	86/2200	98/219 7	RR 0.88 (0.66, 1.16)	6 fewer per 1000 (15 fewer to 7 more)	moder ate
acute kidney injury at end of follow-up – 31.4 months											
1 (perkovic 2019)	RCT	not serio us	not serious	NA ²	serious ¹	NA	2200	2197	HR 0.85 (0.64, 1.13)	Not estimable	moder ate
persistent signs of kidney disease at end of follow-up – 31.4 months											
1 (perkovic 2019)	RCT	NA	NA	NA ²	not serious	NA	118/2202	188/21 99	RR 0.63	32 fewer per 1000	00
					Serious			99	(0.50, 0.78)	(43 fewer to 19	fewer)

Ort BE tables medere. Type E				y aloodoo							
persistent signs of worsening kidney disease at end of follow-up – 31.4 months											
1 (perkovic 2019)	RCT	not serio us	not serious	NA ²	not serious	NA	2202	2199	HR 0.60 (0.48, 0.75)	Not estimable	high
development of end stage kidney disease at end of follow-up – 31.4 months											
1 (perkovic 2019)	RCT	not serio us	not serious	NA ²	serious ¹	NA	116/2202	165/21 99	RR 0.70 (0.56, 0.88)	22 fewer per 1000 (33 fewer to 9 fewer)	moder ate
development of end stage kidney disease at end of follow-up – 31.4 months											
1 (perkovic 2019)	RCT	not serio us	not serious	NA ²	serious ¹	NA	2202	2199	HR 0.68 (0.54, 0.86)	Not estimable	moder ate
death from renal cause at end of follow-up – 31.4 months											
1 (perkovic 2019)	RCT	NA	NA	NA ²	very serious ³	NA	2/2202	5/2199	PETO OR 0.42 (0.10, 1.86)	1 fewer per 100 (4 fewer to 1 mo	

diabetic ketoacidosis at end of follow-up – 28.2 months											
2	RCT	not serio us	not serious	serious ⁴	very serious ³	NA	15/2354	4/2351	RR 3.42 (0.40, 29.37)	4 more per 1000 (1 fewer to 48 more)	very low
diabetic ketoacidosis at end of follow-up – 31.4 months											
1 (perkovic 2019)	RCT	not serio us	not serious	NA ²	not serious	NA	2200	2197	HR 10.80 (1.39, 83.92)	Not estimable	high
hypoglycaemia episodes at end of follow-up – 28.2 months											
2	RCT	not serio us	not serious	not serious	not serious	NA	268/2354	283/23 51	RR 0.95 (0.81, 1.11)	7 fewer per 1000 (23 fewer to 13 more)	high
hypoglycaemia episodes at end of follow-up – 31.4 months											
1 (perkovic 2019)	RCT	not serio us	not serious	NA ²	serious ¹	NA	2200	2197	HR 0.92 (0.77, 1.10)	Not estimable	moder ate
hba1c change (%, lower values are better, change											

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scores) at end of follow-up – 22.8 months											
3	RCT	not serio us	not serious	not serious	not serious	NA	2505	2416	MD -0.20 (-0.32, - 0.08)	MD 0.20 lower (0.32 lower to 0.08 lower)	high
weight change (kg, lower values are better, change scores) at end of follow-up – 22.8 months											
3	RCT	not serio us	not serious	not serious	not serious	NA	2505	2416	MD -0.90 (-1.38, - 0.43)	MD 0.90 lower (1.38 lower to 0.43 lower)	high

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

J.3.2 Adding dapagliflozin compared to adding placebo

Table 15: Clinical evidence profile: Adding dapagliflozin compared to adding placebo

									Relati		
									ve		
		Risk				Other			effect		
	Desig	of	Indirectn	Inconsiste	Imprecisi	considerati	Interventi	Contro	(95%	Absolute	Certain
No of studies	n	bias	ess	ncy	on	ons	on N	ΙN	CI)	effect	ty

