National Institute for Health and Care Excellence

Draft for consultation

Type 2 diabetes in adults: management

[F7] 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 L GRADE tables – Model 5: Type 2 diabetes and higher cardiovascular risk

L.1 Adding

L.1.1 Metformin

L.1.1.1 Adding metformin compared to adding placebo

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

Table 1. Offical evidence prome. Adding	De	Risk			<u>g</u> p	Other			Relative		Cert
	_		1		1			C		Alexalista	
	sig	of	Indire	Inconsi	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ions	ntion N	rol N	CI)	effect	У
all-cause mortality at end of follow up Mean follow-up: 35 month(s)											
	RC	serio	not seriou	serious	very seriou			6/40	PETO OR 1.82	12 more per 1000 (8 fewer to 32	very
2	Т	us ¹	S	2	s^3	NA	11/402	0	(0.69, 4.78)	more)	low
cardiovascular mortality at end of follow											
up											
Mean follow-up: 52 month(s)											
1 (kooy 2009)	RC T	serio us ¹	not seriou s	NA ⁴	very seriou s ³	NA	3/196	1/19 4	RR 2.97 (0.31, 28.30)	10 more per 1000 (4 fewer to 141 more)	very low
hospitalisation for heart failure at end of follow up Mean follow-up: 52 month(s)									,		

GIVADE tables Woder 5. Type 2 diabetes and	riigiici	ouraiove	accarai iic	710				_			
1 (kooy 2009)	RC T	serio us¹	not seriou s	NA ⁴	very seriou s ³	NA	3/196	4/19 4	RR 0.74 (0.17, 3.27)	5 fewer per 1000 (17 fewer to 47 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 14.9 month(s)											
4	RC T	not serio us	not seriou s	not serious	not seriou s	NA	291/39 4	285/ 395	RR 1.03 (0.90, 1.17)	21 more per 1000 (70 fewer to 125 more)	high
severe hypoglycaemic episodes at end of follow up Mean follow-up: 15 month(s)											
2	RC T	not serio us	not seriou s	very serious	very seriou s ³	NA	17/283	8/27 9	RR 2.62 (0.27, 25.56)	46 more per 1000 (21 fewer to 704 more)	very low
hba1c change (%, lower values are better, mean difference) at end of follow up Mean follow-up: 19.6 month(s)											
6	RC T	serio us ¹	not seriou s	very serious	seriou s ⁶	NA	611	610	MD -0.47 (-0.80, - 0.13)	MD 0.47 lower (0.80 lower to 0.13 lower)	very low
weight change (kg, lower values are better, mean difference) at end of follow up Mean follow-up: 14.9 month(s)											
4	RC T	serio us¹	not seriou s	very serious	seriou s ⁷	NA	388	393	MD -1.19 (-3.92, 1.54)	MD 1.19 lower (3.92 lower to 1.54 higher)	very low
bmi change (kg/m2, lower values are better, mean difference) at end of follow up Mean follow-up: 35 month(s)											

GRADE tables - Model 5: Type 2 diabetes and higher cardiovascular risk

										MD 0.99	
		not	not		not				MD -0.99	lower	
	RC	serio	seriou	not	seriou				(-1.18, -	(1.18 lower to	
2	Т	us	S	serious	S	NA	402	400	0.80)	0.80 lower)	high

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. Only one study so no inconsistency
- 5. I2 > 75%
- 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 (-2.40, 2.40)

L.1.1.2 Adding metformin compared to adding insulin

Table 2: Clinical evidence profile: Adding metformin compared to adding insulin

•	De	Risk	•			Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow up Mean follow-up: 6 month(s)											
1 (civera 2008)	RC T	seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	0/12	1/13	PETO OR 0.15 (0.00, 7.39)	77 fewer per 1000 (222 fewer to 68 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 6 month(s)									(, ,	,	
1 (civera 2008)	RC T	seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	0/12	1/13	PETO OR 0.15 (0.00, 7.39)	77 fewer per 1000	very low

GRADE tables - Model 5: Type 2 diabetes and higher cardiovascular risk

										(222 fewer to 68 more)	
hba1c change (%, lower values are better, change scores) at end of follow up											
Mean follow-up: 5.5 month(s)											
1 (civera 2008) weight change (kg, lower values are	RC T	seriou s ¹	not seriou s	NA ²	seriou s ⁴	NA	12	13	MD 0.70 (-0.40, 1.80)	MD 0.70 higher (0.40 lower to 1.80 higher)	low
better, change score) at end of follow up Mean follow-up: 5.5 month(s)											
	RC	seriou	not seriou		seriou				MD -1.30	MD 1.30 lower (3.42 lower to	
1 (civera 2008)	T	s ¹	S	NA ²	s ⁵	NA	12	13	(-3.42, 0.82)	0.82 higher)	low

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

L.1.2 DPP-4 inhibitors

L.1.2.1 Adding alogliptin compared to adding placebo

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

Tubio of Chinesis of Lacrico promot / Lauring and	9	••	Pu. Uu .		. g p. a. c.						
	De	Risk	Indir	Incon	Impr	Other	Interv	Con	Relative		Cer
	sig	of	ectn	sisten	ecisi	consider	entio	trol	effect (95%		tain
No of studies	n	bias	ess	су	on	ations	n N	N	CI)	Absolute effect	ty

all-cause mortality at end of follow up Mean follow-up: 6 month(s)											
4	R CT	very serio us ¹	not serio us	serio us²	very serio us ³	NA	3/148	0/4 30	RD 0.00 (- 0.01, 0.01)	2 more per 1000 (5 fewer to 10 more)	ver y low
cardiovascular mortality at end of follow up Mean follow-up: 6 month(s)											
3	R CT	very serio us ¹	not serio us	serio us ²	very serio us ⁴	NA	2/108 4	0/3	RD 0.00 (- 0.01, 0.01)	2 more per 1000 (6 fewer to 10 more)	ver y low
non-fatal myocardial infarction at end of follow up Mean follow-up: 6 month(s)			5.0	5.5					., ., ., .,		
1 (pratley 2009a)	R CT	not serio us	not serio us	NA ⁵	very serio us ⁶	NA	3/397	0/9 7	PETO OR 3.49 (0.20, 60.57)	8 more per 1000 (1 fewer to 16 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 6 month(s)									,	,	
4	R CT	very serio us ¹	not serio us	not serio us	serio us ⁷	NA	148/1 481	50/ 429	RR 1.07 (0.80, 1.44)	9 more per 1000 (23 fewer to 51 more)	ver y low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)										,	
3	R CT	very serio us ¹	not serio us	serio us ²	very serio us ⁸	NA	3/108 4	3/3 33	RD -0.01 (- 0.02, 0.01)	6 fewer per 1000 (17 fewer to 6 more)	ver y low
hba1c change (%, lower values are better, mean difference) at end of follow up Mean follow-up: 6 month(s)											
3	R CT	very serio us ¹	not serio us	not serio us	serio us ⁹	NA	1084	333	MD -0.53 (- 0.63, -0.42)	MD 0.53 lower (0.63 lower to 0.42 lower)	ver y low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)											
4	R CT	not serio us	not serio us	not serio us	not serio us	NA	1480	430	MD 0.17 (- 0.09, 0.43)	MD 0.17 higher (0.09 lower to 0.43 higher)	hig h

analysis were at high risk of bias

- 2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.5 (0.8-0.9 = serious, <0.8 = very serious).
- 4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.37 (0.8-0.9 = serious, <0.8 = very serious).
- 5. Only one study so no inconsistency
- 6. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 7. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 8. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.58 (0.8-0.9 = serious, <0.8 = very serious).
- 9. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

L.1.2.2 Adding linagliptin compared to adding placebo

Table 4: Clinical evidence profile: Adding linagliptin compared to adding placebo

	De	Risk	Indir	Incon	Impr	Other	Interv	Con	Relative		Cer
	sig	of	ectn	siste	ecisio	consider	entio	trol	effect (95%		tain
No of studies	n	bias	ess	ncy	n	ations	n N	N	CI)	Absolute effect	ty
all-cause mortality at end of follow up Mean											
follow-up: 8.5 month(s)											
	R	not	not		very			380/		2 fewer per 1000	ver
	С	serio	serio	serio	serio		373/5	499	RD -0.00 (-	(12 fewer to 8	у
10	T	us	us	us ¹	us ²	NA	274	6	0.01, 0.01)	more)	low
all-cause mortality at end of follow up Mean											
follow-up: 26.4 month(s)											

GRADE tables – Woder 5. Type 2 diabetes and highe	R	not	not		not						
	C	serio	serio		serio			348	HR 0.98		hig
1 (rosenstock 2019a)	 	us	us	NA ³	us	NA	3494	5	(0.84, 1.14)	Not estimable	h
cardiovascular mortality at end of follow up	1	us	us	INA.	us	INA	3434	3	(0.04, 1.14)	Not estimable	11
Mean follow-up: 8.5 month(s)											
Mean follow-up. 6.5 month(s)	R	not	not		Vorv			266/		2 more per 1000	Wor
	C	not serio	not serio	aaria	very		261/5	499	RD 0.00 (-	(3 fewer to 6	ver
10	<u> </u>			serio us¹	serio us ⁴	NA	274	6	0.00, 0.01)	more)	У
cardiovascular mortality at end of follow up	1	us	us	us.	us.	INA	2/4	0	0.00, 0.01)	more)	low
Mean follow-up: 26.4 month(s)			4		1						
	R	not	not		not			0.40	LID 0 00		
4 (C	serio	serio	NIA2	serio	NI A	0.40.4	348	HR 0.96	N	hig
1 (rosenstock 2019a)	ı	us	us	NA ³	us	NA	3494	5	(0.81, 1.14)	Not estimable	h
4-point mace at end of follow up Mean follow-											
up: 15.9 month(s)								1551			
	R	not	not	not	not			460/		1 more per 1000	
	С	serio	serio	serio	serio		466/3	363	RR 1.01	(13 fewer to 18	hig
2	Т	us	us	us	us	NA	645	7	(0.90, 1.14)	more)	h
4-point mace at end of follow up Mean follow-											
up: 26.4 month(s)											
	R	not	not		not						
	С	serio	serio		serio			348	HR 1.00		hig
1 (rosenstock 2019a)	Т	us	us	NA ³	us	NA	3494	6	(0.88, 1.14)	Not estimable	h
5-point mace at end of follow up Mean follow-											
up: 9.9 month(s)											
	R	very	not		very					9 more per 1000	ver
	С	serio	serio	serio	serio		18/83	11/7	RD 0.01 (-	(5 fewer to 23	У
2	Т	us ⁵	us	us ¹	us ⁶	NA	6	30	0.00, 0.02)	more)	low
non-fatal stroke at end of follow up Mean											
follow-up: 10.7 month(s)											
	R	not	not		very					2 fewer per 1000	ver
	С	serio	serio	serio	serio		67/39	74/3	RD -0.00 (-	(8 fewer to 4	У
4	Т	us	us	us ¹	us ⁷	NA	90	804	0.01, 0.00)	more)	low
non-fatal stroke at end of follow up Mean									,		
follow-up: 26.4 month(s)											

GRADE lables – Model 5: Type 2 diabetes and highe	i car	ulovasci	iiai iisk								
	R	not	not								mo
	С	serio	serio		serio			348	HR 0.88		der
1 (rosenstock 2019a)	Т	us	us	NA^3	us ⁸	NA	3494	5	(0.63, 1.23)	Not estimable	ate
non-fatal myocardial infarction at end of follow											
up Mean follow-up: 10.7 month(s)											
1 ,	R	not	not		very			135/		6 more per 1000	ver
	С	serio	serio	serio	serio		158/3	385	RD 0.01 (-	(3 fewer to 14	V
4	Т	us	us	us ¹	us ⁹	NA	956	6	0.00, 0.01)	more)	low
non-fatal myocardial infarction at end of follow									,		
up Mean follow-up: 26.4 month(s)											
	R	not	not								mo
	С	serio	serio		serio			348	HR 1.15		der
1 (rosenstock 2019a)	Т	us	us	NA^3	us ⁸	NA	3494	5	(0.91, 1.45)	Not estimable	ate
unstable angina at end of follow up Mean											
follow-up: 12.5 month(s)											
	R	not	not		very					1 fewer per 1000	ver
	С	serio	serio	serio	serio		43/38	47/3	RD -0.00 (-	(6 fewer to 4	У
3	Т	us	us	us ¹	us ¹⁰	NA	39	652	0.01, 0.00)	more)	low
unstable angina at end of follow up Mean											
follow-up: 26.4 month(s)											
	R	not	not		very						
	С	serio	serio		serio			348	HR 0.87		
1 (rosenstock 2019a)	Т	us	us	NA^3	us ¹¹	NA	3494	4	(0.57, 1.33)	Not estimable	low
hospitalisation for heart failure at end of follow											
up Mean follow-up: 10.7 month(s)											
	R	not	not		very			228/		5 fewer per 1000	ver
	С	serio	serio	serio	serio		210/4	382	RD -0.00 (-	(15 fewer to 5	У
4	Т	us	us	us ¹	us ¹²	NA	033	5	0.01, 0.01)	more)	low
hospitalisation for heart failure at end of follow											
up Mean follow-up: 26.4 month(s)											
	R	not	not								mo
	С	serio	serio		serio			348	HR 0.90		der
1 (rosenstock 2019a)	Т	us	us	NA^3	us ⁸	NA	3494	4	(0.74, 1.09)	Not estimable	ate
acute kidney injury at end of follow up Mean											
follow-up: 26.4 month(s)											

OTABL tables - Model 6. Type 2 diabetes and highe	R C	not serio	not serio		serio		96/34	102/ 348	RR 0.94	2 fewer per 1000 (8 fewer to 7	mo der
1 (rosenstock 2019a)	T	us	us	NA ³	us ⁸	NA	94	5	(0.71, 1.24)	more)	ate
persistent signs of worsening kidney disease at end of follow up Mean follow-up: 26.4 month(s)									(****, **=*/	,	
	R	not	not		not		700/0	819/ 348	DD 0.00	17 fewer per 1000	1- 1
1 (rosenstock 2019a)	C	serio us	serio us	NA ³	serio us	NA	763/3 494	348 5	RR 0.93 (0.85, 1.01)	(35 fewer to 3 more)	hig h
persistent signs of worsening kidney disease at end of follow up Mean follow-up: 26.4 month(s)	-								(6:66, 1:61)		
	R C	not serio	not serio		serio			348	HR 0.86		mo der
1 (rosenstock 2019a)	Т	us	us	NA ³	us ⁸	NA	3494	5	(0.78, 0.95)	Not estimable	ate
development of end stage kidney disease at end of follow up Mean follow-up: 15.9 month(s)											
	R	not	not		very					0 fewer per 1000	ver
2	Ст	serio us	serio us	serio us ¹	serio us ¹³	NA	63/36 99	64/3 585	RD -0.00 (- 0.01, 0.01)	(6 fewer to 6 more)	y low
death from renal causes at end of follow up Mean follow-up: 26.4 month(s)	•	us	us	us	us	14/4	33	303	0.01, 0.01)	more	IOW
1 (rosenstock 2019a)	R C T	not serio us	not serio us	NA ³	very serio us ¹¹	NA	1/349	1/34 85	PETO OR 1.00 (0.06, 15.95)	0 fewer per 1000 (1 fewer to 1 more)	low
cardiac arrhythmia at end of follow up Mean follow-up: 5.5 month(s)	•	us	u.c		u.c				10.007	merey	1011
·	R C	not serio	not serio		very serio				PETO OR 4.43 (0.07,	6 more per 1000 (6 fewer to 18	
1 (barnett 2013)	Т	us	us	NA ³	us ¹¹	NA	1/162	0/79	288.02)	more)	low
diabetic ketoacidosis at end of follow up Mean follow-up: 5.5 month(s)											
	R	not	not	not	not			0/24	BD 0.00 (0 fewer per 1000	hia
2	C	serio us	serio	serio us	serio us	NA	0/238	0/24	RD 0.00 (- 0.01, 0.01)	(12 fewer to 12 more)	hig h

hypoglycaemia episodes at end of follow up Mean follow-up: 7.2 month(s)											
12	R C	not serio us	not serio us	serio us ¹	very serio us ¹⁴	NA	1450/ 6589	126 1/54 36	RD 0.00 (- 0.01, 0.02)	4 more per 1000 (11 fewer to 20 more)	ver y low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 7.2 month(s)	1	us	us	us	us	INA	0309	30	0.01, 0.02)	more)	IOW
12	R C T	not serio us	not serio us	serio us¹	very serio us ¹⁵	NA	116/6 589	116/ 543 6	RD -0.00 (- 0.01, 0.00)	1 fewer per 1000 (6 fewer to 4 more)	ver y low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 7.2 month(s)											
12	R C T	not serio us	not serio us	serio us ¹⁶	serio us ¹⁷	NA	6495	519 5	MD -0.53 (- 0.62, -0.44)	MD 0.53 lower (0.62 lower to 0.44 lower)	low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
10	R C T	serio us ¹⁸	not serio us	not serio us	not serio us	NA	2783	168 0	MD 0.10 (- 0.08, 0.28)	MD 0.10 higher (0.08 lower to 0.28 higher)	mo der ate

- 1. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 2. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.31 (0.8-0.9 = serious, <0.8 = very serious).
- 3. Only one study so no inconsistency
- 4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.23 (0.8-0.9 = serious, <0.8 = very serious).
- 5. >33.3% of the studies in the meta-analysis were at high risk of bias
- 6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.27 (0.8-0.9 = serious, <0.8 = very serious).

Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.24 (0.8-0.9 = serious, <0.8 = very serious).

- 8. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 9. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.37 (0.8-0.9 = serious, <0.8 = very serious).
- 10. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.15 (0.8-0.9 = serious, <0.8 = very serious).
- 11. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 12. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.54 (0.8-0.9 = serious, <0.8 = very serious).
- 13. 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).
- 14. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.6 (0.8-0.9 = serious, <0.8 = very serious).
- 15. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.55 (0.8-0.9 = serious, <0.8 = very serious).
- 16. I2 between 50% and 75%
- 17. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 18. >33.3% of the studies in the meta-analysis were at moderate risk of bias

L.1.2.3 Adding linagliptin compared to adding metformin

Table 5: Adding linagliptin compared to adding metformin

rable 5: Adding imagilptin compared to adding r	Hetit	/									
	De	Risk	Indir	Incon	Impr	Other	Interv	Con	Relative		Cer
	sig	of	ectn	siste	ecisi	consider	entio	trol	effect (95%		tai
No of studies	n	bias	ess	ncy	on	ations	n N	N	CI)	Absolute effect	nty
	•••	Dias	C33	псу	OII	ations	11 14	14	Cij	Absolute effect	iity
all-cause mortality at end of follow up Mean											
follow-up: 12 month(s)		4	4							0 f 4000	
	R	not	not		very			0.10	DD 0 00 /	0 fewer per 1000	
4.0	С	seri	serio	N 1 A 1	serio		0/05	0/2	RD 0.00 (-	(75 fewer to 75	١.
1 (komorizono 2020)	ı	ous	us	NA ¹	us ²	NA	0/25	5	0.07, 0.07)	more)	low
cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)											
	R	not	not		very					0 fewer per 1000	
	С	seri	serio		serio			0/2	RD 0.00 (-	(75 fewer to 75	
1 (komorizono 2020)	Т	ous	us	NA ¹	us ²	NA	0/25	5	0.07, 0.07)	more)	low
hypoglycaemia episodes at end of follow up									, ,		
Mean follow-up: 12 month(s)											
	R		not		very				PETO OR	5 more per 1000	ver
	C	seri	serio		serio			0/1	5.31 (0.10,	(5 fewer to 16	V
1 (inagaki 2013)	Ť	ous ³	us	NA ¹	us ⁴	NA	1/185	24	289.71)	more)	low
severe hypoglycaemic episodes at end of follow	•	0 0.0	J. J		J. J		.,				1011
up Mean follow-up: 12 month(s)											
	R		not							0 fewer per 1000	
	C	seri	serio		serio			0/1	RD 0.00 (-	(13 fewer to 13	
1 (inagaki 2013)	Ť	ous ³	us	NA ¹	us ²	NA	0/185	24	0.01, 0.01)	more)	low
hba1c change (%, lower values are better, change		340	40		30		3, 103		3.31, 3.31)	1113137	1011
scores and final values) at end of follow up Mean											
follow-up: 12 month(s)											
	R		not	not	not					MD 0.10 higher	mo
	С	seri	serio	serio	serio				MD 0.10	(0.08 higher to	der
2	Т	ous ³	us	us	us	NA	208	165	(0.08, 0.12)	0.12 higher)	ate

GRADE tables - Model 5: Type 2 diabetes and higher cardiovascular risk

weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
	R	not	not							MD 2.60 higher	mo
	С	seri	serio		serio				MD 2.60	(1.21 higher to	der
1 (komorizono 2020)	Т	ous	us	NA ¹	us ⁵	NA	23	25	(1.21, 3.99)	3.99 higher)	ate

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

L.1.2.4 Adding saxagliptin compared to adding placebo

Table 6: Clinical evidence profile: Adding saxagliptin compared to adding placebo

	De	Risk	Indir	Inco	Impr	Other	Inter	Con	Relative		Cer
	sig	of	ectn	nsist	ecisi	consider	venti	trol	effect		tai
No of studies	n	bias	ess	ency	on	ations	on N	N	(95% CI)	Absolute effect	nty
all-cause mortality at end of follow up Mean											
follow-up: 12 month(s)											
	R	very	not		very			381		4 more per 1000	ver
	С	serio	serio	serio	serio		425/1	/92	RD 0.00 (-	(2 fewer to 10	У
7	Τ	us ¹	us	us ²	us ³	NA	0043	46	0.00, 0.01)	more)	low
all-cause mortality at end of follow up Mean											
follow-up: 25.2 month(s)											
	R	very	not						HR 1.11		ver
	С	serio	serio		serio			821	(0.96,		У
1 (scirica 2013)	Т	us ¹	us	NA ⁴	us ⁵	NA	8280	2	1.28)	Not estimable	low
cardiovascular mortality at end of follow up Mean											
follow-up: 11.9 month(s)											

Of the Lables Model of Type 2 diabetes and higher care	R	very	not		very			261		1 more per 1000	ver
	С	serio	serio	serio	serio		271/9	/89	RD 0.00 (-	(4 fewer to 6	у
5	Т	us ¹	us	us ²	us ³	NA	586	33	0.00, 0.01)	more)	low
cardiovascular mortality at end of follow up Mean follow-up: 25.2 month(s)											
	R	very	not		not				HR 1.03		
	С	serio	serio		serio			821	(0.87,		
1 (scirica 2013)	Т	us ¹	us	NA ⁴	us	NA	8280	2	1.22)	Not estimable	low
3-point mace at end of follow up Mean follow-up: 25.2 month(s)											
	R	very	not		not			609	RR 1.00	0 fewer per 1000	
	С	serio	serio		serio		613/8	/82	(0.90,	(8 fewer to 8	
1 (scirica 2013)	Т	us ¹	us	NA ⁴	us	NA	280	12	1.11)	more)	low
3-point mace at end of follow up Mean follow-up: 25.2 month(s)											
	R	very	not		not				HR 1.00		
	С	serio	serio		serio			821	(0.89,		
1 (scirica 2013)	Т	us ¹	us	NA ⁴	us	NA	8280	2	1.12)	Not estimable	low
non-fatal stroke at end of follow up Mean follow- up: 15.3 month(s)											
	R	very	not	not				142	RR 1.10	2 more per 1000	ver
	С	serio	serio	serio	serio		158/8	/84	(0.88,	(2 fewer to 6	у
2	Т	us ¹	us	us	us ⁵	NA	523	60	1.38)	more)	low
non-fatal stroke at end of follow up Mean follow- up: 25.2 month(s)											
	R	very	not						HR 1.11		ver
	С	serio	serio		serio			817	(0.88,		У
1 (scirica 2013)	Т	us ¹	us	NA ⁴	us ⁵	NA	8240	3	1.40)	Not estimable	low
non-fatal myocardial infarction at end of follow up Mean follow-up: 15.6 month(s)											
	R	very	not		not			278	RR 0.95	2 fewer per 1000	Ver
	С	serio	serio	serio	serio		266/8	/84	(0.80,	(6 fewer to 4	У
2	Т	us ¹	us	us ²	us	NA	474	04	1.12)	more)	low
non-fatal myocardial infarction at end of follow up Mean follow-up: 25.2 month(s)											

OTVIDE Lables Wilder 6. Type 2 diabetes and higher said	R	very	not						HR 0.95		ver
	C	serio	serio		serio			817	(0.80,		y
1 (scirica 2013)	T	us ¹	us	NA ⁴	us ⁵	NA	8240	3	1.13)	Not estimable	low
unstable angina at end of follow up Mean follow-	•	us	uo	14/ (uo	14/ (0240		1.10)	140t Cotimable	100
up: 25.2 month(s)											
45. 20.2 monun(0)	R	very	not					81/	RR 1.19	2 more per 1000	ver
	C	serio	serio		serio		97/82	821	(0.89.	(1 fewer to 6	V
1 (scirica 2013)	Ť	us ¹	us	NA ⁴	us ⁵	NA	80	2	1.59)	more)	low
unstable angina at end of follow up Mean follow-									/	/	
up: 25.2 month(s)											
· · · · · · · · · · · · · · · · · · ·	R	very	not						HR 1.19		ver
	С	serio	serio		serio			821	(0.89,		у
1 (scirica 2013)	Т	us ¹	us	NA ⁴	us ⁵	NA	8280	2	1.59)	Not estimable	low
hospitalisation for heart failure at end of follow up											
Mean follow-up: 25.2 month(s)											
	R	very	not					228	RR 1.26	7 more per 1000	ver
	С	serio	serio		serio		289/8	/81	(1.06,	(2 more to 14	У
1 (scirica 2013)	Т	us ¹	us	NA ⁴	us ⁵	NA	240	73	1.49)	more)	low
hospitalisation for heart failure at end of follow up											
Mean follow-up: 25.2 month(s)											
	R	very	not						HR 1.27		ver
	С	serio	serio		serio			817	(1.07,		У
1 (scirica 2013)	Т	us ¹	us	NA ⁴	us ⁵	NA	8240	3	1.51)	Not estimable	low
persistent signs of worsening kidney disease at											
end of follow up Mean follow-up: 25.2 month(s)											
	R	very	not					166	RR 1.09	2 more per 1000	ver
	С	serio	serio		serio		183/8	/82	(0.89,	(2 fewer to 7	У
1 (scirica 2013)	Т	us ¹	us	NA ⁴	us ⁵	NA	280	12	1.35)	more)	low
persistent signs of worsening kidney disease at											
end of follow up Mean follow-up: 25.2 month(s)	_								LID 4 40		1
	R	very	not					004	HR 1.10		ver
4 (ini 2042)	C	serio	serio	NIA4	serio	NIA	0000	821	(0.89,	Niet estimatel	У
1 (scirica 2013)	Т	us ¹	us	NA ⁴	us ⁵	NA	8280	2	1.36)	Not estimable	low
development of end stage kidney disease at end of											
follow up Mean follow-up: 25.2 month(s)											

OTABL tables Woder 5. Type 2 diabetes and higher ear	R	very	not		very			55/	PETO OR	1 fewer per 1000	ver
	С	serio	serio		serio		51/82	821	0.92 (0.63,	(3 fewer to 2	y
1 (scirica 2013)	Т	us ¹	us	NA ⁴	us ⁶	NA	80	2	1.35)	more)	low
development of end stage kidney disease at end of											
follow up Mean follow-up: 25.2 month(s)											
	R	very	not		very				HR 0.90		ver
	С	serio	serio		serio			821	(0.61,		у
1 (scirica 2013)	Т	us ¹	us	NA ⁴	us ⁶	NA	8280	2	1.33)	Not estimable	low
death from renal causes at end of follow up Mean follow-up: 25.2 month(s)											
	R	very	not		very				PETO OR	1 more per 1000	ver
	С	serio	serio		serio		10/82	5/8	1.93 (0.70,	(0 more to 2	у
1 (scirica 2013)	Τ	us ¹	us	NA ⁴	us ⁶	NA	80	212	5.32)	more)	low
cardiac arrhythmia at end of follow up Mean follow-up: 12 month(s)											
	R		not		very				PETO OR	6 fewer per 1000	ver
	С	serio	serio		serio			1/1	0.14 (0.00,	(18 fewer to 6	у
1 (matthaei 2015a)	Τ	us ⁷	us	NA ⁴	us ⁶	NA	0/153	62	7.22)	more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 11.2 month(s)											
. , ,	R	very	not		very		1310/	113		2 more per 1000	ver
	С	serio	serio	serio	serio		1032	4/9	RD 0.00 (-	(10 fewer to 15	у
8	Т	us ¹	us	us ²	us ⁸	NA	8	534	0.01, 0.01)	more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 11 month(s)											
	R	very	not		very			143		4 more per 1000	ver
	С	serio	serio	serio	serio		180/9	/92	RD 0.00 (-	(0 more to 7	у
6	Т	us ¹	us	us ²	us ⁹	NA	818	22	0.00, 0.01)	more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 25.2 month(s)											
	R	very	not						HR 1.22		ver
	С	serio	serio		serio			821	(0.82,		у
1 (scirica 2013)	Т	us ¹	us	NA ⁴	us ⁵	NA	8280	2	1.82)	Not estimable	low
hba1c change (%, lower values are better, change scores and final values) at end of follow up Mean follow-up: 11.2 month(s)											

	R	very	not	very					MD -0.50	MD 0.50 lower	ver
	С	serio	serio	serio	serio		1023	948	(-0.67, -	(0.67 lower to	У
8	Т	us ¹	us	us ¹⁰	us ¹¹	NA	4	7	0.33)	0.33 lower)	low
weight change (kg, lower values are better, change											
scores and final values) at end of follow up Mean											
follow-up: 11.9 month(s)											
	R	very	not		not					MD 0.21 higher	ver
	С	serio	serio	serio	serio			916	MD 0.21 (-	(0.15 lower to	у
6	Т	us ¹	us	us ¹²	us	NA	9545	0	0.15, 0.57)	0.57 higher)	low
bmi change (kg/m2, lower values are better, change											
scores and final values) at end of follow up Mean											
follow-up: 12.2 month(s)											
	R	very	not	not	not					MD 0.02 higher	
	С	serio	serio	serio	serio			884	MD 0.02 (-	(0.06 lower to	
4	Т	us ¹	us	us	us	NA	9035	7	0.06, 0.10)	0.10 higher)	low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.08 (0.8-0.9 = serious, <0.8 = very serious).
- 4. Only one study so no inconsistency
- 5. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 6. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 7. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 8. Precision calculated through Optimal 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).
- 9. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.57 (0.8-0.9 = serious, <0.8 = very serious).
- 10. I2 > 75%

end of the defined MIDs (-0.50, 0.50)

12. I2 between 50% and 75%

L.1.2.5 Adding sitagliptin compared to adding placebo

Table 7: Clinical evidence profile: Adding sitagliptin compared to adding placebo

rable 1. Offical evidence profile. Adding stragifical	De	Risk	Indir	Incon	Impr	Other	Interv	Con	Relative		Cer
					_	consider				Absolute	
	sig	of	ectn	siste	ecisi		entio	trol	effect		tain
No of studies	n	bias	ess	ncy	on	ations	n N	N	(95% CI)	effect	ty
health-related quality of life - overall (iwqol lite scores,											
higher values are better, change scores) at end of follow											
up											
										MD 0.30	
										higher	
	R	very	not		not				MD 0.30	(3.83 lower	
	С	serio	serio		serio				(-3.83,	to 4.43	
1 (gadde 2017)	Т	us ¹	us	NA ²	us	NA	122	61	4.43)	higher)	low
health-related quality of life - subscale well being (dmsat											
well being scores, higher values are better, change											
scores) at end of follow up											
										MD 1.10	
										lower	
	R	very	not		not				MD -1.10	(9.37 lower	
	С	serio	serio		serio				(-9.37,	to 7.17	
1 (gadde 2017)	Τ	us ¹	us	NA ²	us	NA	122	61	7.17)	higher)	low
all-cause mortality at end of follow up										,	
,										1 fewer	
	R	not	not		verv				RD -0.00	per 1000	ver
	C	serio	serio	serio	serio		3/348	6/3	(-0.00,	(3 fewer to	y
16	T	us	us	us ³	us ⁴	NA	3	080	0.00)	2 more)	low
cardiovascular mortality at end of follow up											

Woder 5. Type 2 diabetes and higher dardiovas										1 fewer	
	R C	not serio	not serio	serio	very serio		0/230	3/2	RD -0.00 (-0.00,	per 1000 (5 fewer to	ver
11	+	us	us	us ³	us ⁵	NA	5	087	0.00)	2 more)	y low
non-fatal stroke at end of follow up											
1 (ba 2017)	R C T	not serio us	not serio us	NA ²	very serio us ⁶	NA	0/248	1/2 49	PETO OR 0.14 (0.00, 6.85)	4 fewer per 1000 (12 fewer to 4 more)	low
non-fatal myocardial infarction at end of follow up							0,=,0			,	
3	R C T	serio us ⁷	not serio us	serio us³	very serio us ⁶	NA	1/678	2/7 13	PETO OR 0.56 (0.06, 5.41)	1 fewer per 1000 (6 fewer to 4 more)	ver y low
unstable angina at end of follow up											
2 diabetic ketoacidosis at end of follow up	R C T	not serio us	not serio us	serio us ³	very serio us ⁶	NA	1/570	1/5 68	PETO OR 1.00 (0.06, 15.95)	0 fewer per 1000 (5 fewer to 5 more)	ver y low
diabetic ketoacidosis at end of follow up										3 fewer	
1 (shankar 2017a)	R C T	serio us ⁷	not serio us	NA ²	very serio us ⁶	NA	0/234	1/2 33	RR 0.33 (0.01, 8.11)	per 1000 (4 fewer to 30 more)	ver y low
hypoglycaemia episodes at the end of follow up										40	
20	R C T	not serio us	not serio us	serio us³	very serio us ⁸	NA	608/4 022	535 /34 45	RD 0.02 (0.00, 0.04)	18 more per 1000 (1 more to 35 more)	ver y low
severe hypoglycaemic episodes at the end of follow up											
16	R C T	not serio us	not serio us	serio us³	very serio us ⁹	NA	38/32 52	36/ 300 1	RD 0.00 (-0.01, 0.01)	1 more per 1000 (5 fewer to 6 more)	ver y low
hba1c change (%, lower values are better, mean difference) at end of follow up											

23	R C T	very serio us ¹	not serio us	very serio us ¹⁰	not serio us	NA	4055	356 8	MD -0.71 (-0.80, - 0.61)	MD 0.71 lower (0.80 lower to 0.61 lower)	ver y low
weight change (kg, lower values are better, mean difference) at end of follow up											
20 bmi change (kg/m2, lower values are better, final values)	R C T	not serio us	not serio us	very serio us ¹⁰	not serio us	NA	3221	295 1	MD 0.13 (-0.13, 0.39)	MD 0.13 higher (0.13 lower to 0.39 higher)	low
at end of follow up											
3	R C	very serio us ¹	not serio us	very serio us ¹⁰	serio us ¹¹	NA	237	229	MD -1.50 (-2.35, - 0.66)	MD 1.50 lower (2.35 lower to 0.66 lower)	ver y 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. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.38 (0.8-0.9 = serious, <0.8 = very serious).
- 5. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.71 (0.8-0.9 = serious, <0.8 = very serious).
- 6. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 7. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 8. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.1 (0.8-0.9 = serious, <0.8 = very serious).

9. Precision calculated through Optimal

Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.04 (0.8-0.9 = serious, <0.8 = very serious).

10. I2 > 75%

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

L.1.2.6 Adding sitagliptin compared to adding metformin

Table 8: Clinical evidence profile: Adding sitagliptin compared to adding metformin

Table 6. Chilical evidence profile. Adding Sitag	nptn			, addini	y moun					I	
	De	Risk	Indir	Incon	Impr	Other	Interv	Con	Relative		Cer
	sig	of	ectn	siste	ecisi	consider	entio	trol	effect (95%		tai
No of studies	n	bias	ess	ncy	on	ations	n N	N	CI)	Absolute effect	nty
hypoglycaemia episodes at end of follow-up											
Mean follow-up: 12 month(s)											
	R	very	not		very				PETO OR	27 more per 1000	ver
	С	serio	serio		serio			0/7	7.59 (0.47,	(10 fewer to 63	у
1 (derosa 2010b)	Т	us ¹	us	NA ²	us ³	NA	2/75	6	122.49)	more)	low
hba1c change (%, lower values are better, final											
and change scores) at end of follow-up Mean											
follow-up: 9 month(s)											
	R	very	not	very	very					MD 0.33 lower	ver
	С	serio	serio	serio	serio				MD -0.33 (-	(1.25 lower to	y
2	Т	us ¹	us	us ⁴	us ⁵	NA	104	103	1.25, 0.60)	0.60 higher)	low
weight change (kg, lower values are better, final											
and change values) at end of follow-up Mean											
follow-up: 9 month(s)											
	R	very	not	very						MD 1.47 higher	ver
	С	serio	serio	serio	serio				MD 1.47 (-	(0.53 lower to	у
2	Т	us ¹	us	us ⁴	us ⁶	NA	104	103	0.53, 3.47)	3.47 higher)	low
bmi change (kg/m2, lower values are better, final											
and change values) at end of follow-up Mean											
follow-up: 9 month(s)											

	R	very	not							MD 0.41 higher	ver
	С	serio	serio	serio	serio				MD 0.41	(0.02 higher to	у
2	Т	us ¹	us	us ⁷	us ⁸	NA	104	103	(0.02, 0.80)	0.80 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. 12 > 75%
- 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. I2 between 50% and 75%
- 8. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

L.1.2.7 Adding sitagliptin compared to adding insulin

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

Table 9: Clinical evidence profile: Adding sitag	liptin compai	rea to a	iaaing	ınsuli	<u>n</u>						
					lm						
			Ind		pr			Со			
		Risk	irec	Inco	eci	Other	Inter	ntr	Relative		
		of	tne	nsist	sio	conside	venti	ol	effect		
No of studies	Design	bias	SS	ency	n	rations	on N	N	(95% CI)	Absolute effect	Certainty
health-related quality of life - subscale mental component (sf36, higher values are better, change scores) at end of follow up Mean follow-up: 24 month(s)											
1 (group 2022)	RCT	very serio us ¹	not seri ous	NA ²	not ser iou s	NA	1236	12 09	MD 0.12 (-0.48, 0.72)	MD 0.12 higher (0.48 lower to 0.72 higher)	low
health-related quality of life - subscale physical component (sf36, higher values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (group 2022)	RCT	very serio us ¹	not seri ous	NA ²	not ser iou s	NA	1236	12 09	MD 0.23 (-0.32, 0.78)	MD 0.23 higher (0.32 lower to 0.78 higher)	low
all-cause mortality at end of follow-up Mean follow-up: 33 month(s)											
2	RCT	serio us³	not seri ous	serio us ⁴	ver y ser iou s ⁵	NA	41/1 495	43/ 14 89	PETO OR 0.95 (0.61, 1.47)	1 fewer per 1000 (13 fewer to 10 more)	very low
all-cause mortality at end of follow up Mean follow-up: 60 month(s)											

OTTIBE tables Woder of Type 2 diabetes and higher of		1	1	1		ı					1
					ver						
					٧						
			not		ser				HR 0.98		
		serio	seri		iou			12	(0.68,		
4 / 2000)	БОТ						4007				
1 (group 2022)	RCT	us ³	ous	NA ²	s ⁵	NA	1267	63	1.41)	Not estimable	very low
cardiovascular mortality at end of follow-up											
Mean follow-up: 60 month(s)											
, , , , , , , , , , , , , , , , , , ,					ver						
										O fower per	
					У			.		0 fewer per	
			not		ser			21/	RR 0.99	1000	
		serio	seri		iou		21/1	12	(0.55,	(8 fewer to 14	
1 (group 2022)	RCT	us ³	ous	NA^2	s^5	NA	264	57	1.81)	more)	very low
cardiovascular mortality at end of follow up										/	
Mean follow-up: 60 month(s)											
					ver						
					У						
			not		ser				HR 1.00		
		serio	seri		iou			12	(0.55,		
1 (group 2022)	RCT	us ³		NA ²	s ⁵	NA	1264	57	1.82)	Not estimable	yery levy
1 (group 2022)	RCI	us	ous	INA	S	INA	1204	57	1.02)	Not estimable	very low
3-point mace at end of follow-up											
Mean follow-up: 60 month(s)											
·					ver						
					V					3 more per	
					,			051	DD 4 00		
			not		ser			65/	RR 1.06	1000	
		serio	seri		iou		69/1	12	(0.76,	(12 fewer to 24	
1 (group 2022)	RCT	us ³	ous	NA^2	s ⁵	NA	264	57	1.47)	more)	very low
3-point mace at end of follow up									•	,	
Mean follow-up: 60 month(s)											
Mican follow-up. of month(9)					Wor						
					ver						
					У						
			not		ser				HR 1.06		
		serio	seri		iou			12	(0.76,		
1 (group 2022)	RCT	us ³	ous	NA ²	s ⁵	NA	1264	57	1.48)	Not estimable	very low
4-point mace at end of follow up	1.01	40	040	. */ `		, .	1201	0,		110t Ootiiiiabio	1313 1317
Mean follow-up: 60 month(s)											

Woder 5. Type 2 diabetes and higher e										T =	
1 (group 2022)	RCT	very serio us ¹	not seri ous	NA ²	ser iou s ⁶	NA	78/1 268	71/ 12 63	RR 1.09 (0.80, 1.49)	5 more per 1000 (11 fewer to 28 more)	very low
non-fatal myocardial infarction Mean follow-up: 5.5 month(s)									,	,	
1 (aschner 2012)	RCT	very serio us ¹	not seri ous	NA ²	ver y ser iou s ⁵	NA	1/26 4	0/2 37	PETO OR 6.67 (0.13, 338.11)	4 more per 1000 (4 fewer to 11 more)	very low
unstable angina at the end of follow-up Mean follow-up: 32.8 month(s)											
2	RCT	very serio us ¹	not seri ous	serio us ⁴	y ser iou s ⁵	NA	15/1 532	11/ 15 00	PETO OR 1.35 (0.62, 2.92)	2 more per 1000 (4 fewer to 9 more)	very low
hospitalisation for heart failure at end of follow up Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	serio us³	not seri ous	NA ²	ver y ser iou s ⁵	NA	1264	12 57	HR 1.15 (0.67, 1.96)	Not estimable	very low
hospitalisation for heart failure at end of follow- up Mean follow-up: 60 month(s)											
1 (group 2022)	RCT	serio us³	not seri ous	NA ²	ver y ser iou s ⁵	NA	30/1 264	26/ 12 57	RR 1.15 (0.68, 1.93)	3 more per 1000 (7 fewer to 19 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 16.6 month(s)											

3	RCT	not serio us	not seri ous	not serio us	ser iou s ⁹	NA	60	57	MD -0.39 (-1.00, 0.23)	MD 0.39 lower (1.00 lower to 0.23 higher)	moderate
bmi change (kg/m2, lower values are better, change scores and final values) at end of follow- up Mean follow-up: 7.8 month(s)										N. C.	
7	RCT	very serio us ¹	not seri ous	serio us ⁸	not ser iou s	NA	880	99 8	MD 0.18 (-0.09, 0.46)	MD 0.18 higher (0.09 lower to 0.46 higher)	very low
hba1c change (%, lower values are better, mean difference) at end of follow-up Mean follow-up: 14.4 month(s)							,		/	, ,	,,
up Mean follow-up: 19.2 month(s)	RCT	very serio us ¹	not seri	serio us ⁴	ser iou s ⁶	NA	11/1 821	24/ 17 89	PETO OR 0.47 (0.24, 0.91)	7 fewer per 1000 (14 fewer to 1 fewer)	very low
2 severe hypoglycaemic episodes at end of follow-	RCT	serio us ³	not seri ous	serio us ⁸	not ser iou s	NA	21/4 92	70/ 46 3	RR 0.28 (0.11, 0.71)	108 fewer per 1000 (134 fewer to 43 fewer)	low
1 (group 2022) at night hypoglycaemic episodes Mean follow-up: 5.8 month(s)	RCT	very serio us ¹	not seri ous	NA ²	ser iou s	NA	1253	12 45	HR 0.63 (0.59, 0.67)	Not estimable	low
hypoglycaemia episodes at end of follow-up Mean follow-up: 60 month(s)					not						
5	RCT	very serio us ¹	not seri ous	very serio us ⁷	not ser iou s	NA	398/ 1833	69 1/1 79 5	RR 0.41 (0.23, 0.72)	227 fewer per 1000 (295 fewer to 107 fewer)	very low

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weight change (kg, lower values are better, mean difference) at end of follow-up Mean follow-up: 6.8 month(s)											
6	RCT	very serio us ¹	not seri ous	serio us ⁸	ser iou s ¹⁰	NA	603	57 6	MD -1.89 (-2.62, - 1.16)	MD 1.89 lower (2.62 lower to 1.16 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. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 4. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 5. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 6. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 7.12 > 75%
- 8. I2 between 50% and 75%
- 9. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)
- 10. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

L.1.2.8 Adding vildagliptin compared to adding placebo

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

3											
	De	Risk	Indir	Incon	Impr	Other	Interv	Con	Relative		Cer
	sig	of	ectn	siste	ecisio	consider	entio	trol	effect		tai
No of studies	n	bias	ess	ncy	n	ations	n N	N	(95% CI)	Absolute effect	nty
all-cause mortality at end of follow-up Mean											
follow-up: 6.1 month(s)											
	R	Very	not		very					1 fewer per 1000	ver
	С	serio	serio	serio	serio		3/219	5/1	RD -0.00 (-	(6 fewer to 3	У
12	Т	us ¹	us	us ²	us ³	NA	1	659	0.01, 0.00)	more)	low

cardiovascular mortality at end of follow-up											
Mean follow-up: 6.4 month(s)											
	R		not		very					0 more per 1000	ver
	С	serio	serio	serio	serio		1/130	1/9	RD 0.00 (-	(6 fewer to 6	У
8	Τ	us ⁴	us	us ²	us ⁵	NA	4	71	0.01, 0.01)	more)	low
non-fatal stroke at end of follow-up Mean follow-											
up: 5.5 month(s)	_								5570.00	5 6 4000	
	R		not	_	very				PETO OR	5 fewer per 1000	ver
	С	serio	serio	serio	serio			3/4	0.19 (0.02,	(13 fewer to 2	У
3	Τ	us ⁴	us	us ²	us ⁶	NA	1/797	61	1.48)	more)	low
progression of liver disease at end of follow-up											
Mean follow-up: 5.5 month(s)											
	R	not								0 fewer per 1000	
	С	serio	serio		serio			0/1	RD 0.00 (-	(14 fewer to 14	
1 (strain 2013)	Τ	us	us ⁷	NA ⁸	us ⁹	NA	0/139	39	0.01, 0.01)	more)	low
hypoglycaemia episodes at end of follow-up									,	,	
Mean follow-up: 6.4 month(s)											
	R	very	not		very			93/		4 more per 1000	ver
	С	serio	serio	serio	serio		116/3	222	RD 0.01 (-	(6 fewer to 15	y
15	T	us ¹	us	us ²	us ¹⁰	NA	031	9	0.01, 0.01)	more)	low
severe hypoglycaemic episodes at end of follow-		1.0							10101,0101)		1011
up Mean follow-up: 6.0 month(s)											
ap mountonow aproto month(o)	R		not		very			11/		3 fewer per 1000	ver
	C	serio	serio	serio	serio		6/264	184	RD -0.00 (-	(8 fewer to 2	y
13	-	us ⁴	us	us ²	us ¹¹	NA	2	0	0.01, 0.00)	more)	low
hba1c change (%, lower values are better, mean	<u>'</u>	us	us	us	us	INA	+2	0	0.01, 0.00)	more)	IOW
difference) at end of follow-up Mean follow-up:											
6.0 month(s)	_									MD 0 00 I	_
	R	very	not	very	not _.			400		MD 0.69 lower	ver
	С	serio	serio	serio	serio			189	MD -0.69 (-	(0.77 lower to	У
14	T	us ¹	us	us ¹²	us	NA	2601	4	0.77, -0.62)	0.62 lower)	low
weight change (kg, lower values are better,											
change and final scores) at end of follow-up											
Mean follow-up: 5.8 month(s)											
	R	very	not	very	not					MD 0.7 higher	ver
	С	serio	serio	serio	serio				MD 0.07 (-	(0.89 lower to	у
7	Т	us ¹	us	us ¹²	us	NA	1108	835	0.89, 1.04)	1.04 higher)	ĺow

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.3 (0.8-0.9 = serious, <0.8 = very serious).
- 4. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 5. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.05 (0.8-0.9 = serious, <0.8 = very serious).
- 6. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 7. Largest proportion of studies in the meta-analysis came from partially direct studies
- 8. Only one study so no inconsistency
- 9. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 10. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.07 (0.8-0.9 = serious, <0.8 = very serious).
- 11. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.59 (0.8-0.9 = serious, <0.8 = very serious).
- 12. I2 > 75%

L.1.2.9 Adding vildagliptin compared to adding metformin

Table 11: Clinical evidence profile: Adding vildagliptin compared to adding metformin

Table 11: Clinical evidence profile: Adding	VIIU	agripun (compare	ed to ad	aing me	uormin					
	De	Risk	Indire	Incons		Other			Relative		Cert
	sig	of	ctnes	istenc	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	s	у	cision	ions	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow-up Mean follow-up: 5.5 month(s)											
1 (ji 2016b)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/2562	0/50 0	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (3 fewer to 3 more)	low
cardiovascular mortality at end of follow-up Mean follow-up: 5.5 month(s)											
1 (ji 2016b)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/2562	0/50 0	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (3 fewer to 3 more)	low
acute kidney injury at end of follow-up Mean follow-up: 5.5 month(s)											
1 (filozof 2010b)	RC T	not seriou s	seriou s³	NA ²	very seriou s ⁴	NA	1/456	0/45 8	PETO OR 7.42 (0.15, 374.03)	2 more per 1000 (2 fewer to 6 more)	very low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)											
2	RC T	very seriou s ¹	not seriou s	not seriou s	very seriou s ⁴	NA	27/301 8	9/95 8	RR 0.66 (0.31, 1.41)	3 fewer per 1000 (6 fewer to 4 more)	very low
hba1c change (%, lower values are better, change and final scores) at end of follow-up Mean follow-up: 5.5 month(s)										,	

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weight change (kg, lower values are better, change scores) at end of follow-up	RC T	very seriou s ¹	not seriou s	not seriou s	not seriou s	NA	2957	942	MD -0.14 (-0.20, - 0.08)	MD 0.14 lower (0.20 lower to 0.08 lower)	low
Mean follow-up: 5.5 month(s)											
	RC	very seriou	not seriou		not seriou				MD -0.51 (-0.77, -	MD 0.51 lower (0.77 lower to 0.25	
1 (ji 2016b)	T	s ¹	s	NA ²	s	NA	2501	484	0.25)	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. Largest proportion of studies in the meta-analysis came from partially direct studies
- 4. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

L.1.2.10 Adding vildagliptin compared to adding insulin

Table 12: Clinical evidence profile: Adding vildagliptin compared to adding insulin

	De	Risk	Indir	Incon	Impr	Other	Interv	Con	Relative		Cer
	sig	of	ectn	sisten	ecisi	consider	entio	trol	effect (95%		tain
No of studies	n	bias	ess	су	on	ations	n N	N	CI)	Absolute effect	ty
all-cause mortality at end of follow-up Mean follow-up: 5.5 month(s)											
		very	not		very				PETO OR	13 fewer per 1000	ver
	R	serio	serio		serio			1/7	0.13 (0.00,	(37 fewer to 12	У
1 (forst 2015)	CT	us ¹	us	NA ²	us ³	NA	0/82	9	6.57)	more)	low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)											

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	R	very serio	not serio		serio			23/	RR 0.50	145 fewer per 1000 (213 fewer	ver y
1 (forst 2015)	CT	us ¹	us	NA^2	us ⁴	NA	12/82	79	(0.27, 0.94)	to 18 fewer)	low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)											
		very	not							0 fewer per 1000	ver
	R	serio	serio		serio			0/7	RD 0.00 (-	(24 fewer to 24	у
1 (forst 2015)	CT	us ¹	us	NA^2	us ⁵	NA	0/82	9	0.02, 0.02)	more)	low
hba1c change (%, lower values are better,											
mean difference) at end of follow-up Mean											
follow-up: 5.5 month(s)											
		very	not							MD 0.30 higher	ver
	R	serio	serio		serio				MD 0.30	(0.05 higher to	у
1 (forst 2015)	CT	us ¹	us	NA^2	us ⁶	NA	82	79	(0.05, 0.55)	0.55 higher)	low

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

L.1.2.11 Adding vildagliptin compared to adding saxagliptin

Table 13: Clinical evidence profile: Adding vildagliptin compared to adding saxagliptin

	De	Risk	Indir	Incon	Impr	Other	Interv	Con	Relative		Cer
	sig	of	ectn	sisten	ecisi	consider	entio	trol	effect		tain
No of studies	n	bias	ess	су	on	ations	n N	N	(95% CI)	Absolute effect	ty
all-cause mortality at end of follow-up Mean											
follow-up: 5.5 month(s)											

2	R CT	very serio us ¹	not serio us	not serio us	serio us ²	NA	0/100	0/1 02	RD 0.00 (- 0.03, 0.03)	0 fewer per 1000 (27 fewer to 27 more)	ver y low
cardiovascular mortality at end of follow-up Mean follow-up: 5.5 month(s)									,	,	
2	R CT	very serio us ¹	not serio us	not serio us	serio us ²	NA	0/100	0/1 02	RD 0.00 (- 0.03, 0.03)	0 fewer per 1000 (27 fewer to 27 more)	ver y low
hospitalisation for heart failure at end of follow- up Mean follow-up: 5.5 month(s)											
1 (chen 2016)	R CT	very serio us ¹	not serio us	NA ³	serio us ²	NA	0/37	0/3 6	RD 0.00 (- 0.05, 0.05)	0 fewer per 1000 (52 fewer to 52 more)	ver y low
hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)											
3	R CT	very serio us ¹	not serio us	not serio us	very serio us ⁴	NA	7/157	9/1 62	RR 0.81 (0.25, 2.65)	11 fewer per 1000 (42 fewer to 92 more)	ver y low
at night hypoglycaemic episodes Mean follow- up: 5.5 month(s)											
1 (chen 2016)	R CT	very serio us ¹	not serio us	NA ³	serio us ²	NA	0/37	0/3	RD 0.00 (- 0.05, 0.05)	0 fewer per 1000 (52 fewer to 52 more)	ver y low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)											
2	R CT	very serio us ¹	not serio us	not serio us	serio us ²	NA	0/94	0/9	RD 0.00 (- 0.03, 0.03)	0 fewer per 1000 (29 fewer to 29 more)	ver y low
hba1c change (%, lower values are better, change scores) at end of follow-up Mean follow-up: 5.5 month(s)											
3	R CT	very serio us ¹	not serio us	not serio us	not serio us	NA	157	162	MD -0.08 (-0.20, 0.04)	MD 0.08 lower (0.20 lower to 0.04 higher)	low
weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 5.5 month(s)											

