National Institute for Health and Care Excellence

Draft for consultation

Type 2 diabetes in adults: management

[F6] 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 K Forest plots – Model 5: Type 2 diabetes and higher cardiovascular risk

K.1 Adding

K.1.1 Metformin

K.1.1.1 Adding metformin compared to adding placebo

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

	Metfor	min	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events Total Events Total		Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI		
Kooy 2009	9	196	6	194	87.9%	1.50 [0.53, 4.20]	-
Lundby-Christensen 2016	2	206	0	206	12.1%	7.43 [0.46, 119.11]	-
Total (95% CI)		402		400	100.0%	1.82 [0.69, 4.78]	•
Total events	11		6				
Heterogeneity: Chi² = 1.12, d	lf=1 (P=	0.29); f	² =11%				0.001 0.1 1 10 1000
Test for overall effect: Z = 1.2	1 (P = 0.2	22)					Favours Metformin Favours Placebo

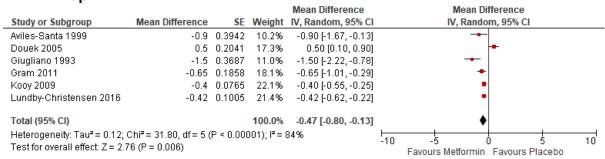
Figure 2: Hypoglycaemia episodes at end of follow up

	Metfor	min	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Aviles-Santa 1999	3	21	3	22	1.0%	1.05 [0.24, 4.62]	
Douek 2005	63	77	48	73	17.3%	1.24 [1.02, 1.51]	-
Gram 2011	69	90	78	94	26.8%	0.92 [0.80, 1.07]	+
Lundby-Christensen 2016	156	206	156	206	54.8%	1.00 [0.90, 1.12]	•
Total (95% CI)		394		395	100.0%	1.02 [0.94, 1.11]	•
Total events	291		285				
Heterogeneity: Chi² = 5.85, o	df = 3 (P =	0.12); (² = 49%				0.01 0.1 10 100
Test for overall effect: $Z = 0.5$	54 (P = 0.5	i9)					0.01 0.1 1 10 100 Favours Metformin Favours Placebo

Figure 3: Severe hypoglycaemic episodes at end of follow up

	Metfor	Metformin Placebo				Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	otal Weight M-H, Random, 95% Cl		M-H, Random, 95% CI
Douek 2005	10	77	1	73	42.8%	9.48 [1.24, 72.22]	
Lundby-Christensen 2016	7	206	7	206	57.2%	1.00 [0.36, 2.80]	-
Total (95% CI)		283		279	100.0%	2.62 [0.27, 25.56]	
Total events	17		8				
Heterogeneity: Tau² = 2.09;	$Chi^2 = 4.09$	9, df = 1	(P = 0.0)	4); ² = '	76%		0.01 0.1 1 10 100
Test for overall effect: $Z = 0.8$	33 (P = 0.4	1)					Favours Metformin Favours Placebo

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



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

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

			Metformin	Placebo		Mean Difference		Mean Difference	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI	
Aviles-Santa 1999	-2.7	1.4656	21	22	24.0%	-2.70 [-5.57, 0.17]			
Douek 2005	1.5	0.6888	71	71	30.2%	1.50 [0.15, 2.85]			
Gram 2011	-1.21	2.8423	90	94	13.8%	-1.21 [-6.78, 4.36]			
Lundby-Christensen 2016	-2.6	0.3749	206	206	31.9%	-2.60 [-3.33, -1.87]		-	
Total (95% CI)			388		100.0%	-1.19 [-3.92, 1.54]		-	
Heterogeneity: Tau² = 5.95; 0 Test for overall effect: Z = 0.8		P < 0.00	001); l² = 89°	%			-10	-5 0 5 Favours Metformin Favours Placebo	10

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

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

			Metformin	Placebo		Mean Difference	Mean Differ	ence
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95	5% CI
Kooy 2009	-1.09	0.1429	196	194	44.6%	-1.09 [-1.37, -0.81]	-	
Lundby-Christensen 2016	-0.91	0.1281	206	206	55.4%	-0.91 [-1.16, -0.66]		
Total (95% CI)			402	400	100.0%	-0.99 [-1.18, -0.80]	•	
Heterogeneity: Chi² = 0.88, c Test for overall effect: Z = 10		0%					-10 -5 0 Favours Metformin Fa	5 10 svours Placebo

K.1.1.2 Adding metformin compared to adding insulin

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

K.1.2 DPP-4 inhibitors

K.1.2.1 Adding alogliptin compared to adding placebo



	Aloglip	otin	Place	bo		Risk Difference		Risk Difference			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fi	xed, 95%	CI	
Nauck 2009A	1	423	0	104	25.5%	0.00 [-0.01, 0.02]			•		
Pratley 2009A	1	397	0	97	23.8%	0.00 [-0.01, 0.02]			•		
Pratley 2009B	0	401	0	99	24.2%	0.00 [-0.01, 0.01]			•		
Rosenstock 2009B	1	260	0	130	26.5%	0.00 [-0.01, 0.02]			†		
Total (95% CI)		1481		430	100.0%	0.00 [-0.01, 0.01]					
Total events	3		0								
Heterogeneity: Chi² =	0.15, df =	3 (P=	0.99); [*=	= 0%			<u> </u>	-0.5	 	0.5	_
Test for overall effect:	Z = 0.60	(P = 0.5)	i5)				-1	Favours Aloglipt	in Favour	0.5 rs Placebo	'

Figure 8: Cardiovascular mortality at end of follow up

	Alogli	otin	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Nauck 2009A	1	423	0	104	33.5%	0.00 [-0.01, 0.02]	•
Pratley 2009B	0	401	0	99	31.8%	0.00 [-0.01, 0.01]	•
Rosenstock 2009B	1	260	0	130	34.7%	0.00 [-0.01, 0.02]	•
Total (95% CI)		1084		333	100.0%	0.00 [-0.01, 0.01]	
Total events	2		0				
Heterogeneity: Chi²=	0.14, df=	2 (P =	0.93); l² :	= 0%			-1 -0.5 0 0.5 1
Test for overall effect:	Z = 0.50	(P = 0.6)	61)				-1 -0.5 0 0.5 1 Favours Alogliptin Favours Placebo

Figure 9: Hypoglycaemia episodes at end of follow up

	Aloglij	otin	Place	ebo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Nauck 2009A	2	423	3	104	6.7%	0.16 [0.03, 0.97]	
Pratley 2009A	25	397	5	97	11.2%	1.22 [0.48, 3.11]	- • -
Pratley 2009B	51	401	11	99	24.5%	1.14 [0.62, 2.11]	-
Rosenstock 2009B	70	260	31	129	57.6%	1.12 [0.78, 1.62]	<u></u>
Total (95% CI)		1481		429	100.0%	1.07 [0.80, 1.44]	+
Total events	148		50				
Heterogeneity: Chi²:	= 4.47, df=	3 (P =	0.22); l²:	= 33%			0.01 0.1 1 10 100
Test for overall effec	t: Z = 0.48	(P = 0.6)	3)				Favours Alogliptin Favours Placebo

Figure 10: Severe hypoglycaemic episodes at end of follow up

_	Aloglij	ptin	Place	bo	•	Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Nauck 2009A	0	423	0	104	33.5%	0.00 [-0.01, 0.01]	•
Pratley 2009B	2	401	1	99	31.8%	-0.01 [-0.03, 0.02]	•
Rosenstock 2009B	1	260	2	130	34.7%	-0.01 [-0.03, 0.01]	•
Total (95% CI)		1084		333	100.0%	-0.01 [-0.02, 0.01]	
Total events	3		3				
Heterogeneity: Chi²=	0.93, df=	2 (P =	0.63); l² :	= 0%			-1 -0.5 0 0.5 1
Test for overall effect:	Z = 0.98	(P = 0.3)	32)				Favours Alogliptin Favours Placebo

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

_			Alogliptin	Placebo		Mean Difference		Mean Dif	ference		
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Fixed, 95% CI		IV, Fixed	, 95% CI		
Nauck 2009A	-0.7	0.1224	423	104	18.0%	-0.70 [-0.94, -0.46]		•			
Pratley 2009B (1)	-0.39	0.1	203	49	26.9%	-0.39 [-0.59, -0.19]		•			
Pratley 2009B (2)	-0.53	0.1	198	50	26.9%	-0.53 [-0.73, -0.33]		•			
Rosenstock 2009B	-0.54	0.0977	260	130	28.2%	-0.54 [-0.73, -0.35]		•			
Total (95% CI)			1084	333	100.0%	-0.53 [-0.63, -0.42]		•			
Heterogeneity: Chi ^z = Test for overall effect:	, ,		3%				-10	-5 Favours Alogliptin	Favours	5 Placebo	10

Footnotes

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

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

up											
-			Alogliptin	Placebo		Mean Difference		Mea	an Differen	ce	
Study or Subgroup M	Mean Difference	SE	Total	Total	Weight	IV, Fixed, 95% CI		IV,	Fixed, 95%	CI	
Nauck 2009A (1)	-0.3	0.3316	210	52	16.2%	-0.30 [-0.95, 0.35]			-		
Nauck 2009A (2)	0	0.3571	213	52	14.0%	0.00 [-0.70, 0.70]			+		
Pratley 2009A (3)	0.42	0.41	197	48	10.6%	0.42 [-0.38, 1.22]			+-		
Pratley 2009A (4)	0.05	0.4	199	49	11.1%	0.05 [-0.73, 0.83]			+		
Pratley 2009B	0.84	0.3109	401	99	18.4%	0.84 [0.23, 1.45]			-		
Rosenstock 2009B	0.05	0.2449	260	130	29.7%	0.05 [-0.43, 0.53]			+		
Total (95% CI)			1480	430	100.0%	0.17 [-0.09, 0.43]			•		
Heterogeneity: Chi ² = 7.5	58, $df = 5$ ($P = 0.18$	8); I ² = 3	4%				100	<u> </u>		<u> </u>	
Test for overall effect: Z:							-10	-5	U :*:	5	10
	(, _,,							Favours Alogi	iptin Favoi	urs Piacebo	

<u>Footnotes</u>

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

K.1.2.2 Adding linagliptin compared to adding placebo

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

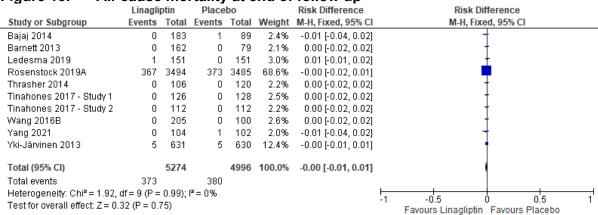


Figure 14: Cardiovascular mortality at end of follow up

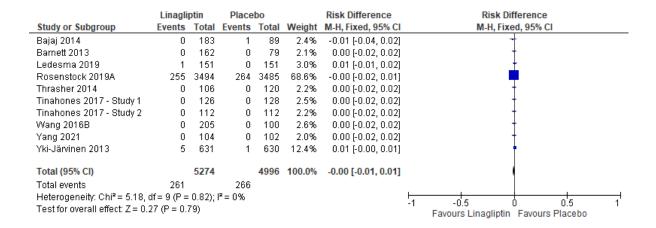


Figure 15: 4-point MACE at end of follow up

	Linagli	ptin	Place	bo		Risk Ratio		Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI		
Ledesma 2019	3	151	1	151	0.2%	3.00 [0.32, 28.52]				
Rosenstock 2019A	463	3494	459	3486	99.8%	1.01 [0.89, 1.14]		—		
Total (95% CI)		3645		3637	100.0%	1.01 [0.90, 1.14]		♦		
Total events	466		460							
Heterogeneity: Chi²=	0.90, df=	1 (P=	0.34); l² =	= 0%			0.01		 10 10	
Test for overall effect:	Z = 0.17	(P = 0.8)	16)				0.01	Favours Linagliptin Favours Pla		JU
								- '		

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

	Linagli	ptin	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Wang 2016B	0	205	0	100	17.6%	0.00 [-0.02, 0.02]	<u> •</u>
Yki-Järvinen 2013	18	631	11	630	82.4%	0.01 [-0.01, 0.03]	
Total (95% CI)		836		730	100.0%	0.01 [-0.00, 0.02]	•
Total events	18		11				
Heterogeneity: Chi²=	1.43, df=	1 (P=	0.23); l² =	= 30%			-1 -0.5 0 0.5 1
Test for overall effect	Z = 1.29	(P = 0.2)	(0)				Favours Linagliptin Favours Placebo

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

		Linagli	ptin	Place	bo		Risk Difference		Risk Difference	
St	udy or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Ва	ajaj 2014	0	183	0	89	3.1%	0.00 [-0.02, 0.02]		+	
Ва	arnett 2013	1	162	0	79	2.7%	0.01 [-0.02, 0.03]		+	
Le	edesma 2019	1	151	1	151	3.9%	0.00 [-0.02, 0.02]		<u> </u>	
R	osenstock 2019A	65	3494	73	3485	90.3%	-0.00 [-0.01, 0.00]		•	
To	otal (95% CI)		3990		3804	100.0%	-0.00 [-0.01, 0.00]			
To	otal events	67		74						
He	eterogeneity: Chi²=	0.60, df=	3 (P=	0.90); l² =	= 0%			-1	-0.5 0 0.5	
Τe	est for overall effect: .	Z = 0.64 ((P = 0.5)	i2)				-1	Favours Linagliptin Favours Placebo	'

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

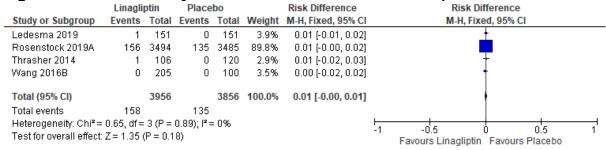


Figure 19: Unstable angina at end of follow up Risk Difference Linagliptin Placebo Risk Difference Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI Bajaj 2014 0 183 0 89 3.2% 0.00 [-0.02, 0.02] Barnett 2013 0 79 0.01 [-0.02, 0.03] 1 162 2.9% Rosenstock 2019A 42 3494 47 3484 93.9% -0.00 [-0.01, 0.00] Total (95% CI) 3839 3652 100.0% -0.00 [-0.01, 0.00] Total events 47 43

-0.5

Favours Linagliptin Favours Placebo

0.5

Figure 20:	Hospitalisation for heart failure at end of follow up
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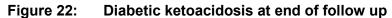
Heterogeneity: $Chi^2 = 0.44$, df = 2 (P = 0.80); $I^2 = 0\%$

Test for overall effect: Z = 0.47 (P = 0.64)

	Linagli	ptin	Place	bo		Risk Difference		Risk Difference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Bajaj 2014	0	183	0	89	3.1%	0.00 [-0.02, 0.02]		+	
Ledesma 2019	1	151	2	151	3.9%	-0.01 [-0.03, 0.02]		<u>+</u>	
Rosenstock 2019A	209	3494	226	3485	89.6%	-0.01 [-0.02, 0.01]			
Wang 2016B	0	205	0	100	3.5%	0.00 [-0.02, 0.02]		†	
Total (95% CI)		4033		3825	100.0%	-0.00 [-0.01, 0.01]		•	
Total events	210		228						
Heterogeneity: Chi² =	0.70, df =	3 (P=	0.87); l² =	= 0%			-1	-0.5 0 0.5	_
Test for overall effect:	Z= 0.91	(P = 0.3)	6)				-1	Favours Linagliptin Favours Placebo	1

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

	Linagli	ptin	Place	bo		Risk Difference		Risk Difference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Rosenstock 2019A	63	3494	64	3485	96.3%	-0.00 [-0.01, 0.01]			
Wang 2016B	0	205	0	100	3.7%	0.00 [-0.02, 0.02]		†	
Total (95% CI)		3699		3585	100.0%	-0.00 [-0.01, 0.01]			
Total events	63		64						
Heterogeneity: Chi²=		,		= 0%			-1	-0.5 0 0.5	
Test for overall effect:	Z = 0.10	(P = 0.9)	12)				'	Favours Linagliptin Favours Placebo	'



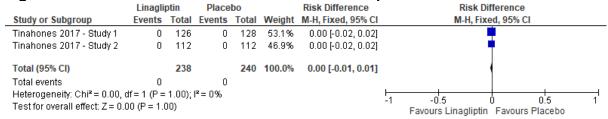
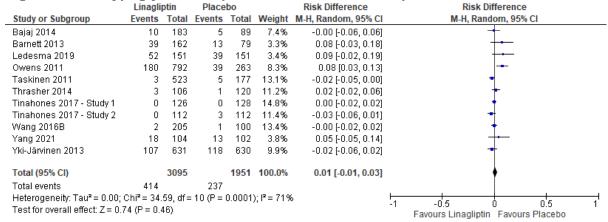


Figure 23: Hypoglycaemia episodes at end of follow up

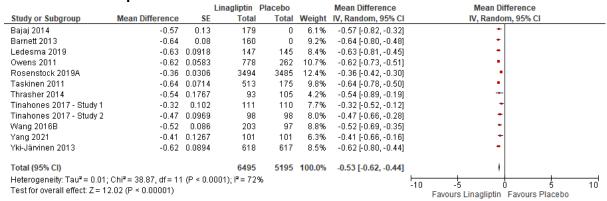


Note: Heterogeneity was not explained by sensitivity analysis, nor subgroup analysis by eGFR subgroup.

Figure 24: Severe hypoglycaemic episodes

	Linagli	ptin	Place	bo		Risk Difference		Risk Difference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Bajaj 2014	0	183	0	89	5.3%	0.00 [-0.02, 0.02]		+	
Barnett 2013	1	162	0	79	4.7%	0.01 [-0.02, 0.03]		+	
Ledesma 2019	2	151	1	151	6.7%	0.01 [-0.02, 0.03]		+	
Owens 2011	5	792	2	263	17.5%	-0.00 [-0.01, 0.01]		•	
Taskinen 2011	0	523	0	177	11.7%	0.00 [-0.01, 0.01]		•	
Thrasher 2014	0	106	0	120	5.0%	0.00 [-0.02, 0.02]		†	
Tinahones 2017 - Study 1	0	126	0	128	5.6%	0.00 [-0.02, 0.02]		†	
Tinahones 2017 - Study 2	0	112	1	112	5.0%	-0.01 [-0.03, 0.02]		†	
Wang 2016B	0	205	0	100	6.0%	0.00 [-0.02, 0.02]		†	
Yang 2021	0	104	0	102	4.6%	0.00 [-0.02, 0.02]		†	
Yki-Järvinen 2013	2	631	4	630	28.0%	-0.00 [-0.01, 0.00]		†	
Total (95% CI)		3095		1951	100.0%	-0.00 [-0.01, 0.00]			
Total events	10		8						
Heterogeneity: Chi² = 1.68, i	df = 10 (P	= 1.00)	; I² = 0%				<u> </u>	-0.5 0 0.5	_
Test for overall effect: $Z = 0.3$	37 (P = 0.1	71)					-1	-0.5 0 0.5 Favours Linagliptin Favours Placebo	1

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



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

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

	•		Linagliptin	Placebo		Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Bajaj 2014	-0.17	0.4545	183	89	4.0%	-0.17 [-1.06, 0.72]	•
Barnett 2013	0.4	0.3362	146	63	7.3%	0.40 [-0.26, 1.06]	•
Owens 2011	0.33	0.19	714	222	22.8%	0.33 [-0.04, 0.70]	•
Taskinen 2011	0.1	0.4001	513	175	5.1%	0.10 [-0.68, 0.88]	+
Thrasher 2014	0	0.82	98	110	1.2%	0.00 [-1.61, 1.61]	†
Tinahones 2017 - Study 1	0.6	0.36	109	109	6.3%	0.60 [-0.11, 1.31]	•
Tinahones 2017 - Study 2	0.1	0.36	98	97	6.3%	0.10 [-0.61, 0.81]	+
Wang 2016B	0.55	0.3336	203	97	7.4%	0.55 [-0.10, 1.20]	•
Yang 2021	-0.02	0.3124	101	101	8.4%	-0.02 [-0.63, 0.59]	•
Yki-Järvinen 2013	-0.28	0.1626	618	617	31.1%	-0.28 [-0.60, 0.04]	•
Total (95% CI)			2783	1680	100.0%	0.10 [-0.08, 0.28]	
Heterogeneity: Chi ² = 11.99	. , , , , ,	= 25%					-100 -50 0 50 100
Test for overall effect: $Z = 1$.	.09 (P = 0.28)						Favours Linagliptin Favours Placebo

K.1.2.3 Adding linagliptin compared to adding metformin

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

	Lina	agliptin		Met	formin			Mean Difference		Mean	Differenc	e	
Study or Subgroup	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV, Fixed, 95% CI [%]		IV, Fixed	I, 95% CI	[%]	
1.5.1 Change scores	s												
Inagaki 2013 Subtotal (95% CI)	-0.8	0.1	185 185		0.1	140 140	99.9% 99.9 %	0.10 [0.08, 0.12] 0.10 [0.08, 0.12]					
Heterogeneity: Not a	pplicable												
Test for overall effect	: Z = 8.93 (P	< 0.0000	01)										
1.5.2 Final scores													
Komorizono 2020 Subtotal (95% CI)	6.8	0.9	23 23	7	1.3	25 25	0.1% 0.1%	-0.20 [-0.83, 0.43] -0.20 [-0.83, 0.43]			•		
Heterogeneity: Not a	nnlicable							5125 [5155, 5115]			٦		
Test for overall effect		= 0.53)											
Total (95% CI)			208			165	100.0%	0.10 [0.08, 0.12]					
Heterogeneity: Chi ² =	0.87, df = 1	(P = 0.3)	5); l² = 1	0%					10	_	 	<u> </u>	
Test for overall effect	: Z = 8.90 (P	< 0.0000	01)						-10	-5 Favours Linaglipti	n Favou	o ure Motformin	10
Test for subgroup dit	ferences: Cl	$hi^2 = 0.87$	'. df = 1	(P = 0.35).	$I^2 = 0\%$					ravvuis Lillagiipii	II FAVOU	no menomini	1

K.1.2.4 Adding saxagliptin compared to adding placebo

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

_	Saxagi	iptin	Place	bo		Risk Difference		Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Barnett 2012	2	304	0	151	2.1%	0.01 [-0.01, 0.02]		•
Chen 2018A	1	232	1	230	2.4%	-0.00 [-0.01, 0.01]		†
DeFronzo 2009	0	564	1	179	2.9%	-0.01 [-0.02, 0.01]		+
Hollander 2009	2	381	0	184	2.6%	0.01 [-0.01, 0.02]		+
Matthaei 2015A	0	153	1	162	1.7%	-0.01 [-0.02, 0.01]		†
Moses 2014	0	129	0	128	1.4%	0.00 [-0.02, 0.02]		<u>+</u>
Scirica 2013	420	8280	378	8212	86.9%	0.00 [-0.00, 0.01]		-
Total (95% CI)		10043		9246	100.0%	0.00 [-0.00, 0.01]		
Total events	425		381					
Heterogeneity: Chi²=	4.29, df=	6 (P = 0)).64); l ² =	0%			-1	-0.5 0 0.5
Test for overall effect:	Z = 1.40 (P = 0.16	6)				-1	-0.5 0 0.5 Favours Saxagliptin Favours Placebo

Figure 29: Cardiovascular mortality at end of follow up

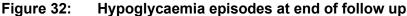
	Saxagl	iptin	Place	bo		Risk Difference		Risk Difference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Chen 2018A	1	232	0	230	2.5%	0.00 [-0.01, 0.02]		+	
DeFronzo 2009	0	564	1	179	3.0%	-0.01 [-0.02, 0.01]		†	
Hollander 2009	1	381	0	184	2.7%	0.00 [-0.01, 0.01]		†	
Moses 2014	0	129	0	128	1.4%	0.00 [-0.02, 0.02]		<u>+</u>	
Scirica 2013	269	8280	260	8212	90.4%	0.00 [-0.00, 0.01]		-	
Total (95% CI)		9586		8933	100.0%	0.00 [-0.00, 0.01]			
Total events	271		261						
Heterogeneity: Chi²=	1.34, df=	4 (P =	0.85); <mark>I</mark> ²=	: 0%			H_	-0.5 0 0.5	_
Test for overall effect:	Z = 0.30	(P = 0.7)	6)				-1	Favours Saxagliptin Favours Placebo	'

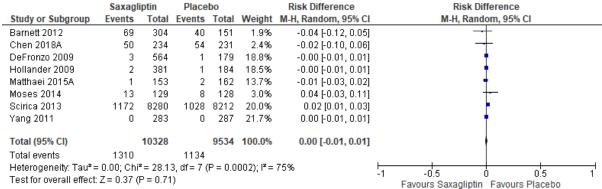
Figure 30: Non-fatal stroke at end of follow up

.9							
	Saxagi	iptin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Scirica 2013	157	8240	141	8173	99.3%	1.10 [0.88, 1.38]	
Yang 2011	1	283	1	287	0.7%	1.01 [0.06, 16.13]	
Total (95% CI)		8523		8460	100.0%	1.10 [0.88, 1.38]	•
Total events	158		142				
Heterogeneity: Chi²=	0.00, df=	1 (P=	0.95); l² =	: 0%			0.01 0.1 1 10 100
Test for overall effect	Z = 0.86 (P = 0.3	9)				0.01 0.1 1 10 100 Favours Saxagliptin Favours Placebo

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

	Saxagi	iptin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Chen 2018A	1	234	0	231	0.2%	2.96 [0.12, 72.33]	
Scirica 2013	265	8240	278	8173	99.8%	0.95 [0.80, 1.12]	•
Total (95% CI)		8474		8404	100.0%	0.95 [0.80, 1.12]	+
Total events	266		278				
Heterogeneity: Chi²=	0.49, df =	1 (P = 1)	0.48); <mark>I</mark> ²=	: 0%			0.01 0.1 1 10 100
Test for overall effect:	Z = 0.62 (P = 0.5	4)				Favours Saxagliptin Favours Placebo





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

Figure 33: Severe hypoglycaemic episodes at end of follow up

		- ··· <i>J</i> r	3- 1						
	Saxagl	iptin	Place	bo		Risk Difference		Risk Difference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Barnett 2012	2	304	3	151	2.1%	-0.01 [-0.04, 0.01]		+	
Chen 2018A	1	234	0	231	2.5%	0.00 [-0.01, 0.02]		†	
DeFronzo 2009	0	564	0	179	2.9%	0.00 [-0.01, 0.01]		†	
Matthaei 2015A	0	153	0	162	1.7%	0.00 [-0.01, 0.01]		<u>+</u>	
Scirica 2013	177	8280	140	8212	87.8%	0.00 [0.00, 0.01]			
Yang 2011	0	283	0	287	3.0%	0.00 [-0.01, 0.01]		ţ	
Total (95% CI)		9818		9222	100.0%	0.00 [-0.00, 0.01]			
Total events	180		143						
Heterogeneity: Chi²=	4.20, df=	5 (P=	0.52); <mark>P</mark> =	: 0%			<u> </u>	-0.5 0 0.5	_
Test for overall effect	: Z= 1.90 ((P = 0.0)	6)				-1	Favours Saxagliptin Favours Placebo	'

Figure 34: HbA1c change at end of follow up

.9			,			~.P				
			Saxagliptin	Placebo		Mean Difference		Mean Dit	fference	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI		IV, Rando	m, 95% CI	
Barnett 2012	-0.37	0.0918	244	124	12.3%	-0.37 [-0.55, -0.19]		•		
Chen 2018A	-0.58	0.0698	229	227	13.0%	-0.58 [-0.72, -0.44]		•		
DeFronzo 2009	-0.75	0.0811	552	175	12.7%	-0.75 [-0.91, -0.59]		•		
Hollander 2009	-0.63	0.1138	372	180	11.5%	-0.63 [-0.85, -0.41]		•		
Matthaei 2015A	-0.42	0.1122	153	162	11.5%	-0.42 [-0.64, -0.20]		•		
Moses 2014	-0.66	0.1054	129	128	11.8%	-0.66 [-0.87, -0.45]		•		
Scirica 2013	-0.2	0.0226	8280	8212	14.1%	-0.20 [-0.24, -0.16]		-		
Yang 2011	-0.42	0.0663	275	279	13.1%	-0.42 [-0.55, -0.29]		•		
Total (95% CI)			10234	9487	100.0%	-0.50 [-0.67, -0.33]		•		
Heterogeneity: Tau ² =		,	P < 0.00001); I	2= 92%			-10	-5) 5	10
Test for overall effect	: Z = 5.65 (P < 0.000	U1)						Favours Saxagliptin	Favours Placebo	

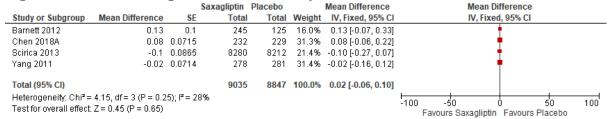
Note: Heterogeneity was not explained by sensitivity analysis, nor subgroup analysis by eGFR subgroup.

Figure 35: Weight change at end of follow up

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			Saxagliptin I	Placebo		Mean Difference		Mear	Differen	ce	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI		IV, Raı	ndom, 95	% CI	
Barnett 2012	0.3	0.2806	245	125	16.4%	0.30 [-0.25, 0.85]			•		
Chen 2018A	0.3	0.2828	232	230	16.3%	0.30 [-0.25, 0.85]			•		
Hollander 2009	0.5	0.3468	381	184	13.6%	0.50 [-0.18, 1.18]			•		
Moses 2014	0.8	0.2683	129	128	17.0%	0.80 [0.27, 1.33]			•		
Scirica 2013	-0.5	0.296	8280	8212	15.7%	-0.50 [-1.08, 0.08]			•		
Yang 2011	-0.07	0.1888	278	281	20.9%	-0.07 [-0.44, 0.30]			†		
Total (95% CI)			9545	9160	100.0%	0.21 [-0.15, 0.57]					
Heterogeneity: Tau ² :	= 0.12; Chi ² = 13.58,	df = 5 (P	$= 0.02$); $I^2 = 63$	3%			100	<u> </u>			
Test for overall effect	T = 1.15 (P = 0.25)						-100			50	100
	(/ - 0.20)							Favours Saxaglip	tin Favo	urs Piacebo	

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

Figure 36: BMI change at end of follow up



K.1.2.5 Adding sitagliptin compared to adding placebo

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

	Sitaglij	ptin	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Ba 2017	0	248	0	249	11.3%	0.00 [-0.01, 0.01]	•
Dobs 2013	0	170	0	92	2.4%	0.00 [-0.02, 0.02]	†
Fonseca 2013	0	157	1	156	2.3%	-0.01 [-0.02, 0.01]	†
Hermansen 2007 - Stratum 1	0	106	0	106	2.1%	0.00 [-0.02, 0.02]	†
Hermansen 2007 - Stratum 2	1	116	0	113	1.2%	0.01 [-0.02, 0.03]	+
Lavalle-Gonzalez 2013A	0	366	0	183	9.8%	0.00 [-0.01, 0.01]	+
Mathieu 2015B	2	329	1	329	6.6%	0.00 [-0.01, 0.01]	•
Moses 2017	0	210	1	212	4.1%	-0.00 [-0.02, 0.01]	†
Nauck 2014 Sitagliptin v Placebo	0	315	0	177	8.7%	0.00 [-0.01, 0.01]	•
Raz 2008	0	96	1	94	0.8%	-0.01 [-0.04, 0.02]	+
Rosenstock 2006	0	175	0	178	5.7%	0.00 [-0.01, 0.01]	†
Roussel 2019	0	373	2	370	8.4%	-0.01 [-0.01, 0.00]	+
Seino 2021	0	70	0	71	0.9%	0.00 [-0.03, 0.03]	+
Shankar 2017A	0	234	0	233	10.0%	0.00 [-0.01, 0.01]	•
Vilsboll 2010	0	322	0	319	18.7%	0.00 [-0.01, 0.01]	•
Yang 2012	0	196	0	198	7.1%	0.00 [-0.01, 0.01]	†
Total (95% CI)		3483		3080	100.0%	-0.00 [-0.00, 0.00]	
Total events	3		6				
Heterogeneity: Chi ² = 3.55, df = 15	(P = 1.00)	$ ^2 = 0.9$	6				1. J. J. J.
Test for overall effect: Z = 0.43 (P =							-1 -0.5 0 0.5 1
	/						Favours Sitagliptin Favours Placebo

Figure 38: Cardiovascular mortality at end of follow up

_	Sitaglij	ptin	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Ba 2017	0	248	0	249	11.5%	0.00 [-0.01, 0.01]	•
Dobs 2013	0	170	0	92	5.5%	0.00 [-0.02, 0.02]	<u>†</u>
Hermansen 2007 - Stratum 1	0	106	0	106	4.9%	0.00 [-0.02, 0.02]	†
Nauck 2014 Sitagliptin v Placebo	0	315	0	177	10.5%	0.00 [-0.01, 0.01]	•
Raz 2008	0	96	1	94	4.4%	-0.01 [-0.04, 0.02]	†
Rosenstock 2006	0	175	0	178	8.2%	0.00 [-0.01, 0.01]	†
Roussel 2019	0	373	2	370	17.2%	-0.01 [-0.01, 0.00]	•
Seino 2021	0	70	0	71	3.3%	0.00 [-0.03, 0.03]	†
Shankar 2017A	0	234	0	233	10.8%	0.00 [-0.01, 0.01]	•
Vilsboll 2010	0	322	0	319	14.8%	0.00 [-0.01, 0.01]	•
Yang 2012	0	196	0	198	9.1%	0.00 [-0.01, 0.01]	•
Total (95% CI)		2305		2087	100.0%	-0.00 [-0.00, 0.00]	
Total events	0		3				
Heterogeneity: Chiz = 1.86, df = 10	P = 1.00	$ I^2 = 09 $	6				14 05 05 1
Test for overall effect: Z = 0.80 (P =	0.42)						-1 -0.5 0 0.5 1 Favours Sitagliptin Favours Placebo

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

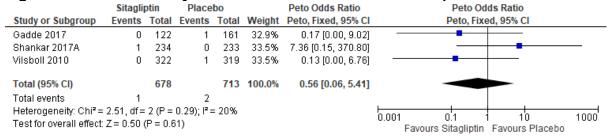


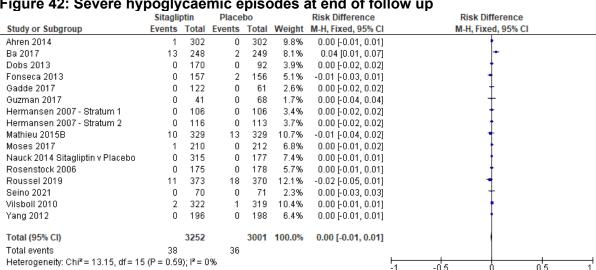
Figure 40: Unstable angina at end of follow up

	Sitagli	ptin	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Ba 2017	1	248	0	249	50.0%	7.42 [0.15, 373.89]	
Vilsboll 2010	0	322	1	319	50.0%	0.13 [0.00, 6.76]	
Total (95% CI)		570		568	100.0%	1.00 [0.06, 15.95]	
Total events	1		1				
Heterogeneity: Chi²=		,		= 50%			0.001 0.1 1 10 1000
Test for overall effect:	Z = 0.00	(P = 1.0	10)				Favours Sitagliptin Favours Placebo