all-cause mortality at end of follow up – Mean follow-up: 21.4 month(s)			ino marioy ar								
4	RCT	very seriou s ¹	not serious	serious ²	not serious	NA	260/3417	320/33 33	RD - 0.01 (-0.03, 0.02)	8 fewer per 1000 (30 fewer to 15 more)	very low
cardiovascular mortality at end of follow up – Mean follow-up: 26.6 month(s)											
3	RCT	seriou s³	not serious	serious ²	very serious ⁴	NA	130/3272	141/31 85	RD - 0.00 (-0.01, 0.01)	4 fewer per 1000 (14 fewer to 6 more)	very low
3-point mace at end of follow up – Mean follow-up: 50.4 month(s)											
1 (wiviott 2019)	RCT	seriou s³	not serious	NA ⁵	not serious	NA	347/2944	372/29 40	RR 0.93 (0.81, 1.07)	9 fewer per 1000 (24 fewer to 9 more)	modera te
hospitalisation for heart failure at end of follow up – Mean follow-up: 50.4 month(s)											
1 (wiviott 2019)	RCT	seriou s³	not serious	NA ⁵	serious ⁶	NA	122/2944	166/29 40	RR 0.73 (0.58, 0.92)	15 fewer per 1000 (23 fewer to 4 fewer)	low
acute kidney injury at end of follow up – Mean follow-up: 24 month(s)											
1 (kohan 2014)	RCT	very seriou s ¹	not serious	NA ⁵	very serious ⁷	NA	0/168	1/84	PETO OR 0.05 (0.00, 3.18)	12 fewer per 1000 (35 fewer to 11 more)	very low

persistent signs of worsening kidney disease at end of follow up – Mean follow-up: 14.8 month(s)											
2	RCT	very seriou s ¹	not serious	serious ²	very serious ⁷	NA	5/313	4/232	PETO OR 0.66 (0.16, 2.65)	1 fewer per 1000 (23 fewer to 20 more)	very low
development of end stage kidney disease at end of follow up – Mean follow-up: 24 month(s)											
1 (kohan 2014)	RCT	very seriou s ¹	not serious	NA ⁵	very serious ⁷	NA	2/168	2/84	RR 0.50 (0.07, 3.49)	12 fewer per 1000 (22 fewer to 59 more)	very low
of follow up – Mean follow-up: 20.5 month(s)											
3	RCT	seriou s³	not serious	serious ²	very serious ⁸	NA	7/3249	6/3249	RD 0.00 (-0.00, 0.00)	0 more per 1000 (2 fewer to 3 more)	very low
hypoglycaemia episodes at end of follow up – Mean follow-up: 11.7 month(s)											
3	RCT	very seriou s ¹	not serious	not serious	serious ⁶	NA	123/473	90/393	RR 0.96 (0.77, 1.20)	9 fewer per 1000 (53 fewer to 46 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 21.4 month(s)											

4	RCT	seriou s³	not serious	serious ²	not serious	NA	27/3417	48/333	RD - 0.01 (-0.01, -0.00)	7 fewer per 1000 (12 fewer to 2 fewer)	low
hba1c change (%, lower values are better, change scores) at end of follow up – Mean follow-up: 11.7 month(s)											
3	RCT	very seriou s ¹	not serious	not serious	not serious	NA	317	310	MD - 0.23 (-0.40, -0.07)	MD 0.23 lower (0.40 lower to 0.07 lower)	low
weight change (kg, lower values are better, change scores) at end of follow up – Mean follow-up: 14.8 month(s)									,		
2	RCT	seriou s³	not serious	very serious ⁹	serious ¹⁰	NA	251	203	MD - 2.15 (-4.22, -0.08)	MD 2.15 lower (4.22 lower to 0.08 lower)	very low
weight change (%, lower values are better, change scores) at end of follow up – Mean follow-up: 5.5 month(s)									,		
1 (pollock 2019)	RCT	very seriou s ¹	not serious	NA ⁵	not serious	NA	144	148	MD - 0.87 (-2.17, 0.43)	MD 0.87 lower (2.17 lower to 0.43 higher)	low

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

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

- 3. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.25 (0.8-0.9 = serious, <0.8 = very serious).
- 5. Only one study so no inconsistency
- 6. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 7. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 8. 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. 12 > 75%
- 10. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

J.3.3 Adding empagliflozin compared to adding placebo

Table 16: Clinical evidence profile: Adding empagliflozin compared to adding placebo

No of studies all-cause mortality at end of follow-up	Desig n	Risk of bias	Indirectnes s	Inconsistenc y	Imprecisio n	Other consideration s	Interventio n N	Control N	Relativ e effect (95% CI)	Absolute effect	Certaint y
– 24.6 months	RCT	not seriou s	not serious	not serious	serious ¹	NA	144/1917	95/107 1	RR 0.77 (0.60, 0.98)	21 fewer per 1000 (36 fewer to 2 fewer)	moderat e