1 (li 2014a)	R CT	very serio us ¹	not serio us	NA ³	not serio us	NA	57	60	MD 0.10 (-0.63, 0.83)	MD 0.10 higher (0.63 lower to 0.83 higher)	low
bmi change (kg/m2, lower values are better, change scores) at end of follow-up Mean follow-up: 5.5 month(s)											
2	R CT	very serio us ¹	not serio us	not serio us	not serio us	NA	94	96	MD -0.01 (-0.25, 0.24)	MD 0.01 lower (0.25 lower to 0.24 higher)	low

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

L.1.3 GLP-1 receptor agonist

L.1.3.1 Adding dulaglutide compared to adding placebo

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

	D							Со			
	es	Risk	Indi	Inco	Impr	Other	Inter	ntr	Relative		Cer
	ig	of	rect	nsist	ecisi	conside	venti	ol	effect	Absolute	tai
No of studies	n	bias	ness	ency	on	rations	on N	N	(95% CI)	effect	nty
health-related quality of life - overall (eq-5d-5l uk index, -											
0.59-1, higher values are better, changes scores) at end of											
follow up Mean follow-up: 6.5 month(s)											
	R	seri	not		very				MD -0.01	MD 0.01 lower	ver
	С	ous	seri		serio			15	(-0.07,	(0.07 lower to	у
1 (pozzilli 2017)	Т	1	ous	NA ²	us ³	NA	150	0	0.05)	0.05 higher)	low

all-cause mortality at end of follow up Mean follow-up: 13.3 month(s)											
10.5 month(s)								34			
	R	not	not		not			9/5	RD -0.01	5 fewer per	mo
	С	seri	seri	serio	serio		320/6	69	(-0.01,	1000 (14 fewer	der
8	Τ	ous	ous	us ⁴	us	NA	428	6	0.00)	to 3 more)	ate
all-cause mortality at end of follow up Mean follow-up: 64.8 month(s)											
	R	not	not						HR 0.90		mo
	С	seri	seri		serio			49	(0.80,		der
1 (gerstein 2019a)	I	ous	ous	NA ²	us ⁵	NA	4949	52	1.01)	Not estimable	ate
cardiovascular mortality at end of follow up Mean follow- up: 17.8 month(s)											
								59			
	R	not	not		not			5/5	RD -0.01	10 fewer per	mo
	С	seri	seri	serio	serio		541/6	69	(-0.02,	1000 (20 fewer	der
8	I	ous	ous	us ⁴	us	NA	428	6	0.00)	to 1 more)	ate
cardiovascular mortality at end of follow up Mean follow- up: 64.8 month(s)											
	R	not	not						HR 0.91		mo
	С	seri	seri		serio		40.40	49	(0.78,		der
1 (gerstein 2019a)	I	ous	ous	NA ²	us ⁵	NA	4949	52	1.06)	Not estimable	ate
3-point mace at end of follow up Mean follow-up: 64.8 month(s)											
								66			
	R	not	not		not			3/4	RR 0.90	14 fewer per	١
1 (maratain 2010a)	С	seri	seri	NA ²	serio	NIA.	594/4	95	(0.81,	1000 (26 fewer	hig
1 (gerstein 2019a) 3-point mace at end of follow up Mean follow-up: 64.8	I	ous	ous	INA ²	us	NA	949	2	0.99)	to 1 fewer)	h
month(s)											
	R	not	not						HR 0.88		mo
4 (С	seri	seri		serio		10.15	49	(0.79,		der
1 (gerstein 2019a)	Τ	ous	ous	NA ²	us ⁵	NA	4949	52	0.99)	Not estimable	ate
non-fatal stroke at end of follow up Mean follow-up: 25.6 month(s)											

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								17			
	R	not	not					5/5	RR 0.78	7 fewer per	
	С	seri	seri	serio	serio		138/5	16	(0.63,	1000 (13 fewer	
3	Т	ous	ous	us ⁴	us ⁵	NA	338	2	0.98)	to 1 fewer)	low
non-fatal stroke at end of follow up Mean follow-up: 64.8											
month(s)											
	R	not	not						HR 0.76		mo
	С	seri	seri		serio			49	(0.61,		der
1 (gerstein 2019a)	Т	ous	ous	NA^2	us ⁵	NA	4949	52	0.95)	Not estimable	ate
non-fatal myocardial infarction at end of follow up Mean											
follow-up: 25.6 month(s)											
								21			
	R	not	not					4/5	RR 0.96	2 fewer per	
	С	seri	seri	serio	serio		206/5	24	(0.80,	1000 (8 fewer	
3	Т	ous	ous	us ⁴	us5	NA	382	2	1.16)	to 6 more)	low
non-fatal myocardial infarction at end of follow up Mean											
follow-up: 64.8 month(s)											
	R	not	not						HR 0.96		mo
	С	seri	seri		serio			49	(0.79,		der
1 (gerstein 2019a)	T	ous	ous	NA^2	us ⁵	NA	4949	52	1.16)	Not estimable	ate
unstable angina at end of follow up Mean follow-up: 25.6											
month(s)											
	R	not	not					79/	RR 1.12	2 more per	
	С	seri	seri	serio	serio		89/53	52	(0.83,	1000 (3 fewer	
3	T	ous	ous	us ⁴	us ⁵	NA	82	42	1.51)	to 8 more)	low
unstable angina at end of follow up Mean follow-up: 64.8									,	•	
month(s)											
• •	R	not	not						HR 1.14		mo
	С	seri	seri		serio			49	(0.84,		der
1 (gerstein 2019a)	Т	ous	ous	NA^2	us ⁵	NA	4949	52	1.54)	Not estimable	ate
hospitalisation for heart failure at end of follow up Mean											
follow-up: 64.8 month(s)											
								22			
	R	not	not					6/4	RR 0.94	3 fewer per	mo
	С	seri	seri		serio		213/4	95	(0.79,	1000 (10 fewer	der
1 (gerstein 2019a)	Т	ous	ous	NA^2	us ⁵	NA	949	2	1.13)	to 6 more)	ate

hospitalisation for heart failure at end of follow up Mean follow-up: 64.8 month(s)											
, , , , , , , , , , , , , , , , , , ,	R	not	not						HR 0.93		mo
	С	seri	seri		serio			49	(0.77,		der
1 (gerstein 2019a)	Т	ous	ous	NA ²	us ⁵	NA	4949	52	1.12)	Not estimable	ate
acute kidney injury at end of follow up Mean follow-up: 35.6 month(s)											
	R	not	not		very			67/	RR 0.91	1 fewer per	Ver
	С	seri	seri	serio	serio		61/50	50	(0.65,	1000 (5 fewer	У
2	Т	ous	ous	us ⁴	us ⁶	NA	93	99	1.29)	to 4 more)	low
persistent signs of worsening kidney disease at end of follow up Mean follow-up: 64.8 month(s)											
								50			
	R	not	not		not			0/4	RR 0.91	9 fewer per	
4 (С	seri	seri	1112	serio		453/4	95	(0.80,	1000 (20 fewer	hig
1 (gerstein 2019a)	I	ous	ous	NA ²	us	NA	949	2	1.02)	to 2 more)	h
persistent signs of worsening kidney disease at end of follow up Mean follow-up: 64.8 month(s)											
Tollow up Mean Tollow-up. 64.6 month(s)	R	not	not						HR 0.89		mo
	C	seri	seri		serio			49	(0.78,		der
1 (gerstein 2019a)	T	ous	ous	NA ²	us ⁵	NA	4949	52	1.01)	Not estimable	ate
development of end stage kidney disease at end of follow up Mean follow-up: 64.8 month(s)			Guo		us		10.0	02	,	THE COLLINGUE	
ap mountained apronomental									PETO OR		
	R	not	not		very			6/4	0.51	1 fewer per	
	С	seri	seri		serio		3/494	95	(0.14,	1000 (2 fewer	
1 (gerstein 2019a)	Т	ous	ous	NA ²	us ⁶	NA	9	2	1.90)	to 1 more)	low
cardiac arrhythmia at end of follow up Mean follow-up: 35.4 month(s)											
								19			
	R	not	not		very			2/5	RD 0.00	5 more per	ver
	С	seri	seri	serio	serio		216/4	00	(-0.00,	1000 (3 fewer	У
2	Т	ous	ous	us ⁴	us ⁷	NA	999	7	0.01)	to 13 more)	low
diabetic ketoacidosis at end of follow up Mean follow-up: 5.8 month(s)											

OTT TEL TABLES Winder 6. Type 2 diabetes and higher bardievase	aidi	1011									
	R	not	not	not	not				RD 0.00	0 fewer per	
	С	seri	seri	serio	serio			0/1	(-0.01,	1000 (12 fewer	hig
2	Т	ous	ous	us	us	NA	0/333	95	0.01)	to 12 more)	h
progression of liver disease at end of follow up Mean										/	
follow-up: 64.8 month(s)											
									PETO OR		
	R	not	not					40/	0.63	3 fewer per	mo
	C	seri	seri		serio		25/49	49	(0.39,	1000 (6 fewer	der
1 (gerstein 2019a)	T	ous	ous	NA ²	us ⁵	NA	49	52	1.02)	to 0 more)	ate
hypoglycaemia episodes at end of follow up Mean	•	ous	ous	14/ \	uo	14/ (170	02	1.02)	to o more)	ate
follow-up: 6 month(s)											
ionow-up. 6 month(s)	R	not	not	not				10	RR 1.22	38 more per	ma
		not	not	not	aaria		159/9	1/6		•	mo der
0	C	seri	seri	serio	serio	NI A			(0.97,	1000 (5 fewer	
6	I	ous	ous	us	us ⁵	NA	20	03	1.54)	to 91 more)	ate
at night hypoglycaemic episodes at end of follow up											
Mean follow-up: 6.1 month(s)											
	R	not	not	not	very			63/	RR 0.94	11 fewer per	
	С	seri	seri	serio	serio		69/53	35	(0.68,	1000 (56 fewer	
3	T	ous	ous	us	us ⁶	NA	3	7	1.29)	to 51 more)	low
severe hypoglycaemic episodes at end of follow up Mean											
follow-up: 14.4 month(s)											
	R	not	not		very			74/	RD -0.00	1 fewer per	ver
	С	seri	seri	serio	serio		66/58	55	(-0.01,	1000 (6 fewer	У
7	Т	ous	ous	us ⁴	us ⁸	NA	69	55	0.00)	to 3 more)	ĺow
hba1c change (%, lower values are better, change scores)										,	
at end of follow up Mean follow-up: 12.5 month(s)											
	R	not	not	very	not				MD -0.90	MD 0.90 lower	
	C	seri	seri	serio	serio			58	(-1.08, -	(1.08 lower to	
9	Ť	ous	ous	us ⁹	us	NA	7034	73	0.73)	0.73 lower)	low
weight change (kg, lower values are better, change	•	Jus	Cuc	40	40	147 (1001	, 0	0.70)	0.1010001)	1011
scores) at end of follow up Mean follow-up: 12.5											
month(s)											
month(s)	В	not	not	not	not				MD -1.44	MD 1.44 lower	
	R	not	not	not	not			67			bie
0	C	seri	seri	serio	serio	NIA	0550	57	(-1.60, -	(1.60 lower to	hig
9	ı	ous	ous	us	us	NA	6559	29	1.27)	1.27 lower)	h

GRADE tables - Model 5: Type 2 diabetes and higher cardiovascular risk

bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 25.6 month(s)											
	R	not	not	not	not				MD -0.53	MD 0.53 lower	
	С	seri	seri	serio	serio			50	(-0.61, -	(0.61 lower to	hig
3	Т	ous	ous	us	us	NA	5053	58	0.46)	1 1	h

- 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 (-0.03, 0.03)
- 4. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 5. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 6. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 7. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.41 (0.8-0.9 = serious, <0.8 = very serious).
- 8. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.3 (0.8-0.9 = serious, <0.8 = very serious).
- 9.12 > 75%

L.1.3.2 Adding dulaglutide compared to adding insulin

Table 15: Clinical evidence profile: Adding dulaglutide compared to adding insulin

Table 101 Chinear Criaciles promot Adding a	<u> </u>	40.40	• · · · · • • · ·		. 						
	De	Risk	Indir	Incon	Impr	Other	Interv	Con	Relative		Cer
	sig	of	ectn	siste	ecisi	consider	entio	trol	effect (95%		tain
No of studies	n	bias	ess	ncy	on	ations	n N	N	CI)	Absolute effect	ty
all-cause mortality at end of follow up Mean											
follow-up: 13.9 month(s)											

GRADE tables – Model 5: Type 2 diabetes and highe	R	very	not		very				PETO OR	4 fewer per 1000	ver
	C	serio	serio	serio	serio		4/164	5/8	0.36 (0.09,	(10 fewer to 2	yeı
3	T	us ¹	us	us ²	us ³	NA	8	11	1.45)	more)	low
cardiovascular mortality at end of follow up		uo	uo	us	us	147.			1.40)	more)	1000
Mean follow-up: 17.7 month(s)											
	R	not	not		very				PETO OR		
	С	serio	serio		serio			0/2	4.40 (0.07,	2 more per 1000	
1 (giorgino 2015)	Т	us	us	NA ⁴	us ³	NA	1/545	62	289.01)	(2 fewer to 5 more)	low
non-fatal stroke at end of follow up Mean											
follow-up: 6 month(s)											
	R	not	not		very				PETO OR	11 more per 1000	
	С	serio	serio		serio			0/1	7.39 (0.46,	(4 fewer to 26	
1 (araki 2015b)	Т	us	us	NA ⁴	us ³	NA	2/181	80	118.59)	more)	low
non-fatal myocardial infarction at end of follow											
up Mean follow-up: 6 month(s)											
	R	not	not		very				PETO OR	6 more per 1000	
	С	serio	serio		serio			0/1	7.35 (0.15,	(5 fewer to 16	
1 (araki 2015b)	Т	us	us	NA ⁴	us ³	NA	1/181	80	370.34)	more)	low
falls requiring hospitalisation at end of follow											
up Mean follow-up: 6 month(s)											
	R	not	not		very			0.44	PETO OR	6 more per 1000	
4 (1:00451)	C	serio	serio		serio		4/404	0/1	7.35 (0.15,	(5 fewer to 16	۱.
1 (araki 2015b)	Т	us	us	NA ⁴	us ³	NA	1/181	80	370.34)	more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 11.9 month(s)											
	R	not	not					297		147 fewer per	
	C	serio	serio	serio	serio		361/1	/69	RR 0.66	1000 (208 fewer to	
3	T	us	us	us ⁵	us ⁶	NA	241	5	(0.51, 0.84)	70 fewer)	low
at night hypoglycaemic episodes at end of											
follow up Mean follow-up: 11.9 month(s)											
	R	not	not	not	not			181		138 fewer per	
	С	serio	serio	serio	serio		156/1	/69	RR 0.47	1000 (159 fewer to	hig
3	Τ	us	us	us	us	NA	241	5	(0.39, 0.57)	112 fewer)	h
severe hypoglycaemic episodes at end of											
follow up Mean follow-up: 11.9 month(s)											

4	R C T	not serio us	not serio us	serio us²	very serio us ⁷	NA	18/18 29	17/ 991	RD -0.00 (- 0.01, 0.01)	4 fewer per 1000 (15 fewer to 7 more)	ver y low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 11.9 month(s)	•	ac	u.c	uc	u.c			001	0.01, 0.01)	e.e,	1011
4	R C T	not serio us	not serio us	very serio us ⁸	serio us ⁹	NA	1819	988	MD -0.33 (- 0.51, -0.15)	MD 0.33 lower (0.51 lower to 0.15 lower)	ver y low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 8 month(s)											
3	R C T	not serio us	not serio us	serio us ⁵	serio us ¹⁰	NA	1638	808	MD -2.60 (- 3.15, -2.05)	MD 2.60 lower (3.15 lower to 2.05 lower)	low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. Only one study so no inconsistency
- 5. I2 between 50% and 75%
- 6. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 7. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.66 (0.8-0.9 = serious, <0.8 = very serious).
- 8.12 > 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)

L.1.3.3 Adding dulaglutide compared to adding exenatide

Table 16: Clinical evidence profile: Adding dulaglutide compared to adding exenatide

Table 16: Clinical evidence profile: Addi	De	Risk	ie comp	Jareu lo	adding e	Other			Relative		Cert
		of	Indino	Inconsi	lmana		Intonio	Cont		Absolute	
No of studios	sig		Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	1.00010.00	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	У
all-cause mortality at end of follow up Mean follow-up: 12 month(s)											
1 (wysham 2014 52 weeks)	RC T	seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	2/559	0/27 6	RR 2.47 (0.12, 51.34)	0 fewer per 1000 (0 more to 0 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)											
1 (wysham 2014 52 weeks)	RC T	seriou s ¹	not seriou s	NA ²	Very seriou s ³	NA	2/559	0/27 6	PETO OR 4.46 (0.23, 85.07)	4 more per 1000 (1 fewer to 9 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 6 month(s)											
1 (wysham 2014 26 weeks)	RC T	seriou s ¹	not seriou s	NA ²	seriou s ⁴	NA	59/559	44/2 76	RR 0.66 (0.46, 0.95)	54 fewer per 1000 (86 fewer to 8 fewer)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											
1 (wysham 2014 52 weeks)	RC T	seriou s ¹	not seriou s	NA ²	seriou s ⁴	NA	0/559	2/27 6	PETO OR 0.05 (0.00, 0.92)	7 fewer per 1000 (17 fewer to 3 more)	low

hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (wysham 2014 52 weeks)	RC T	seriou s ¹	not seriou s	NA ²	not seriou s	NA	559	276	MD -0.13 (-0.32, 0.06)	MD 0.13 lower (0.32 lower to 0.06 higher)	mod erat e
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
1 (wysham 2014 26 weeks)	RC T	seriou s ¹	not seriou s	NA ²	not seriou s	NA	559	276	MD 0.52 (-0.18, 1.22)	MD 0.52 higher (0.18 lower to 1.22 higher)	mod erat e

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

L.1.3.4 Adding dulaglutide compared to adding sitagliptin

Table 17: Clinical evidence profile: Adding dulaglutide compared to adding sitagliptin

Table 17: Clinical evidence profile: Add	ing at	ilagiutio	e comp	ared to a	<u>laaing s</u>	itagiiptin				•	
	De					Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow up											
Mean follow-up: 12 month(s)											
										5 fewer per	
		very	not		very					1000	
	RC	seriou	seriou		seriou			2/31	RR 0.26	(6 fewer to	very
1 (nauck 2014 dulaglutide v sitagliptin)	Т	s ¹	S	NA ²	s ³	NA	1/606	5	(0.02, 2.86)	12 more)	low
cardiovascular mortality at end of follow											
up											
Mean follow-up: 12 month(s)											
										3 fewer per	
		very	not _.		very			4 /0 4	PETO OR	1000	
	RC	seriou	seriou		seriou		0.4000	1/31	0.05	(9 fewer to 3	very
1 (nauck 2014 dulaglutide v sitagliptin)	Т	s ¹	S	NA ²	s ³	NA	0/606	5	(0.00, 3.35)	more)	low
severe hypoglycaemic episodes at end											
of follow up											
Mean follow-up: 12 month(s)										0.6	
										0 fewer per	
	DO	very	not .		not .			0/04	DD 0 00	1000	
4 (RC	seriou	seriou	NIA?	seriou		0/000	0/31	RD 0.00	(5 fewer to 5	
1 (nauck 2014 dulaglutide v sitagliptin)	1	s ¹	S	NA ²	S	NA	0/606	5	(-0.00, 0.00)	more)	low
hba1c change (%, lower values are											
better, change scores) at end of follow											
up											
Mean follow-up: 12 month(s)										MD 0 53	
										MD 0.53	
			not						MD -0.53	lower	
	RC	seriou	not		ooriou					(0.68 lower to 0.38	
1 (nauck 2014 dulaglutida y sitaglintin)	T	seriou s ⁴	seriou	NA ²	seriou s ⁵	NA	606	315	(-0.68, - 0.38)		low
1 (nauck 2014 dulaglutide v sitagliptin)	ı	ა.	S	INA-	ວັ	INA	000	313	0.36)	lower)	low

weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
	RC	very seriou	not seriou		not seriou				MD -0.89 (-1.49, -	MD 0.89 lower (1.49 lower to 0.29	
1 (nauck 2014 dulaglutide v sitagliptin)	Т	s ¹	S	NA^2	S	NA	606	315	0.29)	lower)	low

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

L.1.3.5 Adding exenatide compared to adding placebo

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

rable 18. Chilical evidence profile. Adding exertative con	ipare	tu to a	uuiiig	Diaceb	<u> </u>						
	D							Co			
	es	Risk	Indir	Inco	Impr	Other	Inter	ntr	Relative		Cer
	ig	of	ectn	nsist	ecisi	conside	venti	ol	effect	Absolute	tai
No of studies	n	bias	ess	ency	on	rations	on N	N	(95% CI)	effect	nty
health-related quality of life - overall (iqwol-lite, 0-100, higher values are better, changes scores) at end of follow up Mean follow-up: 6.5 month(s)											
1 (gadde 2017)	R C T	very serio us ¹	not serio us	NA ²	not serio us	NA	181	61	MD -1.00 (-5.13, 3.13)	MD 1.00 lower (5.13 lower to 3.13 higher)	low
health-related quality of life - subscale barriers to activity (diabetes health profile, 0-100, lower values are better, changes scores) at end of follow up Mean follow-up: 6 month(s)									,		
1 (joubert 2021)	R C T	serio us³	not serio us	NA ²	serio us ⁴	NA	28	18	MD -4.30 (-9.75, 1.15)	MD 4.30 lower (9.75 lower to 1.15 higher)	low
health-related quality of life - subscale disinhibited eating (diabetes health profile, 0-100, lower values are better, changes scores) at end of follow up Mean follow-up: 6 month(s)									·		
1 (joubert 2021)	R C T	serio us³	not serio us	NA ²	serio us ⁵	NA	28	18	MD -8.09 (-19.75, 3.57)	MD 8.09 lower (19.75 lower to	low

The tables intouched type 2 diabetes and higher cardiovascular										3.57 higher)	
health-related quality of life - subscale well being (dmsat, 0- 100, higher values are better, changes scores) at end of follow up Mean follow-up: 6.5 month(s)										nignor)	
1 (gadde 2017) health-related quality of life - subscale psychological distress (diabetes health profile, 0-100, lower values are	R C T	very serio us ¹	not serio us	NA ²	serio us ⁶	NA	181	61	MD 7.10 (-0.95, 15.15)	MD 7.10 higher (0.95 lower to 15.15 higher)	ver y low
better, changes scores) at end of follow up Mean follow-up: 6 month(s)											
1 (joubert 2021)	R C T	serio us³	not serio us	NA ²	serio	NA	28	18	MD 2.73 (-3.04, 8.50)	MD 2.73 higher (3.04 lower to 8.50 higher)	low
all-cause mortality at end of follow up Mean follow-up: 10.6 month(s)											
8	R C T	not serio us	not serio us	serio us ⁸	not serio us	NA	508/8 590	587 /81 51	RD -0.01 (-0.02, - 0.00)	9 fewer per 1000 (17 fewer to 2 fewer)	mo der ate
all-cause mortality at end of follow up Mean follow-up: 38.4 month(s)											
1 (holman 2017)	R C T	not serio us	not serio us	NA ²	serio us ⁹	NA	7356	739 6	HR 0.86 (0.77, 0.97)	Not estimable	mo der ate
cardiovascular mortality at end of follow up Mean follow-up: 10.6 month(s)									,		

GNADE tables – Model 3. Type 2 diabetes and higher cardiovascu	iidi iidi									5 fewer	
	R	not	not		not			384	RD -0.01	per 1000	mo
	C	serio	serio	serio	serio		340/8	/81	(-0.01,	(11 fewer	der
8	T	us	us	us ⁸	us	NA	590	51	0.00)	to 1 more)	ate
cardiovascular mortality at end of follow up										, , , , , , , , , , , , , , , , , , , ,	
Mean follow-up: 38.4 month(s)											
	R	not	not						HR 0.88		mo
	С	serio	serio		serio			739	(0.76,	Not	der
1 (holman 2017)	T	us	us	NA ²	us ⁹	NA	7356	6	1.02)	estimable	ate
3-point mace at end of follow up Mean follow-up: 38.4 month(s)											
										8 fewer	
	R	not	not		not			905	RR 0.93	per 1000	
	С	serio	serio		serio		839/7	/73	(0.85,	(18 fewer	hig
1 (holman 2017)	T	us	us	NA ²	us	NA	356	96	1.02)	to 2 more)	h
3-point mace at end of follow up Mean follow-up: 38.4 month(s)											
	R	not	not		not				HR 0.91		
	С	serio	serio		serio			739	(0.83,	Not	hig
1 (holman 2017)	T	us	us	NA ²	us	NA	7356	6	1.00)	estimable	h
non-fatal myocardial infarction at end of follow up Mean follow-up: 6.8 month(s)											
									PETO	3 fewer	
	R	very	not		very				OR 0.36	per 1000	ver
	С	serio	serio	serio	serio			1/1	(0.02,	(15 fewer	У
2	T	us ¹	us	us ⁸	us ¹⁰	NA	1/435	84	7.65)	to 8 more)	low
unstable angina at end of follow up Mean follow-up: 38.4 month(s)											
										3 more per	
	R	not						151	RR 1.14	1000	
	C	serio	serio		serio		171/7	/73	(0.92,	(2 fewer to	
1 (holman 2017)	Т	us	us ¹¹	NA ²	us ⁹	NA	356	96	1.41)	8 more)	low
hospitalisation for heart failure at end of follow up Mean follow-up: 22.2 month(s)											
, , ,	R	not	not					231	RR 0.96		
	С	serio	serio	serio	serio		220/7	/74	(0.80,	1 fewer	
2	Т	us	us	us ⁸	us ⁹	NA	384	14	1.15)	per 1000	low

GIVADE tables Woder 6. Type 2 diabetes and higher cardiovascul										(6 fewer to 5 more)	
hospitalisation for heart failure at end of follow up Mean follow-up: 38.4 month(s)										3 more)	
1 (holman 2017)	R C T	not serio us	not serio us	NA ²	serio us ⁹	NA	7356	739 6	HR 0.94 (0.78, 1.13)	Not estimable	mo der ate
acute kidney injury at end of follow up Mean follow-up: 6.4 month(s)	1	us	us	INA	us	INA	7330	0	1.13)	estimable	ale
1 (guja 2017)	R C T	not serio us	not serio us	NA ²	very serio us ¹⁰	NA	1/232	0/2	PETO OR 7.36 (0.15, 370.79)	4 more per 1000 (4 fewer to 13 more)	low
development of end stage kidney disease at end of follow up Mean follow-up: 38.4 month(s)									,		
1 (holman 2017)	R C T	not serio us	not serio us	NA ²	serio us ⁹	NA	55/73 56	65/ 739 6	PETO OR 0.85 (0.59, 1.22)	1 fewer per 1000 (4 fewer to 2 more)	mo der ate
death from renal causes at end of follow up Mean follow-up: 38.4 month(s)		GO	do	10.0	uc				1.22)	2 mere)	ato
1 (holman 2017)	R C T	not serio us	not serio us	NA ²	very serio us ¹⁰	NA	5/735 6	5/7 396	PETO OR 1.01 (0.29, 3.47)	0 more per 1000 (1 fewer to 1 more)	low
cardiac arrhythmia at end of follow up Mean follow-up: 38.4 month(s)											
1 (holman 2017)	R C T	not serio us	not serio us	NA ²	serio us ⁹	NA	322/7 356	350 /73 96	RR 0.93 (0.80, 1.07)	4 fewer per 1000 (10 fewer to 3 more)	mo der ate
diabetic ketoacidosis at end of follow up Mean follow-up: 5.5 month(s)		30	40		30					(3 0 111010)	ato
2	R C T	very serio us ¹	not serio us	serio us ⁸	very serio us ¹²	NA	1/160	0/4	RD 0.01 (-0.04, 0.05)	5 more per	ver y low

GRADE tables – Model 5: Type 2 diabetes and higher cardiovascula	ai iisr									(38 fewer	
										to 49	
										more)	
hypoglycaemia episodes at end of follow up										more)	
Mean follow-up: 6.9 month(s)											
										56 more	
										per 1000	
	R		not		not			171	RD 0.06	(10 more	
	С	serio	serio	serio	serio		455/2	/13	(0.01,	to 102	
13	Т	us ³	us	us ⁸	us	NA	480	98	0.10)	more)	low
at night hypoglycaemic episodes at end of follow up Mean follow-up: 7 month(s)											
										94 fewer	
	R		not						RR 0.64	per 1000	
	С	serio	serio		serio		23/13	32/	(0.40,	(158 fewer	
1 (buse 2011)	Т	us ³	us	NA^2	us ⁹	NA	7	122	1.03)	to 8 more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 9.5 month(s)											
, , ,										3 more per	
	R	not	not		very			220	RD 0.00	1000	ver
	С	serio	serio	serio	serio		248/9	/85	(-0.00,	(2 fewer to	У
11	Т	us	us	us ⁸	us ¹³	NA	363	14	0.01)	8 more)	low
hba1c change (%, lower values are better, change scores) at											
end of follow up											
Mean follow-up: 10.9 month(s)											
										MD 0.72	
										lower	
									.45 0 70	(0.82	
	R	very	not		not			000	MD -0.72	lower to	ver
12	C	serio	serio	serio	serio	NIA	0000	868	(-0.82, -	0.63	У
hhada ahanga (mmal/l lawar yaluaa ara hattar ahanga	I	us ¹	us	us ¹⁴	us	NA	9820	2	0.63)	lower)	low
hba1c change (mmol/l, lower values are better, change scores) at end of follow up											
Mean follow-up: 5.5 month(s)											
wiedn follow-up. 5.5 month(s)	R		not		not				MD -0.52		mo
	C	serio	serio		serio				(-0.86, -	MD 0.52	der
1 (harreiter 2021)	T	us ³	us	NA ²	us	NA	16	14	0.17)	lower	ate
ו (וומווסונסו בטב ו)		นจ	นอ	11/4-	นอ	INA	10	14	0.17)	IOWEI	alt

weight change (kg, lower values are better, change scores)										(0.86 lower to 0.17 lower)	
at end of follow up											
Mean follow-up: 10.6 month(s) 14 bmi change (kg/m2, lower values are better, change and final scores) at end of follow up Mean follow-up: 7.8 month(s)	R C T	very serio us ¹	not serio us	serio us ¹⁴	not serio us	NA	9846	871 9	MD -1.58 (-2.00, - 1.17)	MD 1.58 lower (2.00 lower to 1.17 lower)	ver y low
3	R C T	very serio us ¹	serio us ¹¹	not serio us	not serio us	NA	125	114	MD -1.28 (-1.51, - 1.06)	MD 1.28 lower (1.51 lower to 1.06 lower)	ver y 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 one end of the defined MIDs (-8.33, 8.33)
- 5. 95% confidence intervals cross one end of the defined MIDs (-11.68, 11.68)
- 6. 95% confidence intervals cross one end of the defined MIDs (-11.43, 11.43)
- 7. 95% confidence intervals cross one end of the defined MIDs (-7.78, 7.78)
- 8. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

end of the defined MIDs (0.80, 1.25)

- 10. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 11. Largest proportion of studies in the meta-analysis came from partially direct studies
- 12. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.21 (0.8-0.9 = serious, <0.8 = very serious).
- 13. 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).
- 14. I2 between 50% and 75%

L.1.3.6 Adding exenatide compared to adding insulin

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

	D							Со			
	es	Risk	Indi	Inco	Impr	Other	Inter	ntr	Relative		Cer
	ig	of	rect	nsist	ecisi	conside	venti	ol	effect		tai
No of studies	n	bias	ness	ency	on	rations	on N	N	(95% CI)	Absolute effect	nty
health-related quality of life - overall (eq-5d, -0.59-1.0,											
higher values are better, change scores) at end of											
follow up Mean follow-up: 20.8 month(s)											
	R	very	not	not	not					MD 0.00 lower	
	С	serio	seri	serio	serio				MD -0.00 (-	(0.03 lower to	
2	Т	us ¹	ous	us	us	NA	450	438	0.03, 0.02)	0.02 higher)	low
health-related quality of life - overall (iwqol, 0-100,											
higher values are better, change scores) at end of											
follow up Mean follow-up: 6.5 month(s)											
	R		not	not	not				MD 3.71	MD 3.71 higher	mo
	С	serio	seri	serio	serio				(1.95,	(1.95 higher to	der
2	Т	us ²	ous	us	us	NA	358	368	5.46)	5.46 higher)	ate

all-cause mortality at end of follow up Mean follow-up: 12.2 month(s)											
, ,	R	very	not		very					2 more per 1000	ver
	С	serio	seri	serio	serio		5/125	2/1	RD 0.00 (-	(3 fewer to 8	у
6	Т	us ¹	ous	us ³	us ⁴	NA	1	224	0.00, 0.01)	more)	low
cardiovascular mortality at end of follow up Mean follow-up: 6.2 month(s)											
	R		not		very					3 more per 1000	ver
	С	serio	seri	serio	serio			0/7	RD 0.00 (-	(4 fewer to 9	у
4	Т	us ²	ous	us ³	us ⁵	NA	2/765	53	0.00, 0.01)	more)	low
non-fatal stroke at end of follow up Mean follow-up: 6 month(s)											
	R	not	not		very				PETO OR	5 more per 1000	
	С	serio	seri		serio			0/2	7.29 (0.14,	(4 fewer to 14	
1 (inagaki 2012)	T	us	ous	NA^6	us ⁷	NA	1/215	12	367.26)	more)	low
non-fatal myocardial infarction at end of follow up Mean follow-up: 7 month(s)											
•	R		not		very				PETO OR	6 fewer per	ver
	С	serio	seri		serio			2/3	0.13 (0.01,	1000 (15 fewer	у
1 (diamant 2014)	Т	us ²	ous	NA ⁶	us ⁷	NA	0/315	12	2.14)	to 2 more)	low
acute kidney injury at end of follow up Mean follow- up: 7 month(s)											
	R		not		very				PETO OR	3 more per 1000	ver
	С	serio	seri		serio			0/3	7.32 (0.15,	(3 fewer to 9	у
1 (diamant 2014)	Т	us ²	ous	NA ⁶	us ⁷	NA	1/315	12	368.87)	more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 7.6 month(s)											
	R		not	not	not			269	RR 0.66	86 fewer per	mo
	С	serio	seri	serio	serio		178/1	/10	(0.56,	1000 (111 fewer	der
8	Т	us ²	ous	us	us	NA	081	71	0.77)	to 58 fewer)	ate
at night hypoglycaemic episodes at end of follow up Mean follow-up: 7.2 month(s)											
	R		not		not			257	RR 0.54	105 fewer per	
	С	serio	seri	serio	serio		150/1	/11	(0.38,	1000 (141 fewer	
6	Т	us ²	ous	us ⁸	us	NA	147	30	0.76)	to 55 fewer)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 10.9 month(s)			_								

	R	very	not		very			21/		6 fewer per	ver
		serio	seri	serio	serio		11/17	170	RD -0.01 (-	1000 (13 fewer	V
10	-					NIA			•	,	1 :
10	<u> </u>	us ¹	ous	us ³	us ⁹	NA	38	4	0.01, 0.00)	to 1 more)	low
hba1c change (%, lower values are better, change											
scores) at end of follow up Mean follow-up: 9.2											
month(s)											
	R		not	very	not					MD 0.09 lower	ver
	С	serio	seri	serio	serio			201	MD -0.09 (-	(0.24 lower to	у
15	Т	us ²	ous	us ¹⁰	us	NA	2059	0	0.24, 0.06)	0.06 higher)	low
weight change (kg, lower values are better, change											
scores) at end of follow up Mean follow-up: 9.2											
month(s)											
, ,	R	very	not	very	not				MD -4.26 (-	MD 4.26 lower	ver
	С	serio	seri	serio	serio			197	5.05, -	(5.05 lower to	v
15	Т	us ¹	ous	us ¹⁰	us	NA	2015	6	3.48)	3.48 lower)	ĺow
bmi change (kg/m2, lower values are better, change									,	,	
scores) at end of follow up Mean follow-up: 7.1											
month(s)											
	R		not	very					MD -1.34 (-	MD 1.34 lower	ver
	С	serio	seri	serio	serio				1.88, -	(1.88 lower to	У
6	Т	us ²	ous	us ¹⁰	us ¹¹	NA	604	594	0.79)	0.79 lower)	ĺow

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 3. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.35 (0.8-0.9 = serious, <0.8 = very serious).
- 5. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.51 (0.8-0.9 = serious, <0.8 = very serious).
- 6. Only one study so no inconsistency
- 7. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

- 8. I2 between 50% and 75%
- 9. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.73 (0.8-0.9 = serious, <0.8 = very serious).
- 10. I2 > 75%
- 11. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

L.1.3.7 Adding exenatide compared to adding liraglutide

Table 20: Clinical evidence profile: Adding exenatide compared to adding liraglutide

rable 20. Chilical evidence profile. Adding ex	De	Risk	Indir	Incon	Impr	Other	Interv	Con	Relative		Cer
	sig	of	ectn	sisten	ecisi	consider	entio	trol	effect (95%		tain
No of studies	n	bias	ess	су	on	ations	n N	N	CI)	Absolute effect	ty
all-cause mortality at end of follow up Mean follow-up: 6 month(s)											
1 (buse 2013)	R CT	serio us¹	not serio us	NA 2	very serio us ³	NA	2/461	2/4 50	PETO OR 0.98 (0.14, 6.95)	0 fewer per 1000 (9 fewer to 8 more)	ver y low
hypoglycaemia episodes at end of follow up Mean follow-up: 6 month(s)											
2	R CT	not serio us	not serio us	not serio us	serio us ⁴	NA	129/6 93	100 /68 5	RR 1.29 (1.02, 1.62)	42 more per 1000 (3 more to 91 more)	mo der ate
severe hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)											
2	R CT	serio us¹	not serio us	serio us ⁵	very serio us ⁶	NA	1/693	0/6 85	RD 0.00 (- 0.00, 0.01)	1 more per 1000 (3 fewer to 6 more)	ver y low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)											
2	R CT	serio us¹	not serio us	not serio us	not serio us	NA	621	621	MD 0.26 (0.16, 0.35)	MD 0.26 higher (0.16 higher to 0.35 higher)	mo der ate

GRADE tables - Model 5: Type 2 diabetes and higher cardiovascular risk

weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)											
			not	not	not					MD 0.69 higher	mo
	R	serio	serio	serio	serio				MD 0.69	(0.30 higher to	der
2	СТ	us ¹	us	us	us	NA	635	633	(0.30, 1.07)	1.07 higher)	ate

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

L.1.3.8 Adding exenatide compared to adding sitagliptin

Table 21: Clinical evidence profile: Adding exenatide compared to adding sitagliptin

Tuble 21. Office evidence profile. Adding exchang	D				gp			Со			
	es	Risk	Indir	Inco	Impr	Other	Inter	ntr	Relative		Cer
	ig	of	ectn	nsist	ecisi	conside	venti	ol	effect		tai
No of studies	n	bias	ess	ency	on	rations	on N	N	(95% CI)	Absolute effect	nty
health-related quality of life - overall (ed-5d index, -											
0.59-1, higher values are better, changes scores)											
Mean follow-up: 6 month(s)											
	R	very	not		very				MD -0.01	MD 0.01 lower	ver
	С	serio	serio		serio				(-0.07,	(0.07 lower to	у
1 (bergenstal 2010)	Т	us ¹	us	NA^2	us ³	NA	129	139	0.05)	0.05 higher)	low
health-related quality of life - overall (iqwol, 0-100,											
higher values are better, changes scores) Mean											
follow-up: 6.5 month(s)											

GRADE tables – Model 3. Type 2 diabetes and higher cardio	1	Talai Holi			4				MD 4.00	MD 4 00 L	
	R		not		not				MD -1.30	MD 1.30 lower	mo
	C	serio	serio		serio				(-4.35,	(4.35 lower to	der
1 (gadde 2017)	T	us ⁴	us	NA ²	us	NA	181	122	1.75)	1.75 higher)	ate
health-related quality of life - subscale well being											
(dmsat, 0-100, higher values are better, changes											
scores) Mean follow-up: 6.5 month(s)											
	R		not		not				MD 8.20	MD 8.20 higher	mo
	С	serio	serio		serio				(1.54,	(1.54 higher to	der
1 (gadde 2017)	Т	us ⁴	us	NA ²	us	NA	181	122	14.86)	14.86 higher)	ate
all-cause mortality at end of follow up Mean follow-									,	, , , , , , , , , , , , , , , , , , ,	
up: 6 month(s)											
	R		not		very				PETO OR	6 fewer per 1000	ver
	C	serio	serio		serio			1/1	0.14 (0.00,	(18 fewer to 6	y
1 (bergenstal 2010)	T	us ⁴	us	NA ²	us ⁵	NA	0/160	66	7.08)	more)	low
cardiovascular mortality at end of follow up Mean							0, 100		1100)		
follow-up: 6 month(s)											
	R		not		very				PETO OR	6 fewer per 1000	ver
	С	serio	serio		serio			1/1	0.14 (0.00,	(18 fewer to 6	y
1 (bergenstal 2010)	T	us ⁴	us	NA ²	us ⁵	NA	0/160	66	7.08)	more)	low
non-fatal myocardial infaRCTion at end of follow up										,	
Mean follow-up: 6.5 month(s)											
(e)	R	not	not							0 fewer per 1000	mo
	C	serio	serio		serio			0/1	RD 0.00 (-	(14 fewer to 14	der
1 (gadde 2017)	ΙŤ	us	us	NA ²	us ⁶	NA	0/181	22	0.01, 0.01)	more)	ate
unstable angina at end of follow up Mean follow-up:			5.5				07.10.		0.01, 0.01)		1000
6 month(s)											
(-)	R		not							0 fewer per 1000	
	С	serio	serio		serio			0/1	RD 0.00 (-	(12 fewer to 12	
1 (bergenstal 2010)	T	us ⁴	us	NA ²	us ⁶	NA	0/160	66	0.01, 0.01)	more)	low
acute kidney injury at end of follow up Mean follow-									, , , , , ,	,	
up: 6 month(s)											
	R		not							0 fewer per 1000	
	С	serio	serio		serio			0/1	RD 0.00 (-	(12 fewer to 12	
1 (bergenstal 2010)	T	us ⁴	us	NA ²	us ⁶	NA	0/160	66	0.01, 0.01)	more)	low
hypoglycaemia episodes at end of follow up Mean							300		, , , , , ,	,	
follow-up: 6.2 month(s)											
TOTION APT SIZ IIIOII(II(O)											

	R		not		very				PETO OR	15 fewer per	ver
	C	serio	serio	serio	serio			6/2	0.35 (0.09,	1000 (33 fewer to	v
2	T	us ⁴	us	us ⁷	us ⁵	NA	2/341	88	1.44)	3 more)	low
severe hypoglycaemic episodes at end of follow up		uo	uo .	uo	uo	14/ (2/011	- 00	1111/	0 111010)	1011
Mean follow-up: 6.2 month(s)											
Mean follow-up. 6.2 month(s)	R		not	not	not					O fower per 1000	mo
	R		not	not	not			0/0	DD 0 00 /	0 fewer per 1000	mo
	<u>C</u>	serio	serio	serio	serio	1		0/2	RD 0.00 (-	(9 fewer to 9	der
2	Т	us ⁴	us	us	us	NA	0/341	88	0.01, 0.01)	more)	ate
hba1c change (%, lower values are better, change											
scores) at end of follow up Mean follow-up: 6.2											
month(s)											
, ,	R	not	not	not					MD -0.44	MD 0.44 lower	mo
	С	serio	serio	serio	serio				(-0.74, -	(0.74 lower to	der
2	T	us	us	us	us ⁸	NA	341	288	0.14)	0.14 lower)	ate
weight change (kg, lower values are better, change				<u> </u>	5.5				J,		10.10
scores) at end of follow up Mean follow-up: 6.2											
month(s)	_										
	R	not	not	very	not				MD -0.69	MD 0.69 lower	
	С	serio	serio	serio	serio				(-2.26,	(2.26 lower to	
2	Т	us	us	us ⁹	us	NA	341	288	0.88)	0.88 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 (-0.03, 0.03)
- 4. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 5. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 6. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 7. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 8. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

L.1.3.9 Adding liraglutide compared to adding placebo

Table 22: Adding liraglutide compared to adding placebo

lable 22: Adding liragiutide compared to adding placebo											
	D	Ris									Се
	е	k	Ind	Inc	lm	Other	Inte	Co	Relativ		rt
	si	of	ire	ons	pre	consi	rve	ntr	e effect		ai
	g	bia	ctn	iste	cisi	derati	ntio	ol	(95%	Absolute	nt
No of studies	n	S	ess	ncy	on	ons	n N	N	CI)	effect	у
health-related quality of life - overall (iwqol, higher values are better, change score) at end of follow-up Mean follow-up: 12.8 month(s)											
		ver									
		У	not						MD	MD 3.23	
	R	seri	ser		not				3.23	higher (1.18	
	С	ous	iou		seri			21	(1.18,	higher to	lo
1 (davies 2015)	Т	1	S	NA ²	ous	NA	615	1	5.28)	5.28 higher)	W
health-related quality of life - subscale barriers to activity (sf-36											
physical role subscale, higher values are better, change score) at end											
of follow-up Mean follow-up: 5.5 month(s)										MD 44.00	
					ver				MD	MD 14.20	
	R	oori	not		y				MD 14.20 (-	higher (5.77 lower to	ve
	C	seri	ser iou		seri ous				5.77,	34.17	ry lo
1 (miras 2019)	T	3	s	NA ²	4	NA	53	27	34.17)	higher)	W
health-related quality of life - subscale barriers to activity (modified	1	-	3	INA		INA	33	21	34.17)	riigriei)	VV
diabetes quality of life clinical trial questionnaire - lifestyle flexibility											
subscale, lower values are better, change score) at end of follow-up											
Mean follow-up: 6 month(s)											
mount on a production (o)			not						MD -	MD 0.10	
	R	seri	ser		seri				0.10 (-	lower (0.51	
	С	ous	iou		ous				0.51,	lower to 0.31	lo
1 (vanderheiden 2016a)	Т	3	s	NA^2	5	NA	32	34	0.31)	higher)	w
health-related quality of life - subscale blood glucose control (modified											
diabetes quality of life clinical trial questionnaire - glycaemia control											

perception subscale, lower values are better, change score) at end of											
follow-up Mean follow-up: 6 month(s)											
Tollow-up Mean follow-up. 6 month(s)			t						MD -	MD 1.10	
	_		not							_	
	R	seri	ser		seri				1.10 (-	lower (1.78	١.
	С	ous	iou		ous				1.78, -	lower to 0.42	lo
1 (vanderheiden 2016a)	Т	3	S	NA ²	6	NA	32	34	0.42)	lower)	W
health-related quality of life - subscale current health perception											
(modified diabetes quality of life clinical trial questionnaire - current											
health perception subscale, lower values are better, change score) at											
end of follow-up Mean follow-up: 6 month(s)											
			not						MD -	MD 0.30	
	R	seri	ser		seri				0.30 (-	lower (0.88	
	С	ous	iou		ous				0.88,`	lower to 0.28	lo
1 (vanderheiden 2016a)	T	3	s	NA ²	7	NA	32	34	0.28)	higher)	w
health-related quality of life - subscale emotional effects (sf-36										.3/	
emotional role functioning subscale, higher values are better, change											
score) at end of follow-up Mean follow-up: 5.5 month(s)											
Score at end of follow-up mean follow-up. 0.0 month(3)					ver					MD 6.30	+
			not						MD	higher (9.49	\/O
	В	o o ri			y						ve
	R	seri	ser		seri				6.30 (-	lower to	ry
4 (; 2040)	C	ous 3	iou		ous			07	9.49,	22.09	lo
1 (miras 2019)	l l	3	S	NA ²	8	NA	53	27	22.09)	higher)	W
health-related quality of life - subscale fatigue (sf-36 vitality subscale,											
higher values are better, change score) at end of follow-up Mean											
follow-up: 5.5 month(s)											
					ver						
			not		у				MD	MD 0.20	ve
	R	seri	ser		seri				0.20 (-	higher (8.77	ry
	С	ous	iou		ous				8.77,`	lower to 9.17	lo
1 (miras 2019)	Т	3	s	NA ²	4	NA	53	27	9.17)	higher)	w
health-related quality of life - subscale general health (sf-36 general									,	<i>J</i> ,	
health perception, higher values are better, change score) at end of											
follow-up Mean follow-up: 5.5 month(s)											
ionow-up mean ionow-up. o.o month(s)										MD 6.20	
			not						MD	higher (1.66	
	D	oori			acri					• (
	R	seri	ser		seri				6.20 (-	lower to	la.
4 (C	ous 3	iou	NIAS	ous	NI A	50	07	1.66,	14.06	lo
1 (miras 2019)	I	3	S	NA ²	9	NA	53	27	14.06)	higher)	W

health related-quality of life - subscale general health (modified diabetes quality of life clinical trial questionnaire - general health perception subscale, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)											
1 (vanderheiden 2016a)	R C T	seri ous	not ser iou s	NA ²	seri ous	NA	32	34	MD - 0.30 (- 0.68, 0.08)	MD 0.30 lower (0.68 lower to 0.08 higher)	lo w
health-related quality of life - subscale hypoglycaemia fear (modified diabetes quality of life clinical trial questionnaire - hypoglycaemia subscale, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)			J			10.	02		0.00)	Tilgilot)	
1 (vanderheiden 2016a)	R C T	seri ous	not ser iou s	NA ²	not seri ous	NA	32	34	MD 0.00 (- 0.27, 0.27)	MD 0.00 lower (0.27 lower to 0.27 higher)	m od er at e
health-related quality of life - lifestyle impact (modified diabetes quality of life clinical trial questionnaire - treatment impact subscale, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)									,		
1 (vanderheiden 2016a)	R C T	seri ous	not ser iou s	NA ²	seri ous	NA	32	34	MD - 0.20 (- 0.41, 0.01)	MD 0.20 lower (0.41 lower to 0.01 higher)	lo w
health-related quality of life - subscale pain (sf-36 bodily pain subscale, higher values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)	1		3	INA		INA	32	34	0.01)	, i	VV
1 (miras 2019)	R C T	seri ous	not ser iou s	NA ²	ver y seri ous	NA	53	27	MD - 3.40 (- 17.95, 11.15)	MD 3.40 lower (17.95 lower to 11.15 higher)	ve ry lo w
health-related quality of life - subscale physical functioning (sf-36 physical function subscale, higher values are better, change scores) at end of follow-up Mean follow-up: 9.2 month(s)									,	J,	

	not seri ous	not ser iou s	not seri ous	not seri ous	NA	251	22 5	MD 0.36 (- 1.00, 1.71)	MD 0.36 higher (1.00 lower to 1.71 higher)	hi
	seri	iou	seri	seri	NA	251		1.00,`	lower to 1.71	hi
	seri	iou	seri	seri	NA	251		1.00,`	lower to 1.71	hi
T					NA	251		,		1 111
1	ous	<u> </u>	ous	ous	INA	231	5	1.7 17		II .
								,	riigriei)	gh
		not						MD -	MD 0.30	
R	seri	ser		seri				0.30 (-	lower (0.57	
С	ous	iou		ous				0.57, -	lower to 0.03	lo
тΙ	3	s	NA ²	13	NA	32	34	0.03)	lower)	w
		_							,	
-										
		4						MD	MD 5 CO	
_				,						ve
										ry
		iou							lower to 5.95	lo
Т	3	s	NA^2	12	NA	53	27	5.95)	higher)	W
		not						MD -	MD 0 30	
ь	cori			cori						
									,	اما
$\frac{1}{2}$			NIA2		NIA	20	24			lo
<u> </u>	J	S	INA	17	INA	32	34	0.04)	nigner)	W
		not						MD	MD 0.30	
R	seri	ser		seri						
								`	,	lo
Ť	3		ΝΔ2	15	ΝΔ	32	34		_	w
T RCT RCT		seri ous 3	not seri ous iou s	seri ous iou s seri ious 3 s NA² not seri ious 3 NA² not seri ious 3 NA² not seri ious 3 NA²	seri ous iou s seri ous 3 s NA2 13 ver y seri ous 12 12 13 14 14 15 15 16 16 16 16 16 16 16 16 16 16 16 16 16	seri ous iou seri ous seri ous 3 s NA² 13 NA NA Ver y seri ous iou s NA² 1² NA NA NA NA NA NA Seri ous iou s NA² 14 NA NA NA NA NA NA NA	seri ous jou s seri ous 3 seri ous 12 NA 53	3 S NA2 13 NA 32 34	3 S NA2 13 NA 32 34 0.03)	3 S NA2 13 NA 32 34 0.03 lower 1

health-related quality of life - subscale wellbeing (sf-36 mental health											
subscale, higher values are better, change score) at end of follow-up											
Mean follow-up: 5.5 month(s)											
			not		ver				MD	MD 0.60	ve
	R	seri	ser		y seri				0.60 (-	higher (7.31	ry
	C	ous	iou		ous				7.31,	lower to 8.51	lo
1 (miras 2019)	T	3	S	NA ²	12	NA	53	27	8.51)	higher)	w
all-cause mortality at end of follow up Mean follow-up: 12.1 month(s)									,	J /	
(-)		ver									
		у	not					45	RD -	1 fewer per	ve
	R	seri	ser	seri	not		387	0/	0.00 (-	1000 (9	ry
	С	ous	iou	ous	seri		/72	58	0.01,	fewer to 6	lo
11	Τ	1	S	16	ous	NA	14	82	0.01)	more)	W
all-cause mortality at end of follow up (hazard ratio) Mean follow-up: 45.6 month(s)											
											m
	_		not						HR		od
	R C	not	ser		seri		468	46	0.85	Not	er
1 (marso 2016a)	 	seri ous	iou s	NA ²	ous 17	NA	8	72	(0.74, 0.98)	estimable	at e
cardiovascular mortality at end of follow up Mean follow-up: 13.5	'	ous	3	INA		INA	0	12	0.90)	CStillable	
month(s)											
			4					07	DD	4.6	m
	Ь	not	not	oori	not		222	27	RD -	1 fewer per	od
	R C	not seri	ser iou	seri ous	not seri		222 /69	8/ 56	0.00 (- 0.01,	1000 (9 fewer to 7	er
9	T	ous	S	16	ous	NA	36	30	0.01,	more)	e
cardiovascular mortality at end of follow up (hazard ratio) Mean follow-up: 45.6 month(s)										,,,,,,	
											m
			not						HR		od
	R	not	ser		seri				0.78		er
4.4	C	seri	iou		ous		468	46	(0.66,	Not	at
1 (marso 2016a)	Τ	ous	S	NA ²	17	NA	8	72	0.92)	estimable	е
3-point mace at end of follow up Mean follow-up: 45.6 month(s)											