Figure 41: Hypoglycaemia at end of follow up

	Sitagli	ptin	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Ahren 2014	5	302	4	101	5.4%	-0.02 [-0.06, 0.02]	+
3a 2017	35	248	17	249	4.4%	0.07 [0.02, 0.13]	-
Charbonnel 2006	6	464	5	237	6.9%	-0.01 [-0.03, 0.01]	†
Derosa 2012A	0	91	0	87	6.8%	0.00 [-0.02, 0.02]	+
Dobs 2013	7	170	1	92	5.7%	0.03 [-0.01, 0.07]	 -
Fonseca 2013	10	157	7	156	4.7%	0.02 [-0.03, 0.07]	+
Gadde 2017	1	122	0	61	6.3%	0.01 [-0.02, 0.04]	+
Hermansen 2007 - Stratum 1	8	106	3	106	4.0%	0.05 [-0.01, 0.11]	
Hermansen 2007 - Stratum 2	19	116	1	113	3.4%	0.15 [0.09, 0.22]	
Mathieu 2015B	93	329	144	329	3.3%	-0.16 [-0.23, -0.08]	
Moses 2017	27	210	7	212	4.6%	0.10 [0.04, 0.15]	
Raz 2008	1	96	0	94	6.4%	0.01 [-0.02, 0.04]	†
Rosenstock 2006	2	175	0	178	7.0%	0.01 [-0.01, 0.03]	<u>†</u>
Roussel 2019	247	373	244	370	3.5%	0.00 [-0.07, 0.07]	+
Seino 2021	0	70	1	71	5.6%	-0.01 [-0.05, 0.02]	+
Shankar 2017A	64	234	51	233	3.0%	0.05 [-0.02, 0.13]	 -
/ilsboll 2010	50	322	25	319	4.7%	0.08 [0.03, 0.13]	-
Wang 2017	4	191	3	189	6.5%	0.01 [-0.02, 0.03]	+
Yang 2012	1	196	3	198	7.0%	-0.01 [-0.03, 0.01]	+
Zhao 2017	28	50	19	50	0.7%	0.18 [-0.01, 0.37]	
Total (95% CI)		4022		3445	100.0%	0.02 [0.00, 0.04]	•
Total events	608		535				
Heterogeneity: Tau ² = 0.00; Chi	²= 83.31.	df= 19	(P < 0.00)	0001): I	²= 77%		I, J. J.
Fest for overall effect: Z = 2.04 (,				-1 -0.5 0 0.5 Favours Sitagliptin Favours Placebo

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



Favours Sitagliptin Favours Placebo

Figure 42: Severe hypoglycaemic episodes at end of follow up

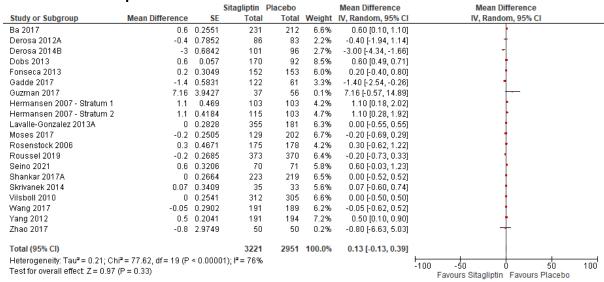
Test for overall effect: Z = 0.21 (P = 0.84)

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

			Sitagliptin	Placebo		Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	Total		Weight	IV, Random, 95% CI	IV, Random, 95% CI
Ba 2017	-0.61	0.0816	243	236	4.9%	-0.61 [-0.77, -0.45]	•
Charbonnel 2006	-0.65	0.0882	453	224	4.8%	-0.65 [-0.82, -0.48]	•
Derosa 2012A	-0.6	0.0245	86	83	5.6%	-0.60 [-0.65, -0.55]	•
Derosa 2014B	-2	0.136	101	96	3.9%	-2.00 [-2.27, -1.73]	•
Dobs 2013	-0.8	0.102	168	88	4.6%	-0.80 [-1.00, -0.60]	+
Fonseca 2013	-0.7	0.0917	152	153	4.7%	-0.70 [-0.88, -0.52]	•
Gadde 2017	-0.35	0.2302	122	61	2.5%	-0.35 [-0.80, 0.10]	-
Guzman 2017	0.48	0.314	7	11	1.7%	0.48 [-0.14, 1.10]	-
Hermansen 2007 - Stratum 1	-0.57	0.1298	103	103	4.1%	-0.57 [-0.82, -0.32]	-
Hermansen 2007 - Stratum 2	-0.89	0.11	115	109	4.4%	-0.89 [-1.11, -0.67]	•
Lavalle-Gonzalez 2013A	-0.66	0.04	354	181	5.5%	-0.66 [-0.74, -0.58]	•
Mathieu 2015B	-0.41	0.0684	329	329	5.1%	-0.41 [-0.54, -0.28]	•
Moses 2017	-0.68	0.0915	129	202	4.7%	-0.68 [-0.86, -0.50]	•
Raz 2008	-1	0.1816	95	92	3.2%	-1.00 [-1.36, -0.64]	-
Rosenstock 2006	-0.7	0.0931	163	174	4.7%	-0.70 [-0.88, -0.52]	•
Roussel 2019	-0.46	0.0707	373	370	5.1%	-0.46 [-0.60, -0.32]	•
Seino 2021	-0.83	0.1134	70	71	4.3%	-0.83 [-1.05, -0.61]	+
Shankar 2017A	-0.4	0.0718	223	219	5.1%	-0.40 [-0.54, -0.26]	•
Skrivanek 2014	-0.71	0.1526	25	28	3.6%	-0.71 [-1.01, -0.41]	-
Vilsboll 2010	-0.6	0.051	312	305	5.4%	-0.60 [-0.70, -0.50]	•
Wang 2017	-0.62	0.1231	191	189	4.2%	-0.62 [-0.86, -0.38]	•
Yang 2012	-0.9	0.102	191	194	4.6%	-0.90 [-1.10, -0.70]	•
Zhao 2017	-1.2	0.1703	50	50	3.4%	-1.20 [-1.53, -0.87]	-
Total (95% CI)			4055	3568	100.0%	-0.71 [-0.80, -0.61]	
Heterogeneity: Tau ² = 0.04; Chi	₹- 190 05 df- 22 0				.001070	5[5.00, -0.01]	
Test for overall effect: Z = 14.50		- 0.000	001),1 - 007	U			-10 -5 Ö 5 1ı
restroi overan ellett. Z = 14.50	(1 5 0.00001)						Favours Sitagliptin Favours Placebo

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

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



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

Figure 45: BMI change (kg/m², lower values are better, final values) at end of follow up

	Sita	iglipti	in	Pla	acebo)		Mean Difference		Mean Di	fference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Rando	m, 95% CI	
Derosa 2012A	27.2	0.6	86	28.1	1.2	83	37.6%	-0.90 [-1.19, -0.61]		-		
Derosa 2014B	27.6	2.3	101	29.1	3	96	30.0%	-1.50 [-2.25, -0.75]		-		
Zhao 2017	26.4	1.2	50	28.6	1.9	50	32.4%	-2.20 [-2.82, -1.58]		-		
Total (95% CI)			237			229	100.0%	-1.50 [-2.35, -0.66]		•		
Heterogeneity: Tau² = Test for overall effect					= 0.0	0007); I	²= 86%		-10	-5 Favours Sitagliptin) 5 Favours Placeb	10

K.1.2.6 Adding sitagliptin compared to adding metformin

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

Olia	O	,,,,	** 4	Μ						
	Sita	iglipti	n	Me	tformi	n		Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
1.2.1 Change scores										
Ohira 2014B	-1.54	1.5	35	-0.69	1.01	35	44.9%	-0.85 [-1.45, -0.25]	-	
Subtotal (95% CI)			35			35	44.9%	-0.85 [-1.45, -0.25]	•	
Heterogeneity: Not ap	plicable									
Test for overall effect:	Z = 2.78	(P=	0.005)							
1.2.2 Final scores										
Derosa 2010B	7.1	0.3	69	7	0.2	68	55.1%	0.10 [0.01, 0.19]	•	
Subtotal (95% CI)			69			68	55.1%	0.10 [0.01, 0.19])	
Heterogeneity: Not ap	plicable									
Test for overall effect:	Z = 2.30	(P=	0.02)							
Total (95% CI)			104			103	100.0%	-0.33 [-1.25, 0.60]	•	
Heterogeneity: Tau ² =	0.40; C	hi² = !	9.47, di	f=1 (P=	= 0.00	2); $I^2 = 0$	39%		<u> </u>	
Test for overall effect:	Z = 0.69) (P =	0.49)	•					-10 -5 0 5	10
Test for subgroup diff	erences	: Chi	$^{2} = 9.47$	7, df = 1	(P = 0)	.002), P	= 89.4%		Favours Sitagliptin Favours Metformir	1

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

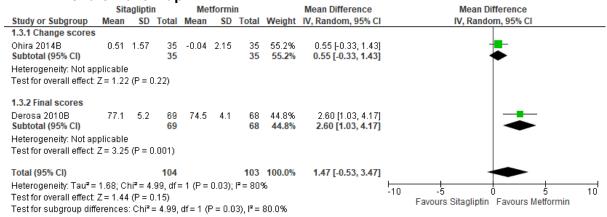


Figure 48: BMI change (kg/m², lower values are better, change and final scores) at end of follow up

	• • • •		-	•						
	Sitagliptin Metformin					n		Mean Difference	Mean D	ifference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Rando	om, 95% CI
1.4.1 Change scores										
Ohira 2014B	0.2	0.59	35	0	0.86	35	47.1%	0.20 [-0.15, 0.55]		*
Subtotal (95% CI)			35			35	47.1%	0.20 [-0.15, 0.55]		*
Heterogeneity: Not ap	plicable	!								
Test for overall effect:	Z = 1.13	(P = 0	0.26)							
1.4.2 Final scores										
Derosa 2010B	27.3	1	69	26.7	0.7	68	52.9%	0.60 [0.31, 0.89]		
Subtotal (95% CI)			69			68	52.9%	0.60 [0.31, 0.89]		♦
Heterogeneity: Not ap	plicable	!								
Test for overall effect:	Z = 4.07	'(P < 0	0.0001))						
Total (95% CI)			104			103	100.0%	0.41 [0.02, 0.80]		•
Heterogeneity: Tau ² =	0.05; C	hi²=3	.03, df	= 1 (P =	0.08);	l ² = 67°		-10 -5	0 5 10	
Test for overall effect:	Z = 2.08	6 (P = 0	0.04)							Favours Metformin
Test for subgroup diffe	erences	: Chi²:	= 3.03,	df = 1 (F	o.0 = 9	18), I ² =	67.0%		Favours Sitagripuir	Favours Medioillilli

K.1.2.7 Adding sitagliptin compared to adding insulin

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



Figure 50: Unstable angina at end of follow up

_	Sitagli	ptin	Insul	lin		Peto Odds Ratio	Peto Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI		
Aschner 2012	0	264	2	237	7.7%	0.12 [0.01, 1.94]	<u> </u>		
Group 2022	15	1268	9	1263	92.3%	1.65 [0.74, 3.69]	-		
Total (95% CI)		1532		1500	100.0%	1.35 [0.62, 2.92]	•		
Total events	15		11						
Heterogeneity: Chi²=	3.15, df=	1 (P=	0.08); l² :	0.001 0.1 1 10 10	000				
Test for overall effect:	Z = 0.76	(P = 0.4)	15)		Favours Sitagliptin Favours Insulin	100			

Figure 51: Hypoglycaemia episodes at end of follow up

	Sitagliptin Insulin					Risk Ratio	Risk Ratio
Study or Subgroup Even		Events Total		Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Aschner 2012	35	264	108	237	26.0%	0.29 [0.21, 0.41]	
Group 2022	328	1253	474	1245	28.4%	0.69 [0.61, 0.77]	•
Hong 2012	5	61	11	63	15.2%	0.47 [0.17, 1.27]	
Philis-Tsimikas 2013	29	228	96	226	25.5%	0.30 [0.21, 0.43]	-
Yan 2019	1	27	2	24	4.9%	0.44 [0.04, 4.60]	
Total (95% CI)		1833		1795	100.0%	0.41 [0.23, 0.72]	•
Total events	398		691				
Heterogeneity: Tau ² = 0	.29; Chi ^z :	= 36.94	df = 4 (F)	o.00	$(001); I^2 = 3$	89%	0.04 0.4 40 400
Test for overall effect: Z	= 3.08 (P	= 0.000	2)				0.01 0.1 1 10 100 Favours Sitagliptin Favours Insulin

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

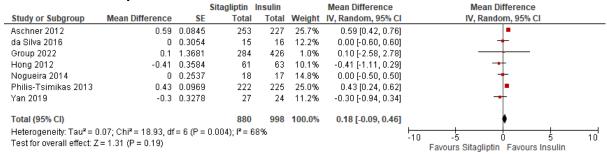
Figure 52: At night hypoglycaemic episodes at end of follow up

	Sitagli	ptin	Insul	in		Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI			
Aschner 2012	8	264	41	237	47.8%	0.18 [0.08, 0.37]	-			
Philis-Tsimikas 2013	13	228	29	226	52.2%	0.44 [0.24, 0.83]				
Total (95% CI)		492		463	100.0%	0.28 [0.11, 0.71]	•			
Total events	21		70							
Heterogeneity: Tau² = 0 Test for overall effect: Z			•	= 0.06)	; I² = 72%		0.01 0.1 10 Favours Sitagliptin Favours Insulin	100		

Figure 53: Severe hypoglycaemic episodes at end of follow up

	Sitagli	ptin	insul	in		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Aschner 2012	1	264	3	237	11.5%	0.33 [0.05, 2.34]	
Group 2022	9	1268	16	1263	71.6%	0.57 [0.26, 1.24]	■ +
Hong 2012	1	61	4	63	14.0%	0.30 [0.05, 1.78]	
Philis-Tsimikas 2013	0	228	1	226	2.9%	0.13 [0.00, 6.76]	
Total (95% CI)		1821		1789	100.0%	0.47 [0.24, 0.91]	•
Total events	11		24				
Heterogeneity: Chi² = 0.	.98, df = 3	(P = 0.	81); $I^2 = 0$		0.001 0.1 1 10 1000		
Test for overall effect: Z	= 2.24 (P	= 0.02))		Favours Sitagliptin Favours Insulin		

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



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

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

			Sitagliptin	Insulin		Mean Difference		Mea	n Differen	ce	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI		IV, Ra	ndom, 95	% CI	
Aschner 2012	-1.52	0.2201	253	227	37.0%	-1.52 [-1.95, -1.09]			•		
da Silva 2016	-6.2	4.1262	15	16	0.8%	-6.20 [-14.29, 1.89]			-		
Hong 2012	-1.8	0.5261	61	63	22.9%	-1.80 [-2.83, -0.77]			•		
Nogueira 2014	-4.1	3.6854	18	17	1.0%	-4.10 [-11.32, 3.12]			+		
Philis-Tsimikas 2013	-2.75	0.4031	229	229	28.3%	-2.75 [-3.54, -1.96]			•		
Yan 2019	-0.5	1.023	27	24	10.1%	-0.50 [-2.51, 1.51]			†		
Total (95% CI)			603	576	100.0%	-1.89 [-2.62, -1.16]					
Heterogeneity: Tau ² = 0	0.32; Chi² = 10.30, df	= 5 (P =	0.07); $I^2 = 5$	1%			100	<u> </u>			400
Test for overall effect: Z	C = 5.10 (P < 0.00001)					-100	-50 Favours Sitaglii	U Stip Four	50	100
	•	•						ravours Sitagii	oun ravo	urs msuim	

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

Figure 56: BMI change (kg/m², lower values are better, change scores and final values) at end of follow up

	Sita	glipti	in	Insulin			Mean Difference			Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI		
da Silva 2016	26.6	3.1	15	27.9	2.8	16	8.7%	-1.30 [-3.38, 0.78]				
Nogueira 2014	26.8	2.6	18	27.8	2.8	17	11.8%	-1.00 [-2.79, 0.79]				
Yan 2019	-0.6	0.9	27	-0.4	1.5	24	79.5%	-0.20 [-0.89, 0.49]		-		
Total (95% CI)			60			57	100.0%	-0.39 [-1.00, 0.23]		•		
Heterogeneity: Chi² = Test for overall effect:		,		-10	-5 0 5 Favours Sitagliptin Favours Insulin	10						

K.1.2.8 Adding vildagliptin compared to adding placebo

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

	Vildagli	iptin	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Ahren 2004	0	56	0	51	2.9%	0.00 [-0.04, 0.04]	+
Bosi 2007	0	360	0	181	13.1%	0.00 [-0.01, 0.01]	•
Fonseca 2007	1	144	1	152	8.0%	0.00 [-0.02, 0.02]	†
Garber 2008	0	339	0	176	12.6%	0.00 [-0.01, 0.01]	•
Kothny 2013	0	228	1	221	12.2%	-0.00 [-0.02, 0.01]	•
Lukashevich 2011 moderate renal impairment	1	163	1	129	7.8%	-0.00 [-0.02, 0.02]	<u>†</u>
Lukashevich 2014	0	157	1	160	8.6%	-0.01 [-0.02, 0.01]	<u>†</u>
Macauley 2015	0	22	0	22	1.2%	0.00 [-0.08, 0.08]	
Ning 2016	0	146	0	147	8.0%	0.00 [-0.01, 0.01]	<u>†</u>
Pan 2012B	0	294	0	146	10.6%	0.00 [-0.01, 0.01]	†
Strain 2013	1	139	1	139	7.5%	0.00 [-0.02, 0.02]	†
Yang 2015	0	143	0	135	7.5%	0.00 [-0.01, 0.01]	<u>†</u>
Total (95% CI)		2191		1659	100.0%	-0.00 [-0.01, 0.00]	
Total events	3		5				
Heterogeneity: $Chi^2 = 0.91$, $df = 11$ (P = 1.00); $I^2 = 0$	1%						-1 -0.5 0 0.5 1
Test for overall effect: Z = 0.53 (P = 0.60)							Favours Vildagliptin Favours Placebo

Figure 58: Cardiovascular mortality at end of follow up

	Vildagli	ptin	Place	bo	Risk Difference			Risk Difference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Ahren 2004	0	56	0	51	4.9%	0.00 [-0.04, 0.04]		+	
Bosi 2007	0	360	0	181	22.3%	0.00 [-0.01, 0.01]		•	
Fonseca 2007	0	144	1	152	13.7%	-0.01 [-0.02, 0.01]		+	
Macauley 2015	0	22	0	22	2.0%	0.00 [-0.08, 0.08]		+	
Ning 2016	0	146	0	147	13.5%	0.00 [-0.01, 0.01]		†	
Pan 2012B	0	294	0	144	17.9%	0.00 [-0.01, 0.01]		†	
Strain 2013	1	139	0	139	12.8%	0.01 [-0.01, 0.03]		†	
Yang 2015	0	143	0	135	12.8%	0.00 [-0.01, 0.01]		†	
Total (95% CI)		1304		971	100.0%	0.00 [-0.01, 0.01]			
Total events	1		1						
Heterogeneity: Chi² = 1.01, df = 7 (P = 0.99); l² = 0%								-0.5 0 0.5	_
Test for overall effect: Z = 0.01 (P = 0.99)							-1	Favours Vildagliptin Favours Placebo	'

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

_	Vildagli	iptin	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Bosi 2007	1	360	1	181	48.6%	0.47 [0.03, 8.98]	
Pan 2012B	0	294	1	144	24.1%	0.05 [0.00, 3.10]	
Yang 2015	0	143	1	136	27.3%	0.13 [0.00, 6.49]	-
Total (95% CI)		797		461	100.0%	0.19 [0.02, 1.48]	
Total events	1		3				
Heterogeneity: Chi²=	: 0.83, df=	2 (P=	0.66); l ^z =	0.001 0.1 1 10 1000			
Test for overall effect	: Z = 1.58 (P = 0.1	1)	0.001 0.1 1 10 1000 Favours Vildagliptin Favours Placebo			

Figure 60: Hypoglycaemia episodes at end of follow up

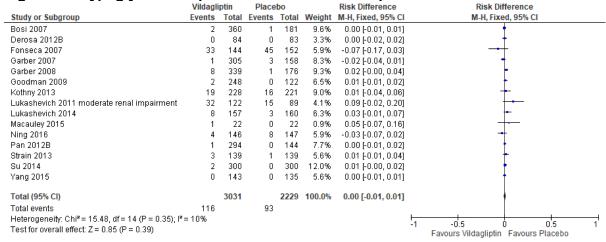


Figure 61: Severe hypoglycaemic episodes at end of follow up

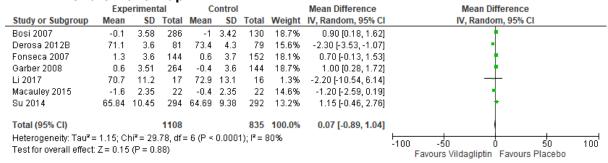
	Vildagli	iptin	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Bosi 2007	0	360	0	181	11.4%	0.00 [-0.01, 0.01]	•
Fonseca 2007	0	144	4	152	7.0%	-0.03 [-0.05, 0.00]	+
Garber 2007	0	305	0	158	9.9%	0.00 [-0.01, 0.01]	•
Garber 2008	0	339	1	176	11.0%	-0.01 [-0.02, 0.01]	+
Goodman 2009	0	248	0	122	7.7%	0.00 [-0.01, 0.01]	†
Kothny 2013	2	228	2	221	10.6%	-0.00 [-0.02, 0.02]	†
Li 2017	0	17	0	16	0.8%	0.00 [-0.11, 0.11]	+
Lukashevich 2011 moderate renal impairment	2	122	3	89	4.9%	-0.02 [-0.06, 0.03]	+
Lukashevich 2014	1	157	0	160	7.5%	0.01 [-0.01, 0.02]	†
Ning 2016	0	146	1	147	6.9%	-0.01 [-0.03, 0.01]	†
Pan 2012B	1	294	0	144	9.2%	0.00 [-0.01, 0.02]	•
Strain 2013	0	139	0	139	6.6%	0.00 [-0.01, 0.01]	†
Yang 2015	0	143	0	135	6.6%	0.00 [-0.01, 0.01]	†
Total (95% CI)		2642		1840	100.0%	-0.00 [-0.01, 0.00]	
Total events	6		11				
Heterogeneity: $Chi^2 = 6.94$, $df = 12$ (P = 0.86); $I^2 = 0$	1%						1. J. J. J.
Test for overall effect: Z = 1.20 (P = 0.23)							-1 -0.5 0 0.5 1 Favours Vildagliptin Favours Placebo

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

			Vildagliptin	Placebo		Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Bosi 2007	-0.9	0.1226	286	130	5.7%	-0.90 [-1.14, -0.66]	•
Derosa 2012B	-0.5	0.0251	81	79	12.9%	-0.50 [-0.55, -0.45]	•
Fonseca 2007	-0.3	0.1412	140	149	4.8%	-0.30 [-0.58, -0.02]	+
Garber 2007	-0.6	0.1228	305	158	5.7%	-0.60 [-0.84, -0.36]	+
Garber 2008	-0.675	0.1119	264	144	6.3%	-0.68 [-0.89, -0.46]	*
Goodman 2009	-0.77	0.1345	248	122	5.1%	-0.77 [-1.03, -0.51]	+
Kothny 2013	-0.7	0.0094	228	221	13.6%	-0.70 [-0.72, -0.68]	•
Li 2017	-1.3	0.3785	17	16	0.9%	-1.30 [-2.04, -0.56]	
Macauley 2015	-0.7	0.0094	22	22	13.6%	-0.70 [-0.72, -0.68]	•
Ning 2016	-0.7	0.1697	146	147	3.7%	-0.70 [-1.03, -0.37]	*
Pan 2012B	-0.45	0.0981	292	144	7.2%	-0.45 [-0.64, -0.26]	•
Strain 2013	-0.6	0.1071	137	137	6.6%	-0.60 [-0.81, -0.39]	•
Su 2014	-1.61	0.1004	294	292	7.0%	-1.61 [-1.81, -1.41]	•
Yang 2015	-0.5	0.1	141	133	7.1%	-0.50 [-0.70, -0.30]	*
Total (95% CI)			2601	1894	100.0%	-0.69 [-0.77, -0.62]	
Heterogeneity: Tau ² =	: 0.01; Chi² = 167.84	, df = 13	(P < 0.00001); I²= 92%			
Test for overall effect:	•		•				-10 -5 0 5 10 Favours Vildagliptin Favours Placebo
							. areare rinaugilpair ravourer raccore

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

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



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

K.1.2.9 Adding vildagliptin compared to adding metformin

Figure 64: Hypoglycaemia episodes at end of follow up

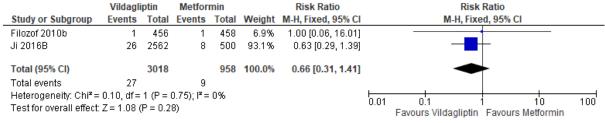


Figure 65: HbA1c change (%, lower values are better, change and final scores) at end of follow up

			Vildagliptin	Metformin		Mean Difference		Mean D	ifference		
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Fixed, 95% CI		IV, Fixed	d, 95% CI		
Filozof 2010b	-0.14	0.0485	456	458	42.4%	-0.14 [-0.24, -0.04]					
Ji 2016B	-0.14	0.0416	2501	484	57.6%	-0.14 [-0.22, -0.06]		•			
Total (95% CI)			2957	942	100.0%	-0.14 [-0.20, -0.08]					
Heterogeneity: Chi² = Test for overall effect:	, ,		%				-10	-5 Favours Vildagliptin	0 Favours M	5 letformin	10

K.1.2.10 Adding vildagliptin compared to adding insulin

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

K.1.2.11 Adding vildagliptin compared to adding saxagliptin

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

	Vildagli	ptin	Saxagi	iptin		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Chen 2016	0	37	0	36	36.1%	0.00 [-0.05, 0.05]	+
Li 2014B	0	63	0	66	63.9%	0.00 [-0.03, 0.03]	•
Total (95% CI)		100		102	100.0%	0.00 [-0.03, 0.03]	+
Total events	0		0				
Heterogeneity: Chi² = Test for overall effect:		,			-1 -0.5 0 0.5 1 Favours Vildagliptin Favours Saxagliptin		

Figure 67: Cardiovascular mortality at end of follow up

_	Vildagli	iptin	Saxagl	iptin	_	Risk Difference	Risk Difference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
Chen 2016	0	37	0	36	36.1%	0.00 [-0.05, 0.05]	+	
Li 2014B	0	63	0	66	63.9%	0.00 [-0.03, 0.03]	•	
Total (95% CI)		100		102	100.0%	0.00 [-0.03, 0.03]	•	
Total events	0		0					
Heterogeneity: Chi²=	0.00, df=	1 (P = 1)	1.00); $I^2 =$	0%		-1 -05 0 05 1	 	
Fest for overall effect: Z = 0.00 (P = 1.00)							Favours Vildagliptin Favours Saxagliptin	1

Figure 68: Hypoglycaemia episodes at end of follow up

	Vildagli	ptin	Saxagi	iptin		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95% CI	
Chen 2016	1	37	2	36	22.2%	0.49 [0.05, 5.13]		•	
Li 2014A	5	57	3	60	52.0%	1.75 [0.44, 7.01]		- •	
Li 2014B	1	63	4	66	25.8%	0.26 [0.03, 2.28]			
Total (95% CI)		157		162	100.0%	0.81 [0.25, 2.65]			
Total events	7		9						
Heterogeneity: Tau ² =				P = 0.30); I²= 189	%	0.01	0.1 1 10	100
Test for overall effect:	Z = 0.35 (P = 0.7	3)				0.01	Favours Vildagliptin Favours Saxagliptin	

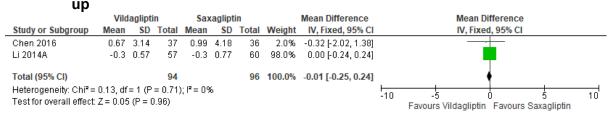
Figure 69: Severe hypoglycaemic episodes at end of follow up

	Vildagli	iptin	Saxagl	iptin		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	I M-H, Fixed, 95% CI
Chen 2016	0	37	0	36	38.4%	0.00 [-0.05, 0.05]	†
Li 2014A	0	57	0	60	61.6%	0.00 [-0.03, 0.03]] 📍
Total (95% CI)		94		96	100.0%	0.00 [-0.03, 0.03]	1
Total events	0		0				
Heterogeneity: Chi²=	0.00, df =	1 (P = 1)	1.00); l² =		-1 -05 0 05 1		
Test for overall effect:	Z = 0.00 ((P = 1.0	0)		Favours Vildagliptin Favours Saxagliptin		

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

up												
	Vild	Vildagliptin		Saxagliptin			Mean Difference			Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI		
Chen 2016	-1.22	0.4	37	-1.07	0.36	36	47.5%	-0.15 [-0.32, 0.02]				
Li 2014A	-1.25	0.45	57	-1.23	0.48	60	50.9%	-0.02 [-0.19, 0.15]		•		
Li 2014B	-1.34	2.76	63	-1.21	2.85	66	1.5%	-0.13 [-1.10, 0.84]				
Total (95% CI)			157			162	100.0%	-0.08 [-0.20, 0.04]				
Heterogeneity: $Chi^2 = 1.11$, $df = 2$ $(P = 0.57)$; $I^2 = 0\%$ Test for overall effect: $Z = 1.36$ $(P = 0.17)$										-5 0 5 Favours Vildagliptin Favours Saxagliptin	10	

Figure 71: BMI change (kg/m², lower values are better, change scores) at end of follow



K.1.3 GLP-1 receptor agonist

K.1.3.1 Adding dulaglutide compared to adding placebo

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

_	Dulaglu	ıtida	Place	ho		Risk Difference	Risk Difference
Study or Subgroup	Events				Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Dungan 2016	1	239	0	60	1.6%	0.00 [-0.02, 0.03]	+
Frias 2018	0	54	1	51	0.9%	-0.02 [-0.07, 0.03]	-
Frias 2023	0	50	1	55	0.9%	-0.02 [-0.07, 0.03]	+
Gerstein 2019A	317	4949	346	4952	84.5%	-0.01 [-0.02, 0.00]	
Ludvik 2018	0	283	0	140	3.2%	0.00 [-0.01, 0.01]	Ŧ
Pozzilli 2017	0	150	0	150	2.6%	0.00 [-0.01, 0.01]	†
Wang 2023	0	144	1	147	2.5%	-0.01 [-0.03, 0.01]	+
Wysham 2014 26 weeks	2	559	0	141	3.8%	0.00 [-0.01, 0.01]	†
Total (95% CI)		6428		5696	100.0%	-0.01 [-0.01, 0.00]	
Total events	320		349				
Heterogeneity: Chi ² = 5.01,	df = 7 (P :	= 0.66);	$I^2 = 0\%$				1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1
Test for overall effect: Z = 1	.22 (P = 0	.22)		-1 -0.5 0 0.5 1 Favours Dulaglutide Favours Placebo			

Figure 73: Cardiovascular mortality at end of follow up

	Dulaglu	ıtide	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Dungan 2016	1	239	0	60	1.6%	0.00 [-0.02, 0.03]	+
Frias 2018	0	54	1	51	0.9%	-0.02 [-0.07, 0.03]	+
Frias 2023	0	50	1	55	0.9%	-0.02 [-0.07, 0.03]	<u>±</u>
Gerstein 2019A	536	4949	592	4952	84.5%	-0.01 [-0.02, 0.00]	
Ludvik 2018	2	283	0	140	3.2%	0.01 [-0.01, 0.02]	†
Pozzilli 2017	0	150	0	150	2.6%	0.00 [-0.01, 0.01]	†
Wang 2023	0	144	1	147	2.5%	-0.01 [-0.03, 0.01]	†
Wysham 2014 26 weeks	2	559	0	141	3.8%	0.00 [-0.01, 0.01]	<u>†</u>
Total (95% CI)		6428		5696	100.0%	-0.01 [-0.02, 0.00]	•
Total events	541		595				
Heterogeneity: Chi ² = 13.9	6, df = 7 (F	9 = 0.05		1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1			
Test for overall effect: $Z = 1$.76 (P = 0	.08)		-1 -0.5 0 0.5 Favours Dulaglutide Favours Placebo			

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

	Dulaglutide	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events Tot	al Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Dungan 2016	1 2	39 0	60	0.5%	0.76 [0.03, 18.49]	
Gerstein 2019A	135 49	9 175	4952	99.3%	0.77 [0.62, 0.96]	
Pozzilli 2017	2 1	50 0	150	0.3%	5.00 [0.24, 103.28]	
Total (95% CI)	533	88	5162	100.0%	0.78 [0.63, 0.98]	•
Total events	138	175				
Heterogeneity: Chi ² = Test for overall effect:			0%			0.001 0.1 10 1000 Favours Dulaglutide Favours Placebo

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

_	Dulaglu	itide	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Gerstein 2019A	205	4949	212	4952	98.2%	0.97 [0.80, 1.17]	
Ludvik 2018	0	283	2	140	1.5%	0.10 [0.00, 2.05]	
Pozzilli 2017	1	150	0	150	0.2%	3.00 [0.12, 73.06]	
Total (95% CI)		5382		5242	100.0%	0.96 [0.80, 1.16]	+
Total events	206		214				
Heterogeneity: Chi²=	2.65, df=	2(P = 1)	0.27); l ^z =		0.001 0.1 1 10 1000		
Test for overall effect:	Z = 0.44 (P = 0.6	6)		Favours Dulaglutide Favours Placebo		

Figure 76: Unstable angina at end of follow up

	Dulaglu	itide	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Gerstein 2019A	88	4949	77	4952	96.2%	1.14 [0.84, 1.55]	
Ludvik 2018	0	283	1	140	2.5%	0.17 [0.01, 4.04]	
Pozzilli 2017	1	150	1	150	1.3%	1.00 [0.06, 15.84]	
Total (95% CI)		5382		5242	100.0%	1.12 [0.83, 1.51]	•
Total events	89		79				
Heterogeneity: Chi² = Test for overall effect:				: 0%			0.001 0.1 1 10 1000
	,		.,				Favours Dulaglutide Favours Placebo

Figure 77: Acute kidney injury at end of follow up

i iguie i i . Acc	ILC KIU	ii i C y	ıııjuı y	ale	ilu Ol	ionow up	
	Dulaglu	itide	Place	Placebo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Gerstein 2019A	60	4949	67	4952	99.3%	0.90 [0.63, 1.27]	•
Wang 2023	1	144	0	147	0.7%	3.06 [0.13, 74.55]	
Total (95% CI)		5093		5099	100.0%	0.91 [0.65, 1.29]	*
Total events	61		67				
Heterogeneity: Chi²=	0.56, df =	1 (P=	0.45); l ² =		0.01 0.1 1 10 100		
Test for overall effect:	Z = 0.53 (P = 0.6	0)	0.01 0.1 1 10 100 Eavours Duladutide Favours Placebo			

Figure 78: Cardiac arrhythmia at end of follow up

	Dulaglu	ıtide	Place	bo		Risk Difference		Risk Difference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Frias 2023	0	50	0	55	1.0%	0.00 [-0.04, 0.04]		<u>±</u>	
Gerstein 2019A	216	4949	192	4952	99.0%	0.00 [-0.00, 0.01]		-	
Total (95% CI)		4999		5007	100.0%	0.00 [-0.00, 0.01]			
Total events	216		192						
Heterogeneity: Chi²=	0.07, df=	1 (P = 1)	0.80); l² =	: 0%			H_	-0.5 0 0.5	
Test for overall effect:	Z = 1.22 (P = 0.2	2)				-1	Favours Dulaglutide Favours Placebo	'