all-cause mortality at end of follow-up	71										
- 37.2 months											
1 (zinman 2015) cardiovascular	RCT	not seriou s	not serious	NA ²	serious ¹	NA	1498	752	HR 0.76 (0.59, 0.98)	Not estimable	moderat e
mortality at end of follow-up – 37.2 months											
1 (zinman 2015)	RCT	not seriou s	not serious	NA ²	serious ¹	NA	94/1498	65/752	RR 0.73 (0.54, 0.98)	24 fewer per 1000 (40 fewer to 1 fewer)	moderat e
cardiovascular mortality at end of follow up – 37.2 months											
1 (zinman 2015)	RCT	not seriou s	not serious	NA ²	serious ¹	NA	1498	752	HR 0.71 (0.52, 0.97)	Not estimable	moderat e
hospitalisation for heart failure at end of follow-up – 37.2 months											
1 (zinman 2015)	RCT	not seriou s	not serious	NA ²	serious ¹	NA	66/1498	53/752	RR 0.63 (0.44, 0.89)	26 fewer per 1000 (39 fewer to 8 fewer)	moderat e
hospitalisation for heart failure at end of follow up – 37.2 months											

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1 (zinman 2015)	RCT	not seriou s	not serious	NA ²	serious¹	NA	1498	752	HR 0.61 (0.42, 0.89)	Not estimable	moderat e
cardiac arrhythmia at end of follow-up – 12 months									,		
1 (barnett 2014)	RCT	not seriou s	not serious	NA ²	very serious ³	NA	3/419	5/319	PETO OR 0.45 (0.11, 1.85)	9 fewer per 1000 (24 fewer to 7 more)	low
hypoglycaemia episodes at end of follow-up – 12 months											
1 (barnett 2014)	RCT	not seriou s	not serious	NA ²	serious ¹	NA	114/419	88/319	RR 0.99 (0.78, 1.25)	4 fewer per 1000 (61 fewer to 69 more)	moderat e
severe hypoglycaemia episodes at end of follow-up – 12 months	1,61				55.1545			36/6/16	1123	e.e,	
1 (barnett 2014)	RCT	not seriou s	not serious	NA ²	very serious ³	NA	6/419	6/319	RR 0.76 (0.25, 2.34)	4 fewer per 1000 (14 fewer to 25 more)	low
hba1c change (%, lower values are better, change scores) at end of follow-up – 12 months											

GRADE tables - Model 3: Type 2 diabetes and chronic kidney disease

1 (barnett 2014) weight change (kg, lower values are better, change scores) at end of follow-up – 12 months	RCT	not seriou s	not serious	NA ²	serious ⁴	NA	419	319	MD - 0.46 (- 0.59, - 0.33)	MD 0.46 lower (0.59 lower to 0.33 lower)	moderat e
1 (barnett 2014)	RCT	not seriou s	not serious	NA ²	not serious	NA	419	319	MD - 1.55 (- 2.00, - 1.10)	MD 1.55 lower (2.00 lower to 1.10 lower)	high

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

J.3.4 Adding empagliflozin compared to adding linagliptin

Table 17: Clinical evidence profile: Adding empagliflozin compared to adding linagliptin

						 					
									Relativ		
		Risk				Other			e effect		
	Desi	of	Indirectn	Inconsiste	Imprecis	considerati	Intervent	Contr	(95%		Certai
No of studies	gn	bias	ess	ncy	ion	ons	ion N	ol N	CI)	Absolute effect	nty
hypoglycaemia episodes at											
end of follow up - 12 months											

GRADE tables - Model 3: Type 2 diabetes and chronic kidney disease

1 (Raman 2022)	RCT	very seriou s ¹	not serious	NA ²	serious ³	NA	23/52	16/55	RR 1.52 (0.91, 2.54)	151 more per 1000 (26 fewer to 448 more)	very low
hba1c change (%, lower values are better, final scores) at end of follow up – 12 months											
1 (Raman 2022)	RCT	very seriou s ¹	not serious	NA ²	serious ⁴	NA	52	55	MD - 0.34 (-0.67, - 0.01)	MD 0.34 lower (-0.67 lower to - 0.01 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)

J.3.5 Adding ertugliflozin compared to adding placebo

Table 18: Clinical evidence profile: Adding ertugliflozin compared to adding placebo

No	of studies	Desi gn	Risk of bias	Indirectn ess	Inconsiste ncy	Imprecis ion	Other considerati ons	Intervent ion N	Contr ol N	Relativ e effect (95% CI)	Absolute effect	Certai nty
	cause mortality at end of low up – 12 months											