GNADE tables – Model 3. Type 2 diabetes and higher cardiovascular risk									ı	•	
											m
			not					69	RR	18 fewer per	od
	R	not	ser		seri		608	4/	0.88	1000 (31	er
	С	seri	iou		ous		/46	46	(0.79,	fewer to 4	at
1 (marso 2016a)	Т	ous	s	NA ²	17	NA	68	72	0.97)	fewer)	е
3-point mace at end of follow up (hazard ratio) Mean follow-up: 45.6									,	,	
month(s)											
											m
			not						HR		od
	R	not	ser		seri				0.87		er
	C	seri	iou		ous		466	46	(0.78,	Not	at
1 (marso 2016a)	T	ous	s	NA ²	17	NA	8	72	0.97)	estimable	e
	'	Ous	3	14/1		14/4	-	12	0.01)	Command	
non-fatal stroke at end of follow up Mean follow-up: 28.8 month(s)											
	_		not					17	RR	4 fewer per	
	R	not	ser	seri	seri		159	8/	0.89	1000 (10	
	С	seri	iou	ous	ous		/49	48	(0.72,	fewer to 4	lo
2	Т	ous	S	16	17	NA	52	14	1.10)	more)	W
non-fatal stroke at end of follow up (hazard ratio) Mean follow-up: 45.6											
month(s)											
											m
			not						HR		od
	R	not	ser		seri				0.89		er
	С	seri	iou		ous		466	46	(0.72,	Not	at
1 (marso 2016a)	Т	ous	s	NA^2	17	NA	8	72	1.10)	estimable	е
non-fatal myocardial infarction at end of follow up Mean follow-up:											
28.8 month(s)											
, ,			not					31	RR	7 fewer per	
	R	not	ser	seri	seri		282	7/	0.89	1000 (16	
	С	seri	iou	ous	ous		/49	48	(0.76,	fewer to 2	lo
2	Т	ous	S	16	17	NA	52	14	1.04)	more)	W
non-fatal myocardial infarction at end of follow up (hazard ratio) Mean										,	
follow-up: 45.6 month(s)											
											m
			not						HR		od
	R	not	ser		seri				0.88		er
	C	seri	iou		ous		466	46	(0.75,	Not	at
1 (marso 2016a)	T	ous	S	NA ²	17	NA	8	72	1.03)	estimable	e
1 (maiso 2010a)	ı	ous	3	IN/\		INA	U	12	1.00)	Collinable	<u></u>

GRADE tables – Woder 5. Type 2 diabetes and higher cardiovascular risk											
unstable angina at end of follow up Mean follow-up: 28.8 month(s)											
					ver			4.0		0.6	
			not		У		400	12	RD -	0 fewer per	ve
	R	not	ser	seri	seri		122	4/	0.00 (-	1000 (7	ry
	C	seri	iou	OUS 16	0US 18	NIA	/49	48	0.01,	fewer to 6	lo
2 unotable engine at and of follow up (horord ratio). Mach follow up 45 C	I	ous	S	10	10	NA	52	14	0.01)	more)	W
unstable angina at end of follow up (hazard ratio) Mean follow-up: 45.6 month(s)											
					ver						
			not		У				HR		
	R	not	ser		seri				0.98		
4.4	C	seri	iou		ous		466	46	(0.76,	Not	lo
1 (marso 2016a)	T	ous	S	NA ²	19	NA	8	72	1.26)	estimable	W
hospitalisation for heart failure at end of follow up Mean follow-up: 45.6 month(s)											
Total months (c)											m
			not					24	RR	6 fewer per	od
	R	not	ser		seri		218	8/	0.88	1000 (14	er
	С	seri	iou		ous		/46	46	(0.74,	fewer to 3	at
1 (marso 2016a)	Т	ous	s	NA^2	17	NA	68	72	1.05)	more)	е
hospitalisation for heart failure at end of follow up (hazard ratio) Mean follow-up: 45.6 month(s)											
Tollow-up: 45.0 Month(5)											m
			not						HR		od
	R	not	ser		seri				0.87		er
	C	seri	iou		ous		466	46	(0.73,	Not	at
1 (marso 2016a)	ΙŤ	ous	S	NA ²	17	NA	8	72	1.04)	estimable	e
acute kidney injury at end of follow up Mean follow-up: 21.2 month(s)									, , ,		
			not					10	RR	2 more per	
	R	not	ser	seri	seri		112	0/	1.11	1000 (3	
	С	seri	iou	ous	ous		/51	49	(0.85,	fewer to 9	lo
3	Т	ous	s	16	17	NA	54	14	1.44)	more)	W
persistent signs of worsening kidney disease at end of follow up Mean follow-up: 25.6 month(s)											
	R	not		seri	seri		269				
	С	seri	not	ous	ous		/47	33	RR	15 fewer per	lo
2	Т	ous	ser	16	17	NA	21	7/	0.80	1000 (23	W

GNADE lables – Model 3. Type 2 diabetes and higher cardiovascular risk							1	10	(0.00		
			iou					46	(0.68,	fewer to 5	
			S					99	0.93)	fewer)	
persistent signs of worsening kidney disease at end of follow up											
(hazard ratio) Mean follow-up: 45.6 month(s)											
											m
			not						HR		od
	R	not	ser		seri				0.78		er
							466	46		Not	
4 / 2010)	С	seri	iou		OUS			46	(0.67,		at
1 (marso 2016a)	l l	ous	S	NA ²	17	NA	8	72	0.91)	estimable	е
development of end stage kidney disease at end of follow up Mean follow-up: 29.2 month(s)											
· · · · · · · · · · · · · · · · · · ·					ver						
			not		y			64	RR	2 fewer per	ve
	R	not	ser	seri	seri		57/	/4	0.88	1000 (5	ry
	C	seri	iou	ous	ous		530	88	(0.62,	fewer to 3	lo
	T			16	19	N I A		4			
2	I	ous	S	10	15	NA	0	4	1.25)	more)	W
development of end stage kidney disease at end of follow up (hazard ratio) Mean follow-up: 45.6 month(s)											
											m
			not						HR		od
	R	not	ser		seri				0.87		er
	C	seri	iou		ous		466	46	(0.61,	Not	at
1 (marso 2016a)	-	ous	s	NA ²	17	NA	8	72	1.24)	estimable	e
	<u> </u>	ous	3	INA		INA	0	12	1.24)	estimable	6
death from renal causes at end of follow up Mean follow-up: 34.8 month(s)											
		ver			ver				PETO		
		y	not		у				OR	1 more per	ve
	R	seri	ser	seri	seri			5/	1.63	1000 (1	ry
	C	ous	iou	ous	ous		9/5	47	(0.56,	fewer to 2	lo
2	T	1	s	16	19	NA	392	93	4.74)	more)	W
	1		5			INA	392	93	4.74)	more)	VV
death from renal causes at end of follow up (hazard ratio) Mean follow- up: 45.6 month(s)											
		ver			ver						
		У	not		у				HR		ve
	R	seri	ser		seri				1.59		ry
	C	ous	iou		ous		466	46	(0.52,	Not	lo
1 (marso 2016a)	T	1	s	NA ²	19	NA	8	72	4.86)	estimable	
1 (111a150 20 10a)	ı		5	INA		INA	0	12	4.00)	estillianie	W

hypoglycaemia episodes at end of follow up Mean follow-up: 12.1 month(s)											
montality			not					24 17	RR	69 more per	
	R C	not seri	ser iou	seri ous	seri ous		252 7/7	/6 18	1.18 (1.02,	1000 (6 more to 142	lo
13	T	ous	S	20	17	NA	762	3	1.36)	more)	W
at night hypoglycaemic episodes at end of follow up Mean follow-up: 7.2 month(s)											
	R C	not seri	not ser iou	seri ous	seri ous	NIA	6/3 57	11 /2	RD - 0.02 (- 0.10,	16 fewer per 1000 (95 fewer to 63	lo
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12.1 month(s)		ous	S	10		NA	31	44	0.06)	more)	W
13	R C T	not seri ous	not ser iou s	seri ous	not seri ous	NA	129 /81 33	15 7/ 60 51	RD - 0.01 (- 0.01, - 0.00)	5 fewer per 1000 (10 fewer to 0 more)	m od er at e
hba1c change (mmol/mol, lower values are better, change score) at end of follow up Mean follow-up: 6 month(s)											
1 (bizino 2019)	R C T	ver y seri ous	not ser iou s	NA ²	seri ous	NA	23	26	MD - 2.90 (- 8.09, 2.29)	MD 2.90 lower (8.09 lower to 2.29 higher)	ve ry lo w
hba1c change (%, lower values are better, change scores and final values) at end of follow up Mean follow-up: 9.9 month(s)									,	,	
19	R C T	ver y seri ous	not ser iou s	ver y seri ous	not seri ous	NA	795 0	58 70	MD - 0.88 (- 1.03, - 0.72)	MD 0.88 lower (1.03 lower to 0.72 lower)	ve ry lo w
weight change (kg, lower values are better, change scores and final values) at end of follow up Mean follow-up: 8.8 month(s)									,	,	

				ver							
			not	у					MD -	MD 2.02	ve
	R	seri	ser	seri	seri				2.02 (-	lower (2.85	ry
	С	ous	iou	ous	ous		727	54	2.85, -	lower to 1.20	lo
19	Т	3	S	23	24	NA	6	96	1.20)	lower)	W
bmi change (kg/m2, lower values are better, change scores and final											
values) at end of follow up Mean follow-up: 7.4 month(s)											
			not						MD -	MD 1.08	
	R	not	ser	seri	seri				1.08 (-	lower (1.37	
	С	seri	iou	ous	ous		147	28	1.37, -	lower to 0.79	lo
9	Т	ous	S	20	25	NA	1	29	0.79)	lower)	W

- 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 (-2.00, 2.00)
- 5. 95% confidence intervals cross one end of the defined MIDs (-0.38, 0.38)
- 6. 95% confidence intervals cross one end of the defined MIDs (-0.55, 0.55)
- 7. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 8. 95% confidence intervals cross both ends of the defined MIDs (-4.00, 4.00)
- 9. 95% confidence intervals cross one end of the defined MIDs (-2.00, 2.00)
- 10. 95% confidence intervals cross one end of the defined MIDs (-0.40, 0.40)
- 11. 95% confidence intervals cross one end of the defined MIDs (-0.33, 0.33)
- 12. 95% confidence intervals cross both ends of the defined MIDs (-3.00, 3.00)
- 13. 95% confidence intervals cross one end of the defined MIDs (-0.35, 0.35)
- 14. 95% confidence intervals cross one end of the defined MIDs (-0.42, 0.42)

end of the defined MIDs (-0.53, 0.53)

- 16. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 17. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 18. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.07 (0.8-0.9 = serious, <0.8 = very serious).
- 19. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 20. I2 between 50% and 75%
- 21. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.81 (0.8-0.9 = serious, <0.8 = very serious).
- 22. 95% confidence intervals cross one end of the defined MIDs (-5.50, 5.50)
- 23. I2 > 75%
- 24. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)
- 25. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

L.1.3.10 Adding liraglutide compared to adding insulin

Table 23: Adding liraglutide compared to adding insulin

	De	Risk	Indir	Incon	Impr	Other	Interv	Con	Relative	Ab l	Cer
	sig	of	ectn	sisten	ecisio	consider	entio	trol	effect	Absolute	tain
No of studies	n	bias	ess	су	n	ations	n N	N	(95% CI)	effect	ty
health-related quality of life - subscale mental											
component (SF-36, higher values are better, change											
score) at end of follow-up											
Mean follow-up: 15 month(s)											
		very	not	not	not				MD 0.04		
	R	serio	serio	serio	serio			127	(-0.10,	MD 0.04	
2	CT	us ¹	us	us	us	NA	1277	0	0.18)	higher	low

GRADE tables – Model 5: Type 2 diabetes and higher cardio	vascu	iai iisk								(0.40.1	
										(0.10 lower	
										to 0.18	
										higher)	
health-related quality of life -subscale physical											
component (SF-36, higher values are better, change											
score) at end of follow-up											
Mean follow-up: 9 month(s)											
										MD 0.48	
										higher	
		very	not	very	not				MD 0.48	(0.29 lower	ver
	R	serio	serio	serio	serio			127	(-0.29,	to 1.24	у
2	СТ	us ¹	us	us ²	us	NA	1277	0	1.24)	higher)	low
all-cause mortality at end of follow up			2.0						,	15	
Mean follow-up: 18 month(s)											
										2 fewer per	
			not		very				RD -0.00	1000	ver
	R	serio	serio	serio	serio		29/20	43/2	(-0.01,	(12 fewer	У
5	СТ	us ³	us	us ⁴	us ⁵	NA	23	022	0.01)	to 8 more)	ĺow
all-cause mortality at end of follow-up (hazard ratio)										,	
Mean follow-up: 60 month(s)											
mountenent aproximental(e)			not						HR 0.65		
	R	serio	serio		serio			126	(0.40,	Not	
1 (group 2022)	СТ	us ³	us	NA ⁶	us ⁷	NA	1262	3	1.05)	estimable	low
cardiovascular mortality at end of follow up	01	us	us	IN/A	us	INA	1202	3	1.00)	CSUITIADIC	IOW
Mean follow-up: 21 month(s)											
wiean follow-up: 21 month(s)										0 f	
			4						DD 0.00	3 fewer per	
			not				0/407	04/4	RD -0.00	1000	ver
	R	serio	serio	serio	serio	1	9/187	21/1	(-0.01,	(12 fewer	У
4	СТ	us ³	us	us ⁴	us ⁸	NA	6	879	0.01)	to 6 more)	low
cardiovascular mortality at end of follow-up (hazard											
ratio)											
Mean follow-up: 60 month(s)											
			not						HR 0.43		
	R	serio	serio		serio			125	(0.20,	Not	
1 (group 2022)	CT	us ³	us	NA ⁶	us ⁷	NA	1251	7	0.95)	estimable	low
3-point mace at end of follow up											
Mean follow-up: 36 month(s)											

GNADE tables – Model 5. Type 2 diabetes and higher cardio	774304	iai iisit	1								
										10 fewer	
			not	not					RR 0.75	per 1000	
	R	serio	serio	serio	serio		49/16	66/1	(0.52,	(19 fewer	
2	СТ	us ³	us	us	us ⁷	NA	65	670	1.07)	to 3 more)	low
	CI	us	us	us	us [,]	INA	05	670	1.07)	to 3 more)	IOW
3-point mace at end of follow up (hazard ratio)											
Mean follow-up: 60 month(s)											
			not						HR 0.74		
	R	serio	serio		serio			125	(0.51,	Not	
1 (group 2022)	СТ	us ³	us	NA ⁶	us ⁷	NA	1251	7	1.07)	estimable	low
	CI	us	us	INA	us [,]	INA	1231	1	1.07)	estimable	IOW
4-point mace at end of follow up											
Mean follow-up: 60 month(s)											
										13 fewer	
		very	not						RR 0.76	per 1000	ver
	R	serio	serio		serio		54/12	71/1	(0.54,	(26 fewer	
4 (NIA6		NIA.			, ,	`	У
1 (group 2022)	СТ	us ¹	us	NA ⁶	us ⁷	NA	62	263	1.07)	to 4 more)	low
non-fatal myocardial infarction at end of follow up											
Mean follow-up: 12 month(s)											
									PETO OR	0 fewer per	
		not	not		very				1.00	1000	
	Ь							1/41			
4.4	R	serio	serio		serio				(0.06,	(7 fewer to	١.
1 (gough 2014)	СТ	us	us	NA ⁶	us ⁹	NA	1/414	3	15.98)	7 more)	low
unstable angina at end of follow up											
Mean follow-up: 33 month(s)											
									PETO OR	2 fewer per	
		von	not		Vorv				0.70	1000	vor
		very	not .		very		7/4.4.4	40/4			ver
	R	serio	serio	serio	serio		7/144	10/1	(0.27,	(8 fewer to	У
2	CT	us ¹	us	us ⁴	us ⁹	NA	2	442	1.82)	4 more)	low
non-fatal stroke at end of follow up											
Mean follow-up: 5.8 month(s)											
mount on one aprior monthly									PETO OR	5 more per	
			4								
			not		very				3.34	1000	ver
	R	serio	serio	serio	serio			1/66	(0.57,	(2 fewer to	У
2	CT	us ³	us	us ⁴	us ⁹	NA	4/661	3	19.37)	11 more)	low
hospitalisation for heart failure at end of follow up										,	
Mean follow-up: 60 month(s)											
weatt tollow-up. or infolicits)											

GNADE tables – Model 3. Type 2 diabetes and higher cardio	R	serio	not serio		serio		14/12	26/1	RR 0.54 (0.28,	9 fewer per 1000 (15 fewer	
1 (group 2022)	СТ	us ³	us	NA ⁶	us ⁷	NA	51	257	1.03)	to 1 more)	low
hospitalisation for heart failure at end of follow-up (hazard ratio) Mean follow-up: 60 month(s)											
1 (group 2022)	R CT	serio us ³	not serio us	NA ⁶	serio us ⁷	NA	1251	125 7	HR 0.54 (0.28, 1.04)	Not estimable	low
acute kidney injury at end of follow up Mean follow-up: 6 month(s)											
1 (pasquel 2021)	R CT	very serio us ¹	serio us ¹⁰	NA ⁶	very serio us ⁹	NA	1/136	3/13 7	RR 0.34 (0.04, 3.19)	15 fewer per 1000 (21 fewer to 48 more)	ver y low
hypoglycaemia episodes at end of follow up Mean follow-up: 11.9 month(s)											
9	R	not serio us	not serio us	very serio us ²	not serio us	NA	527/2 781	100 0/27 99	RR 0.46 (0.31, 0.68)	193 fewer per 1000 (246 fewer to 115 fewer)	low
hypoglycaemia episodes at end of follow-up (hazard ratio) Mean follow-up: 60 month(s)											
1 (group 2022)	R CT	very serio us ¹	not serio us	NA ⁶	not serio us	NA	1233	124 5	HR 0.61 (0.53, 0.70)	Not estimable	low
at night hypoglycaemic episodes at end of follow up Mean follow-up: 5.8 month(s)											
3	R CT	not serio us	not serio us	serio us ⁴	not serio us	NA	15/89 1	93/8 95	RD -0.06 (-0.23, 0.12)	57 fewer per 1000 (234 fewer to 121 more)	mo der ate

severe hypoglycaemic episodes at end of follow up Mean follow-up: 13.6 month(s)											
7	R CT	very serio us ¹	not serio us	serio us ⁴	very serio us ¹¹	NA	22/26 08	23/2 615	RD -0.00 (-0.01, 0.00)	0 fewer per 1000 (6 fewer to 5 more)	ver y low
hba1c change (%, lower values are better, change scores and final values) at end of follow up Mean follow-up: 12.6 month(s)											
9 weight change (kg, lower values are better, change	R CT	not serio us	not serio us	serio us ¹²	not serio us	NA	1697	180 4	MD -0.10 (-0.29, 0.09)	MD 0.10 lower (0.29 lower to 0.09 higher)	mo der ate
scores) at end of follow up Mean follow-up: 6.7 month(s)											
8	R CT	not serio us	not serio us	serio us ¹²	not serio us	NA	1352	137 6	MD -4.13 (-4.81, - 3.45)	MD 4.13 lower (4.81 lower to 3.45 lower)	mo der ate
bmi change (kg/m2, lower values are better, change scores and final values) at end of follow up Mean follow-up: 8 month(s)											
3	R CT	serio us³	not serio us	not serio us	serio us ¹³	NA	95	94	MD -1.18 (-1.73, - 0.63)	MD 1.18 lower (1.73 lower to 0.63 lower)	low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. I2 > 75%
- 3. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 4. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

5. Precision calculated through Optimal

Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.65 (0.8-0.9 = serious, <0.8 = very serious).

- 6. Only one study so no inconsistency
- 7. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 8. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.87 (0.8-0.9 = serious, <0.8 = very serious).
- 9. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 10. Largest proportion of studies in the meta-analysis came from partially direct studies
- 11. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.04 (0.8-0.9 = serious, <0.8 = very serious).
- 12. I2 between 50% and 75%
- 13. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

L.1.3.11 Adding liraglutide compared to adding dulaglutide

Table 24: Adding liraglutide compared to adding dulaglutide

	De	Risk	Indir	Incon	Impr	Other	Interv	Con	Relative		Cer
	sig	of	ectn	sisten	ecisi	consider	entio	trol	effect (95%		tain
No of studies	n	bias	ess	су	on	ations	n N	N	CI)	Absolute effect	ty
all-cause mortality at end of follow up Mean											
follow-up: 6 month(s)											
		not	not		not					0 fewer per 1000	
	R	serio	serio		serio			0/3	RD 0.00 (-	(7 fewer to 7	hig
1 (dungan 2014)	CT	us	us	NA^1	us	NA	0/299	00	0.01, 0.01)	more)	h
cardiovascular mortality at end of follow up											
Mean follow-up: 6 month(s)											

OTTIBLE tables Model 6. Type 2 diabetes and high		not	not		not					0 fewer per 1000	
	R	serio	serio		serio			0/3	RD 0.00 (-	(7 fewer to 7	hig
1 (dungan 2014)	CT	us	us	NA ¹	us	NA	0/299	00	0.01, 0.01)	more)	h
falls requiring hospitalisation at end of follow											
up Mean follow-up: 6 month(s)											
		not	not		very				PETO OR	3 more per 1000	
	R	serio	serio		serio			0/3	7.41 (0.15,	(3 fewer to 10	
1 (dungan 2014)	СТ	us	us	NA ¹	us ²	NA	1/299	00	373.63)	more)	low
hypoglycaemia episodes at end of follow up											
Mean follow-up: 6 month(s)											
		not	not							30 more per 1000	mo
	R	serio	serio		serio		26/29	17/	RR 1.53	(8 fewer to 100	der
1 (dungan 2014)	СТ	us	us	NA ¹	us ³	NA	9	300	(0.85, 2.77)	more)	ate
at night hypoglycaemic episodes at end of											
follow up Mean follow-up: 6 month(s)											
		not	not		very					7 fewer per 1000	
	R	serio	serio		serio			6/3	RR 0.67	(16 fewer to 27	
1 (dungan 2014)	СТ	us	us	NA ¹	us ²	NA	4/299	00	(0.19, 2.35)	more)	low
severe hypoglycaemic episodes at end of											
follow up Mean follow-up: 6 month(s)											
		not	not		not					0 fewer per 1000	
	R	serio	serio		serio			0/3	RD 0.00 (-	(7 fewer to 7	hig
1 (dungan 2014)	СТ	us	us	NA ¹	us	NA	0/299	00	0.01, 0.01)	more)	h
hba1c change (%, lower values are better,											
change score) at end of follow up Mean											
follow-up: 6 month(s)											
		not	not		not					MD 0.06 lower	
	R	serio	serio		serio				MD -0.06 (-	(0.20 lower to 0.08	hig
1 (dungan 2014)	СТ	us	us	NA ¹	us	NA	299	300	0.20, 0.08)	higher)	h
weight change (kg, lower values are better,											
change scores) at end of follow up Mean											
follow-up: 6 month(s)											
		not	not		not					MD 0.71 higher	
	R	serio	serio		serio				MD 0.71	(0.16 higher to	hig
1 (dungan 2014)	CT	us	us	NA ¹	us	NA	299	300	(0.16, 1.26)	1.26 higher)	h

1. Only one study so no inconsistency

- 2. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 3. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

L.1.3.12 Adding liraglutide compared to adding saxagliptin

Table 25: Clinical evidence profile: Adding liraglutide compared to adding saxagliptin

Table 23. Chilical evidence profile. Addi		agiuliue	Compa	eu to au	uning sa						
	De					Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ions	ntion N	rol N	CI)	effect	у
hypoglycaemia episodes at the end of											
follow-up											
Mean follow-up: 5.5 month(s)											
										16 more per	
		very	not		very					1000	
	RC	seriou	seriou		seriou				RR 1.31	(35 fewer to	very
1 (li 2014a)	Т	s ¹	S	NA ²	s ³	NA	4/61	3/60	(0.31, 5.61)	231 more)	low
severe hypoglycaemic episodes at the											
end of follow-up											
Mean follow-up: 5.5 month(s)											
										0 fewer per	
		very	not							1000	
	RC	seriou	seriou		seriou				RD 0.00	(32 fewer to	very
1 (li 2014a)	T	s ¹	S	NA ²	s ⁴	NA	0/61	0/60	(-0.03, 0.03)	32 more)	low
hba1c change (%, lower values are											
better, final values) at the end of follow-											
up											
Mean follow-up: 5.5 month(s)											
										MD 0.27	
										lower	
		very	not		not				MD -0.27	(0.47 lower	
	RC	seriou	seriou		seriou				(-0.47, -	to 0.07	
1 (li 2014a)	Т	s ¹	S	NA ²	S	NA	61	60	0.07)	lower)	low

weight change (kg, lower values are better, change scores) at end of follow-											
up											
Mean follow-up: 5.5 month(s)											
1 (li 2014a) bmi change (kg/m2, lower values are	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	61	60	MD -5.10 (-6.01, - 4.19)	MD 5.10 lower (6.01 lower to 4.19 lower)	low
better, change scores) at end of follow-											
up											
Mean follow-up: 5.5 month(s)											
	RC	very seriou	not seriou		not seriou				MD -1.80 (-2.11, -	MD 1.80 lower (2.11 lower to 1.49	
1 (li 2014a)	Т	s ¹	S	NA ²	s	NA	61	60	1.49)	lower)	low

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

adding sitagliptin

Table 22: Clinical evidence profile: Adding liraglutide compared to adding sitagliptin (adding therapy)

No of studies health-related quality of life - subscale mental component (SF-36, higher values are better, change scores) at end of follow up	De sig n	of	Indire ctness				Interve ntion N	Relative effect (95% CI)	Absolute effect	Cert aint y
Mean follow-up: 24 month(s)										
1 (group 2022) health-related quality of life - subscale physical component (SF-36, higher values are better, change scores) at end of follow up Mean follow-up: 12 month(s)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s		1218	MD -0.27	MD 0.27 lower (0.85 lower to 0.31 higher)	low
	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	1218	MD 0.66	MD 0.66 higher (0.11 higher to 1.21 higher)	low
4	RC T	seriou s³	not seriou s		not seriou s		28/220 8	RD -0.01	8 fewer per 1000	low

GRADE tables – Model 5: Type 2 diabetes and higher cardiovascular	IIION										
									(-0.02, - 0.00)	(16 fewer to 0 more)	
all-cause mortality at the end of follow-up											
Mean follow-up: 60 month(s)											
mean ronow-up. oo month(s)											
	RC.	seriou	not seriou		seriou				HR 0.66		
1 (group 2022)	T	s ³		NA ²		NA	1262	1267	(0.41, 1.07)	Not estimable	low
cardiovascular mortality at the end of follow-up											
Mean follow-up: 26 month(s)											
Mean follow-up. 20 month(s)											
										6 fewer per 1000	
			not _.		not _.			00/4	RD -0.01		
3		seriou s³	seriou s	seriou s ⁴	seriou s	NA	9/1873	23/1 667	(-0.01, 0.00)	(13 fewer to 1 more)	low
cardiovascular mortality at the end of follow-up										,	
Mean follow-up: 60 month(s)											
	DO		not						HR 0.44		
1 (group 2022)		seriou s³	seriou s	NA ²	seriou s ⁵	NA	1251	1264	(0.20, 0.95)	Not estimable	low
3-point mace at end of follow-up											
·											
Mean follow-up: 60 month(s)											
			not							16 fewer per 1000	
	RC	seriou	not seriou		seriou		48/125	69/1	RR 0.70	(28 fewer to 0	
1 (group 2022)	Т	s^3	s	NA ²		NA	1		(0.49, 1.01)		low

GRADE lables – Model 5: Type 2 diabetes and higher cardiovascular r	ISIN										
3-point mace at the end of follow-up											
Mean follow-up: 60 month(s)											
			not						HR 0.70		
		seriou			seriou						
1 (group 2022)	Т	s ³	S	NA ²	s ⁵	NA	1251	1264	(0.48, 1.02)	Not estimable	low
4-point mace at end of follow-up											
Mean follow-up: 60 month(s)											
										19 fewer per	
		very	not						DD 0.70	1000	
		seriou			seriou		54/126	78/1		(31 fewer to 2	very
1 (group 2022)	T	s ¹	s	NA ²	s ⁵	NA	2	268	(0.50, 0.98)	fewer)	low
non-fatal stroke at the end of follow-up											
Mean follow-up: 6 month(s)											
										5 fewer per	
		not	not		very				PETO OR	1000	
	RC	seriou			seriou			1/18	0.14	(16 fewer to 5	
1 (zang 2016)	Т	S	S	NA ²	s ⁶	NA	0/183	4	(0.00, 6.86)	more)	low
non-fatal myocardial infarction at the end of follow-up											
Mean follow-up: 6 month(s)											
										26 fewer per	
		not	not		Vor.				PETO OR	1000	
	RC	not seriou	seriou		very seriou				0.14	(77 fewer to	
1 (webb 2020)	Т	s	s	NA ²	s ⁶	NA	0/38	1/38	(0.00, 6.82)	25 more)	low
unstable angina at end of follow-up											

GRADE tables – Model 3. Type 2 diabetes and higher cardiovascular i										
Mean follow-up: 60 month(s)										
1 (group 2022) hospitalisation for heart failure at the end of follow-up	RC T	seriou	not seriou s	seriou s ⁵	NA	7/1262	15/1	RR 0.47	6 fewer per 1000 (10 fewer to 2 more)	e very low
Mean follow-up: 60 month(s)										
1 (group 2022)	RC T	seriou	not seriou s	seriou s ⁵	NA	14/125 1	30/1	RR 0.47 (0.25, 0.88)	13 fewer per 1000 (18 fewer to 3 fewer)	low
hospitalisation for heart failure at the end of follow-up										
Mean follow-up: 60 month(s)										
1 (group 2022)		seriou	not seriou s	seriou s ⁵		1262		HR 0.47 (0.25, 0.88)	Not estimable	low
cardiac arrhythmia at the end of follow-up Mean follow-up: 6 month(s)										
1 (zang 2016)	RC T	seriou	not seriou s	very seriou s ⁶	NA	0/183		PETO OR 0.14	5 fewer per 1000 (16 fewer to 5 more)	low
diabetic ketoacidosis at the end of follow-up Mean follow-up: 6 month(s)										

1 (zang 2016) hypoglycaemia episodes at the end of follow-up Mean follow-up: 14.5 month(s)	RC T	not seriou s	not seriou s	NA ²	very seriou s ⁶		1/183	0/18	PETO OR 7.43 (0.15, 374.43)	5 more per 1000 (5 fewer to 16 more)	low
7 hypoglycaemia episodes at end of follow up	RC T	very seriou s ¹	not seriou s	seriou s ⁷	very seriou s ⁶		361/22 91	387/	RR 0.84 (0.50, 1.39)	30 fewer per 1000 (92 fewer to 72 more)	very low
Mean follow-up: 60 month(s) 1 (group 2022) at night hypoglycaemic episodes at the end of follow-up	RC T	very seriou s ¹	not seriou s		not seriou s	NA	1233		HR 0.97 (0.84, 1.12)	Not estimable	low
Mean follow-up: 6 month(s) 1 (zang 2016)	RC T	not seriou s		NA ²	not seriou s	NA	0/183	0/18 4	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (11 fewer to 11 more)	high
severe hypoglycaemic episodes at the end of follow-up Mean follow-up: 15.9 month(s)											

GRADE tables – Model 5: Type 2 diabetes and higher cardiovascular r	ISN								1		
6	RC	seriou		seriou	very seriou s ⁸			10/2 084	RD 0.00 (-0.00, 0.01)	2 more per 1000 (3 fewer to 6 more)	very low
hba1c change (%, lower values are better, final values) at the end of follow-up Mean follow-up: 13.4 month(s)											
8		seriou	not seriou s	very seriou s ⁹	seriou s ¹⁰	NA	1335		MD -0.33 (-0.56, -	MD 0.33 lower (0.56 lower to 0.10 lower)	very
weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 6.8 month(s)											
6		seriou	not seriou s	seriou s ⁷		NA	975	786	MD -2.10	MD 2.10 lower (2.65 lower to 1.55 lower)	very low
bmi change (kg/m2, lower values are better, change scores) at end of follow-up Mean follow-up: 5.8 month(s)											
4		seriou	not seriou s		seriou s ¹²	NA	274		MD -0.68 (-1.01, -	MD 0.68 lower (1.01 lower to 0.35 lower)	very

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. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 5. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 6. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 7. I2 between 50% and 75%
- 8. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.13 (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. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)
- 12. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

L.1.3.14 Adding liraglutide compared to adding vildagliptin

Table 23: Clinical evidence profile: Adding liraglutide compared to adding vildagliptin

	De					Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ions	ntion N	rol N	CI)	effect	у
hypoglycaemia episodes at the end of											
follow-up											
Mean follow-up: 5.5 month(s)											
		very	not		very						
	RC	seriou	seriou		seriou				RR 0.75	22 fewer per	very
1 (li 2014a)	Т	s ¹	s	NA ²	s^3	NA	4/61	5/57	(0.21, 2.65)	1000	low

GRADE lables – Woder 5. Type 2 diabetes and	riigiici	Cardiova	asculai III	DIV.				_		•	
										(69 fewer to 144 more)	
anyone by negly comic enjoydes at the										144 more)	
severe hypoglycaemic episodes at the end of follow-up											
Mean follow-up: 5.5 month(s)											
mean follow-up: 5.5 month(s)										0 fewer per	
		very	not							1000	
	RC	seriou	seriou		seriou				RD 0.00	(33 fewer to	very
1 (li 2014a)	T	s ¹	S	NA ²	s ⁴	NA	0/61	0/57	(-0.03, 0.03)	33 more)	low
hba1c change (%, lower values are	•	Ū.		101		10,	0,01	0,01	(0.00, 0.00)	oo more)	1011
better, final values) at the end of follow-											
up											
Mean follow-up: 5.5 month(s)											
										MD 0.25	
										lower	
		very	not		not				MD -0.25	(0.45 lower	
	RC	seriou	seriou		seriou				(-0.45, -	to 0.05	
1 (li 2014a)	Т	s ¹	S	NA ²	S	NA	61	57	0.05)	lower)	low
weight change (kg, lower values are											
better, change scores) at end of follow-											
up											
Mean follow-up: 5.5 month(s)										MD 5 00	
										MD 5.20	
		\/on/	not		not				MD -5.20	lower (6.08 lower	
	RC	very seriou	not seriou		not seriou				(-6.08, -	to 4.32	
1 (li 2014a)	T	seriou s ¹	S	NA ²	Seriou	NA	61	57	4.32)	lower)	low
bmi change (kg/m2, lower values are	1	3	3	INA	3	INA	01	37	4.02)	lower	IOW
better, change scores) at end of follow-											
up											
Mean follow-up: 5.5 month(s)											
										MD 1.80	
										lower	
		very	not		not				MD -1.80	(2.09 lower	
	RC	seriou	seriou		seriou				(-2.09, -	to 1.51	
1 (li 2014a)	T	s ¹	S	NA ²	s	NA	61	57	1.51)	lower)	low

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.

L.1.3.15 Adding lixisenatide compared to adding placebo

Table 26: Clinical evidence profile: Adding lixisenatide compared to adding placebo

Table 20. Chilical evidence prome. Adding historiatide	, 0011	ipaica	to aac	iiig pia	0000					1	
	De	Risk	Indir	Incon	Impr	Other	Interv	Con	Relative		Cer
	sig	of	ectn	siste	ecisi	consider	entio	trol	effect	Absolute	tain
No of studies	n	bias	ess	ncy	on	ations	n N	N	(95% CI)	effect	ty
health-related quality of life - subscale physical component (sf-12 scores, higher values are better, mean difference) at end of follow-up Mean follow-up: 5.3 month(s)											
1 (meneilly 2017) health-related quality of life - subscale mental	R C T	not serio us	not serio us	NA ¹	serio us²	NA	175	173	MD 1.73 (0.01, 3.45)	MD 1.73 higher (0.01 higher to 3.45 higher)	mo der ate
component (sf-12 scores, higher values are better, mean difference) at end of follow-up											
Mean follow-up: 5.3 month(s)										MD 0.33	
	R C	not serio	not serio		not serio				MD 0.33 (-1.57,	higher (1.57 lower to 2.23	hig
1 (meneilly 2017)	T	us	us	NA ¹	us	NA	175	173	2.23)	higher)	h
all-cause mortality at end of follow-up											

Mean follow-up: 6.7 month(s)											
10	R C T	not serio us	not serio us	serio us³	very serio us ⁴	NA	5/303 0	8/1 914	RD -0.00 (-0.01, 0.00)	3 fewer per 1000 (7 fewer to 1 more)	ver y low
cardiovascular mortality at end of follow-up Mean follow-up: 5.5 month(s)											
9	R C T	not serio us	not serio us	serio us³	very serio us ⁵	NA	2/270 8	2/1 754	RD -0.00 (-0.00, 0.00)	0 fewer per 1000 (4 fewer to 3 more)	ver y low
non-fatal stroke at end of follow-up Mean follow-up: 5.5 month(s)											
2	R C T	not serio us	not serio us	not serio us	very serio us ⁶	NA	3/350	0/3 51	PETO OR 7.49 (0.78, 72.21)	9 more per 1000 (1 fewer to 18 more)	low
non-fatal myocardial infarction at end of follow-up Mean follow-up: 5.5 month(s)											
1 (pan 2014)	R C T	not serio us	not serio us	NA ¹	very serio us ⁶	NA	1/196	0/1 94	PETO OR 7.31 (0.15, 368.62)	5 more per 1000 (5 fewer to 15 more)	low
hypoglycaemia episodes at end of follow-up Mean follow-up: 6.7 month(s)											
10	R C T	not serio us	not serio us	not serio us	serio us ⁷	NA	396/3 030	191 /19 14	RR 1.44 (1.18, 1.76)	44 more per 1000 (18 more to 76 more)	mo der ate
severe hypoglycaemic episodes at end of outcome Mean follow-up: 6.7 month(s)											
10	R C T	not serio us	not serio us	serio us³	not serio us	NA	7/303 0	0/1 914	RD 0.00 (-0.00, 0.01)	2 more per 1000 (1 fewer to 6 more)	mo der ate
hba1c change (%, lower values are better, mean difference) at end of follow-up											

Mean follow-up: 6.7 month(s)											
										MD 0.51	
										lower	
	R	not	not						MD -0.51	(0.63 lower	
	С	serio	serio	serio	serio			188	(-0.63, -	to 0.40	
10	Т	us	us	us ⁸	us ⁹	NA	2977	9	0.40)	lower)	low
weight change (kg, lower values are better, mean											
difference) at end of follow-up											
Mean follow-up: 6.7 month(s)											
										MD 0.74	
										lower	
	R	not	not	not	not				MD -0.74	(1.02 lower	
	С	serio	serio	serio	serio			189	(-1.02, -	to 0.46	hig
10	Т	us	us	us	us	NA	3012	8	0.46)	lower)	h

- 1. Only one study so no inconsistency
- 2. 95% confidence intervals cross one end of the defined MIDs (-2.00, 2.00)
- 3. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.65 (0.8-0.9 = serious, <0.8 = very serious).
- 5. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.09 (0.8-0.9 = serious, <0.8 = very serious).
- 6. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 7. 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)

adding insulin

Table 27: Clinical evidence profile: Adding lixisenatide compared to adding insulin

Tuble 27. Officer evidence profile. Add	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow up Mean follow-up: 6.2 month(s)											
3	RC T	serio us ¹	not seriou s	serious	very seriou s ³	NA	2/707	5/14 11	RD -0.00 (-0.01, 0.00)	1 fewer per 1000 (6 fewer to 5 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 6.2 month(s)											
3	RC T	serio us ¹	not seriou s	serious 2	very seriou s ⁴	NA	1/707	3/14 11	RD -0.00 (-0.01, 0.00)	1 fewer per 1000 (6 fewer to 4 more)	very low
non-fatal stroke at end of follow up Mean follow-up: 7 month(s)											
1 (rosenstock 2016b)	RC T	serio us ¹	not seriou s	NA ⁵	very seriou s ⁶	NA	1/233	1/46 7	RR 2.00 (0.13, 31.90)	2 more per 1000 (2 fewer to 66 more)	very low
unstable angina at end of follow up Mean follow-up: 7 month(s)											
1 (rosenstock 2016b)	RC T	serio us ¹	not seriou s	NA ⁵	very seriou s ⁶	NA	0/233	1/46 7	PETO OR 0.22 (0.00, 14.30)	2 fewer per 1000 (6 fewer to 2 more)	very low
hospitalisation for heart failure at end of follow up Mean follow-up: 7 month(s)											

1 (rosenstock 2016b) hypoglycaemia episodes at end of follow up Mean follow-up: 6.2 month(s)	RC T	serio us ¹	not seriou s	NA ⁵	very seriou s ⁶	NA	0/233	2/46	PETO OR 0.22 (0.01, 4.23)	4 fewer per 1000 (10 fewer to 2 more)	very low
3	RC T	serio us ¹	not seriou s	very serious	not seriou s	NA	125/70 7	618/ 1411	RR 0.29 (0.12, 0.71)	310 fewer per 1000 (386 fewer to 126 fewer)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 6.2 month(s)											
3	RC T	serio us ¹	not seriou s	serious 2	very seriou s ⁶	NA	1/707	4/14 11	PETO OR 0.55 (0.09, 3.51)	1 fewer per 1000 (5 fewer to 2 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 6.2 month(s)											
3	RC T	not serio us	not seriou s	serious	seriou s ⁹	NA	700	1402	MD 0.36 (0.17, 0.54)	MD 0.36 higher (0.17 higher to 0.54 higher)	low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6.2 month(s)											
3	RC T	not serio us	not seriou s	very serious	seriou s ¹⁰	NA	703	1402	MD -2.73 (-3.59, - 1.87)	MD 2.73 lower (3.59 lower to 1.87 lower)	very low

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

2. Downgraded for heterogeneity due to

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

- 3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.06 (0.8-0.9 = serious, <0.8 = very serious).
- 4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.08 (0.8-0.9 = serious, <0.8 = very serious).
- 5. Only one study so no inconsistency
- 6. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 7.12 > 75%
- 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)

L.1.3.17 Adding lixisenatide compared to adding liraglutide

Table 28: Clinical evidence profile: Adding lixisenatide compared to adding liraglutide

	De	Risk				Other			Relative		Cert
	sig	of	Indire	Incons	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	istency	cision	ions	ntion N	rol N	CI)	effect	У
cardiac arrhythmia at end of follow-up											
Mean follow-up: 6 month(s)											
1 (nauck 2016b)	RC	very seriou s ³	not seriou	NA ¹	very seriou s ²	NA	1/202	0/20	PETO OR 7.39 (0.15, 372.38)	5 more per 1000 (5 fewer to 15 more)	very
hypoglycaemia episodes at end of follow-	'	3	3	INA	3	INA	1/202		312.30)	more)	IOW
up Mean follow-up: 6 month(s)											

1 (nauck 2016b)	RC T	not seriou s	not seriou s	NA ¹	very seriou s ²	NA	5/202	3/20	RR 1.67 (0.40, 6.88)	10 more per 1000 (9 fewer to 87 more)	low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 6 month(s)											
1 (nauck 2016b)	RC T	very seriou s ³	not seriou s	NA ¹	not seriou s	NA	0/202	0/20	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (10 fewer to 10 more)	low
hba1c change (%, lower values are better, mean difference) at end of follow- up Mean follow-up: 6 month(s)											
1 (nauck 2016b)	RC T	not seriou s	not seriou s	NA ¹	seriou s ⁴	NA	202	202	MD 0.60 (0.40, 0.80)	MD 0.60 higher (0.40 higher to 0.80 higher)	mod erat e
weight change (kg, lower values are better, mean difference) at end of follow- up Mean follow-up: 6 month(s)											
1 (nauck 2016b)	RC T	not seriou s	not seriou s	NA ¹	not seriou s	NA	0	0	MD 0.60 (-0.18, 1.38)	MD 0.60 higher (0.18 lower to 1.38 higher)	high

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

adding exenatide

Table 29: Clinical evidence profile: Adding lixisenatide compared to adding exenatide

	De	Risk				Other					Cert
	sig	of	Indire	Inconsi	Impre	considerat	Interve	Cont	Relative effect	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ions	ntion N	rol N	(95% CI)	effect	У
all-cause mortality at end of follow up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2013)	RC T	not serio us	not seriou s	NA ¹	very seriou s ²	NA	1/318	1/31 6	PETO OR 0.99 (0.06, 15.92)	0 fewer per 1000 (9 fewer to 9 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2013)	RC T	not serio us	not seriou s	NA ¹	not seriou s	NA	8/318	25/3 16	RD -0.05 (-0.09, -0.02)	54 fewer per 1000 (88 fewer to 20 fewer)	high
severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2013)	RC T	not serio us	not seriou s	NA ¹	not seriou s	NA	0/318	0/31 6	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	high
hba1c change (%, lower values are better, change score) at end of follow- up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2013)	RC T	not serio us	not seriou	NA ¹	not seriou	NA	315	315	MD 0.17 (0.03, 0.31)	MD 0.17 higher (0.03 higher to 0.31 higher)	high

GRADE tables – Model 5: Type 2 diabetes and higher cardiovascular risk

weight change (kg, lower vaues are better, change score) at end of follow- up Mean follow-up: 5.5 month(s)											
	RC	not serio	not seriou		not seriou				MD 1.02	MD 1.02 higher (0.46 higher to 1.58	
1 (rosenstock 2013)	T	us	S	NA ¹	S	NA	315	315	(0.46, 1.58)	higher)	high

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

L.1.3.19 Adding lixisenatide compared to adding sitagliptin

Table 30: Clinical evidence profile: Adding lixisenatide compared to adding sitagliptin

						a.i			5 l .·		
	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ions	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow-up Mean follow-up: 5.5 month(s)											
1 (van gaal 2014)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s³	NA	0/158	0/16 1	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	very low
cardiovascular mortality at end of follow- up Mean follow-up: 5.5 month(s)											
1 (van gaal 2014)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s³	NA	0/158	0/16	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	very low

ONADE tables - Model 5. Type 2 diabetes and	riigiio	odraiove	doddiai iid								
hypoglycaemia episodes at end of follow-											
up											
Mean follow-up: 5.5 month(s)											
1 (van gaal 2014)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ⁴	NA	1/158	3/16	RR 0.34 (0.04, 3.23)	12 fewer per 1000 (18 fewer to 42 more)	very low
severe hypoglycaemic episodes at end of									,	,	
follow-up											
Mean follow-up: 5.5 month(s)											
1 (van gaal 2014)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s³	NA	0/158	0/16 1	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	very low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (van gaal 2014)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	158	161	MD 0.00 (-0.28, 0.28)	MD 0.00 lower (0.28 lower to 0.28 higher)	low
weight change (kg, lower values are better, mean difference) at end of follow- up Mean follow-up: 5.5 month(s)											
1 (van gaal 2014)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	152	160	MD -1.30 (-2.10, - 0.50)	MD 1.30 lower (2.10 lower to 0.50 lower)	low

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

L.1.3.20 Adding semaglutide compared to adding placebo

Table 31: Clinical evidence profile: Adding semaglutide compared to adding placebo

	De	Risk	Indir	Incon	Impr	Other	Interv	Con	Relative		Cer
	sig	of	ectn	siste	ecisi	consider	entio	trol	effect		tai
No of studies	n	bias	ess	ncy	on	ations	n N	N	(95% CI)	Absolute effect	nty
health-related quality of life - subscale mental component (sf-36, higher values are better, change scores) at end of follow-up Mean follow-up: 12.7 month(s)											
5	R C T	not seri ous	not serio us	not serio us	not serio us	NA	3286	242 9	MD 0.75 (0.28, 1.22)	MD 0.75 higher (0.28 higher to 1.22 higher)	hig h
health-related quality of life - subscale physical component (sf-36, higher values are better, change scores) at end of follow-up Mean follow-up: 12.7 month(s)											
5	R C T	not seri ous	not serio us	not serio us	not serio us	NA	3286	242 9	MD 0.55 (0.17, 0.93)	MD 0.55 higher (0.17 higher to 0.93 higher)	hig h
all-cause mortality at end of follow up Mean follow-up: 11.3 month(s)											
10	R C T	not seri ous	not serio us	serio us ¹	not serio us	NA	94/59 21	107 /43 82	RD -0.00 (- 0.01, 0.00)	4 fewer per 1000 (9 fewer to 2 more)	mo der ate
all-cause mortality at end of follow up Mean follow-up: 20.4 month(s)											
2	R C T	not seri ous	not serio us	very serio us ²	very serio us ³	NA	3239	324 1	HR 0.75 (0.37, 1.52)	Not estimable	ver y low
cardiovascular mortality at end of follow up Mean follow-up: 11.3 month(s)	,	340	40	40	40		3200		1.02)	THE COMMISSION	1000

OTT DE tables Model 6. Type 2 diabetes and higher of	R	not	not		not			76/		4 fewer per 1000	mo
	С	seri	serio	serio	serio		60/45	376	RD -0.00 (-	(10 fewer to 2	der
7	Т	ous	us	us ¹	us	NA	40	6	0.01, 0.00)	more)	ate
cardiovascular mortality at end of follow up Mean follow-up: 20.4 month(s)											
	R	not	not		very				HR 0.72		ver
	С	seri	serio	serio	serio			324	(0.37,		У
2	Т	ous	us	us ⁴	us ³	NA	3239	1	1.41)	Not estimable	low
3-point mace at end of follow up Mean follow-up: 20.4 month(s)											
	R	not	not	not				222	RR 0.76	16 fewer per	mo
	С	seri	serio	serio	serio		169/3	/32	(0.63,	1000 (26 fewer to	der
2	Т	ous	us	us	us ⁵	NA	239	41	0.92)	5 fewer)	ate
3-point mace at end of follow up Mean follow-up: 20.4 month(s)											
	R	not	not	not					HR 0.76		mo
	С	seri	serio	serio	serio			324	(0.62,		der
2	Т	ous	us	us	us ⁵	NA	3239	1	0.92)	Not estimable	ate
5-point mace at end of follow up Mean follow-up: 20.4 month(s)											
	R	not	not	not				364	RR 0.78	25 fewer per	mo
	С	seri	serio	serio	serio		282/3	/32	(0.67,	1000 (37 fewer to	der
2	Т	ous	us	us	us ⁵	NA	239	41	0.90)	12 fewer)	ate
5-point mace at end of follow up Mean follow-up: 20.4 month(s)											
	R	not	not	not					HR 0.76		mo
	С	seri	serio	serio	serio			324	(0.65,		der
2	T	ous	us	us	us ⁵	NA	3239	1	0.88)	Not estimable	ate
non-fatal stroke at end of follow up Mean follow-up: 13 month(s)											
	R	not	not					65/	PETO OR	8 fewer per 1000	
	С	seri	serio	serio	serio		47/48	377	0.64 (0.44,	(13 fewer to 3	
6	Т	ous	us	us ¹	us ⁵	NA	92	1	0.93)	rewer)	low
non-fatal stroke at end of follow up Mean follow-up: 20.4 month(s)											

Try to Labeta Wooder 6. Type 2 diabetes and higher bar	_		1						LID 0.04		
	R	not	not	not					HR 0.64		mo
	С	seri	serio	serio	serio			324	(0.43,		der
2	Т	ous	us	us	us ⁵	NA	3239	1	0.96)	Not estimable	ate
non-fatal myocardial infarction at end of follow up											
Mean follow-up: 14.2 month(s)											
mount tonout april 112 months(o)	R	not	not					98/		3 fewer per 1000	
	C		serio	aaria	aaria		91/46	363	RD -0.00 (-		
_		seri		serio	serio				`	(10 fewer to 4	
5	Т	ous	us	us ¹	us ⁶	NA	29	8	0.01, 0.00)	more)	low
non-fatal myocardial infarction at end of follow up											
Mean follow-up: 20.4 month(s)											
	R	not	not		very				HR 0.91		ver
	C	seri	serio	serio	serio			324	(0.58,		v
2	ΙŤ	ous	us	us ⁴	us ³	NA	3239	1	1.43)	Not estimable	low
	-	ous	us	us	us	INA	3233	'	1.43)	Not estimable	IOW
unstable angina at end of follow up											
Mean follow-up: 17.6 month(s)											
	R	not	not		very			34/	PETO OR	0 fewer per 1000	ver
	С	seri	serio	serio	serio		34/35	338	0.99 (0.61,	(5 fewer to 4	У
3	lΤ	ous	us	us ¹	us ³	NA	24	3	1.60)	more)	low
unstable angina at end of follow up										,	
Mean follow-up: 20.4 month(s)											
Mean follow-up. 20.4 month(s)	В	not	not	not) (OF) (HR 0.97		
	R	not .	not .	not .	very			004			
	С	seri	serio	serio	serio			324	(0.60,		
2	Т	ous	us	us	us ³	NA	3239	1	1.56)	Not estimable	low
hospitalisation for heart failure at end of follow up											
Mean follow-up: 14.9 month(s)											
	R	not	not		very			79/	RR 1.02	0 more per 1000	ver
	C	seri	serio	serio	serio		83/40	355	(0.75,	(6 fewer to 8	
4	T					NIA				`	У
4		ous	us	us ¹	us ³	NA	48	8	1.38)	more)	low
hospitalisation for heart failure at end of follow up											
Mean follow-up: 20.4 month(s)											
	R	not	not	not	very				HR 1.03		
	С	seri	serio	serio	serio			324	(0.76,		
2	ΙŤ	ous	us	us	us ³	NA	3239	1	1.41)	Not estimable	low
acute kidney injury at end of follow up		040	40	30	40		0200		,	1101 Ootiiiiabio	1011
Mean follow-up: 14.6 month(s)											

GNADE lables – Model 5. Type 2 diabetes and higher can	1							T			
	R	not	not		very			108		1 fewer per 1000	ver
	С	seri	serio	serio	serio		107/5	/41	RD -0.00 (-	(8 fewer to 5	У
6	Т	ous	us	us ¹	us ⁷	NA	024	20	0.01, 0.01)	more)	low
persistent signs of worsening kidney disease at									,	,	
end of follow up											
Mean follow-up: 25.2 month(s)											
mean follow up: 20:2 month(0)	R	not	not					100	RR 0.62	23 fewer per	mo
	C	seri	serio		serio		62/16	/16	(0.46,	1000 (33 fewer to	der
1 (marga 2016h)	T			NA ⁸	us ⁵	NA	48	49			
1 (marso 2016b)	I	ous	us	INA	us°	INA	40	49	0.85)	9 fewer)	ate
persistent signs of worsening kidney disease at											
end of follow up											
Mean follow-up: 25.2 month(s)											
	R	not	not						HR 0.64		mo
	С	seri	serio		serio			164	(0.46,		der
1 (marso 2016b)	Т	ous	us	NA ⁸	us ⁵	NA	1648	9	0.89)	Not estimable	ate
cardiac arrhythmia at end of follow up									ĺ		
Mean follow-up: 25.2 month(s)											
	R	not	not		very			58/	RR 0.86	5 fewer per 1000	
	C	seri	serio		serio		50/16	164	(0.59,	(14 fewer to 9	
1 (marso 2016b)	ΙŤ	ous	us	NA ⁸	us ³	NA	48	9	1.25)	more)	low
hypoglycaemia episodes at end of follow up	-	Ous	us	11/1	us	I IV/X	70	3	1.20)	inorc)	IOW
Mean follow-up: 9.3 month(s)											
Mean follow-up: 9.5 month(s)								00/	DD 4 04	00	
	R	not _.	not _.		very		000/0	82/	RR 1.31	26 more per 1000	ver
	С	seri	serio	serio	serio		288/2	100	(0.77,	(19 fewer to 102	У
7	Т	ous	us	us ⁴	us ³	NA	418	8	2.25)	more)	low
severe hypoglycaemic episodes at end of follow up											
Mean follow-up: 11.4 month(s)											
	R	not	not		very			371		11 more per 1000	ver
	С	seri	serio	serio	serio		431/4	/38	RD 0.01 (-	(1 fewer to 23	V
7	T	ous	us	us ¹	us ⁹	NA	801	08	0.00, 0.02)	more)	low
hba1c change (%, lower values are better, change				3.0	2.0				1100, 0102)		
scores) at end of follow up											
Mean follow-up: 12.6 month(s)											
mean follow-up. 12.6 month(5)	В	not	not	1/05/	not				MD 1.04	MD 1 04 lower	
	R	not	not	very	not			000	MD -1.04	MD 1.04 lower	
	С	seri	serio	serio	serio			269	(-1.26, -	(1.26 lower to	
1	ľ	ous	us	us ²	us	NA	4203	6	0.82)	0.82 lower)	low

hba1c change (mmol/mol, lower values are better, change scores) at end of follow up Mean follow-up: 6.2 month(s)											
2	R C T	seri ous ¹	not serio us	very serio us ²	serio us ¹¹	NA	71	50	MD -14.67 (-27.41, - 1.94)	MD 14.67 lower (27.41 lower to 1.94 lower)	ver y low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 11.2 month(s)											
9	R C T	not seri ous	not serio us	very serio us ²	not serio us	NA	4275	274 7	MD -3.59 (-4.24, - 2.94)	MD 3.59 lower (4.24 lower to 2.94 lower)	low
bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 11.8 month(s)									·	,	
4	R C T	not seri ous	not serio us	very serio us ²	not serio us	NA	1741	844	MD -1.26 (-1.60, - 0.91)	MD 1.26 lower (1.60 lower to 0.91 lower)	low

- 1. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 2. 12 > 75%
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. I2 between 50% and 75%
- 5. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.87 (0.8-0.9 = serious, <0.8 = very serious).
- 7. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.59 (0.8-0.9 = serious, <0.8 = very serious).
- 8. Only one study so no inconsistency

9. Precision calculated through Optimal

Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.41 (0.8-0.9 = serious, <0.8 = very serious).