Figure 79: Diabetic ketoacidosis at end of follow up

	Dulaglu	itide	Place	bo		Risk Difference		Risk Difference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Frias 2023	0	50	0	55	21.9%	0.00 [-0.04, 0.04]		<u>+</u>	
Ludvik 2018	0	283	0	140	78.1%	0.00 [-0.01, 0.01]		•	
Total (95% CI)		333		195	100.0%	0.00 [-0.01, 0.01]		•	
Total events	0		0						
Heterogeneity: Chi²=	0.00, df =	1 (P =	1.00); l² =	:0%			H_	-0.5 0 0.5	
Test for overall effect:	Z = 0.00 (P = 1.0	0)				-1	Favours Dulaglutide Favours Placebo	'

Figure 80: Hypoglycaemia episodes at end of follow up

_		Dulaglu	tide	Place	bo		Risk Ratio	Risk	Ratio	
Study or	r Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixe	d, 95% CI	
Dungan	2016	50	239	2	60	3.1%	6.28 [1.57, 25.07]			
Frias 20	118	2	54	2	51	2.0%	0.94 [0.14, 6.46]			
Frias 20	123	2	50	2	55	1.8%	1.10 [0.16, 7.52]			
Ludvik 2	:018	10	283	4	140	5.2%	1.24 [0.39, 3.87]		-	
Pozzilli 2	2017	53	150	45	150	43.7%	1.18 [0.85, 1.63]	-	-	
Wang 2	023	42	144	46	147	44.2%	0.93 [0.66, 1.32]	-	-	
Total (9	5% CI)		920		603	100.0%	1.22 [0.97, 1.54]		•	
Total ev	ents	159		101						
Heterog	eneity: Chi²=	7.83, df=	5 (P = 1)	0.17); $I^2 =$	36%			0.01 0.1	10	100
Test for	overall effect:	Z=1.72 (P = 0.0	8)				Favours Dulaglutide		100

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

	Dulaglu	itide	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Dungan 2016	16	239	1	60	2.5%	4.02 [0.54, 29.69]	
Pozzilli 2017	42	150	43	150	67.8%	0.98 [0.68, 1.40]	-
Wang 2023	11	144	19	147	29.7%	0.59 [0.29, 1.20]	
Total (95% CI)		533		357	100.0%	0.94 [0.68, 1.29]	+
Total events	69		63				
Heterogeneity: Chi²=	3.73, df=	2 (P =	0.16); l ^z =	46%			0.04 0.4 10 100
Test for overall effect	Z = 0.39 (P = 0.7	0)				0.01 0.1 1 10 100 Favours Duladutide Favours Placebo

Figure 82: Severe hypoglycaemic episodes at end of follow up

	Dulaglu	tide	Place	bo		Risk Difference		Risk Difference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Dungan 2016	0	239	0	60	1.7%	0.00 [-0.02, 0.02]		+	
Frias 2018	0	54	0	51	0.9%	0.00 [-0.04, 0.04]		+	
Frias 2023	0	50	0	55	0.9%	0.00 [-0.04, 0.04]		<u>±</u>	
Gerstein 2019A	64	4949	74	4952	87.9%	-0.00 [-0.01, 0.00]			
Ludvik 2018	1	283	0	140	3.3%	0.00 [-0.01, 0.02]		†	
Pozzilli 2017	1	150	0	150	2.7%	0.01 [-0.01, 0.02]		†	
Wang 2023	0	144	0	147	2.6%	0.00 [-0.01, 0.01]		†	
Total (95% CI)		5869		5555	100.0%	-0.00 [-0.01, 0.00]			
Total events	66		74						
Heterogeneity: Chi²=	1.46, df=	6 (P = 1)	0.96); l²=	: 0%			-1	-0.5 0 0.5	_
Test for overall effect:	Z = 0.69 (P = 0.4	9)				-1	Favours Dulaglutide Favours Placebo	'

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

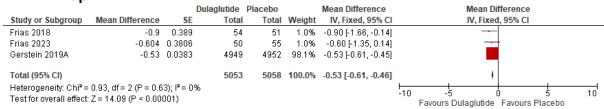
-			Dulaglutide	Placebo		Mean Difference		Mean Difference	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI	
Dungan 2016	-1.3	0.1531	239	60	9.8%	-1.30 [-1.60, -1.00]		•	
Frias 2018	-1.2	0.2193	54	51	7.5%	-1.20 [-1.63, -0.77]		-	
Frias 2023	-0.67	0.1837	50	55	8.7%	-0.67 [-1.03, -0.31]		-	
Gerstein 2019A	-0.61	0.0179	4949	4952	13.7%	-0.61 [-0.65, -0.57]		•	
Ludvik 2018	-0.74	0.0737	283	140	12.6%	-0.74 [-0.88, -0.60]		•	
Nauck 2014 Dulaglutide v Placebo	-1.14	0.0801	606	177	12.4%	-1.14 [-1.30, -0.98]		•	
Pozzilli 2017	-0.765	0.1046	150	150	11.6%	-0.77 [-0.97, -0.56]		•	
Wang 2023	-0.9	0.1064	144	147	11.5%	-0.90 [-1.11, -0.69]		•	
Wysham 2014 26 weeks	-0.94	0.0905	559	141	12.1%	-0.94 [-1.12, -0.76]		•	
Total (95% CI)			7034	5873	100.0%	-0.90 [-1.08, -0.73]		•	
Heterogeneity: Tau ² = 0.06; Chi ² = 83		001); l² =	= 90%				-10	-5 0 5	10
Test for overall effect: Z = 10.07 (P <	0.00001)							Favours Dulaglutide Favours Placebo	

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

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

			Dulaglutide	Placebo		Mean Difference		Mean Dif	ference		
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Fixed, 95% CI		IV, Fixed	, 95% CI		
Dungan 2016	-0.675	0.4362	239	60	3.8%	-0.68 [-1.53, 0.18]		-			
Frias 2018	-2.3	1.1245	54	51	0.6%	-2.30 [-4.50, -0.10]					
Frias 2023	-1.7	1.0714	50	55	0.6%	-1.70 [-3.80, 0.40]			-		
Gerstein 2019A	-1.46	0.1071	4949	4952	63.1%	-1.46 [-1.67, -1.25]					
Ludvik 2018	-0.75	0.3675	283	140	5.4%	-0.75 [-1.47, -0.03]		-			
Pozzilli 2017	-2.41	0.3954	150	150	4.6%	-2.41 [-3.18, -1.64]					
Skrivanek 2014	-1.5	0.2855	131	33	8.9%	-1.50 [-2.06, -0.94]		-			
Wang 2023	-1.2	0.2826	144	147	9.1%	-1.20 [-1.75, -0.65]		-			
Wysham 2014 26 weeks	-1.79	0.4259	559	141	4.0%	-1.79 [-2.62, -0.96]					
Total (95% CI)			6559	5729	100.0%	-1.44 [-1.60, -1.27]		•			
Heterogeneity: Chi² = 14.74		² = 46%					-10	-5	l	5	10
Test for overall effect: $Z = 1$	0.88 (P < 0.00001)							Favours Dulaglutide	Favours Pla	acebo	

Figure 85: BMI change (kg/m², lower values are better, change scores) at end of follow up



K.1.3.2 Adding dulaglutide compared to adding insulin

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

	Dulaglu	ıtide	Insul	in		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Blonde 2015	2	588	3	296	55.8%	0.30 [0.05, 1.95]	
Giorgino 2015	1	545	2	262	33.0%	0.21 [0.02, 2.35]	
Wang 2019B	1	515	0	253	11.1%	4.44 [0.07, 287.54]	-
Total (95% CI)		1648		811	100.0%	0.36 [0.09, 1.45]	•
Total events	4		5				
Heterogeneity: Chi²=	1.62, df=	2(P = 1)	0.44); 2 =	0%			0.001 0.1 1 10 1000
Test for overall effect	Z = 1.44 ((P = 0.1)	5)				Favours Dulaglutide Favours Insulin

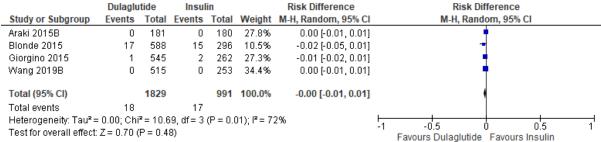
Figure 87: Hypoglycaemia episodes at end of follow up

	Dulaglu	ıtide	Insul	in		Risk Ratio	Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Rand	om, 95% CI	
Araki 2015B	47	181	86	180	28.4%	0.54 [0.41, 0.73]	+		
Giorgino 2015	205	545	123	262	38.8%	0.80 [0.68, 0.95]			
Wang 2019B	109	515	88	253	32.8%	0.61 [0.48, 0.77]	•		
Total (95% CI)		1241		695	100.0%	0.66 [0.51, 0.84]	•		
Total events	361		297						
Heterogeneity: Tau ² =	: 0.03; Chi	$i^2 = 6.80$	f = 2 (1)	P = 0.03	3); I ² = 71°	%	0.04 0.4	10	100
Test for overall effect	Z = 3.41 (P = 0.0	007)				0.01 0.1 Favours Dulaglutide	Favours Insulin	100

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

	Dulaglu	ıtide	Insul	lin		Risk Ratio	Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixe	ed, 95% CI	
Araki 2015B	16	181	48	180	21.2%	0.33 [0.20, 0.56]	-		
Giorgino 2015	111	545	98	262	58.2%	0.54 [0.43, 0.68]	-		
Wang 2019B	29	515	35	253	20.6%	0.41 [0.25, 0.65]	-		
Total (95% CI)		1241		695	100.0%	0.47 [0.39, 0.57]	•		
Total events	156		181						
Heterogeneity: Chi²=	: 3.63, df=	2 (P =	0.16); l ^z =	45%			0.01 0.1	1 10	100
Test for overall effect	Z = 7.65	(P < 0.0	0001)				Favours Dulaglutide	1 10 Favours Insulin	100

Figure 89: Severe hypoglycaemic episodes at end of follow up



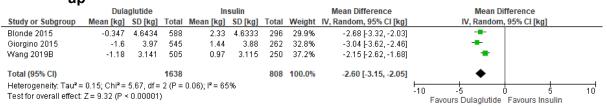
Note: Heterogeneity was not explained by sensitivity analysis, nor subgroup analysis by eGFR subgroup.

Figure 90: HbA1c change (%, lower values are better, change scores) at end of follow

սբ	,												
_	Dula	aglutide		In	sulin			Mean Difference		Mean D	fferen	ce	
Study or Subgroup	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV, Random, 95% CI [%]		IV, Randon	ı, 95% (CI [%]	
Araki 2015B	-1.44	0.6727	181	-0.9	0.6708	180	27.2%	-0.54 [-0.68, -0.40]		•			
Blonde 2015	-1.45	1.393	588	-1.23	1.399	296	23.5%	-0.22 [-0.42, -0.02]					
Giorgino 2015	-0.76	1.16	545	-0.59	1.13	262	25.3%	-0.17 [-0.34, -0.00]			•		
Wang 2019B	-1.25	1.226	505	-0.89	1.2649	250	23.9%	-0.36 [-0.55, -0.17]		•			
Total (95% CI)			1819			988	100.0%	-0.33 [-0.51, -0.15]		•			
Heterogeneity: Tau ² =	= 0.03; Chi² =	= 13.34, 0	f= 3 (F	P = 0.004); F	² = 78%				-10	-5	<u> </u>	- Į	10
Test for overall effect	Z = 3.56 (P	= 0.0004)							vours Dulaglutide	Favou	ırs İnsulin	10

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

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



K.1.3.3 Adding dulaglutide compared to adding exenatide

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

K.1.3.4 Adding dulaglutide compared to adding sitagliptin

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

K.1.3.5 Adding exenatide compared to adding placebo

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

	Exena	tide	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Buse 2011	0	137	1	122	1.6%	-0.01 [-0.03, 0.01]	+
Guja 2017	0	232	1	231	2.8%	-0.00 [-0.02, 0.01]	<u>+</u>
Holman 2017	507	7356	584	7396	89.1%	-0.01 [-0.02, -0.00]	
Joubert 2021	0	28	0	18	0.3%	0.00 [-0.09, 0.09]	+
Kadowaki 2011	0	144	0	35	0.7%	0.00 [-0.04, 0.04]	+
Liutkus 2010	0	111	0	54	0.9%	0.00 [-0.03, 0.03]	+
Rosenstock 2018A	1	306	1	154	2.5%	-0.00 [-0.02, 0.01]	†
Wysham 2014 26 weeks	0	276	0	141	2.3%	0.00 [-0.01, 0.01]	†
Total (95% CI)		8590		8151	100.0%	-0.01 [-0.02, -0.00]	(
Total events	508		587				
Heterogeneity: Chi² = 4.83,	df= 7 (P	= 0.68)	$ I^2 = 0\% $				1 1 1 1
Test for overall effect: $Z = 2$.40 (P = 0	1.02)					-1 -0.5 0 0.5 1 Favours Exenatide Favours Placebo

Figure 93: Cardiovascular mortality at end of follow up

	Exena	tide	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Buse 2011	0	137	1	122	1.6%	-0.01 [-0.03, 0.01]	+
Guja 2017	0	232	0	231	2.8%	0.00 [-0.01, 0.01]	<u> </u>
Holman 2017	340	7356	383	7396	89.1%	-0.01 [-0.01, 0.00]	
Joubert 2021	0	28	0	18	0.3%	0.00 [-0.09, 0.09]	+
Kadowaki 2011	0	144	0	35	0.7%	0.00 [-0.04, 0.04]	+
Liutkus 2010	0	111	0	54	0.9%	0.00 [-0.03, 0.03]	+
Rosenstock 2018A	0	306	0	154	2.5%	0.00 [-0.01, 0.01]	<u> </u>
Wysham 2014 26 weeks	0	276	0	141	2.3%	0.00 [-0.01, 0.01]	†
Total (95% CI)		8590		8151	100.0%	-0.01 [-0.01, 0.00]	
Total events	340		384				
Heterogeneity: Chi ² = 3.52,	df = 7 (P :	= 0.83)	I² = 0%				-1 -05 0 05 1
Test for overall effect: $Z = 1$.	60 (P = 0	.11)					-1 -0.5 0 0.5 1 Favours Exenatide Favours Placebo

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

	Exena	tide	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Buse 2004	1	254	0	123	53.8%	4.41 [0.07, 288.49]	
Gadde 2017	0	181	1	61	46.2%	0.02 [0.00, 1.73]	—
Total (95% CI)		435		184	100.0%	0.36 [0.02, 7.65]	
Total events	1		1				
Heterogeneity: Chi² =	3.02, df=	1 (P=	0.08); l² =	= 67%			0.001 0.1 1 10 1000
Test for overall effect:	Z = 0.66	(P = 0.5)	51)				Favours Exenatide Favours Placebo

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

	Exena	tide	Place	bo		RISK Ratio		RISK	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed	d, 95% CI	
Holman 2017	219	7356	231	7396	99.7%	0.95 [0.79, 1.14]				
Joubert 2021	1	28	0	18	0.3%	1.97 [0.08, 45.77]			-	_
Total (95% CI)		7384		7414	100.0%	0.96 [0.80, 1.15]		•	,	
Total events	220		231							
Heterogeneity: Chi²=	0.20, df=	1 (P=	0.65); l² =	= 0%			0.01	n'1 1	10	100
Test for overall effect:	Z = 0.49	(P = 0.8)	i3)				0.01	Favours Exenatide	Favours Placebo	100

Figure 96: Diabetic ketoacidosis at end of follow up

	Exena	tide	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	I M-H, Fixed, 95% CI
Harreiter 2021	0	16	0	14	21.0%	0.00 [-0.12, 0.12]	<u>+</u>
Kadowaki 2011	1	144	0	35	79.0%	0.01 [-0.03, 0.05]	ij <u> </u>
Total (95% CI)		160		49	100.0%	0.01 [-0.04, 0.05]	•
Total events	1		0				
Heterogeneity: Chi²=	0.01, df =	1 (P=	0.91); l² :	= 0%			-1 -0.5 0 0.5 1
Test for overall effect:	Z = 0.25	(P = 0.8)	30)				Favours Exenatide Favours Placebo

Figure 97: Hypoglycaemia episodes at end of follow up

	Exena	tide	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Buse 2004	64	254	4	123	8.1%	0.22 [0.16, 0.28]	
Buse 2011	34	137	35	122	6.2%	-0.04 [-0.15, 0.07]	
DeFronzo 2005	11	223	6	113	8.5%	-0.00 [-0.05, 0.05]	+
Derosa 2012C	0	86	0	85	9.3%	0.00 [-0.02, 0.02]	+
Gadde 2017	0	181	0	61	9.3%	0.00 [-0.02, 0.02]	+
Guja 2017	81	232	77	231	7.1%	0.02 [-0.07, 0.10]	+
Harreiter 2021	0	16	0	14	5.7%	0.00 [-0.12, 0.12]	
Joubert 2021	0	28	0	18	7.1%	0.00 [-0.09, 0.09]	+
Kadowaki 2011	79	144	8	35	4.4%	0.32 [0.16, 0.48]	
Kendall 2005	114	486	31	247	8.3%	0.11 [0.05, 0.16]	-
Liutkus 2010	4	111	1	54	8.5%	0.02 [-0.03, 0.07]	+
Rosenstock 2018A	24	306	4	154	8.9%	0.05 [0.01, 0.09]	
Wysham 2014 26 weeks	44	276	5	141	8.4%	0.12 [0.07, 0.18]	+
Total (95% CI)		2480		1398	100.0%	0.06 [0.01, 0.10]	◆
Total events	455		171				
Heterogeneity: Tau ² = 0.01	: Chi² = 13	33.04. d	f= 12 (P	< 0.000	001); I²=	91%	I. J. J. J.
Test for overall effect: Z = 2	•		•				-1 -0.5 0 0.5 Favours Exenatide Favours Placebo

Note: Heterogeneity was not explained by sensitivity analysis

Figure 98: Severe hypoglycaemic episodes at end of follow up

J	Exena	tide	Place	bo	•	Risk Difference		Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Buse 2004	0	254	0	123	1.9%	0.00 [-0.01, 0.01]		+
Buse 2011	0	137	1	122	1.5%	-0.01 [-0.03, 0.01]		+
DeFronzo 2005	0	223	0	113	1.7%	0.00 [-0.01, 0.01]		†
Gadde 2017	0	181	0	61	1.0%	0.00 [-0.02, 0.02]		†
Guja 2017	0	232	0	231	2.6%	0.00 [-0.01, 0.01]		†
Harreiter 2021	0	16	0	14	0.2%	0.00 [-0.12, 0.12]		
Holman 2017	247	7356	219	7396	84.1%	0.00 [-0.00, 0.01]		
Joubert 2021	0	28	0	18	0.2%	0.00 [-0.09, 0.09]		+
Kadowaki 2011	0	144	0	35	0.6%	0.00 [-0.04, 0.04]		+
Kendall 2005	1	486	0	247	3.7%	0.00 [-0.01, 0.01]		†
Rosenstock 2018A	0	306	0	154	2.3%	0.00 [-0.01, 0.01]		†
Total (95% CI)		9363		8514	100.0%	0.00 [-0.00, 0.01]		
Total events	248		220					
Heterogeneity: Chi ² =	2.83, df=	10 (P	= 0.99); P	2=0%			<u> </u>	0.5
Test for overall effect:	Z = 1.34	(P = 0.1	8)				-1	-0.5 0 0.5 1 Favours Exenatide Favours Placebo

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

-			Exenatide	Placebo		Mean Difference		Mean Difference	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI	
Buse 2004	-0.78	0.122	254	123	7.9%	-0.78 [-1.02, -0.54]		•	
Buse 2011	-0.7	0.1269	137	122	7.6%	-0.70 [-0.95, -0.45]		+	
DeFronzo 2005	-0.7	0.1228	223	113	7.8%	-0.70 [-0.94, -0.46]		+	
Derosa 2012C	-0.6	0.0399	81	82	13.6%	-0.60 [-0.68, -0.52]		•	
Gadde 2017	-0.73	0.2195	181	61	3.9%	-0.73 [-1.16, -0.30]		-	
Guja 2017	-0.73	0.102	231	230	9.2%	-0.73 [-0.93, -0.53]		-	
Holman 2017	-0.53	0.0204	7362	7313	14.5%	-0.53 [-0.57, -0.49]		•	
Joubert 2021	-0.695	0.2781	28	18	2.7%	-0.69 [-1.24, -0.15]			
Kadowaki 2011	-1.2	0.1696	144	35	5.5%	-1.20 [-1.53, -0.87]		-	
Kendall 2005	-0.89	0.0881	486	247	10.2%	-0.89 [-1.06, -0.72]		•	
Liutkus 2010	-0.74	0.3054	111	54	2.3%	-0.74 [-1.34, -0.14]			
Rosenstock 2018A (1)	-1	0.27	153	72	2.8%	-1.00 [-1.53, -0.47]		-	
Rosenstock 2018A (2)	-1.1	0.27	153	71	2.8%	-1.10 [-1.63, -0.57]			
Wysham 2014 26 weeks	-0.53	0.1001	276	141	9.3%	-0.53 [-0.73, -0.33]		-	
Total (95% CI)			9820	8682	100.0%	-0.72 [-0.82, -0.63]		-	
Heterogeneity: Tau ² = 0.02;	$Chi^2 = 45.96, df = 1$	3 (P < 0.	$0001); I^2 = 7$	2%			-10	+ + +	10
Test for overall effect: $Z = 14$	4.45 (P < 0.00001)						-10	Favours Exenatide Favours Placebo	

<u>Footnotes</u>

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

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

	-		Exenatide	Placebo		Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Buse 2004	-0.66	0.366	254	125	9.4%	-0.66 [-1.38, 0.06]	
Buse 2011	-2.74	0.5111	137	122	7.4%	-2.74 [-3.74, -1.74]	
DeFronzo 2005	-1.91	0.4407	223	113	8.3%	-1.91 [-2.77, -1.05]	
Derosa 2012C	-5.6	1.1401	81	82	2.7%	-5.60 [-7.83, -3.37]	
Gadde 2017	-1.3	0.5831	181	61	6.6%	-1.30 [-2.44, -0.16]	
Guja 2017	-1.5	0.3393	231	230	9.8%	-1.50 [-2.17, -0.83]	
Harreiter 2021	-2.45	1.5255	16	14	1.7%	-2.45 [-5.44, 0.54]	
Holman 2017	-1.27	0.0663	7372	7334	12.9%	-1.27 [-1.40, -1.14]	•
Joubert 2021	-3.85	0.9592	28	18	3.6%	-3.85 [-5.73, -1.97]	 -
Kadowaki 2011	-0.5	0.4383	144	35	8.4%	-0.50 [-1.36, 0.36]	-+
Kendall 2005	-0.7	0.2447	486	247	11.1%	-0.70 [-1.18, -0.22]	+
Liutkus 2010	-0.6	0.9161	111	54	3.8%	-0.60 [-2.40, 1.20]	
Rosenstock 2018A (1)	-2	1.03	153	71	3.2%	-2.00 [-4.02, 0.02]	
Rosenstock 2018A (2)	-1.3	1.03	153	72	3.2%	-1.30 [-3.32, 0.72]	
Wysham 2014 26 weeks	-2.31	0.47	276	141	7.9%	-2.31 [-3.23, -1.39]	
Total (95% CI)			9846	8719	100.0%	-1.58 [-2.00, -1.17]	•
Heterogeneity: Tau ² = 0.34;	Chi ² = 50.26, df = 1	4 (P < 0.	00001); I ² =	72%			1 <u>1</u>
Test for overall effect: $Z = 7$.	47 (P < 0.00001)	•					-10 -5 0 5 10
	,						Favours Exenatide Favours Placebo

Footnotes

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

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

	-		Exenatide	Placebo		Mean Difference	Mean Difference
Study or Subgro	oup Mean Difference	SE	Total	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Derosa 2012C	-1.3	0.1236	81	82	86.9%	-1.30 [-1.54, -1.06]	
Harreiter 2021	-0.62	0.5536	16	14	4.3%	-0.62 [-1.71, 0.47]	
Joubert 2021	-1.45	0.3903	28	18	8.7%	-1.45 [-2.21, -0.69]	
Total (95% CI)			125	114	100.0%	-1.28 [-1.51, -1.06]	•
Heterogeneity: C	Chi ² = 1.64, df = 2 (P = 0.4	4); ² = 0	%				-10 -5 0 5 10
Test for overall e	effect: Z = 11.14 (P < 0.00	001)					Favours Exenatide Favours Placebo

^{(1) 40} mcg daily arm. N placebo was halved

^{(2) 60} mcg daily arm. N placebo was halved

^{(1) 60} mcg daily arm. N for placebo arm was halved

^{(2) 40} mcg daily arm. N for placebo arm was halved.

K.1.3.6 Adding exenatide compared to adding insulin

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

	F	xenatide			Insulin			Mean Difference		Mean D	fference	Δ.	
Study or Subgroup	Mean	SD		Mean		Total	Weight	IV, Fixed, 95% CI		IV, Fixe		_	
Diamant 2010	0.02	0.3053	233	0	0.2987	223	20.0%	0.02 [-0.04, 0.08]		_	<u> </u>		
Heine 2005	0.02	0.1473	217	0.03	0.1466	215	80.0%	-0.01 [-0.04, 0.02]					
Total (95% CI)			450			438	100.0%	-0.00 [-0.03, 0.02]					
Heterogeneity: Chi² = Test for overall effect:				²= 0%					-10	-5 Favours Insulin	0 Favour	5 s Exenatide	10

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

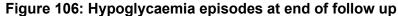
	E	xenatide			Insulin			Mean Difference		Mean	Differen	ice	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fix	ed, 95%	CI	
Davies 2013	6.2	10.6326	111	2.8	10.8513	105	37.4%	3.40 [0.53, 6.27]			—	_	
Diamant 2014	4.4	12.573	247	0.51	12.9738	263	62.6%	3.89 [1.67, 6.11]			-	_	
Total (95% CI)			358			368	100.0%	3.71 [1.95, 5.46]			-	•	
Heterogeneity: Chi ² = Test for overall effect		•		= 0%					-10	-5	 	_ 5	10
restror overall effect	2 - 4.1-	r (i - 0.00	01/							Favours Insul	n Favo	urs Exenat	ide

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

_	Exena	tide	Insu	lin	Risk Difference			Risk Difference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Bergenstal 2009	0	124	0	124	10.0%	0.00 [-0.02, 0.02]		+	
Davies 2013	0	111	0	105	8.7%	0.00 [-0.02, 0.02]		†	
Diamant 2010	1	233	1	223	18.4%	-0.00 [-0.01, 0.01]		<u> </u>	
Diamant 2014	1	315	0	312	25.3%	0.00 [-0.01, 0.01]		•	
Inagaki 2012	1	215	0	212	17.3%	0.00 [-0.01, 0.02]		†	
Nauck 2007A	2	253	1	248	20.2%	0.00 [-0.01, 0.02]		†	
Total (95% CI)		1251		1224	100.0%	0.00 [-0.00, 0.01]			
Total events	5		2						
Heterogeneity: Chi²=	0.53, df=	5 (P =	0.99); l²:	= 0%			<u> </u>	-0.5 0 0.5	_
Test for overall effect	Z = 0.88	(P = 0.3)	38)				- 1	Favours Exenatide Favours Insulin	'

Figure 105: Cardiovascular mortality at end of follow up

_	Exenatide		Insulin		Risk Difference		Risk Difference				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fix	ked, 95%	CI	
Bergenstal 2009	0	124	0	124	16.3%	0.00 [-0.02, 0.02]			•		
Davies 2013	0	111	0	105	14.2%	0.00 [-0.02, 0.02]			+		
Diamant 2014	1	315	0	312	41.3%	0.00 [-0.01, 0.01]			•		
Inagaki 2012	1	215	0	212	28.1%	0.00 [-0.01, 0.02]			•		
Total (95% CI)		765		753	100.0%	0.00 [-0.00, 0.01]					
Total events	2		0								
Heterogeneity: Chi²=	3 (P =	0.96); l² :		<u></u>	0.5	 	0.5				
Test for overall effect	(P = 0.4)	12)	-1	-0.5 Favours Exenatid	u e Favoi		'				



	Exenatide In		Insul	sulin Ris		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Bergenstal 2009	25	124	49	124	18.2%	0.51 [0.34, 0.77]	
Bunck 2009	3	36	8	33	3.1%	0.34 [0.10, 1.19]	
Davies 2009	37	118	42	116	15.7%	0.87 [0.60, 1.24]	
Davies 2013	5	111	6	105	2.3%	0.79 [0.25, 2.51]	
Diamant 2014	95	315	127	312	47.3%	0.74 [0.60, 0.92]	=
Gallwitz 2011	11	135	28	137	10.3%	0.40 [0.21, 0.77]	
Inagaki 2012	1	215	4	212	1.5%	0.25 [0.03, 2.19]	
Zhang 2020B	1	27	5	32	1.7%	0.24 [0.03, 1.91]	· ·
Total (95% CI)		1081		1071	100.0%	0.66 [0.56, 0.77]	•
Total events	178		269				
Heterogeneity: Chi²=	9.98, df=	7 (P=	0.01 0.1 1 10 100				
Test for overall effect:	Z = 5.17	(P < 0.0	Favours Exenatide Favours Insulin				

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

_	Exenatide Insulin		in	-	Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Davies 2009	14	118	34	116	19.7%	0.40 [0.23, 0.71]	
Davies 2013	1	111	1	105	1.5%	0.95 [0.06, 14.93]	
Diamant 2014	84	315	128	312	35.3%	0.65 [0.52, 0.82]	-
Gallwitz 2011	5	135	10	137	8.7%	0.51 [0.18, 1.45]	
Inagaki 2012	2	215	22	212	5.2%	0.09 [0.02, 0.38]	
Nauck 2007A	44	253	62	248	29.5%	0.70 [0.49, 0.98]	-
Total (95% CI)		1147		1130	100.0%	0.54 [0.38, 0.76]	•
Total events	150		257				
Heterogeneity: Tau² =	0.08; Ch	$i^2 = 10.3$	36, df = 5	(P = 0.	$07); I^2 = 5$	2%	0.01 0.1 1 10 100
Test for overall effect:	Z = 3.50	(P = 0.0)	1005)			Favours Exenatide Favours Insulin	

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

Figure 108: Severe hypoglycaemic episodes at end of follow up

	Exenatide		Insulin		Risk Difference		Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Bergenstal 2009	0	124	4	124	7.2%	-0.03 [-0.07, 0.00]	-
Bunck 2009	0	36	0	33	2.0%	0.00 [-0.05, 0.05]	+
Davies 2009	5	118	6	116	6.8%	-0.01 [-0.06, 0.04]	+
Diamant 2010	0	233	0	223	13.2%	0.00 [-0.01, 0.01]	†
Diamant 2014	2	315	7	312	18.2%	-0.02 [-0.03, 0.00]	•
Gallwitz 2011	0	135	0	137	7.9%	0.00 [-0.01, 0.01]	†
Heine 2005	4	282	4	267	15.9%	-0.00 [-0.02, 0.02]	†
Inagaki 2012	0	215	0	212	12.4%	0.00 [-0.01, 0.01]	†
Nauck 2007A	0	253	0	248	14.6%	0.00 [-0.01, 0.01]	†
Zhang 2020B	0	27	0	32	1.7%	0.00 [-0.06, 0.06]	+
Total (95% CI)		1738		1704	100.0%	-0.01 [-0.01, 0.00]	
Total events	11		21				
Heterogeneity: Chi ² =	10.25, df	= 9 (P :	= 0.33); P	-1 -0.5 0 0.5 1			
Test for overall effect:	Z=1.68 ((P = 0.0)	19)	-1 -0.5 0 0.5 1 Favours Exenatide Favours Insulin			

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

	-		Exenatide	Insulin		Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Bergenstal 2009	0.59	0.1956	124	124	5.7%	0.59 [0.21, 0.97]	+
Bunck 2009	-0.1	0.2236	36	33	5.1%	-0.10 [-0.54, 0.34]	+
Davies 2009	0.01	0.1273	98	102	7.3%	0.01 [-0.24, 0.26]	+
Davies 2013	-0.42	0.1102	111	105	7.7%	-0.42 [-0.64, -0.20]	•
Diamant 2010	-0.2	0.0944	233	223	8.1%	-0.20 [-0.39, -0.01]	+
Diamant 2014	-0.025	0.0689	315	312	8.6%	-0.03 [-0.16, 0.11]	+
Gallwitz 2011	0.144	0.075	181	173	8.5%	0.14 [-0.00, 0.29]	•
Gurkan 2014	0.05	0.2713	17	17	4.2%	0.05 [-0.48, 0.58]	+
Heine 2005	0.017	0.0714	275	260	8.6%	0.02 [-0.12, 0.16]	<u> </u>
Inagaki 2012	-0.43	0.0849	215	212	8.3%	-0.43 [-0.60, -0.26]	•
Kang 2021	-1.012	0.2833	79	80	4.0%	-1.01 [-1.57, -0.46]	
Nauck 2007A	-0.15	0.0922	253	248	8.1%	-0.15 [-0.33, 0.03]	1
Sawidou 2016	0.4	0.1162	55	48	7.6%	0.40 [0.17, 0.63]	<u>+</u>
Wang 2020A	-0.37	0.2094	40	41	5.4%	-0.37 [-0.78, 0.04]	-
Zhang 2020B	-0.22	0.3711	27	32	2.8%	-0.22 [-0.95, 0.51]	+
Total (95% CI)			2059	2010	100.0%	-0.09 [-0.24, 0.06]	
Heterogeneity: Tau ² =	0.06; Chi² = 82.40,	df = 14 (P < 0.00001); I ² = 839	6		<u> </u>
Test for overall effect:		Ì					-10 -5 0 5 10 Favours Exenatide Favours Insulin

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

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

		•	Exenatide	Insulin		Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Bergenstal 2009	-4.7	0.4701	124	124	8.1%	-4.70 [-5.62, -3.78]	•
Bunck 2009	-4.6	1	36	33	5.8%	-4.60 [-6.56, -2.64]	•
Davies 2009	-5.71	0.4384	100	104	8.3%	-5.71 [-6.57, -4.85]	•
Davies 2013	-3.5	0.4968	111	105	8.0%	-3.50 [-4.47, -2.53]	•
Diamant 2010	-4.51	0.3674	233	223	8.5%	-4.51 [-5.23, -3.79]	•
Diamant 2014	-4.5	0.3316	315	312	8.6%	-4.50 [-5.15, -3.85]	•
Gallwitz 2011	-5.1	0.3111	135	137	8.7%	-5.10 [-5.71, -4.49]	•
Gurkan 2014	-0.87	4.7009	17	17	0.7%	-0.87 [-10.08, 8.34]	
Heine 2005	-4.05	0.2806	275	260	8.8%	-4.05 [-4.60, -3.50]	•
Inagaki 2012	-2.01	0.2296	215	212	8.9%	-2.01 [-2.46, -1.56]	•
Kang 2021	-4.73	1.1474	79	80	5.2%	-4.73 [-6.98, -2.48]	•
Nauck 2007A	-5.4	0.2828	253	248	8.8%	-5.40 [-5.95, -4.85]	•
Sawidou 2016	-9.3	2.379	55	48	2.2%	-9.30 [-13.96, -4.64]	-
Wang 2020A	2.29	1.9794	40	41	2.8%	2.29 [-1.59, 6.17]	-
Zhang 2020B	-3.78	0.8423	27	32	6.5%	-3.78 [-5.43, -2.13]	•
Total (95% CI)			2015	1976	100.0%	-4.26 [-5.05, -3.48]	- 1
Heterogeneity: Tau ² =	: 1.76; Chi² = 149.98	3, df = 14	(P < 0.0000	1); I ² = 91	%		1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Test for overall effect:	Z=10.62 (P < 0.00	001)					-100 -50 0 50 100 Favours Exenatide Favours Insulin