				1		1				1	
1 (grunberger 2018)	RCT	very seriou s ¹	not serious	NA ²	very serious ³	NA	7/313	3/154	RR 1.15 (0.30, 4.38)	3 more per 1000 (14 fewer to 66 more)	very low
hypoglycaemia episodes at end of follow up – 12 months											
1 (grunberger 2018)	RCT	very seriou s ¹	not serious	NA ²	very serious ³	NA	67/313	35/15 4	RR 0.94 (0.66, 1.35)	13 fewer per 1000 (78 fewer to 80 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up – 29 months											
2	RCT	very seriou s ¹	not serious	not serious	not serious	NA	800	372	MD - 0.14 (-0.30, 0.02)	MD 0.14 lower (0.30 lower to 0.02 higher)	low
weight change (kg, lower values are better, change scores) at end of follow up – 29 months											
2	RCT	very seriou s ¹	not serious	not serious	serious ⁴	NA	691	318	MD - 2.05 (-2.53, - 1.57)	MD 2.05 lower (2.53 lower to 1.57 lower)	very low

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 (-2.40, 2.40)

J.4 Sulphonylureas

J.4.1 Adding glimepiride compared to adding insulin

Table 19: Clinical evidence profile: Adding glimepiride compared to adding insulin

	Desig	Risk of	Indirectn	Inconsiste	Imprecisi	Other considerati	Interventi	Contr	Relati ve effect (95%	Absolute	Certain
No of studies	n	bias	ess	ncy	on	ons	on N	ol N	CI)	effect	ty
hypoglycaemia episodes at end of follow up - 5.5 months				,					,		,
1 (Li 2014c)	RCT	very seriou s ¹	not serious	NA ²	not serious	NA	7/29	19/26	RR 0.33 (0.17, 0.66)	489 fewer per 1000 (609 fewer to 251 fewer)	low
hba1c change (%, lower values are better, final scores) at end of follow up - 5.5 months											
1 (li 2014c)	RCT	very seriou s ¹	not serious	NA ²	serious ³	NA	29	26	MD - 0.60 (-1.29, 0.09)	MD 0.60 lower (1.29 lower to 0.09 higher)	very low
weight change (kg, lower values are better, final											

GRADE tables - Model 3: Type 2 diabetes and chronic kidney disease

scores) at end of follow up - 5.5 months											
		very							MD - 2.90 (-	MD 2.90 lower (11.66 lower	
		seriou	not		very				11.66,	to 5.86	very
1 (li 2014c)	RCT	s ¹	serious	NA ²	serious4	NA	29	26	5.86)	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 (-3.00, 3.00)

J.5 Thiazolidinediones

J.5.1 Adding pioglitazone compared to adding placebo

Table 20: Clinical evidence profile: Adding pioglitazone compared to adding placebo

No of studies hypoglycaemia episodes at end of follow up - 6 months	Desig n	Risk of bias	Indirectne ss	Inconsisten cy	Imprecisi on	Other consideratio ns	Interventi on N	Contr ol N	Relativ e effect (95% CI)	Absolute effect	Certaint y
1 (galle 2012) severe hypoglycaemic	RCT	very seriou s ¹	not serious	NA ²	very serious ³	NA	2/20	2/19	RR 0.95 (0.15, 6.08)	5 fewer per 1000 (90 fewer to 535 more)	very low

GRADE tables - Model 3: Type 2 diabetes and chronic kidney disease

episodes at end of follow up - 6 months											
1 (galle 2012) hba1c change (%, lower is better, scores) at end of follow up - 6 months	RCT	very seriou s ¹	not serious	NA ²	very serious ⁴	NA	0/20	0/19	RD 0.00 (-0.09, 0.09)	0 fewer per 10 (95 fewer to 9	
1 (galle 2012)	RCT	very seriou s ¹	not serious	NA ²	serious ⁵	NA	19	17	MD - 0.81 (-1.46, -0.16)	MD 0.81 lower (1.46 lower to 0.16 lower)	very low

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

J.6 Combinations

J.6.1 Adding dapagliflozin + saxagliptin compared to adding placebo

Table 21 Clinical evidence profile: Adding dapagliflozin + saxagliptin compared to adding placebo

			0 1 0		<u> </u>						
		Risk				Other			Relative		
	Desig	of	Indirectn	Inconsiste	Imprecisi	considerati	Interventi	Contr	effect	Absolute	Certain
No of studies	n	bias	ess	ncy	on	ons	on N	ol N	(95% CI)	effect	ty