- 10. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 11. 95% confidence intervals cross one end of the defined MIDs (-5.50, 5.50)

L.1.3.21 Adding semaglutide compared to adding insulin

Table 32: Clinical evidence profile: Adding semagluitde compared to adding insulin

	De	Risk	Indir	Incon	Impr	Other	Interv	Con	Relative		Cer
	sig	of	ectn	siste	ecisi	consider	entio	trol	effect	Absolute	tain
No of studies	n	bias	ess	ncy	on	ations	n N	N	(95% CI)	effect	ty
health-related quality of life - subscale mental											
component (sf-36 v2, higher values are better, change											
scores) at end of follow-up											
Mean follow-up: 12 month(s)											
										MD 0.59 higher	
	R	very	not		not				MD 0.59	(0.14 lower	
	C	serio	serio		serio				(-0.14,	to 1.32	
1 (kellerer 2022)	T	us ¹	us	NA ²	us	NA	874	874	1.32)	higher)	low
health-related quality of life - subscale physical										,	
component (sf-36 v2, higher values are better, change											
scores) at end of follow-up											
Mean follow-up: 12 month(s)											
										MD 0.95	
										higher	
	R	very	not		not				MD 0.95	(0.37 higher to	
	C	serio	serio		serio				(0.37,	1.53	
1 (kellerer 2022)	T	us ¹	us	NA ²	us	NA	874	874	1.53)	higher)	low
all-cause mortality at end of follow up										,	
Mean follow-up: 9.5 month(s)											

										_	
									PETO OR	8 more per	
	R		not		not				3.32	1000	
	С	serio	serio	serio	serio		16/15	3/1	(1.32,	(2 more to	
	T	us ³	us	us ⁴	us	NA	96	224	8.31)	13 more)	low
cardiovascular mortality at end of follow up Mean follow-up: 7 month(s)											
									PETO OR	1 fewer per	
	R	very	not		very				0.74	1000	ver
	С	serio	serio		serio			2/3	(0.11,	(10 fewer	у
l (aroda 2017)	T	us ¹	us	NA^2	us ⁵	NA	3/722	60	4.76)	to 8 more)	low
unstable angina at end of follow up Mean follow-up: 12 month(s)											
• , ,									PETO OR	0 fewer per	
	R		not		very				0.99	1000	ver
	С	serio	serio		serio			1/8	(0.06,	(3 fewer to	У
(kellerer 2022)	ΙŤ	us ³	us	NA ²	us ⁵	NA	1/874	64	15.82)	3 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 12 month(s)											
. ,										235 fewer	
										per 1000	
	R		not		not			527	RR 0.62	(271 fewer	mo
	C	serio	serio		serio		328/8	/86	(0.56,	to 195	der
(kellerer 2022)	ΙŤ	us ³	us	NA ²	us	NA	74	4	0.68)	fewer)	ate
at night hypoglycaemic episodes at end of follow up		J. J	U. U		5.5				0.00)	,	
Mean follow-up: 7 month(s)											
, , ,										13 fewer	
	R	very	not						RR 0.44	per 1000	ver
	С	serio	serio		serio			8/3	(0.16,	(19 fewer	У
l (aroda 2017)	T	us ¹	us	NA ²	us ⁶	NA	7/722	60	1.19)	to 4 more)	low
severe hypoglycaemic episodes at end of follow up										.,	
Mean follow-up: 9.5 month(s)											
. , , ,										19 fewer	
										per 1000	
	R	very	not	not	not			45/	RR 0.48	(25 fewer	
	C	serio	serio	serio	serio		40/15	122	(0.32,	to 10	

hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 8.7 month(s)											
2	R C T	very serio us ¹	not serio us	very serio us ⁷	serio us ⁸	NA	1596	123 4	MD -0.49 (-0.79, - 0.19)	MD 0.49 lower (0.79 lower to 0.19 lower)	ver y low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 8.7 month(s)											
2	R C T	very serio us ¹	not serio us	very serio us ⁷	not serio us	NA	1596	123 4	MD -6.69 (-8.73, - 4.65)	MD 6.69 lower (8.73 lower to 4.65 lower)	ver y low
bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (kellerer 2022)	R C T	very serio us ¹	not serio us	NA ²	not serio us	NA	874	874	MD -2.54 (-2.69, - 2.39)	MD 2.54 lower (2.69 lower to 2.39 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. I2 between 50% and 75%
- 5. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 6. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 7. 12 > 75%

end of the defined MIDs (-0.50, 0.50)

L.1.3.22 Adding semaglutide compared to adding dulaglutide

Table 33: Clinical evidence profile: Adding semaglutide compared to adding dulaglutide

Table 33: Clinical evidence profile: Adding semagiuti											
	De	Risk	Indir	Incon	Impr	Other	Interv	Con	Relative		Cer
	sig	of	ectn	sisten	ecisi	consider	entio	trol	effect	Absolute	tain
No of studies	n	bias	ess	су	on	ations	n N	N	(95% CI)	effect	ty
health-related quality of life - subscale mental component (sf-36-v2, higher values are better, change scores) at end of follow-up Mean follow-up: 12 month(s)											
1 (yabe 2020)	R C T	very serio us ¹	not serio us	NA ²	not serio us	NA	393	65	MD 0.26 (-0.86, 1.38)	MD 0.26 higher (0.86 lower to 1.38 higher)	low
health-related quality of life - subscale physical component (sf-36-v2, higher values are better, change scores) at end of follow-up Mean follow-up: 12 month(s)											
1 (yabe 2020)	R C T	very serio us ¹	not serio us	NA ²	not serio us	NA	393	65	MD -0.12 (-0.88, 0.64)	MD 0.12 lower (0.88 lower to 0.64 higher)	low
all-cause mortality at end of follow up Mean follow-up: 11.2 month(s)											
2	R C T	not serio us	not serio us	serio us³	very serio us ⁴	NA	2/994	4/6 63	RD -0.00 (-0.01, 0.00)	3 fewer per 1000 (10 fewer to 5 more)	ver y low
cardiovascular mortality at end of follow up Mean follow-up: 11.2 month(s)											

GNADE tables – Model 5. Type 2 diabetes and higher cardiova	Joodie	ai iioit					_			1 4 6	
	R C	not serio	not serio	serio	very serio	NIA.	4/004	2/6	RD -0.00 (-0.01,	1 fewer per 1000 (7 fewer to	ver y
2	Т	us	us	us ³	us ⁵	NA	1/994	63	0.00)	4 more)	low
acute kidney injury at end of follow up Mean follow-up: 12 month(s)											
1 (yabe 2020)	R C T	not serio us	not serio us	NA ²	not serio us	NA	0/393	0/6 5	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (21 fewer to 21 more)	hig h
death from renal causes at end of follow up Mean follow-up: 12 month(s)											
1 (yabe 2020)	R C T	not serio us	not serio us	NA ²	not serio us	NA	0/393	0/6 5	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (21 fewer to 21 more)	hig h
hypoglycaemia episodes at end of follow up Mean follow-up: 9 month(s)											
2	R C T	not serio us	not serio us	serio us ³	very serio us ⁶	NA	67/40 9	13/ 81	RD -0.03 (-0.12, 0.07)	26 fewer per 1000 (118 fewer to 67 more)	ver y low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 11.2 month(s)											
2	R C T	not serio us	not serio us	serio us³	very serio us ⁷	NA	7/994	8/6 63	PETO OR 0.87 (0.31, 2.41)	5 fewer per 1000 (15 fewer to 5 more)	ver y low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 9.1 month(s)									,	,	
3	R C T	serio us ⁸	not serio us	very serio us ⁹	serio us ¹⁰	NA	1010	679	MD -0.25 (-0.56, 0.06)	MD 0.25 lower	ver y low

										(0.56 lower to 0.06 higher)	
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 9.1 month(s)											
3	R C T	not serio us	not serio us	serio us ¹¹	serio us ¹²	NA	1010	679	MD -2.45 (-3.26, - 1.64)	MD 2.45 lower (3.26 lower to 1.64 lower)	low
bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 11.3 month(s)											
2	R C T	serio us ⁸	not serio us	very serio us ⁹	serio us ¹³	NA	994	663	MD -0.74 (-1.05, - 0.43)	MD 0.74 lower (1.05 lower to 0.43 lower)	ver y 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. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.45 (0.8-0.9 = serious, <0.8 = very serious).
- 5. 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).
- 6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.03 (0.8-0.9 = serious, <0.8 = very serious).
- 7. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.32 (0.8-0.9 = serious, <0.8 = very serious).

analysis were at moderate risk of bias

- 9. 12 > 75%
- 10. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 11. I2 between 50% and 75%
- 12. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)
- 13. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

L.1.3.23 Adding semaglutide compared to adding exenatide

Table 34: Clinical evidence profile: Adding semaglutide compared to adding exenatide

у по	De	Risk	Indir	Incon	Impr	Other	Interv	Con	Relative		Cer
	sig	of	ectn	sisten	ecisi	consider	entio	trol	effect	Absolute	tain
No of studies	n	bias	ess	су	on	ations	n N	N	(95% CI)	effect	ty
health-related quality of life - subscale mental component (sf-36, higher values are better, change scores) at end of follow-up Mean follow-up: 12 month(s)											
1 (ahmann 2018)	R CT	very serio us ¹	not serio us	NA ²	not serio us	NA	404	405	MD 0.16 (-1.14, 1.46)	MD 0.16 higher (1.14 lower to 1.46 higher)	low
health-related quality of life - subscale physical component (sf-36, higher values are better, change scores) at end of follow-up Mean follow-up: 12 month(s)									,	y /	
	R	very serio	not serio		not serio				MD 0.46 (-0.64,	MD 0.46	
1 (ahmann 2018)	СТ	us ¹	us	NA ²	us	NA	404	405	1.56)	higher	low

GRADE tables – Model 5: Type 2 diabetes and higher cardio	/ascui	ai iisk									
										(0.64 lower	
										to 1.56	
										higher)	
all-cause mortality at end of follow up											
Mean follow-up: 12 month(s)											
wiean follow-up. 12 month(5)									DETO OD	T f	
									PETO OR	5 fewer per	
		very	not		very				0.13	1000	ver
	R	serio	serio		serio			2/4	(0.01,	(12 fewer	У
1 (ahmann 2018)	CT	us ¹	us	NA^2	us ³	NA	0/405	04	2.16)	to 2 more)	low
severe hypoglycaemic episodes at end of follow up									,	,	
Mean follow-up: 12 month(s)											
mount onew up: 12 month(c)										0 more per	
										1000	
									DD 4 00		
		very	not		very				RR 1.00	(30 fewer	ver
	R	serio	serio		serio		33/40	33/	(0.63,	to 48	У
1 (ahmann 2018)	CT	us ¹	us	NA^2	us ³	NA	4	405	1.59)	more)	low
hba1c change (%, lower values are better, change											
scores) at end of follow up											
Mean follow-up: 12 month(s)											
mican follow-up. 12 month(3)										MD 0.60	
										lower	
		very	not						MD -0.60	(0.77 lower	ver
	R	serio	serio		serio				(-0.77, -	to 0.43	У
1 (ahmann 2018)	CT	us ¹	us	NA^2	us ⁴	NA	404	405	0.43)	lower)	low
weight change (kg, lower values are better, change											
scores) at end of follow up											
Mean follow-up: 12 month(s)											
mount tollow up. 12 month(0)										MD 3.70	
										lower	
			4		4				MD 0.70		
		very	not		not				MD -3.70	(4.50 lower	
	R	serio	serio		serio				(-4.50, -	to 2.90	
1 (ahmann 2018)	CT	us ¹	us	NA ²	us	NA	404	405	2.90)	lower)	low
bmi change (kg/m2, lower values are better, change											
scores) at end of follow up											
Mean follow-up: 12 month(s)											

										MD 1.40	
	1									lower	
	1	very	not		not				MD -1.40	(1.68 lower	
	R	serio	serio		serio				(-1.68, -	to 1.12	
1 (ahmann 2018)	СТ	us ¹	us	NA^2	us	NA	404	405	1.12)	lower)	low

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

L.1.3.24 Adding semaglutide compared to adding liraglutide

Table 35: Clinical evidence profile: Adding semaglutide compared to adding liraglutide

	De	Risk	Indir	Incon	Impr	Other	Interv	Con	Relative		Cer
	sig	of	ectn	sisten	ecisi	consider	entio	trol	effect	Absolute	tain
No of studies	n	bias	ess	су	on	ations	n N	N	(95% CI)	effect	ty
health-related quality of life - subscale mental											
component (sf-36 v2, higher values are better, change											
scores) at end of follow-up											
Mean follow-up: 7 month(s)											
										MD 1.00	
										higher	
	R	very	not		not				MD 1.00	(0.11 lower	
	С	serio	serio		serio				(-0.11,	to 2.11	
1 (capehorn 2020)	Т	us ¹	us	NA ²	us	NA	290	287	2.11)	higher)	low
health-related quality of life - subscale physical											
component (sf-36 v2, higher values are better, change											
scores) at end of follow-up											
Mean follow-up: 7 month(s)											

1 (capehorn 2020) all-cause mortality at end of follow up	R C T	very serio us ¹	not serio us	NA ²	not serio us	NA	290	287	MD 0.70 (-0.41, 1.81)	MD 0.70 higher (0.41 lower to 1.81 higher)	low
Mean follow-up: 9.5 month(s)										2.6	
2	R C T	very serio us ¹	not serio us	serio us³	very serio us ⁴	NA	3/575	4/5 71	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (11 fewer to 8 more)	ver y low
cardiovascular mortality at end of follow up Mean follow-up: 9.5 month(s)											
2	R C T	very serio us ¹	not serio us	serio us³	very serio us ⁵	NA	1/575	2/5 71	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (9 fewer to 5 more)	ver y low
non-fatal stroke at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2019)	R C T	not serio us	not serio us	NA ²	very serio us ⁶	NA	2/285	0/2 84	PETO OR 7.39 (0.46, 118.42)	7 more per 1000 (3 fewer to 17 more)	low
non-fatal myocardial infarction at end of follow up Mean follow-up: 12 month(s)										·	
1 (pratley 2019)	R C T	not serio us	not serio us	NA ²	very serio us ⁶	NA	0/285	1/2	PETO OR 0.13 (0.00, 6.80)	4 fewer per 1000 (10 fewer to 3 more)	low
unstable angina at end of follow up Mean follow-up: 12 month(s)										- ,	
1 (pratley 2019)	R C T	not serio us	not serio us	NA ²	very serio us ⁶	NA	1/285	0/2	PETO OR 7.36 (0.15, 371.08)	4 more per 1000 (3 fewer to 10 more)	low
acute kidney injury at end of follow up Mean follow-up: 12 month(s)									,	,	

Woder of Type 2 diabetes and higher saratev									PETO OR	4 fewer per	
	R	not	not		very			4 /0	0.13	1000	
1 (pratley 2019)	C	serio us	serio us	NA ²	serio us ⁶	NA	0/285	1/2 84	(0.00, 6.80)	(10 fewer to 3 more)	low
hypoglycaemia episodes at end of follow up	•	us	us	14/3	us	INA	0/200	04	0.00)	to o more)	IOW
Mean follow-up: 9.5 month(s)											
										12 fewer	
	R	very	not serio	not serio	aaria			14/	RR 0.50	per 1000	ver
2	T	serio us ¹	us	us	serio us ⁷	NA	7/575	571	(0.20, 1.22)	(20 fewer to 5 more)	y low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 7 month(s)		u.c	us	GG .	us	14.	17010	011	1.22)	10 0 111010)	
·										0 fewer per	
	R	very	not .		not .			0.40	RD 0.00	1000	
1 (capehorn 2020)	C	serio us ¹	serio us	NA ²	serio us	NA	0/290	0/2 87	(-0.01, 0.01)	(7 fewer to 7 more)	low
hba1c change (%, lower values are better, change		us	us	INA	us	INA	0/290	01	0.01)	7 more)	IOW
scores) at end of follow up											
Mean follow-up: 6.5 month(s)											
										MD 0.41 lower	
	R	very	not	very					MD -0.41	(0.99 lower	ver
	C	serio	serio	serio	serio				(-0.99,	to 0.17	y
2	Т	us ¹	us	us ⁸	us ⁹	NA	568	559	Ò.17)	higher)	ĺow
weight change (kg, lower values are better, change											
scores) at end of follow up Mean follow-up: 6.5 month(s)											
mount tonest up? ote menun(e)										MD 2.55	
										lower	
	R	not	not serio	very	aaric				MD -2.55	(5.03 lower to 0.07	ver
2	C	serio us	serio	serio us ⁸	serio us ¹⁰	NA	568	558	(-5.03, - 0.07)	lower)	y low
bmi change (kg/m2, lower values are better, change		40	ao	40	40	14/1	300	000	0.01)	10001)	10 00
scores) at end of follow up											
Mean follow-up: 9.5 month(s)											

										MD 0.90	
										lower	
	R	very	not	very					MD -0.90	(1.68 lower	ver
	С	serio	serio	serio	serio				(-1.68, -	to 0.12	у
2	Т	us ¹	us	us ⁸	us ¹¹	NA	565	556	0.12)	lower)	low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.08 (0.8-0.9 = serious, <0.8 = very serious).
- 5. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.13 (0.8-0.9 = serious, <0.8 = very serious).
- 6. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 7. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 8. I2 > 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)
- 11. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

Table 36: Clinical evidence profile - Semaglutide v sitagliptin

	De	Risk	Indir	Incon	Impr	Other	Interv	Con	Relative		Cer
	sig	of	ectn	sisten	ecisi	consider	entio	trol	effect	Absolute	tain
No of studies	n	bias	ess	су	on	ations	n N	N	(95% CI)	effect	ty
health-related quality of life - subscale mental component (sf36 v2, higher values are better, change scores) at end of follow-up Mean follow-up: 16.5 month(s)											
2	R CT	not serio us	not serio us	not serio us	not serio us	NA	1649	718	MD 0.05 (-0.52, 0.63)	MD 0.05 higher (0.52 lower to 0.63 higher)	hig h
health-related quality of life - subscale physical component (sf36 v2, higher values are better, change scores) at end of follow-up Mean follow-up: 16.5 month(s)											
2	R CT	not serio us	not serio us	not serio us	not serio us	NA	1649	718	MD 0.09 (-0.33, 0.52)	MD 0.09 higher (0.33 lower to 0.52 higher)	hig h
all-cause mortality at end of follow up Mean follow-up: 12.5 month(s)											
4	R CT	not serio us	not serio us	serio us ¹	very serio us ²	NA	14/30 44	8/1 413	PETO OR 0.74 (0.30, 1.87)	1 fewer per 1000 (6 fewer to 4 more)	ver y low
cardiovascular mortality at end of follow up Mean follow-up: 12.5 month(s)									,	,	
4	R CT	not serio us	not serio us	serio us ¹	very serio us ²	NA	7/304 4	4/1 413	PETO OR 0.90 (0.25, 3.19)	1 fewer per 1000 (4 fewer to 3 more)	ver y low

1 (rosenstock 2019c)	non-fatal stroke at end of follow up Mean follow-up: 18 month(s)											
Mean follow-up: 18 month(s)	1 (rosenstock 2019c)		serio	serio	NA ³	serio	NA			2.24 (0.53,	1000 (2 fewer to	low
1 (rosenstock 2019c)												
Mean follow-up: 18 month(s)			serio	serio	NA ³	serio	NA		-	0.64 (0.10,	1000 (8 fewer to	low
1 (rosenstock 2019c)												
Mean follow-up: 15 month(s)	·		serio	serio	NA ³	serio	NA		-	1.78 (0.32,	1000 (3 fewer to	low
Not serio												
Acute kidney injury at end of follow up Mean follow-up: 15 month(s)	•		serio	serio		serio	NA			0.42 (0.10,	1000 (9 fewer to	у
Not Not Serio Serio Serio Serio Serio Serio Us Us Us NA NA NA NA NA NA NA N	acute kidney injury at end of follow up										,	
Mean follow-up: 18 month(s) Image: Control of the contro			serio	serio		serio	NA			1.32 (0.40,	1000 (4 fewer to	у
Not Not Not Not Serio Serio Serio Not Not Serio Not No												
	·		serio	serio	N14.2	serio				3.80 (0.04,	1000 (1 fewer to	
hypoglycaemia episodes at end of follow up		CT	us	us	NA ³	us ²	NA	5	66	350.01)	2 more)	low

GRADE tables – Wodel 3. Type 2 diabetes and higher cardiov	ascuie	11131									
Mean follow-up: 12.7 month(s)											
3	R CT	not serio us	not serio us	not serio us	not serio us	NA	358/2 791	124 /11 63	RR 0.99 (0.83, 1.19)	1 fewer per 1000 (18 fewer to 20 more)	hig h
at night hypoglycaemic episodes at end of follow up Mean follow-up: 15 month(s)											
2	R CT	not serio us	not serio us	not serio us	very serio us ²	NA	20/16 48	7/7 16	RR 1.21 (0.51, 2.87)	2 more per 1000 (5 fewer to 18 more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 14 month(s)											
3	R CT	not serio us	not serio us	serio us ¹	not serio us	NA	1/246 6	6/1 123	RD -0.01 (-0.01, - 0.00)	5 fewer per 1000 (11 fewer to 0 more)	mo der ate
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 13.1 month(s)											
4	R CT	not serio us	not serio us	very serio us ⁴	serio us ⁵	NA	3045	141 5	MD -0.39 (-0.61, - 0.17)	MD 0.39 lower (0.61 lower to 0.17 lower)	ver y low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 13.1 month(s)											
4	R CT	not serio us	not serio us	very serio us ⁴	serio	NA	3045	141 5	MD -2.03 (-2.77, - 1.30)	MD 2.03 lower (2.77 lower to 1.30 lower)	ver y low
bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 13.1 month(s)											

										MD 0.75	
										lower	
		not	not	very					MD -0.75	(1.02 lower	ver
	R	serio	serio	serio	serio			141	(-1.02, -	to 0.49	у
4	CT	us	us	us ⁴	us ⁷	NA	3045	5	0.49)	lower)	low

- 1. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 2. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 3. Only one study so no inconsistency
- 4. I2 > 75%
- 5. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 6. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)
- 7. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

L.1.3.26 Adding SC semaglutide compared to adding oral semaglutide

Table 37: Clinical evidence profile: Adding SC semaglutide compared to adding oral semaglutide

	De	Risk	Indir	Incon	Impr	Other	Interv	Con	Relative		Cer
	sig	of	ectn	sisten	ecisio	consider	ention	trol	effect	Absolute	tain
No of studies	n	bias	ess	су	n	ations	N	N	(95% CI)	effect	ty
health-related quality of life - subscale mental component (sf-36, higher values are better, change scores) at follow-up Mean follow-up: 6 month(s)											
1 (davies 2017)	R CT	very serio us ¹	not serio us	NA ²	not serio us	NA	69	490	MD -0.43 (-2.63, 1.77)	MD 0.43 lower (2.63 lower to 1.77 higher)	low

health-related quality of life - subscale physical component (sf-36, higher values are better, change scores) at follow-up Mean follow-up: 6 month(s)											
1 (davies 2017) all-cause mortality at end of follow up	R CT	very serio us ¹	not serio us	NA ²	not serio us	NA	69	490	MD 0.22 (-1.30, 1.74)	MD 0.22 higher (1.30 lower to 1.74 higher)	low
Mean follow-up: 6 month(s)											
1 (davies 2017)	R CT	very serio us ¹	not serio us	NA ²	not serio us	NA	0/69	0/49	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	low
cardiovascular mortality at end of follow up Mean follow-up: 6 month(s)											
1 (davies 2017)	R CT	very serio us ¹	not serio us	NA ²	not serio us	NA	0/69	0/49	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	low
non-fatal stroke at end of follow up Mean follow-up: 6 month(s)											
1 (davies 2017)	R CT	very serio us ¹	not serio us	NA ²	not serio us	NA	0/69	0/49	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	low
non-fatal myocardial infaRCTion at end of follow up Mean follow-up: 6 month(s)											
1 (davies 2017)	R CT	very serio us ¹	not serio us	NA ²	very serio us ³	NA	0/69	2/49	PETO OR 0.32 (0.00, 21.63)	4 fewer per 1000 (10 fewer to 2 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 6 month(s)									,	,	

1 (davies 2017) severe hypoglycaemic episodes at end of follow up	R CT	very serio us ¹	not serio us	NA ²	very serio us ³	NA	12/69	63/4 90	RR 1.35 (0.77, 2.38)	45 more per 1000 (30 fewer to 177 more)	very low
Mean follow-up: 6 month(s) 1 (davies 2017)	R CT	very serio us ¹	not serio us	NA ²	very serio us ³	NA	1/69	1/49	PETO OR 32.67 (0.48, 2216.41)	12 more per 1000 (16 fewer to 41 more)	very
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)											
1 (davies 2017)	R CT	very serio us ¹	not serio us	NA ²	serio us ⁴	NA	69	490	MD -0.41 (-0.62, - 0.20)	MD 0.41 lower (0.62 lower to 0.20 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)											
1 (davies 2017)	R CT	very serio us ¹	not serio us	NA ²	not serio us	NA	69	490	MD -1.12 (-2.29, 0.05)	MD 1.12 lower (2.29 lower to 0.05 higher)	low

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

agonists

L.1.4.1 Adding tirzepatide compared to adding placebo

Table 38: Clinical evidence profile: Adding tirzepatide compared to adding placebo

rable 30. Official evidence profile. Adding the epatide co				.g p.a.		0.1					
	D		Indi			Other		Со			Се
	es	Ris	rect	Inco	Impr	consid	Inter	ntr	Relative		rta
	ig	k of	nes	nsist	ecisi	eration	venti	ol	effect		int
No of studies	n	bias	s	ency	on	s	on N	N	(95% CI)	Absolute effect	у
health-related quality of life - subscale physical functioning											
(sf-36 physical function scores, higher values are better) at											
end of follow-up Mean follow-up: 18 month(s)											
	R	not	not		not				MD 2.00	MD 2.00 higher	
	С	seri	seri		serio			31	(1.04,	(1.04 higher to	hig
1 (garvey 2023)	Т	ous	ous	NA^1	us	NA	623	5	2.96)	2.96 higher)	h
all-cause mortality at end of follow-up Mean follow-up:											
10.4 month(s)											
	R	not	not		very				RD -0.00	0 fewer per	ver
	С	seri	seri	serio	serio		2/12	1/5	(-0.01,	1000 (8 fewer	у
4	Т	ous	ous	us ²	us ³	NA	34	10	0.01)	to 7 more)	low
cardiovascular mortality at end of follow-up Mean follow-											
up: 8.8 month(s)											
	R	not	not	not	not				RD 0.00	0 fewer per	
	С	seri	seri	serio	serio		0/40	0/1	(-0.01,	1000 (14 fewer	hig
2	Т	ous	ous	us	us	NA	0	48	0.01)	to 14 more)	h
4-point mace at end of follow-up Mean follow-up: 11											
month(s)											
	R	not	not		very				RR 0.68	3 fewer per	
	С	seri	seri		serio		2/35	1/1	(0.06,	1000 (8 fewer	
1 (dahl 2022)	Т	ous	ous	NA ¹	us ⁴	NA	5	20	7.39)	to 53 more)	low
cardiac arrhythmia at end of follow-up Mean follow-up: 18											
month(s)											
	R	not	not		very				RR 2.53	5 more per	
	С	seri	seri		serio		5/62	1/3	(0.30,	1000 (2 fewer	
1 (garvey 2023)	Т	ous	ous	NA ¹	us ⁴	NA	3	15	21.55)	to 65 more)	low

GNADE lables – Model 3. Type 2 diabetes and higher cardiovascu	iiai iik) N									
persistent signs of worsening kidney disease at end of											
follow-up Mean follow-up: 18 month(s)											
	R	not	not		very				RR 1.52	2 more per	
	С	seri	seri		serio		3/62	1/3	(0.16,	1000 (3 fewer	
1 (garvey 2023)	Т	ous	ous	NA^1	us ⁴	NA	3	15	14.52)	to 43 more)	low
progression of liver disease at end of follow-up Mean											
follow-up: 18 month(s)											
									PETO OR		
	R	not	not		very				4.51	3 more per	
	С	seri	seri		serio		2/62	0/3	(0.24,	1000 (1 fewer	
1 (garvey 2023)	Т	ous	ous	NA^1	us ⁴	NA	3	15	85.06)	to 8 more)	low
hypoglycaemia episodes at end of follow-up Mean follow-									,		
up: 10.4 month(s)											
. ,	R	not	not		very			94/	RR 1.74	136 more per	ver
	С	seri	seri	serio	serio		318/	51	(0.75,	1000 (45 fewer	V
4	ΙT	ous	ous	us ⁵	us ⁴	NA	1234	4	4.04)	to 556 more)	low
severe hypoglycaemic episodes at end of follow-up Mean	-								,		
follow-up: 10.4 month(s)											
	R	not	not		very				RD 0.00	2 more per	ver
	C	seri	seri	serio	serio		3/12	0/5	(-0.00,	1000 (4 fewer	v
4	T	ous	ous	us ²	us ⁶	NA	34	14	0.01)	to 9 more)	low
hba1c change (%, lower values are better, change scores)	-								, , ,	,	
at end of follow-up Mean follow-up: 11.3 month(s)											
at one of the mount of the mount of	R	not	not	not	not				MD -1.53	MD 1.53 lower	
	C	seri	seri	serio	serio			48	(-1.65, -	(1.65 lower to	hig
3	Ť	ous	ous	us	us	NA	1189	6	1.42)	1.42 lower)	h
hba1c change (mmol/mol, lower values are better, change		0.0.0	3 3.3	5.0	5.5		1.00		/		
scores) at end of follow-up Mean follow-up: 6.5 month(s)											
									MD -		
	R	seri	not		not				25.50 (-	MD 25.50 lower	mo
	C	ous	seri		serio				26.02, -	(26.02 lower to	der
1 (heise 2022)	T	7	ous	NA ¹	us	NA	41	24	24.98)	24.98 lower)	ate
weight change (kg, lower values are better, change scores)			540	.,,,	40				21.00)	200 1011017	alo
at end of follow-up Mean follow-up: 10.1 month(s)											
at one of follow up moun follow up. 10.1 month(3)	R	not	not	very					MD -6.55	MD 6.55 lower	ver
	C	seri	seri	serio	serio			67	(-12.94, -	(12.94 lower to	y
4	T	ous	ous	us ⁸	us ⁹	NA	1070	0	0.16)	0.16 lower)	low
4		ous	ous	นร	นร	INA	1070	U	0.10)	0.10 lower)	IUW

GRADE tables - Model 5: Type 2 diabetes and higher cardiovascular risk

bmi change (kg/m2, lower values are better, change scores) at end of follow-up Mean follow-up: 12 month(s)											
	R	not	not	very	very				MD -0.83	MD 0.83 lower	ver
	С	seri	seri	serio	serio			52	(-6.76,	(6.76 lower to	у
2	Т	ous	ous	us ⁸	us ¹⁰	NA	674	6	5.10)	5.10 higher)	low

- 1. Only one study so no inconsistency
- 2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.04 (0.8-0.9 = serious, <0.8 = very serious).
- 4. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 5. I2 between 50% and 75%
- 6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.54 (0.8-0.9 = serious, <0.8 = very serious).
- 7. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 8. I2 > 75%
- 9. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)
- 10. 95% confidence intervals cross both ends of the defined MIDs (-0.80, 0.80)

L.1.4.2 Adding tirzepatide compared to adding insulin

Table 39: Clinical evidence profile: Adding tirzepatide compared to adding insulin

Table 05: Officer evidence profile: Addi	ng m	Zepatia	c comp	aica to a	ading n	13uiiii					
	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow-up											
Mean follow-up: 11 month(s)											

GRADE lables – Model 5. Type 2 diabetes and	ringiic	Caraiov	ascalal I	ISIX	1		_				
										5 fewer per	
			not							1000	
	RC	seriou	seriou	not	seriou		12/248	15/1	RR 0.55	(9 fewer to 2	
3	Т	s ¹	s	serious	s ²	NA	1	288	(0.26, 1.18)	more)	low
cardiovascular mortality at end of follow-											
up											
Mean follow-up: 10.5 month(s)											
										2 fewer per	
			not		very				PETO OR	1000	
	RC	seriou	seriou	serious	seriou			2/58	0.25	(7 fewer to 3	very
2	Т	s ¹	s	3	s ⁴	NA	2/1764	0	(0.03, 2.45)	more)	low
4-point mace at end of follow-up									,	,	
Mean follow-up: 10.5 month(s)											
										1 more per	
		not	not		very					1000	
	RC	seriou	seriou	not	seriou		15/176	4/58	RR 1.11	(4 fewer to 17	
2	T	S	S	serious	s ⁴	NA	4	0	(0.36, 3.44)	more)	low
non-fatal stroke at end of follow-up										,	
Mean follow-up: 9 month(s)											
										5 more per	
			not		very					1000	
	RC	seriou	seriou		seriou			2/22	RR 1.60	(6 fewer to 57	very
1 (gao 2023)	T	s ¹	s	NA ⁵	s ⁴	NA	10/687	0	(0.35, 7.25)	more)	low
non-fatal myocardial infaRCTion at end							10,001		(0.00, 1.20)		
of follow-up											
Mean follow-up: 9 month(s)											
mount one apromotion (e)									PETO OR	1 more per	
			not		very				3.74	1000	
	RC	seriou	seriou		seriou			0/22	(0.04,	(1 fewer to 4	very
1 (gao 2023)	T	s ¹	S	NA ⁵	s ⁴	NA	1/687	0	362.44)	more)	low
cardiac arrhythmia at end of follow-up	•		3		3	.,,	1,001		552.11)	11.510)	.011
Mean follow-up: 9 month(s)											
										5 fewer per	
			not		very				PETO OR	1000	
	RC	seriou	seriou		seriou			1/22	0.02	(13 fewer to 4	very
1 (gao 2023)	T	s ¹	S	NA ⁵	s ⁴	NA	0/687	0	(0.00, 1.57)	more)	low
. (3)		_		, .		, .	0,001		(5.55, 1.57)	515/	

GIADE lables - Model 5. Type 2 diabetes and	ringine	i oaraiov	accarar r	IOIX							
hospitalisation for heart failure at end of											
follow-up											
Mean follow-up: 9 month(s)											
,									PETO OR	1 more per	
			not		very				3.74	1000	
	RC	seriou	seriou		seriou			0/22	(0.04,	(1 fewer to 4	very
1 (gao 2023)	T	s ¹	S	NA ⁵	s ⁴	NA	1/687	0	362.44)	more)	low
acute kidney injury				1 1 1		101	17001		002:11)	merej	1011
Mean follow-up: 12 month(s)											
									PETO OR	1 more per	
			not		very				7.30	1000	
	RC	seriou	seriou		seriou			0/70	(0.14,	(1 fewer to 4	very
1 (rosenstock 2023)	Т	s ¹	s	NA ⁵	s ⁴	NA	1/717	8	367.77)	more)	low
hypoglycaemia episodes at end of											
follow-up											
Mean follow-up: 11 month(s)											
										312 fewer per	
			not	very	not					1000	
	RC	seriou	seriou	serious	seriou		413/24	607/	RR 0.34	(394 fewer to	very
3	Т	s ¹	s	6	s	NA	81	1288	(0.16, 0.70)	141 fewer)	low
severe hypoglycaemic episodes at end										,	
of follow-up											
Mean follow-up: 11 month(s)											
										17 fewer per	
			not		not				RD -0.02	1000	
	RC	seriou	seriou	serious	seriou			30/1	(-0.02, -	(24 fewer to	
3	T	s ¹	S	3	S	NA	4/2481	288	0.01)	10 fewer)	low
hba1c change (%, lower values are							.,,				
better, change scores) at end of follow-											
up											
Mean follow-up: 11 month(s)											
										MD 1.08	
			not	very	not				MD -1.08	lower	
	RC	seriou	seriou	serious	seriou				(-1.46, -	(1.46 lower to	very
3	Т	s ¹	S	6	S	NA	2479	1287	0.70)	0.70 lower)	low
									,		

weight change (kg, lower values are better, change scores) at end of follow- up Mean follow-up: 11 month(s)											
3	RC T	seriou s ¹	not seriou s	very serious	not seriou s	NA	2479	1287	MD -10.90 (-14.29, - 7.52)	MD 10.90 lower (14.29 lower to 7.52 lower)	very 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. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 4. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 5. Only one study so no inconsistency
- 6. I2 > 75%

L.1.4.3 Adding tirzepatide compared to adding dulaglutide

Table 40: Clinical evidence profile: Adding tirzepatide compared to adding dulaglutide

	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 Mean follow-up: 6 month(s)											
1 (frias 2018)	RC T	not seriou	not seriou	NA ¹	seriou s ²	NA	0/211	0/54	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (26 fewer to 26 more)	mod erat e
hypoglycaemia episodes at end of follow up Mean follow-up: 6 month(s)									(= = = ; = = = = ;		

OT VIDE tables Woder o. Type 2 diabetes and	mgmon	caratore	4000101 11					1			
1 (frias 2018)	RC T	not seriou s	not seriou s	NA ¹	very seriou s³	NA	14/211	2/54	RR 1.79 (0.42, 7.65)	29 more per 1000 (21 fewer to 246 more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)											
1 (frias 2018)	RC T	not seriou s	not seriou s	NA ¹	seriou s²	NA	0/211	0/54	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (26 fewer to 26 more)	mod erat e
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)											
1 (frias 2018)	RC T	not seriou s	not seriou s	NA ¹	seriou s ⁴	NA	211	54	MD -0.68 (-0.86, - 0.50)	MD 0.68 lower (0.86 lower to 0.50 lower)	mod erat e
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)											
1 (frias 2018)	RC T	not seriou s	not seriou s	NA ¹	seriou s ⁵	NA	211	54	MD -2.07 (-3.96, - 0.18)	MD 2.07 lower (3.96 lower to 0.18 lower)	mod erat e
bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)											
1 (frias 2018)	RC T	not seriou s	not seriou s	NA ¹	seriou s ⁶	NA	211	54	MD -1.30 (-1.93, - 0.67)	MD 1.30 lower (1.93 lower to 0.67 lower)	mod erat e

1. Only one study so no inconsistency

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. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 5. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)
- 6. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

L.1.4.4 Adding tirzepatide compared to adding semaglutide

Table 41: Clinical evidence profile: Adding tirezepatide compared to adding semaglutide

Table 41. Official evidence profile. Adding thez							leton.	Con	Dolotivo		Con
	De	Risk	Indir	Incon	Impr	Other	Interv	Con	Relative		Cer
	sig	of	ectn	siste	ecisi	consider	entio	trol	effect (95%		tain
No of studies	n	bias	ess	ncy	on	ations	n N	N	CI)	Absolute effect	ty
all-cause mortality at end of follow up Mean follow-up: 7.8 month(s)											
2	R C T	serio us ¹	not serio us	serio us ²	very serio us ³	NA	12/14 54	1/5 13	RD 0.01 (- 0.00, 0.01)	6 more per 1000 (1 fewer to 13 more)	ver y low
cardiovascular mortality at end of follow up Mean follow-up: 7.8 month(s)										,	
2	R C T	serio us ¹	not serio us	serio us ²	very serio us ⁴	NA	5/145 5	0/5 13	RD 0.00 (- 0.00, 0.01)	3 more per 1000 (2 fewer to 8 more)	ver y low
non-fatal myocardial infaRCTion at end of follow up Mean follow-up: 9 month(s)									·		
1 (frias 2021)	R C T	serio us ¹	not serio us	NA ⁵	very serio us ⁶	NA	3/140 9	0/4 69	PETO OR 3.80 (0.28, 51.93)	2 more per 1000 (0 more to 5 more)	ver y low
cardiac arrhythmia at end of follow up Mean follow-up: 9 month(s)											
1 (frias 2021)	R C T	serio us ¹	not serio us	not serio us	very serio us ⁶	NA	2/140 9	0/4 69	PETO OR 3.79 (0.15, 93.33)	1 more per 1000 (1 fewer to 3 more)	ver y low

hypoglycaemia episodes at end of follow up Mean follow-up: 6.5 month(s)											
2	R C T	serio us ¹	not serio us	not serio us	very serio us ⁶	NA	15/14 54	3/5 13	PETO OR 2.00 (0.71, 5.64)	4 more per 1000 (4 fewer to 13 more)	ver y low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 7.8 month(s)											
2	R C T	serio us ¹	not serio us	serio us ²	very serio us ⁷	NA	2/145 4	0/5 13	RD 0.00 (- 0.00, 0.01)	1 more per 1000 (3 fewer to 6 more)	ver y low
hba1c change (%, lower values are better, mean difference) at end of follow up Mean follow-up: 9 month(s)											
1 (frias 2021)	R C T	serio us ¹	not serio us	NA ⁵	serio us ⁸	NA	1408	468	MD -0.33 (- 0.51, -0.16)	MD 0.33 lower (0.51 lower to 0.16 lower)	low
hba1c change (mmol/mol, lower values are better, change scores) at end of follow up Mean follow-up: 6.5 month(s)											
1 (heise 2022)	R C T	serio us ¹	not serio us	NA ⁵	serio us ⁹	NA	41	43	MD -4.50 (- 6.99, -2.01)	MD 4.50 lower (6.99 lower to 2.01 lower)	low
weight change (kg, lower values are better, mean difference) at end of follow up Mean follow-up: 8.4 month(s)											
2	R C T	serio us¹	not serio us	very serio us ¹⁰	not serio us	NA	1449	511	MD -3.82 (- 5.24, -2.41)	MD 3.82 lower (5.24 lower to 2.41 lower)	ver y low

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.79 (0.8-0.9 = serious, <0.8 = very serious).
- 4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.74 (0.8-0.9 = serious, <0.8 = very serious).

5. Only one study so no inconsistency

- 6. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 7. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.38 (0.8-0.9 = serious, <0.8 = very serious).
- 8. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 9. 95% confidence intervals cross one end of the defined MIDs (-5.50, 5.50)
- 10. I2 > 75%

L.1.5 SGLT2 inhibitors

L.1.5.1 Adding canagliflozin compared to adding placebo

Table 42: Clinical evidence profile: Adding canagliflozin compared to adding placebo

Table 121 chines of the promote promot	De					Other			Relative		Cert
	sig	Risk	Indire	Inconsi	Imprec	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	of bias	ctness	stency	ision	ions	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow up Mean follow-up: 9.9 month(s)											
6	RC T	very seriou s ¹	not seriou s	serious	very serious	NA	3/1930	0/86 7	RD 0.00 (-0.00, 0.01)	2 more per 1000 (3 fewer to 6 more)	very low
all-cause mortality at end of follow up Mean follow-up: 43 month(s)											
1 (mahaffey 2018)	RC T	not seriou s	not seriou s	NA ⁴	serious 5	NA	5795	4347	HR 0.87 (0.75, 1.01)	Not estimable	mod erat e
cardiovascular mortality at end of follow up Mean follow-up: 10.7 month(s)											

GRADE lables – Model 5. Type 2 diabetes and	riigiic	, caralov	asculai II	31(1	1				1	
5	RC T	very seriou s ¹	not seriou s	serious	very serious	NA	2/1195	0/68 4	RD 0.00 (-0.00, 0.01)	2 more per 1000 (4 fewer to 7 more)	very low
cardiovascular mortality at end of follow											
up Mean follow-up: 43 month(s)											
. ,		not	not								mod
	RC	seriou	seriou		serious				HR 0.87	Not	erat
1 (mahaffey 2018)	T	S	S	NA ⁴	5	NA	5795	4347	(0.71, 1.06)	estimable	е
3-point mace at end of follow up Mean follow-up: 43 month(s)											
		not	not								mod
	RC	seriou	seriou		serious				HR 0.85	Not	erat
1 (mahaffey 2018)	Т	s	S	NA ⁴	5	NA	5795	4347	(0.75, 0.97)	estimable	е
non-fatal stroke at end of follow up											
Mean follow-up: 43 month(s)											
		not	not								mod
	RC	seriou	seriou		serious				HR 0.90	Not	erat
1 (mahaffey 2018)	Т	S	S	NA ⁴	5	NA	5795	4347	(0.71, 1.15)	estimable	е
non-fatal myocardial infaRCTion at end of follow up Mean follow-up: 43 month(s)											
mean follow-up: 40 month(3)		not	not								mod
	RC	seriou	seriou		serious				HR 0.85	Not	erat
1 (mahaffey 2018)	T	S	s	NA ⁴	5	NA	5795	4347	(0.69, 1.05)	estimable	e
hospitalisation for heart failure at end of follow up							0.00		(6:66, 1:66)		
Mean follow-up: 43 month(s)											
		not .	not .								mod
4 (RC	seriou	seriou	NIA4	serious 5	NIA	F70F	4047	HR 0.67	Not	erat
1 (mahaffey 2018)	Т	S	S	NA ⁴	5	NA	5795	4347	(0.52, 0.87)	estimable	е
persistent signs of worsening kidney disease at end of follow up											
Mean follow-up: 43 month(s)											

GNADE tables – Woder 5. Type 2 diabetes and	riigiic	not	not	JI.							
	RC	seriou	seriou		not				HR 0.73	Not	
1 (mahaffey 2018)	Т	s	s	NA ⁴	serious	NA	5795	4347	(0.67, 0.79)	estimable	high
development of end stage kidney											
disease at end of follow up											
Mean follow-up: 43 month(s)		4									
	RC	not seriou	not seriou		very serious				HR 0.77	Not	
1 (mahaffey 2018)	T	S	S	NA ⁴	7	NA	5795	4347	(0.30, 1.97)	estimable	low
cardiac arrhythmia at end of follow up Mean follow-up: 43 month(s)	•	J		TW V		10.	0.00	1011	(0.00, 1.01)	Communic	1011
mount to now up. 10 month (c)										2 more per	
		not	not							1000	mod
	RC	seriou	seriou		serious		125/57	84/4	RR 1.12	(3 fewer to 9	erat
1 (mahaffey 2018)	Т	S	S	NA ⁴	5	NA	95	347	(0.85, 1.47)	more)	е
cardiac arrhythmia at end of follow up Mean follow-up: 43 month(s)											
		not	not								mod
4 () (5 0040)	RC	seriou	seriou	NIA4	serious 5		F70F	40.47	HR 0.84	Not	erat
1 (mahaffey 2018) diabetic ketoacidosis at end of follow up	Т	S	S	NA ⁴	3	NA	5795	4347	(0.64, 1.12)	estimable	е
Mean follow-up: 5.8 month(s)											
			,							0 fewer per	
	RC	very seriou	not seriou	not	not			0/17	RD 0.00	1000	
2	T	seriou s ¹	seriou	serious	serious	NA	0/178	6	(-0.02, 0.02)	(16 fewer to 16 more)	low
diabetic ketoacidosis at end of follow up Mean follow-up: 43 month(s)		3	3	Scrious	3011003	N/A	0/1/0		(-0.02, 0.02)	10 more)	IOW
		not	not		very						
	RC	seriou	seriou		serious				HR 1.57	Not	
1 (mahaffey 2018)	Т	s	s	NA ⁴	7	NA	1447	2039	(0.40, 6.16)	estimable	low
hypoglycaemia episodes at end of follow											
up Maan fallow up: 44.9 month(a)											
Mean follow-up: 11.9 month(s)		very	not								
	RC	seriou	seriou	serious	not		205/96	73/5	RD 0.04	45 more per	very
4	T	s ¹	s	2	serious	NA	8	69	(-0.03, 0.12)	1000	low

GRADE tables – Model 5: Type 2 diabetes and	riigiie	Cardiov	asculai II	SK						(32 fewer to	
										121 more)	
hypoglycaemia episodes at end of follow up Mean follow-up: 43 month(s)											
1 (mahaffey 2018)	RC T	not seriou	not seriou s	NA ⁴	very serious	NA	1447	2039	HR 1.04 (0.78, 1.39)	Not estimable	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 14 month(s)		S	5	IVA		INA	1447	2039	(0.76, 1.39)	езшпаше	IOW
3	RC T	seriou s ⁸	seriou s ⁹	serious	very serious	NA	13/898	9/50 1	RD -0.01 (-0.02, 0.01)	5 fewer per 1000 (20 fewer to 9 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 12.7 month(s)											
8	RC T	very seriou s ¹	not seriou s	very serious	not serious	NA	7672	5152	MD -0.71 (-0.87, - 0.54)	MD 0.71 lower (0.87 lower to 0.54 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12.1 month(s)											
7	RC T	very seriou s ¹	not seriou s	very serious	serious	NA	7253	4991	MD -2.16 (-2.67, - 1.65)	MD 2.16 lower (2.67 lower to 1.65 lower)	very low
weight change (%, lower values are better, change scores) Mean follow-up: 24 month(s)											

										MD 2.93	
										lower	
			not						MD -2.93	(3.89 lower	
	RC	seriou	seriou		serious				(-3.89, -	to 1.97	
1 (bode 2013)	Т	s ⁸	s	NA^4	13	NA	425	170	1.97)	lower)	low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.55 (0.8-0.9 = serious, <0.8 = very serious).
- 4. Only one study so no inconsistency
- 5. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.43 (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. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 9. Largest proportion of studies in the meta-analysis came from partially direct studies
- 10. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.11 (0.8-0.9 = serious, <0.8 = very serious).
- 11. I2 > 75%
- 12. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)
- 13. 95% confidence intervals cross one end of the defined MIDs (-3.00, 3.00)

to adding sitagliptin

Table 43: Clinical evidence profile: Adding canagliflozin compared to adding sitagliptin

Table 43. Chilical evidence profile. Adding can						Other					
		Risk	Indir	Incon	Impr	consid	Inter		Relative		Cert
	Desi	of	ectn	sisten	ecisi	eratio	venti	Cont	effect (95%		aint
No of studies	gn	bias	ess	су	on	ns	on N	rol N	CI)	Absolute effect	y
all-cause mortality at end of follow up Mean follow-up: 12 month(s)											
2	RCT	very serio us ¹	not serio us	seriou s²	very serio us ³	NA	3/111	1/74 4	PETO OR 2.03 (0.27, 15.26)	1 more per 1000 (3 fewer to 5 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)											
1 (schernthaner 2013)	RCT	very serio us ¹	not serio us	NA ⁴	very serio us ³	NA	2/377	0/37	PETO OR 2.03 (0.27, 15.26)	5 more per 1000 (2 fewer to 13 more)	very
hypoglycaemia episodes at end of follow up Mean follow-up: 12 month(s)									,	,	
2	RCT	very serio us ¹	not serio us	seriou s ⁵	serio us ⁶	NA	213/1 112	169/ 744	RR 1.22 (0.81, 1.86)	51 more per 1000 (44 fewer to 196 more)	very
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)										,	
2	RCT	very serio us ¹	not serio us	not seriou s	very serio us ³	NA	16/11 12	14/7 44	RR 1.10 (0.54, 2.21)	2 more per 1000 (9 fewer to 23 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
2	RCT	very serio us ¹	not serio us	very seriou s ⁷	serio us ⁸	NA	1102	732	MD -0.22 (-0.51, 0.07)	MD 0.22 lower (0.51 lower to 0.07 higher)	very low

weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
		not	not	not					MD -2.31	MD 2.31 lower	mod
		serio	serio	seriou	serio				(-2.77, -	(2.77 lower to	erat
2	RCT	us	us	S	us ⁹	NA	1102	733	1.86)	1.86 lower)	е