Figure 111: BMI change (kg/m², lower values are better, change and final scores) at end of follow up

		•	Exenatide	Insulin		Mean Difference		Mean Difference	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI	
Davies 2013	-1.3	0.1701	111	105	23.4%	-1.30 [-1.63, -0.97]		•	
Diamant 2014	-1.65	0.1276	315	312	24.3%	-1.65 [-1.90, -1.40]		•	
Gurkan 2014	0.96	1.4972	17	17	3.1%	0.96 [-1.97, 3.89]		- •	
Kang 2021	-1.95	0.3146	79	80	19.3%	-1.95 [-2.57, -1.33]		 -	
Sawidou 2016	-2.4	0.8979	55	48	7.0%	-2.40 [-4.16, -0.64]			
Zhang 2020B	-0.5	0.19	27	32	22.9%	-0.50 [-0.87, -0.13]		•	
Total (95% CI)			604	594	100.0%	-1.34 [-1.88, -0.79]		•	
Heterogeneity: Tau² = Test for overall effect:			o < 0.00001);	I²= 85%			-10	-5 0 5 Favours Exenatide Favours Insulin	10

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

K.1.3.7 Adding exenatide compared to adding liraglutide

Figure 112: Hypoglycaemia episodes at end of follow up

	Exena	tide	Liraglu	tide		Risk Ratio		Risk Ratio)	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95	5% CI	
Buse 2009	78	232	60	235	59.6%	1.32 [0.99, 1.75]		-		
Buse 2013	51	461	40	450	40.4%	1.24 [0.84, 1.84]		-		
Total (95% CI)		693		685	100.0%	1.29 [1.02, 1.62]		•		
Total events	129		100							
Heterogeneity: Chi² = Test for overall effect:		•		= 0%			0.01	0.1 1 Favours Exenatide Favo	10 ours Liraglutide	100

Figure 113: Severe hypoglycaemic episodes at end of follow up

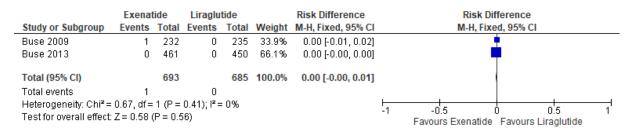


Figure 114: HbA1c change (%, lower values are better, change scores) at end of follow

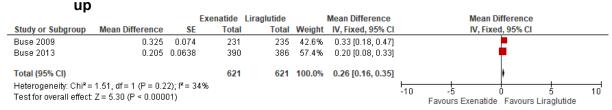


Figure 115: Weight change (kg, lower values are better, change scores) at end of follow up

			Exenatide	Liraglutide		Mean Difference		Mea	an Differenc	e	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Fixed, 95% CI		IV, I	Fixed, 95% C	1	
Buse 2009	0.38	0.3112	231	235	40.7%	0.38 [-0.23, 0.99]			-		
Buse 2013	0.895	0.2577	404	398	59.3%	0.90 [0.39, 1.40]			-		
Total (95% CI)			635	633	100.0%	0.69 [0.30, 1.07]			•		
Heterogeneity: Chi² = Test for overall effect:			3%				-10 F	-5 avours Exena	0 tide Favou	5 rs Liraglutid	10 le

K.1.3.8 Adding exenatide compared to adding sitagliptin

Figure 116: Hypoglycaemia episodes at end of follow up



Figure 117: Severe hypoglycaemic episodes at end of follow up

	Exena	tide	Sitagli	ptin		Risk Difference		Risk Difference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Bergenstal 2010	0	160	0	166	52.8%	0.00 [-0.01, 0.01]		•	
Gadde 2017	0	181	0	122	47.2%	0.00 [-0.01, 0.01]		•	
Total (95% CI)		341		288	100.0%	0.00 [-0.01, 0.01]			
Total events	0		0						
Heterogeneity: Chi²=		,		= 0%			-1	-0.5 0 0.5	
Test for overall effect:	Z = 0.00	(P = 1.0)	00)				•	Favours Exenatide Favours Sitagliptin	·

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

up													
	Exe	natide		Sita	gliptin			Mean Difference		Mean D	ifference	е	
Study or Subgroup	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV, Fixed, 95% CI [%]		IV, Fixed,	95% CI [%]	
Bergenstal 2010	-1.5	0.9607	160	-0.8	4.3068	166	19.8%	-0.70 [-1.37, -0.03]		-	1		
Gadde 2017	-1.13	1.4799	181	-0.75	1.4359	122	80.2%	-0.38 [-0.71, -0.05]		•			
Total (95% CI)			341			288	100.0%	-0.44 [-0.74, -0.14]		•			
Heterogeneity: Chi²=	•	•)%					-10	- 5	 	+	10
Test for overall effect:	Z= 2.91 (P	= 0.004)							-10	Favours Exenatide	Favour	s Sitagliptin	

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

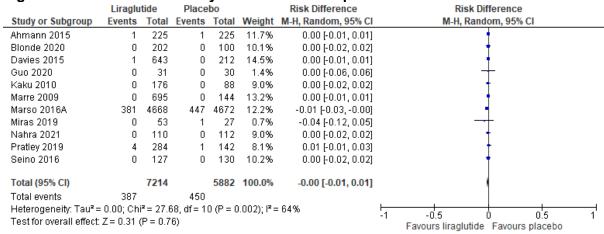
		_											
	Exe	natide		Sita	gliptin			Mean Difference		Mean	Differer	ice	
Study or Subgroup	Mean [kg]	SD [kg]	Total	Mean [kg]	SD [kg]	Total	Weight	IV, Random, 95% CI [kg]		IV, Randor	n, 95%	CI [kg]	
Bergenstal 2010	-2.3	3.8428	160	-0.8	4.3068	166	49.5%	-1.50 [-2.39, -0.61]			•		
Gadde 2017	-1.1	4.0361	181	-1.2	3.3136	122	50.5%	0.10 [-0.73, 0.93]			•		
Total (95% CI)			341			288	100.0%	-0.69 [-2.26, 0.88]			•		
Heterogeneity: Tau² = Test for overall effect:			1 (P =	0.010); I² = 8	35%				-100	-50 Favours Exenatide	0 e Favo	50 urs Sitagliptin	100

K.1.3.9 Adding liraglutide compared to adding placebo

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

	-		Liraglutide	Placebo		Mean Difference		Mean Difference	
Study or Subgroup	Mean Difference	SE	Tota	l Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI	
Garvey 2020	0.39	0.6939	198	198	98.6%	0.39 [-0.97, 1.75]			
Miras 2019	-2.1	5.8583	53	27	1.4%	-2.10 [-13.58, 9.38]			
Total (95% CI)			251	225	100.0%	0.36 [-1.00, 1.71]			
Heterogeneity: Chi² = Test for overall effect			%				-100	-50 0 50 100	Í

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



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

Figure 122: Cardiovascular mortality at end of follow-up

•	Liraglu	tide	Place	bo	_	Risk Difference	•	Risk Difference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95% CI	
Blonde 2020	0	202	0	100	10.9%	0.00 [-0.02, 0.02]		+	
Davies 2015	1	643	0	212	16.3%	0.00 [-0.01, 0.01]		•	
Guo 2020	0	31	0	30	1.4%	0.00 [-0.06, 0.06]		+	
Kaku 2010	0	176	0	88	9.7%	0.00 [-0.02, 0.02]		†	
Marre 2009	0	695	0	144	14.7%	0.00 [-0.01, 0.01]		•	
Marso 2016A	219	4668	278	4672	15.1%	-0.01 [-0.02, -0.00]		•	
Nahra 2021	0	110	0	112	9.6%	0.00 [-0.02, 0.02]		†	
Pratley 2019	2	284	0	142	11.4%	0.01 [-0.01, 0.02]		<u>†</u>	
Seino 2016	0	127	0	130	11.0%	0.00 [-0.02, 0.02]		†	
Total (95% CI)		6936		5630	100.0%	-0.00 [-0.01, 0.01]			
Total events	222		278						
Heterogeneity: Tau ² =				(P = 0.1	003); I²=	65%	-1	-0.5 0 0.5	⊣ 1
Test for overall effect:	Z = 0.221	(P = 0.8)	3)					Favours liraglutide Favours placebo	

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

	Liraglu	tide	Place	bo		Risk Ratio			Risk	Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI			M-H, Fixe	d, 95% (CI		
Marso 2016A	159	4668	177	4672	98.9%	0.90 [0.73, 1.11]			-	-			
Pratley 2019	0	284	1	142	1.1%	0.17 [0.01, 4.08]	←	•					
Total (95% CI)		4952		4814	100.0%	0.89 [0.72, 1.10]			•	-			
Total events	159		178										
Heterogeneity: Chi2=	1.06, df=	1 (P=	0.30); l ² =	- 6%			<u> </u>	0.2	0.5	<u> </u>	<u> </u>	<u> </u>	10
Test for overall effect:	Z=1.08 (P = 0.2	8)				0.1		v.o rs liraglutide	Favour	: s placeb	0	10

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

	Liraglu	tide	Place	bo		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
Marso 2016A	281	4668	317	4672	99.8%	0.89 [0.76, 1.04]		
Pratley 2019	1	284	0	142	0.2%	1.51 [0.06, 36.72]		
Total (95% CI)		4952		4814	100.0%	0.89 [0.76, 1.04]	•	
Total events	282		317					
Heterogeneity: Chi² = Test for overall effect:		•		: 0%			0.01 0.1 1 Favours liraglutide Favours	 100

Figure 125: Unstable angina at end of follow-up

_	Liraglu	tide	Place	bo		Risk Difference		Risk Difference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Marso 2016A	122	4668	124	4672	96.1%	-0.00 [-0.01, 0.01]			
Pratley 2019	0	284	0	142	3.9%	0.00 [-0.01, 0.01]		Ŧ	
Total (95% CI)		4952		4814	100.0%	-0.00 [-0.01, 0.01]			
Total events	122		124						
Heterogeneity: Chi2=	0.01, df =	1 (P=	0.94); l² =	: 0%			<u> </u>	-0.5 0 0.5	_
Test for overall effect:	Z = 0.12 ((P = 0.9)	0)				-1	Favours liraglutide Favours placebo	1

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

	Liraglu	tide	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Blonde 2020	0	202	1	100	2.0%	0.17 [0.01, 4.03]	<u> </u>
Marso 2016A	111	4668	99	4672	97.4%	1.12 [0.86, 1.47]	
Pratley 2019	1	284	0	142	0.7%	1.51 [0.06, 36.72]	
Total (95% CI)		5154		4914	100.0%	1.11 [0.85, 1.44]	•
Total events	112		100				
Heterogeneity: Chi²=	1.40, df=	2(P =	0.50); l² =	: 0%			0.01 0.1 1 10 100
Test for overall effect:	Z = 0.74 (P = 0.4	6)				Favours liraglutide Favours placebo

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

_	Liraglu	tide	Place	bo	_	Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Marso 2016A	268	4668	337	4672	99.8%	0.80 [0.68, 0.93]	
Miras 2019	1	53	0	27	0.2%	1.56 [0.07, 36.96]	
Total (95% CI)		4721		4699	100.0%	0.80 [0.68, 0.93]	•
Total events	269		337				
Heterogeneity: Chi ² =	0.17, df =	1 (P=	0.68); l ^z =	: 0%			0.01 0.1 1 10 100
Test for overall effect:	Z = 2.86 (P = 0.0	04)				Favours liradutide Favours placeho

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

	Favours lirag	lutide	Place	bo		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fix	ed, 95% CI	
Davies 2015	1	632	0	212	1.2%	1.01 [0.04, 24.69]		<u>_</u>		
Marso 2016A	56	4668	64	4672	98.8%	0.88 [0.61, 1.25]		1	•	
Total (95% CI)		5300		4884	100.0%	0.88 [0.62, 1.25]		•	•	
Total events	57		64							
Heterogeneity: Chi²=	0.01, $df = 1$ (P =	= 0.93); I	$^{2} = 0\%$				0.01	0.4	1 10	100
Test for overall effect:	Z = 0.72 (P = 0.00)	.47)					0.01	Favours liraglutide	Favours placebo	

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

	Liraglu	tide	Place	bo		Peto Odds Ratio		Peto Oc	lds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI		Peto, Fix	ed, 95% CI		
Marso 2016A	8	4668	5	4672	96.4%	1.59 [0.54, 4.72]		_			
Nauck 2009B	1	724	0	121	3.6%	3.21 [0.01, 864.96]	_		· ·		→
Total (95% CI)		5392		4793	100.0%	1.63 [0.56, 4.74]		-			
Total events	9		5								
Heterogeneity: Chi ² =	0.06, df=	1 (P =	0.81); I ²=	: 0%			0.01	01	 		100
Test for overall effect:	Z = 0.90	(P = 0.3)	17)				0.01	Favours liraglutide		~	100

Figure 130: Hypoglycaemia episodes at end of follow-up

	Liraglu	tide	Place	DO		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Ahmann 2015	41	225	28	225	7.7%	1.46 [0.94, 2.28]	-
Blonde 2020	6	202	7	100	1.8%	0.42 [0.15, 1.23]	
Davies 2015	92	632	14	212	5.7%	2.20 [1.28, 3.78]	
3arvey 2020	140	195	140	197	21.4%	1.01 [0.89, 1.15]	+
3uo 2020	1	31	1	30	0.3%	0.97 [0.06, 14.78]	
Marso 2016A	2039	4668	2130	4672	24.8%	0.96 [0.92, 1.00]	•
Miras 2019	4	53	2	27	0.8%	1.02 [0.20, 5.22]	
Nauck 2009B	32	724	3	121	1.5%	1.78 [0.55, 5.73]	- ·
Pratley 2019	7	284	3	142	1.2%	1.17 [0.31, 4.44]	
Russell-Jones 2009	63	230	19	114	7.3%	1.64 [1.04, 2.61]	-
3eino 2016	42	127	36	130	9.7%	1.19 [0.82, 1.73]	 -
/anderheiden 2016A	30	35	25	36	14.4%	1.23 [0.96, 1.59]	 -
Zinman 2009	30	356	9	177	3.6%	1.66 [0.80, 3.41]	
Fotal (95% CI)		7762		6183	100.0%	1.18 [1.02, 1.36]	•
Fotal events	2527		2417				
Heterogeneity: Tau ² = 0	.02; Chi²:	= 27.57	, df = 12	P = 0.0	$(06); I^2 = 5$	6%	
Fest for overall effect: Z							0.01 0.1 1 10 10 Favours liraglutide Favours placebo

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

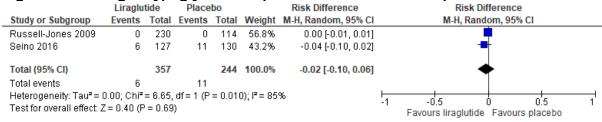


Figure 132: Severe hypoglycaemic episodes at end of follow up

	Liraglu	tide	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Blonde 2020	0	202	0	100	2.1%	0.00 [-0.02, 0.02]	†
Davies 2015	5	632	0	212	4.9%	0.01 [-0.00, 0.02]	†
Garvey 2020	3	195	2	197	3.0%	0.01 [-0.02, 0.03]	+
Guo 2020	0	31	0	30	0.5%	0.00 [-0.06, 0.06]	+
Kaku 2010	0	174	0	88	1.8%	0.00 [-0.02, 0.02]	†
Lind 2015	0	64	0	60	1.0%	0.00 [-0.03, 0.03]	+
Marre 2009	1	695	0	114	3.0%	0.00 [-0.01, 0.01]	<u> </u>
Marso 2016A	114	4668	153	4672	72.0%	-0.01 [-0.02, -0.00]	
Nauck 2009B	1	724	1	121	3.2%	-0.01 [-0.02, 0.01]	†
Russell-Jones 2009	5	230	0	114	2.4%	0.02 [-0.00, 0.04]	+
3eino 2016	0	127	0	130	2.0%	0.00 [-0.02, 0.02]	†
Vanderheiden 2016A	0	35	1	36	0.5%	-0.03 [-0.10, 0.05]	+
Zinman 2009	0	356	0	177	3.6%	0.00 [-0.01, 0.01]	†
Total (95% CI)		8133		6051	100.0%	-0.01 [-0.01, -0.00]	
Total events	129		157				
Heterogeneity: Chi² = 1	8.31, df=	12 (P =	0.11); l ² :	= 34%			1 15 15 1
Test for overall effect: Z	= 2.03 (P	= 0.04)	1				-1 -0.5 0 0.5 1 Favours liraglutide Favours placebo

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

			Liraglutide	Placebo		Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Ahmann 2015	-1.2	0.1	225	225	5.5%	-1.20 [-1.40, -1.00]	•
Blonde 2020	-0.68	0.1	202	100	5.5%	-0.68 [-0.88, -0.48]	•
Davies 2015	-0.93	0.0581	615	411	5.8%	-0.93 [-1.04, -0.82]	•
Garvey 2020	-0.5	0.13	198	198	5.2%	-0.50 [-0.75, -0.25]	•
Guo 2020	-0.6	0.2259	31	30	4.0%	-0.60 [-1.04, -0.16]	+
Kaku 2010	-0.96	0.49	86	44	1.8%	-0.96 [-1.92, 0.00]	-
Kaku 2010	-1.33	0.15	87	44	5.0%	-1.33 [-1.62, -1.04]	+
Lind 2015	-1.12	0.1632	63	59	4.8%	-1.12 [-1.44, -0.80]	-
Marre 2009	-1.14	0.0822	695	234	5.7%	-1.14 [-1.30, -0.98]	•
Marso 2016A	-0.4	0.03	3810	3640	6.0%	-0.40 [-0.46, -0.34]	•
Miras 2019	-1.05	0.27	53	27	3.5%	-1.05 [-1.58, -0.52]	-
Nahra 2021	-0.72	0.1423	110	112	5.1%	-0.72 [-1.00, -0.44]	*
Nauck 2009B	-0.8	0.1143	724	121	5.4%	-0.80 [-1.02, -0.58]	•
Pratley 2019	-0.9	0.1416	272	134	5.1%	-0.90 [-1.18, -0.62]	+
Russell-Jones 2009	-1.09	0.1416	230	114	5.1%	-1.09 [-1.37, -0.81]	+
Seino 2016	-0.81	0.09	127	129	5.6%	-0.81 [-0.99, -0.63]	•
Vanderheiden 2016A	-0.9	0.2962	32	34	3.3%	-0.90 [-1.48, -0.32]	-
van Eyk 2019	-0.4	0.26	22	25	3.7%	-0.40 [-0.91, 0.11]	-
Wagner 2019	-1	0.2942	12	12	3.3%	-1.00 [-1.58, -0.42]	-
Zinman 2009	-1	0.14	178	89	5.1%	-1.00 [-1.27, -0.73]	•
Zinman 2009	-0.9	0.08	178	88	5.7%	-0.90 [-1.06, -0.74]	•
Total (95% CI)			7950	5870	100.0%	-0.88 [-1.03, -0.72]	•
Heterogeneity: Tau² =			o < 0.00001);	I² = 91%			-10 -5 0 5 10
Test for overall effect: 2	Z = 11.06 (P < 0.0000	01)					Favours liraglutide Favours placebo

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

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

	,						
			Liraglutide			Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Ahmann 2015	-3.1	0.38	225	225	5.6%	-3.10 [-3.84, -2.36]	
Bizino 2019	-4.4	0.9318	23	26	4.6%	-4.40 [-6.23, -2.57]	
Blonde 2020	-0.82	0.46	202	100	5.5%	-0.82 [-1.72, 0.08]	
Davies 2015	-3.37	0.4755	615	211	5.5%	-3.37 [-4.30, -2.44]	
Garvey 2020	-4.3	0.59	198	198	5.3%	-4.30 [-5.46, -3.14]	
Guo 2020	-4.5	0.8791	31	30	4.7%	-4.50 [-6.22, -2.78]	
Kaku 2010	1.18	0.28	88	44	5.7%	1.18 [0.63, 1.73]	-
Kaku 2010	0.75	0.28	88	44	5.7%	0.75 [0.20, 1.30]	-
Lind 2015	-3.82	0.529	63	59	5.4%	-3.82 [-4.86, -2.78]	
Marre 2009	0.37	0.4648	695	114	5.5%	0.37 [-0.54, 1.28]	
Marso 2016A	-2.3	0.13	3835	3680	5.8%	-2.30 [-2.55, -2.05]	•
Miras 2019	-3.94	1.22	53	27	3.9%	-3.94 [-6.33, -1.55]	
Nahra 2021	-2.65	0.7554	110	112	4.9%	-2.65 [-4.13, -1.17]	
Pratley 2019	-2.6	0.3603	271	134	5.6%	-2.60 [-3.31, -1.89]	
Russell-Jones 2009	-1.38	0.5104	230	114	5.4%	-1.38 [-2.38, -0.38]	
Seino 2016	-0.35	0.28	127	130	5.7%	-0.35 [-0.90, 0.20]	-
Vanderheiden 2016A	-2.4	0.9544	32	34	4.5%	-2.40 [-4.27, -0.53]	
van Eyk 2019	-3.5	0.89	22	25	4.7%	-3.50 [-5.24, -1.76]	
Wagner 2019	-7.5	7.2056	12	12	0.3%	-7.50 [-21.62, 6.62]	-
Zinman 2009	0.9	0.3682	356	177	5.6%	0.90 [0.18, 1.62]	-
Total (95% CI)			7276	5496	100.0%	-2.02 [-2.85, -1.20]	•
Heterogeneity: Tau ² = 3	3.03; Chi ² = 390.37,	df = 19 (F	o < 0.00001)	I² = 95%			1. <u> </u>
Test for overall effect: Z			,				-10 -5 0 5 Favours liraglutide Favours placebo

Figure 135: BMI change (kg/m², lower values are better, change scores and final values) at end of follow-up

Vai	acs, at cha	01.10	/110 W-uj	9					
	•		Liraglutide	Placebo		Mean Difference		Mean Difference	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI		IV, Random, 95% (CI
Ahmann 2015	-1.2	0.1	225	225	5.5%	-1.20 [-1.40, -1.00]		•	
Blonde 2020	-0.68	0.1	202	100	5.5%	-0.68 [-0.88, -0.48]		-	
Davies 2015	-0.93	0.0581	615	411	5.8%	-0.93 [-1.04, -0.82]		•	
Garvey 2020	-0.5	0.13	198	198	5.2%	-0.50 [-0.75, -0.25]		+	
Guo 2020	-0.6	0.2259	31	30	4.0%	-0.60 [-1.04, -0.16]		-	
Kaku 2010	-0.96	0.49	86	44	1.8%	-0.96 [-1.92, 0.00]			
Kaku 2010	-1.33	0.15	87	44	5.0%	-1.33 [-1.62, -1.04]		+	
Lind 2015	-1.12	0.1632	63	59	4.8%	-1.12 [-1.44, -0.80]		+	
Marre 2009	-1.14	0.0822	695	234	5.7%	-1.14 [-1.30, -0.98]		•	
Marso 2016A	-0.4	0.03	3810	3640	6.0%	-0.40 [-0.46, -0.34]		-	
Miras 2019	-1.05	0.27	53	27	3.5%	-1.05 [-1.58, -0.52]			
Nahra 2021	-0.72	0.1423	110	112	5.1%	-0.72 [-1.00, -0.44]		-	
Nauck 2009B	-0.8	0.1143	724	121	5.4%	-0.80 [-1.02, -0.58]		-	
Pratley 2019	-0.9	0.1416	272	134	5.1%	-0.90 [-1.18, -0.62]		-	
Russell-Jones 2009	-1.09	0.1416	230	114	5.1%	-1.09 [-1.37, -0.81]		+	
Seino 2016	-0.81	0.09	127	129	5.6%	-0.81 [-0.99, -0.63]		•	
Vanderheiden 2016A	-0.9	0.2962	32	34	3.3%	-0.90 [-1.48, -0.32]			
van Eyk 2019	-0.4	0.26	22	25	3.7%	-0.40 [-0.91, 0.11]		- 	
Wagner 2019	-1	0.2942	12	12	3.3%	-1.00 [-1.58, -0.42]		-	
Zinman 2009	-1	0.14	178	89	5.1%	-1.00 [-1.27, -0.73]		+	
Zinman 2009	-0.9	0.08	178	88	5.7%	-0.90 [-1.06, -0.74]		•	
Total (95% CI)			7950	5870	100.0%	-0.88 [-1.03, -0.72]		•	
Heterogeneity: Tau ² =	0.10; Chi ² = 223.57,	df = 20 (F	o < 0.00001);	I²= 91%			100	-5 0	<u> </u>
Test for overall effect:			,,				-10		5 1
		•						Favours liraglutide Favours	piace00

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

K.1.3.10 Adding liraglutide compared to adding insulin

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

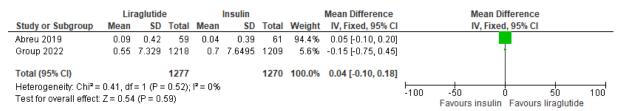


Figure 137: Health-related quality of life -subscale physical component (SF-36, 0, 100, higher values are better, change scores) at end of follow-up

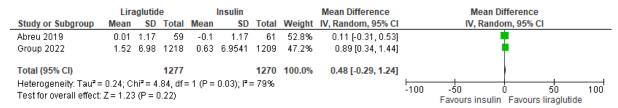
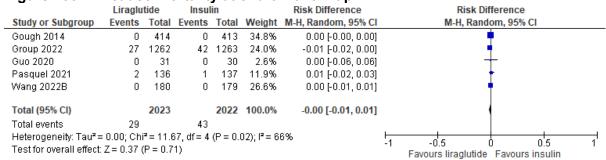


Figure 138: All-cause mortality at end of follow-up



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

Figure 139: Cardiovascular mortality at end of follow-up

	Liraglu	tide	Insul	lin		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Gough 2014	0	414	0	413	39.7%	0.00 [-0.00, 0.00]	•
Group 2022	9	1251	21	1257	31.6%	-0.01 [-0.02, -0.00]	•
Guo 2020	0	31	0	30	1.9%	0.00 [-0.06, 0.06]	+
Wang 2022B	0	180	0	179	26.7%	0.00 [-0.01, 0.01]	†
Total (95% CI)		1876		1879	100.0%	-0.00 [-0.01, 0.01]	
Total events	9		21				
Heterogeneity: Tau ² =	= 0.00; Chi	$i^2 = 8.83$	3, df = 3 (P = 0.0	3); I ² = 66		-1 -05 0 05 1
Test for overall effect:	Z = 0.67	P = 0.5	0)			-	-1 -0.5 0 0.5 1 Favours liraglutide Favours insulin

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

	Liraglu	tide	Insul	in		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Gough 2014	1	414	1	413	1.5%	1.00 [0.06, 15.90]	
Group 2022	48	1251	65	1257	98.5%	0.74 [0.52, 1.07]	=
Total (95% CI)		1665		1670	100.0%	0.75 [0.52, 1.07]	•
Total events	49		66				
Heterogeneity: Chi²=	0.04, df=	1 (P=	0.84); ²=	: 0%			0.01 0.1 1 10 100
Test for overall effect:	Z = 1.59 (P = 0.1	1)				Favours liraglutide Favours insulin

Figure 141: Unstable angina at end of follow-up

	Liraglu	tide	Insul	in		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events Total Weight Peto, Fixed, 95% CI		Peto, Fixed, 95% CI	Peto, Fixed, 95% CI	
Group 2022	7	1262	9	1263	94.1%	0.78 [0.29, 2.08]	-
Wang 2022B	0	180	1	179	5.9%	0.13 [0.00, 6.78]	
Total (95% CI)		1442		1442	100.0%	0.70 [0.27, 1.82]	•
Total events	7		10				
Heterogeneity: Chi²=	0.72, df=	1 (P=	0.39);	: 0%			0.001 0.1 1 10 1000
Test for overall effect:	Z = 0.73 ((P = 0.4)	7)				Favours liraglutide Favours insulin

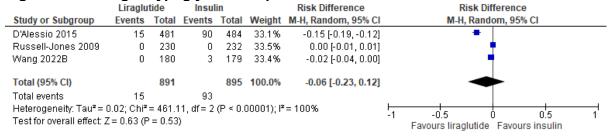
Figure 142: Non-fatal stroke at end of follow-up

	Liraglu	tide	Insul	in		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Events Total Weig		Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
D'Alessio 2015	0	481	1	484	20.1%	0.14 [0.00, 6.86]	<u> </u>
Wang 2022B	4	180	0	179	79.9%	7.47 [1.04, 53.49]	
Total (95% CI)		661		663	100.0%	3.34 [0.57, 19.37]	-
Total events	4		1				
Heterogeneity: Chi²=	3.20, df =	1 (P=	0.07);	69%			0.001 0.1 1 10 1000
Test for overall effect:	Z = 1.34 ((P = 0.1)	8)				Favours liraglutide Favours insulin

Figure 143: Hypoglycaemia episodes at end of follow-up

	Liraglu	tide	Insul	in		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Abreu 2019	19	54	37	56	14.7%	0.53 [0.35, 0.80]	
D'Alessio 2015	85	481	219	484	16.6%	0.39 [0.31, 0.48]	+
Gough 2014	28	412	159	412	15.1%	0.18 [0.12, 0.26]	
Group 2022	312	1233	474	1245	17.3%	0.66 [0.59, 0.75]	•
Guo 2020	1	31	3	30	2.6%	0.32 [0.04, 2.93]	
Pasquel 2021	18	136	31	137	13.2%	0.58 [0.34, 0.99]	-
Russell-Jones 2009	63	230	67	232	16.0%	0.95 [0.71, 1.27]	+
Wang 2022B	1	180	8	179	3.0%	0.12 [0.02, 0.98]	
Yan 2019	0	24	2	24	1.6%	0.20 [0.01, 3.96]	-
Total (95% CI)		2781		2799	100.0%	0.46 [0.31, 0.68]	•
Total events	527		1000				
Heterogeneity: Tau² =	0.23; Chi²	= 71.89	9, df = 8 (P < 0.0	0001); l²=	: 89%	0.01 0.1 1 10 100
Test for overall effect: 2	Z = 3.91 (F	° < 0.00	01)				Favours liraglutide Favours insulin

Figure 144: At night hypoglycaemic episodes





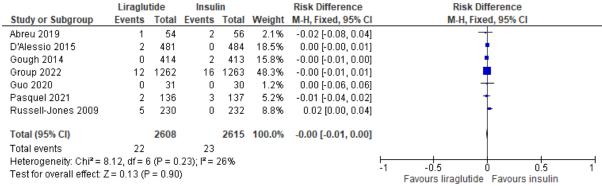


Figure 146: HbA1c change (%, lower values are better, change scores and final values) at end of follow-up

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

- ,	,	,	J				
			Liraglutide	Insulin		Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Abreu 2019	0.7	0.4592	59	61	3.8%	0.70 [-0.20, 1.60]	nj • -
D'Alessio 2015	0.15	0.0708	481	484	21.3%	0.15 [0.01, 0.29]	oj
Gough 2014	0.1	0.073	415	414	21.2%	0.10 [-0.04, 0.24]	F] •
Group 2022	0	1.4384	337	426	0.5%	0.00 [-2.82, 2.82]	2] — —
Guo 2020	-0.2	0.269	31	30	8.5%	-0.20 [-0.73, 0.33]	8] -
lkonomidis 2020	-0.4	0.2247	40	40	10.6%	-0.40 [-0.84, 0.04]	ı)
Pasquel 2021	-0.55	0.2277	80	93	10.4%	-0.55 [-1.00, -0.10])] -
Russell-Jones 2009	-0.24	0.127	230	232	17.1%	-0.24 [-0.49, 0.01]] •
Yan 2019	-0.3	0.3227	24	24	6.6%	-0.30 [-0.93, 0.33]	n +
Total (95% CI)			1697	1804	100.0%	-0.10 [-0.29, 0.09]	g (
Heterogeneity: Tau² = Test for overall effect:		lf=8 (P:	= 0.004); 2 =	64%			-10 -5 0 5 10 Favours liraglutide Favours insulin

ps.