TO E GIGI	l	I	l alocaco							
		not		very					,	very
RCT	s ¹	serious	NA ²	serious ³	NA	1/152	0/148	362.84)	19 more)	low
								PETO	13 more per	
	very							OR 2.67	1000	
	seriou	not		very				(0.37,	(13 fewer to	very
RCT	s ¹	serious	NA ²	serious ³	NA	3/152	1/148	19.17)	39 more)	low
									0 fewer per	
	very							RD 0.00	1000	
	seriou	not						(-0.01,	(13 fewer to	very
RCT	s ¹	serious	NA ²	serious ⁴	NA	0/152	0/148		13 more)	low
								,	/	
									133 more	
	very							RR 1.68		
		not					29/14			very
RCT	s ¹		NA ²	serious ⁵	NA	50/152	8			low
								,	,	
								PETO	6 more per	
	very							OR 1.90	1000	
	,									
	seriou	not		very				(0.20,	(16 fewer to	very
	RCT	RCT very seriou s1 RCT very seriou s1 Very seriou s1 Very seriou s1 Very seriou s1 Very seriou s1	RCT very serious not serious very serious not serious	RCT serious not serious NA2 Very seriou not serious NA2 RCT very seriou not serious NA2	Very seriou serious NA2 very serious³ RCT very serious serious NA2 very serious³ RCT very serious serious NA2 serious³ RCT very seriou serious NA2 serious⁴ RCT very seriou serious NA2 serious⁴ RCT very seriou serious NA2 serious⁴	RCT very seriou serious NA2 very serious³ NA Very seriou serious NA2 very serious³ NA	RCT serious not serious NA2 very serious NA 1/152 RCT very seriou sorious NA2 very serious NA 3/152 RCT very seriou sorious NA2 serious NA 3/152 RCT very seriou sorious NA2 serious NA 0/152 RCT very seriou sorious NA2 serious NA 50/152	RCT very seriou s ¹ not serious NA ² very serious ³ NA 1/152 0/148 RCT very seriou s ¹ not serious NA ² very serious ³ NA 3/152 1/148 RCT very seriou s ¹ not serious NA ² serious ⁴ NA 0/152 0/148 RCT very seriou s ¹ not serious NA ² serious ⁵ NA 50/152 29/14 RCT serious NA 50/152 8	Very seriou serious NA2 Very serious NA3 NA3	Very seriou sorious

GRADE tables - Model 3: Type 2 diabetes and chronic kidney disease

hba1c change (%, lower values are better, change scores) at end of follow up – 34 months											
1 (pollock 2019)	RCT	very seriou s ¹	not serious	NA ²	serious ⁶	NA	151	145	MD - 0.58 (-0.80, - 0.36)	MD 0.58 lower (0.80 lower to 0.36 lower)	very low
weight change (%, lower values are better, change scores) at end of follow up – 34 months											
1 (pollock 2019)	RCT	very seriou s ¹	not serious	NA ²	not serious	NA	152	148	MD - 0.04 (-1.32, 1.24)	MD 0.04 lower (1.32 lower to 1.24 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 (0.80, 1.25)
- 6. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

J.6.2 Adding dapagliflozin + saxagliptin compared to adding dapagliflozin

Table 22: Clinical evidence

profile: Adding dapagliflozin + saxagliptin compared to adding dapagliflozin

profile: Adding dapaglifiozin + saxagliptin compared to adding dapaglifiozin												
		Risk				Other			Relative			
	Desig	of	Indirectne	Inconsisten	Imprecisi	considerati	Interventi	Contr	effect	Absolute	Certain	
No of studies	n	bias	ss	су	on	ons	on N	ol N	(95% CI)	effect	ty	
all-cause mortality at end of follow up												
1 (pollock 2019)	RCT	very seriou s ¹	not serious	NA ²	very serious ³	NA	1/152	1/145	PETO OR 0.95 (0.06, 15.33)	0 fewer per 1000 (19 fewer to 18 more)	very low	
persistent signs of worsening kidney disease at end of follow up – 34 months												
1 (pollock 2019)	RCT	very seriou s ¹	not serious	NA ²	very serious ³	NA	3/152	0/145	PETO OR 7.15 (0.74, 69.32)	20 more per 1000 (2 fewer to 42 more)	very low	
diabetic ketoacidosis at end of follow up – 34 months												
1 (pollock 2019)	RCT	very seriou s ¹	not serious	NA ²	very serious ³	NA	0/152	1/145	PETO OR 0.13 (0.00, 6.51)	7 fewer per 1000 (20 fewer to 7 more)	very low	
hypoglycaemia episodes at end of follow up – 34 months												
1 (pollock 2019)	RCT	very seriou s ¹	not serious	NA ²	serious ⁴	NA	50/152	35/14 5	RR 1.36 (0.94, 1.97)	88 more per 1000 (14 fewer to 234 more)	very low	
severe hypoglycaemic episodes at end of follow up – 34 months												

Ì										PETO	13 more per	
			very							OR 7.10	1000	
			seriou	not		very				(0.44,	(5 fewer to 31	very
	1 (pollock 2019)	RCT	s ¹	serious	NA^2	serious ³	NA	2/152	0/145	114.19)	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 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)