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. Only one study so no inconsistency
- 5. I2 between 50% and 75%
- 6. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 7.12 > 75%
- 8. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 9. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

L.1.5.3 Adding canagliflozin compared to adding semaglutide

Table 44: Clinical evidence profile: Adding canagliflozin compared to adding semaglutide

	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	У
all-cause mortality at end of follow up Mean follow-up: 12 month(s)											
	RC	not serio	not seriou		very seriou		0/00/	1/39	PETO OR 0.13	3 fewer per 1000 (8 fewer to 2	
1 (lingvay 2019)	T	us	S	NA ¹	S ²	NA	0/394	2	(0.00, 6.79)	more)	low

cardiovascular mortality at end of follow											
up											
Mean follow-up: 12 month(s)											
			_						DETO 00	3 fewer per	
		not	not		very			4/00	PETO OR	1000	
1 (lingvay 2019)	RC T	serio us	seriou s	NA ¹	seriou s ²	NA	0/394	1/39 2	0.13 (0.00, 6.79)	(8 fewer to 2 more)	low
acute kidney injury at end of follow up	l	us	5	INA.	5-	INA	0/394		(0.00, 6.79)	more)	IOW
Mean follow-up: 12 month(s)											
										10 fewer per	
		not	not _.					4/00	PETO OR	1000	mod
4 (1:	RC	serio	seriou	NIA1	seriou	NIA .	0/004	4/39	0.13	(20 fewer to 0	erat
1 (lingvay 2019)	Т	us	S	NA ¹	s ³	NA	0/394	2	(0.02, 0.95)	more)	е
hypoglycaemia episodes at end of follow up											
Mean follow-up: 12 month(s)											
·										54 fewer per	
		not	not							1000	mod
	RC	serio	seriou		seriou			53/3	RR 0.60	(82 fewer to	erat
1 (lingvay 2019)	Т	us	S	NA ¹	s ³	NA	32/394	92	(0.40, 0.91)	12 fewer)	е
severe hypoglycaemic episodes at end											
of follow up Mean follow-up: 12 month(s)											
mean follow-up: 12 month(s)										3 fewer per	
		not	not		very				PETO OR	1000	
	RC	serio	seriou		seriou			1/39	0.13	(8 fewer to 2	
1 (lingvay 2019)	Т	us	S	NA ¹	s ²	NA	0/394	2	(0.00, 6.79)	more)	low
hba1c change (%, lower values are									,	,	
better, change scores) at end of follow											
up											
Mean follow-up: 12 month(s)											
										MD 0.50	
		not	not							higher	mad
	RC	not serio	not seriou		seriou				MD 0.50	(0.38 higher to 0.62	mod erat
1 (lingvay 2019)	T	us	S	NA ¹	s ⁴	NA	394	394	(0.38, 0.62)	higher)	e

GRADE tables - Model 5: Type 2 diabetes and higher cardiovascular risk

weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (lingvay 2019)	RC T	not serio us	not seriou s	NA ¹	not seriou s	NA	394	394	MD 1.10 (0.41, 1.79)	MD 1.10 higher (0.41 higher to 1.79 higher)	high

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

L.1.5.4 Adding dapagliflozin compared to adding placebo

Table 45: Clinical evidence profile: Adding dapagliflozin compared to adding placebo

	De	Risk	Indir	Incon		Other	Interv	Cont	Relative		Cert
	sig	of	ectn	sisten	Impre	consider	ention	rol	effect	Absolute	aint
No of studies	n	bias	ess	су	cision	ations	N	N	(95% CI)	effect	у
health-related quality of life - overall (eq-5d, -0.59-											
1.0, higher values are better, change scores) at end											
of follow up											
Mean follow-up: 17.8 month(s)											
										MD 0.00	
										higher	
			not	not	very				MD 0.00	(0.03 lower	
	R	seriou	serio	seriou	seriou				(-0.03,	to 0.04	very
2	CT	s ¹	us	S	s ²	NA	176	178	0.04)	higher)	low
all-cause mortality at end of follow up											
Mean follow-up: 17.2 month(s)											

11 all-cause mortality at end of follow up	R CT	seriou s ¹	not serio us	seriou s ³	not seriou s	NA	540/1 1353	572/ 100 61	RD -0.00 (-0.01, 0.00)	4 fewer per 1000 (10 fewer to 3 more)	low
Mean follow-up: 50.4 month(s)											
1 (wiviott 2019)	R CT	seriou s ¹	not serio us	NA ⁴	not seriou s	NA	8582	857 8	HR 0.98 (0.82, 1.17)	Not estimable	mo der ate
cardiovascular mortality at end of follow up Mean follow-up: 18.9 month(s)											
7	R CT	seriou s ¹	not serio us	seriou s³	very seriou s ⁵	NA	252/1 0596	251/ 944 5	RD -0.00 (-0.00, 0.00)	0 fewer per 1000 (5 fewer to 4 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 50.4 month(s)											
1 (wiviott 2019)	R CT	seriou s ¹	not serio us	NA ⁴	not seriou s	NA	8582	857 8	HR 0.92 (0.82, 1.04)	Not estimable	mo der ate
3-point mace at end of follow up Mean follow-up: 50.4 month(s)											
1 (wiviott 2019) 3-point mace at end of follow up Mean follow-up: 50.4 month(s)	R CT	seriou s ¹	not serio us	NA ⁴	not seriou s	NA	756/8 582	803/ 857 8	RR 0.94 (0.86, 1.03)	6 fewer per 1000 (13 fewer to 3 more)	mo der ate
1 (wiviott 2019)	R CT	seriou s ¹	not serio us	NA ⁴	not seriou s	NA	8582	857 8	HR 0.93 (0.84, 1.03)	Not estimable	mo der ate
non-fatal stroke at end of follow up Mean follow-up: 30.8 month(s)											
2	R CT	seriou s ¹	not serio us	seriou s³	not seriou s	NA	236/9 032	231/ 872 4	PETO OR 1.02 (0.85, 1.23)	0 fewer per 1000 (5 fewer to 4 more)	low

non-fatal stroke at end of follow up Mean follow-up: 50.4 month(s)											
1 (wiviott 2019)	R CT	seriou s ¹	not serio us	NA ⁴	not seriou s	NA	8582	857 8	HR 1.01 (0.84, 1.21)	Not estimable	mo der ate
non-fatal myocardial infarction at end of follow up Mean follow-up: 50.4 month(s)											
1 (wiviott 2019)	R CT	seriou s ¹	not serio us	NA ⁴	seriou s ⁶	NA	393/8 582	441/ 857 8	RR 0.89 (0.78, 1.02)	6 fewer per 1000 (11 fewer to 1 more)	low
non-fatal myocardial infarction at end of follow up Mean follow-up: 50.4 month(s)											
1 (wiviott 2019)	R CT	seriou s ¹	not serio us	NA ⁴	seriou s ⁶	NA	8582	857 8	HR 0.89 (0.77, 1.02)	Not estimable	low
unstable angina at end of follow up Mean follow-up: 50.4 month(s)											
1 (wiviott 2019)	R CT	seriou s ¹	not serio us	NA ⁴	not seriou s	NA	243/8 582	238/ 857 8	RR 1.02 (0.86, 1.22)	1 more per 1000 (4 fewer to 6 more)	mo der ate
hospitalisation for heart failure at end of follow up Mean follow-up: 50.4 month(s)									,		
1 (wiviott 2019)	R CT	seriou s ¹	not serio us	NA ⁴	seriou s ⁶	NA	212/8 582	286/ 857 8	RR 0.74 (0.62, 0.88)	9 fewer per 1000 (13 fewer to 4 fewer)	low
hospitalisation for heart failure at end of follow up Mean follow-up: 50.4 month(s)											
1 (wiviott 2019)	R CT	seriou s ¹	not serio us	NA ⁴	seriou s ⁶	NA	8582	857 8	HR 0.73 (0.61, 0.88)	Not estimable	low
acute kidney injury at end of follow up Mean follow-up: 50.4 month(s)									,		

GRADE tables – Model 5: Type 2 diabetes and higher car	ulova	Sculai 115	N.							6 fewer per	
	_		not				405/0	175/	RR 0.71	1000	
1 (wiviott 2019)	R CT	seriou s ¹	serio us	NA ⁴	seriou s ⁶	NA	125/8 582	857 8	(0.57, 0.90)	(9 fewer to 2 fewer)	low
acute kidney injury at end of follow up	01	3	us	INA	3	INA	302	0	0.90)	2 lewel)	IOW
Mean follow-up: 50.4 month(s)			4						LID 0 00		
	R	seriou	not serio		seriou			857	HR 0.69 (0.55,	Not	
1 (wiviott 2019)	СТ	s ¹	us	NA ⁴	s ⁶	NA	8582	8	0.87)	estimable	low
persistent signs of worsening kidney disease at end of follow up											
Mean follow-up: 27.2 month(s)											
								000/	DD 0 57	11 fewer	
	R	seriou	not serio	not seriou	not seriou		149/1	230/ 905	RR 0.57 (0.46,	per 1000 (14 fewer to	mo der
4	СТ	s ¹	us	S	S	NA	0051	8	0.71)	7 fewer)	ate
persistent signs of worsening kidney disease at											
end of follow up Mean follow-up: 50.4 month(s)											
mount offer aprover mental(e)			not		not				HR 0.54		mo
4 (white # 2040)	R	seriou s ¹	serio	NA ⁴	seriou	NIA	0500	857	(0.43,	Not	der
1 (wiviott 2019) development of end stage kidney disease at end of	CI	S	us	NA ⁺	S	NA	8582	8	0.67)	estimable	ate
follow up											
Mean follow-up: 20.5 month(s)											
			not		not				RD -0.00	1 fewer per 1000	
	R	seriou	serio	seriou	seriou		7/901	20/8	(-0.00, -	(3 fewer to	
3	СТ	s ¹	us	s ³	s	NA	8	856	0.00)	0 more)	low
development of end stage kidney disease at end of follow up											
Mean follow-up: 50.4 month(s)											
			not		not				HR 0.31		mo
1 (wiviott 2019)	R CT	seriou s ¹	serio us	NA ⁴	seriou s	NA	8582	857 8	(0.13, 0.78)	Not estimable	der ate
death from renal causes at end of follow up		5	us	INA.	5	INA	0302	0	0.70)	csumanie	alt
Mean follow-up: 50.4 month(s)											

1 (wiviott 2019)	R	seriou	not serio us	NA ⁴	very seriou s ⁷	NA	10/85 82	6/85 78	PETO OR 1.65 (0.62, 4.39)	0 more per 1000 (0 more to 1 more)	very
death from renal causes at end of follow up		3	us	INA	3	INA	02	70	4.55)	T more)	IOW
Mean follow-up: 50.4 month(s)											
1 (wiviott 2019)	R CT	seriou s ¹	not serio us	NA ⁴	very seriou s ⁷	NA	8582	857 8	HR 0.60 (0.22, 1.65)	Not estimable	very
cardiac arrhythmia at end of follow up Mean follow-up: 50.4 month(s)	0,		us			10.	0002		1.00)	Communic	1011
1 (wiviott 2019)	R	seriou s ¹	not serio us	NA ⁴	seriou s ⁶	NA	94/85 82	121/ 857 8	RR 0.78 (0.59, 1.01)	3 fewer per 1000 (6 fewer to 0 more)	low
diabetic ketoacidosis at end of follow up Mean follow-up: 22.6 month(s)			us			10.1	02		1.0.7	e merey	1011
3	R CT	seriou s ¹	not serio us	seriou s³	not seriou s	NA	27/87 53	12/8 745	RD 0.00 (0.00, 0.00)	2 more per 1000 (0 more to 3 more)	low
diabetic ketoacidosis at end of follow up Mean follow-up: 50.4 month(s)									,		
1 (wiviott 2019)	R CT	seriou s ¹	not serio us	NA ⁴	seriou s ⁶	NA	8582	857 8	HR 2.18 (1.10, 4.30)	Not estimable	low
progression of liver disease at end of follow up Mean follow-up: 50.4 month(s)											
1 (wiviott 2019)	R CT	seriou s ¹	not serio us	NA ⁴	very seriou s ⁷	NA	82/85 82	87/8 578	PETO OR 0.94 (0.70, 1.27)	1 fewer per 1000 (4 fewer to 2 more)	very low
progression of liver disease at end of follow up Mean follow-up: 50.4 month(s)									,		
1 (wiviott 2019)	R CT	seriou s ¹	not serio us	NA ⁴	seriou s ⁶	NA	8582	857 8	HR 0.92 (0.68, 1.25)	Not estimable	low

hypoglycaemia episodes at end of follow up Mean follow-up: 13.7 month(s)											
11	R CT	seriou s ¹	not serio us	seriou s³	not seriou s	NA	501/2 803	181/ 151 7	RD 0.01 (-0.01, 0.03)	13 more per 1000 (8 fewer to 34 more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 17.2 month(s)											
11	R CT	seriou s ¹	not serio us	seriou s³	not seriou s	NA	62/11 353	84/1 006 1	RD -0.00 (-0.00, 0.00)	2 fewer per 1000 (5 fewer to 0 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 15.8 month(s)											
12	R CT	seriou s ¹	not serio us	very seriou s ⁸	seriou s ⁹	NA	10903	981	MD -0.54 (-0.62, - 0.45)	MD 0.54 lower (0.62 lower to 0.45 lower)	very low
hba1c change (mmol/mol, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (brown 2020)	R CT	not seriou s	not serio us	NA ⁴	seriou s ¹⁰	NA	32	34	MD -5.49 (-10.13, - 0.85)	MD 5.49 lower (10.13 lower to 0.85 lower)	mo der ate
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 14.5 month(s)											
13	R CT	very seriou s ¹¹	not serio us	seriou s ¹²	not seriou s	NA	10679	986 7	MD -1.80 (-2.12, - 1.49)	MD 1.80 lower (2.12 lower to 1.49 lower)	very low

bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 8.8 month(s)											
										MD 0.45	
										lower	
		not	not		very				MD -0.45	(2.85 lower	
	R	seriou	serio	seriou	seriou				(-2.85,	to 1.94	very
2	CT	s	us	s ¹²	s ¹³	NA	82	84	1.94)	higher)	low

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. 95% confidence intervals cross both ends of the defined MIDs (-0.03, 0.03)
- 3. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 4. Only one study so no inconsistency
- 5. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.43 (0.8-0.9 = serious, <0.8 = very serious).
- 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. I2 > 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 (-5.50, 5.50)
- 11. >33.3% of the studies in the meta-analysis were at high risk of bias
- 12. I2 between 50% and 75%
- 13. 95% confidence intervals cross both ends of the defined MIDs (-0.80, 0.80)

L.1.5.5

to adding exenatide

Table 46: Clinical evidence profile: Adding dapagliflozin compared to adding exenatide

Table 46: Clinical evidence profile: Add	ing u	apayımı	ZIII COII	ipareu it	auding	exematice					
	De					Other			Relative		Cert
	sig	Risk	Indire	Inconsi	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	of bias	ctness	stency	cision	ions	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow up Mean follow-up: 24 month(s)											
1 (frias 2016)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	2/233	1/23 0	PETO OR 1.93 (0.20, 18.63)	4 more per 1000 (10 fewer to 19 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 24 month(s)											
1 (frias 2016)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	1/233	1/23 0	PETO OR 0.99 (0.06, 15.83)	0 fewer per 1000 (12 fewer to 12 more)	very low
acute kidney injury at end of follow up Mean follow-up: 24 month(s)											
1 (frias 2016)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	3/233	2/23 0	RR 1.48 (0.25, 8.78)	4 more per 1000 (15 fewer to 23 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 24 month(s)											
1 (frias 2016)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	1/233	0/23	PETO OR 7.29 (0.14, 367.65)	4 more per 1000 (4 fewer to 13 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 24 month(s)											

GRADE tables - Model 5: Type 2 diabetes and higher cardiovascular risk

1 (frias 2016)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/233	0/23	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	low
hba1c change (%, lower values are better, change scores) at end of follow										·	
up Mean follow-up: 24 month(s)											
1 (frias 2016)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s ⁴	NA	230	227	MD 0.23 (-0.10, 0.56)	MD 0.23 higher (0.10 lower to 0.56 higher)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 24 month(s)											
1 (frias 2016)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s ⁵	NA	230	227	MD -2.22 (-3.55, - 0.89)	MD 2.22 lower (3.55 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 both ends of the defined MIDs (0.80, 1.25)
- 4. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 5. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

L.1.5.6 Adding dapagliflozin compared to adding liraglutide

Table 47: Clinical evidence profile: Adding dapagliflozin compared to adding liraglutide

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

all-cause mortality at end of follow up Mean follow-up: 5.5 month(s)											
1 (jiang 2021b)	RC T	very seriou s ¹	seriou s²	NA ³	seriou s ⁴	NA	0/79	0/77	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (25 fewer to 25 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 5.5 month(s)											
1 (jiang 2021b)	RC T	very seriou s ¹	seriou s²	NA ³	seriou s ⁴	NA	0/79	0/77	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (25 fewer to 25 more)	very low
non-fatal myocardial infarction at end of follow up Mean follow-up: 5.5 month(s)											
1 (hao 2022)	RC T	very seriou s ¹	not seriou s	NA ³	seriou s ⁴	NA	0/166	0/14	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (13 fewer to 13 more)	very low
unstable angina at end of follow up Mean follow-up: 5.5 month(s)										,	
1 (hao 2022)	RC T	very seriou s ¹	not seriou s	NA ³	very seriou s ⁵	NA	2/166	2/14 3	RR 0.86 (0.12, 6.04)	2 fewer per 1000 (12 fewer to 70 more)	very low
hospitalisation for heart failure at end of follow up Mean follow-up: 5.5 month(s)											
1 (hao 2022)	RC T	very seriou s ¹	not seriou	NA ³	seriou s ⁴	NA	0/166	0/14	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (13 fewer to 13 more)	very
diabetic ketoacidosis at end of follow up Mean follow-up: 5.5 month(s)							3		, ,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	, , , , ,	

1 (jiang 2021b)	RC T	very seriou s ¹	seriou s²	NA ³	seriou s ⁴	NA	0/79	0/77	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (25 fewer to 25 more)	very low
hypoglycaemia episodes at end of follow up											
Mean follow-up: 5.5 month(s)											
1 (hao 2022)	RC T	very seriou s ¹	not seriou s	NA ³	very seriou s ⁵	NA	29/166	21/1 43	RR 1.19 (0.71, 1.99)	28 more per 1000 (42 fewer to 146 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.5 month(s)											
2	RC T	very seriou s ¹	not seriou s	not serious	not seriou s	NA	0/245	0/22	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)										,	
1 (hao 2022)	RC T	very seriou s ¹	not seriou s	NA ³	seriou s ⁶	NA	166	143	MD 0.36 (-0.01, 0.73)	MD 0.36 higher (0.01 lower to 0.73 higher)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
2	RC T	very seriou s ¹	not seriou s	not serious	not seriou s	NA	245	220	MD -0.24 (-1.92, 1.43)	MD 0.24 lower (1.92 lower to 1.43 higher)	low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Largest proportion of studies in the meta-analysis came from partially direct studies

- 3. Only one study so no inconsistency
- 4. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 5. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 6. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

L.1.5.7 Adding dapagliflozin compared to adding saxagliptin

Table 48: Clinical evidence profile: Adding dapagliflozin compared to adding saxagliptin

Table 46. Chilical evidence prome. Addi			2111 0011	iparca t	l				Buluit i		
	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	У
all-cause mortality at end of follow up Mean follow-up: 5.5 month(s)											
2	RC T	not seriou s	not seriou s	serious	very seriou s ²	NA	2/472	0/47	RD 0.00 (-0.00, 0.01)	4 more per 1000 (4 fewer to 13 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 5.5 month(s)											
2	RC T	not seriou s	not seriou s	serious	very seriou s ²	NA	2/472	0/47	RD 0.00 (-0.00, 0.01)	4 more per 1000 (4 fewer to 13 more)	very low
persistent signs of worsening kidney disease at end of follow up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2015a)	RC T	seriou s³	not seriou s	NA ⁴	not seriou s	NA	0/179	0/17 6	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (11 fewer to 11 more)	mod erat e
diabetic ketoacidosis at end of follow up Mean follow-up: 5.5 month(s)											

		1					1	т —		1	
	RC	not seriou	not seriou		not seriou			0/29	RD 0.00	0 fewer per 1000 (7 fewer to 7	
1 (rosenstock 2019d)	Т	S	S	NA ⁴	S	NA	0/293	5	(-0.01, 0.01)	more)	high
hypoglycaemia episodes at end of follow											
up											
Mean follow-up: 5.5 month(s)											
2	RC T	not seriou s	not seriou s	not serious	very seriou s ⁵	NA	2/472	5/47 1	PETO OR 0.42 (0.10, 1.87)	6 fewer per 1000 (17 fewer to 5 more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.5 month(s)											
2	RC T	not seriou s	not seriou s	serious	very seriou s ⁶	NA	0/472	1/47	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (9 fewer to 5 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
2	RC T	not seriou s	not seriou s	very serious	not seriou s	NA	431	431	MD -0.12 (-0.50, 0.25)	MD 0.12 lower (0.50 lower to 0.25 higher)	low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2015a)	RC T	seriou s³	not seriou s	NA ⁴	seriou s ⁸	NA	152	145	MD -2.40 (-3.10, - 1.70)	MD 2.40 lower (3.10 lower to 1.70 lower)	low

^{1.} Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

2. Precision calculated through Optimal

Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.52 (0.8-0.9 = serious, <0.8 = very serious).

- 3. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 4. Only one study so no inconsistency
- 5. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.29 (0.8-0.9 = serious, <0.8 = very serious).
- 7. I2 > 75%
- 8. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

L.1.5.8 Adding dapagliflozin compared to adding sitagliptin

Table 49: Clinical evidence profile: Adding dapagliflozin compared to adding sitagliptin

					<u> </u>	J					
	De	Risk	Indire	Incons		Other			Relative		Cert
	sig	of	ctnes	istenc	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	S	У	cision	ions	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow up Mean follow-up: 5.5 month(s)											
1 (scott 2018)	RC T	not seriou s	not seriou s	NA ¹	not seriou s	NA	0/306	0/30	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	high
cardiovascular mortality at end of follow up Mean follow-up: 5.5 month(s)											
1 (scott 2018)	RC T	not seriou s	not seriou s	NA ¹	not seriou s	NA	0/306	0/30	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	high
hospitalisation for heart failure at end of follow up											

Mean follow-up: 24 month(s)	91101 0	ai dio vao	Jaiai Hok								
weari follow-up: 24 month(s)											
1 (hong 2023)	RC T	seriou s ²	not seriou s	NA ¹	very seriou s ³	NA	0/26	0/26	RD 0.00 (-0.07, 0.07)	0 fewer per 1000 (72 fewer to 72 more)	very low
diabetic ketoacidosis at end of follow up Mean follow-up: 5.5 month(s)											
1 (lee 2022)	RC T	very seriou s ⁴	not seriou s	NA ¹	very seriou s ³	NA	0/30	0/30	RD 0.00 (-0.06, 0.06)	0 fewer per 1000 (63 fewer to 63 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 14.8 month(s)											
2	RC T	not seriou s	not seriou s	not seriou s	very seriou s ⁵	NA	20/332	21/3 33	RR 0.95 (0.53, 1.72)	3 fewer per 1000 (30 fewer to 46 more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 14.8 month(s)											
	RC	not seriou	not seriou	not seriou	very seriou			2/33	PETO OR 1.50	3 more per 1000 (10 fewer to	
hba1c change (%, lower values are better, change and final scores) at end of follow up Mean follow-up: 11.7 month(s)	T	S	S	S	s ⁵	NA	3/332	3	(0.26, 8.74)	16 more)	low
3	RC T	not seriou s	not seriou s	not seriou s	not seriou s	NA	361	362	MD 0.05 (-0.21, 0.31)	MD 0.05 higher (0.21 lower to 0.31 higher)	high
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											

GRADE tables - Model 5: Type 2 diabetes and higher cardiovascular risk

1 (lee 2022)	RC T	very seriou s ⁴	not seriou s	NA ¹	seriou s ⁶	NA	30	30	MD -1.59 (-2.70, - 0.48)	MD 1.59 lower (2.70 lower to 0.48 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
1 (lee 2022)	RC T	very seriou s ⁴	not seriou	NA¹	seriou s ⁷	NA	30	30	MD -1.59 (-2.70, - 0.48)	MD 1.59 lower (2.70 lower to 0.48 lower)	very low

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

L.1.5.9 Adding empagliflozin compared to adding placebo

Table 50: Clinical evidence profile: Adding empagliflozin compared to adding placebo

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

health-related quality of life - overall (eq-5d-5l, higher values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (yabe 2023)	R CT	not serio us	not serio us	NA ¹	seriou s²	NA	65	64	MD 0.05 (0.01, 0.09)	MD 0.05 higher (0.01 higher to 0.09 higher)	mod erat e
all-cause mortality at end of follow up Mean follow-up: 13.1 month(s)											
9 cardiovascular mortality at end of follow up	R CT	very serio us ³	not serio us	seriou s ⁴	very seriou s ⁵	NA	7/2447	3/12 95	RD 0.00 (-0.00, 0.01)	1 more per 1000 (4 fewer to 5 more)	very low
Mean follow-up: 11.6 month(s)											
5	R CT	very serio us ³	not serio us	seriou s ⁴	very seriou s ⁶	NA	2/1356	0/71	RD 0.00 (-0.00, 0.01)	1 more per 1000 (4 fewer to 7 more)	very low
non-fatal stroke at end of follow up Mean follow-up: 12 month(s)											
1 (kawamori 2018)	R CT	not serio us	not serio us	NA¹	very seriou s ⁷	NA	0/182	1/93	PETO OR 0.05 (0.00, 3.27)	11 fewer per 1000 (32 fewer to 10 more)	low
unstable angina at end of follow up Mean follow-up: 12 month(s)											
1 (sone 2019)	R CT	not serio us	not serio us	NA ¹	very seriou s ⁷	NA	0/176	1/90	PETO OR 0.05 (0.00, 3.28)	11 fewer per 1000 (33 fewer to 11 more)	low
hospitalisation for heart failure at end of follow up Mean follow-up: 12 month(s)											

1 (kawamori 2018) acute kidney injury at end of follow up	R CT	not serio us	not serio us	NA ¹	seriou s ⁸	NA	0/182	0/93	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (17 fewer to 17 more)	mod erat e
Mean follow-up: 8.8 month(s) 2 persistent signs of worsening kidney disease at	R CT	not serio us	not serio us	seriou s ⁴	very seriou s ⁹	NA	3/328	0/16	RD 0.01 (-0.01, 0.03)	9 more per 1000 (8 fewer to 26 more)	very
end of follow up Mean follow-up: 8.9 month(s)											
2	R CT	not serio us	not serio us	not seriou s	seriou s ⁸	NA	0/145	0/14	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (19 fewer to 19 more)	mod erat e
diabetic ketoacidosis at end of follow up Mean follow-up: 10.1 month(s)											
7	R CT	not serio us	not serio us	seriou s ⁴	very seriou s ¹⁰	NA	0/1195	1/67	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (9 fewer to 5 more)	very low
progression of liver disease at end of follow up Mean follow-up: 12 month(s)											
1 (yabe 2023)	R CT	not serio us	not serio us	NA ¹	very seriou s ⁷	NA	2/65	0/64	PETO OR 7.39 (0.46, 119.47)	31 more per 1000 (11 fewer to 73 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 11.7 month(s)											
12	R CT	not serio us	not serio us	seriou s ⁴	not seriou s	NA	517/28 95	247/ 158 1	RR 1.08 (0.96, 1.22)	13 more per 1000 (7 fewer to 34 more)	mod erat e
severe hypoglycaemic episodes at end of follow up											

Mean follow-up: 11.8 month(s)											
9	R CT	very serio us ³	not serio us	seriou s ⁴	very seriou s ⁵	NA	9/2260	4/12 03	RD 0.00 (-0.00, 0.01)	0 more per 1000 (5 fewer to 6 more)	very low
hba1c change (%, lower values are better, change scores and final values) at end of follow up Mean follow-up: 11.3 month(s)											
weight change (kg, lower values are better, change scores) at end of follow up	R CT	not serio us	not serio us	very seriou s ¹¹	seriou s ¹²	NA	2471	131 4	MD -0.74 (-0.99, - 0.49)	MD 0.74 lower (0.99 lower to 0.49 lower)	very low
Mean follow-up: 10.6 month(s)	R	not serio us	not serio us	very seriou s ¹¹	seriou s ¹³	NA	2526	134	MD -2.22 (-2.62, -	MD 2.22 lower (2.62 lower to 1.81 lower)	very
bmi change (kg/m2, lower values are better, change scores and final values) at end of follow up Mean follow-up: 8.8 month(s)									,	,	
2	R CT	not serio us	not serio us	not seriou s	seriou s ¹⁴	NA	100	102	MD -0.58 (-0.92, - 0.24)	MD 0.58 lower (0.92 lower to 0.24 lower)	mod erat e

- 1. Only one study so no inconsistency
- 2. 95% confidence intervals cross one end of the defined MIDs (-0.03, 0.03)
- 3. >33.3% of the studies in the meta-analysis were at high risk of bias
- 4. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

5. Precision calculated through Optimal

Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.07 (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 = 0.44 (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. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 9. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.57 (0.8-0.9 = serious, <0.8 = very serious).
- 10. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.38 (0.8-0.9 = serious, <0.8 = very serious).
- 11. I2 > 75%
- 12. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 13. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)
- 14. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

L.1.5.10 Adding empagliflozin compared to adding insulin

Table 51: Clinical evidence profile: Adding empagliflozin compared to adding insulin

	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
hba1c change (%, lower values are											
better, final scores) at end of follow up											
Mean follow-up: 12 month(s)											

GRADE tables - Model 5: Type 2 diabetes and higher cardiovascular risk

1 (ikonomidis 2020)	RC T	seriou s ¹	not seriou s	NA ²	very seriou s³	NA	40	40	MD 0.00 (-0.50, 0.50)	MD 0.00 lower (0.50 lower to 0.50 higher)	very low
weight change (kg, lower values are better, final scores) at end of follow up											
Mean follow-up: 12 month(s)											
1 (ikonomidis 2020)	RC T	seriou s ¹	not seriou s	NA ²	seriou s ⁴	NA	40	40	MD -2.90 (-7.07, 1.27)	MD 2.90 lower (7.07 lower to 1.27 higher)	low
bmi change (kg/m2, lower values are better, final scores) at end of follow up Mean follow-up: 12 month(s)											
1 (ikonomidis 2020)	RC T	seriou s ¹	not seriou s	NA ²	seriou s ⁵	NA	40	40	MD -1.20 (-2.32, - 0.08)	MD 1.20 lower (2.32 lower to 0.08 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 (-0.50, 0.50)
- 4. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)
- 5. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

L.1.5.11 Adding empagliflozin compared to adding linagliptin

Table 52: Clinical evidence profile: Adding empagliflozin compared to adding linagliptin

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

GRADE tables – Model 3. Type 2 diabetes and	RC	not seriou	not seriou	SK.	seriou				RD 0.00	0 fewer per 1000 (36 fewer to	mod erat
1 (liu 2021)	Т	S	S	NA ¹	s ²	NA	0/53	0/53	(-0.04, 0.04)	36 more)	е
cardiovascular mortality at end of follow up Mean follow-up: 5.5 month(s)											
1 (liu 2021)	RC T	not seriou s	not seriou s	NA ¹	seriou s ²	NA	0/53	0/53	RD 0.00 (-0.04, 0.04)	0 fewer per 1000 (36 fewer to 36 more)	mod erat e
diabetic ketoacidosis at end of follow up Mean follow-up: 5.5 month(s)											
1 (liu 2021)	RC T	not seriou s	not seriou s	NA ¹	very seriou s ³	NA	1/53	0/53	PETO OR 7.39 (0.15, 372.38)	19 more per 1000 (18 fewer to 56 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 5.5 month(s)											
1 (liu 2021)	RC T	not seriou	not seriou s	NA¹	very seriou s ³	NA	5/53	5/53	RR 1.00 (0.31, 3.25)	0 fewer per 1000 (65 fewer to 213 more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.5 month(s)	•	3	3	147.		10.1	- Groo	0,00	(0.01, 0.20)	210 more)	low
1 (liu 2021)	RC T	not seriou s	not seriou s	NA ¹	seriou s ²	NA	0/53	0/53	RD 0.00 (-0.04, 0.04)	0 fewer per 1000 (36 fewer to 36 more)	mod erat e
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
1 (liu 2021)	RC T	not seriou s	not seriou s	NA ¹	seriou s ⁴	NA	51	53	MD -0.95 (-1.41, - 0.49)	MD 0.95 lower	mod erat e

GRADE tables - Model 5: Type 2 diabetes and higher cardiovascular risk

										(1.41 lower to 0.49 lower)	
weight change (kg, lower values are											
better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
(2)										MD 1.70	
										lower	
	DC	not	not						MD -1.70	(2.58 lower	mod
1 (liu 2021)	RC	seriou	seriou	NA ¹	seriou s ⁵	NA	51	53	(-2.58, - 0.82)	to 0.82	erat
1 (IIU 2021)	ı	S	5	INA'	S	INA	וט	ეე	0.02)	lower)	е

- 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. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 5. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

L.1.5.12 Adding empagliflozin compared to adding liraglutide

Table 53: Clinical evidence profile: Adding empagliflozin compared to adding liraglutide

	De	Risk	Indire	Incons		Other			Relative		Cert
	sig	of	ctnes	istenc	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	S	у	cision	ions	ntion N	rol N	CI)	effect	У
severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.5 month(s)											
1 (nakaguchi 2020)	RC T	not serio us	not seriou s	NA ¹	very seriou s ²	NA	0/31	0/30	RD 0.00 (-0.06, 0.06)	0 fewer per 1000 (62 fewer to 62 more)	low
hba1c change (%, lower values are better, change and final scores) at end of follow up											

Mean follow-up: 8.8 month(s)											
2	RC T	not serio us	not seriou s	very seriou s ³	seriou s ⁴	NA	71	70	MD 0.46 (-0.41, 1.33)	MD 0.46 higher (0.41 lower to 1.33 higher)	very low
weight change (kg, lower values are better, final scores) at end of follow up Mean follow-up: 8.8 month(s)											
2	RC T	not serio us	not seriou s	not seriou s	not seriou s	NA	71	70	MD -0.34 (-1.30, 0.61)	MD 0.34 lower (1.30 lower to 0.61 higher)	high
bmi change (kg/m2, lower values are better, final scores) at end of follow up Mean follow-up: 8.8 month(s)											
2	RC T	not serio us	not seriou s	seriou s ⁵	seriou s ⁶	NA	71	70	MD -0.51 (-1.55, 0.53)	MD 0.51 lower (1.55 lower to 0.53 higher)	low

- 1. Only one study so no inconsistency
- 2. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 3. I2 > 75%
- 4. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 5. I2 between 50% and 75%
- 6. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

to adding semaglutide

Table 54: Clinical evidence profile: Adding empagliflozin compared to adding semaglutide

rable 54. Chilical evidence prome. Adding empagni	De	Risk	Indir	Incon	_	Other	Interv	Con	Relative		Cer
	_				Impr					Absolute	
No of studios	sig	of	ectn	sisten	ecisi	consider	entio	trol	effect	Absolute	tain
No of studies	n	bias	ess	су	on	ations	n N	N	(95% CI)	effect	ty
health-related quality of life - subscale mental											
component (sf36, higher values are better, change											
scores) at end of follow-up Mean follow-up: 12 month(s)											A .
Mean follow-up. 12 month(s)										MD 0.20	
										lower	
			not		not				MD -0.20	(1.33 lower	mo
	R	serio	serio		serio				(-1.33,	to 0.93	der
1 (rodbard 2019)	СТ	us ¹	us	NA ²	us	NA	409	409	0.93)	higher)	ate
health-related quality of life - subscale physical									, , , ,		
component (sf-36, higher values are better, change											A .
scores) at end of follow-up											A .
Mean follow-up: 12 month(s)											
										MD 1.00	
										higher	
										(0.12	
			not		not				MD 1.00	higher to	mo
4 (- 11 1 0040)	R	serio	serio	NIA?	serio	NIA	440	400	(0.12,	1.88	der
1 (rodbard 2019)	СТ	us ¹	us	NA ²	us	NA	410	409	1.88)	higher)	ate
all-cause mortality at end of follow up Mean follow-up: 12 month(s)											
Mean follow-up. 12 month(s)									PETO OR	2 more per	
		not	not		verv				7.41	1000	
	R	serio	serio		serio			0/4	(0.15,	(2 fewer to	
1 (rodbard 2019)	СТ	us	us	NA ²	us ³	NA	1/409	10	373.30)	7 more)	low
cardiovascular mortality at end of follow up		3.0	2.0		3.0		,,		270.00)		
Mean follow-up: 12 month(s)											
1 , 7		not	not		very						
	R	serio	serio		serio			0/4	PETO OR	2 more per	
1 (rodbard 2019)	CT	us	us	NA ²	us ³	NA	1/409	10	7.41	1000	low

GRADE tables – Model 3. Type 2 diabetes and higher cardion	raccar	ai rioit							(0.15,	(2 fewer to	
									373.30)	7 more)	
hospitalisation for heart failure at end of follow up									0.0.00)	1 111616)	
Mean follow-up: 12 month(s)											
·									PETO OR	2 fewer per	
		not	not		very				0.51	1000	
	R	serio	serio		serio			2/4	(0.05,	(11 fewer to	
1 (rodbard 2019)	СТ	us	us	NA ²	us ³	NA	1/409	10	4.95)	6 more)	low
acute kidney injury at end of follow up Mean follow-up: 12 month(s)											
									PETO OR	2 fewer per	
		not	not		very				0.51	1000	
4 (11 10040)	R	serio	serio		serio		44400	2/4	(0.05,	(11 fewer to	
1 (rodbard 2019)	СТ	us	us	NA ²	us ³	NA	1/409	10	4.95)	6 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 12 month(s)											
										14 fewer	
	_	not	not		very				RR 0.87	per 1000	
4 (- 11 1 0040)	R	serio	serio	N142	serio	NIA.	39/40	45/	(0.58,	(46 fewer to	
1 (rodbard 2019)	СТ	us	us	NA ²	us ³	NA	9	410	1.30)	33 more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											
										0 more per	
		not _.	not .		very			1,,,	RR 1.00	1000	
4 (R	serio	serio	NIA2	serio	NI A	4/400	1/4	(0.06,	(2 fewer to	
1 (rodbard 2019)	СТ	us	us	NA ²	us ³	NA	1/409	10	15.97)	37 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up											
Mean follow-up: 12 month(s)											
- mountonow up. 12 month(o)										MD 0.40	
										higher	
										(0.30	
		not	not		not				MD 0.40	higher to	
	R	serio	serio		serio				(0.30,	0.50	hig
1 (rodbard 2019)	СТ	us	us	NA ²	us	NA	410	411	0.50)	higher)	h
weight change (kg, lower values are better, change scores) at end of follow up											

GRADE tables - Model 5: Type 2 diabetes and higher cardiovascular risk

Mean follow-up: 12 month(s)											
	R	not serio	not serio		not serio				MD 0.20 (-0.50,	MD 0.20 higher (0.50 lower to 0.90	hig
1 (rodbard 2019)	CT	us	us	NA ²	us	NA	410	411	0.90)	higher)	h
bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
	R	not serio	not serio		not serio				MD 0.10 (-0.15,	MD 0.10 higher (0.15 lower to 0.35	hig
1 (rodbard 2019)	CT	us	us	NA^2	us	NA	410	411	0.35)	higher)	h

- 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)

L.1.5.14 Adding empagliflozin compared to adding sitagliptin

Table 55: Clinical evidence profile: Adding empagliflozin compared to adding sitagliptin

	De	Risk	Indire	Incons		Other			Relative		Cert
	sig	of	ctnes	istenc	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	S	у	cision	ions	ntion N	rol N	CI)	effect	У
hba1c change (mmol/mol, lower values are											
better, change scores) at end of follow up											
Mean follow-up: 6 month(s)											
										MD 1.70	
										lower	
		very	not		not				MD -1.70	(3.20 lower	
	RC	seriou	seriou		seriou				(-3.20, -	to 0.20	
1 (nesti 2022)	Т	s ¹	S	NA^2	s	NA	22	22	0.20)	lower)	low

GRADE tables – Model 5: Type 2 diabetes and higher cardiovascular risk

weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)											
	RC	very seriou	not seriou		very seriou				MD 0.30 (-4.26,	MD 0.30 higher (4.26 lower to 4.86	very
1 (nesti 2022)	Т	s ¹	S	NA ²	s^3	NA	22	22	4.86)	higher)	low

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

L.1.5.15 Adding empagliflozin compared to adding vildagliptin

Table 56: Clinical evidence profile: Adding empagliflozin compared to adding vildagliptin

•				_							
	De					Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
hba1c change (%, lower values are											
better, change scores) at end of follow											
up											
Mean follow-up: 5.5 month(s)											
										MD 0.15	
		very	not							lower	
	RC	seriou	seriou		seriou				MD -0.15	(0.61 lower to	very
1 (khan 2022)	Τ	s ¹	S	NA ²	s^3	NA	53	54	(-0.61, 0.31)	0.31 higher)	low
weight change (kg, lower values are											
better, change scores) at end of follow											
up											
Mean follow-up: 5.5 month(s)											
										MD 0.12	
		very	not		not					lower	
	RC	seriou	seriou		seriou				MD -0.12	(1.44 lower to	
1 (khan 2022)	T	s ¹	s	NA ²	s	NA	53	54	(-1.44, 1.20)	1.20 higher)	low

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)

L.1.5.16 Adding ertugliflozin compared to adding placebo

Table 57: Clinical evidence profile: Adding ertugliflozin compared to adding placebo

rable 57. Chilical evidence profile. Addi	iig ci	tugiiioz	LIII COIII	pared to	adding	Diacebo					
	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	y
all-cause mortality at end of follow up Mean follow-up: 8 month(s)											
3	RC T	not seriou s	not seriou s	not serious	not seriou s	NA	0/1060	0/52 9	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (5 fewer to 5 more)	high
cardiovascular mortality at end of follow up Mean follow-up: 8 month(s)											
3	RC T	not seriou	not seriou s	not serious	not seriou s	NA	0/1060	0/52 9	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (5 fewer to 5 more)	high
diabetic ketoacidosis at end of follow up Mean follow-up: 12 month(s)											J
1 (dagogo-jack 2017)	RC T	not seriou s	not seriou s	NA ¹	not seriou s	NA	0/309	0/15 3	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (10 fewer to 10 more)	high
hypoglycaemia episodes at end of follow up Mean follow-up: 8 month(s)											

3	RC T	not seriou s	not seriou s	not serious	seriou s²	NA	66/106 0	20/5 29	RR 1.65 (1.01, 2.69)	25 more per 1000 (0 more to 64 more)	mod erat e
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											
1 (dagogo-jack 2017)	RC T	not seriou s	not seriou s	NA ¹	very seriou s ³	NA	0/309	1/15	PETO OR 0.05 (0.00, 3.14)	7 fewer per 1000 (19 fewer to 6 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 8 month(s)										·	
3	RC T	not seriou s	not seriou s	not serious	not seriou s	NA	1060	529	MD -0.73 (-0.81, - 0.64)	MD 0.73 lower (0.81 lower to 0.64 lower)	high
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 8 month(s)											
2	RC T	not seriou s	not seriou	not serious	not seriou s	NA	648	320	MD -1.94 (-2.26, - 1.62)	MD 1.94 lower (2.26 lower to 1.62 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)

adding sitagliptin

Table 58: Clinical evidence profile: Adding ertugliflozin compared to adding sitagliptin

rable 56. Chilical evidence prome. Add	De					Other			Relative		Cert
	sig	Risk	Indire	Inconsi	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	of bias	ctness	stency	cision	ions	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RC T	not seriou s	not seriou s	NA ¹	very seriou s ²	NA	1/498	0/24 7	PETO OR 4.46 (0.07, 286.95)	2 more per 1000 (2 fewer to 6 more)	low
cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RC T	not seriou s	not seriou s	NA ¹	very seriou s ²	NA	1/498	0/24 7	PETO OR 4.46 (0.07, 286.95)	2 more per 1000 (2 fewer to 6 more)	low
diabetic ketoacidosis at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RC T	not seriou s	not seriou s	NA ¹	not seriou s	NA	0/498	0/24 7	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	high
hypoglycaemia episodes at end of follow up Mean follow-up: 12 month(s)										,	J
1 (pratley 2018a)	RC T	very seriou s ³	not seriou s	NA ¹	very seriou s ²	NA	15/498	7/24 7	RR 1.06 (0.44, 2.57)	2 more per 1000 (16 fewer to 45 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											

								_			
1 (pratley 2018a)	RC T	very seriou s ³	not seriou	NA ¹	very seriou s ²	NA	2/498	0/24	PETO OR 4.47 (0.24, 85.11)	4 more per 1000 (2 fewer to 10 more)	very
hba1c change (%, lower values are									,		
better, change scores) at end of follow											
up											
Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RC T	very seriou s ³	not seriou s	NA ¹	not seriou s	NA	498	247	MD -0.10 (-0.28, 0.08)	MD 0.10 lower (0.28 lower to 0.08 higher)	low
weight change (kg, lower values are											
better, change scores) at end of follow											
up											
Mean follow-up: 12 month(s)											
	RC	very seriou	not seriou		seriou				MD -2.70 (-3.41, -	MD 2.70 lower (3.41 lower to	very
1 (pratley 2018a)	T	s^3	S	NA^1	s ⁴	NA	498	247	1.99)	1.99 lower)	low

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

L.1.6.1 Adding gliclazide compared to adding vildagliptin

Table 59: Clinical evidence profile: Adding gliclazide compared to adding vildagliptin

Table 39. Chilical evidence profile. Add	De	Risk	- Compa		lanig vii	Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ions	ntion N	rol N	CI)	effect	y
all-cause mortality at end of follow up Mean follow-up: 12 month(s)				,							-
2	RC T	seriou s¹	not seriou s	serious 2	very seriou s ³	NA	2/514	1/53 1	RR 1.70 (0.23, 12.67)	1 more per 1000 (1 fewer to 22 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)											
1 (vianna 2018)	RC T	seriou s ¹	not seriou s	NA ⁴	very seriou s ³	NA	1/21	0/21	PETO OR 7.39 (0.15, 372.38)	48 more per 1000 (43 fewer to 139 more)	very low
non-fatal stroke at end of follow up Mean follow-up: 12 month(s)											
1 (vianna 2018)	RC T	seriou s ¹	not seriou s	NA ⁴	very seriou s ³	NA	0/21	1/21	PETO OR 0.14 (0.00, 6.82)	48 fewer per 1000 (139 fewer to 43 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											
1 (vianna 2018)	RC T	seriou s ¹	not seriou s	NA ⁴	very seriou s ⁵	NA	0/21	0/21	RD 0.00 (-0.09, 0.09)	0 fewer per 1000 (88 fewer to 88 more)	very low
hypoglycaemia episodes at end of follow up											

Mean follow-up: 12 month(s)											
1 (vianna 2018)	RC T	seriou s ¹	not seriou s	NA ⁴	seriou s ⁵	NA	7/21	2/21	RR 3.50 (0.82, 14.93)	238 more per 1000 (17 fewer to 1326 more)	low
hba1c change (%, lower values are better, change scores) at end of follow									,	,	
up Mean follow-up: 12 month(s)											
2	RC T	very seriou s ⁶	not seriou s	not serious	not seriou s	NA	414	407	MD -0.07 (-0.23, 0.09)	MD 0.07 lower (0.23 lower to 0.09 higher)	low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 8.8 month(s)											
2	RC T	very seriou s ⁶	not seriou	not serious	not seriou s	NA	512	532	MD 1.22 (0.47, 1.97)	MD 1.22 higher (0.47 higher to 1.97 higher)	low

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

L.1.6.2

adding placebo

Table 60: Clinical evidence profile: Adding glimepiride compared to adding placebo

rable 60. Chilical evidence profile. Adding gilliephilde	COL	iparec	i to au	unig p	lacebo		1				
	D							Co			
	es	Risk	Indi	Inco	Impr	Other	Inter	ntr	Relative		Cer
	ig	of	rect	nsist	ecisi	conside	venti	ol	effect		tai
	_	_						J			
No of studies	n	bias	ness	ency	on	rations	on N	N	(95% CI)	Absolute effect	nty
health-related quality of life - overall health utilities index											
mark 3 (higher values are better, change scores) at end											
of follow-up Mean follow-up: 6 month(s)											
	R	very	not							MD 0.03 higher	ver
	С	seri	seri		serio				MD 0.03 (-	(0.02 lower to	У
1 (roberts 2005)	Т	ous ¹	ous	NA^2	us ³	NA	82	77	0.02, 0.08)	0.08 higher)	low
all-cause mortality at end of follow up Mean follow-up:									,	,	
5.8 month(s)											
on menan(o)	R	very	not	not						0 fewer per	ver
	C	seri	seri	serio	serio		0/15	0/1	RD 0.00 (-	1000 (18 fewer	y
2	T	ous ¹	ous	us	us ⁴	NA	4	46	0.02, 0.02)	to 18 more)	low
cardiovascular mortality at end of follow up Mean	•	ous	ous	uo	uo	14/ (T	70	0.02, 0.02)	to ro more)	low
follow-up: 5.8 month(s)											
Tollow-up. 5.6 month(s)	R	1/05/	not	not						O fower nor	\ \(\sigma\)
		very	not	not			0/45	0/4	DD 0 00 /	0 fewer per	ver
	C	seri	seri	serio	serio	NIA.	0/15	0/1	RD 0.00 (-	1000 (18 fewer	У
2	I	ous ¹	ous	us	us ⁴	NA	4	46	0.02, 0.02)	to 18 more)	low
non-fatal stroke at end of follow up Mean follow-up: 5.5 month(s)											
··	R	very	not		very				PETO OR	14 more per	ver
	С	seri	seri		serio			0/6	6.59 (0.13,	1000 (13 fewer	V
1 (riddle 1998)	Т	ous ¹	ous	NA^2	us ⁵	NA	1/70	2	334.58)	to 42 more)	ĺow
non-fatal myocardial infarction at end of follow up Mean									,	,	
follow-up: 5.8 month(s)											
	R	very	not		very				RR 0.41	12 fewer per	ver
	C	seri	seri	serio	serio		1/15	3/1	(0.06,	1000 (19 fewer	V
2	Т	ous ¹	ous	us ⁶	us ⁵	NA	4	46	2.72)	to 35 more)	low
death from renal causes at end of follow up Mean		Jus	Jus	us	us	14/7	7	70	2.12)	to 55 more)	IOW
follow-up: 24 month(s)											

	R C	very seri	not seri		not serio		0/24	0/1	RD 0.00 (-	0 fewer per 1000 (13 fewer	
1 (nauck 2009b)	T	ous ¹	ous	NA ²	us	NA	2	21	0.01, 0.01)	to 13 more)	low
hypoglycaemia episodes at end of follow up Mean									,	,	
follow-up: 14.9 month(s)								201	55.55	470	
	R	very	not _.	very			404/	23/	RR 3.75	172 more per	ver
4	C	seri	seri	serio	serio us ⁸	NIA.	164/ 703	36	(1.25,	1000 (15 more	У
4	l	ous ¹	ous	us ⁷	usº	NA	703	8	11.25)	to 641 more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 14.9 month(s)											
(e)	R	very	not		very				RD -0.00	1 fewer per	ver
	С	seri	seri	serio	serio		1/70	1/5	(-0.01,	1000 (9 fewer	V
4	Т	ous ¹	ous	us ⁶	us ⁹	NA	3	69	0.01)	to 8 more)	low
hba1c change (%, lower values are better, change scores									,	,	
and final values) at end of follow up Mean follow-up:											
10.6 month(s)											
	R	very	not	very					MD -0.69	MD 0.69 lower	ver
	С	seri	seri	serio	serio			27	(-1.10, -	(1.10 lower to	У
4	Τ	ous ¹	ous	us ⁷	us ¹⁰	NA	419	5	0.29)	0.29 lower)	low
weight change (kg, lower values are better, change											
scores and final values) at end of follow up Mean											
follow-up: 5.8 month(s)											
	R	very	not _.	very	very			1,0	MD -0.24	MD 0.24 lower	ver
	C	seri	seri	serio	serio	N.A.	450	13	(-8.30,	(8.30 lower to	У
2	I	ous ¹	ous	us ⁷	us ¹¹	NA	152	9	7.81)	7.81 higher)	low
bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)											
	R	very	not						MD 1.09	MD 1.09 higher	ver
	С	seri	seri		serio				(0.65,	(0.65 higher to	У
1 (roberts 2005)	Т	ous ¹	ous	NA ²	us ¹²	NA	82	77	1.53)	1.53 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 (-0.05, 0.05)

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

- 5. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 6. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)7. I2 > 75%
- 8. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 9. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.04 (0.8-0.9 = serious, <0.8 = very serious).
- 10. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 11. 95% confidence intervals cross both ends of the defined MIDs (-2.40, 2.40)
- 12. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

L.1.6.3 Adding glimepiride compared to adding metformin

Table 61: Clinical evidence profile: Adding glimepiride compared to adding metformin

	De	Risk				Other			Relative		Cert
	sig	of	Indirec	Inconsi	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	tness	stency	cision	ions	ntion N	rol N	CI)	effect	У
hypoglycaemia episodes at end of follow up Mean follow-up: 5.5 month(s)											
1 (park 2014)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s³	NA	20/34	15/3 3	RR 1.29 (0.81, 2.07)	134 more per 1000 (86 fewer to 485 more)	very low
at night hypoglycaemic episodes at end of follow up Mean follow-up: 5.5 month(s)	•						20,01		(6:6:, 2:6:)	.sc mercy	
1 (park 2014)	RC T	very seriou s ¹	not serious	NA ²	very seriou s ⁴	NA	6/34	3/33	RR 1.94 (0.53, 7.13)	86 more per 1000	very low

										(43 fewer to 557 more)	
severe hypoglycaemic episodes at end of follow up											
Mean follow-up: 5.5 month(s)											
1 (park 2014) hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)	RC T	very seriou s ¹	not serious	NA ²	very seriou s ⁵	NA	0/34	0/33	RD 0.00 (-0.06, 0.06)	0 fewer per 1000 (56 fewer to 56 more)	very low
										MD 0.05	
	RC	very	not		very				MD 0.05	higher	Vorv
1 (park 2014)	T	seriou s ¹	not serious	NA ²	seriou s ⁶	NA	32	32	(-0.52, 0.62)	(0.52 lower to 0.62 higher)	very low

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

adding insulin

Table 62: Clinical evidence profile: Adding glimepiride compared to adding insulin