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

			Liraglutide	Insulin		Mean Difference		Mean Di	fference		
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI		IV, Rando	m, 95% CI		
Abreu 2019	-2.5	1.0428	59	61	8.1%	-2.50 [-4.54, -0.46]					
D'Alessio 2015	-5	0.245	481	484	26.1%	-5.00 [-5.48, -4.52]		-			
Gough 2014	-4.6	0.2612	414	414	25.6%	-4.60 [-5.11, -4.09]		-			
Guo 2020	-4.2	1.0141	31	30	8.4%	-4.20 [-6.19, -2.21]					
lkonomidis 2020	-2.2	2.3717	40	40	2.0%	-2.20 [-6.85, 2.45]			 		
Pasquel 2021	-5.37	1.4854	73	91	4.6%	-5.37 [-8.28, -2.46]	-	-			
Russell-Jones 2009	-3.4	0.4666	230	232	19.5%	-3.40 [-4.31, -2.49]		-			
Yan 2019	-2.4	1.3174	24	24	5.7%	-2.40 [-4.98, 0.18]		-	1		
Total (95% CI)			1352	1376	100.0%	-4.13 [-4.81, -3.45]		•			
Heterogeneity: Tau² = 1 Test for overall effect: 2			= 0.01); I² = 6	0%			-10	-5 Favours liraglutide	0 5	i ulin	10

Figure 148: BMI change (kg/m², lower values are better, change scores and final values) at end of follow-up

	<u>.</u>		Liraglutide	Insulin		Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Guo 2020	-1.5	0.4956	31	30	31.8%	-1.50 [-2.47, -0.53]	-
Ikonomidis 2020	-2	0.6708	40	40	17.4%	-2.00 [-3.31, -0.69]	
Yan 2019	-0.7	0.3921	24	24	50.8%	-0.70 [-1.47, 0.07]	
Total (95% CI)			95	94	100.0%	-1.18 [-1.73, -0.63]	•
Heterogeneity: Chi² = Test for overall effect:	1%				-10 -5 0 5 10 Favours liraglutide Favours insulin		

K.1.3.11 Adding liraglutide compared to adding dulaglutide

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

K.1.3.12 Adding liraglutide compared to adding saxagliptin

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

K.1.3.13 Adding liraglutide compared to adding sitagliptin

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

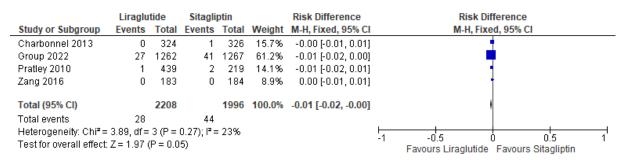


Figure 150: Cardiovascular mortality at end of follow up

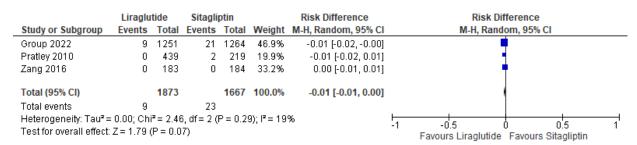
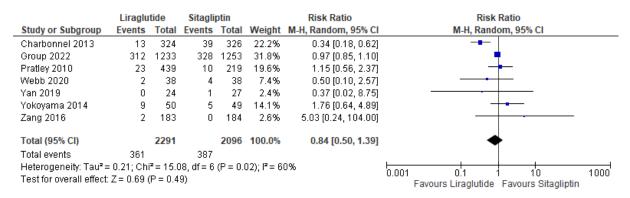


Figure 151: Hypoglycaemia episodes at end of follow up



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

Figure 152: Severe hypoglycaemic episodes at end of follow up

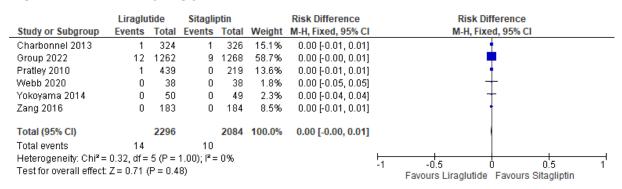


Figure 153: HbA1c change (%, lower values are better, mean difference) at end of follow up

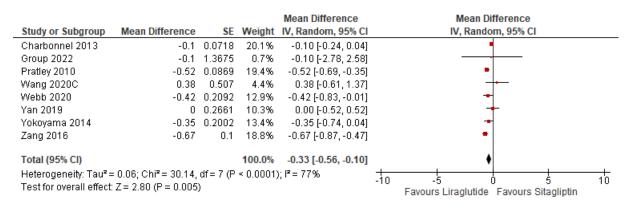
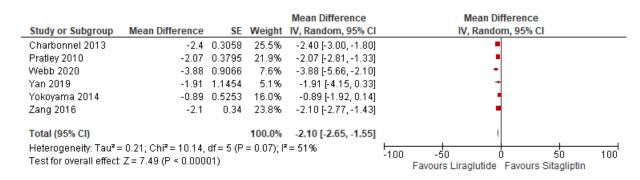
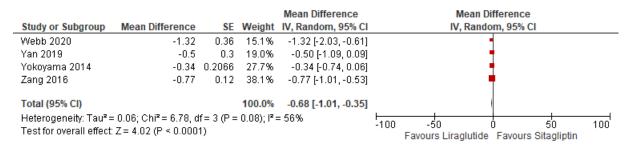


Figure 154: Weight change (kg, lower values are better, mean difference) at end of follow up



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

Figure 155: BMI change (kg/m², lower values are better, mean difference) at end of follow up



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

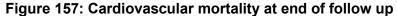
K.1.3.14 Adding liraglutide compared to adding vildagliptin

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

K.1.3.15 Adding lixisenatide compared to adding placebo

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

	Lixisena	atide	Place	Placebo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Ahren 2013	0	510	0	170	11.3%	0.00 [-0.01, 0.01]	•
Bolli 2014	3	322	2	160	9.5%	-0.00 [-0.02, 0.02]	†
Meneilly 2017	0	176	1	174	7.8%	-0.01 [-0.02, 0.01]	<u>†</u>
Pan 2014	0	196	0	194	8.6%	0.00 [-0.01, 0.01]	<u>†</u>
Pinget 2013	0	323	2	161	9.5%	-0.01 [-0.03, 0.01]	+
Riddle 2013A	1	328	0	167	9.8%	0.00 [-0.01, 0.01]	†
Riddle 2013B	0	223	2	223	9.9%	-0.01 [-0.02, 0.01]	+
Rosenstock 2014A	1	574	0	285	16.9%	0.00 [-0.00, 0.01]	†
Seino 2012	0	154	1	157	6.9%	-0.01 [-0.02, 0.01]	†
Yang 2018B	0	224	0	223	9.9%	0.00 [-0.01, 0.01]	†
Total (95% CI)		3030		1914	100.0%	-0.00 [-0.01, 0.00]	
Total events	5		8				
Heterogeneity: Chi ^z =	5.82, df=	9 (P = 0)	1.76); l ^z =	0%			1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1
Test for overall effect:	Z = 1.26 (P = 0.21)				-1 -0.5 0 0.5 1 Favours Lixisenatide Favours Placebo
							I avours Livischaude Favours Flacebo



	Lixisen	atide	Place	bo	o Risk Difference			Risk Difference		
Study or Subgroup	Events	Total	Events				M-H, Fixed, 95% CI			
Ahren 2013	0	510	0	170	12.5%	0.00 [-0.01, 0.01]		•		
Meneilly 2017	0	176	0	174	8.6%	0.00 [-0.01, 0.01]		†		
Pan 2014	0	196	0	194	9.5%	0.00 [-0.01, 0.01]		•		
Pinget 2013	0	323	1	161	10.5%	-0.01 [-0.02, 0.01]		†		
Riddle 2013A	1	328	0	167	10.8%	0.00 [-0.01, 0.01]		<u>†</u>		
Riddle 2013B	0	223	1	223	10.9%	-0.00 [-0.02, 0.01]		†		
Rosenstock 2014A	1	574	0	285	18.6%	0.00 [-0.00, 0.01]		<u>†</u>		
Seino 2012	0	154	0	157	7.6%	0.00 [-0.01, 0.01]		†		
Yang 2018B	0	224	0	223	10.9%	0.00 [-0.01, 0.01]		†		
Total (95% CI)		2708		1754	100.0%	-0.00 [-0.00, 0.00]		(
Total events	2		2							
Heterogeneity: Chi²=	1.85, df=	8 (P = 0).99); l ^z =	0%			<u> </u>	- J ₅ - J ₅ - J ₅	_	
Test for overall effect:	Z = 0.27 (P = 0.78	3)				-1	-0.5 0 0.5 Favours Lixisenatide Favours Placebo	1	

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

	Lixisen	Lixisenatide Placebo				Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Pan 2014	1	196	0	194	33.4%	7.31 [0.15, 368.62]	-
Seino 2012	2	154	0	157	66.6%	7.58 [0.47, 121.81]	
Total (95% CI)		350		351	100.0%	7.49 [0.78, 72.21]	
Total events	3		0				
Heterogeneity: Chi ² =	0.00, df =	1 (P = 0)).99); l ^z =	0%			0.001 0.1 1 10 1000
Test for overall effect:	Z=1.74 (P = 0.08	3)				Favours Lixisenatide Favours Placebo

Figure 159: Hypoglycaemia episodes at end of follow up

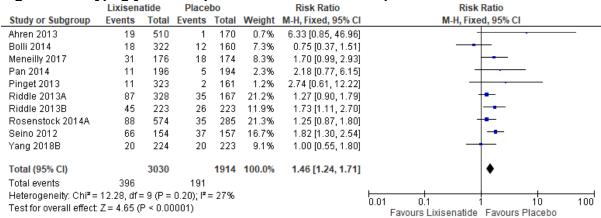


Figure 160: Severe hypoglycaemic episodes at end of follow up

	Lixisena	atide	Place	Placebo Risk Difference			Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Ahren 2013	0	510	0	170	11.3%	0.00 [-0.01, 0.01]	
Bolli 2014	0	322	0	160	9.5%	0.00 [-0.01, 0.01]	•
Meneilly 2017	1	1 176		0 174		0.01 [-0.01, 0.02]	†
Pan 2014	0	196	0	194	8.6%	0.00 [-0.01, 0.01]	†
Pinget 2013	0	323	0	161	9.5%	0.00 [-0.01, 0.01]	•
Riddle 2013A	4	328	0	167	9.8%	0.01 [-0.00, 0.03]	•
Riddle 2013B	1	223	0	223	9.9%	0.00 [-0.01, 0.02]	•
Rosenstock 2014A	1	574	0	285	16.9%	0.00 [-0.00, 0.01]	†
Seino 2012	0	154	0	157	6.9%	0.00 [-0.01, 0.01]	†
Yang 2018B	0	224	0	223	9.9%	0.00 [-0.01, 0.01]	†
Total (95% CI)		3030		1914	100.0%	0.00 [-0.00, 0.01]	
Total events	7		0				
Heterogeneity: Chi ^z =	3.37, df=	9(P = 0)).95); l² =	0%			1 1 1 1
Test for overall effect:	Z=1.39 (P = 0.16	5)				-1 -0.5 0 0.5 1 Favours Lixisenatide Favours Placebo

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

			Lixisenatide	Placebo		Mean Difference		Mean Difference	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI	
Ahren 2013	-0.43	0.0879	483	164	11.1%	-0.43 [-0.60, -0.26]		•	
Bolli 2014	-0.3	0.1144	322	160	9.5%	-0.30 [-0.52, -0.08]		•	
Meneilly 2017	-0.64	0.08	175	173	11.6%	-0.64 [-0.80, -0.48]		•	
Pan 2014	-0.36	0.1	195	193	10.4%	-0.36 [-0.56, -0.16]		•	
Pinget 2013	-0.56	0.0867	308	148	11.2%	-0.56 [-0.73, -0.39]		•	
Riddle 2013A	-0.3	0.1414	327	166	8.0%	-0.30 [-0.58, -0.02]		-	
Riddle 2013B	-0.3	0.1414	223	223	8.0%	-0.30 [-0.58, -0.02]		-	
Rosenstock 2014A	-0.75	0.0922	574	285	10.9%	-0.75 [-0.93, -0.57]		•	
Seino 2012	-0.88	0.1225	146	154	9.0%	-0.88 [-1.12, -0.64]		+	
Yang 2018B	-0.5	0.102	224	223	10.3%	-0.50 [-0.70, -0.30]		•	
Total (95% CI)			2977	1889	100.0%	-0.51 [-0.63, -0.40]		•	
Heterogeneity: Tau ² =	0.02; Chi ² = 29.46,	df = 9 (P	= 0.0005); I ² =	69%			 	<u> </u>	
Test for overall effect			/				-10	-5 0 5 Favours Lixisenatide Favours Placebo	10

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

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

			Lixisenatide	Placebo		Mean Difference	Mean Difference	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI	
Ahren 2013	-0.4	0.383	510	170	7.2%	-0.40 [-1.15, 0.35]	jj 	
Bolli 2014	-0.8	0.4424	322	160	5.4%	-0.80 [-1.67, 0.07]	'] - 	
Meneilly 2017	-1.32	0.24	175	173	18.3%	-1.32 [-1.79, -0.85]	ij 	
Pan 2014	-0.27	0.26	195	193	15.6%	-0.27 [-0.78, 0.24]	ıj -	
Pinget 2013	-0.41	0.3163	308	148	10.6%	-0.41 [-1.03, 0.21]] 	
Riddle 2013A	-1.3	0.3606	327	166	8.1%	-1.30 [-2.01, -0.59]	j 	
Riddle 2013B	-0.9	0.4243	223	223	5.9%	-0.90 [-1.73, -0.07]	·j —	
Rosenstock 2014A	-0.83	0.3048	574	285	11.4%	-0.83 [-1.43, -0.23]	ıj -	
Seino 2012	-0.44	0.25	154	157	16.9%	-0.44 [-0.93, 0.05]	ij 	
Yang 2018B	-1.5	1.282	224	223	0.6%	-1.50 [-4.01, 1.01]	1	
Total (95% CI)			3012	1898	100.0%	-0.74 [-0.94, -0.53]	ı •	
Heterogeneity: Chi ² =	: 15.43. df = 9 (P = 0.	(08) : $I^2 = 4$	42%				- <u> </u>	1
Test for overall effect							-10 -5 0 5 10	
		/					Favours Lixisenatide Favours Placebo	

K.1.3.16 Adding lixisenatide compared to adding insulin

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



Figure 164: Cardiovascular mortality at end of follow up

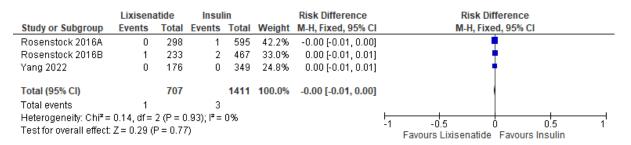


Figure 165: Hypoglycaemia episodes at end of follow up

	Lixisen	Lixisenatide I		Insulin		Risk Ratio	Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Rando	om, 95% CI	
Rosenstock 2016A	98	298	347	595	35.8%	0.56 [0.47, 0.67]	•		
Rosenstock 2016B	15	233	110	467	32.4%	0.27 [0.16, 0.46]			
Yang 2022	12	176	161	349	31.8%	0.15 [0.08, 0.26]	-		
Total (95% CI)		707		1411	100.0%	0.29 [0.12, 0.71]	•		
Total events	125		618						
Heterogeneity: Tau² =	0.57; Chi	2 = 28.5	6, df = 2	$(P \le 0.0$	0001); l²:	= 93%	0.01 0.1 1	10	100
Test for overall effect: Z = 2.71 (P = 0.007)						Favours Lixisenatide	Favours Insulin	100	

Figure 166: Severe hypoglycaemic episodes at end of follow up

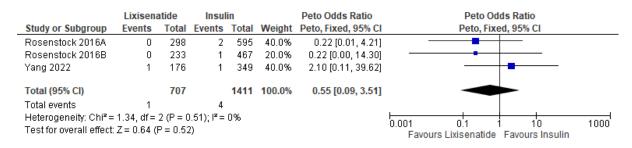


Figure 167: HbA1c change (%, lower values are better, change scores) at end of follow

۷. ۲													
_	Lixis	xisenatide Insulin					Mean Difference	Mean Difference					
Study or Subgroup	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV, Random, 95% CI [%]		IV, Ra	ndom, 95% (CI [%]	
Rosenstock 2016A	-0.6	1.71	292	-0.7	1.72	587	25.9%	0.10 [-0.14, 0.34]			+		
Rosenstock 2016B	-0.9	0.7632	233	-1.3	0.8635	466	37.9%	0.40 [0.27, 0.53]			-		
Yang 2022	-0.9	0.7937	175	-1.4	0.7473	349	36.2%	0.50 [0.36, 0.64]			•		
Total (95% CI)			700			1402	100.0%	0.36 [0.17, 0.54]			*		
Heterogeneity: Tau ² = Test for overall effect:	•			= 0.02); l² =	75%				-10 Favo	-5 ours Lixisen	0 atide Favou	5 Irs Insulin	10

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

	-	-								
	Lixisenatide							Mean Difference	Mean Difference	
Study or Subgroup	Mean [kg]	SD [kg]	Total	Mean [kg]	SD [kg]	Total	Weight	IV, Random, 95% CI [kg]	IV, Random, 95% CI [kg]	
Rosenstock 2016A	-0.6	5.15	295	1.2	5.15	587	29.7%	-1.80 [-2.52, -1.08]	-	
Rosenstock 2016B	-2.3	0.3	233	1.1	0.2	466	37.5%	-3.40 [-3.44, -3.36]	•	
Yang 2022	-1.7	2.9103	175	1.12	2.989	349	32.8%	-2.82 [-3.35, -2.29]	-	
Total (95% CI)			703			1402	100.0%	-2.73 [-3.59, -1.87]	•	
Heterogeneity: Tau² = Test for overall effect:				< 0.00001); I	²= 91%				-10 -5 0 5 Favours Lixisenatide Favours Insul	10 lin

K.1.3.17 Adding lixisenatide compared to adding exenatide

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

K.1.3.18 Adding lixisenatide compared to adding liraglutide

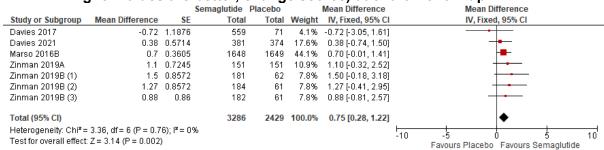
There are no forest plots for this comparison (all outcomes include a single study).

K.1.3.19 Adding lixisenatide compared to adding sitagliptin

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

K.1.3.20 Adding semaglutide compared to adding placebo

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



Footnotes

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

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

			Semaglutide	Placebo		Mean Difference		Mean Difference	e	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% (CI	
Davies 2017	-0.29	0.8427	559	71	5.4%	-0.29 [-1.94, 1.36]				
Davies 2021	1.14	0.5408	381	374	13.1%	1.14 [0.08, 2.20]		-		
Marso 2016B	0.6	0.2884	1648	1649	45.9%	0.60 [0.03, 1.17]		-		
Zinman 2019A	1.25	0.6378	151	151	9.4%	1.25 [-0.00, 2.50]		•		
Zinman 2019B (1)	0.12	0.6582	184	61	8.8%	0.12 [-1.17, 1.41]		_		
Zinman 2019B (2)	-0.3	0.6531	181	62	9.0%	-0.30 [-1.58, 0.98]		-		
Zinman 2019B (3)	0.48	0.6735	182	61	8.4%	0.48 [-0.84, 1.80]		+		
Total (95% CI)			3286	2429	100.0%	0.55 [0.17, 0.93]		*		
Heterogeneity: Chi² = Test for overall effect:			%				-10 -5	0 Placebo Favou	5 Semanlutid	10

Footnotes

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

Figure 171: All-cause mortality at end of follow up

_	Semagl	utide	Place	bo	Risk Difference		Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Davies 2017	0	559	0	71	2.6%	0.00 [-0.02, 0.02]	+
Davies 2021	2	804	1	402	11.3%	0.00 [-0.01, 0.01]	•
Heise 2022	0	44	0	28	0.7%	0.00 [-0.06, 0.06]	+
Husain 2019	23	1591	45	1592	33.4%	-0.01 [-0.02, -0.00]	•
Marso 2016B	62	1648	60	1649	34.6%	0.00 [-0.01, 0.01]	•
Pratley 2019	3	285	1	142	4.0%	0.00 [-0.01, 0.02]	†
Rodbard 2018	0	263	0	133	3.7%	0.00 [-0.01, 0.01]	†
Sivalingam 2023	1	30	0	30	0.6%	0.03 [-0.05, 0.12]	+
Zinman 2019A	0	151	0	151	3.2%	0.00 [-0.01, 0.01]	†
Zinman 2019B	3	546	0	184	5.8%	0.01 [-0.00, 0.02]	†
Total (95% CI)		5921		4382	100.0%	-0.00 [-0.01, 0.00]	
Total events	94		107				
Heterogeneity: Chi ² =	11.05, df :	= 9 (P =	0.27);	= 19%			1, 1 ₂ 1, 1 ₃
Test for overall effect:	Z = 1.19 (P = 0.23	3)				-1 -0.5 0 0.5 1 Favours Semaglutide Favours Placebo

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



Figure 173: Cardiovascular mortality at end of follow-up

_	Semagl	utide	Placebo		Risk Difference		Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Davies 2017	0	559	0	71	3.2%	0.00 [-0.02, 0.02]	+
Heise 2022	0	44	0	28	0.9%	0.00 [-0.06, 0.06]	+
Husain 2019	15	1591	30	1592	40.6%	-0.01 [-0.02, -0.00]	•
Marso 2016B	44	1648	46	1649	42.1%	-0.00 [-0.01, 0.01]	•
Pratley 2019	1	285	0	142	4.8%	0.00 [-0.01, 0.02]	•
Rodbard 2018	0	263	0	133	4.5%	0.00 [-0.01, 0.01]	†
Zinman 2019A	0	150	0	151	3.8%	0.00 [-0.01, 0.01]	†
Total (95% CI)		4540		3766	100.0%	-0.00 [-0.01, 0.00]	
Total events	60		76				
Heterogeneity: Chi ² =	4.33, df=	6 (P = 0)	.63); l ² =	0%			-1 -05 0 05 1
Test for overall effect:	Z=1.39 (P = 0.17	")				-1 -0.5 0 0.5 1 Favours Semaglutide Favours Placebo

Figure 174: Cardiovascular mortality at end of follow-up

			Semaglutide	Placebo		Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Husain 2019	-0.7133	0.3041	1591	1592	44.9%	0.49 [0.27, 0.89]	
Marso 2016B	-0.0202	0.2095	1648	1649	55.1%	0.98 [0.65, 1.48]	-
Total (95% CI)			3239	3241	100.0%	0.72 [0.37, 1.41]	•
Heterogeneity: Tau² = Test for overall effect:		= 1 (P =	0.06); I²= 72%				0.01 0.1 1 10 100 Favours Semaglutide Favours Placebo

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

	Semagl	utide	Place	bo		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
Husain 2019	61	1591	76	1592	34.2%	0.80 [0.58, 1.12]		
Marso 2016B	108	1648	146	1649	65.8%	0.74 [0.58, 0.94]	-	
Total (95% CI)		3239		3241	100.0%	0.76 [0.63, 0.92]	•	
Total events	169		222					
Heterogeneity: Chi²=	1 (P = 0)	.69); l²=	0%			0.01 0.1 1 10	100	
Test for overall effect:	Z = 2.76 (P = 0.00	16)				Favours Semaglutide Favours Placebo	100

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

			Semaglutide	Placebo		Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Husain 2019	-0.2357	0.1665	1591	1592	35.8%	0.79 [0.57, 1.09]	-
Marso 2016B	-0.3011	0.1243	1648	1649	64.2%	0.74 [0.58, 0.94]	
Total (95% CI)			3239	3241	100.0%	0.76 [0.62, 0.92]	•
Heterogeneity: Chi ^z = Test for overall effect:			6				0.01 0.1 1 10 100 Favours Semaglutide Favours Placebo

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

	Semagl	utide	Place	bo		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
Husain 2019	83	1591	100	1592	27.5%	0.83 [0.63, 1.10]		
Marso 2016B	199	1648	264	1649	72.5%	0.75 [0.64, 0.89]	•	
Total (95% CI)		3239		3241	100.0%	0.78 [0.67, 0.90]	•	
Total events	282		364					
Heterogeneity: Chi²=	0.33, df =	1 (P = 0)	.57); l² =	0%			0.01 0.1 1 10	100
Test for overall effect:	Z = 3.41 (P = 0.00	06)				Favours Semaglutide Favours Place	

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

			Semaglutide	Placebo		Hazard Ratio	Hazaro	l Ratio	
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Fixed, 95% CI	IV, Fixed	, 95% CI	
Husain 2019	-0.1985	0.1509	1591	1592	26.4%	0.82 [0.61, 1.10]		-	
Marso 2016B	-0.3011	0.0903	1648	1649	73.6%	0.74 [0.62, 0.88]			
Total (95% CI)			3239	3241	100.0%	0.76 [0.65, 0.88]	•		
Heterogeneity: Chi² = Test for overall effect:			6				0.01 0.1 Favours Semaglutide	10 Favours Placebo	100

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

	Semagl	utide	Place	cebo Peto Odds Ratio Peto Odds Ratio					
Study or Subgroup	Events	Total	Events	Total	Weight	eight Peto, Fixed, 95% CI Peto, Fixed, 95% C		ed, 95% CI	
Davies 2017	0	559	1	71	0.4%	0.00 [0.00, 0.07]	← —		
Husain 2019	12	1591	16	1592	25.9%	0.75 [0.36, 1.58]	-	 -	
Marso 2016B	27	1648	44	1649	64.8%	0.61 [0.38, 0.98]	-	-	
Pratley 2019	2	285	1	142	2.5%	1.00 [0.09, 11.07]			
Rodbard 2018	1	263	0	133	0.8%	4.51 [0.07, 285.89]		•	_
Zinman 2019B	5	546	3	184	5.6%	0.52 [0.10, 2.57]			
Total (95% CI)		4892		3771	100.0%	0.64 [0.44, 0.93]	•		
Total events	47		65						
Heterogeneity: Chi ² =	8.35, df=	5 (P = 0)	$.14$); $I^2 =$	40%			0.001 0.1	10	4000
Test for overall effect:	Z = 2.32 (P = 0.02	!)				0.001 0.1 Favours Semaglutide		1000

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

9		••••				~.p			
			Semaglutide	Placebo		Hazard Ratio	Hazaro	Ratio	
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Fixed, 95% CI	IV, Fixed	, 95% CI	
Husain 2019	-0.3011	0.382	1591	1592	28.6%	0.74 [0.35, 1.56]		_	
Marso 2016B	-0.4943	0.2415	1648	1649	71.4%	0.61 [0.38, 0.98]	-		
Total (95% CI)			3239	3241	100.0%	0.64 [0.43, 0.96]	•		
Heterogeneity: Chi²=	0.18, $df = 1$ (P = 0.63	7); $I^2 = 0^4$	%				0.01 0.1	10	100
Test for overall effect:	Z = 2.15 (P = 0.03)						Composition	Ferrenza Diagona	100

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

_	Semaglutide		Place	bo		Risk Difference		Risk Difference		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI		
Davies 2017	2	559	1	71	3.3%	-0.01 [-0.04, 0.02]		+		
Husain 2019	37	1591	31	1592	41.5%	0.00 [-0.01, 0.01]		•		
Marso 2016B	47	1648	64	1649	43.0%	-0.01 [-0.02, 0.00]		•		
Pratley 2019	0	285	0	142	4.9%	0.00 [-0.01, 0.01]		†		
Zinman 2019B	5	546	2	184	7.2%	-0.00 [-0.02, 0.02]		†		
Total (95% CI)		4629		3638	100.0%	-0.00 [-0.01, 0.00]				
Total events	91		98							
Heterogeneity: Chi²=	3.81, df=	4 (P = 0)	1.43); I ² =	0%			-1	-0.5 0 0.5		
Test for overall effect: $Z = 0.94$ (P = 0.35)							-1	-0.5 0 0.5 Favours Semaglutide Favours Placebo	1	

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

			Semaglutide	Placebo		Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Husain 2019	0.1655	0.245	1591	1592	44.5%	1.18 [0.73, 1.91]	
Marso 2016B	-0.3011	0.1899	1648	1649	55.5%	0.74 [0.51, 1.07]	
Total (95% CI)			3239	3241	100.0%	0.91 [0.58, 1.43]	•
Heterogeneity: Tau ² = Test for overall effect:		= 1 (P =	0.13); I ^z = 56%	1			0.01 0.1 10 100 Favours Semaglutide Favours Placebo

Figure 183: Unstable angina at end of follow-up

_	Semagl	utide	Place	Placebo		Peto Odds Ratio	Peto Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI	
Husain 2019	11	1591	7	1592	26.7%	1.56 [0.62, 3.95]	-	
Marso 2016B	22	1648	27	1649	72.0%	0.81 [0.46, 1.43]	-	
Pratley 2019	1	285	0	142	1.3%	4.47 [0.07, 286.69]	-	→
Total (95% CI)		3524		3383	100.0%	0.99 [0.61, 1.60]	*	
Total events	34		34					
Heterogeneity: Chi²=	1.91, df=	2(P = 0)	.39); l² =	0%			0.01 0.1 1 10	100
Test for overall effect:	Z = 0.04 (P = 0.97	")				Favours Semaglutide Favours Placebo	100

Figure 184: Unstable angina at end of follow-up

J			Semaglutide	Placebo		Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Husain 2019	0.4447	0.4875	1591	1592	25.3%	1.56 [0.60, 4.06]	
Marso 2016B	-0.1985	0.284	1648	1649	74.7%	0.82 [0.47, 1.43]	
Total (95% CI)			3239	3241	100.0%	0.97 [0.60, 1.56]	*
Heterogeneity: Chi ² = Test for overall effect		5); I² = 23	3%				0.01 0.1 1 10 100 Favours Semaglutide Favours Placebo



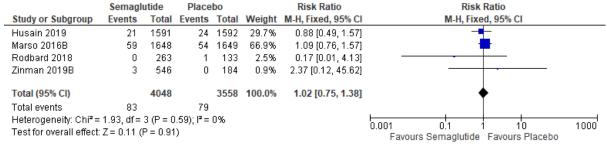


Figure 186: Hospitalisation for heart failure at end of follow-up

			Semaglutide	Placebo		Hazard Ratio	Hazaro	d Ratio	
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Fixed, 95% CI	IV, Fixed	I, 95% CI	
Husain 2019	-0.1508	0.2975	1591	1592	28.2%	0.86 [0.48, 1.54]	-		
Marso 2016B	0.1044	0.1866	1648	1649	71.8%	1.11 [0.77, 1.60]	4	-	
Total (95% CI)			3239	3241	100.0%	1.03 [0.76, 1.41]	•		
Heterogeneity: Chi² = Test for overall effect		7); I² = 0%	•				0.01 0.1 Favours Semaglutide	10 Favours Placebo	100

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

	Semagl	utide	Place	ho		DO L DOG	Dial Difference
Semaglutide Placebo		DU		Risk Difference	Risk Difference		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Davies 2021	6	804	2	402	12.2%	0.00 [-0.01, 0.01]	•
Husain 2019	32	1591	37	1592	36.2%	-0.00 [-0.01, 0.01]	•
Marso 2016B	65	1648	69	1649	37.5%	-0.00 [-0.02, 0.01]	•
Pratley 2019	0	285	0	142	4.3%	0.00 [-0.01, 0.01]	†
Zinman 2019A	1	150	0	151	3.4%	0.01 [-0.01, 0.02]	†
Zinman 2019B	3	546	0	184	6.3%	0.01 [-0.00, 0.02]	†
Total (95% CI)		5024		4120	100.0%	-0.00 [-0.01, 0.01]	
Total events	107		108				
Heterogeneity: Chi ² =	3.24, df=	5(P = 0)	.66); l ² =	0%			1 1 1 1 1 1
Test for overall effect:	Z= 0.35 (P = 0.72	2)				-1 -0.5 0 0.5 Favours Semaglutide Favours Placebo

Figure 188: Hypoglycaemia episodes at end of follow-up

J	<i>J</i>	J	-				· · · · · · · · · · · · · · · · · · ·				
	Semagl	utide	Place	bo		Risk Ratio	Risk Ratio				
Study or Subgroup	Events	Events Total		Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI				
Davies 2017	75	559	8	71	21.1%	1.19 [0.60, 2.36]	-				
Davies 2021	45	804	12	402	22.4%	1.88 [1.00, 3.50]	-				
Heise 2022	1	44	0	28	2.7%	1.93 [0.08, 45.86]					
Pratley 2019	2	285	3	142	7.1%	0.33 [0.06, 1.97]					
Sivalingam 2023	1	30	2	30	4.5%	0.50 [0.05, 5.22]					
Zinman 2019A	17	150	3	151	12.3%	5.70 [1.71, 19.06]					
Zinman 2019B	147	546	54	184	29.9%	0.92 [0.70, 1.19]	+				
Total (95% CI)		2418		1008	100.0%	1.31 [0.77, 2.25]	•				
Total events	288		82								
Heterogeneity: Tau ² =	0.23; Chi	² = 14.6	6, df = 6 (P = 0.0	2); l² = 59	1%	0.01 0.1 1 10 100				
est for overall effect: Z = 1.00 (P = 0.32)							Favours Semaglutide Favours Placebo				

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

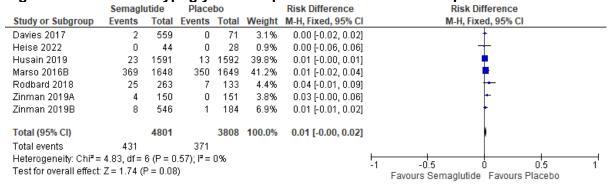


Figure 190: HbA1c change (%, lower values are better, change scores) at end of follow up

			Semaglutide	Placebo		Mean Difference	Mean D	ifference	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Rando	om, 95% CI	
Davies 2017	-1.24	0.1075	559	71	9.1%	-1.24 [-1.45, -1.03]	•		
Davies 2021	-1.1503	0.1223	757	374	8.9%	-1.15 [-1.39, -0.91]	-		
Marso 2016B (1)	-0.66	0.0714	826	824	9.5%	-0.66 [-0.80, -0.52]	•		
Marso 2016B (2)	-1.05	0.0714	822	825	9.5%	-1.05 [-1.19, -0.91]	•		
Pratley 2019	-1	0.1414	278	134	8.6%	-1.00 [-1.28, -0.72]	-		
Rodbard 2018 (3)	-1.35	0.1327	132	67	8.7%	-1.35 [-1.61, -1.09]	-		
Rodbard 2018 (4)	-1.75	0.1327	131	66	8.7%	-1.75 [-2.01, -1.49]	+		
Zinman 2019A	-1.42	0.0969	151	151	9.3%	-1.42 [-1.61, -1.23]	•		
Zinman 2019B (5)	-0.6	0.102	182	61	9.2%	-0.60 [-0.80, -0.40]	•		
Zinman 2019B (6)	-0.4	0.102	184	61	9.2%	-0.40 [-0.60, -0.20]	-	-	
Zinman 2019B (7)	-0.9	0.102	181	62	9.2%	-0.90 [-1.10, -0.70]	•		
Total (95% CI)			4203	2696	100.0%	-1.04 [-1.26, -0.82]	•		
Heterogeneity: Tau ² =	: 0.13; Chi ² = 137.74	df= 10	(P < 0.00001);	l² = 93%			L	<u> </u>	
Test for overall effect:	•						-10 -5 Favours Semaglutide	U 5 Favours Placebo	10

Footnotes

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

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

			Semaglutide	Placebo		Mean Difference		Mea	n Diffe	rence	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI		IV, Ra	ndom,	, 95% CI	
Heise 2022	-21	1.4213	43	24	51.3%	-21.00 [-23.79, -18.21]					
Sivalingam 2023	-8	2.55	28	26	48.7%	-8.00 [-13.00, -3.00]			-		
Total (95% CI)			71	50	100.0%	-14.67 [-27.41, -1.94]		<	▶		
Heterogeneity: Tau²: Test for overall effect			P < 0.00001); i²	²= 95%			-100 Fa	-50 vours Semaglut	0 ide F	50 avours Placebo	100

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

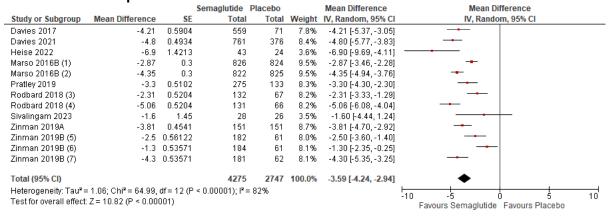
	•		Semaglutide	Placebo		Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Davies 2017	-4.21	0.5904	559	71	7.8%	-4.21 [-5.37, -3.05]	
Davies 2021	-4.8	0.4934	761	376	8.4%	-4.80 [-5.77, -3.83]	
Heise 2022	-6.9	1.4213	43	24	3.6%	-6.90 [-9.69, -4.11]	
Marso 2016B (1)	-2.87	0.3	826	824	9.5%	-2.87 [-3.46, -2.28]	-
Marso 2016B (2)	-4.35	0.3	822	825	9.5%	-4.35 [-4.94, -3.76]	
Pratley 2019	-3.3	0.5102	275	133	8.3%	-3.30 [-4.30, -2.30]	
Rodbard 2018 (3)	-2.31	0.5204	132	67	8.2%	-2.31 [-3.33, -1.29]	
Rodbard 2018 (4)	-5.06	0.5204	131	66	8.2%	-5.06 [-6.08, -4.04]	
Sivalingam 2023	-1.6	1.45	28	26	3.5%	-1.60 [-4.44, 1.24]	
Zinman 2019A	-3.81	0.4541	151	151	8.7%	-3.81 [-4.70, -2.92]	
Zinman 2019B (5)	-2.5	0.56122	182	61	8.0%	-2.50 [-3.60, -1.40]	
Zinman 2019B (6)	-1.3	0.53571	184	61	8.1%	-1.30 [-2.35, -0.25]	
Zinman 2019B (7)	-4.3	0.53571	181	62	8.1%	-4.30 [-5.35, -3.25]	
Total (95% CI)			4275	2747	100.0%	-3.59 [-4.24, -2.94]	•
Heterogeneity: Tau ² =	= 1.06; Chi² = 64.99,	df = 12 (P	< 0.00001); l ² :	= 82%			
Test for overall effect:	Z = 10.82 (P < 0.00	001)	,,				-10 -5 0 5 10
		/					Favours Semaglutide Favours Placebo

<u>Footnotes</u>

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

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

Figure 193: BMI change (kg/m², lower values are better, change scores) at end of follow up



Footnotes

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

K.1.3.21 Adding semaglutide compared to adding insulin

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

_	Semaglutide Insulin			Peto Odds Ratio	Peto Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Aroda 2017	4	722	2	360	29.1%	1.00 [0.18, 5.47]	
Kellerer 2022	12	874	1	864	70.9%	5.43 [1.82, 16.18]	_
Total (95% CI)		1596		1224	100.0%	3.32 [1.32, 8.31]	•
Total events	16		3				
Heterogeneity: Chi²=	2.70, df=	1 (P = 0)	.10); l² =	63%			0.01 0.1 1 10 100
Test for overall effect:	Z = 2.56 (I	P = 0.01)				Favours Semaglutide Favours Insulin