	De	Risk	Indir	Incon	Impr	Other	Interv	Con	Relative		Cer
	sig	of	ectn	sisten	ecisi	consider	entio	trol	effect	Absolute	tain
No of studies	n	bias	ess	су	on	ations	n N	N	(95% CI)	effect	ty
health-realted quality of life - subscale mental component (sf-36, higher values are better, change scores) at end of follow up Mean follow-up: 24 month(s)											
1 (group 2022)	R CT	very serio us ¹	not serio us	NA ²	not serio us	NA	1222	120 9	MD 0.18 (-0.42, 0.78)	MD 0.18 higher (0.42 lower to 0.78 higher)	low
health-realted quality of life - subscale physical component (sf-36, higher values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (group 2022)	R	very serio us ¹	not serio us	NA ²	not serio us	NA	1222	120 9	MD 0.00 (-0.55, 0.55)	MD 0.00 lower (0.55 lower to 0.55 higher)	low
all-cause mortality at end of follow up Mean follow-up: 60 month(s)									·		
1 (group 2022)	R CT	serio us³	not serio us	NA ²	very serio us ⁴	NA	43/12 51	41/ 126 1	RR 1.06 (0.69, 1.61)	2 more per 1000 (10 fewer to 20 more)	ver y low
all-cause mortality at end of follow up Mean follow-up: 60 month(s)											
4 (2022)	R	serio	not serio	N1A2	very serio	NIA	4047	125	HR 1.04 (0.68,	Not	ver y
1 (group 2022)	СТ	us ³	us	NA ²	us ⁴	NA	1247	7	1.58)	estimable	low
cardiovascular mortality at end of follow up											

Mean follow-up: 60 month(s)											
1 (group 2022) cardiovascular mortality at end of follow-up	R CT	serio us³	not serio us	NA ²	very serio us ⁴	NA	16/12 44	21/ 125 5	RR 0.77 (0.40, 1.47)	4 fewer per 1000 (10 fewer to 8 more)	ver y low
Mean follow-up: 60 month(s)											
1 (group 2022)	R CT	serio us³	not serio us	NA ²	very serio us ⁴	NA	1247	125 7	HR 0.78 (0.40, 1.48)	Not estimable	ver y low
3-point mace at end of follow up Mean follow-up: 60 month(s)											
1 (group 2022)	R CT	serio us³	not serio us	NA ²	very serio us ⁴	NA	59/12 44	65/ 125 5	RR 0.92 (0.65, 1.29)	4 fewer per 1000 (18 fewer to 15 more)	ver y low
3-point mace at end of follow up Mean follow-up: 60 month(s)											
1 (group 2022)	R CT	serio us ³	not serio us	NA ²	very serio us ⁴	NA	1247	125 7	HR 0.92 (0.65, 1.30)	Not estimable	ver y low
4-point mace at end of follow up Mean follow-up: 60 month(s)											
1 (group 2022)	R	very serio us ¹	not serio us	NA ²	very serio us ⁴	NA	67/12 54	71/ 126 3	RR 0.95 (0.69, 1.31)	3 fewer per 1000 (18 fewer to 18 more)	ver y low
unstable angina at end of follow up Mean follow-up: 60 month(s)											
1 (group 2022)	R CT	very serio us ¹	not serio us	NA ²	very serio us ⁴	NA	12/12 54	15/ 126 8	RR 0.81 (0.38, 1.72)	2 fewer per 1000 (7 fewer to 9 more)	ver y low
hospitalisation for heart failure at end of follow up Mean follow-up: 60 month(s)									,	,	

GRADE tables – Model 5: Type 2 diabetes and higher cardio	rascui	ai iisk								3 more per	
			not		very			26/	RR 1.16	1000	ver
1 (group 2022)	R	serio us³	serio	NA ²	serio us ⁴	NA	30/12 44	125 5	(0.69, 1.96)	(6 fewer to 20 more)	y low
1 (group 2022) hospitalisation for heart failure at end of follow up	CI	us°	us	INA	us	INA	44	5	1.90)	20 more)	IOW
Mean follow-up: 60 month(s)											
			not		very				HR 1.16		ver
	R	serio	serio		serio			126	(0.69,	Not	У
1 (group 2022)	СТ	us ³	us	NA ²	us ⁴	NA	1247	4	1.96)	estimable	low
hypoglycaemia episodes at end of follow up Mean follow-up: 54 month(s)											
										155 more	
		Verv	not	not	not			484	RR 1.41	per 1000 (110 more	
	R	very serio	serio	serio	serio		673/1	/12	(1.29,	to 203	
2	СТ	us ¹	us	us	us	NA	265	83	1.54)	more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 60 month(s)									,		
. , ,		very	not		not				HR 1.61		
	R	serio	serio		serio			124	(1.43,	Not	
1 (group 2022)	СТ	us ¹	us	NA ²	us	NA	1231	5	1.81)	estimable	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 54 month(s)											
								40/	DD 0.04	9 more per	
	R	very serio	not serio	serio	very serio		28/12	16/ 130	RD 0.01 (-0.00,	1000 (1 fewer to	ver
2	СТ	us ¹	us	us ⁵	us ⁶	NA	88	130	0.02)	19 more)	y low
hba1c change (%, lower values are better, change		5.5	J. J	5.0	0.0				0.02)	,	
scores and final values) at end of follow up Mean follow-up: 35.5 month(s)											
,										MD 0.00	
										higher	
	Р	very	not	not	very				MD 0.00	(0.56 lower to 0.57	ver
2	R	serio us ¹	serio	serio us	serio us ⁷	NA	344	464	(-0.56, 0.57)	higher)	y low
weight change (kg, lower values are better, change		45	u.o	40	45	1773	77	157	5.57	/ iigiioi /	1.5 **
scores) at end of follow up											

GRADE tables - Model 5: Type 2 diabetes and higher cardiovascular risk

Mean follow-up: 11 month(s)											
										MD 1.70	
										lower	
		very	not						MD -1.70	(3.05 lower	ver
	R	serio	serio		serio				(-3.05, -	to 0.35	y
1 (moon 2014)	СТ	us ¹	us	NA ²	us ⁸	NA	34	38	0.35)	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. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.75 (0.8-0.9 = serious, <0.8 = very serious).
- 7. 95% confidence intervals cross both ends of the defined MIDs (-0.50, 0.50)
- 8. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

L.1.6.5 Adding glimepiride compared to adding canagliflozin

Table 63: Clinical evidence profile: Adding glimepiride compared to adding canagliflozin

	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ions	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow up Mean follow-up: 24 month(s)											
	RC	not seriou	not seriou		very seriou			2/96	RR 2.01 (0.28,	2 more per 1000 (1 fewer to 27	
1 (cefalu 2013)	Т	S	S	NA ¹	s^2	NA	2/482	8	14.21)	more)	low

cardiovascular mortality at end of follow	riigiie	Cardiov	asculai II	JK .							
up											
Mean follow-up: 24 month(s)											
, , ,	RC	not seriou	not seriou		seriou			0/96	PETO OR 20.30 (1.07,	4 more per 1000 (2 fewer to 10	mod erat
1 (cefalu 2013)	T	S	S	NA ¹	s ³	NA	2/482	8	385.05)	more)	е
death from renal causes at end of follow									,	,	
up Mean follow-up: 24 month(s)											
1 (cefalu 2013)	RC T	not seriou s	not seriou	NA¹	very seriou s ²	NA	0/482	1/96	PETO OR 0.22 (0.00, 14.33)	1 fewer per 1000 (3 fewer to 1 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 24 month(s)									,	,	
	RC	not seriou	not seriou		not seriou		197/48	71/9	RR 5.57	335 more per 1000 (245 more to	
1 (cefalu 2013)	Т	s	S	NA ¹	S	NA	2	68	(4.35, 7.14)	451 more)	high
severe hypoglycaemic episodes at end of follow up Mean follow-up: 24 month(s)											
	RC	not seriou	not seriou	2124	not seriou		40/400	4/96	RR 8.03 (2.70,	29 more per 1000 (7 more to 95	
1 (cefalu 2013) hba1c change (%, lower values are	I	S	S	NA ¹	S	NA	16/482	8	23.90)	more)	high
better, change scores) at end of follow											
Mean follow-up: 24 month(s)											
	RC	very seriou	not seriou		not seriou				MD 0.14	MD 0.14 higher (0.05 higher to 0.22	
1 (cefalu 2013,cefalu 2013)	Т	s ⁴	S	NA ¹	S	NA	482	968	(0.05, 0.22)	higher)	low

weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 24 month(s)											
1 (cefalu 2013,cefalu 2013)	RC	very seriou s ⁴	not seriou	NA ¹	not seriou s	NA	482	968	MD 5.15 (4.76, 5.54)	MD 5.15 higher (4.76 higher to 5.54 higher)	low

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

L.1.6.6 Adding glimepiride compared to adding dapagliflozin

Table 64: Clinical evidence profile: Adding glimepiride compared to adding dapagliflozin

No of studies	Des ign		Indirec tness	Inconsis tency	Impreci sion	Other consideratio	Interven tion N	Contr	Relative effect (95% CI)	Absolute effect	Certa
140 of studies	ıgıı	Dias	tiless	cericy	31011	113	CIOIIIV	OI IV	(3378 CI)	Absolute ellect	iiity
all-cause mortality at end of follow up Mean follow-up: 12 month(s)											
1 (park 2023)			not serious	NA ¹	serious ²	NA	0/61		RD 0.00	` .	mode rate
cardiovascular mortality at end of follow up											

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Mean follow-up: 12 month(s)											
1 (park 2023) hospitalisation for heart failure at end of follow up Mean follow-up: 12 month(s)	RC T		not serious	NA ¹	serious ²	NA	0/61	0/60	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (32 fewer to 32 more)	mode rate
1 (muller-wieland 2018) hypoglycaemia episodes at end of follow up Mean follow-up: 10.2 month(s)	RC T		not serious	NA ¹	very serious ³	NA	1/312		7.41	3 more per 1000 (3 fewer to 9 more)	low
	RC T		not serious	serious ⁴	not serious	NA	22/403		PETO OR 4.87 (2.18, 10.84)	47 more per 1000 (24 more to 71 more)	mode rate
			not serious	NA ¹	not serious	NA	0/312		RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	high

Mean follow-up: 10.2 month(s)										
3			very serious ⁵	serious ⁶	NA	394	397	MD 0.14	MD 0.14 higher (0.29 lower to 0.57 higher)	very low
weight change (kg, lower values are better, change score) at end of follow up Mean follow-up: 10.2 month(s)										
3			very serious ⁵	very serious ⁷	NA	397	399	MD 1.59	MD 1.59 higher (4.00 lower to 7.18 higher)	very low
bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)										
1 (park 2023)		not serious		not serious	NA	56		MD 1.37	MD 1.37 higher (1.00 higher to 1.74 higher)	high

- 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. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 5. I2 > 75%
- 6. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 7. 95% confidence intervals cross both ends of the defined MIDs (-2.40, 2.40)

adding empagliflozin

Table 65: Clinical evidence profile: Adding glimepiride compared to adding empagliflozin

No of studies						Other	Interven tion N	Contr ol N	Relative effect (95% CI)	Absolute effect	Certa inty
all-cause mortality at end of follow up											
Mean follow-up: 48 month(s)											
			not		very				RR 0.98	0 fewer per 1000 (5 fewer to 16	
1 (ridderstrale 2014)	Т	serious	serious	NA ¹	serious ²	NA	5/780	5/765	(0.29, 3.37)	more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 48 month(s)											
1 (ridderstrale 2014)	RC T		not serious		not serious	NA	189/780	19/76	RR 9.76	217 more per 1000 (128 more to 359 more)	high
hba1c change (%, lower values are better, change scores) at end of follow up											
Mean follow-up: 48 month(s)											
1 (ridderstrale 2014)			not serious		not serious		780		MD 0.11	MD 0.11 higher (0.03 higher to 0.19 higher)	high

weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 48 month(s)								
1 (ridderstrale 2014)	RC T	not serious	not serious	NA	780	MD 4.61	MD 4.61 higher (4.18 higher to 5.04 higher)	high

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

L.1.6.8 Adding glimepiride compared to adding ertugliflozin

Table 66: Clinical evidence profile: Adding glimepiride compared to adding ertugliflozin

Table 66. Officer evidence profile. Add	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ions	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow up Mean follow-up: 12 month(s)											
1 (hollander 2018)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s³	NA	0/437	6/88 8	PETO OR 0.22 (0.04, 1.23)	7 fewer per 1000 (12 fewer to 1 fewer)	very low
cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)											
1 (hollander 2018)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ⁴	NA	0/435	1/88 0	PETO OR 0.22 (0.00, 14.46)	1 fewer per 1000 (3 fewer to 1 more)	very low
acute kidney injury at end of follow up Mean follow-up: 12 month(s)									·		

1 (hollander 2018)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ⁴	NA	0/437	1/88 8	RR 0.68 (0.03, 16.57)	0 fewer per 1000 (1 fewer to 18 more)	very low
diabetic ketoacidosis at end of follow up Mean follow-up: 12 month(s)											
1 (hollander 2018)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ⁴	NA	0/437	1/88 8	PETO OR 0.22 (0.00, 14.54)	1 fewer per 1000 (3 fewer to 1 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 12 month(s)											
1 (hollander 2018)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	84/437	37/8 88	RR 4.61 (3.19, 6.67)	151 more per 1000 (91 more to 236 more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											
1 (hollander 2018)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	10/437	2/88 8	RR 10.16 (2.24, 46.17)	21 more per 1000 (3 more to 102 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (hollander 2018)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	437	888	MD -0.10 (-0.17, - 0.03)	MD 0.10 lower (0.17 lower to 0.03 lower)	low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											

										MD 4.10	
										higher	
		very	not		not					(3.67 higher	
	RC	seriou	seriou		seriou				MD 4.10	to 4.53	
1 (hollander 2018)	T	s ¹	S	NA^2	S	NA	437	888	(3.67, 4.53)	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)

L.1.6.9 Adding glimepiride compared to adding exenatide

Table 67: Clinical evidence profile: Adding glimepiride compared to adding exenatide

33	De	Risk	Indire	Incons		Other	Interve	Cont	Relative		Cert
	sig	of	ctnes	istenc	Impre	considera	ntion	rol	effect (95%	Absolute	aint
No of studies	n	bias	S	у	cision	tions	N	N	CI)	effect	У
all-cause mortality at end of follow up Mean follow-up: 36 month(s)											
1 (gallwitz 2012b)	RC T	not serio us	not seriou s	NA ¹	very seriou s ²	NA	5/508	5/51 1	RR 1.01 (0.29, 3.45)	0 more per 1000 (7 fewer to 24 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 24 month(s)											
2	RC T	not serio us	not seriou s	seriou s³	not seriou s	NA	341/56 2	186/ 568	RR 1.84 (1.62, 2.10)	276 more per 1000 (202 more to 360 more)	high
at night hypoglycaemic episodes at end of follow up Mean follow-up: 36 month(s)										,	y

GRADE lables - Model 5: Type 2 diabetes and higher	Laiu	iovascu	iai iisk								
1 (gallwitz 2012b)	RC T	not serio us	not seriou s	NA¹	seriou s 4	NA	82/508	53/5 11	RR 1.56 (1.13, 2.15)	58 more per 1000 (13 more to 119 more)	mod erat e
severe hypoglycaemic episodes at end of follow up Mean follow-up: 36 month(s)											
1 (gallwitz 2012b)	RC T	not serio us	not seriou s	NA ¹	very seriou s ²	NA	0/508	1/51 1	PETO OR 0.14 (0.00, 6.86)	2 fewer per 1000 (6 fewer to 2 more)	low
hba1c change (%, lower values are better, change scores and final values) at end of follow up Mean follow-up: 24 month(s)											
2	RC T	not serio us	not seriou s	very seriou s ⁵	not seriou s	NA	246	234	MD 0.03 (-0.04, 0.10)	MD 0.03 higher (0.04 lower to 0.10 higher)	low
weight change (kg, lower values are better, change scores and final values) at end of follow up Mean follow-up: 24 month(s)											
2	RC T	not serio us	not seriou s	very seriou s ⁵	not seriou s	NA	560	560	MD -4.03 (-4.61, - 3.45)	MD 4.03 lower (4.61 lower to 3.45 lower)	low
bmi change (kg/m2, lower values are better, change scores and final values) at end of follow up Mean follow-up: 24 month(s)											
2	RC T	not serio us	not seriou s	not seriou s	not seriou s	NA	560	0	MD 1.79 (1.53, 2.04)	MD 1.79 higher (1.53 higher to 2.04 higher)	high

1. Only one study so no inconsistency

- 2. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 3. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 4. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 5. I2 > 75%

L.1.6.10 Adding glimepiride compared to adding gliclazide

Table 68: Clinical evidence profile: Adding glimepiride compared to adding gliclazide

	De	Risk	Indir	Incon	Impr	Other	Interv	Con	Relative		Cer
	sig	of	ectn	sisten	ecisi	consider	entio	trol	effect (95%		tain
No of studies	n	bias	ess	су	on	ations	n N	N	CI)	Absolute effect	ty
all-cause mortality at end of follow up Mean											
follow-up: 5.5 month(s)											
	R	very	not		not					0 fewer per 1000	
	С	serio	serio		serio			0/5	RD 0.00 (-	(4 fewer to 4	
1 (xu 2017)	T	us ¹	us	NA ²	us	NA	0/549	50	0.00, 0.00)	more)	low
cardiovascular mortality at end of follow up											
Mean follow-up: 5.5 month(s)											
	R	very	not		not					0 fewer per 1000	
	С	serio	serio		serio			0/5	RD 0.00 (-	(4 fewer to 4	
1 (xu 2017)	Т	us ¹	us	NA ²	us	NA	0/549	50	0.00, 0.00)	more)	low
non-fatal stroke at end of follow up Mean											
follow-up: 5.5 month(s)											
	R	very	not		not					0 fewer per 1000	
	С	serio	serio		serio			0/5	RD 0.00 (-	(4 fewer to 4	
1 (xu 2017)	Т	us ¹	us	NA ²	us	NA	0/549	50	0.00, 0.00)	more)	low
non-fatal myocardial infaRCTion at end of											
follow up Mean follow-up: 5.5 month(s)											

,	R	very	not		very				PETO OR	4 fewer per 1000	ver
	С	serio	serio		serio			2/5	0.14 (0.01,	(9 fewer to 1	У
1 (xu 2017)	Т	us ¹	us	NA ²	us ³	NA	0/549	50	2.17)	more)	low
diabetic ketoacidosis at end of follow up Mean follow-up: 5.5 month(s)											
	R C	very serio	not serio		very serio			1/5	PETO OR 0.14 (0.00,	2 fewer per 1000 (5 fewer to 2	ver v
1 (xu 2017)	Ť	us ¹	us	NA ²	us ³	NA	0/549	50	6.83)	more)	low
falls requiring hospitalisation at end of follow-									,	,	
up Mean follow-up: 5.5 month(s)											
	R C	very serio	not serio		not serio			0/5	RD 0.00 (-	0 fewer per 1000 (4 fewer to 4	
1 (xu 2017)	Т	us ¹	us	NA ²	us	NA	0/549	50	0.00, 0.00)	more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 5.5 month(s)											
1 (/// 2017)	R C	very serio	not serio	NA ²	not serio	NA	49/54	20/ 550	RR 2.45	53 more per 1000 (17 more to 112	low
1 (xu 2017)	ı	us ¹	us	INA ²	us	NA	9	550	(1.48, 4.07)	more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.5 month(s)											
	R C	very serio	not serio		very serio			0/5	RR 3.01 (0.12,	0 fewer per 1000	ver y
1 (xu 2017)	ΙŤ	us ¹	us	NA ²	us ³	NA	1/549	50	73.62)	(0 more to 0 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)									,		
	R C	very serio	not serio		not serio				MD 0.05 (-	MD 0.05 higher (0.11 lower to 0.21	
1 (xu 2017)	Т	us ¹	us	NA ²	us	NA	414	418	0.11, 0.21)	higher)	low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
	R C	not serio	not serio		not serio				MD 0.24	MD 0.24 higher (0.05 higher to	hig
1 (xu 2017)	T	us	us	NA ²	us	NA	549	550	(0.05, 0.43)	0.43 higher)	hig h

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

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

L.1.6.11 Adding glimepiride compared to adding linagliptin

Table 69: Clinical evidence profile: Adding climepiride compared to adding linagliptin

rable 69: Cliffical evidence profile: Addi	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow up Mean follow-up: 49.8 month(s)											
2	RC T	not serio us	not seriou s	not serious	seriou s ¹	NA	340/37 85	312/ 3799	RR 1.09 (0.95, 1.27)	8 more per 1000 (4 fewer to 22 more)	mod erat e
all-cause mortality at end of follow up Mean follow-up: 75.6 month(s)											
1 (rosenstock 2019b)	RC T	not serio us	not seriou s	NA ²	seriou s ¹	NA	3023	3010	HR 1.10 (0.94, 1.28)	Not estimable	mod erat e
cardiovascular mortality at end of follow up Mean follow-up: 49.8 month(s)											
2	RC T	not serio us	not seriou s	not serious	not seriou s	NA	170/37 85	171/ 3799	RR 1.00 (0.81, 1.23)	0 fewer per 1000 (8 fewer to 10 more)	high
cardiovascular mortality at end of follow up Mean follow-up: 75.6 month(s)											
1 (rosenstock 2019b)	RC T	not serio us	not seriou s	NA ²	not seriou s	NA	3023	3010	HR 1.00 (0.81, 1.23)	Not estimable	high

4-point mace at end of follow up	ingile	Jaiaioi	, addurant								
Mean follow-up: 75.6 month(s)											
1 (rosenstock 2019b)	RC T	not serio us	not seriou s	NA ²	not seriou s	NA	401/30 10	398/ 3023	RR 1.01 (0.89, 1.15)	2 more per 1000 (15 fewer to 20 more)	high
4-point mace at end of follow up Mean follow-up: 75.6 month(s)											
1 (rosenstock 2019b)	RC T	not serio us	not seriou s	NA ²	not seriou s	NA	3010	3023	HR 1.01 (0.88, 1.16)	Not estimable	high
non-fatal stroke at end of follow up Mean follow-up: 49.8 month(s)											
2	RC T	not serio us	not seriou s	serious	very seriou s ⁴	NA	115/37 85	94/3 799	RR 1.73 (0.58, 5.14)	18 more per 1000 (10 fewer to 103 more)	very low
non-fatal stroke at end of follow up Mean follow-up: 75.6 month(s)											
1 (rosenstock 2019b)	RC T	not serio us	not seriou s	NA ²	seriou s ¹	NA	3010	3023	HR 1.15 (0.87, 1.52)	Not estimable	mod erat e
non-fatal myocardial infarction at end of follow up Mean follow-up: 24 month(s)											
1 (gallwitz 2012a)	RC T	not serio us	not seriou	NA ²	very seriou s ⁴	NA	10/775	6/77 6	RR 1.67 (0.61, 4.57)	5 more per 1000 (3 fewer to 28 more)	low
non-fatal myocardial infarction at end of follow-up							19,110		(5:5:4)		
Mean follow-up: 75.6 month(s)		not	not		very						
1 (rosenstock 2019b)	RC T	serio	seriou	NA ²	seriou s ⁴	NA	142	145	HR 0.99 (0.78, 1.26)	Not estimable	low
unstable angina at end of follow up Mean follow-up: 49.8 month(s)	•			10.		7.0.1			(0.10, 1.20)	. 101 0041114010	10.17

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	RC	not serio	not seriou	not	very seriou		59/378	63/3	RR 0.94	1 fewer per 1000 (6 fewer to 6	
2	Т	us	S	serious	s ⁴	NA	5	799	(0.66, 1.34)	more)	low
unstable angina at end of follow-up Mean follow-up: 75.6 month(s)											
4/ 4 4 4 00401)	RC	not serio	not seriou		very seriou		50	00	HR 0.93		
1 (rosenstock 2019b)	ı	us	S	NA ²	s ⁴	NA	56	60	(0.65, 1.33)	Not estimable	low
hospitalisation for heart failure at end of follow up Mean follow-up: 49.8 month(s)											
2	RC T	not serio us	not seriou s	not serious	seriou s ¹	NA	94/378 5	115/ 3799	RR 0.82 (0.63, 1.07)	5 fewer per 1000 (11 fewer to 2 more)	mod erat e
hospitalisation for heart failure at end of follow-up Mean follow-up: 75.6 month(s)											
1 (rosenstock 2019b)	RC T	not serio us	not seriou s	NA ²	seriou s ¹	NA	92	112	HR 0.83 (0.63, 1.09)	Not estimable	mod erat e
falls requiring hospitalisation at end of follow up Mean follow-up: 24 month(s)											
1 (gallwitz 2012a)	RC T	not serio us	not seriou s	NA ²	very seriou s ⁴	NA	2/775	3/77 6	RR 0.67 (0.11, 3.98)	1 fewer per 1000 (3 fewer to 12 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 49.8 month(s)											
2	RC T	not serio us	not seriou s	very serious	not seriou s	NA	1412/3 785	378/ 3799	RR 4.05 (3.00, 5.45)	303 more per 1000 (199 more to 443 more)	low

hypoglycaemia episodes at end of follow											
up Mean follow-up: 75.6 month(s)											
1 (rosenstock 2019b)	RC T	not serio us	not seriou s	NA ²	not seriou s	NA	3010	3023	HR 4.35 (3.85, 4.91)	Not estimable	high
severe hypoglycaemic episodes at end of follow up Mean follow-up: 49.8 month(s)											
2	RC T	not serio us	not seriou s	not serious	not seriou s	NA	77/378 5	11/3 799	RR 7.03 (3.74, 13.20)	17 more per 1000 (8 more to 35 more)	high
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 75.6 month(s)											
1 (rosenstock 2019b)	RC T	not serio us	not seriou s	NA ²	not seriou s	NA	3010	3023	HR 5.63 (4.76, 6.67)	Not estimable	high
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 49.8 month(s)											
2	RC T	not serio us	not seriou s	very serious	not seriou s	NA	3765	3787	MD -0.09 (-0.30, 0.11)	MD 0.09 lower (0.30 lower to 0.11 higher)	low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 49.8 month(s)											
2	RC T	not serio us	not seriou	very serious	seriou s ⁶	NA	3786	3798	MD 2.10 (0.96, 3.24)	MD 2.10 higher (0.96 higher to 3.24 higher)	very low

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

2. Only one study so no inconsistency

- 3. I2 between 50% and 75%
- 4. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 5. I2 > 75%
- 6. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

L.1.6.12 Adding glimepiride compared to adding liraglutide

Table 70: Clinical evidence profile: Adding glimepiride compared to adding liraglutide

gg	De	Risk	Indir	Incon	Impr	Other	Interv	Con	Relative		Cer
	sig	of	ectn	sisten	ecisi	consider	entio	trol	effect	Absolute	tain
No of studies	n	bias	ess	су	on	ations	n N	N	(95% CI)	effect	ty
health-related quality of life - subscale mental component (sf36, higher values are better, change scores) at end of follow up Mean follow-up: 24 month(s)											
1 (group 2022)	R CT	very serio us ¹	not serio us	NA ²	not serio us	NA	1222	121 8	MD 0.33 (-0.25, 0.91)	MD 0.33 higher (0.25 lower to 0.91 higher)	low
health-related quality of life - subscale physical component (sf36, higher values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (group 2022)	R CT	very serio us ¹	not serio us	NA ²	not serio us	NA	1222	121 8	MD -0.89 (-1.44, - 0.34)	MD 0.89 lower (1.44 lower to 0.34 lower)	low
all-cause mortality at end of follow up Mean follow-up: 60 month(s)									3.0.)	,	

GRADE tables – Model 5. Type 2 diabetes and higher card	10 4 4 5 6 4 1	Idi Hok								13 more	
			not					27/	RR 1.60	per 1000	
	R	serio	serio		serio		43/12	126	(1.00,	(0 more to	
1 (group 2022)	CT	us ³		NA ²	us ⁴	NA	54	2		34 more)	lovy
1 (group 2022)	<u> </u>	us	us	INA	us	INA	54		2.58)	34 more)	low
all-cause mortality at end of follow up											
Mean follow-up: 60 month(s)			4						LID 4 04		
			not					400	HR 1.61	N1.4	
4 (0000)	R	serio	serio	NIA2	serio	l NIA	4054	126	(1.00,	Not	1
1 (group 2022)	СТ	us ³	us	NA ²	us ⁴	NA	1254	2	2.59)	estimable	low
cardiovascular mortality at end of follow up Mean follow-up: 60 month(s)											
										6 more per	
			not		very				RR 1.78	1000	ver
	R	serio	serio		serio		16/12	9/1	(0.79,	(2 fewer to	у
1 (group 2022)	CT	us ³	us	NA ²	us ⁵	NA	47	251	4.02)	22 more)	low
cardiovascular mortality at end of follow up											
Mean follow-up: 60 month(s)											
·			not		very				HR 1.78		ver
	R	serio	serio		serio			125	(0.79,	Not	у
1 (group 2022)	CT	us ³	us	NA ²	us ⁵	NA	1247	1	4.01)	estimable	low
3-point mace at end of follow up											
Mean follow-up: 60 month(s)											
										9 more per	
			not					48/	RR 1.23	1000	
	R	serio	serio		serio		59/12	125	(0.85,	(6 fewer to	
1 (group 2022)	СТ	us ³	us	NA ²	us ⁴	NA	47	1	1.79)	30 more)	low
3-point mace at end of follow-up											
Mean follow-up: 60 month(s)											
			not						HR 1.24		
	R	serio	serio		serio			125	(0.85,	Not	
1 (group 2022)	СТ	us ³	us	NA ²	us ⁴	NA	1247	1	1.81)	estimable	low
4-point mace at end of follow-up Mean follow-up: 60 month(s)									,		
(*)										11 more	
		very	not					54/	RR 1.25	per 1000	ver
	R	serio	serio		serio		67/12	126	(0.88,	(5 fewer to	y
1 (group 2022)	СТ	us ¹	us	NA ²	us ⁴	NA	54	2	1.77)	33 more)	low
1 (group 2022)	U	us	us	IN/A-	us	INA	34		1.77)	100 HIDIE)	IUW

hospitalisation for heart failure at end of follow up											
Mean follow-up: 60 month(s)	R	serio us ³	not serio	NA ²	serio	NIA	30/12	14/	RR 2.15 (1.15,	13 more per 1000 (2 more to	1
1 (group 2022) hospitalisation for heart failure at end of follow-up Mean follow-up: 60 month(s)	CI	us°	us	INA ²	us ⁴	NA	44	9	4.04)	34 more)	low
1 (group 2022) unstable angina at end of follow up	R CT	serio us³	not serio us	NA ²	serio us ⁴	NA	1254	126 2	HR 2.16 (1.14, 4.09)	Not estimable	low
Mean follow-up: 60 month(s)	R	very	not serio		very		12/12	7/1	RR 1.73 (0.68,	4 more per 1000 (2 fewer to	ver
1 (group 2022) death from renal causes at end of follow up	CT	us ¹	us	NA ²	us ⁵	NA	54	262	4.37)	19 more)	low
Mean follow-up: 24 month(s) 1 (nauck 2009b) hypoglycaemia episodes at end of follow up	R CT	very serio us ¹	not serio us	NA ²	very serio us ⁵	NA	0/242	1/7 24	PETO OR 0.26 (0.00, 24.26)	1 fewer per 1000 (4 fewer to 1 more)	ver y low
Mean follow-up: 42 month(s)	R	very serio us ¹	not serio us	very serio us ⁶	very serio us ⁵	NA	660/1 473	344 /19 57	RR 1.17 (0.32, 4.24)	29 more per 1000 (119 fewer to 569 more)	ver y low
hypoglycaemia episodes at end of follow up Mean follow-up: 60 month(s)	0,	30	30	30			11.0	J.	,		1011
1 (group 2022)	R CT	very serio us ¹	not serio us	NA ²	not serio us	NA	1231	123 3	HR 2.64 (2.32, 3.00)	Not estimable	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 42 month(s)									·		

	R	very serio	not serio	not serio	serio		28/14	13/ 198	RR 2.27 (1.18,	8 more per 1000 (1 more to	ver y
2	CT	us ¹	us	us	us ⁴	NA	96	6	4.37)	22 more)	low
hba1c change (%, lower values are better, change scores and final values) at end of follow up Mean follow-up: 42 month(s)											
2	R CT	very serio us ¹	not serio us	not serio us	not serio us	NA	552	106	MD 0.00 (-0.23, 0.23)	MD 0.00 higher (0.23 lower to 0.23 higher)	low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Only one study so no inconsistency
- 3. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 4. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 5. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 6. 12 > 75%

L.1.6.13 Adding glimepiride compared to adding saxagliptin

Table 71: Clinical evidence profile: Adding glimepiride compared to adding saxagliptin

No of studies	Des ign	Indirec tness	Inconsis tency	Impreci sion	Other consideratio ns	Interven tion N	Relative effect (95% CI)	Absolute effect	Certa inty
all-cause mortality at end of follow up Mean follow-up: 12 month(s)			•				, , ,		

1 (schernthaner 2015a) cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)	RC T	serious	not serious	NA ²	very serious ³	NA	1/359		RR 1.00	0 fewer per 1000 (3 fewer to 42 more)	very low
	RC T	serious	not serious	NA ²	very serious ³	NA	0/359		0.14	3 fewer per 1000 (8 fewer to 3 more)	very low
non-fatal myocardial infaRCTion at end of follow up Mean follow-up: 11 month(s)											
1 (gu 2019)	RC T		not serious	NA ²	very serious ³	NA	1/188		7.51	5 more per 1000 (5 fewer to 16 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 11.5 month(s)										000	
2	RC T	serious	not serious	not serious	not serious	NA	l 	27/55 0	RR 5.54	`	mode rate
severe hypoglycaemic episodes at end of follow up Mean follow-up: 11 month(s)											

Of the Education in the Education and ingride										
1 (gu 2019)			not serious	NA ²	very serious ³	NA	1/188	RR 1.02	0 more per 1000 (5 fewer to 79 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 11 month(s)										
			not serious		not serious	NA	187		MD 0.06 lower (0.23 lower to 0.11 higher)	high
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 11.5 month(s)										
2	RC T	serious	not serious	not serious	not serious	NA	472	MD 1.70 (1.32, 2.08)	MD 1.70 higher (1.32 higher to 2.08 higher)	mode rate

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

L.1.6.14 Adding glimepiride compared to adding sitagliptin

Table 72: Clinical evidence profile: Adding glimepiride compared to adding sitagliptin

Table 121 Chillian Citation Control 1 talaning S						9					
	De		Indire	Incons		Other	Interve	Cont	Relative		Cert
	sig	Risk of	ctnes	istenc	Impre	considera	ntion	rol	effect (95%	Absolute	aint
No of studies	n	bias	S	у	cision	tions	N	N	CI)	effect	У

all-cause mortality at end of follow up	J. 001										
Mean follow-up: 33.5 month(s)	RC T	seriou s ¹	not seriou	seriou s ²	very seriou s ³	NA	44/177	41/1 781	RR 1.08 (0.71, 1.64)	2 more per 1000 (7 fewer to 15 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 33.5 month(s)										,	
2	RC T	seriou s ¹	not seriou s	seriou s ²	very seriou s ³	NA	17/176 3	21/1 778	RR 0.82 (0.44, 1.54)	2 fewer per 1000 (7 fewer to 6 more)	very low
3-point mace at end of follow up Mean follow-up: 60 month(s)											
1 (group 2022)	RC T	seriou s¹	not seriou s	NA ⁴	seriou s ⁵	NA	59/124 4	69/1 262	RR 0.87 (0.62, 1.22)	7 fewer per 1000 (21 fewer to 12 more)	low
non-fatal stroke at end of follow up Mean follow-up: 5.5 month(s)											
1 (xiao 2016)	RC T	very seriou s ⁶	not seriou s	NA ⁴	very seriou s ⁷	NA	0/18	0/23	RD 0.00 (-0.09, 0.09)	0 fewer per 1000 (92 fewer to 92 more)	very low
non-fatal myocardial infarction at end of follow up Mean follow-up: 5.5 month(s)											
1 (xiao 2016)	RC T	very seriou s ⁶	not seriou s	NA ⁴	very seriou s ⁷	NA	0/18	0/23	RD 0.00 (-0.09, 0.09)	0 fewer per 1000 (92 fewer to 92 more)	very low
hospitalisation for heart failure at end of follow up Mean follow-up: 32.8 month(s)											
2	RC T	seriou s ¹	not seriou s	seriou s²	very seriou s ⁸	NA	30/126 2	30/1 285	RD 0.00 (-0.01, 0.01)	0 more per 1000	very low

GNADE tables – Model 3. Type 2 diabetes and high	01 001	10 (4004)	ar riott							(12 fewer to	
										12 more)	
hypoglycaemia episodes at end of follow up Mean follow-up: 12.2 month(s)											
3	RC T	not seriou s	not seriou s	seriou s ⁹	not seriou s	NA	146/82 4	43/1 031	RR 4.17 (1.73, 10.03)	132 more per 1000 (30 more to 377 more)	mod erat e
severe hypoglycaemic episodes at end of follow up Mean follow-up: 24.1 month(s)											
4	RC T	very seriou s ⁶	not seriou s	seriou s ²	not seriou s	NA	39/228 5	11/2 299	RR 3.12 (1.59, 6.11)	10 more per 1000 (3 more to 24 more)	very low
hba1c change (%, lower values are better, change scores and final values) at end of follow up Mean follow-up: 6 month(s)											
3	RC T	very seriou s ⁶	not seriou s	very seriou s ¹⁰	seriou s ¹¹	NA	732	745	MD 0.18 (-0.17, 0.53)	MD 0.18 higher (0.17 lower to 0.53 higher)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)									,	y /	
3	RC T	very seriou s ⁶	not seriou s	very seriou s ¹⁰	seriou s ¹²	NA	739	752	MD 1.52 (0.48, 2.56)	MD 1.52 higher (0.48 higher to 2.56 higher)	very low
bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)										,	

										MD 0.39	
										higher	
		very	not		not					(0.15 higher	
	RC	seriou	seriou		seriou				MD 0.39	to 0.63	
1 (kesavadev 2017)	T	s 6	S	NA ⁴	S	NA	205	213	(0.15, 0.63)	higher)	low

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. Only one study so no inconsistency
- 5. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 6. >33.3% of the studies in the meta-analysis were at high risk of bias
- 7. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 8. 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).
- 9. I2 between 50% and 75%
- 10. I2 > 75%
- 11. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 12. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

adding vildagliptin

Table 73: Clinical evidence profile: Adding glimepiride compared to adding vildagliptin

Table 73: Clinical evidence profile: Adding g	De	Risk	Indire	Incons	ling viia	Other	Interve	Cont	Relative		Cert
	sig	of	ctnes	istenc	Impre	considera	ntion	rol	effect (95%	Absolute	aint
No of studies	n	bias	s	У	cision	tions	N	N	CI)	effect	У
all-cause mortality at end of follow up Mean follow-up: 9 month(s)											
2	RC T	seriou s ¹	not seriou s	not seriou s	very seriou s ²	NA	9/2929	9/29 42	RR 1.00 (0.40, 2.53)	0 more per 1000 (2 fewer to 5 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)											
1 (ferrannini 2009) cardiac arrhythmia at end of follow up	RC T	very seriou s ³	not seriou s	NA ⁴	very seriou s ²	NA	1/1383	2/13 89	RR 0.50 (0.05, 5.53)	1 fewer per 1000 (1 fewer to 7 more)	very low
Mean follow-up: 12 month(s)											
1 (ferrannini 2009)	RC T	very seriou s ³	not seriou s	NA ⁴	very seriou s ²	NA	5/1383	3/13 89	RR 1.67 (0.40, 6.99)	1 more per 1000 (1 fewer to 13 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 9 month(s)											
2	RC T	seriou s ¹	not seriou s	not seriou s	not seriou s	NA	505/29 29	58/2 942	RR 8.75 (6.70, 11.42)	153 more per 1000 (112 more to 205 more)	mod erat e
severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.8 month(s)											
2	RC T	seriou s ¹	not seriou s	seriou s ⁵	not seriou s	NA	15/156 8	0/15 75	RD 0.01 (0.00, 0.01)	10 more per 1000	low

										// 22222 12	
										(4 more to 15 more)	
hba1c change (%, lower values are better, change values and final scores) at end of follow up Mean follow-up: 11.9 month(s)											
4	RC T	very seriou s ³	not seriou s	not seriou s	not seriou s	NA	2720	278 5	MD -0.13 (-0.21, - 0.05)	MD 0.13 lower (0.21 lower to 0.05 lower)	low
weight change (kg, lower values are better, change scores and final values) at end of follow up Mean follow-up: 11.8 month(s)											
3	RC T	very seriou s ³	not seriou s	not seriou s	not seriou s	NA	1648	166 7	MD 1.50 (1.23, 1.78)	MD 1.50 higher (1.23 higher to 1.78 higher)	low
bmi change (kg/m2, lower values are better, final values) at end of follow up Mean follow-up: 6 month(s)										,	
1 (derosa 2014a)	RC T	very seriou s ³	not seriou s	NA ⁴	seriou s ⁶	NA	70	83	MD 0.60 (0.13, 1.07)	MD 0.60 higher (0.13 higher to 1.07 higher)	very low

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

end of the defined MIDs (-0.80, 0.80)

L.1.6.16 Adding glipizide compared to adding placebo

Table 74: Clinical evidence profile: Adding glipizide compared to adding placebo

Table 74: Clinical evidence profile: Add	umg ç	Jiipiziae	compar	eu to au	ung pia	ceno					
	De					Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow up											
Mean follow-up: 6 month(s)											
1 (wilding 2013b)	RC T	seriou s ¹	not seriou s	NA ²	seriou s ³	NA	0/93	0/87	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (22 fewer to 22 more)	low
cardiovascular mortality at end of										,	
follow up											
Mean follow-up: 6 month(s)											
1 (wilding 2013b)	RC T	seriou s¹	not seriou s	NA ²	seriou s³	NA	0/93	0/87	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (22 fewer to 22 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 6 month(s)											
1 (wilding 2013b)	RC T	seriou s¹	not seriou s	NA ²	not seriou s	NA	6/93	0/87	PETO OR 7.32 (1.44, 37.16)	65 more per 1000 (15 more to 115 more)	mod erate
severe hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)											
1 (wilding 2013b)	RC T	seriou s ¹	not seriou s	NA ²	seriou s ⁴	NA	1/93	1/87	RR 0.94 (0.06, 14.73)	1 fewer per 1000	low

										(11 fewer to 158 more)	
hba1c change (%, lower values are better, final values) at end of follow up Mean follow-up: 36 month(s)											
1 (camerini-davalos 1994)	RC	very seriou	not seriou	NA ²	seriou s ⁴	NA	34	27	MD -0.90 (-1.78, - 0.02)	MD 0.90 lower (1.78 lower to 0.02 lower)	Very low

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. Only one study so no inconsistency
- 3. 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)
- 5. >33.3% of the studies in the meta-analysis were at high risk of bias

L.1.6.17 Adding glipizide compared to adding metformin

Table 75: Clinical evidence profile: Adding glipizide compared to adding metformin

·	De		•			Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
hba1c change (%, lower values are better, change scores) at end of follow up											
Mean follow-up: 12 month(s)											
4 (11 11 1 0007)	RC	very seriou	not seriou	1142	seriou		45	00	MD 0.50	MD 0.50 higher (0.34 lower to	very
1 (vähätalo 2007)	T	S ¹	S	NA ²	s^3	NA	15	26	(-0.34, 1.34)	1.34 higher)	low

GRADE tables – Model 5: Type 2 diabetes and higher cardiovascular risk

weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
										MD 1.30	
		very	not							higher	
	RC	seriou	seriou		seriou				MD 1.30	(1.35 lower to	very
1 (vähätalo 2007)	Т	s ¹	s	NA ²	s ⁴	NA	15	26	(-1.35, 3.95)	3.95 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 one end of the defined MIDs (-2.40, 2.40)

L.1.6.18 Adding glipizide compared to adding alogliptin

Table 76: Clinical evidence profile: Adding glipizide compared to adding alogliptin

	De					Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No. of an aller	_				•				•		
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	У
all-cause mortality at end of follow up											
Mean follow-up: 24 month(s)											
										2 more per	
		very	not		very					1000	
	RC	seriou	seriou		seriou			6/17	RR 1.68	(2 fewer to 15	very
1 (del prato 2014)	Т	s ¹	S	NA^2	s^3	NA	5/869	51	(0.51, 5.49)	more)	low
cardiovascular mortality at end of follow									,	•	
up											
Mean follow-up: 24 month(s)											
		very	not		very						
	RC	seriou	seriou		seriou			4/17	RR 2.01	2 more per	very
1 (del prato 2014)	Т	s ¹	s	NA^2	s^3	NA	4/869	51	(0.51, 8.04)	1000	low

The tables Medero. Type 2 diabetes and										(1 fewer to 16 more)	
3-point mace at end of follow up Mean follow-up: 24 month(s)											
1 (del prato 2014)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	11/869	14/1 751	RR 1.58 (0.72, 3.47)	5 more per 1000 (2 fewer to 20 more)	very low
non-fatal stroke at end of follow up Mean follow-up: 24 month(s)											
1 (del prato 2014)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	3/869	5/17 51	RR 1.21 (0.29, 5.05)	1 more per 1000 (2 fewer to 12 more)	very low
non-fatal myocardial infaRCTion at end of follow up Mean follow-up: 24 month(s)											
1 (del prato 2014)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	4/869	5/17 51	RR 1.61 (0.43, 5.99)	2 more per 1000 (2 fewer to 14 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 24 month(s)											
1 (del prato 2014)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	202/86 9	34/1 751	RR 11.97 (8.40, 17.06)	213 more per 1000 (144 more to 312 more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 24 month(s)											
1 (del prato 2014)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s ⁴	NA	5/869	1/17 51	RR 10.07 (1.18, 86.10)	5 more per 1000 (0 more to 49 more)	very low

very not RC seriou seriou t seriou se	ı NA²	not seriou	NA	336	753	MD 0.11 (0.02, 0.20)	MD 0.11 higher (0.02 higher to 0.20 higher)	low

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

L.1.6.19 Adding glipizide compared to adding dapagliflozin

Table 77: Clinical evidence profile: Adding glipizide compared to adding dapagliflozin

	De	Risk	•			Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ions	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow up											
Mean follow-up: 48 month(s)											
	RC	very seriou	not seriou		very seriou			2/40	RR 2.49 (0.49,	7 more per 1000 (3 fewer to 58	very
1 (nauck 2011)	Т	s ¹	s	NA ²	s ³	NA	5/408	6	12.75)	more)	low
hypoglycaemia episodes at end of follow											
up											
Mean follow-up: 12 month(s)											

1 (nauck 2011)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	147/40 8	7/40 6	RR 20.90 (9.91, 44.05)	343 more per 1000 (154 more to 742 more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											
1 (nauck 2011)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	3/408	0/40 6	PETO OR 7.39 (0.77, 71.24)	7 more per 1000 (1 fewer to 16 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 48 month(s)											
1 (nauck 2011)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s ⁴	NA	401	400	MD 0.30 (0.08, 0.52)	MD 0.30 higher (0.08 higher to 0.52 higher)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 48 month(s)											
1 (nauck 2011)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	401	400	MD 4.38 (3.45, 5.31)	MD 4.38 higher (3.45 higher to 5.31 higher)	low

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

L.1.6.20 Adding glipizide compared to adding saxagliptin

Table 78: Clinical evidence profile: Adding glipizide compared to adding saxagliptin

Table 78: Clinical evidence profile: Addi		ipiziae c	compare	ed to add	ing sax						
	De					Other			Relative		Cert
	sig	Risk	Indire	Inconsi	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	of bias	ctness	stency	cision	ions	ntion N	rol N	CI)	effect	У
all-cause mortality at end of follow up											
Mean follow-up: 24 month(s)											
										5 fewer per	
		very	not .		not			4/40		1000	
4 (~= 100 0040)	RC	seriou	seriou	NIA2	seriou	NIA .	2/420	4/42	RD -0.00	(16 fewer to 6	lave
1 (göke 2010)	ı	s ¹	S	NA ²	S	NA	2/430	8	(-0.02, 0.01)	more)	low
cardiovascular mortality at end of follow											
up Mean follow-up: 24 month(s)											
wear follow-up. 24 month(s)										2 more per	
		very	not		not					1000	
	RC	seriou	seriou		seriou			1/42	RD 0.00	(6 fewer to 10	
1 (göke 2010)	Т	s ¹	s	NA ²	s	NA	2/430	8	(-0.01, 0.01)	more)	low
hypoglycaemia episodes at end of follow									,	,	
up											
Mean follow-up: 24 month(s)											
									PETO OR	91 more per	
		very	not		not				8.07	1000	
4 (" 00 40)	RC	seriou	seriou		seriou		00/400	0/42	(4.25,	(64 more to	
1 (göke 2010)	Т	s ¹	S	NA ²	S	NA	39/430	8	15.33)	118 more)	low
hba1c change (%, lower values are											
better, change scores) at end of follow											
up Mean follow-up: 24 month(s)											
Mean follow-up. 24 month(s)										MD 0.06	
		very	not		not					higher	
	RC	seriou	seriou		seriou				MD 0.06	(0.05 lower to	
1 (göke 2010)	T	s ¹	S	NA ²	S	NA	423	423	(-0.05, 0.17)	0.17 higher)	low

weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 24 month(s)											
	RC	very seriou	not seriou		seriou				MD 2.80	MD 2.80 higher (2.25 higher to 3.35	very
1 (göke 2010)	T	s ¹	S	NA^2	s^3	NA	426	424	(2.25, 3.35)	higher)	low

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

L.1.6.21 Adding glipizide compared to adding sitagliptin

Table 79: Clinical evidence profile: Adding glipizide compared to adding sitagliptin

Table 10. Ollinodi ovidence promo: Add	De	Risk				Other			Relative		Cert
	_	_	1 12	•	•					Alexal II	
	sig	of	Indire	Inconsi	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ions	ntion N	rol N	CI)	effect	У
all-cause mortality at end of follow up											
Mean follow-up: 24 month(s)											
										12 more per	
		very	not						RR 8.05	1000	
	RC	seriou	seriou		seriou			1/58	(1.01,	(0 more to	very
1 (nauck 2007b)	T	s ¹	s	NA^2	s ³	NA	8/584	8	64.20)	107 more)	low
cardiovascular mortality at end of follow											
up											
Mean follow-up: 24 month(s)											
									PETO OR	5 more per	
		very	not		very				7.47	1000	
	RC	seriou	seriou		seriou			0/58	(0.78,	(1 fewer to 11	very
1 (nauck 2007b)	Т	s ¹	s	NA^2	s ⁴	NA	3/584	8	71.91)	more)	low

hypoglycaemia episodes at end of follow											
up Mean follow-up: 24 month(s)											
1 (nauck 2007b)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	448/58 4	31/5 88	RR 14.55 (10.30, 20.56)	714 more per 1000 (490 more to 1031 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 24 month(s)											
1 (nauck 2007b)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	584	588	HR 20.00 (11.11, 33.33)	Not estimable	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 24 month(s)											
1 (nauck 2007b)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	22/584	2/58 8	RR 11.08 (2.62, 46.89)	34 more per 1000 (5 more to 156 more)	low
severe hypoglycaemia episodes at end of follow-up Mean follow-up: 24 month(s)											
1 (nauck 2007b)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	584	588	HR 12.50 (2.13, 100)	Not estimable	low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 24 month(s)											
1 (nauck 2007b)	RC T	very seriou s ¹	not seriou	NA ²	not seriou s	NA	559	576	MD -0.02 (-0.14, 0.10)	MD 0.02 lower (0.14 lower to 0.10 higher)	low
weight change (kg, lower values are better, change scores) at end of follow up								0.0	(3111, 3110)	51.70 mg.151)	7511

GRADE tables - Model 5: Type 2 diabetes and higher cardiovascular risk

Mean follow-up: 24 month(s)											
										MD 2.30	
										higher	
		very	not							(1.38 higher	
	RC	seriou	seriou		seriou				MD 2.30	to 3.22	very
1 (nauck 2007b)	T	s ¹	S	NA ²	s ⁵	NA	559	576	(1.38, 3.22)	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. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

L.1.7 Thiazolidinediones

L.1.7.1 Adding pioglitazone compared to adding placebo

Table 80: Clinical evidence profile: Adding pioglitazone compared to adding placebo

	De	Risk	Indire	Incons		Other	Interv	Con	Relative		Cert
	sig	of	ctnes	istenc	Impre	considera	ention	trol	effect (95%	Absolute	aint
No of studies	n	bias	S	у	cision	tions	N	N	CI)	effect	У
all-cause mortality at end of follow up Mean follow-up: 7 month(s)											
		very	not		very				RD -0.00		
	RC	seriou	seriou	seriou	seriou			6/11	(-0.01,	2 fewer per	very
6	Т	s ¹	S	s^2	s^3	NA	5/1168	66	0.00)	1000	low

GRADE tables – Model 5: Type 2 diabetes and high	or care	Jiovascu	iai iisk							(8 fewer to 5	
										more)	
cardiovascular mortality at end of follow up										more)	
Mean follow-up: 6 month(s)											
4	RC T	very seriou s ¹	not seriou s	seriou s²	very seriou s ⁴	NA	1/749	1/90	RD 0.00 (-0.01, 0.01)	0 more per 1000 (6 fewer to 6 more)	very low
3-point mace at end of follow up Mean follow-up: 8.7 month(s)											
2	RC T	very seriou s ¹	not seriou s	seriou s ⁵	seriou s ⁶	NA	45/619	15/6 56	RR 1.36 (0.38, 4.88)	8 more per 1000 (14 fewer to 89 more)	very low
non-fatal stroke at end of follow up Mean follow-up: 5.4 month(s)											
1 (punthakee 2012)	RC T	very seriou s ¹	not seriou s	NA ⁷	very seriou s ⁸	NA	2/392	2/54 1	PETO OR 1.39 (0.19, 10.15)	1 more per 1000 (7 fewer to 10 more)	very low
non-fatal myocardial infarction at end of follow up Mean follow-up: 5.7 month(s)									ŕ		
2	RC T	seriou s ⁹	not seriou s	seriou s ²	very seriou s ⁸	NA	5/494	7/64 7	RR 0.81 (0.27, 2.42)	2 fewer per 1000 (8 fewer to 15 more)	very low
hospitalisation for heart failure at end of follow up Mean follow-up: 6.2 month(s)											
2	RC T	very seriou s ¹	not seriou s	seriou s ²	very seriou s ¹⁰	NA	2/537	1/69 5	RD 0.00 (-0.00, 0.01)	2 more per 1000 (4 fewer to 9 more)	very low
persistent signs of worsening kidney disease at end of follow up Mean follow-up: 5.4 month(s)											