Figure 195: Severe hypoglycaemic episodes at end of follow up

	Semagl	utide	Insul	in		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
Aroda 2017	36	722	38	360	87.8%	0.47 [0.30, 0.73]	-	
Kellerer 2022	4	874	7	864	12.2%	0.56 [0.17, 1.92]	-	
Total (95% CI)		1596		1224	100.0%	0.48 [0.32, 0.73]	•	
Total events	40		45					
Heterogeneity: Chi²=	0.07, df =	1 (P = 0)).79); l²=	0%			0.01 0.1 1 10	100
Test for overall effect:	Z= 3.45 (P = 0.00	006)				Favours Semaglutide Favours Insulin	100

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

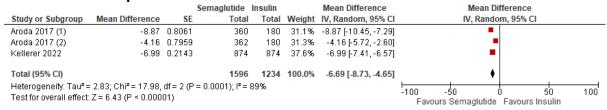
			Semaglutide	Insulin		Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Aroda 2017 (1)	-0.38	0.07	362	180	33.0%	-0.38 [-0.52, -0.24]	•
Aroda 2017 (2)	-0.81	0.0765	360	180	32.6%	-0.81 [-0.96, -0.66]	•
Kellerer 2022	-0.29	0.0459	874	874	34.4%	-0.29 [-0.38, -0.20]	•
Total (95% CI)			1596	1234	100.0%	-0.49 [-0.79, -0.19]	♦
Heterogeneity: Tau² = Test for overall effect:			< 0.00001); ² =	94%			-10 -5 0 5 10 Favours Semaglutide Favours Insulin

Footnotes

(1) 0.5 mg semaglutide v placebo

(2) 1.0 mg semaglutide v insulin

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



Footnotes

(1) 1.0 mg semaglutide v insulin

(2) 0.5 mg semaglutide v insulin

K.1.3.22 Adding semaglutide compared to adding dulaglutide

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

	Semagl	utide	Dulaglu	ıtide		Risk Difference		Ris	k Differend	e	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H,	Fixed, 95%	CI	
Pratley 2018B	2	601	4	598	84.3%	-0.00 [-0.01, 0.00]					
Yabe 2020	0	393	0	65	15.7%	0.00 [-0.02, 0.02]			†		
Total (95% CI)		994		663	100.0%	-0.00 [-0.01, 0.00]			(
Total events	2		4								
Heterogeneity: Chi²=	0.09, df=	1 (P = 0)	.77); I * =	0%			1	-0.5	 	0.5	
Test for overall effect:	Z = 0.74 (1	P = 0.48	i)				-1	Favours Semaglu	tide Favoi		'

Figure 199: Cardiovascular mortality at end of follow up

	Semagl	utide	Dulaglu	ıtide		Risk Difference		Ris	sk Differenc	e	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H	, Fixed, 95%	CI	
Pratley 2018B	1	601	2	598	84.3%	-0.00 [-0.01, 0.00]					
Yabe 2020	0	393	0	65	15.7%	0.00 [-0.02, 0.02]			†		
Total (95% CI)		994		663	100.0%	-0.00 [-0.01, 0.00]					
Total events	1		2								
Heterogeneity: Chi²=	0.03, df=	1 (P = 0)).87); I²=	0%			<u> </u>	0.5	_ 	0.5	
Test for overall effect	Z = 0.48 (P = 0.63	3)				-1	-0.5 Favours Semagli	utide Favou	0.5 ırs Dulaglutide	1

Figure 200: Hypoglycaemia episodes at end of follow up

	Semagl	utide	Dulaglu	ıtide		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
lijima 2023	0	16	0	16	12.5%	0.00 [-0.11, 0.11]	
Yabe 2020	67	393	13	65	87.5%	-0.03 [-0.13, 0.07]	-
Total (95% CI)		409		81	100.0%	-0.03 [-0.12, 0.07]	•
Total events	67		13				
Heterogeneity: Chi²=	0.20, df=	1 (P = 0)	1.65); I²=	0%			-1 -05 0 05 1
Test for overall effect	: Z= 0.55 (P = 0.58	3)				Favours Semaglutide Favours Dulaglutide

Figure 201: Severe hypoglycaemic episodes at end of follow up

_	Semagli	utide	Dulaglu	ıtide	-	Risk Difference		Risk E	ifference		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fix	ced, 95% CI		
Pratley 2018B	7	601	8	598	84.3%	-0.00 [-0.01, 0.01]					
Yabe 2020	0	393	0	65	15.7%	0.00 [-0.02, 0.02]			†		
Total (95% CI)		994		663	100.0%	-0.00 [-0.01, 0.01]			•		
Total events	7		8								
Heterogeneity: Chi²=	0.02, df =	1 (P = 0	.89); l²=	0%			-1	-0.5	 	0.5	
Test for overall effect:	Z = 0.26 (f	P = 0.80))				-1	Favours Semaglutid	e Favours		'

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

	Sema	aglutide		Dula	glutide			Mean Difference	Me	ean Difference	,	
Study or Subgroup	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV, Random, 95% CI [%]	IV, Ra	andom, 95% CI	[%]	
lijima 2023	-0.42	0.49	16	0	0.34	16	29.4%	-0.42 [-0.71, -0.13]		-		
Pratley 2018B	-1.65	1.04	601	-1.25	1	598	37.8%	-0.40 [-0.52, -0.28]		-		
Yabe 2020	-1.33	1.19	393	-1.4	0.81	65	32.7%	0.07 [-0.16, 0.30]		•		
Total (95% CI)			1010			679	100.0%	-0.25 [-0.56, 0.06]		•		
Heterogeneity: Tau ² = Test for overall effect:			df = 2 (F	P = 0.001); I	²= 85%				-10 -5 Favours Semag	0 lutide Favours	5 S Dulaglutide	10

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

		-										
	Sem	aglutide		Dula	glutide			Mean Difference		Mean Dif	ference	
Study or Subgroup	Mean [kg]	SD [kg]	Total	Mean [kg]	SD [kg]	Total	Weight	IV, Random, 95% CI [kg]		IV, Random,	95% CI [kg]	
lijima 2023	-2.6	3.6	16	-0.1	2.7	16	11.3%	-2.50 [-4.70, -0.30]		•		
Pratley 2018B	-5.55	4.86	601	-2.65	4.67	598	50.8%	-2.90 [-3.44, -2.36]				
Yabe 2020	-0.83	3.49	393	1	3.23	65	37.9%	-1.83 [-2.69, -0.97]		•		
Total (95% CI)			1010			679	100.0%	-2.45 [-3.26, -1.64]		1		
Heterogeneity: Tau ² = Test for overall effect:				0.12); I² = 53	3%				-100	-50 0 Favours Semaglutide	50 Favours Dulagluti	100 ide

BMI change (kg/m², lower values are better, change scores) at end of Figure 204: follow up

	-		Semaglutide	Dulaglutide		Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Pratley 2018B	-1	0.0999	601	598	29.7%	-1.00 [-1.20, -0.80]	
Yabe 2020 (1)	-0.7	0.18	132	22	23.4%	-0.70 [-1.05, -0.35]	
Yabe 2020 (2)	-0.9	0.18	130	22	23.4%	-0.90 [-1.25, -0.55]	
Yabe 2020 (3)	-0.3	0.18	131	21	23.4%	-0.30 [-0.65, 0.05]	
Total (95% CI)			994	663	100.0%	-0.74 [-1.05, -0.43]	•
Heterogeneity: Tau ² =	= 0.07; Chi2 = 12.23,	df = 3 (F	P = 0.007); $P = 7$	5%			
Test for overall effect:	Z = 4.72 (P < 0.000)	01)					-1 -0.5 0 0.5 1 Favours Semaglutide Favours Dulaglutide

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

Adding semaglutide compared to adding exenatide K.1.3.23

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

K.1.3.24 Adding semaglutide compared to adding liraglutide

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

	Semagli	utide	Liraglu	tide		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Capehorn 2020	0	290	0	287	50.3%	0.00 [-0.01, 0.01]	•
Pratley 2019	3	285	4	284	49.7%	-0.00 [-0.02, 0.01]	•
Total (95% CI)		575		571	100.0%	-0.00 [-0.01, 0.01]	
Total events	3		4				
Heterogeneity: Chi²=	0.30, df =	1 (P = 0)	.58); (2=	0%			-1 -0.5 0 0.5 1
Test for overall effect:	Z = 0.36 (f	P = 0.72	?)				Favours Semaglutide Favours Liraglutide

Figure 206: Cardiovascular mortality at end of follow up

	Semagli	utide	Liraglu	tide		Risk Difference		Risk	Difference		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fi	xed, 95% CI		
Capehorn 2020	0	290	0	287	50.3%	0.00 [-0.01, 0.01]			•		
Pratley 2019	1	285	2	284	49.7%	-0.00 [-0.02, 0.01]			•		
Total (95% CI)		575		571	100.0%	-0.00 [-0.01, 0.01]			1		
Total events	1		2								
Heterogeneity: Chi²=	0.34, df=	1 (P = 0)	.56); l² = 1	0%			1	-0.5	+	 	
Test for overall effect:	Z = 0.50 (F	P = 0.61)				-1	Favours Semaglutio	u la Favoure I	U.5 iradutida	'
								i avours sernagium	ic lavouis i	Liragiuliue	



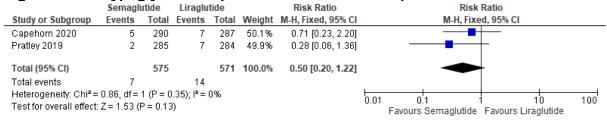


Figure 208: HbA1c change (%, lower values are better, change scores) at end of follow up

			Semaglutide	Liraglutide		Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Capehorn 2020	-0.69	0.0663	290	287	52.2%	-0.69 [-0.82, -0.56]	
Pratley 2019	-0.1	0.1416	278	272	47.8%	-0.10 [-0.38, 0.18]	•
Total (95% CI)			568	559	100.0%	-0.41 [-0.99, 0.17]	•
Heterogeneity: Tau² = Test for overall effect:			= 0.0002); I ^z = 9	33%			-10 -5 0 5 10 Favours Semaglutide Favours Liraglutide

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

	-		Semaglutide L	Liraglutide		Mean Difference	Mean Di	fference	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Rando	m, 95% CI	
Capehorn 2020	-3.83	0.3776	290	287	49.5%	-3.83 [-4.57, -3.09]	-		
Pratley 2019	-1.3	0.2825	278	271	50.5%	-1.30 [-1.85, -0.75]	•		
Total (95% CI)			568	558	100.0%	-2.55 [-5.03, -0.07]	-		
Heterogeneity: Tau² = Test for overall effect:			< 0.00001); I² =	97%			-10 -5 Favours Semaglutide		10 de

Figure 210: BMI change (kg/m², lower values are better, change scores) at end of follow up

	-		Semaglutide Lii	iraglutide		Mean Difference	Mean Difference	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
Capehorn 2020	-3.83	0.3776	290	287	49.5%	-3.83 [-4.57, -3.09]	-	
Pratley 2019	-1.3	0.2825	278	271	50.5%	-1.30 [-1.85, -0.75]	-	
Total (95% CI)			568	558	100.0%	-2.55 [-5.03, -0.07]	-	
Heterogeneity: Tau² = Test for overall effect:		df = 1 (P	< 0.00001); I ² = 9	97%			-10 -5 0 5 1 Favours Semaglutide Favours Liraglutide	10

K.1.3.25 Adding semaglutide compared to adding sitagliptin

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

			Semaglutide	Sitagliptin		Mean Difference		Mean	Difference	е	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Fixed, 95% CI		IV, Fix	ed, 95% Cl	I	
Pieber 2019	-0.17	0.7296	253	251	16.2%	-0.17 [-1.60, 1.26]		_	•		
Rosenstock 2019C (1)	0.23	0.5561	465	156	27.9%	0.23 [-0.86, 1.32]			-		
Rosenstock 2019C (2)	-0.12	0.5612	465	155	27.4%	-0.12 [-1.22, 0.98]		-	-		
Rosenstock 2019C (3)	0.17	0.551	466	156	28.4%	0.17 [-0.91, 1.25]		•	+		
Total (95% CI)			1649	718	100.0%	0.05 [-0.52, 0.63]			*		
Heterogeneity: Chi² = 0.3	33, df = 3 (P = 0.95);	l² = 0%					-10	- L	 	_	10
Test for overall effect: Z =	= 0.18 (P = 0.86)						-10	-5 Favours Sitanlinti	n Favour	c Semanlutide	10

<u>Footnotes</u>

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

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

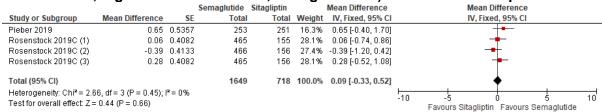


Figure 213: All-cause mortality at end of follow up

•	Semagl	utide	Sitagli	ptin		Peto Odds Ratio	Peto Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI	
Ahrén 2017	3	818	3	407	29.4%	0.47 [0.09, 2.57]		
Ji 2021A	2	578	0	290	9.9%	4.50 [0.24, 85.07]	-	
Pieber 2019	0	253	2	250	11.1%	0.13 [0.01, 2.14]		
Rosenstock 2019C	9	1395	3	466	49.7%	1.00 [0.27, 3.71]	-	
Total (95% CI)		3044		1413	100.0%	0.74 [0.30, 1.87]	•	
Total events	14		8					
Heterogeneity: Chi ² =	3.40, df=	3(P = 0)	.33); I²=	12%			0.004	4000
Test for overall effect:	Z = 0.63 (P = 0.53)				0.001 0.1 1 10 Favours Semaglutide Favours Sitagliptin	1000

Figure 214: Cardiovascular mortality at end of follow up

	Semagl	utide	Sitagli	ptin		Peto Odds Ratio	Peto Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI	
Ahrén 2017	3	818	2	407	46.3%	0.74 [0.11, 4.75]		
Ji 2021A	1	578	0	290	9.3%	4.49 [0.07, 286.30]		_
Pieber 2019	0	253	2	250	20.9%	0.13 [0.01, 2.14]		
Rosenstock 2019C	3	1395	0	466	23.5%	3.80 [0.28, 51.87]		
Total (95% CI)		3044		1413	100.0%	0.90 [0.25, 3.19]	-	
Total events	7		4					
Heterogeneity: Chi ² =	3.61, df=	3(P = 0)	.31); I²=	17%			0.001 0.1 1 10	1000
Test for overall effect:	Z= 0.17 (P = 0.87)				Favours Semaglutide Favours Sitagliptin	1000

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

	Semagl	utide	Sitagli	ptin		Peto Odds Ratio	Peto O	dds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fix	red, 95% CI	
Pieber 2019	0	253	1	250	14.3%	0.13 [0.00, 6.74]	<u> </u>	 	
Rosenstock 2019C	5	1395	3	466	85.7%	0.51 [0.10, 2.55]			
Total (95% CI)		1648		716	100.0%	0.42 [0.10, 1.87]	-	-	
Total events	5		4						
Heterogeneity: Chi²=	0.39, df=	1 (P = 0)	.53); l² =	0%			0.001 0.1	1 10	1000
Test for overall effect: .	Z = 1.14 (I	P = 0.26)				Favours Semaglutide		1000

^{(1) 14} mg semaglutide v sitagliptin

^{(2) 3} mg semaglutide v sitagliptin (3) 7 mg semaglutide v sitagliptin



	Semagl	utide	Sitagli	ptin		Peto Odds Ratio	Peto Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI	
Pieber 2019	1	253	0	250	9.3%	7.30 [0.14, 368.02]		
Rosenstock 2019C	10	1395	3	466	90.7%	1.11 [0.32, 3.91]	— <mark>—</mark> —	
Total (95% CI)		1648		716	100.0%	1.32 [0.40, 4.39]	-	
Total events	11		3					
Heterogeneity: Chi²=	0.80, df =	1 (P = 0)	.37); I² =	0%			0.001 0.1 1 10	1000
Test for overall effect:	Z = 0.46 (P = 0.65)				Favours Semaglutide Favours Sitagliptin	

Figure 217: Hypoglycaemia episodes at end of follow up

	Semagl	utide	Sitagli	ptin		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Ahrén 2017	9	818	5	407	3.6%	0.90 [0.30, 2.66]	
Ji 2021A	8	578	7	290	5.1%	0.57 [0.21, 1.57]	
Rosenstock 2019C	341	1395	112	466	91.3%	1.02 [0.84, 1.22]	—
Total (95% CI)		2791		1163	100.0%	0.99 [0.83, 1.19]	•
Total events	358		124				
Heterogeneity: Chi ² =	1.25, df=	2(P = 0)	.54); I² =	0%			0.01 0.1 1 10 100
Test for overall effect:	Z = 0.11 (P = 0.91)				Favours Semaglutide Favours Sitagliptin

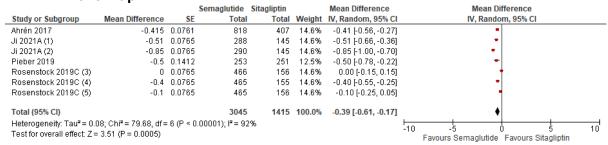
Figure 218: At night hypoglycaemic episodes at end of follow up

	Semagl	utide	Sitagli	ptin		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% C	1	
Pieber 2019	3	253	2	250	21.2%	1.48 [0.25, 8.79]			
Rosenstock 2019C	17	1395	5	466	78.8%	1.14 [0.42, 3.06]			
Total (95% CI)		1648		716	100.0%	1.21 [0.51, 2.87]	•		
Total events	20		7						
Heterogeneity: Chi²=	0.07, df =	1 (P = 0)	.80); l²=	0%			0.01 0.1 1	10	100
Test for overall effect:	Z = 0.43 (I	P = 0.67	")				Favours Semaglutide Favours	Sitagliptin	100

Figure 219: Severe hypoglycaemic episodes at end of follow up

•								
	Semagl	utide	Sitagli	ptin		Risk Difference	Risk Difference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
Ahrén 2017	0	818	2	407	36.4%	-0.00 [-0.01, 0.00]	•	
Pieber 2019	0	253	0	250	16.8%	0.00 [-0.01, 0.01]	•	
Rosenstock 2019C	1	1395	4	466	46.8%	-0.01 [-0.02, 0.00]	•	
Total (95% CI)		2466		1123	100.0%	-0.01 [-0.01, -0.00]		
Total events	1		6					
Heterogeneity: Chi ² =	2.24, df=	2(P = 0)	.33); I²=	11%			1 05	
Test for overall effect:	Z = 2.12 (I	P = 0.03)				-1 -0.5 0 0.5 Favours Semaglutide Favours Sitagliptin	1

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



<u>Footnotes</u>

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

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

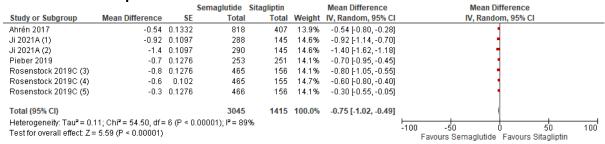
Figure 221: Weight change (kg, lower values are better, change scores) at end of follow up

			Semaglutide	Sitagliptin		Mean Difference		Mean D	ifference		
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI		IV, Rande	om, 95% CI		
Ahrén 2017	-1.375	0.366	818	407	14.0%	-1.38 [-2.09, -0.66]			•		
Ji 2021A (1)	-2.48	0.2959	288	145	14.7%	-2.48 [-3.06, -1.90]			•		
Ji 2021A (2)	-3.79	0.2959	290	145	14.7%	-3.79 [-4.37, -3.21]					
Pieber 2019	-1.9	0.3605	253	251	14.0%	-1.90 [-2.61, -1.19]			•		
Rosenstock 2019C (3)	-1.7	0.3316	465	156	14.3%	-1.70 [-2.35, -1.05]			•		
Rosenstock 2019C (4)	-0.8	0.3571	466	156	14.1%	-0.80 [-1.50, -0.10]			•		
Rosenstock 2019C (5)	-2.1	0.3316	465	155	14.3%	-2.10 [-2.75, -1.45]		1	•		
Total (95% CI)			3045	1415	100.0%	-2.03 [-2.77, -1.30]					
Heterogeneity: Tau² = 0.8			.00001); I²= 89	%			-100	-50	0 50	1	100
Test for overall effect: Z =	: 5.45 (P < 0.00001)							Favours Semaglutide			

Footnotes

- (1) 0.5 mg semaglutide v sitagliptin
- (2) 1.0 mg semaglutide v sitagliptin
- (3) 7 mg semaglutide v sitagliptin
- (4) 3 mg semaglutide v sitagliptin (5) 14 mg semaglutide v sitagliptin
- Note: Heterogeneity was not explained by sensitivity analysis nor subgroup analysis by eGFR subgroup.

Figure 222: BMI change (kg/m², lower values are better, change scores) at end of follow up



Footnotes

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

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

K.1.3.26 Adding subcutaneous semaglutide compared to adding oral semaglutide

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

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

K.1.4.1 Adding tirzepatide compared to adding placebo

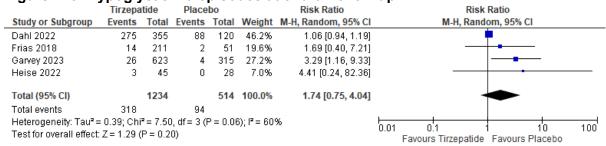
Figure 223: All-cause mortality at end of follow up

_	Tirzepa	itide	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Dahl 2022	0	355	0	120	25.2%	0.00 [-0.01, 0.01]	•
Frias 2018	0	211	1	51	11.6%	-0.02 [-0.07, 0.03]	- -
Garvey 2023	2	623	0	311	58.4%	0.00 [-0.00, 0.01]	
Heise 2022	0	45	0	28	4.9%	0.00 [-0.06, 0.06]	+
Total (95% CI)		1234		510	100.0%	-0.00 [-0.01, 0.01]	1
Total events	2		1				
Heterogeneity: Chi ² =	1.80, df=	3 (P=	0.61); l ^z =	: 0%			-1 -05 0 05 1
Test for overall effect:	Z = 0.10	(P = 0.9)	2)				-1 -0.5 0 0.5 1 Favours Tirzepatide Favours Placebo

Figure 224: Cardiovascular mortality at end of follow up

	Tirzepa	itide	Placebo		Placebo Risk Difference		Risk Difference		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Dahl 2022	0	355	0	120	83.9%	0.00 [-0.01, 0.01]			
Heise 2022	0	45	0	28	16.1%	0.00 [-0.06, 0.06]		+	
Total (95% CI)		400		148	100.0%	0.00 [-0.01, 0.01]		•	
Total events	0		0						
Heterogeneity: Chi²=	0.00, df=	1 (P=	1.00); l²=		-1	-0.5 0 0.5	_		
Test for overall effect:	Z = 0.00 (P = 1.0	0)				-1	Favours Tirzepatide Favours Placebo	'

Figure 225: Hypoglycaemia episodes at end of follow up





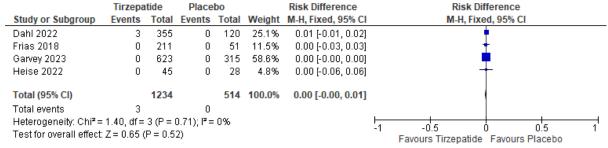


Figure 227: HbA1c change (%, lowr values are better, change scores) at end of follow

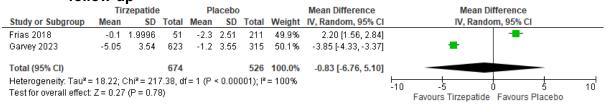
up									
	Tirzepatide			F	Placebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Dahl 2022	-2.29	0.94	355	-0.86	0.91	120	38.2%	-1.43 [-1.62, -1.24]	•
Frias 2018	-1.68	1.31	211	0.1	1.1426	51	10.6%	-1.78 [-2.14, -1.42]	+
Garvey 2023	-2.07	1.15	623	-0.51	1.24	315	51.2%	-1.56 [-1.72, -1.40]	•
Total (95% CI)	1189 486					486	100.0%	-1.53 [-1.65, -1.42]	•
Heterogeneity: Chi ^z = Test for overall effect:		•			%				-10 -5 0 5 10 Favours Tirzepatide Favours Placebo

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

	Tirzepatide			Placebo			Mean Difference			Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Rando	om, 95	% CI	
Dahl 2022	-7.25	6.45	355	1.6	6.36	120	25.3%	-8.85 [-10.17, -7.53]		•			
Frias 2018	-0.4	5.7846	51	-4.77	8.28	211	25.0%	4.37 [2.43, 6.31]			•		
Garvey 2023	-13.75	9.79	623	-3.2	8.87	315	25.3%	-10.55 [-11.80, -9.30]		•			
Heise 2022	-11.2	5.3889	41	0	5.7628	24	24.4%	-11.20 [-14.03, -8.37]		•			
Total (95% CI)			1070			670	100.0%	-6.55 [-12.94, -0.16]		•	•		
Heterogeneity: Tau² : Test for overall effect				= 3 (P <	0.00001); I ² = 9	8%		-100	-50 Favours Tirzepatide	0 Favo	50 ours Placebo	100

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

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



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K.1.4.2 Adding tirzepatide compared to adding insulin

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

	Tirzepa	tide	Insul	lin		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
Gao 2023	1	687	2	220	17.7%	0.16 [0.01, 1.76]	-	
Ludvik 2021	4	1077	2	360	17.5%	0.67 [0.12, 3.63]		
Rosenstock 2023	7	717	11	708	64.7%	0.63 [0.24, 1.61]		
Total (95% CI)		2481		1288	100.0%	0.55 [0.26, 1.18]	•	
Total events	12		15					
Heterogeneity: Chi ² =	1.15, df=	2 (P = 1)	0.56); l ^z =	: 0%			0.01 0.1 1 10	100
Test for overall effect:	Z = 1.52 (P = 0.1	3)				Favours Tirzepatide Favours Insulin	100

Figure 231: Cardiovascular mortality at end of follow up

	Tirzepatide Insulin		Tirzepatide		in		Peto Odds Ratio	Peto Od	ds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fix	ed, 95% CI		
Gao 2023	1	687	2	220	74.5%	0.10 [0.01, 1.39]		_		
Ludvik 2021	1	1077	0	360	25.5%	3.80 [0.04, 349.83]		-	_	
Total (95% CI)		1764		580	100.0%	0.25 [0.03, 2.45]				
Total events	2		2							
Heterogeneity: Chi²=	1.86, df=	1 (P=	0.17); I² =	46%			0.001 0.1	1 10	1000	
Test for overall effect:	Z = 1.19 ((P = 0.2)	3)				Favours Tirzepatide		1000	

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

	Tirzepatide		irzepatide Insulin			Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	
Gao 2023	8	687	1	220	29.7%	2.56 [0.32, 20.37]		
Ludvik 2021	7	1077	3	360	70.3%	0.78 [0.20, 3.00]		
Total (95% CI)		1764		580	100.0%	1.11 [0.36, 3.44]	-	
Total events	15		4					
Heterogeneity: Tau² = Test for overall effect:				P = 0.34	4); I² = 0%	•	0.01 0.1 10 10 Favours Tirzepatide Favours Insulin	ō

Figure 233: Hypoglycaemia episodes at end of follow up

	Tirzepa	atide	Insu	lin		Risk Ratio	-	Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Rando	om, 95% CI	
Gao 2023	207	687	97	220	33.5%	0.68 [0.57, 0.82]		-		
Ludvik 2021	130	1077	170	360	33.4%	0.26 [0.21, 0.31]		-		
Rosenstock 2023	76	717	340	708	33.1%	0.22 [0.18, 0.28]		-		
Total (95% CI)		2481		1288	100.0%	0.34 [0.16, 0.70]				
Total events	413		607							
Heterogeneity: Tau ² =	= 0.40; Chi	$i^2 = 77.7$	1, df = 2	(P < 0.1	00001); I ²	= 97%	<u> </u>	0.2 0.5	1 1	10
Test for overall effect	: Z= 2.92 ((P = 0.0)	03)				0.1	Favours Tirzepatide	Favours Insulin	10

Figure 234: Severe hypoglycaemic episodes at end of follow up

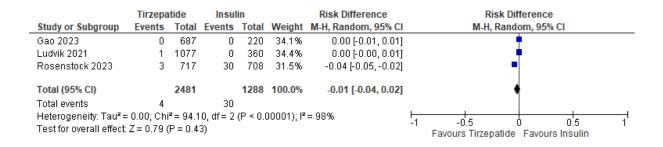
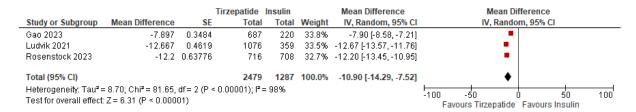


Figure 235: HbA1c change (%, lower values are better, change scores) at end of follow up

			Tirzepatide	Insulin		Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Gao 2023	-1.44	0.0809	687	220	33.3%	-1.44 [-1.60, -1.28]	•
Rosenstock 2023	-0.98	0.09694	716	708	32.5%	-0.98 [-1.17, -0.79]	•
Ludvik 2021	-0.827	0.0577	1076	359	34.2%	-0.83 [-0.94, -0.71]	•
Total (95% CI)			2479	1287	100.0%	-1.08 [-1.46, -0.70]	•
Heterogeneity: Tau² = Test for overall effect:		•	< 0.00001); P	= 95%			-10 -5 0 5 10 Favours Tirzepatide Favours Insulin

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

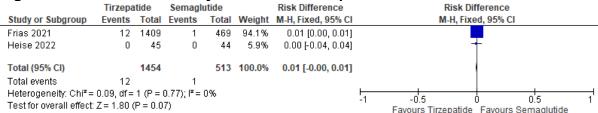


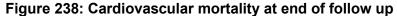
K.1.4.3 Adding tirzepatide compared to adding dulaglutide

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

K.1.4.4 Adding tirzepatide compared to adding semaglutide

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





	Tirzepa	atide	Semagl	utide		Risk Difference		F	Risk Differenc	e	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M	-H, Fixed, 95%	CI	
Frias 2021	5	1410	0	469	94.1%	0.00 [-0.00, 0.01]					
Heise 2022	0	45	0	44	5.9%	0.00 [-0.04, 0.04]			+		
Total (95% CI)		1455		513	100.0%	0.00 [-0.00, 0.01]					
Total events	5		0								
Heterogeneity: Chi²:		,		0%			-1	-0.5		0.5	
Test for overall effec	t: Z= 1.34 ((P = 0.1)	8)				'		patide Favou	ırs Semaglutide	

Figure 239: Hypoglycaemia episodes at end of follow up

	Tirzepa	itide	Semagl	utide		Peto Odds Ratio		Peto Od	lds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI		Peto, Fix	ed, 95% CI	
Frias 2021	12	1409	2	469	73.0%	1.78 [0.53, 5.98]		_	_	
Heise 2022	3	45	1	44	27.0%	2.75 [0.37, 20.22]			•	-
Total (95% CI)		1454		513	100.0%	2.00 [0.71, 5.64]		-		
Total events	15		3							
Heterogeneity: Chi²=	0.14, df=	1 (P = 1)	0.71); I²=	0%			0.04	0.4	10	100
Test for overall effect	Z= 1.31 (P = 0.1	9)				0.01	Favours Tirzepatide	Favours Semaglu	

Figure 240: Severe hypoglycaemic episodes at end of follow up

	Tirzepa	ıtide	Semagl	utide		Risk Difference		Ri	isk Differend	e	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-l	H, Fixed, 95%	CI	
Frias 2021	2	1409	0	469	94.1%	0.00 [-0.00, 0.01]					
Heise 2022	0	45	0	44	5.9%	0.00 [-0.04, 0.04]			+		
Total (95% CI)		1454		513	100.0%	0.00 [-0.00, 0.01]					
Total events	2		0								
Heterogeneity: Chi ² =	0.01, df=	1 (P = 1)	0.94); $I^2 =$	0%			<u> </u>				_
Test for overall effect	Z = 0.60 (P = 0.5	5)				-1	-0.5 Favours Tirzep	atide Favou	0.5 ırs Semaglutide	1

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

			Tirzepatide	Semaglutide		Mean Difference	Mean	Difference	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Rar	ndom, 95% CI	
Frias 2021 (1)	-1.9	0.4592	470	156	29.2%	-1.90 [-2.80, -1.00]	-		
Frias 2021 (2)	-3.6	0.0612	469	156	33.0%	-3.60 [-3.72, -3.48]			
Frias 2021 (3)	-6.4	0.9184	469	156	21.5%	-6.40 [-8.20, -4.60]			
Heise 2022	-4.3	1.2728	41	43	16.3%	-4.30 [-6.79, -1.81]			
Total (95% CI)			1449	511	100.0%	-3.82 [-5.24, -2.41]	•		
Heterogeneity: Tau² =	: 1.58; Chi² = 23.24,	df= 3 (P	< 0.0001); I ² =	87%			-10 -5	 	10
Test for overall effect:	Z = 5.29 (P < 0.000	01)						de Favours Semaglutide	

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

(3) Tirzepatide 15 mg daily

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

K.1.5 SGLT2 inhibitors

K.1.5.1 Adding canagliflozin compared to adding placebo

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

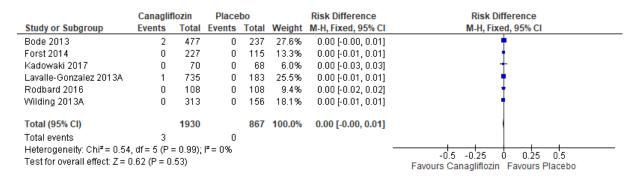


Figure 243: Cardiovascular mortality at end of follow up

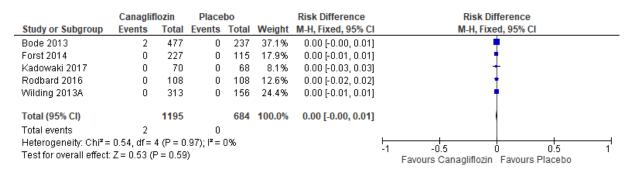


Figure 244: Diabetic ketoacidosis at end of follow up

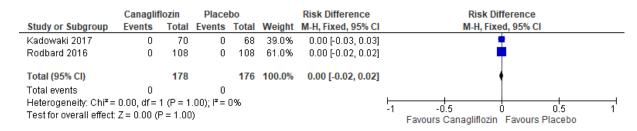
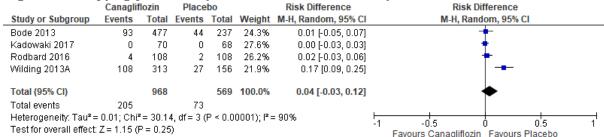


Figure 245: Hypoglycaemia episodes at end of follow up



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



	Canaglif	flozin	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Bode 2013	11	477	8	237	50.0%	-0.01 [-0.04, 0.02]	•
Rodbard 2016	0	108	0	108	17.1%	0.00 [-0.02, 0.02]	†
Wilding 2013A	2	313	1	156	32.9%	-0.00 [-0.02, 0.02]	•
Total (95% CI)		898		501	100.0%	-0.01 [-0.02, 0.01]	•
Total events	13		9				
Heterogeneity: Chi²=	0.96, df =	2(P = 0)	.62); l²=	0%			-1 -0.5 0 0.5 1
Test for overall effect:	Z = 0.72 (1	P = 0.47	")				Favours Canagliflozin Favours Placebo

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

ωp										
-			Canagliflozin	Placebo		Mean Difference		Mean Diff	ference	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI		IV, Randon	n, 95% CI	
Bode 2013	-0.48	0.0981	425	170	11.2%	-0.48 [-0.67, -0.29]		•		
Cusi 2019	-0.75	0.1895	24	27	7.9%	-0.75 [-1.12, -0.38]				
Forst 2014 (1)	-0.76	0.23	114	57	6.7%	-0.76 [-1.21, -0.31]		-		
Forst 2014 (2)	-0.62	0.19	113	58	7.9%	-0.62 [-0.99, -0.25]		+		
Kadowaki 2017	-0.87	0.1414	70	68	9.6%	-0.87 [-1.15, -0.59]		*		
Lavalle-Gonzalez 2013A	-0.7	0.0663	725	181	12.2%	-0.70 [-0.83, -0.57]		•		
Mahaffey 2018	-0.39	0.0283	5795	4347	13.0%	-0.39 [-0.45, -0.33]		•		
Rodbard 2016	-0.89	0.1531	99	94	9.2%	-0.89 [-1.19, -0.59]		-		
Wilding 2013A (3)	-0.75	0.102	155	75	11.1%	-0.75 [-0.95, -0.55]		•		
Wilding 2013A (4)	-0.97	0.102	152	75	11.1%	-0.97 [-1.17, -0.77]		*		
Total (95% CI)			7672	5152	100.0%	-0.71 [-0.87, -0.54]		•		
Heterogeneity: Tau² = 0.09		9 (P < 0.	00001); I² = 879	%			-10	-5	<u> </u>	10
Test for overall effect: Z =	8.36 (P < 0.00001)							vours Canagliflozin	Favours Placebo	

Footnotes

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

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

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

	•		Canagliflozin	Placebo		Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Cusi 2019	-3.4	0.9431	24	27	5.2%	-3.40 [-5.25, -1.55]	
Forst 2014	-3.2	0.1533	227	115	15.8%	-3.20 [-3.50, -2.90]	•
Kadowaki 2017	-1.51	0.3183	69	67	13.4%	-1.51 [-2.13, -0.89]	
Lavalle-Gonzalez 2013A	-2.4	0.245	725	181	14.6%	-2.40 [-2.88, -1.92]	-
Mahaffey 2018	-2.4	0.1204	5795	4347	16.2%	-2.40 [-2.64, -2.16]	•
Rodbard 2016	-1.55	0.4337	103	104	11.4%	-1.55 [-2.40, -0.70]	
Wilding 2013A (1)	-2.05	0.4337	154	75	11.4%	-2.05 [-2.90, -1.20]	
Wilding 2013A (2)	-1	0.4082	156	75	11.9%	-1.00 [-1.80, -0.20]	
Total (95% CI)			7253	4991	100.0%	-2.16 [-2.67, -1.65]	•
Heterogeneity: Tau ² = 0.40	; Chi² = 51.57, df = 1	7 (P < 0.	00001); I ² = 869	Х6			
Test for overall effect: Z = 8	.30 (P < 0.00001)						-10 -5 0 5 10 Favours Canagliflozin Favours Placebo

Footnotes

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

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

K.1.5.2 Adding canagliflozin compared to adding semaglutide

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

K.1.5.3 Adding canagliflozin compared to adding sitagliptin

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

K.1.5.4 Adding dapagliflozin compared to adding placebo

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

			Dapagliflozin	Placebo		Mean Difference			Mean Di	fference		
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Fixed, 95% CI			IV, Fixed	I, 95% CI		
Bolinder 2012	-0.013	0.0273	68	70	46.6%	-0.01 [-0.07, 0.04]						
Matthaei 2015B	0.02	0.0255	108	108	53.4%	0.02 [-0.03, 0.07]			•			
Total (95% CI)			176	178	100.0%	0.00 [-0.03, 0.04]						
Heterogeneity: Chi² = Test for overall effect:			%				-10	-5 Favours D	(apagliflozin) Favours PI	5 acebo	10

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

	Dapaglit	flozin	Place	bo		Risk Difference		Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Bailey 2010	2	409	1	137	2.0%	-0.00 [-0.02, 0.01]		+
Bolinder 2012	1	91	0	91	0.9%	0.01 [-0.02, 0.04]		+
Jabbour 2014	0	225	1	226	2.2%	-0.00 [-0.02, 0.01]		†
Mathieu 2015A	1	160	0	160	1.5%	0.01 [-0.01, 0.02]		†
Matthaei 2015B	0	109	0	109	1.0%	0.00 [-0.02, 0.02]		†
Rosenstock 2012	1	281	0	139	1.8%	0.00 [-0.01, 0.02]		†
Strojek 2011	3	450	0	146	2.1%	0.01 [-0.01, 0.02]		†
Wilding 2012	3	610	0	197	2.9%	0.00 [-0.00, 0.01]		<u> </u>
Wiviott 2019	529	8582	570	8578	82.5%	-0.00 [-0.01, 0.00]		
Yang 2016	0	297	0	145	1.9%	0.00 [-0.01, 0.01]		†
Yang 2018A	0	139	0	133	1.3%	0.00 [-0.01, 0.01]		†
Total (95% CI)		11353		10061	100.0%	-0.00 [-0.01, 0.00]		
Total events	540		572					
Heterogeneity: Chi²=	10.18, df	= 10 (P =	= 0.42); l²	= 2%			H	-0.5 0 0.5 1
Test for overall effect:	Z = 1.15 (P = 0.25)				-1	-0.5 0 0.5 1 Favours Dapagliflozin Favours Placebo

Figure 251: Cardiovascular mortality at end of follow up

.ga.o _ 0 o.					ity at	Dick Difference	•
	Dapagli	IIOZIII	Place	DO		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Bailey 2010	2	409	2	137	2.1%	-0.01 [-0.03, 0.01]	+
Matthaei 2015B	0	109	0	109	1.1%	0.00 [-0.02, 0.02]	†
Strojek 2011	2	450	0	146	2.3%	0.00 [-0.01, 0.02]	†
Wilding 2012	3	610	0	197	3.1%	0.00 [-0.00, 0.01]	<u>+</u>
Wiviott 2019	245	8582	249	8578	88.1%	-0.00 [-0.01, 0.00]	
Yang 2016	0	297	0	145	2.0%	0.00 [-0.01, 0.01]	†
Yang 2018A	0	139	0	133	1.4%	0.00 [-0.01, 0.01]	†
Total (95% CI)		10596		9445	100.0%	-0.00 [-0.00, 0.00]	
Total events	252		251				
Heterogeneity: Chi ² =	2.69 df=	6/P = 0	85): 13=	N96			
				0 70			-1 -0.5 0 0.5
Test for overall effect:	Z = 0.17 (P = 0.87)				Favours Dapagliflozin Favours Placebo

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

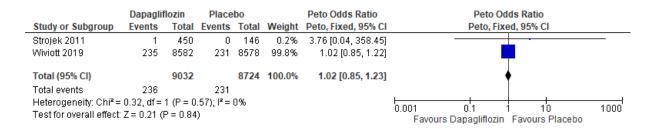


Figure 253: Persistent signs of worsening kidney disease at end of follow up

	Dapagli	flozin	Place	bo		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
Bailey 2010	12	409	2	137	1.3%	2.01 [0.46, 8.87]	- ·	
Strojek 2011	2	450	3	146	1.9%	0.22 [0.04, 1.28]		
Wilding 2012	15	610	4	197	2.6%	1.21 [0.41, 3.61]		
Wiviott 2019	120	8582	221	8578	94.2%	0.54 [0.44, 0.68]	•	
Total (95% CI)		10051		9058	100.0%	0.57 [0.46, 0.71]	•	
Total events	149		230					
Heterogeneity: Chi² =	5.94, df=	3(P = 0)	.11); l² =	49%			0.01 0.1 1 10	100
Test for overall effect:	Z = 5.20 (P < 0.00	001)				Favours Dapagliflozin Favours Placebo	100

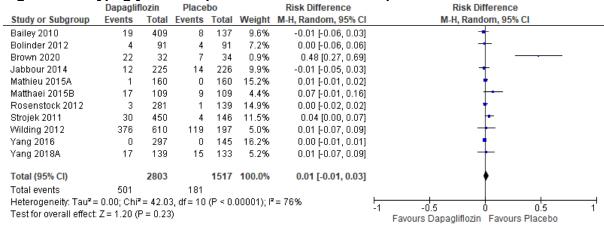
Figure 254: Development of end stage kidney disease at end of follow up

	Dapaglit	flozin	Place	ebo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Wiviott 2019	6	8582	19	8578	96.3%	-0.00 [-0.00, -0.00]	
Yang 2016	0	297	0	145	2.2%	0.00 [-0.01, 0.01]	†
Yang 2018A	1	139	1	133	1.5%	-0.00 [-0.02, 0.02]	†
Total (95% CI)		9018		8856	100.0%	-0.00 [-0.00, -0.00]	
Total events	7		20				
Heterogeneity: Chi²=	0.09, df=	2(P = 0)	.95); l² =		-1 -0.5 0 0.5 1		
Test for overall effect	Z = 2.46 (P = 0.01)				Favours Dapagliflozin Favours Placebo

Figure 255: Diabetic ketoacidosis at end of follow up

	Dapagli	flozin	Place	bo		Risk Difference		Risk Difference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Brown 2020	0	32	0	34	0.4%	0.00 [-0.06, 0.06]		<u>±</u>	
Wiviott 2019	27	8582	12	8578	98.1%	0.00 [0.00, 0.00]			
Yang 2018A	0	139	0	133	1.6%	0.00 [-0.01, 0.01]		Ŧ	
Total (95% CI)		8753		8745	100.0%	0.00 [0.00, 0.00]			
Total events	27		12						
Heterogeneity: Chi ² =	= 0.06, df=	2(P = 0)	.97); l ² =		<u> </u>	-0.5 0 0.5			
Test for overall effect	: Z = 2.34 (P = 0.02	2)			-1	Favours Danadiflozin Favours Placeho	'	

Figure 256: Hypoglycaemia episodes at end of follow up



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

Figure 257: Severe hypoglycaemic episodes at end of follow up

	Dapaglit	flozin	Place	ebo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	I M-H, Fixed, 95% CI
Bailey 2010	0	409	0	137	2.0%	0.00 [-0.01, 0.01]]
Bolinder 2012	0	91	0	91	0.9%	0.00 [-0.02, 0.02]	1 +
Jabbour 2014	1	225	1	226	2.2%	0.00 [-0.01, 0.01]	1
Mathieu 2015A	0	160	0	160	1.5%	0.00 [-0.01, 0.01]]
Matthaei 2015B	0	109	0	109	1.0%	0.00 [-0.02, 0.02]	1 †
Rosenstock 2012	0	281	0	139	1.8%	0.00 [-0.01, 0.01]	1 †
Strojek 2011	1	450	0	146	2.1%	0.00 [-0.01, 0.01]	1
Wilding 2012	2	610	0	197	2.9%	0.00 [-0.01, 0.01]	1 <u>+</u>
Wiviott 2019	58	8582	83	8578	82.5%	-0.00 [-0.01, -0.00]]
Yang 2016	0	297	0	145	1.9%	0.00 [-0.01, 0.01]]
Yang 2018A	0	139	0	133	1.3%	0.00 [-0.01, 0.01]	1 †
Total (95% CI)		11353		10061	100.0%	-0.00 [-0.00, 0.00]	1
Total events	62		84				
Heterogeneity: Chi²=	3.45, df=	10 (P=	0.97); l² =	: 0%			1 05 0 05 1
Test for overall effect:	Z = 1.91 (P = 0.06)				-1 -0.5 0 0.5 1
	,		•				Favours Dapagliflozin Favours Placebo

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

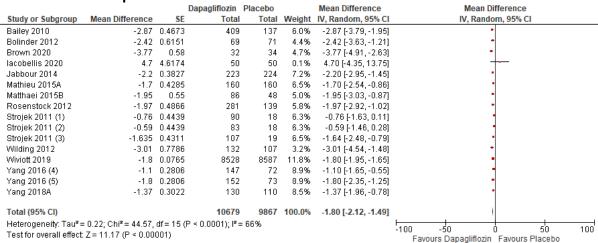
•			Dapagliflozin	Placebo		Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Bailey 2010	-0.627	0.1211	409	137	5.3%	-0.63 [-0.86, -0.39]	•
Bolinder 2012	-0.418	0.0995	60	49	6.1%	-0.42 [-0.61, -0.22]	•
lacobellis 2020	-0.3	0.153	50	50	4.2%	-0.30 [-0.60, -0.00]	<u>*</u>
Jabbour 2014	-0.7	0.102	223	224	6.0%	-0.70 [-0.90, -0.50]	•
Mathieu 2015A	-0.805	0.1313	160	160	4.9%	-0.81 [-1.06, -0.55]	+
Matthaei 2015B	-0.7	0.1414	84	48	4.6%	-0.70 [-0.98, -0.42]	+
Rosenstock 2012	-0.54	0.0963	281	139	6.2%	-0.54 [-0.73, -0.35]	•
Strojek 2011 (1)	-0.37	0.1173	83	19	5.4%	-0.37 [-0.60, -0.14]	•
Strojek 2011 (2)	-0.7	0.1173	107	18	5.4%	-0.70 [-0.93, -0.47]	•
Strojek 2011 (3)	-0.525	0.1148	90	18	5.5%	-0.53 [-0.75, -0.30]	+
Wilding 2012 (4)	-0.385	0.1046	128	36	5.9%	-0.39 [-0.59, -0.18]	•
Wilding 2012 (5)	-0.35	0.102	139	36	6.0%	-0.35 [-0.55, -0.15]	•
Wilding 2012 (6)	-0.21	0.102	132	35	6.0%	-0.21 [-0.41, -0.01]	•
Wiviott 2019	-0.42	0.0128	8528	8587	9.1%	-0.42 [-0.45, -0.39]	•
Yang 2016 (7)	-0.59	0.0867	147	73	6.6%	-0.59 [-0.76, -0.42]	•
Yang 2016 (8)	-0.62	0.0867	152	72	6.6%	-0.62 [-0.79, -0.45]	•
Yang 2018A	-0.9	0.0965	130	110	6.2%	-0.90 [-1.09, -0.71]	*
Total (95% CI)			10903	9811	100.0%	-0.54 [-0.62, -0.45]	•
Heterogeneity: Tau ² :	= 0.02; Chi ² = 66.26,	df = 16 (i	P < 0.00001); P	= 76%			
Test for overall effect		,					-10 -5 0 5 10
	,						Favours Dapagliflozin Favours Placebo

Footnotes

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

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

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

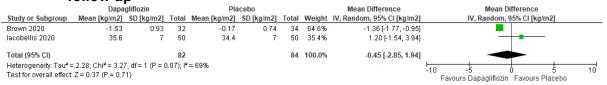


<u>Footnotes</u>

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

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

Figure 260: BMI change (kg/m², lower values are better, change scores) at end of follow up



K.1.5.5 Adding dapagliflozin compared to adding exenatide

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

K.1.5.6 Adding dapagliflozin compared to adding liraglutide

Figure 261: Severe hypoglycaemic episodes at end of follow up

	Dapaglif	lozin	Liraglu	ıtide		Risk Difference		Risk Dif	ference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	ed, 95% CI	
Hao 2022	0	166	0	143	66.3%	0.00 [-0.01, 0.01]				
Jiang 2021B	0	79	0	77	33.7%	0.00 [-0.02, 0.02]		•	•	
Total (95% CI)		245		220	100.0%	0.00 [-0.01, 0.01]				
Total events	0		0							
Heterogeneity: Chi²=	0.00, df =	1 (P = 1	=1;(00.	0%			<u> </u>	-0.5	 D 0.5	
Test for overall effect:	Z = 0.00 (F	P = 1.00))				-1	Favours Dapagliflozin		'

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



K.1.5.7 Adding dapagliflozin compared to adding saxagliptin

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



Figure 264: Cardiovascular mortality at end of follow up



Figure 265: Hypoglycaemia episodes at end of follow up

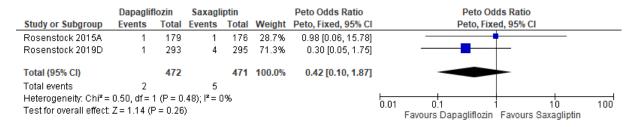


Figure 266: Severe hypoglycaemic episodes at end of follow up

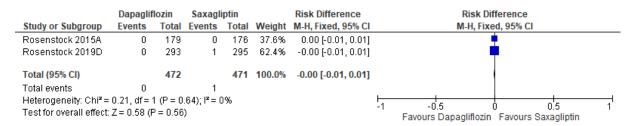
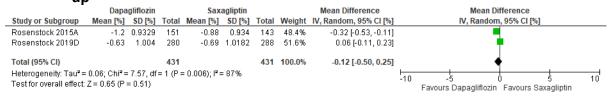


Figure 267: HbA1c change (%, lower values are better, change scores) at end of follow



K.1.5.8 Adding dapagliflozin compared to adding sitagliptin

Figure 268: Hypoglycaemia episodes at end of follow up

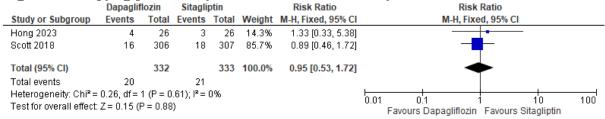


Figure 269: Severe hypoglycaemic episodes at end of follow up

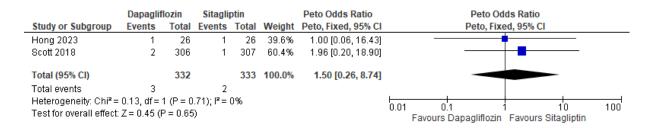
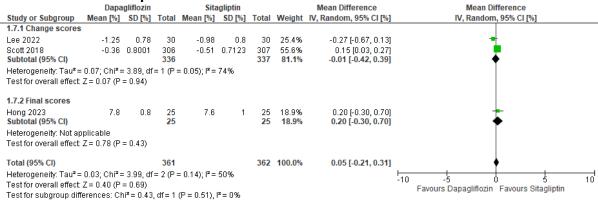


Figure 270: HbA1c change (%, lower values are better, change and final scores) at end of follow up



K.1.5.9 Adding empagliflozin compared to adding placebo

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

				_			
	Empagli	flozin	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Ferdinand 2019	0	80	0	77	4.7%	0.00 [-0.02, 0.02]	+
Haring 2013	1	441	0	225	17.7%	0.00 [-0.01, 0.01]	†
Haring 2014	0	431	0	206	16.6%	0.00 [-0.01, 0.01]	†
Kovacs 2014	4	333	1	165	13.1%	0.01 [-0.01, 0.02]	†
Rosenstock 2014B	1	375	0	188	14.9%	0.00 [-0.01, 0.01]	†
Rosenstock 2015B	0	324	1	170	13.3%	-0.01 [-0.02, 0.01]	†
Softeland 2017	0	222	0	110	8.8%	0.00 [-0.01, 0.01]	†
Sone 2019	1	176	0	90	7.1%	0.01 [-0.01, 0.03]	+
Yabe 2023	0	65	1	64	3.8%	-0.02 [-0.06, 0.03]	+
Total (95% CI)		2447		1295	100.0%	0.00 [-0.00, 0.01]	
Total events	7		3				
Heterogeneity: Chi ² =	2.33, df=	8 (P = 0	.97); ² =	0%			I
Test for overall effect	•	,					-1 -0.5 0 0.5 1
. COLICI CYCIAII CIICOL	0.20 (= 5.00	/				Favours Empagliflozin Favours Placebo

Figure 272: Cardiovascular mortality at end of follow up

	Empagli	flozin	Place	bo		Risk Difference		Risk Difference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Ferdinand 2019	0	80	0	77	8.5%	0.00 [-0.02, 0.02]		+	
Haring 2013	1	441	0	225	32.2%	0.00 [-0.01, 0.01]		•	
Haring 2014	0	431	0	206	30.1%	0.00 [-0.01, 0.01]		•	
Kawamori 2018	1	182	0	93	13.3%	0.01 [-0.01, 0.03]		<u>†</u>	
Softeland 2017	0	222	0	110	15.9%	0.00 [-0.01, 0.01]		†	
Total (95% CI)		1356		711	100.0%	0.00 [-0.00, 0.01]			
Total events	2		0						
Heterogeneity: Chi²=	0.40, df =	4 (P = 0)	.98); I²=	0%			H_	-0.5 0 0.5	
Test for overall effect:	Z = 0.54 (8	P = 0.59)				-1	-0.5 0 0.5 Favours Empagliflozin Favours Placebo	'



	Empagli	flozin	Place	bo		Risk Difference		Risk Difference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Ji 2023	3	146	0	73	44.2%	0.02 [-0.01, 0.05]		+	
Kawamori 2018	0	182	0	93	55.8%	0.00 [-0.02, 0.02]		*	
Total (95% CI)		328		166	100.0%	0.01 [-0.01, 0.03]		•	
Total events	3		0						
Heterogeneity: Chi²=	1.69, df=	1 (P = 0)	.19); (21.	41%			H	-0.5 0 0.5	
Test for overall effect	Z = 1.07 (8)	P = 0.29)				-1	Favours Empagliflozin Favours Placebo	'

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

	Empagli	flozin	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Ferdinand 2019	0	80	0	77	54.9%	0.00 [-0.02, 0.02]	•
Yabe 2023	0	65	0	64	45.1%	0.00 [-0.03, 0.03]	•
Total (95% CI)		145		141	100.0%	0.00 [-0.02, 0.02]	•
Total events	0		0				
Heterogeneity: Chi ² =	0.00, df =	1 (P = 1	$= ^{2}l;(00)$	0%			1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1
Test for overall effect:	Z = 0.00 (F	P = 1.00)				-1 -0.5 0 0.5 1 Favours Empagliflozin Favours Placebo

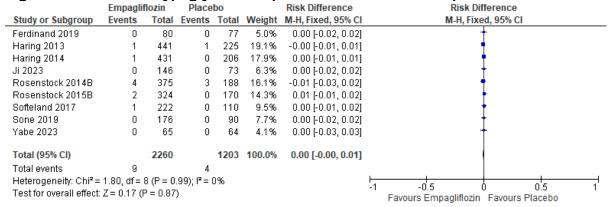
Figure 275: Diabetic ketoacidosis at end of follow up

	Empagli	flozin	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Ferdinand 2019	0	80	0	77	9.2%	0.00 [-0.02, 0.02]	+
Ji 2023	0	146	0	73	11.4%	0.00 [-0.02, 0.02]	†
Kawamori 2018	0	182	0	93	14.4%	0.00 [-0.02, 0.02]	<u> </u>
Rosenstock 2015B	0	324	0	170	26.2%	0.00 [-0.01, 0.01]	•
Softeland 2017	0	222	0	110	17.3%	0.00 [-0.01, 0.01]	•
Sone 2019	0	176	1	90	14.0%	-0.01 [-0.04, 0.02]	+
Yabe 2023	0	65	0	64	7.6%	0.00 [-0.03, 0.03]	†
Total (95% CI)		1195		677	100.0%	-0.00 [-0.01, 0.01]	
Total events	0		1				
Heterogeneity: Chi²=	0.71, df=	6 (P = 0)	$.99); I^2 = I$	0%			-1 -0.5 0 0.5 1
Test for overall effect:	Z = 0.44 (F	o = 0.66)				Favours Empagliflozin Favours Placebo

Figure 276: Hypoglycaemia episodes at end of follow up

_	<i>-</i>	, ,					•
	Empagli	flozin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Babar 2021	8	120	6	120	1.8%	1.33 [0.48, 3.73]	
Ferdinand 2019	3	80	0	77	0.2%	6.74 [0.35, 128.38]	
Haring 2013	95	441	35	225	14.2%	1.38 [0.97, 1.97]	 -
Haring 2014	18	431	7	206	2.9%	1.23 [0.52, 2.90]	 -
Ji 2023	20	146	8	73	3.3%	1.25 [0.58, 2.70]	
Kawamori 2018	0	182	1	93	0.6%	0.17 [0.01, 4.16]	
Kovacs 2014	8	333	7	165	2.9%	0.57 [0.21, 1.53]	
Rosenstock 2014B	204	375	109	188	44.4%	0.94 [0.81, 1.09]	•
Rosenstock 2015B	117	324	60	170	24.1%	1.02 [0.80, 1.31]	+
Softeland 2017	3	222	0	110	0.2%	3.48 [0.18, 66.87]	- ·
Sone 2019	40	176	13	90	5.3%	1.57 [0.89, 2.79]	 •
Yabe 2023	1	65	1	64	0.3%	0.98 [0.06, 15.41]	
Total (95% CI)		2895		1581	100.0%	1.08 [0.96, 1.22]	•
Total events	517		247				
Heterogeneity: Chi²=	12.38, df=	= 11 (P =	= 0.34); l ²	= 11%			0.001 0.1 1 10 1000
Test for overall effect:	Z = 1.25 (P = 0.21)				0.001 0.1 1 10 1000 Favours Empagliflozin Favours Placebo
							r avours Empayimozin Favours Flacebo

Figure 277: Severe hypoglycaemic episodes at end of follow up



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

	•		Empagliflozin	Placebo		Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Babar 2021	-1.58	0.0414	120	120	6.6%	-1.58 [-1.66, -1.50]	•
Ferdinand 2019	-0.78	0.198	78	72	5.7%	-0.78 [-1.17, -0.39]	-
Haring 2013	-0.8	0.1224	213	76	6.2%	-0.80 [-1.04, -0.56]	+
Haring 2014	-0.8	0.1227	248	70	6.2%	-0.80 [-1.04, -0.56]	+
Hattori 2018	0.02	0.1715	51	51	5.9%	0.02 [-0.32, 0.36]	+
Ji 2023	-0.99	0.1196	145	73	6.3%	-0.99 [-1.22, -0.76]	+
Kawamori 2018	-1.22	0.1173	182	93	6.3%	-1.22 [-1.45, -0.99]	*
Kovacs 2014 (1)	-0.59	0.09949	165	83	6.4%	-0.59 [-0.78, -0.40]	•
Kovacs 2014 (2)	-0.69	0.096939	168	82	6.4%	-0.69 [-0.88, -0.50]	•
Rosenstock 2014B	-0.41	0.0943	375	188	6.4%	-0.41 [-0.59, -0.23]	•
Rosenstock 2015B	-0.55	0.1227	237	112	6.2%	-0.55 [-0.79, -0.31]	•
Softeland 2017 (3)	-0.7	0.119879	100	44	6.3%	-0.70 [-0.93, -0.47]	+
Softeland 2017 (4)	-0.79	0.119879	100	44	6.3%	-0.79 [-1.02, -0.56]	•
Sone 2019	-0.93	0.0851	176	90	6.4%	-0.93 [-1.10, -0.76]	•
Tanaka 2019	-0.32	0.1212	48	52	6.2%	-0.32 [-0.56, -0.08]	+
Yabe 2023	-0.57	0.11	65	64	6.3%	-0.57 [-0.79, -0.35]	•
Total (95% CI)			2471	1314	100.0%	-0.74 [-0.99, -0.49]	•
Heterogeneity: Tau2:	= 0.25; Chi ^z = 378.23	3, df = 15 (P	< 0.00001); I ² =	96%			-10 -5 0 5 10
Test for overall effect	: Z = 5.77 (P < 0.000	01)					-10 -5 0 5 10 Favours Empagliflozin Favours Placebo
							i avours Empayimozin Favours Flacebo

<u>Footnotes</u>

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

^{(1) 10} mg Empagliflozin v Placebo

^{(2) 25} mg Empagliflozin v Placebo

^{(3) 25} mg Empagliflozin v Placebo

Empagliflozin Placebo Mean Difference Mean Difference Study or Subgroup Mean Difference SE Total Total Weight IV, Random, 95% CI IV, Random, 95% CI -3.8 0.2309 Babar 2021 120 8.3% -3.80 (-4.25, -3.35) Ferdinand 2019 -1.23 0.5869 78 5.3% -1.23 (-2.38, -0.08) Gullaksen 2023 -4.3 1.2784 17 2.0% -4.30 [-6.81, -1.79] 18 Haring 2013 -1.61 0.4527 214 77 6.4% -1.61 [-2.50, -0.72] Haring 2014 -2.4 D 4527 251 70 6.4% -2.40 [-3.29, -1.51] -1.66 [-2.21, -1.11] Ji 2023 -1.66 0.2827 146 73 7.9% Kawamori 2018 93 7.4% -1.53 0.34 182 -1.53 [-2.20, -0.86] -1.9 0.2916 Kovacs 2014 333 165 7.8% -1.90 [-2.47, -1.33] Rosenstock 2014B -2.43 0.5091 375 188 5.9% -2.43 [-3.43, -1.43] Rosenstock 2015B -2.8 0.6123 324 170 5.1% -2.80 [-4.00, -1.60] Softeland 2017 (1) -27 0.36 98 44 7.2% -2.70 [-3.41, -1.99] 97 44 8.8% Softeland 2017 (2) -2.2 0.17 -2.20 [-2.53, -1.87] Sone 2019 -1.85 0.2956 176 90 7.8% -1.85 (-2.43, -1.27) Tanaka 2019 -1.65 0.4862 50 52 6.1% -1.65 [-2.60, -0.70] Yabe 2023 -2.37 0.3539 7.3% -2.37 [-3.06, -1.68] 1340 100.0% -2.22 [-2.62, -1.81] Total (95% CI) 2526 Heterogeneity: Tau 2 = 0.45; Chi 2 = 68.91, df = 14 (P < 0.00001); I^2 = 80% <u>⊢</u> -10 10 Test for overall effect: Z = 10.77 (P < 0.00001) Favours Empagliflozin Favours Placebo

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

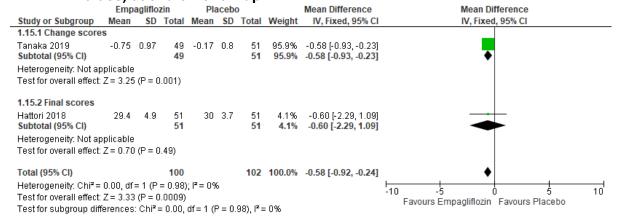
Footnotes

(1) 10 mg Empagliflozin v Placebo

(2) 25 mg Empagliflozin v Placebo

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

Figure 280: BMI change (kg/m², lower values are better, change scores and final values) at end of follow up



K.1.5.10 Adding empagliflozin compared to adding insulin

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

K.1.5.11 Adding empagliflozin compared to adding linagliptin

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

K.1.5.12 Adding empagliflozin compared to adding liraglutide

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

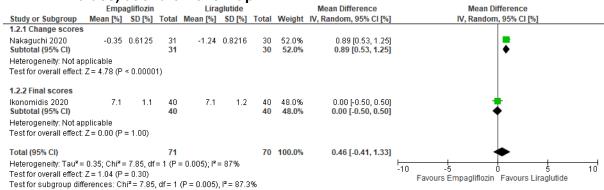


Figure 282: Weight change (kg, lower scores are better, change scores and final values) at end of follow up

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CICILCE	
5% CI [kg]	
-	
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<u> </u>	
5 Favoure Liradutido	10
ravours Erragiunide	
-	% CI [kg]

Figure 283: BMI change (kg/m², lower scores are better, change scores and final values) at end of follow up

	Empa	gliflozin		Lira	glutide			Mean Difference	Mean D	Mean Difference		
Study or Subgroup N	Mean [kg/m2]	SD [kg/m2]	Total	Mean [kg/m2]	SD [kg/m2]	Total	Weight	IV, Random, 95% CI [kg/m2]	IV, Random, 9	95% CI [kg/m2]		
1.4.1 Change scores												
Nakaguchi 2020	-0.6	0.5568	31	-0.5	0.5477	30	62.6%	-0.10 [-0.38, 0.18]				
Subtotal (95% CI)			31			30	62.6%	-0.10 [-0.38, 0.18]	•	†		
Heterogeneity: Not appli	icable											
Test for overall effect: Z =	= 0.71 (P = 0.4	8)										
1.4.2 Final scores												
Ikonomidis 2020	28.4	2	40	29.6	3	40	37.4%	-1.20 [-2.32, -0.08]	-	-		
Subtotal (95% CI)			40			40	37.4%	-1.20 [-2.32, -0.08]	•	4		
Heterogeneity: Not appli	icable											
Test for overall effect: Z =	= 2.10 (P = 0.0	4)										
Total (95% CI)			71			70	100.0%	-0.51 [-1.55, 0.53]	◀	+		
Heterogeneity: Tau ² = 0.	.43; Chi² = 3.51	I, df = 1 (P = 0)	0.06); I ^z	= 71%					10	 	40	
Test for overall effect: Z =	= 0.96 (P = 0.3	4)							-10 -5 Favours Empagliflozin	Favoure Liradutide	10	
Test for subgroup differe	ences: Chi² = 3	3.51, df = 1 (P	= 0.06)), I ² = 71.5%					i avoura Empagiilloziii	i avoura ciragiuliue		

K.1.5.13 Adding empagliflozin compared to adding semaglutide

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

K.1.5.14 Adding empagliflozin compared to adding sitagliptin

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

K.1.5.15 Adding empagliflozin compared to adding vildagliptin

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

K.1.5.16 Adding ertugliflozin compared to adding placebo

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

	Ertuglifl	ozin	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Dagogo-Jack 2017	0	309	0	153	29.0%	0.00 [-0.01, 0.01]	•
Ji 2019	0	339	0	167	31.7%	0.00 [-0.01, 0.01]	•
Rosenstock 2018B	0	412	0	209	39.3%	0.00 [-0.01, 0.01]	<u>†</u>
Total (95% CI)		1060		529	100.0%	0.00 [-0.01, 0.01]	
Total events	0		0				
Heterogeneity: Chi²=	0.00, df =	2 (P = 1)	1.00); I ²=	0%			-1 -05 0 05 1
Test for overall effect:	Z = 0.00 (P = 1.0	0)				-1 -0.5 0 0.5 1 Favours Ertugliflozin Favours Placebo

Figure 285: Cardiovascular mortality at end of follow up

	Ertugliflozin Placebo					Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Dagogo-Jack 2017	0	309	0	153	29.0%	0.00 [-0.01, 0.01]	•
Ji 2019	0	339	0	167	31.7%	0.00 [-0.01, 0.01]	•
Rosenstock 2018B	0	412	0	209	39.3%	0.00 [-0.01, 0.01]	†
Total (95% CI)		1060		529	100.0%	0.00 [-0.01, 0.01]	
Total events	0		0				
Heterogeneity: Chi²=	0.00, df =	2 (P = 1)	1.00); l ² =	0%			-1 -0.5 0 0.5 1
Test for overall effect:	Z = 0.00 (P = 1.0	0)	Favours Ertugliflozin Favours Placebo			

Figure 286: Hypoglycaemia episodes at end of follow up



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

	Ertug	gliflozin		Pla	cebo			Mean Difference	Mean Difference
Study or Subgroup	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV, Fixed, 95% CI [%]	IV, Fixed, 95% CI [%]
Dagogo-Jack 2017	-0.9	0.86	309	-0.3	0.9	153	24.4%	-0.60 [-0.77, -0.43]	•
Ji 2019	-0.95	0.66	339	-0.2	0.65	167	49.2%	-0.75 [-0.87, -0.63]	■
Rosenstock 2018B	-0.8	0.734	412	0	1.1	209	26.4%	-0.80 [-0.97, -0.63]	•
Total (95% CI)			1060			529	100.0%	-0.73 [-0.81, -0.64]	1
Heterogeneity: Chi²=	2.99, df = 2	(P = 0.22)	$2); 1^2 = 3$	33%					-10 -5 0 5 10
Test for overall effect	Z = 16.78 (F	° < 0.000	101)						Favours Ertugliflozin Favours Placebo