GRADE tables – Model 5: Type 2 diabetes and high	ei car	ulovascu	ai 115K					1		1	1
1 (punthakee 2012)	RC T	very seriou s ¹	not seriou s	NA ⁷	seriou s ⁶	NA	8/392	20/5 41	RR 0.55 (0.25, 1.24)	17 fewer per 1000 (28 fewer to 9 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 7.3 month(s)											
7	RC T	very seriou s ¹	not seriou s	very seriou s ¹¹	seriou s ⁶	NA	232/74	107/ 598	RR 2.10 (1.12, 3.95)	198 more per 1000 (21 more to 529 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 8.7 month(s)											
2	RC T	very seriou s ¹	not seriou s	not seriou s	seriou s ⁶	NA	5/669	0/65	PETO OR 6.33 (0.98, 40.83)	7 more per 1000 (1 more to 14 more)	very low
hba1c change (%, lower values are better, change scores and final values) at end of follow up Mean follow-up: 7.2 month(s)											
12	RC T	very seriou s ¹	not seriou s	very seriou s ¹¹	seriou s ¹²	NA	1384	137	MD -0.70 (-0.91, - 0.48)	MD 0.70 lower (0.91 lower to 0.48 lower)	very low
weight change (kg, lower values are better, change scores and final values) at end of follow up Mean follow-up: 7.2 month(s)											
9	RC T	very seriou s ¹	not seriou s	seriou s ⁵	not seriou s	NA	1149	123 0	MD 3.55 (2.54, 4.55)	MD 3.55 higher (2.54 higher to 4.55 higher)	very low
bmi change (kg/m2, lower values are better, final values) at end of follow up Mean follow-up: 5.8 month(s)											

									MD 1.03	
									higher	
	very	not	not						(0.42 higher	
RC	seriou	seriou	seriou	seriou				MD 1.03	to 1.65	very
4 T	s ¹	s	S	s ¹³	NA	538	678	(0.42, 1.65)	higher)	low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 3. 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).
- 4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.04 (0.8-0.9 = serious, <0.8 = very serious).
- 5. I2 between 50% and 75%
- 6. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 7. Only one study so no inconsistency
- 8. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 9. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 10. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.2 (0.8-0.9 = serious, <0.8 = very serious).
- 11. I2 > 75%
- 12. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 13. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

adding metformin

Table 81: Clinical evidence profile: Adding pioglitazone compared to adding metformin

rable of Chilical evidence profile. Adding pr	De	Risk	Indire	Incons	<u>gc</u>	Other	Interve	Cont	Relative		Cert
	sig	of	ctnes	istenc	Impre	considera	ntion	rol	effect (95%	Absolute	aint
No of studies	n	bias	s	v	cision	tions	N	N	CI)	effect	y
all-cause mortality at end of follow up Mean follow-up: 12 month(s)				,							
2	RC T	very seriou s ¹	not seriou s	seriou s²	very seriou s³	NA	1/351	3/35 1	PETO OR 0.36 (0.05, 2.60)	6 fewer per 1000 (17 fewer to 5 more)	very low
unstable angina at end of follow up Mean follow-up: 12 month(s)											
1 (morikawa 2011)	RC T	very seriou s ¹	not seriou s	NA ⁴	very seriou s ³	NA	1/32	0/31	PETO OR 7.16 (0.14, 361.11)	31 more per 1000 (29 fewer to 92 more)	very low
hospitalisation for heart failure at end of follow up Mean follow-up: 5.5 month(s)											
1 (van der meer 2009)	RC T	very seriou s ¹	not seriou s	NA ⁴	seriou s ⁵	NA	0/39	0/39	RD 0.00 (-0.05, 0.05)	0 fewer per 1000 (49 fewer to 49 more)	very low
persistent signs of worsening kidney disease at end of follow up Mean follow-up: 12 month(s)											
1 (morikawa 2011)	RC T	very seriou s ¹	not seriou s	NA ⁴	very seriou s ³	NA	2/32	6/31	RR 0.32 (0.07, 1.48)	131 fewer per 1000 (180 fewer to 93 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 15 month(s)											

TVADE tables Woder 9. Type 2 diabetes and highe			ai non							40 fewer per	
		very	not	not						1000	
	RC	seriou	seriou	seriou	seriou			59/3	RR 0.75	(77 fewer to	very
2	<u>T</u>	s ¹	S	S	s ⁶	NA	44/359	62	(0.53, 1.08)	13 more)	low
severe hypoglycaemic episodes at end of											
follow up Mean follow-up: 12 month(s)											
mean follow up: 12 month(5)										0 fewer per	
		very	not		not				RD 0.00	1000	
	RC	seriou	seriou		seriou			0/32	(-0.01,	(6 fewer to 6	
1 (hanefeld 2004)	<u>T</u>	s ¹	S	NA ⁴	S	NA	0/319	0	0.01)	more)	low
hba1c change (%, lower values are better, change scores and final values) at end of											
follow up											
Mean follow-up: 11 month(s)											
										MD 0.10	
										higher	
	D0	very	not	not	not				MD 0.10	(0.02 lower	
7	RC T	seriou s ¹	seriou s	seriou s	seriou s	NA	525	525	(-0.02, 0.22)	to 0.22 higher)	low
weight change (kg, lower values are better,	•	3	3	3	3	INA	323	323	0.22)	riigriei)	IOVV
change scores and final values) at end of											
follow up											
Mean follow-up: 9.8 month(s)											
										MD 2.47	
		verv	not	not					MD 2.47	higher (0.96 lower	
	RC	seriou	seriou	seriou	seriou				(-0.96,	to 5.89	very
3	Т	s ¹	s	s	s ⁷	NA	377	382	5.89)	higher)	low
bmi change (kg/m2, lower values are better,											
final values) at end of follow up											
Mean follow-up: 9.8 month(s)										MD 0.80	
										higher	
		verv	not	very	very				MD 0.80	(1.56 lower	
	RC	seriou	seriou	seriou	seriou				(-1.56,	to 3.17	very
3	Т	s ¹	S	s ⁸	s ⁹	NA	150	103	3.17)	higher)	low

analysis were at high risk of bias

- 2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. Only one study so no inconsistency
- 5. 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 (0.80, 1.25)
- 7. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)
- 8. 12 > 75%
- 9. 95% confidence intervals cross both ends of the defined MIDs (-0.80, 0.80)

L.1.7.3 Adding pioglitazone compared to adding insulin

Table 82: Clinical evidence profile: Adding pioglitazone compared to adding insulin

	De	Risk	Indire	Incons		Other	Interve	Cont	Relative		Cert
	sig	of	ctnes	istenc	Impre	considera	ntion	rol	effect (95%	Absolute	aint
No of studies	n	bias	S	У	cision	tions	N	N	CI)	effect	У
hypoglycaemia episodes at end of follow up Mean follow-up: 8.2 month(s)											
2	RC T	very seriou s ¹	not seriou	not seriou	seriou s ²	NA	7/140	14/1 34	RR 0.47 (0.24, 0.93)	56 fewer per 1000 (80 fewer to 7 fewer)	very
severe hypoglycaemic episodes at end of follow up Mean follow-up: 8.2 month(s)									(6.2.1, 6.66)		
2	RC T	very seriou s ¹	not seriou s	seriou s³	very seriou s ⁴	NA	1/140	4/13 4	RD -0.02 (-0.06, 0.01)	23 fewer per 1000 (58 fewer to 12 more)	very low

hba1c change (%, lower values are better, change scores and final values) at end of follow up Mean follow-up: 7.5 month(s)											
3	RC T	very seriou s ¹	not seriou s	not seriou s	seriou s ⁵	NA	155	149	MD 0.57 (0.32, 0.81)	MD 0.57 higher (0.32 higher to 0.81 higher)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
1 (hartemann-heurtier 2009)	RC T	very seriou s ¹	not seriou s	NA ⁶	seriou	NA	14	13	MD 1.30 (-0.75, 3.35)	MD 1.30 higher (0.75 lower to 3.35 higher)	very low
bmi change (kg/m2, lower values are better, final values) at end of follow up Mean follow-up: 6 month(s)									,	y ,	
1 (dorkhan 2009)	RC T	very seriou s ¹	not seriou s	NA ⁶	very seriou s ⁸	NA	15	15	MD -0.60 (-4.93, 3.73)	MD 0.60 lower (4.93 lower to 3.73 higher)	very low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 3. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.51 (0.8-0.9 = serious, <0.8 = very serious).
- 5. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 6. Only one study so no inconsistency

end of the defined MIDs (-2.40, 2.40)

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

L.1.7.4 Adding pioglitazone compared to adding dapagliflozin

Table 83: Clinical evidence profile: Adding pioglitazone compared to adding dapagliflozin

Table 03. Chilical evidence profile. Add	De			iparca te	daanig				Polotivo		Cort
		Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	У
hypoglycaemia episodes at end of follow											
up											
Mean follow-up: 6.5 month(s)											
										0 fewer per	
		not	not		very					1000	
	RC	serio	seriou		seriou				RD 0.00	(57 fewer to	
1 (kinoshita 2020)	Т	us	S	NA ¹	s ²	NA	0/33	0/33	(-0.06, 0.06)	57 more)	low
hba1c change (%, lower values are											
better, change scores) at end of follow											
up											
Mean follow-up: 6.5 month(s)											
										MD 0.04	
		not	not		not					higher	
	RC	serio	seriou		seriou				MD 0.04	(0.38 lower to	
1 (kinoshita 2020)	T	us	S	NA ¹	S	NA	33	32	(-0.38, 0.46)	0.46 higher)	high
weight change (kg, lower values are											
better, change scores) at end of follow											
up											
Mean follow-up: 6.5 month(s)											
		not	not		not						
	RC	serio	seriou		seriou				MD 5.30	MD 5.30	
1 (kinoshita 2020)	T	us	S	NA ¹	S	NA	33	32	(4.32, 6.28)	higher	high

 			_		
				(4.32 higher	
				to 6.28	
				higher)	

- 1. Only one study so no inconsistency
- 2. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.

L.1.7.5 Adding pioglitazone compared to adding empagliflozin

Figure 1: Clinical evidence profile: Adding pioglitazone compared to adding empagliflozin

gare is a second process of the second proce					<u>g</u>						
	De	Risk	Indire	Incons		Other	Interve	Cont	Relative		Cert
	sig	of	ctnes	istenc	Impre	considera	ntion	rol	effect (95%	Absolute	aint
No of studies	n	bias	S	У	cision	tions	N	N	CI)	effect	У
non-fatal stroke at end of follow up Mean follow-up: 5.5 month(s)											
1 (attaran 2023)	RC T	serio us ¹	not seriou s	NA 2	very seriou s ³	NA	0/36	1/37	PETO OR 0.14 (0.00, 7.01)	27 fewer per 1000 (79 fewer to 25 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 5.5 month(s)											
2	RC T	serio us¹	not seriou	seriou s ⁴	very seriou s ⁵	NA	2/91	0/95	RD 0.02 (-0.05, 0.08)	18 more per 1000 (47 fewer to 83 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.5 month(s)											
2	RC T	serio us¹	not seriou	not seriou s	seriou s ⁶	NA	0/91	0/95	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (30 fewer to 30 more)	low

hba1c change (%, lower values are better, change scores and final values) at end of follow up Mean follow-up: 5.5 month(s)											
2	RC T	serio us ¹	not seriou s	not seriou s	not seriou s	NA	91	95	MD 0.07 (-0.20, 0.35)	MD 0.07 higher (0.20 lower to 0.35 higher)	mod erat e
bmi change (kg/m2, lower values are better, change scores and final values) at end of follow up Mean follow-up: 5.5 month(s)											
2	RC T	serio	not seriou s	not seriou s	not seriou s	NA	91	95	MD 1.73 (1.32, 2.14)	MD 1.73 higher (1.32 higher to 2.14 higher)	mod erat e

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. Only one study so no inconsistency
- 3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 4. 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 = 0.53 (0.8-0.9 = serious, <0.8 = very serious).
- 6. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.

L.1.7.6

adding exenatide

Table 84: Clinical evidence profile: Adding pioglitazone compared to adding exenatide

	De	Risk	Indir	Incons		Other	Interv	Con	Relative		Cert
	sig	of	ectne	istenc	Impre	considera	ention	trol	effect	Absolute	aint
No of studies	n	bias	SS	у	cision	tions	N	N	(95% CI)	effect	у
health-related quality of life - overall (eq-5d, higher values better, change scores) at end of follow-up Mean follow-up: 6 month(s)											
1 (bergenstal 2010)	RC T	very seriou s ¹	not serio us	NA ²	very seriou s ³	NA	130	129	MD -0.02 (-0.08, 0.04)	MD 0.02 lower (0.08 lower to 0.04 higher)	very low
all-cause mortality at end of follow up Mean follow-up: 6 month(s)											
1 (bergenstal 2010)	RC T	very seriou s ¹	not serio us	NA ²	seriou s ⁴	NA	0/165	0/16 0	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 6 month(s)											
1 (bergenstal 2010)	RC T	very seriou s ¹	not serio us	NA ²	seriou s ⁴	NA	0/165	0/16	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	very low
unstable angina at end of follow up Mean follow-up: 6 month(s)											
1 (bergenstal 2010)	RC T	very seriou s ¹	not serio us	NA ²	very seriou s ⁵	NA	1/165	0/16 0	PETO OR 7.17 (0.14, 361.44)	6 more per 1000 (6 fewer to 18 more)	very low
acute kidney injury at end of follow up Mean follow-up: 6 month(s)									,	,	

	RC	very seriou	not serio		very seriou			0/16	PETO OR 7.17 (0.14,	6 more per 1000 (6 fewer to	very
1 (bergenstal 2010)	Τ	s ¹	us	NA ²	s ⁵	NA	1/165	0	361.44)	18 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 6 month(s)											
1 (bergenstal 2010)	RC T	very seriou s ¹	not serio us	NA ²	very seriou s ⁵	NA	1/165	2/16 0	PETO OR 0.50 (0.05, 4.80)	6 fewer per 1000 (27 fewer to 14 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)											
1 (bergenstal 2010)	RC T	very seriou s ¹	not serio us	NA ²	seriou s ⁴	NA	0/165	0/16 0	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)											
1 (bergenstal 2010)	RC T	seriou s ⁶	not serio us	NA ²	seriou s ⁷	NA	165	160	MD 0.30 (0.05, 0.55)	MD 0.30 higher (0.05 higher to 0.55 higher)	low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)											
1 (bergenstal 2010)	RC T	seriou s ⁶	not serio us	NA ²	not seriou s	NA	165	160	MD 5.10 (4.26, 5.94)	MD 5.10 higher (4.26 higher to 5.94 higher)	mod erat e

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

ends of the defined MIDs (-0.03, 0.03)

- 4. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 5. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 6. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 7. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

L.1.7.7 Adding pioglitazone compared to adding gliclazide

Table 85: Clinical evidence profile: Adding pioglitazone compared to adding gliclazide

Table 60: Gilliear evidence prome. Add	De					Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	y
all-cause mortality at end of follow up Mean follow-up: 12 month(s)											
1 (matthews 2005)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	0/317	2/31 3	PETO OR 0.13 (0.01, 2.13)	6 fewer per 1000 (15 fewer to 2 more)	very low
non-fatal myocardial infaRCTion at end of follow up Mean follow-up: 12 month(s)										,	
1 (matthews 2005)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	1/317	0/31	PETO OR 7.30 (0.14, 367.74)	3 more per 1000 (3 fewer to 9 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 24 month(s)											
1 (matthews 2005)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	7/317	36/3 13	RR 0.19 (0.09, 0.42)	93 fewer per 1000 (105 fewer to 66 fewer)	low

severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											
1 (matthews 2005) hba1c change (%, lower values are better, change scores) at end of follow	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/317	0/31	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	low
up Mean follow-up: 24 month(s)											
1 (matthews 2005)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	317	313	MD -0.12 (-0.31, 0.07)	MD 0.12 lower (0.31 lower to 0.07 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)

L.1.7.8 Adding pioglitazone compared to adding glimepiride

Table 86: Clinical evidence profile: Adding pioglitazone compared to adding glimepiride

	De	Risk	Indire	Incons		Other	Interv	Con	Relative		Cert
	sig	of	ctnes	istenc	Impre	considera	ention	trol	effect (95%	Absolute	aint
No of studies	n	bias	S	у	cision	tions	N	N	CI)	effect	у
all-cause mortality at end of follow up Mean follow-up: 18 month(s)											
	RC	very seriou	seriou		very seriou			0/22	PETO OR 7.33 (0.15,	4 more per 1000 (4 fewer to	very
1 (mazzone 2006)	Т	S ¹	s ²	NA ³	s ⁴	NA	1/230	8	369.17)	13 more)	low
cardiovascular mortality at end of follow up Mean follow-up: 18 month(s)											

1 (mazzone 2006)	RC T	very seriou s ¹	seriou s²	NA ³	not seriou s	NA	0/230	0/22	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	very low
3-point mace at end of follow up Mean follow-up: 18 month(s)											
1 (mazzone 2006)	RC T	very seriou s ¹	seriou s ²	NA ³	very seriou s ⁴	NA	0/230	2/22 8	PETO OR 0.13 (0.01, 2.14)	9 fewer per 1000 (21 fewer to 3 more)	very low
non-fatal stroke at end of follow up Mean follow-up: 11.8 month(s)											
2	RC T	very seriou s ¹	seriou s ²	seriou s ⁵	very seriou s ⁴	NA	1/261	1/26 0	PETO OR 1.01 (0.06, 16.18)	0 fewer per 1000 (11 fewer to 11 more)	very low
non-fatal myocardial infarction at end of follow up Mean follow-up: 11.8 month(s)											
2	RC T	very seriou s ¹	seriou s ²	not seriou s	very seriou s ⁴	NA	0/261	2/26 0	PETO OR 0.14 (0.01, 2.19)	8 fewer per 1000 (18 fewer to 3 more)	very low
unstable angina at end of follow up Mean follow-up: 18 month(s)											
1 (mazzone 2006)	RC T	very seriou s ¹	seriou s ²	NA ³	not seriou s	NA	0/230	0/22	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	very low
hospitalisation for heart failure at end of follow up Mean follow-up: 8.2 month(s)											
5	RC T	very seriou s ¹	not seriou s	seriou s ⁵	very seriou s ⁶	NA	5/657	2/63 8	RD 0.00 (-0.01, 0.01)	4 more per 1000 (6 fewer to 15 more)	very low
acute kidney injury at end of follow up									,	,	

Mean follow-up: 5.5 month(s)											
1 (pfützner 2011b)	RC T	seriou	not seriou s	NA ³	very seriou s ⁴	NA	0/142	1/14	PETO OR 0.14 (0.00, 7.01)	7 fewer per 1000 (20 fewer to 7 more)	very low
falls requiring hospitalisation at end of follow up Mean follow-up: 6 month(s)											
1 (kim 2020)	RC T	seriou s ⁷	not seriou s	NA ³	very seriou s ⁴	NA	2/69	0/66	PETO OR 7.18 (0.44, 116.06)	29 more per 1000 (11 fewer to 69 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 8.5 month(s)											
7	RC T	very seriou s ¹	not seriou s	very seriou s ⁸	seriou s ⁹	NA	81/753	140/ 738	RR 0.49 (0.24, 0.99)	98 fewer per 1000 (145 fewer to 2 fewer)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.8 month(s)											
3	RC T	very seriou s ¹	not seriou s	not seriou s	not seriou s	NA	0/285	0/26	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	low
hba1c change (%, lower values are better, change scores and final values) at end of follow up Mean follow-up: 6.9 month(s)											
12	RC T	very seriou s ¹	not seriou s	seriou s ¹⁰	not seriou s	NA	801	778	MD -0.07 (-0.19, 0.05)	MD 0.07 lower (0.19 lower to 0.05 higher)	very low
weight change (kg, lower values are better, change scores and final values) at end of follow up											

Mean follow-up: 8.2 month(s)											
bmi change (kg/m2, lower values are better, change scores and final values) at end of	RC T	very seriou s ¹	not seriou s	seriou s ¹⁰	not seriou s	NA	663	656	MD 0.88 (0.02, 1.74)	MD 0.88 higher (0.02 higher to 1.74 higher)	very low
follow up Mean follow-up: 7.6 month(s)											
	DC.	very	not	not	not				MD 0.32	MD 0.32 higher (0.14 lower	
7	RC T	seriou s ¹	seriou s	seriou s	seriou s	NA	441	419	(-0.14, 0.79)	to 0.79 higher)	low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Largest proportion of studies in the meta-analysis came from partially direct studies
- 3. Only one study so no inconsistency
- 4. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 5. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.34 (0.8-0.9 = serious, <0.8 = very serious).
- 7. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 8. I2 > 75%
- 9. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 10. I2 between 50% and 75%

L.1.7.9

adding glipizide

Table 87: Clinical evidence profile: Adding pioglitazone compared to adding glipizide

	De					Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	У
hba1c change (%, lower values better, final values) at end of follows:	ow up										
Mean follow-up: 5.5 month(s	5)										
										MD 0.58	
		very	not							higher	
	RC	seriou	seriou		seriou				MD 0.58	(0.34 higher to	very
1 (xiao 2015)	T	s ¹	S	NA ²	s^3	NA	34	36	(0.34, 0.82)	0.82 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)

L.1.7.10 Adding pioglitazone compared to adding sitagliptin

Table 88: Clinical evidence profile: Adding pioglitazone compared to adding sitagliptin

9					. 9	<u> </u>				4	
	De	Risk	Indir	Incon		Other	Interv	Con	Relative		Cert
	sig	of	ectne	sisten	Impre	considera	ention	trol	effect	Absolute	aint
No of studies	n	bias	SS	су	cision	tions	N	N	(95% CI)	effect	у
health-related quality of life - overall (eq-5d,											
higher values are better, change scores) at end											
of follow-up											
Mean follow-up: 6 month(s)											
		very	not						MD -0.03		
	RC	seriou	serio		seriou				(-0.09,	MD 0.03	very
1 (bergenstal 2010)	T	s ¹	us	NA ²	s^3	NA	130	139	0.03)	lower	low

GRADE lables – Model 5: Type 2 diabetes and higher	Cardio	vasculai	IISK	1		1			ı	T	
										(0.09 lower	
										to 0.03	
										higher)	
all-cause mortality at end of follow up										,	
Mean follow-up: 6 month(s)											
									PETO OR	6 fewer per	
		very	not		very				0.14	1000	
	RC	seriou	serio		seriou			1/16	(0.00,	(18 fewer to	very
1 (bergenstal 2010)	T	s ¹	us	NA ²	s ⁴	NA	0/165	6	6.86)	6 more)	low
unstable angina at end of follow up	+-	3	us	14/3	3	TNA	0/103	10	0.00)	o more)	IOW
Mean follow-up: 6 month(s)											
wean follow-up: 6 month(s)									DETO OD	0	-
			4						PETO OR	6 more per	
		very	not		very				7.43	1000	
	RC	seriou	serio		seriou			0/16	(0.15,	(6 fewer to	very
1 (bergenstal 2010)	T	s ¹	us	NA ²	s ⁴	NA	1/165	6	374.66)	18 more)	low
acute kidney injury at end of follow up											
Mean follow-up: 6 month(s)											
									PETO OR	6 more per	
		very	not		very				7.43	1000	
	RC	seriou	serio		seriou			0/16	(0.15,	(6 fewer to	very
1 (bergenstal 2010)	T	s ¹	us	NA ²	s ⁴	NA	1/165	6	374.66)	18 more)	low
hypoglycaemia episodes at end of follow up									,	/	
Mean follow-up: 5.7 month(s)											
mount remain aprion month(e)										17 fewer per	
			not	not	very				RR 0.62	1000	
	RC	seriou	serio	seriou	seriou			13/2	(0.26,	(33 fewer to	Vorv
3	T	seriou s ⁵			seriou s ⁴	NA	8/290	91		•	low
		S°	us	S	5.	INA	0/290	91	1.45)	20 more)	IOW
severe hypoglycaemic episodes at end of follow											
up											
Mean follow-up: 5.7 month(s)											
										0 fewer per	
		very	not	not	not				RD 0.00	1000	
	RC	seriou	serio	seriou	seriou			0/29	(-0.01,	(12 fewer to	
3	T	s ¹	us	S	S	NA	0/290	1	0.01)	12 more)	low
11 4 1 (0/ 1 1 1 1/4											
hba1c change (%, lower values are better,											
hba1c change (%, lower values are better, change scores) at end of follow up											

4	RC T	seriou s ⁵	not serio us	very seriou s ⁶	not seriou s	NA	391	396	MD -0.12 (-0.37, 0.14)	MD 0.12 lower (0.37 lower to 0.14 higher)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 7.2 month(s)											
4	RC T	seriou s ⁵	not serio us	very seriou s ⁶	not seriou s	NA	391	396	MD 1.62 (1.52, 1.73)	MD 1.62 higher (1.52 higher to 1.73 higher)	very low
bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (khaloo 2019)	RC T	very seriou s ¹	not serio us	NA ²	not seriou s	NA	110	112	MD 3.50 (2.62, 4.38)	MD 3.50 higher (2.62 higher to 4.38 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 (-0.03, 0.03)
- 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 moderate risk of bias
- 6. I2 > 75%

adding vildagliptin

Table 89: Clinical evidence profile: Adding pioglitazone compared to adding vildagliptin

rable 69. Chilical evidence profile. Addi			1	iparca te	adding						
	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
non-fatal stroke at end of follow up											
Mean follow-up: 12 month(s)											
										4 more per	
		not	not		very				RR 2.11	1000	
	RC	serio	seriou		seriou			1/29	(0.19,	(3 fewer to 75	
1 (bolli 2008)	Т	us	S	NA ¹	s ²	NA	2/280	5	23.11)	more)	low
hypoglycaemia episodes at end of follow											
up											
Mean follow-up: 12 month(s)											
										0 more per	
		not	not		very				RR 1.05	1000	
	RC	serio	seriou		seriou			1/29	(0.07,	(3 fewer to 53	
1 (bolli 2008)	Т	us	S	NA ¹	s ²	NA	1/280	5	16.76)	more)	low
severe hypoglycaemic episodes at end											
of follow up											
Mean follow-up: 12 month(s)											
										0 fewer per	
		not	not		not					1000	
	RC	serio	seriou		seriou			0/29	RD 0.00	(7 fewer to 7	
1 (bolli 2008)	Т	us	S	NA ¹	S	NA	0/280	5	(-0.01, 0.01)	more)	high
hba1c change (%, lower values are											
better, change scores) at end of follow											
up											
Mean follow-up: 12 month(s)											
										MD 0.00	
		not	not		not					lower	
	RC	serio	seriou		seriou				MD 0.00	(0.18 lower to	
1 (bolli 2008)	T	us	S	NA ¹	S	NA	281	295	(-0.18, 0.18)	0.18 higher)	high

weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (bolli 2008)	RC T	not serio us	not seriou s	NA¹	seriou s³	NA	281	295	MD 2.40 (1.69, 3.11)	MD 2.40 higher (1.69 higher to 3.11 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. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

L.1.8 Insulin combinations

L.1.8.1 Adding insulin degludec/liraglutide compared to adding placebo

Table 90: Clinical evidence profile: Adding insulin degludec/liraglutide compared to adding placebo

	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ions	ntion N	rol N	CI)	effect	У
all-cause mortality at end of follow up Mean follow-up: 6 month(s)											
1 (rodbard 2017)	RC T	not seriou s	not seriou s	NA ²	very seriou s ⁴	NA	1/288	0/14 6	PETO OR 4.51 (0.07, 285.77)	3 more per 1000 (3 fewer to 10 more)	low
non-fatal myocardial infaRCTion at end of follow up Mean follow-up: 6 month(s)									,	,	

GRADE lables – Model 5: Type 2 diabetes and	riigiic	Cardiova	asculai II	3N				_			
1 (rodbard 2017)	RC T	not seriou	not seriou	NA ²	very seriou s ⁴	NA	1/288	0/14	PETO OR 4.51 (0.07, 285.77)	3 more per 1000 (3 fewer to 10 more)	low
hypoglycaemia episodes at end of follow	-	_								,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	
up Mean follow-up: 6 month(s)											
1 (rodbard 2017)	RC T	not seriou s	not seriou s	NA ²	not seriou s	NA	120/28	25/1 46	RR 2.43 (1.66, 3.57)	245 more per 1000 (113 more to 439 more)	high
at night hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)											
1 (rodbard 2017)	RC T	not seriou s	not seriou s	NA ²	seriou s ⁵	NA	34/288	10/1 46	RR 1.72 (0.88, 3.39)	50 more per 1000 (8 fewer to 164 more)	mod erat e
severe hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)											
1 (rodbard 2017)	RC T	not seriou s	not seriou s	NA ²	very seriou s ⁴	NA	2/288	0/14 6	PETO OR 4.53 (0.24, 85.38)	7 more per 1000 (3 fewer to 17 more)	low
hba1c change (%, lower values are better, mean difference) at end of follow up Mean follow-up: 6 month(s)											
1 (rodbard 2017)	RC T	seriou s ¹	not seriou s	NA ²	not seriou s	NA	289	146	MD -1.02 (-1.18, - 0.86)	MD 1.02 lower (1.18 lower to 0.86 lower)	mod erat e
weight change (kg, lower values are better, mean difference) at end of follow up Mean follow-up: 6 month(s)											

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										MD 1.48	
										higher	
		very	not		not					(0.90 higher	
	RC	seriou	seriou		seriou				MD 1.48	to 2.06	
1 (rodbard 2017)	Τ	s^3	s	NA ²	s	NA	289	146	(0.90, 2.06)	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. >33.3% of the studies in the meta-analysis were at high risk of bias
- 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 (0.80, 1.25)

L.1.8.2 Adding insulin degludec/liraglutide compared to adding insulin

Table 91: Clinical evidence profile: Adding insulin degludec/liraglutide compared to adding insulin

	D							Co			
	es	Risk	Indir	Inco	Impr	Other	Inter	ntr	Relative		Cer
	ig	of	ectn	nsist	ecisi	conside	venti	ol	effect	Absolute	tai
No of studies	n	bias	ess	ency	on	rations	on N	N	(95% CI)	effect	nty
health-related quality of life - overall eq-5d-5l index score											
(higher scores are better, final values) at end of follow up Mean follow-up: 6 month(s)											
mean follow-up. o month(s)										MD 0.03	
										higher	
									MD 0 00	(0.00	
	R	corio	not serio		serio				MD 0.03 (-0.00,	lower to 0.06	
1 (watada 2019)	T	serio us¹	us	NA ²	us ³	NA	105	105	(- 0.00, 0.06)	higher)	low
health-related quality of life - subscale mental component									,	J /	
(sf-36 v2, 0-100, higher scores are better, change scores and											
final values) at end of follow up											
Mean follow-up: 6 month(s)											

2 health-related quality of life - subscale physical component (sf-36 v2, 0-100, higher scores are better, change scores and	R C T	very serio us ⁴	not serio us	very serio us ⁵	serio us ⁶	NA	516	512	MD 0.57 (-1.91, 3.05)	MD 0.57 higher (1.91 lower to 3.05 higher)	ver y low
final values) at end of follow up Mean follow-up: 6 month(s)											
2	R C T	very serio us ⁴	not serio us	very serio us ⁵	serio	NA	515	512	MD 0.55 (-1.81, 2.92)	MD 0.55 higher (1.81 lower to 2.92 higher)	ver y low
all-cause mortality at end of follow up Mean follow-up: 8.6 month(s)											
9	R C T	not serio us	not serio us	serio us ⁸	very serio us ⁹	NA	4/293 2	7/2 180	RD -0.00 (-0.00, 0.00)	2 fewer per 1000 (5 fewer to 2 more)	ver y low
cardiovascular mortality at end of follow up Mean follow-up: 8.6 month(s)											
9 3-point mace at end of follow up	R C T	not serio us	not serio us	serio us ⁸	very serio us ¹⁰	NA	2/293	5/2 180	RD -0.00 (-0.00, 0.00)	2 fewer per 1000 (5 fewer to 2 more)	ver y low
Mean follow-up: 8 month(s)											
3	R C T	not serio us	not serio us	not serio us	very serio us ¹¹	NA	9/134 3	5/7 74	PETO OR 1.11 (0.37, 3.32)	0 more per 1000 (7 fewer to 7 more)	low
non-fatal stroke at end of follow up Mean follow-up: 8.9 month(s)											

GNADE tables – Woder 5. Type 2 diabetes and higher cardiovascula	AI 1131	\							DETO	1	
									PETO	1 more	
	R	not _.	not _.		very		7/470	4.14	OR 1.21	per 1000	ver
	С	serio	serio	serio	serio		7/173	4/1	(0.36,	(3 fewer	У
6	Т	us	us	us ⁸	us ¹¹	NA	2	398	4.11)	to 5 more)	low
non-fatal myocardial infarction at end of follow up											
Mean follow-up: 9.4 month(s)											
									PETO	1 more	
	R	not	not		very				OR 1.48	per 1000	ver
	С	serio	serio	serio	serio		9/240	5/1	(0.51,	(2 fewer	У
7	Т	us	us	us ⁸	us ¹¹	NA	5	835	4.30)	to 4 more)	low
unstable angina at end of follow up											
Mean follow-up: 12 month(s)											
									PETO	3 more	
	R	very	not		very				OR 3.47	per 1000	ver
	С	serio	serio	serio	serio		5/111	1/9	(0.69,	(1 fewer	у
3	Т	us ⁴	us	us ⁸	us ¹¹	NA	9	36	17.50)	to 8 more)	ĺow
hospitalisation for heart failure at end of follow up											
Mean follow-up: 15 month(s)											
									PETO	1 fewer	
	R	very	not		very				OR 0.51	per 1000	ver
	С	serio	serio	serio	serio			2/7	(0.05,	(6 fewer	у
2	Т	us ⁴	us	us ⁸	us ¹¹	NA	1/758	57	4.93)	to 3 more)	low
acute kidney injury at end of follow up									,	Í	
Mean follow-up: 6 month(s)											
									PETO	5 fewer	
	R	not	not		very				OR 0.14	per 1000	
	С	serio	serio		serio			1/2	(0.00,	(14 fewer	
1 (philis-tsimikas 2019)	Т	us	us	NA 2	us ¹¹	NA	0/209	10	6.85)	to 5 more)	low
persistent signs of worsening kidney disease at end of									,		
follow up											
Mean follow-up: 6 month(s)											
									PETO	5 fewer	
	R	not	not		very				OR 0.14	per 1000	
	C	serio	serio		serio			1/2	(0.00,	(14 fewer	
1 (philis-tsimikas 2019)	ΙŤ	us	us	NA ²	us ¹¹	NA	0/209	10	6.85)	to 5 more)	low
development of end stage kidney disease at end of follow up							0,200		0.00)	15 5 111515)	
Mean follow-up: 24 month(s)											
ivicali follow-up. 24 illoliti(5)											

GNADE lables – Model 5. Type 2 diabetes and higher cardiovascula	11101								DETA	1 .	
									PETO	2 more	
	R	very	not		very				OR 7.36	per 1000	ver
	С	serio	serio		serio			0/5	(0.15,	(2 fewer	У
1 (aroda 2019a)	Т	us ⁴	us	NA ²	us ¹¹	NA	1/506	04	370.92)	to 6 more)	low
cardiac arrhythmia at end of follow up											
Mean follow-up: 15 month(s)											
									PETO	0 fewer	
	R	very	not		very				OR 1.00	per 1000	ver
	С	serio	serio	serio	serio			2/7	(0.14,	(5 fewer	У
2	T	us ⁴	us	us ⁸	us ¹¹	NA	2/758	57	7.11)	to 5 more)	ĺow
hypoglycaemia episodes at end of follow up Mean follow-up: 7 month(s)											
										82 fewer	
										per 1000	
	R	not	not	not				473	RR 0.78	(109	mo
	C	serio	serio	serio	serio		561/2	/12	(0.70,	fewer to	der
6	ΙŤ	us	us	us	us ¹²	NA	033	85	0.86)	52 fewer)	ate
at night hypoglycaemic episodes at end of follow up	-	us	us	us	us	INA	000	00	0.00)	JZ lewel)	alc
Mean follow-up: 6 month(s)											
mean tenew up. o menting)										58 fewer	
										per 1000	
	R	not							RR 0.47	(87 fewer	ver
	C	serio	serio	serio	serio		29/81	69/	(0.20,	to 10	
	-		us ¹³	us ¹⁴	us ¹²	NIA		631	, ,		У
3	I	us	usio	us	us	NA	2	031	1.09)	more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.9 month(s)											
										2 fewer	
	R	not	not		very			20/	RD -0.00	per 1000	ver
	С	serio	serio	serio	serio		16/10	117	(-0.01,	(14 fewer	У
6	Т	us	us	us ⁸	us ¹⁵	NA	62	6	0.01)	to 9 more)	low
hba1c change (%, lower values are better, change scores) at											
end of follow up											
Mean follow-up: 6.5 month(s)											
				_						MD 0.65	_
	R		not	very					MD -0.65	lower	ver
	С	serio	serio	serio	serio			255	(-0.82, -	(0.82	У
11	Т	us ¹	us	us ⁵	us ¹⁶	NA	3121	1	0.48)	lower to	ĺow

										0.48 lower)	
hba1c change (mmol/mol, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)										,	
1 (wang 2022b) weight change (kg, lower values are better, change scores and final values) at end of follow up	R C T	not serio us	not serio us	NA ²	serio us ¹⁷	NA	361	179	MD -6.50 (-7.96, - 5.04)	MD 6.50 lower (7.96 lower to 5.04 lower)	mo der ate
Mean follow-up: 8 month(s)											
	R C	not serio	not serio	very serio	serio			298	MD -2.21 (-2.79, -	MD 2.21 lower (2.79 lower to 1.63	ver y
12	Т	us	us	us ⁵	us ¹⁸	NA	3736	2	1.63)	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 one end of the defined MIDs (-0.03, 0.03)
- 4. >33.3% of the studies in the meta-analysis were at high risk of bias
- 5. I2 > 75%
- 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 (-2.00, 2.00)
- 8. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 9. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.5 (0.8-0.9 = serious, <0.8 = very serious).

10. Precision calculated through

Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.56 (0.8-0.9 = serious, <0.8 = very serious).

- 11. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 12. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 13. Largest proportion of studies in the meta-analysis came from partially direct studies
- 14. I2 between 50% and 75%
- 15. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.07 (0.8-0.9 = serious, <0.8 = very serious).
- 16. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 17. 95% confidence intervals cross one end of the defined MIDs (-5.50, 5.50)
- 18. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

L.1.8.3 Adding insulin degludec/liraglutide compared to adding liraglutide

Table 92: Clinical evidence profile: Adding insulin degludec/liraglutide compared to adding liraglutide

	De	Risk	Indire	Incons		Other			Relative		Cert
	sig	of	ctnes	istenc	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	S	у	cision	ions	ntion N	rol N	CI)	effect	У
all-cause mortality at end of follow up Mean follow-up: 9 month(s)											
2	RC T	not serio us	not seriou s	seriou s ¹	very seriou s ²	NA	2/1194	0/59 4	RD 0.00 (-0.00, 0.01)	2 more per 1000 (3 fewer to 6 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)											

GRADE tables – Model 5: Type 2 diabetes and nig	grier c	aruiovas	Culai 113N						PETO OR	2 more per	
	RC	not serio	not seriou		very			0/41	4.47 (0.24,	1000 (1 fewer to 6	
1 (gough 2014)	T	us	seriou	NA ³	seriou s ⁴	NA	2/833	4	84.97)	more)	low
3-point mace at end of follow up Mean follow-up: 12 month(s)									,	,	
1 (gough 2014)	RC T	not serio us	not seriou s	NA ³	very seriou s ⁴	NA	4/833	1/41 4	RR 1.99 (0.22, 17.73)	2 more per 1000 (2 fewer to 40 more)	low
non-fatal stroke at end of follow up Mean follow-up: 6 month(s)											
1 (wang 2022b)	RC T	not serio us	not seriou	NA ³	very seriou s ⁴	NA	2/361	4/18 0	RR 0.25 (0.05, 1.35)	17 fewer per 1000 (21 fewer to 8 more)	low
non-fatal myocardial infaRCTion at end of follow up Mean follow-up: 12 month(s)							2,33.				
1 (gough 2014)	RC T	not serio us	not seriou s	NA ³	very seriou s ⁴	NA	2/833	1/41	RR 0.99 (0.09, 10.93)	0 fewer per 1000 (2 fewer to 24 more)	low
unstable angina at end of follow up Mean follow-up: 6 month(s)											
1 (wang 2022b)	RC T	not serio us	not seriou s	NA ³	not seriou s	NA	0/361	0/18 0	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	high
hypoglycaemia episodes at end of follow up Mean follow-up: 8 month(s)											
3	RC T	not serio us	not seriou	very seriou s ⁵	not seriou s	NA	389/14 61	35/8 65	RR 8.77 (3.03, 25.43)	315 more per 1000 (82 more to 988 more)	low
at night hypoglycaemic episodes at end of follow up									/	,	

Mean follow-up: 6 month(s)											
1 (wang 2022b)	RC T	not serio us	seriou s ⁶	NA ³	very seriou s ⁴	NA	5/361	0/18	PETO OR 4.53 (0.70, 29.28)	14 more per 1000 (2 more to 26 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)											
1 (gough 2014)	RC T	not serio us	not seriou s	NA ³	very seriou s ⁴	NA	3/825	0/41	PETO OR 4.50 (0.41, 49.66)	4 more per 1000 (0 more to 8 more)	low
hba1c change (%, lower values are better, mean difference) at end of follow up Mean follow-up: 9 month(s)											
2	RC T	not serio us	not seriou s	not seriou s	seriou	NA	1195	688	MD -0.54 (-0.62, - 0.45)	MD 0.54 lower (0.62 lower to 0.45 lower)	mod erat e
hba1c change (mmol/mol, lower values are better, mean difference) at end of follow up Mean follow-up: 6 month(s)											
1 (wang 2022b)	RC T	not serio us	not seriou s	NA ³	seriou s ⁸	NA	361	180	MD -6.87 (-8.32, - 5.42)	MD 6.87 lower (8.32 lower to 5.42 lower)	mod erat e
weight change (kg, lower values are better, mean difference) at end of follow up Mean follow-up: 8 month(s)											
3	RC T	not serio us	not seriou s	very seriou s ⁵	seriou s ⁹	NA	1470	867	MD 2.96 (2.17, 3.75)	MD 2.96 higher (2.17 higher to 3.75 higher)	very low

^{1.} Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

2. Precision calculated through Optimal

Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.41 (0.8-0.9 = serious, <0.8 = very serious).

- 3. Only one study so no inconsistency
- 4. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 5. I2 > 75%
- 6. Largest proportion of studies in the meta-analysis came from partially direct studies
- 7. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 8. 95% confidence intervals cross one end of the defined MIDs (-5.50, 5.50)
- 9. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

L.1.8.4 Adding insulin glargine/lixisenatide compared to adding insulin

Table 93: Clinical evidence profile: Adding insulin glargine/lixisenatide compared to adding insulin

	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow up Mean follow-up: 6.3 month(s)											
	RC	seriou	not seriou	serious	very seriou			5/20	RD -0.00	0 fewer per 1000 (4 fewer to 3	very
7	Т	s ¹	S	2	s^3	NA	4/2070	73	(-0.00, 0.00)	more)	low
cardiovascular mortality at end of follow											
up											
Mean follow-up: 6.3 month(s)											
			not		very					2 more per 1000	
	RC	seriou	seriou	serious	seriou		50/207	46/2	RD 0.00	(7 fewer to	very
7	T	s ¹	S	2	s ⁴	NA	0	073	(-0.01, 0.01)	11 more)	low

GRADE lables – Model 5: Type 2 diabetes and	Highe	Cardiov	asculai II	3K	_						
non-fatal stroke at end of follow up Mean follow-up: 7 month(s)											
1 (rosenstock 2016b)	RC T	seriou s ¹	not seriou s	NA ⁵	very seriou s ⁶	NA	0/469	1/46 7	PETO OR 0.13 (0.00, 6.79)	2 fewer per 1000 (6 fewer to 2 more)	very low
non-fatal myocardial infaRCTion at end of follow up Mean follow-up: 7 month(s)											
1 (rosenstock 2016b)	RC T	seriou s ¹	not seriou s	NA ⁵	not seriou s	NA	0/469	0/46 7	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (4 fewer to 4 more)	mod erat e
unstable angina at end of follow up Mean follow-up: 7 month(s)											
1 (rosenstock 2016b)	RC T	seriou s ¹	not seriou s	NA ⁵	very seriou s ⁶	NA	1/469	1/46 7	PETO OR 1.00 (0.06, 15.94)	0 fewer per 1000 (6 fewer to 6 more)	very low
hospitalisation for heart failure at end of follow up Mean follow-up: 7 month(s)											
1 (rosenstock 2016b)	RC T	seriou s ¹	not seriou s	NA ⁵	very seriou s ⁶	NA	0/469	2/46 7	PETO OR 0.13 (0.01, 2.15)	4 fewer per 1000 (10 fewer to 2 more)	very low
death from renal causes at end of follow up Mean follow-up: 6.9 month(s)											
1 (yuan 2022)	RC T	not seriou s	not seriou s	NA ⁵	not seriou s	NA	0/211	0/21	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	high
hypoglycaemia episodes at end of follow up Mean follow-up: 6.3 month(s)											J

7	RC T	not seriou s	not seriou s	serious	not seriou s	NA	399/20 69	397/ 2073	RR 1.01 (0.90, 1.12)	1 more per 1000 (19 fewer to 24 more)	mod erat e
severe hypoglycaemic episodes at end of follow up Mean follow-up: 6.3 month(s)											
7	RC T	seriou s ¹	not seriou s	serious	very seriou s ⁷	NA	7/2069	6/20 73	RD 0.00 (-0.00, 0.00)	0 more per 1000 (3 fewer to 4 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 6.3 month(s)											
7	RC T	not seriou s	not seriou s	very serious	seriou s ⁹	NA	2068	2070	MD -0.50 (-0.64, - 0.35)	MD 0.50 lower (0.64 lower to 0.35 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6.3 month(s)											
7	RC T	not seriou	not seriou	not serious	not seriou s	NA	2068	2070	MD -1.16 (-1.32, - 0.99)	MD 1.16 lower (1.32 lower to 0.99 lower)	high

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.07 (0.8-0.9 = serious, <0.8 = very serious).
- 4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.09 (0.8-0.9 = serious, <0.8 = very serious).

5. Only one study so no inconsistency

- 6. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 7. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.06 (0.8-0.9 = serious, <0.8 = very serious).
- 8. 12 > 75%
- 9. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

L.1.8.5 Adding insulin glargine/lixisenatide compared to adding lixisenatide

Table 94: Clinical evidence profile: Adding insulin glargine/lixisenatide compared to adding lixisenatide

Tubic of Temporal of Gorden Promot Pr	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow up Mean follow-up: 6.2 month(s)											
	RC	serio	not seriou	serious	very seriou			1/40	RD -0.00	0 fewer per 1000 (7 fewer to 7	very
2	T	us ¹	S	2	s ³	NA	2/817	9	(-0.01, 0.01)	more)	low
cardiovascular mortality at end of follow										,	
up Mean follow-up: 6.2 month(s)											
2	RC T	serio us ¹	not seriou s	serious	very seriou s ⁴	NA	1/817	1/40 9	PETO OR 0.47 (0.02, 8.90)	1 fewer per 1000 (7 fewer to 4 more)	very low
non-fatal stroke at end of follow up Mean follow-up: 7 month(s)											
1 (resencted 2016h)	RC	serio	not seriou	NA ⁵	very seriou s ⁶	NA	0/460	1/23	PETO OR 0.05	4 fewer per 1000 (13 fewer to 4	very
1 (rosenstock 2016b)	I	us ¹	S	INA ⁵	S	INA	0/469	3	(0.00, 3.16)	more)	low

GRADE tables – Model 5: Type 2 diabetes and higher cardiovascular risk

non-fatal myocardial infaRCTion at end	J										
of follow up Mean follow-up: 7 month(s)											
1 (rosenstock 2016b)	RC T	serio us¹	not seriou s	NA ⁵	not seriou s	NA	0/469	0/23	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	mod erat e
unstable angina at end of follow up Mean follow-up: 7 month(s)											
1 (rosenstock 2016b)	RC T	serio us ¹	not seriou s	NA ⁵	very seriou s ⁶	NA	1/469	0/23	PETO OR 4.47 (0.07, 286.86)	2 more per 1000 (2 fewer to 6 more)	very low
hospitalisation for heart failure at end of follow up Mean follow-up: 7 month(s)											
1 (rosenstock 2016b)	RC T	serio us ¹	not seriou s	NA ⁵	not seriou s	NA	0/469	0/23	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	mod erat e
hypoglycaemia episodes at end of follow up Mean follow-up: 6.2 month(s)											
2	RC T	serio us ¹	not seriou s	serious	not seriou s	NA	291/81 7	27/4 09	RR 5.41 (3.71, 7.87)	291 more per 1000 (179 more to 454 more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 6.2 month(s)											
2	RC T	serio us ¹	not seriou	serious	very seriou s ⁴	NA	1/817	1/40	RD -0.00 (-0.01, 0.01)	1 fewer per 1000 (8 fewer to 5 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up									,	,	

GRADE tables - Model 5: Type 2 diabetes and higher cardiovascular risk

Mean follow-up: 6.2 month(s)											
2	RC T	not serio us	not seriou s	very serious	not seriou s	NA	816	408	MD -0.85 (-1.14, - 0.55)	MD 0.85 lower (1.4 lower to 0.55 lower)	low
weight change (kg, lower values are better, change scores) at end of follow up											
Mean follow-up: 6.2 month(s)										MD 4 92	
	RC	serio	not seriou	not	not seriou				MD 1.83	MD 1.83 higher (1.40 higher to 2.25	mod erat
2	I	us ¹	S	serious	S	NA	643	581	(1.40, 2.25)	higher)	е

- 1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.03 (0.8-0.9 = serious, <0.8 = very serious).
- 4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.1 (0.8-0.9 = serious, <0.8 = very serious).
- 5. Only one study so no inconsistency
- 6. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 7. I2 between 50% and 75%
- 8.12 > 75%.

compared to adding dapagliflozin

Table 95: Clinical evidence profile: Adding dapagliflozin + exenatide compared to adding dapagliflozin

Tuble 50. Offined Cytachice profile. Add	De					Other	,pg		Relative		Cert
	sig	Risk	Indire	Inconsi	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	of bias	ctness	stency	cision	ions	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow up Mean follow-up: 24 month(s)											
1 (frias 2016)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	3/231	2/23 3	RR 1.51 (0.26, 8.97)	4 more per 1000 (6 fewer to 68 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 24 month(s)											
1 (frias 2016)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	1/231	1/23	RR 1.01 (0.06, 16.03)	0 more per 1000 (4 fewer to 65 more)	very low
acute kidney injury at end of follow up Mean follow-up: 24 month(s)											
1 (frias 2016)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	0/231	3/23 3	PETO OR 0.14 (0.01, 1.31)	13 fewer per 1000 (27 fewer to 2 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 24 month(s)											
1 (frias 2016)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	4/231	1/23 3	RR 4.03 (0.45, 35.83)	13 more per 1000 (2 fewer to 149 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 24 month(s)											

GRADE tables - Model 5: Type 2 diabetes and higher cardiovascular risk

1 (frias 2016)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/231	0/23	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	low
hba1c change (%, lower values are									, ,	·	
better, change scores) at end of follow up											
Mean follow-up: 24 month(s)											
1 (frias 2016)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s ⁴	NA	228	230	MD -0.64 (-0.96, - 0.32)	MD 0.64 lower (0.96 lower to 0.32 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow											
up											
Mean follow-up: 24 month(s)											
										MD 0.51	
	DC	very	not		not				MD 0 54	higher	
1 (fries 2016)	RC	seriou	seriou	NIA2	seriou	NIA	220	220	MD 0.51	(0.77 lower to	lave
1 (frias 2016)	I	S ¹	S	NA^2	S	NA	228	230	(-0.77, 1.79)	1.79 higher)	low

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

L.1.8.7 Adding dapagliflozin + exenatide compared to adding exenatide

Table 96: Clinical evidence profile: Adding dapagliflozin + exenatide compared to adding exenatide

	De					Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	У
all-cause mortality at end of follow up											
Mean follow-up: 24 month(s)											

GRADE tables – Model 5: Type 2 diabetes and higher cardiovascular risk

GRADE lables - Model 5. Type 2 diabetes and	riigiic	i odralovi	aboular ik	311				_			
1 (frias 2016)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	3/231	1/23 0	PETO OR 2.72 (0.38, 19.46)	9 more per 1000 (8 fewer to 26 more)	very low
cardiovascular mortality at end of follow											
up											
Mean follow-up: 24 month(s)									DETO 00		
1 (frias 2016)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	1/231	1/23 0	PETO OR 1.00 (0.06, 15.97)	0 fewer per 1000 (12 fewer to 12 more)	very low
acute kidney injury at end of follow up Mean follow-up: 24 month(s)											
1 (frias 2016)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	0/231	2/23 0	PETO OR 0.13 (0.01, 2.15)	9 fewer per 1000 (21 fewer to 3 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 24 month(s)											
1 (frias 2016)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s ⁴	NA	4/231	0/23	PETO OR 7.45 (1.04, 53.26)	17 more per 1000 (1 more to 34 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 24 month(s)										·	
1 (frias 2016)	RC T	very seriou s ¹	not seriou	NA ²	not seriou s	NA	0/231	0/23	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 24 month(s)								3	, ,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	,	

GRADE tables - Model 5: Type 2 diabetes and higher cardiovascular risk

1 (frias 2016)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s ⁵	NA	228	227	MD -0.41 (-0.73, - 0.09)	MD 0.41 lower (0.73 lower to 0.09 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow up											
Mean follow-up: 24 month(s)											
	RC	very seriou	not seriou		seriou				MD -1.71 (-2.96, -	MD 1.71 lower (2.96 lower to 0.46	very
1 (frias 2016)	T	s ¹	S	NA ²	s^6	NA	228	227	0.46)	lower)	low

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

L.1.8.8 Adding dapagliflozin + saxagliptin compared to adding dapagliflozin

Table 97: Clinical evidence profile: Adding dapagliflozin + Saxagliptin compared to adding dapagliflozin

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

GRADE tables – Model 5: Type 2 diabetes and higher cardiovascular risk

GRADE lables - Model 5. Type 2 diabetes and	riigiic	Cardiov	asculai i	ISIN							
2	RC T	not seriou s	not seriou s	serious	very seriou s ²	NA	1/472	2/47 2	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (10 fewer to 6 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 5.5 month(s)											
2	RC T	not seriou s	not seriou s	serious	very seriou s ³	NA	0/472	2/47	RD -0.00 (-0.01, 0.00)	4 fewer per 1000 (13 fewer to 4 more)	very low
hospitalisation for heart failure at end of follow up Mean follow-up: 12 month(s)											
1 (muller-wieland 2018)	RC T	not seriou s	not seriou s	NA ⁴	not seriou s	NA	0/312	0/31	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	high
persistent signs of worsening kidney disease at end of follow up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2015a)	RC T	seriou s ⁵	not seriou s	NA ⁴	not seriou s	NA	0/179	0/17 9	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (11 fewer to 11 more)	mod erat e
diabetic ketoacidosis at end of follow up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2019d)	RC T	not seriou	not seriou	NA ⁴	not seriou	NA	0/293	0/29	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	high
hypoglycaemia episodes at end of follow up Mean follow-up: 7.7 month(s)							5,233				
3	RC T	not seriou s	not seriou s	serious	seriou s ⁶	NA	9/784	3/78	PETO OR 2.74 (0.88, 8.54)	8 more per 1000	low

GRADE tables - Model 5: Type 2 diabetes and higher cardiovascular risk

										(1 fewer to 16 more)	
severe hypoglycaemic episodes at end of follow up											
Mean follow-up: 7.7 month(s)	RC T	not seriou	not seriou	serious	very seriou s ⁷	NA	1/784	1/78	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (5 fewer to 5 more)	very
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 7.7 month(s)	•						.,, .		(3.55, 5.50)		
3	RC T	not seriou s	not seriou s	not serious	not seriou s	NA	753	740	MD -0.37 (-0.46, - 0.27)	MD 0.37 lower (0.46 lower to 0.27 lower)	high
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 8.8 month(s)											
2	RC T	not seriou s	not seriou s	not serious	not seriou s	NA	471	463	MD 0.31 (-0.12, 0.74)	MD 0.31 higher (0.12 lower to 0.74 higher)	high

- 1. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 2. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.13 (0.8-0.9 = serious, <0.8 = very serious).
- 3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.52 (0.8-0.9 = serious, <0.8 = very serious).
- 4. Only one study so no inconsistency
- 5. >33.3% of the studies in the meta-analysis were at moderate risk of bias

end of the defined MIDs (0.80, 1.25)

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

L.1.8.9 Adding dapagliflozin + saxagliptin compared to adding glimepiride

Table 98: Clinical evidence profile: Adding dapagliflozin + saxagliptin compared to adding glimepiride

Table 96. Chilical evidence profile. Addi	De			, agn p an		Other	<u> </u>		Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow up Mean follow-up: 36 month(s)											
1 (frias 2020)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	1/227	3/21 6	PETO OR 0.35 (0.05, 2.48)	9 fewer per 1000 (27 fewer to 8 more)	very low
hospitalisation for heart failure at end of follow up Mean follow-up: 12 month(s)											
2	RC T	not seriou s	not seriou s	serious	very seriou s ⁵	NA	0/539	1/52 8	RD -0.00 (-0.01, 0.00)	2 fewer per 1000 (8 fewer to 4 more)	very low
diabetic ketoacidosis at end of follow up Mean follow-up: 12 month(s)											
1 (frias 2020)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/227	0/21 6	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 24 month(s)											
2	RC T	very seriou s ¹	not seriou s	serious 6	seriou s ⁷	NA	20/539	66/5 25	RR 0.22 (0.06, 0.87)	98 fewer per 1000	very low

GRADE tables - Model 5: Type 2 diabetes and higher cardiovascular risk

The late of the la										(119 fewer to 16 fewer)	
severe hypoglycaemic episodes at end of follow up Mean follow-up: 24 month(s)											
2	RC T	not seriou s	not seriou s	serious	very seriou s ⁸	NA	0/539	3/52 5	RD -0.01 (-0.02, 0.01)	6 fewer per 1000 (24 fewer to 13 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 24 month(s)											
2	RC T	not seriou s	not seriou s	serious	seriou s ⁹	NA	529	517	MD -0.34 (-0.65, - 0.02)	MD 0.34 lower (0.65 lower to 0.02 lower)	low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 24 month(s)											
2	RC T	not seriou s	not seriou s	very serious	seriou s ¹¹	NA	536	522	MD -4.12 (-6.12, - 2.12)	MD 4.12 lower (6.12 lower to 2.12 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. 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 = 0.3 (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. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.69 (0.8-0.9 = serious, <0.8 = very serious).
- 9. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 10. I2 > 75%
- 11. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

L.1.8.10 Adding dapagliflozin + saxagliptin compared to adding insulin

Table 99: Clinical evidence profile: Adding dapagliflozin + saxagliptin compared to adding insulin

Tubic 50: Gilliour Struction promo: Adding dapagimozin - Suxuş	,										
	D		Indi			Other		Со			Се
	es	Risk	rect	Inco	Imp	consid	Inter	ntr	Relative		rta
	ig	of	nes	nsist	reci	eration	venti	ol	effect	Absolute	int
No of studies	n	bias	s	ency	sion	s	on N	N	(95% CI)	effect	у
health-related quality of life - subscale net benefit score (phase v health outcomes information systems diabetes module, higher scores are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (vilsboll 2019)	R C T	not seri ous	not seri	NA¹	not seri ous	NA	324	31 9	MD 1.10 (-0.84, 3.04)	MD 1.10 higher (0.84 lower to 3.04 higher)	hig h
health-related quality of life - subscale regimen acceptance score (phase v health outcomes information systems diabetes module, higher scores are better, change scores) at end of follow up Mean follow-up: 12 month(s)		Jus	Jus	IVA	Jus	INA	324	9	0.04)	riighei)	11
	R	not	not		not						
	С	seri	seri		seri			31	MD	MD 4.20	hig
1 (vilsboll 2019)	T	ous	ous	NA ¹	ous	NA	324	9	4.20	higher	h

GRADE tables – Model 5: Type 2 diabetes and higher cardiovascular risk

GRADE tables – Model 5: Type 2 diabetes and higher cardiovascular risk											
									(1.98,	(1.98	
									6.42)	higher to	
										6.42	
										higher)	
health-related quality of life - subscale satisfaction (phase v health											
outcomes information systems diabetes module, higher scores are											
better, change scores) at end of follow up											
Mean follow-up: 12 month(s)											
										MD 3.40	
										higher	
									MD	(1.46	
	R	not	not		not				3.40	higher to	
	С	seri	seri		seri			31	(1.46,	5.34	hig
1 (vilsboll 2019)	Т	ous	ous	NA ¹	ous	NA	324	9	5.34)	higher)	h
all-cause mortality at end of follow up									,		
Mean follow-up: 12 month(s)											
										6 more	
									PETO	per 1000	
	R	not	not		very				OR 7.30	(2 fewer	
	С	seri	seri		seri		2/32	0/3	(0.46,	to 15	lo
1 (vilsboll 2019)	Т	ous	ous	NA ¹	ous ²	NA	4	19	116.95)	more)	w
cardiovascular mortality at end of follow up										·	
Mean follow-up: 12 month(s)											
										0 fewer	
										per 1000	
	R	not	not		not				RD 0.00	(6 fewer	
	С	seri	seri		seri		0/32	0/3	(-0.01,	to 6	hig
1 (vilsboll 2019)	Т	ous	ous	NA ¹	ous	NA	4	19	0.01)	more)	h
acute kidney injury at end of follow up											
Mean follow-up: 12 month(s)											
										0 fewer	
										per 1000	
	R	not	not		not				RR 0.00	(0 more	
	С	seri	seri		seri		0/32	0/3	(0.00,	to 0	hig
1 (vilsboll 2019)	Т	ous	ous	NA ¹	ous	NA	4	19	0.00)	more)	h
diabetic ketoacidosis at end of follow up											
Mean follow-up: 12 month(s)											

GRADE tables – Model 5: Type 2 diabetes and higher cardiovascular risk

GNADE tables – Model 5. Type 2 diabetes and higher cardiovascular risk		1		1	1	1					
										3 fewer	
									PETO	per 1000	
	R	not	not		very				OR 0.13	(9 fewer	
	С	seri	seri		seri		0/32	1/3	(0.00,	to 3	lo
1 (vilsboll 2019)	Т	ous	ous	NA ¹	ous ²	NA	4	19	6.72)	more)	W
hypoglycaemia episodes at end of follow up											A
Mean follow-up: 12 month(s)											
										174	
										fewer per	
										1000	
										(228	
	R	not	not		not			14	RR 0.62	fewer to	
	С	seri	seri		seri		93/3	7/3	(0.51,	107	hig
1 (vilsboll 2019)	Т	ous	ous	NA ¹	ous	NA	24	19	0.77)	fewer)	h
severe hypoglycaemic episodes at end of follow up											
Mean follow-up: 12 month(s)											
										9 fewer	
	_								PETO	per 1000	
	R	not	not		very				OR 0.13	(20 fewer	١.
	С	seri	seri		seri		0/32	3/3	(0.01,	to 1	lo
1 (vilsboll 2019)	Τ	ous	ous	NA ¹	ous ²	NA	4	19	1.28)	more)	W
hba1c change (%, lower values are better, change scores) at end of											
follow up											
Mean follow-up: 12 month(s)										145 0 05	4
										MD 0.25	
										lower	
					4				MD -	(0.40	
	R	very	not		not			47	0.25	lower to	
4 (.: - - 0040)	C	seri	seri	NIA1	seri	NIA	040	17	(-0.40, -	0.10	lo
1 (vilsboll 2019)	I	ous ³	ous	NA ¹	ous	NA	212	7	0.10)	lower)	W
weight change (kg, lower values are better, change scores) at end											
of follow up											
Mean follow-up: 12 month(s)									MD	MD 4.00	
									MD -	MD 4.60	
	R	very	not		not			47	4.60	lower	
4 (.: - - 0040)	C	seri	seri	NIA1	seri	NIA	040	17	(-5.37, -	(5.37	lo
1 (vilsboll 2019)	I	ous ³	ous	NA ¹	ous	NA	212	8	3.83)	lower to	W

					3.83	
					lower)	

- 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

L.1.8.11 Adding dapagliflozin + saxagliptin compared to adding saxagliptin

Table 100: Clinical evidence profile: Adding dapagliflozin + saxagliptin compared to adding saxagliptin

Table 100. Official evidence profile. Add				June 1	<u></u>		g caxa;	Jp t			
	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow up											
Mean follow-up: 5.5 month(s)											
										2 more per	
		not	not		very					1000	
	RC	seriou	seriou	serious	seriou			0/47	RD 0.00	(5 fewer to 9	very
2	Т	s	s	1	s ²	NA	1/472	1	(-0.01, 0.01)	more)	low
cardiovascular mortality at end of follow											
up											
Mean follow-up: 5.5 month(s)											
										0 fewer per	
		not	not		not					1000	
	RC	seriou	seriou	not	seriou			0/47	RD 0.00	(6 fewer to 6	
2	Т	s	s	serious	s	NA	0/472	1	(-0.01, 0.01)	more)	high
persistent signs of worsening kidney											
disease at end of follow up											
Mean follow-up: 5.5 month(s)											
										0 fewer per	_
			not		not					1000	mod
	RC	seriou	seriou		seriou			0/17	RD 0.00	(11 fewer to	erat
1 (rosenstock 2015a)	Т	s^3	s	NA ⁴	s	NA	0/179	6	(-0.01, 0.01)	11 more)	е

GRADE tables – Model 5: Type 2 diabetes and higher cardiovascular risk

GRADE lables – Model 5. Type 2 diabetes and	mgmo	1 Odlalov	asoaiai ii	OIX				_			
diabetic ketoacidosis at end of follow up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2019d)	RC T	not seriou s	not seriou s	NA ⁴	not seriou s	NA	0/293	0/29 5	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	high
hypoglycaemia episodes at end of follow up Mean follow-up: 5.5 month(s)											
2	RC T	not seriou s	not seriou s	not serious	very seriou s ⁵	NA	8/472	6/47	RR 1.33 (0.47, 3.81)	4 more per 1000 (7 fewer to 36 more)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.5 month(s)											
2	RC T	not seriou s	not seriou s	serious	very seriou s ²	NA	1/472	0/46 9	RD 0.00 (-0.01, 0.01)	2 more per 1000 (5 fewer to 9 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
2	RC T	not seriou s	not seriou s	very serious	seriou s ⁷	NA	443	431	MD -0.75 (-1.61, 0.12)	MD 0.75 lower (1.61 lower to 0.12 higher)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)										y ,	
2	RC T	not seriou	not seriou s	not serious	not seriou s	NA	443	433	MD -1.79 (-2.22, - 1.36)	MD 1.79 lower (2.22 lower to 1.36 lower)	high

^{1.} 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 = 0.29 (0.8-0.9 = serious, <0.8 = very serious).

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

L.1.8.12 Adding dapagliflozin + saxagliptin compared to adding sitagliptin

Table 101: Clinical evidence profile: Adding dapagliflozin + saxagliptin compared to adding sitagliptin

	De			<u>-</u>		Other	3 3-		Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow up Mean follow-up: 12 month(s)											
4.44	RC	very seriou	not seriou	N14.2	not seriou		0/000	0/22	RD 0.00	0 fewer per 1000 (8 fewer to 8	
1 (handelsman 2019)	1	s ¹	S	NA ²	S	NA	0/232	9	(-0.01, 0.01)	more)	low
cardiovascular mortality at end of follow											
up Mean follow-up: 12 month(s)											
1 (handelsman 2019)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	0/232	0/22 9	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	low
acute kidney injury at end of follow up Mean follow-up: 12 month(s)									, , ,	,	

GRADE tables – Model 5: Type 2 diabetes and higher cardiovascular risk

OTABL tables Woder 5. Type 2 diabetes and	Ingilo	- cararer	l accuration					1	DETO OB	1 4	
		om/	not		l von				PETO OR 7.29	4 more per 1000	
	RC	very seriou	not seriou		very seriou			0/22	(0.14,	(4 fewer to	very
1 (handelsman 2019)	T	s ¹	S	NA ²	s ³	NA	1/232	9	367.63)	13 more)	low
cardiac arrhythmia at end of follow up				10,		101	17202		007.007	10 111010)	1011
Mean follow-up: 12 month(s)											
										18 fewer per	
		very	not		very				PETO OR	1000	
4 (1 1 1 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	RC	seriou	seriou		seriou		4/000	5/22	0.26	(38 fewer to	very
1 (handelsman 2019)	ı	s ¹	S	NA ²	s ³	NA	1/232	9	(0.05, 1.28)	3 more)	low
hypoglycaemia episodes at end of follow up											
Mean follow-up: 12 month(s)											
										12 more per	
		very	not		very					1000	
	RC	seriou	seriou		seriou			9/22	RR 1.32	(17 fewer to	very
1 (handelsman 2019)	Т	s ¹	S	NA ²	s ³	NA	12/232	9	(0.57, 3.06)	81 more)	low
severe hypoglycaemic episodes at end											
of follow up Mean follow-up: 12 month(s)											
mean follow-up: 12 month(3)										0 fewer per	
		very	not		not					1000	
	RC	seriou	seriou		seriou			0/22	RD 0.00	(8 fewer to 8	
1 (handelsman 2019)	Т	s ¹	s	NA ²	s	NA	0/232	9	(-0.01, 0.01)	more)	low
hba1c change (%, lower values are											
better, change scores) at end of follow											
up Mean follow-up: 12 month(s)											
Mean follow-up. 12 month(s)										MD 0.48	
										lower	
		very	not						MD -0.48	(0.72 lower	
	RC	seriou	seriou		seriou				(-0.72, -	to 0.24	very
1 (handelsman 2019)	Т	s ¹	S	NA ²	s ⁴	NA	232	229	0.24)	lower)	low
weight change (kg, lower values are											
better, change scores) at end of follow											
up Mean follow-up: 12 month(s)											
mount on a prinz monthly											

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										MD 1.50	
										lower	
		very	not		not				MD -1.50	(2.33 lower	
	RC	seriou	seriou		seriou				(-2.33, -	to 0.67	
1 (handelsman 2019)	Τ	s ¹	S	NA^2	s	NA	232	229	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. 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)

L.1.8.13 Adding empagliflozin + liraglutide compared to adding empagliflozin

Table 102: Clinical evidence profile: Adding empagliflozin + liraglutide compared to adding empagliflozin

	D-	Diele				Othor			Dolotivo		Cont
	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	У
hba1c change (%, lower values are better, final scores) at end of follow up Mean follow-up: 12 month(s)											
1 (ikonomidis 2020)	RC T	seriou s ¹	not seriou s	NA ²	seriou s³	NA	40	40	MD -0.70 (-1.12, - 0.28)	MD 0.70 lower (1.12 lower to 0.28 lower)	low
weight change (kg, lower values are better, final scores) at end of follow up Mean follow-up: 12 month(s)											
1 (ikonomidis 2020)	RC T	seriou s ¹	not seriou s	NA ²	very seriou s ⁴	NA	40	40	MD 1.10 (-3.07, 5.27)	MD 1.10 higher (3.07 lower to 5.27 higher)	very low
bmi change (kg/m2, lower values are better, final scores) at end of follow up Mean follow-up: 12 month(s)											

GRADE tables - Model 5: Type 2 diabetes and higher cardiovascular risk

										MD 1.10	
			not							lower	
	RC	seriou	seriou		seriou				MD -1.10	(2.49 lower to	
1 (ikonomidis 2020)	T	s ¹	S	NA^2	s ⁵	NA	40	40	(-2.49, 0.29)	0.29 higher)	low

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

L.1.8.14 Adding empagliflozin + liraglutide compared to adding insulin

Table 103: Clinical evidence profile: Adding empagliflozin + liraglutide compared to adding insulin

rable 100: Officer evidence profile: Ad	·····	<u> </u>		ag.at.	<u> </u>	tarea to ada					
	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
hba1c change (%, lower values are											
better, final scores) at end of follow up											
Mean follow-up: 12 month(s)											
										MD 0.70	
			not						MD -0.70	lower	
	RC	seriou	seriou		seriou				(-1.15, -	(1.15 lower to	
1 (ikonomidis 2020)	Т	s ¹	s	NA ²	s^3	NA	40	40	0.25)	0.25 lower)	low
weight change (kg, lower values are											
better, final scores) at end of follow up											
Mean follow-up: 12 month(s)											
										MD 1.80	
			not							lower	
	RC	seriou	seriou		seriou				MD -1.80	(5.74 lower to	
1 (ikonomidis 2020)	Т	s ¹	s	NA ²	s ⁴	NA	40	40	(-5.74, 2.14)	2.14 higher)	low
bmi change (kg/m2, lower values are											
better, final scores) at end of follow up											

GRADE tables - Model 5: Type 2 diabetes and higher cardiovascular risk

Mean follow-up: 12 month(s)											
										MD 2.30	
			not						MD -2.30	lower	
	RC	seriou	seriou		seriou				(-3.85, -	(3.85 lower to	
1 (ikonomidis 2020)	Т	s ¹	S	NA ²	s ⁵	NA	40	40	0.75)	0.75 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 one end of the defined MIDs (-0.50, 0.50)
- 4. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)
- 5. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

L.1.8.15 Adding empagliflozin + liraglutide compared to adding liraglutide

Table 104: Clinical evidence profile: Adding empagliflozin + liraglutide compared to adding liraglutide

	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
hba1c change (%, lower values are											
better, final scores) at end of follow up											
Mean follow-up: 12 month(s)											i
1 (ikonomidis 2020)	RC T	seriou s ¹	not seriou s	NA ²	seriou s³	NA	40	40	MD -0.30 (-0.67, 0.07)	MD 0.30 lower (0.67 lower to 0.07 higher)	low
weight change (kg, lower values are better, final scores) at end of follow up Mean follow-up: 12 month(s)											
1 (ikonomidis 2020)	RC T	seriou s ¹	not seriou s	NA ²	very seriou s ⁴	NA	40	40	MD 0.40 (-4.25, 5.05)	MD 0.40 higher (4.25 lower to 5.05 higher)	very low

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bmi change (kg/m2, lower values are better, final scores) at end of follow up Mean follow-up: 12 month(s)											
										MD 0.30	
			not		very					lower	
	RC	seriou	seriou		seriou				MD -0.30	(1.85 lower to	very
1 (ikonomidis 2020)	Т	s ¹	s	NA ²	s ⁵	NA	40	40	(-1.85, 1.25)	1.25 higher)	low

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

L.1.8.16 Adding ertugliflozin + sitagliptin compared to adding ertugliflozin

Table 105: Clinical evidence profile: Adding ertugliflozin + sitagliptin compared to adding ertugliflozin

	De					Other			Relative		Cert
	sig	Risk	Indire	Inconsi	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	of bias	ctness	stency	cision	ions	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RC	not seriou	not seriou	NA ¹	very seriou s ²	NA	1/487	1/49 8	PETO OR 1.02 (0.06, 16.37)	0 more per 1000 (6 fewer to 6 more)	low
cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)		3	3	10.1	3		17401	<u> </u>	10.07)	more	1000
1 (pratley 2018a)	RC T	not seriou s	not seriou s	NA ¹	very seriou s ²	NA	0/487	1/49 8	PETO OR 0.14 (0.00, 6.97)	2 fewer per 1000 (6 fewer to 2 more)	low

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diabetic ketoacidosis at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RC T	not seriou s	not seriou s	NA¹	very seriou s ²	NA	1/487	0/49	PETO OR 7.56 (0.15, 380.98)	2 more per 1000 (2 fewer to 6 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RC T	very seriou s ³	not seriou s	NA ¹	very seriou s ²	NA	22/487	15/4 98	RR 1.50 (0.79, 2.86)	15 more per 1000 (6 fewer to 56 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RC T	very seriou s ³	not seriou s	NA ¹	very seriou s ²	NA	0/487	2/49 8	PETO OR 0.14 (0.01, 2.21)	4 fewer per 1000 (10 fewer to 2 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RC T	very seriou s ³	not seriou s	NA¹	seriou s ⁴	NA	487	498	MD -0.50 (-0.64, - 0.36)	MD 0.50 lower (0.64 lower to 0.36 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)										,	
	RC	very seriou	not seriou	NIA 1	not seriou	NA	407	400	MD 0.20	MD 0.20 higher (0.37 lower to	law
1 (pratley 2018a)	Т	s ³	S	NA ¹	S	NA	487	498	(-0.37, 0.77)	0.77 higher)	low

1. Only one study so no inconsistency

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

L.1.8.17 Adding ertugliflozin + sitagliptin compared to adding sitagliptin

Table 106: Clinical evidence profile: Adding ertugliflozin + sitagliptin compared to adding sitagliptin

Table 106. Cliffical evidence profile. Add		l	2111 - 01	lagnpun	Oompar		Jonagne		Dalativa		Cont
	De					Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RC T	not seriou s	not seriou s	NA ¹	very seriou s ²	NA	1/487	0/24 7	PETO OR 4.51 (0.07, 285.75)	2 more per 1000 (2 fewer to 6 more)	low
cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RC T	not seriou s	not seriou s	NA ¹	not seriou s	NA	0/487	0/24 7	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	high
diabetic ketoacidosis at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RC T	not seriou s	not seriou s	NA ¹	very seriou s ²	NA	1/487	0/24 7	PETO OR 4.51 (0.07, 285.75)	2 more per 1000 (2 fewer to 6 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 12 month(s)											

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71				1						1	
1 (pratley 2018a)	RC T	very seriou s ³	not seriou s	NA ¹	very seriou s ²	NA	22/487	7/24 7	RR 1.59 (0.69, 3.68)	17 more per 1000 (9 fewer to 76 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RC T	very seriou s ³	not seriou s	NA ¹	not seriou s	NA	0/487	0/24	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RC T	very seriou s ³	not seriou s	NA¹	seriou s ⁴	NA	487	247	MD -0.60 (-0.77, - 0.43)	MD 0.60 lower (0.77 lower to 0.43 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RC T	very seriou s ³	not seriou s	NA ¹	seriou s ⁵	NA	487	247	MD -2.50 (-3.23, - 1.77)	MD 2.50 lower (3.23 lower to 1.77 lower)	very low

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

end of the defined MIDs (-2.40, 2.40)

L.1.8.18 Adding glimepiride + metformin compared to adding glimepiride

Table 107: Clinical evidence profile: Adding glimepiride + metformin compared to adding glimepiride

Table 107: Clinical evidence profile: Add		Jiiiicpiii	uc · 1110	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	Compan		giiiicpii	lac	5.1		
	De					Other			Relative		Cert
	sig	Risk	Indire	Inconsi	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	of bias	ctness	stency	cision	ions	ntion N	rol N	CI)	effect	У
hypoglycaemia episodes at end of follow											
up											
Mean follow-up: 5.5 month(s)										F7 (
		1/05/	not		Von					57 fewer per 1000	
	RC	very seriou	not seriou		very seriou			20/3	RR 0.90	(243 fewer to	very
1 (park 2014)	T	s ¹	S	NA ²	s ³	NA	17/32	4	(0.59, 1.39)	229 more)	low
at night hypoglycaemic episodes at end		J	<u> </u>	147 (J	10.0	11702		(0.00, 1.00)	ZZO IIIOIO)	1000
of follow up											
Mean follow-up: 5.5 month(s)											
										83 fewer per	
		very	not		very					1000	
	RC	seriou	seriou	0	seriou				RR 0.53	(151 fewer to	very
1 (park 2014)	Т	s ¹	S	NA ²	s ³	NA	3/32	6/34	(0.14, 1.95)	167 more)	low
severe hypoglycaemic episodes at end											
of follow up											
Mean follow-up: 5.5 month(s)										0 fewer per	
		very	not		very					1000	
	RC	seriou	seriou		seriou				RD 0.00	(57 fewer to	very
1 (park 2014)	T	s ¹	S	NA^2	s ⁴	NA	0/32	0/34	(-0.06, 0.06)	57 more)	low
hba1c change (%, lower values are									,,,	,	
better, change scores) at end of follow											
up											
Mean follow-up: 5.5 month(s)											
		very	not						MD -0.71		
4 (1 0044)	RC	seriou	seriou	N1A2	seriou		00	00	(-1.20, -	MD 0.71	very
1 (park 2014)	Т	s ¹	S	NA ²	s ⁵	NA	32	32	0.22)	lower	low

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										(1.20 lower to 0.22 lower)	
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
1 (park 2014)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	32	32	MD 0.12 (-1.25, 1.49)	MD 0.12 higher (1.25 lower to 1.49 higher)	low

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

L.1.8.19 Adding glimepiride + metformin compared to adding metformin

Table 108: Clinical evidence profile: Adding glimepiride + metformin compared to adding metformin

	De					Other			Relative		Cert
	sig	Risk	Indire	Inconsi	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	of bias	ctness	stency	cision	ions	ntion N	rol N	CI)	effect	у
hypoglycaemia episodes at end of follow											
up											
Mean follow-up: 5.5 month(s)											
										57 fewer per	
		very	not		very					1000	
	RC	seriou	seriou		seriou			20/3	RR 0.90	(243 fewer to	very
1 (park 2014)	Т	s ¹	s	NA ²	s^3	NA	17/32	4	(0.59, 1.39)	229 more)	low

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at night hypoglycaemic episodes at end of follow up Mean follow-up: 5.5 month(s)											
1 (park 2014)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	3/32	6/34	RR 0.53 (0.14, 1.95)	83 fewer per 1000 (151 fewer to 167 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.5 month(s)											
1 (park 2014)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ⁴	NA	0/32	0/34	RD 0.00 (-0.06, 0.06)	0 fewer per 1000 (57 fewer to 57 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
1 (park 2014)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s ⁵	NA	32	32	MD -0.71 (-1.20, - 0.22)	MD 0.71 lower (1.20 lower to 0.22 lower)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
1 (park 2014)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	32	32	MD 0.12 (-1.25, 1.49)	MD 0.12 higher (1.25 lower to 1.49 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. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.

end of the defined MIDs (-0.50, 0.50)

L.1.8.20 Adding glimepiride + metformin slow release compared to adding glimepiride + metformin standard release

Table 109: Clinical evidence profile: Adding glimepiride + metformin slow release compared to adding glimepiride + metformin standard release

1010030											
						Other			Relative		
	Des	Risk of	Indirec	Inconsis	Impreci	consideratio	Interven	Contr	effect (95%	Absolute	Certa
No of studies	ign	bias	tness	tency	sion	ns	tion N	ol N	CI)	effect	inty
hypoglycaemia episodes at end of follow up Mean follow-up: 5.8 month(s)											
1 (kim 2018)	RC T	very serious	not serious	NA ²	serious	NA	19/86	10/86	RR 1.90 (0.94, 3.85)	105 more per 1000 (7 fewer to 331 more)	very low
at night hypoglycaemic episodes at end of follow up Mean follow-up: 5.8 month(s)											
1 (kim 2018)	RC T	very serious	not serious	NA ²	very serious	NA	3/86	5/86	RR 0.60 (0.15, 2.43)	23 fewer per 1000 (50 fewer to 83 more)	very low

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

compared to adding metformin

Table 110: Clinical evidence profile: Adding liraglutide + metformin compared to adding metformin

	De					Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	У
hba1c change (%, lower values are better, final values) at end of follow up Mean follow-up: 6 month(s)											
1 (iacobellis 2017)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s³	NA	49	36	MD -0.80 (-1.13, - 0.47)	MD 0.80 lower (1.13 lower to 0.47 lower)	very low
bmi change (kg/m2, lower values are better, final values) at end of follow up Mean follow-up: 6 month(s)											
1 (iacobellis 2017)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	49	36	MD 4.00 (1.92, 6.08)	MD 4.00 higher (1.92 higher to 6.08 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)

compared to adding pioglitazone

Table 111: Clinical evidence profile: Adding pioglitazone + alogliptin compared to adding pioglitazone

Table 111. Chilical evidence profile. Ad	De					Other	, progrita.		Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow up Mean follow-up: 6 month(s)											
1 (defronzo 2012)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	0/780	1/38 7	PETO OR 0.05 (0.00, 3.15)	3 fewer per 1000 (8 fewer to 2 more)	very low
cardiovascular mortality at end of follow up Mean follow-up: 6 month(s)											
1 (defronzo 2012)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	0/780	1/38 7	PETO OR 0.05 (0.00, 3.15)	3 fewer per 1000 (8 fewer to 2 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 6 month(s)											
1 (defronzo 2012)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	10/780	8/38 7	RR 0.62 (0.25, 1.56)	8 fewer per 1000 (16 fewer to 12 more)	very low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)											
1 (defronzo 2012)	RC T	very seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	1/780	2/38 7	PETO OR 0.22 (0.02, 2.44)	4 fewer per 1000 (11 fewer to 4 more)	very low
hba1c change (%, lower values are better, change scores) at end of follow up											

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Mean follow-up: 6 month(s)											
	RC	very seriou	not seriou		seriou				MD -0.50 (-0.62, -	MD 0.50 lower (0.62 lower to 0.38	very
1 (defronzo 2012)	Т	s ¹	S	NA ²	s ⁴	NA	659	274	0.38)	lower)	low

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

L.1.8.23 Adding pioglitazone + exenatide compared to adding insulin

Table 112: Clinical evidence profile: Adding pioglitazone + exenatide compared to adding insulin

	De	Risk			•	Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
all-cause mortality at end of follow up Mean follow-up: 36 month(s)											
1 (abdul-ghani 2017)	RC T	seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	1/146	2/14 0	PETO OR 0.49 (0.05, 4.75)	7 fewer per 1000 (31 fewer to 16 more)	very low
non-fatal stroke at end of follow up Mean follow-up: 36 month(s)											
1 (abdul-ghani 2017)	RC T	seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	0/146	2/14 0	PETO OR 0.13 (0.01, 2.07)	14 fewer per 1000 (34 fewer to 5 more)	very low
hospitalisation for heart failure at end of follow up											

GRADE tables - Model 5: Type 2 diabetes and higher cardiovascular risk

Mean follow-up: 36 month(s)											
1 (abdul-ghani 2017)	RC T	seriou s ¹	not seriou s	NA ²	seriou s ⁴	NA	0/146	0/14 0	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 36 month(s)											
1 (abdul-ghani 2017)	RC T	seriou s ¹	not seriou s	NA ²	seriou s ⁴	NA	99/146	125/ 140	RR 0.76 (0.67, 0.86)	215 fewer per 1000 (295 fewer to 124 fewer)	low
severe hypoglycaemic episodes at end of follow up Mean follow-up: 36 month(s)											
1 (abdul-ghani 2017)	RC T	seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	0/146	1/14 0	PETO OR 0.13 (0.00, 6.54)	7 fewer per 1000 (21 fewer to 7 more)	very low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 36 month(s)											
1 (abdul-ghani 2017)	RC T	seriou s ¹	not seriou s	NA ²	not seriou s	NA	146	140	MD -4.40 (-4.73, - 4.07)	MD 4.40 lower (4.73 lower to 4.07 lower)	mod erat e

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

L.1.8.24 Adding pioglitazone + exenatide compared to adding pioglitazone

Table 113: Clinical evidence profile: Adding pioglitazone + exenatide compared to adding pioglitazone

rable 113. Chilical evidence profile. Ac	uning	piogiita	ZUITE T E	zxenanu	Compa	red to addin	ig ploglite	azone			
	De					Other			Relative		Cert
	sig	Risk of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	У
hba1c change (%, lower values are better, final values) at end of follow up Mean follow-up: 12 month(s)											
1 (sathyanarayana 2011)	RC T	very seriou s ¹	seriou s ²	NA ³	seriou s ⁴	NA	11	10	MD -0.50 (-0.80, - 0.20)	MD 0.50 lower (0.80 lower to 0.20 lower)	very low
weight change (kg, lower values are better, final values) at end of follow up Mean follow-up: 12 month(s)											
1 (sathyanarayana 2011)	RC T	very seriou s ¹	seriou s ²	NA ³	very seriou s ⁵	NA	11	10	MD -1.10 (-6.54, 4.34)	MD 1.10 lower (6.54 lower to 4.34 higher)	very low
bmi change (kg/m2, lower values are better, final values) at end of follow up Mean follow-up: 12 month(s)											
1 (sathyanarayana 2011)	RC T	very seriou s ¹	seriou s ²	NA ³	not seriou s	NA	11	10	MD 3.40 (1.83, 4.97)	MD 3.40 higher (1.83 higher to 4.97 higher)	very low

- 1. >33.3% of the studies in the meta-analysis were at high risk of bias
- 2. Largest proportion of studies in the meta-analysis came from partially direct studies
- 3. Only one study so no inconsistency

end of the defined MIDs (-0.50, 0.50)

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

L.1.8.25 Adding pioglitazone + metformin compared to adding metformin

Table 114: Clinical evidence profile: Adding pioglitazone + metformin compared to adding metformin

- 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	and it is considered promotive and programation														
	De	Risk				Other			Relative		Cert				
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint				
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у				
hypoglycaemia episodes at end of															
follow up															
Mean follow-up: 6 month(s)															
										68 more per					
			not		very					1000					
	RC	seriou	seriou		seriou				RR 1 32	(83 fewer to	very				
1 (hanefeld 2011)	T	s ¹	S	NA ²	s ³	NA	11/39	9/42	(0.61, 2.83)	392 more)	low				
hba1c change (%, lower values are															
Mean follow-up: 6 month(s)															
. , ,										MD 0.38					
			not						MD -0.38	lower					
	RC	seriou	seriou		seriou				(-0.70	(0.70 lower to					
1 (hanefeld 2011)	T			NA ²	s ⁴	NA	37	39		,	low				
hba1c change (%, lower values are better, final values) at end of follow up	RC T	seriou s ¹ seriou s ¹	seriou s	NA ²	seriou s³	NA NA	11/39	9/42		(83 fewer to 392 more) MD 0.38					

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

compared to adding pioglitazone

Table 115: Clinical evidence profile: Adding pioglitazone + metformin compared to adding pioglitazone

Table 110. Chimodi Ovidence prome. At	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
hypoglycaemia episodes at end of follow up Mean follow-up: 6 month(s)											
1 (hanefeld 2011)	RC T	seriou s ¹	not seriou s	NA ²	very seriou s ³	NA	11/39	8/40	RR 1.41 (0.64, 3.13)	82 more per 1000 (73 fewer to 426 more)	very low
hba1c change (%, lower values are better, final values) at end of follow up Mean follow-up: 6 month(s)											
1 (hanefeld 2011)	RC T	seriou s ¹	not seriou s	NA ²	seriou s ⁴	NA	37	37	MD -0.34 (-0.68, - 0.00)	MD 0.34 lower (0.68 lower to 0.00 lower)	low

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

L.2 Switching

L.2.1 Metformin

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

Table 116: Clinical evidence profile: Switching to metformin slow release compared to staying on metformin standard release

Table 110. Official evidence pr						Other			Relative		
	D	Diele ef	1		•	0.000		C		A la a a la a la	C
	Des	Risk of	Indirec	Inconsis	Impreci	consideratio	Interven	Contr	effect (95%	Absolute	Certa
No of studies	ign	bias	tness	tency	sion	ns	tion N	ol N	CI)	effect	inty
all-cause mortality at end of											
follow up											
Mean follow-up: 6 month(s)											
										7 more per	
		very			very				PETO OR	1000	
	RC	serious	not		serious				4.54	(7 fewer to	verv
1 (fujioka 2003)	Т	1	serious	NA ²	3	NA	1/146	0/75	(0.07, 285.16)	20 more)	low
hypoglycaemia episodes at									,	,	
end of follow up											
Mean follow-up: 6 month(s)											
										6 fewer per	
		very			very					1000	
	RC	serious	not		serious				RR 0.51	(13 fewer to	very
1 (fujioka 2003)	T	1	serious	NA ²	3	NA	1/146	1/75	(0.03, 8.10)	95 more)	low
severe hypoglycaemic	-						.,		(0.00)		
episodes at end of follow up											
Mean follow-up: 6 month(s)											
mountaines apromonanto										0 fewer per	
		very								1000	
	RC	serious	not		serious				RD 0.00	(20 fewer to	very
1 (fujioka 2003)	T	1	serious	NA ²	4	NA	0/146	0/75	(-0.02, 0.02)	20 more)	low
i (lujioka 2000)			Scrious	INA		11/7	0/170	0//3	(-0.02, 0.02)	20 111016)	IUW

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

^{2.} Only one study so no inconsistency

3. 95% confidence intervals cross both

ends of the defined MIDs (0.80, 1.25)

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

L.2.2 DPP-4 inhibitors

L.2.2.1 Switching to sitagliptin compared to switching to placebo

Table 117: Clinical evidence profile: Switching to sitagliptin compared to switching to placebo

	_					Other		_	Relative		
	Des	Risk of	Indirec	Inconsi	Imprec	considerati	Interve	Cont	effect (95%		Cert
No of studies	ign	bias	tness	stency	ision	ons	ntion N	rol N	CI)	Absolute effect	ainty
hypoglycaemia episodes											
at end of follow up											
		very			very						
	RC	serious	seriou		serious				RR 1.10	9 more per 1000 (84	very
1 (retnakaran 2010)	Т	1	s ²	NA ³	4	NA	1/10	1/11	(0.08, 15.36)	fewer to 1305 more)	low

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

L.2.2.2 Switching to vildagliptin compared to switching to alogliptin

Table 118: Clinical evidence profile: Switching to vildagliptin compared to Switching to alogliptin

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

GRADE tables – Model 5: Type 2 diabetes and higher cardiovascular risk

hypoglycaemia episodes at end of follow-up											
Mean follow-up: 5.5 month(s)											
1 (tanaka 2017)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	68/68	62/6 2	RR 1.00 (0.97, 1.03)	0 fewer per 1000 (29 fewer to 30 more)	low
severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)										,	
1 (tanaka 2017)	RC T	very seriou s ¹	not seriou s	NA ²	seriou s³	NA	0/68	0/62	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (30 fewer to 30 more)	very low
hba1c change (%, lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (tanaka 2017)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	63	62	MD -0.20 (-0.43, 0.03)	MD 0.20 lower (0.43 lower to 0.03 higher)	low
weight change (kg, lower values are better, change scores) at end of follow- up Mean follow-up: 5.5 month(s)											
1 (tanaka 2017)	RC T	very seriou s ¹	not seriou s	NA ²	not seriou s	NA	63	62	MD -0.10 (-0.74, 0.54)	MD 0.10 lower (0.74 lower to 0.54 higher)	low

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

L.2.3.1 Switching to liraglutide compared to staying on sitagliptin

Table 119: Clinical evidence profile: Switching to liraglutide compared to staying on sitagliptin

Table 119: Clinical evidence profile: Swi		_	giutiae	compare	d to sta		giiptin				Ι
	De	Risk				Other		_	Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	У
all-cause mortality at the end of follow-up											
Mean follow-up: 5.5 month(s)										_	
									PETO OR	5 more per	
		_	not		very				7.32	1000	
	RC	seriou	seriou		seriou	1		0/20	(0.15,	(5 fewer to	very
1 (bailey 2016)	Т	s ¹	S	NA ²	s ³	NA	1/204	2	368.77)	14 more)	low
hypoglycaemia episodes at the end of											
follow-up											
Mean follow-up: 5.5 month(s)											
									5555 65	15 fewer per	
			not _.		very			0.400	PETO OR	1000	
4 (1 11 0040)	RC	seriou	seriou		seriou		0/004	3/20	0.13	(32 fewer to	very
1 (bailey 2016)	Т	s ¹	S	NA ²	s ³	NA	0/204	2	(0.01, 1.28)	2 more)	low
severe hypoglycaemic episodes at the											
end of follow-up											
Mean follow-up: 5.5 month(s)											
										0 fewer per	١.
	D O		not .		not .			0.400	DD 0 00	1000	mod
4 (- 1 0040)	RC	seriou	seriou	NIA?	seriou		0/004	0/20	RD 0.00	(10 fewer to	erat
1 (bailey 2016)	I	s ¹	S	NA ²	S	NA	0/204	2	(-0.01, 0.01)	10 more)	е
hba1c change (%, lower values are											
better, final values) at the end of follow-											
up											
Mean follow-up: 5.5 month(s)										MD 0 C4	4
										MD 0.61	
									MD 0.04	lower	
	D0		not						MD -0.61	(0.82 lower	
4 (1 - 11 0040)	RC	seriou	seriou	NIA?	seriou	N10	004	000	(-0.82, -	to 0.40	
1 (bailey 2016)	T	s ¹	S	NA ²	s ⁴	NA	204	202	0.40)	lower)	low

GRADE tables – Model 5: Type 2 diabetes and higher cardiovascular risk

weight change (kg, lower values are better, change scores) at end of follow- up Mean follow-up: 5.5 month(s)											
1 (bailey 2016)	RC T	seriou s ¹	not seriou s	NA ²	not seriou s	NA	204	202	MD -1.67 (-2.34, - 1.00)	MD 1.67 lower (2.34 lower to 1.00 lower)	mod erat e

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

L.2.3.2 Switching to semagluitde compared to switching to dulaglutide

Table 120: Clinical evidence profile: Switching to semaglutide compared to switching to dulaglutide

	De	Risk		•		Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
hypoglycaemia episodes at end of follow											
up											
Mean follow-up: 6 month(s)											
1 (lijima 2023)	RC T	seriou	not seriou s	NA 2	very seriou s ³	NA	0/16	0/16	RD 0.00 (-0.11, 0.11)	0 fewer per 1000 (114 fewer to 114 more)	very
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)	•	-			3		3, 13	3, 10	(5, 6.11)		15.7

GRADE tables - Model 5: Type 2 diabetes and higher cardiovascular risk

1 (lijima 2023)	RC T	seriou s ¹	not seriou s	NA ²	seriou s ⁴	NA	16	16	MD -0.42 (-0.71, - 0.13)	MD 0.42 lower (0.71 lower to 0.13 lower)	low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)											
1 (lijima 2023)	RC T	seriou s¹	not seriou s	NA ²	seriou s ⁵	NA	16	16	MD -2.50 (-4.70, -	MD 2.50 lower (4.70 lower to 0.30 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. 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)
- 5. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

L.2.3.3 Switching to semaglutide compared to staying on sitagliptin

Table 121: Clinical evidence profile - Switching to semaglutide compared to staying on sitagliptin

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint v
all-cause mortality at end of follow up Mean follow-up: 12 month(s)				,					•		
1 (buse 2020)	RC T	not serio us	not seriou s	NA ¹	seriou s²	NA	0/100	0/97	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	mod erat e

GRADE tables – Model 5: Type 2 diabetes and higher cardiovascular risk

GNADE lables – Wodel 5. Type 2 diabetes and	riigiic	Caraiov	asculai II	31(_			
cardiovascular mortality at end of follow											
up											
Mean follow-up: 12 month(s)											
										0 fewer per	
		not	not							1000	mod
	RC	serio	seriou		seriou				RD 0.00	(20 fewer to	erat
1 (buse 2020)	Т	us	S	NA ¹	s ²	NA	0/100	0/97	(-0.02, 0.02)	20 more)	е
non-fatal myocardial infaRCTion at end of											
follow up											
Mean follow-up: 12 month(s)											
										0 fewer per	
		not	not							1000	mod
	RC	serio	seriou		seriou				RD 0.00	(20 fewer to	erat
1 (buse 2020)	Т	us	S	NA ¹	s ²	NA	0/100	0/97	(-0.02, 0.02)	20 more)	е
hospitalisation for heart failure at end of											
follow up											
Mean follow-up: 12 month(s)											
										10 fewer per	
		not _.	not _.		very				PETO OR	1000	
4 (1 0000)	RC	serio	seriou		seriou		0/400	4.07	0.13	(30 fewer to	١. ا
1 (buse 2020)	I	us	S	NA ¹	s ³	NA	0/100	1/97	(0.00, 6.62)	10 more)	low
acute kidney injury at end of follow up											
Mean follow-up: 12 month(s)										0.6	
										0 fewer per	
	- DO	not	not						DD 0 00	1000	mod
4 (1 0000)	RC	serio	seriou	N 1 A 1	seriou	NIA.	0/400	0.07	RD 0.00	(20 fewer to	erat
1 (buse 2020)	ı	us	S	NA ¹	s ²	NA	0/100	0/97	(-0.02, 0.02)	20 more)	е
at night hypoglycaemic episodes at end											
of follow up											
Mean follow-up: 12 month(s)										0 f	
		not	not							0 fewer per	med
	DC	not	not						DD 0 00	1000	mod
1 (huga 2020)	RC	serio	seriou	NIA1	seriou s ²	NIA	0/400	0/07	RD 0.00	(20 fewer to	erat
1 (buse 2020)	I	us	S	NA ¹	S ²	NA	0/100	0/97	(-0.02, 0.02)	20 more)	е
severe hypoglycaemic episodes at end of											
follow up											
Mean follow-up: 12 month(s)											

GRADE tables - Model 5: Type 2 diabetes and higher cardiovascular risk

1 (buse 2020)	RC T	not serio us	not seriou s	NA ¹	seriou s ²	NA	0/100	0/97	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	mod erat e
hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (buse 2020)	RC T	serio us ⁴	not seriou s	NA ¹	seriou s ⁵	NA	100	98	MD -0.30 (-0.60, 0.00)	MD 0.30 lower (0.60 lower to 0.00 higher)	low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (buse 2020)	RC T	serio us ⁴	not seriou s	NA ¹	seriou s ⁶	NA	100	98	MD -1.50 (-2.85, - 0.15)	MD 1.50 lower (2.85 lower to 0.15 lower)	low
bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (buse 2020)	RC T	serio us ⁴	not seriou s	NA ¹	seriou s ⁷	NA	100	98	MD -0.40 (-0.90, 0.10)	MD 0.40 lower (0.90 lower to 0.10 higher)	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 one end of the defined MIDs (-0.50, 0.50)
- 6. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

end of the defined MIDs (-0.80, 0.80)

L.2.4 SGLT2 inhibitors

L.2.4.1 Switching to canagliflozin compared to switching to liraglutide

Table 122: Clinical evidence profile: Switching to canagliflozin compared to switching to liraglutide

Table 122. Official evidence profile: Owitching to carr	De	Risk	Indir	Incon	Impr	Other	Interv	Con	Relative		Cer
					•				effect	Absoluto	
A. 6 . 19	sig	of	ectn	siste	ecisi	consider	entio	trol		Absolute	tain
No of studies	n	bias	ess	ncy	on	ations	n N	N	(95% CI)	effect	ty
health-related quality of life - overall (diabetes therapy-											
related qol, 0-100, higher values are better, change											
scores) at end of follow up											
Mean follow-up: 5.5 month(s)										145 0 50	
										MD 6.50	
									MD 0 50	higher	
	R	very	not						MD 6.50	(0.14 higher	ver
1 (and a 2021)	C	serio	serio	NIA2	serio us ³	NIA	47	47	(0.14,	to 12.86	У
1 (ando 2021)	I	us ¹	us	NA ²	us	NA	17	17	12.86)	higher)	low
severe hypoglycaemic episodes at end of follow up											
Mean follow-up: 5.5 month(s)										O former non	
	Ь								RD 0.00	0 fewer per	
	R C	very	not		very serio			0/1		1000 (95 fewer to	ver
1 (ando 2021)	 	serio us ¹	serio	NA ²	us ⁴	NA	0/20	9	(-0.09, 0.09)	95 newer to	У
	ı	us.	us	INA-	us.	INA	0/20	9	0.09)	95 more)	low
hba1c change (%, lower values are better, change scores) at end of follow up											
Mean follow-up: 5.5 month(s)											
weam follow-up. 5.5 month(5)										MD 0.10	
										higher	
	R	very	not						MD 0.10	(0.30 lower	ver
	C	serio	serio		serio				(-0.30,	to 0.50	
1 (ando 2021)	Т	us ¹	us	NA ²	us ⁵	NA	17	17	0.50)	higher)	y low
weight change (kg, lower values are better, change		us	us	INA	us	IVA	17	17	0.00)	riigiici j	1000
scores) at end of follow up											
Scores at end of follow up											

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Mean follow-up: 5.5 month(s)											
1 (ando 2021)	R C T	very serio us ¹	not serio us	NA ²	not serio us	NA	17	17	MD 0.20 (-1.89, 2.29)	MD 0.20 higher (1.89 lower to 2.29 higher)	low
bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
1 (ando 2021)	R C T	very serio us ¹	not serio us	NA ²	serio us ⁶	NA	17	17	MD 0.10 (-0.61, 0.81)	MD 0.10 higher (0.61 lower to 0.81 higher)	ver y 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 (-4.95, 4.95)
- 4. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 5. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 6. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

L.2.1 Sulfonylureas

L.2.1.1 Switching to glimepiride compared to switching to liraglutide

	Des	Risk of	Indirec	Inconsi	Impre	Other considerati	Interve	Cont	Relative effect (95%	Absolute	Cert
No of studies	ign	bias	tness	stency	cision	ons	ntion N	rol N	CI)	effect	ainty
hba1c change (%, lower values are better) at end of follow-up											
Mean follow-up: 12 month(s)											

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		very	not							MD 0.42 higher	
	RC	serious	seriou		seriou				MD 0.42	(0.21 higher to	very
1 (garber 2009)	Т	1	S	NA^2	s^3	NA	154	320	(0.21, 0.63)	0.63 higher)	low

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

L.2.2 Thiazolidinediones

L.2.2.1 Staying on pioglitazone compared to switching to dapagliflozin

Table 123: Clinical evidence profile: Staying on pioglitazone compared to switching to dapagliflozin

Table 120. Officer evidence profile. Of			J	<u> </u>	100.00			1			
	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	у
hypoglycaemia episodes at end of											
follow up											
Mean follow-up: 5.5 month(s)											
			not		very					63 more per 1000	
	RC	seriou	seriou		seriou				RR 1.32	(87 fewer to	very
1 (cho 2019)	Т	s ¹	s	NA ²	s^3	NA	9/35	7/36	(0.55, 3.16)	420 more)	low
severe hypoglycaemic episodes at end											
of follow up											
Mean follow-up: 5.5 month(s)											
	RC	seriou	not seriou		seriou				RD 0.00	0 fewer per 1000 (53 fewer to	
1 (cho 2019)	Т	s ¹	s	NA ²	s^4	NA	0/35	0/36	(-0.05, 0.05)	53 more)	low
hba1c change (%, lower values are											
better, final values) at end of follow up											

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Mean follow-up: 5.5 month(s)											
1 (cho 2019)	RC T	seriou s ¹	not seriou s	NA ²	not seriou s	NA	35	36	MD 0.10 (-0.25, 0.45)	MD 0.10 higher (0.25 lower to 0.45 higher)	mod erat e
weight change (kg, lower values are better, final values) at end of follow up Mean follow-up: 5.5 month(s)											
1 (cho 2019)	RC T	seriou s ¹	not seriou s	NA ²	very seriou s ⁵	NA	35	36	MD 3.90 (-2.85, 10.65)	MD 3.90 higher (2.85 lower to 10.65 higher)	very low

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

L.2.2.2 Switching to pioglitazone compared to switching to glimepiride

Table 124: Clinical evidence profile: Switching to pioglitazone compared with switching to glimepiride

	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	У
hypoglycaemia episodes at end of follow											
up											
Mean follow-up: 12 month(s)											
	DC.	not	not		aariau			20/4	DD 0.51	152 fewer per 1000	mod
1 (tan 2004)	RC T	seriou s	seriou s	NA ¹	seriou s ²	NA	19/121	38/1	RR 0.51 (0.31, 0.83)	(213 fewer to 53 fewer)	erat e

GRADE tables - Model 5: Type 2 diabetes and higher cardiovascular risk

hba1c change (%, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
mean renew up 12 menange,										MD 0.10	
		not	not		very					lower	
	RC	seriou	seriou		seriou				MD -0.10	(1.49 lower to	
1 (tan 2004)	Т	S	S	NA ¹	s^3	NA	109	109	(-1.49, 1.29)	1.29 higher)	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 (-0.50, 0.50)

L.2.3 Combinations

L.2.3.1 Switching to fixed-dose combination glimepiride/metformin slow release compared to staying on fixed-dose combination glimepiride/metformin standard release

Table 125: Clinical evidence profile: Fixed-dose combination glimepiride/metformin slow release compared to staying on fixed-dose

combination glimepiride/metformin standard release

	Des	Risk of	Indirec	Inconsis	Impreci	Other consideratio	Interven	Contr	Relative effect (95%	Absolute	Certa
No of studies	ign	bias	tness	tency	sion	ns	tion N	ol N	CI)	effect	inty
hypoglycaemia episodes at end of follow up Mean follow-up: 5.8 month(s)											
1 (kim 2018)	RC T	very serious	not serious	NA ²	serious	NA	19/86	10/86	RR 1.90 (0.94, 3.85)	105 more per 1000 (7 fewer to 331 more)	very low
at night hypoglycaemic episodes at end of follow up Mean follow-up: 5.8 month(s)										,	

GRADE tables - Model 5: Type 2 diabetes and higher cardiovascular risk

										23 fewer per	
		very			very					1000	
	RC	serious	not		serious				RR 0.60	(50 fewer to	very
1 (kim 2018)	T	1	serious	NA ²	4	NA	3/86	5/86	(0.15, 2.43)	83 more)	low

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