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

	•		Ertugliflozin	Placebo		Mean Difference		Mean Di	fference		
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Fixed, 95% CI		IV, Fixed	I, 95% CI		
Dagogo-Jack 2017	-2.15	0.3931	309	153	17.4%	-2.15 [-2.92, -1.38]					
Ji 2019 (1)	-1.8	0.2551	170	84	41.3%	-1.80 [-2.30, -1.30]		-			
Ji 2019 (2)	-2	0.2551	169	83	41.3%	-2.00 [-2.50, -1.50]		-			
Total (95% CI)			648	320	100.0%	-1.94 [-2.26, -1.62]		•			
Heterogeneity: Chi ^z = Test for overall effect:			%				-10	-5 (Favours Ertugliflozin	Favours Plac	cebo	10

Footnotes

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

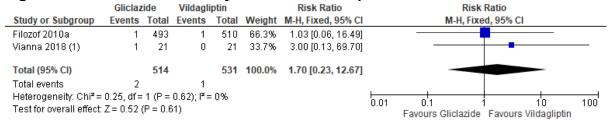
K.1.5.17 Adding ertugliflozin compared to adding sitagliptin

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

K.1.6 Sulfonylureas

K.1.6.1 Adding gliclazide compared to adding vildagliptin

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



<u>Footnotes</u>

(1) Modified release formulation

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

		•									
	Glic	lazide		Vilda	agliptin			Mean Difference		Mean Difference	
Study or Subgroup	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV, Fixed, 95% CI [%]		IV, Fixed, 95% CI [%]	
Filozof 2010a	-0.85	1.19	393	-0.81	1.18	386	91.8%	-0.04 [-0.21, 0.13]			
Vianna 2018	-0.8	0.92	21	-0.39	0.92	21	8.2%	-0.41 [-0.97, 0.15]			
Total (95% CI)			414			407	100.0%	-0.07 [-0.23, 0.09]		•	
Heterogeneity: Chi² = Test for overall effect:		,	1);	36%					-10	-5 0 5 Favours Gliclazide Favours Vildagliptin	10

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

	•		Gliclazide	Vildagliptin		Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Filozof 2010a	1.28	0.39	494	513	96.2%	1.28 [0.52, 2.04]	
Vianna 2018	-0.2	1.9496	18	19	3.8%	-0.20 [-4.02, 3.62]	
Total (95% CI)			512	532	100.0%	1.22 [0.47, 1.97]	•
Heterogeneity: Chi² = Test for overall effect	, ,		%				-10 -5 0 5 10 Favours Gliclazide Favours Vildagliptin

K.1.6.2 Adding glimepiride compared to adding placebo

Figure 292: All-cause mortality

	Glimepri	mide	Place	bo		Risk Difference	Risk Difference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
Riddle 1998	0	70	0	62	43.9%	0.00 [-0.03, 0.03]	•	
Roberts 2005	0	84	0	84	56.1%	0.00 [-0.02, 0.02]	•	
Total (95% CI)		154		146	100.0%	0.00 [-0.02, 0.02]		
Total events	0		0					
Heterogeneity: Chi² =	0.00, df =	1 (P = 1	=°l ;(00.	0%			-1 -05 0 05 1	
Test for overall effect:	Z = 0.00 (F)	° = 1.00)				Favours Glimeprimide Favours Placebo	

Figure 293: Cardiovascular mortality

	Glimepri	mide	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Riddle 1998	0	70	0	62	43.9%	0.00 [-0.03, 0.03]	•
Roberts 2005	0	84	0	84	56.1%	0.00 [-0.02, 0.02]	•
Total (95% CI)		154		146	100.0%	0.00 [-0.02, 0.02]	
Total events	0		0				
Heterogeneity: Chi²=	0.00, df =	1 (P = 1	$(00); I^2 = I$	0%			-1 -05 0 05 1
Test for overall effect:	Z = 0.00 (F	P = 1.00)			Favours Glimeprimide Favours Placebo	

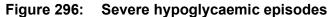
Figure 294: Non-fatal myocardial infarction

	Glimepri	mide	Place	bo		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
Riddle 1998	0	70	1	62	44.3%	0.30 [0.01, 7.13]		
Roberts 2005	1	84	2	84	55.7%	0.50 [0.05, 5.41]		
Total (95% CI)		154		146	100.0%	0.41 [0.06, 2.72]		
Total events	1		3					
Heterogeneity: Chi²=	0.07, df=	1 (P = 0)	$ \mathbf{s}_{0} _{1}^{2} = 1$	0%			0.01 0.1 1 10	100
Test for overall effect:	Z = 0.92 (f	P = 0.36)				0.01 0.1 1 10 Favours Glimeprimide Favours Placet	

Figure 295: Hypoglycaemia episodes

J	<i>J</i> 1 - 1	· ·	-						
	Glimepri	mide	Place	bo		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI		
Ahren 2014	55	307	4	101	24.5%	4.52 [1.68, 12.17]			
Nauck 2009B	58	242	3	121	23.0%	9.67 [3.09, 30.22]			
Riddle 1998	8	70	9	62	25.5%	0.79 [0.32, 1.92]			
Roberts 2005	43	84	7	84	26.9%	6.14 [2.93, 12.87]			
Total (95% CI)		703		368	100.0%	3.75 [1.25, 11.25]	-		
Total events	164		23						
Heterogeneity: Tau ² =	= 1.03; Chi ²	$^2 = 16.98$	3, df = 3 (P = 0.0	007); l²=	82%	0.01 0.1 10	100	
Test for overall effect:	Z = 2.35 (f	P = 0.02)				0.01 0.1 1 10 Favours Glimeprimide Favours Placebo	100	

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



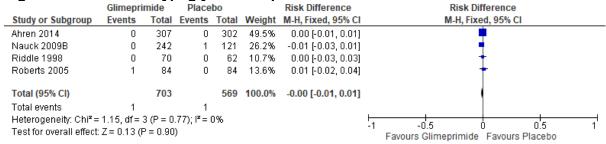
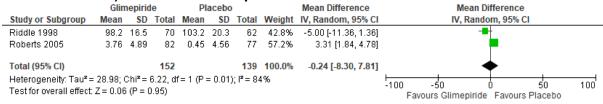


Figure 297: HbA1c change (%, lower values are better, change scores and final values) at end of follow up

	Glimepiride			Pla	aceb	0		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
McCluskey 2004	-1.2	0.5	25	-0.3	0.8	15	21.6%	-0.90 [-1.35, -0.45]	*
Nauck 2009B	-0.5	1.56	242	0.3	1.1	121	26.0%	-0.80 [-1.08, -0.52]	•
Riddle 1998	7.6	0.8	70	7.7	1	62	25.2%	-0.10 [-0.41, 0.21]	*
Roberts 2005	-1.31	0.72	82	-0.33	0.7	77	27.2%	-0.98 [-1.20, -0.76]	•
Total (95% CI)			419			275	100.0%	-0.69 [-1.10, -0.29]	♦
Heterogeneity: Tau² = 0.14; Chi² = 21.41, df = 3 (P < 0.0001); l² Test for overall effect: Z = 3.39 (P = 0.0007)						001); l²	= 86%		-10 -5 0 5 10 Favours Glimepiride Favours Placebo

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

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



K.1.6.3 Adding glimepiride compared to adding metformin

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

K.1.6.4 Adding glimepiride compared to adding insulin

Figure 299: Hypoglycaemia episodes at end of follow up

J	Glimepi	_	Insulin			Risk Ratio	Risk I	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixe	d, 95% CI	
Group 2022	654	1231	474	1245	98.0%	1.40 [1.28, 1.52]			
Moon 2014	19	34	10	38	2.0%	2.12 [1.15, 3.91]		_	
Total (95% CI)		1265		1283	100.0%	1.41 [1.29, 1.54]		•	
Total events	673		484						
Heterogeneity: Chi²= 1	1.78, df=	1 (P = 0)	0.18); l² =	44%			0.01 0.1 1	10	100
Test for overall effect: 2	Z = 7.72 (P < 0.0	0001)				Favours Glimepiride		100

Figure 300: Severe hypoglycaemic episodes at end of follow up

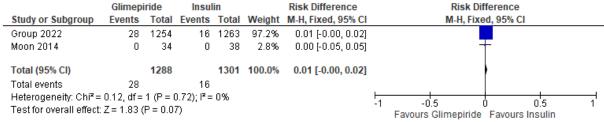
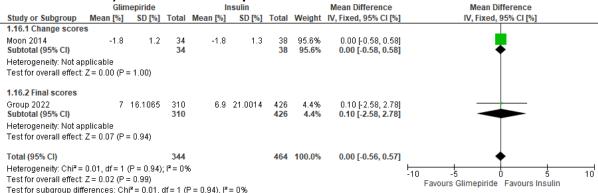


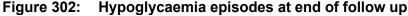
Figure 301: HbA1c change (%, lower values are better, change scores and final values) at end of follow up



K.1.6.5 Adding glimepiride compared to adding canagliflozin

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

K.1.6.6 Adding glimepiride compared to adding dapagliflozin



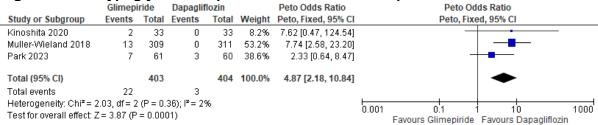


Figure 303: HbA1c change (%, lower values are better, change scores) at end of follow up

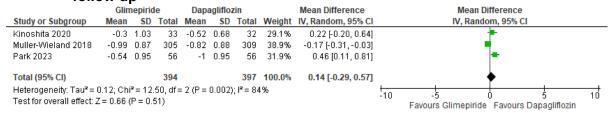


Figure 304: Weight change (kg, lower values are better, change score) at end of follow up

	Glimepiride				aglifloz	zin		Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI		
Kinoshita 2020	-2.8	1.7	33	1.4	2.3	32	33.3%	-4.20 [-5.19, -3.21]		•		
Muller-Wieland 2018	1.8	3.51	308	-3.5	3.53	311	33.5%	5.30 [4.75, 5.85]		•		
Park 2023	1.26	2.67	56	-2.38	2.69	56	33.3%	3.64 [2.65, 4.63]		-		
Total (95% CI)			397			399	100.0%	1.59 [-4.00, 7.18]		*		
Heterogeneity: Tau 2 = 24.22; Chi 2 = 272.29, df = 2 (P < 0.00001); Test for overall effect: Z = 0.56 (P = 0.58)					0001); I	²= 99%		-100	-50 0 50 10 Favours Glimepiride Favours Dapagliflozin	JO		

K.1.6.7 Adding glimepiride compared to adding empagliflozin

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

K.1.6.8 Adding glimepiride compared to adding ertugliflozin

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

K.1.6.9 Adding glimepiride compared to adding exenatide

Figure 305: Hypoglycaemia episodes at end of follow up

	Glimepi	iride	Exena	tide		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
Derosa 2011B	3	54	0	57	0.3%	7.38 [0.39, 139.65]	 	
Gallwitz 2012B	338	508	186	511	99.7%	1.83 [1.60, 2.08]		
Total (95% CI)		562		568	100.0%	1.84 [1.62, 2.10]	•	
Total events	341		186					
Heterogeneity: Chi²=1	0.87, df=	1 (P = 0)	0.35); <mark>I² =</mark>	0%			0.001 0.1 1 10	1000
Test for overall effect: 2	Z= 9.20 (P < 0.0	0001)				Favours Glimepiride Favours Exenatide	1000

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

	Glim	epiride		Exe	natide	Mean Difference	Mean Difference		
Study or Subgroup	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV, Random, 95% CI [%]	IV, Random, 95% CI [%]
Derosa 2011B	7.4	0.2	49	7.5	0.3	52	49.8%	-0.10 [-0.20, -0.00]	
Gallwitz 2012B	-0.21	0.5	197	-0.36	0.44	182	50.2%	0.15 [0.06, 0.24]	•
Total (95% CI)			246			234	100.0%	0.03 [-0.22, 0.27]	•
Heterogeneity: Tau ² =	0.03; Chi ² =	= 12.81, (df = 1 (f	P = 0.0003);	r= 92%	5			10 10 10
Test for overall effect:	Z = 0.20 (P	= 0.84)							-10 -5 0 5 10 Favours Glimeniride Favours Exenatide

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

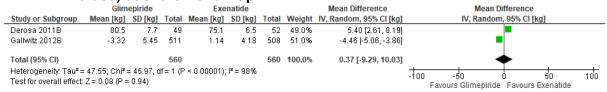
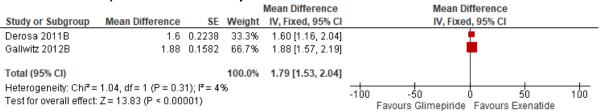


Figure 308: BMI change (kg/m², lower values are better, change scores and final values) at end of follow up



K.1.6.10 Adding glimepiride compared to adding gliclazide

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

K.1.6.11 Adding glimepiride compared to adding linagliptin

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



Figure 310: Cardiovascular mortality at end of follow up

	Glimepi	ride	Linagli	ptin		Risk Ratio			Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H	, Fixed, 95%	CI	
Gallwitz 2012A	2	775	2	776	1.2%	1.00 [0.14, 7.09]			\pm	_	
Rosenstock 2019B	168	3010	169	3023	98.8%	1.00 [0.81, 1.23]					
Total (95% CI)		3785		3799	100.0%	1.00 [0.81, 1.23]			•		
Total events	170		171								
Heterogeneity: Chi² = Test for overall effect:				0%			0.01	0.1 Glimen	iride Linaq	10 liptin	100

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

	Glimepi	ride	Linagli	ptin		Risk Ratio		Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95	% CI	
Gallwitz 2012A	11	775	3	776	35.2%	3.67 [1.03, 13.11]				
Rosenstock 2019B	104	3010	91	3023	64.8%	1.15 [0.87, 1.51]		+		
Total (95% CI)		3785		3799	100.0%	1.73 [0.58, 5.14]		-	-	
Total events	115		94							
Heterogeneity: Tau² = Test for overall effect:				P = 0.08	3); I = 679	6	0.01	0.1 Glimepiride Linag	10 liptin	100

Figure 312: Unstable angina at end of follow up

	Glimep	iride	Linagli	ptin		Risk Ratio		Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	ed, 95% CI		
Gallwitz 2012A	3	775	3	776	4.8%	1.00 [0.20, 4.95]					
Rosenstock 2019B	56	3010	60	3023	95.2%	0.94 [0.65, 1.34]		-			
Total (95% CI)		3785		3799	100.0%	0.94 [0.66, 1.34]		•			
Total events	59		63								
Heterogeneity: Chi ^z = Test for overall effect:				0%			0.01	0.1 Glimepiride		10	100

Figure 313: Hospitalisation for heart failure at follow up

	Glimepi	iride	Linagli	ptin		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Gallwitz 2012A	2	775	3	776	2.6%	0.67 [0.11, 3.98]			
Rosenstock 2019B	92	3010	112	3023	97.4%	0.82 [0.63, 1.08]			
Total (95% CI)		3785		3799	100.0%	0.82 [0.63, 1.07]		•	
Total events	94		115						
Heterogeneity: Chi²=	0.05, df =	1 (P = 1)	0.82); <mark>I²=</mark>	0%			0.01	04 4 40	100
Test for overall effect:	Z = 1.44 (P = 0.1	5)				0.01	0.1 1 10 Glimepiride Linagliptin	100

Figure 314: Hypoglycaemia episodes at end of follow up

	Glimep	iride	Linagli	ptin		Risk Ratio		Ris	sk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Ra	ndom, 95% CI	
Gallwitz 2012A	280	775	58	776	42.2%	4.83 [3.71, 6.30]			-	
Rosenstock 2019B	1132	3010	320	3023	57.8%	3.55 [3.17, 3.98]			•	
Total (95% CI)		3785		3799	100.0%	4.05 [3.00, 5.45]			•	
Total events	1412		378							
Heterogeneity: Tau ² =	•		. ,	P = 0.04	1); $I^2 = 779$	6	0.01	0.1	1 10	100
Test for overall effect:	Z=9.18 (P < 0.0	0001)					Glimepirio	le Linagliptin	

Figure 315: Severe hypoglycaemic episodes at end of follow up

	Glimep	iride	Linagli	ptin		Risk Ratio			Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H	Fixed, 95%	CI	
Gallwitz 2012A	12	775	1	776	9.1%	12.02 [1.57, 92.18]					
Rosenstock 2019B	65	3010	10	3023	90.9%	6.53 [3.36, 12.68]				_	
Total (95% CI)		3785		3799	100.0%	7.03 [3.74, 13.20]				•	
Total events	77		11								
Heterogeneity: Chi²=		,		0%			0.01	0.1	+	10	100
Test for overall effect:	Z = 6.06 ((P < 0.0	UUU1)					Glimepi	ride Linag	liptin	

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

			Glimepiride	Linagliptin		Mean Difference		Mea	an Differei	nce	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI		IV, R	andom, 95	% CI	
Gallwitz 2012A	-0.2	0.05	755	764	48.2%	-0.20 [-0.30, -0.10]			•		
Rosenstock 2019B	0.0088	0.03	3010	3023	51.8%	0.01 [-0.05, 0.07]			•		
Total (95% CI)			3765	3787	100.0%	-0.09 [-0.30, 0.11]			•		
Heterogeneity: Tau² : Test for overall effect			(P = 0.0003);	I²= 92%			-10	-5 Glimepi	0 ride Lina	5 gliptin	10

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

			Glimepiride	Linagliptin		Mean Difference		Me	an Differer	ice	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI		IV, F	Random, 95	% CI	
Gallwitz 2012A	2.7	0.2551	776	775	48.2%	2.70 [2.20, 3.20]			•		
Rosenstock 2019B	1.54	0.1327	3010	3023	51.8%	1.54 [1.28, 1.80]			•		
Total (95% CI)			3786	3798	100.0%	2.10 [0.96, 3.24]					
Heterogeneity: Tau² : Test for overall effect			< 0.0001); l² =	= 94%			-100	-50 Glimep	0 Diride Lina	50 gliptin	100

K.1.6.12 Adding glimepiride compared to adding liraglutide

Figure 318: Hypoglycaemia episodes at end of follow up

J	<i>J</i> 1	J					
	Glimepi	Glimepiride Liraglutide				Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Group 2022	654	1231	312	1233	55.4%	2.10 [1.88, 2.34]	
Nauck 2009b	6	242	32	724	44.6%	0.56 [0.24, 1.33]	ı - •
Total (95% CI)		1473		1957	100.0%	1.17 [0.32, 4.24]	
Total events	660		344				
Heterogeneity: Tau ² =	0.78; Chi	$^2 = 8.99$	9, df = 1 (F	P = 0.00	i3); l² = 89	3%	0.01 0.1 1 10 100
Test for overall effect:	Z = 0.23 (P = 0.8	2)				Favours Glimepiride Favours Liraglutide

Figure 319: Severe hypoglycaemic episodes at end of follow up

	Glimepi	iride	Liraglu	tide		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	ed, 95% CI	
Group 2022	28	1254	12	1262	94.1%	2.35 [1.20, 4.60]				
Nauck 2009b	0	242	1	724	5.9%	0.99 [0.04, 24.33]				
Total (95% CI)		1496		1986	100.0%	2.27 [1.18, 4.37]			•	
Total events	28		13							
Heterogeneity: Chi²=	0.27, df =	1 (P = 0)	0.61); l² =	0%			0.01	0.1	10	100
Test for overall effect:	Z = 2.45 (P = 0.0	1)				0.01	Favours Glimepiride		100

K.1.6.13 Adding glimepiride compared to adding saxagliptin

Figure 320: Hypoglycaemia episodes at end of follow up

_	Glimep	iride	Saxagl	iptin		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	ed, 95% CI	
Gu 2019	24	188	6	191	22.1%	4.06 [1.70, 9.72]				
Schernthaner 2015A	125	359	21	359	77.9%	5.95 [3.84, 9.23]			-	
Total (95% CI)		547		550	100.0%	5.54 [3.74, 8.18]			•	
Total events	149		27							
Heterogeneity: Chi² = 0	0.59, df = 1	I(P = 0.	$(44); I^2 = 0$	0%			0.04	04	1, 1,	100
Test for overall effect: 2	Z = 8.58 (F	o.00	001)				0.01	0.1 Favours Glimepiride	1 10 Favours Saxagliptin	100

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

	Glim	epiride		Sax	agliptin			Mean Difference		Mean Dif	ference	•	
Study or Subgroup	Mean [kg]	SD [kg]	Total	Mean [kg]	SD [kg]	Total	Weight	IV, Fixed, 95% CI [kg]		IV, Fixed, 9	5% CI [k	(g]	
Gu 2019	0.9	2.8	187	-0.7	2.6	186	48.2%	1.60 [1.05, 2.15]					
Schernthaner 2015A	1	3	285	-0.8	3.45	289	51.8%	1.80 [1.27, 2.33]					
Total (95% CI)			472			475	100.0%	1.70 [1.32, 2.08]					
Heterogeneity: Chi² = 0 Test for overall effect: 2			²= 0%						-100	-50 C Favours Glimepiride	Favour	50 s Saxagliptin	100

K.1.6.14 Adding glimepiride compared to adding sitagliptin

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

_	Glimepiride Sitagliptin				Risk Ratio	Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	ed, 95% CI	
Arechavaleta 2011	1	519	0	516	1.2%	2.98 [0.12, 73.05]			<u> </u>	
Group 2022	43	1254	41	1267	98.8%	1.06 [0.70, 1.61]		-	-	
Total (95% CI)		1773		1783	100.0%	1.08 [0.71, 1.64]		•	•	
Total events	44		41							
Heterogeneity: Chi ² =	0.40, df=	1 (P = 0)	0.53); <mark>l² =</mark>	0%			0.01	01	1 10	100
Test for overall effect:	Z= 0.38 (P = 0.7	1)				0.01	Favours Glimepiride		100

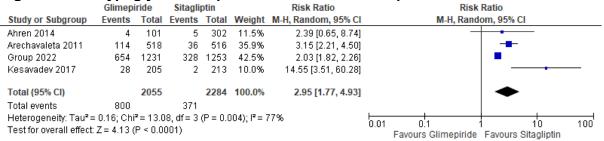
Figure 323: Cardiovascular mortality at end of follow up

_	Glimep	iride	Sitagli	ptin	_	Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	ed, 95% CI	
Arechavaleta 2011	1	519	0	516	2.3%	2.98 [0.12, 73.05]				
Group 2022	16	1244	21	1262	97.7%	0.77 [0.41, 1.47]		-	-	
Total (95% CI)		1763		1778	100.0%	0.82 [0.44, 1.54]		<	-	
Total events	17		21							
Heterogeneity: Chi ² =	0.66, df =	1 (P = 0)	0.42); $I^2 =$	0%					1 10	100
Test for overall effect:	Z = 0.60 (P = 0.5	5)				0.01	Favours Glimepiride	1 10 Favours Sitagliptin	100

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

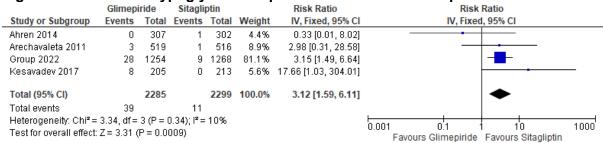
	Glimep	iride	Sitagli	ptin		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Group 2022	30	1244	30	1262	98.4%	0.00 [-0.01, 0.01]	
Xiao 2016	0	18	0	23	1.6%	0.00 [-0.09, 0.09]	
Total (95% CI)		1262		1285	100.0%	0.00 [-0.01, 0.01]	
Total events	30		30				
Heterogeneity: Chi²=	= 0.00, df=	1 (P = 0)	0.99); l² =	0%			-1 -0.5 0 0.5 1
Test for overall effect	Z = 0.06 ((P = 0.9)	6)				Favours Glimepiride Favours Sitagliptin

Figure 325: Hypoglycaemia episodes at end of follow up



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

Figure 326: Severe hypoglycaemic episodes at end of follow up



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

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

	Glimepiride Sitagliptin							Mean Difference	Mean Difference
Study or Subgroup	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV, Random, 95% CI [%]	IV, Random, 95% CI [%]
Arechavaleta 2011	-0.52	1.15	509	-0.46	0.92	509	36.7%	-0.06 [-0.19, 0.07]	•
Group 2022	7	16.1065	310	7	15.4107	284	1.7%	0.00 [-2.54, 2.54]	
Kesavadev 2017	-0.31	0.65	205	-0.7	0.63	213	36.8%	0.39 [0.27, 0.51]	<u> </u>
Xiao 2016	6.47	0.7	18	6.25	0.62	23	24.8%	0.22 [-0.19, 0.63]	†
Total (95% CI)			1042			1029	100.0%	0.18 [-0.17, 0.52]	•
Heterogeneity: Tau² = Test for overall effect:			= 3 (P	< 0.0001); i²	²= 88%				-10 -5 0 5 10 Favours Glimepiride Favours Sitagliptin

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

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

	Glimepiride Sitagliptin							Mean Difference	Mean Difference
Study or Subgroup	Mean [kg]	SD [kg]	Total	Mean [kg]	SD [kg]	Total	Weight	IV, Random, 95% CI [kg]	IV, Random, 95% CI [kg]
Arechavaleta 2011	1.2	3.47	516	-0.8	3.47	516	43.5%	2.00 [1.58, 2.42]	•
Kesavadev 2017	0.54	1.86	205	-0.3	1.79	213	44.5%	0.84 [0.49, 1.19]	•
Xiao 2016	78.1	4.3	18	75.8	4	23	12.0%	2.30 [-0.27, 4.87]	•
Total (95% CI)			739			752	100.0%	1.52 [0.48, 2.56]	
Heterogeneity: Tau² = Test for overall effect:			= 2 (P =	= 0.0001); l² =	= 89%				-100 -50 0 50 100 Favours Glimepiride Favours Sitagliptin

K.1.6.15 Adding glimepiride compared to adding vildagliptin

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

	Glimepi	iride	Vildagli	iptin		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	ed, 95% CI	
Ferrannini 2009	3	1383	2	1389	22.2%	1.51 [0.25, 9.00]			-	
Matthews 2010	6	1546	7	1553	77.8%	0.86 [0.29, 2.56]			_	
Total (95% CI)		2929		2942	100.0%	1.00 [0.40, 2.53]		⋖		
Total events	9		9							
Heterogeneity: Chi² = Test for overall effect:		,		0%			0.01	0.1 Favours Glimepiride	1 10 Favours Vildagliptin	100

Figure 330: Hypoglycaemia episodes at end of follow up

	Glimepi	iride	Vildagli	iptin		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	ed, 95% CI	
Ferrannini 2009	224	1383	23	1389	39.7%	9.78 [6.41, 14.93]			-	
Matthews 2010	281	1546	35	1553	60.3%	8.06 [5.72, 11.38]			-	
Total (95% CI)		2929		2942	100.0%	8.75 [6.70, 11.42]			•	
Total events	505		58							
Heterogeneity: Chiz=	0.48, df =	1 (P = 0)	0.49); $I^2 =$	0%					<u> </u>	400
Test for overall effect:	Z=15.93	(P < 0.	00001)				0.01	0.1 Favours Glimepiride	Tu Favours Vildagliptin	100

Figure 331: Severe hypoglycaemic episodes at end of follow up

	Glimep	iride	Vildagli	iptin		Risk Difference		Risi	(Differen	ce	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H,	Fixed, 959	% CI	
Berndt-Zipfel 2013	0	22	0	22	1.4%	0.00 [-0.08, 0.08]			\pm		
Matthews 2010	15	1546	0	1553	98.6%	0.01 [0.00, 0.01]					
Total (95% CI)		1568		1575	100.0%	0.01 [0.00, 0.01]					
Total events	15		0								
Heterogeneity: Chi ² =	0.05, df =	1 (P = 1)	0.82); $I^2 =$	0%			<u> </u>				
Test for overall effect:	Z=3.66 (P = 0.0	003)				-1	-0.5 Favours Glimepir	u ide Favo	0.5 urs Vildagliptin	1

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

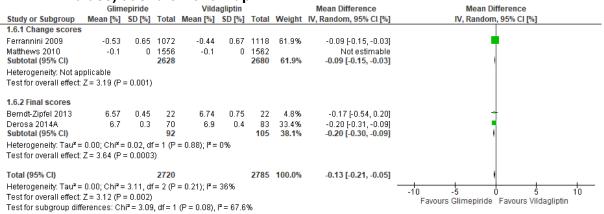
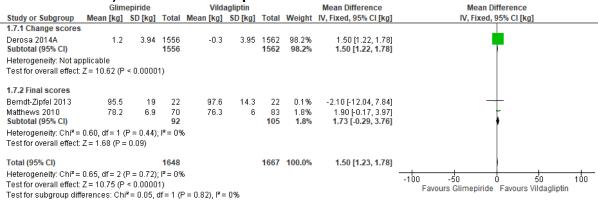


Figure 333: Weight change (kg, lower values are better, change scores and final values) at end of follow up



K.1.6.16 Adding glipizide compared to adding placebo

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

K.1.6.17 Adding glipizide compared to adding metformin

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

K.1.6.18 Adding glipizide compared to adding alogliptin

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

K.1.6.19 Adding glipizide compared to adding dapagliflozin

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

K.1.6.20 Adding glipizide compared to adding saxagliptin

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

K.1.6.21 Adding glipizide compared to adding sitagliptin

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

K.1.7 Thiazolidinediones

K.1.7.1 Adding pioglitazone compared to adding placebo

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

	Pioglita	zone	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events Total		Events Total		Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Charpentier 2009	1	145	0	154	13.3%	0.01 [-0.01, 0.03]	+
Genovese 2013	0	110	0	103	9.5%	0.00 [-0.02, 0.02]	+
Henriksen 2011	0	102	0	106	9.3%	0.00 [-0.02, 0.02]	†
Home 2015	3	277	1	115	14.5%	0.00 [-0.02, 0.02]	+
Mattoo 2005	0	142	1	147	12.9%	-0.01 [-0.03, 0.01]	+
Punthakee 2012	1	392	4	541	40.5%	-0.00 [-0.01, 0.00]	•
Total (95% CI)		1168		1166	100.0%	-0.00 [-0.01, 0.00]	
Total events	5		6				
Heterogeneity: Chi ² =	1.80, df=	5 (P = 0)).88); I² =	0%			1 1 1 1
Test for overall effect:	Z= 0.50 (P = 0.62	2)				-1 -0.5 0 0.5 1 Favours Pioglitazone Favours Placebo

Figure 335: Cardiovascular mortality at end of follow up

	Pioglita	zone	Place	bo		Risk Difference		Risk Difference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Charpentier 2009	1	145	0	154	18.3%	0.01 [-0.01, 0.03]		•	
Genovese 2013	0	110	0	103	13.1%	0.00 [-0.02, 0.02]		†	
Henriksen 2011	0	102	0	106	12.8%	0.00 [-0.02, 0.02]		†	
Punthakee 2012	0	392	1	541	55.8%	-0.00 [-0.01, 0.00]		•	
Total (95% CI)		749		904	100.0%	0.00 [-0.01, 0.01]			
Total events	1		1						
Heterogeneity: Chi ^z =	1.01, df=	3(P = 0)	0.80); I ^z =	0%			<u> </u>	-0.5 0 0.5	_
Test for overall effect:	Z = 0.08 (P = 0.94	4)				-1	-0.5 0 0.5 Favours Pioglitazone Favours Placebo	1

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

i igui c occ.	o-pon	16 1417	70L 0		u 01 10	JIIOW up		
	Pioglita	zone	Place	bo		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	
Home 2015	43	227	10	115	65.5%	2.18 [1.14, 4.17]	-	
Punthakee 2012	2	392	5	541	34.5%	0.55 [0.11, 2.83]		
Total (95% CI)		619		656	100.0%	1.36 [0.38, 4.88]		
Total events	45		15					
Heterogeneity: Tau ²	= 0.54; Chi	² = 2.34	, df = 1 (F	P = 0.13	i); l² = 579	6	0.01 0.1 1 10	100
Test for overall effect	t: $Z = 0.47$ (P = 0.64	4)				Favours Pioglitazone Favours Placebo	100

Figure 337: Non-fatal myocardial infarction at follow up

			- J					
	Piogllita	zone	Place	bo		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
Henriksen 2011	5	102	5	106	70.0%	1.04 [0.31, 3.48]		
Punthakee 2012	0	392	2	541	30.0%	0.28 [0.01, 5.73]		
Total (95% CI)		494		647	100.0%	0.81 [0.27, 2.42]		
Total events	5		7					
Heterogeneity: Chi ² =	0.65, df=	1(P = 0)	$(42); I^2 =$	0%				100
Test for overall effect	Z = 0.38 (F	P = 0.71)				0.01 0.1 1 10 Favours Pioglitazone Favours Placebo	100

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

	Pioglita:	zone	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Charpentier 2009	0	145	0	154	24.7%	0.00 [-0.01, 0.01]	•
Punthakee 2012	2	392	1	541	75.3%	0.00 [-0.00, 0.01]	•
Total (95% CI)		537		695	100.0%	0.00 [-0.00, 0.01]	
Total events	2		1				
Heterogeneity: Chi²=	0.18, df=	1 (P = 0)).68); l² =	0%			-1 -0.5 0 0.5 1
Test for overall effect:	Z = 0.71 (P = 0.48	3)				Favours Pioglitazone Favours Placebo

Figure 339: Hypoglycaemia episodes at end of follow up

	Pioglita:	zone	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Charpentier 2009	35	145	11	154	19.9%	3.38 [1.78, 6.40]	
DePaoli 2014	7	60	0	61	4.1%	15.25 [0.89, 261.16]	
Fernandez 2008	4	10	6	10	16.4%	0.67 [0.27, 1.66]	
Home 2015	87	277	13	115	21.1%	2.78 [1.62, 4.77]	
Kaku 2009A	1	83	0	86	3.4%	3.11 [0.13, 75.21]	
Mattoo 2005	90	142	75	147	24.3%	1.24 [1.02, 1.52]	<u>+</u>
Sridhar 2013	8	25	2	25	10.8%	4.00 [0.94, 17.00]	
Total (95% CI)		742		598	100.0%	2.10 [1.12, 3.95]	•
Total events	232		107				
Heterogeneity: Tau²=	0.42; Chi	= 26.8	6, df = 6 (P = 0.0	1002); l²=	78%	0.01 0.1 1 10 100
Test for overall effect:	Z = 2.31 (P = 0.02	2)				Favours Pioglitazone Favours Placebo

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

Figure 340: Severe hypoglycaemic episodes at end of follow up

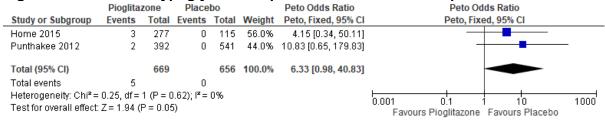


Figure 341: HbA1c change (%, lower values are better, change scores and final values) at end of follow up

	-		Pioglitazone	Placebo		Mean Difference		Mean Difference	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI	
Charpentier 2009	-1.18	0.11	142	147	9.2%	-1.18 [-1.40, -0.96]		•	
DePaoli 2014	-0.76	0.1771	44	41	8.0%	-0.76 [-1.11, -0.41]		+	
Fernandez 2008	-0.3	0.1	10	10	9.3%	-0.30 [-0.50, -0.10]		•	
Genovese 2013	-0.55	0.0957	110	103	9.4%	-0.55 [-0.74, -0.36]		•	
Grey 2014	-0.5	0.1584	43	43	8.4%	-0.50 [-0.81, -0.19]		-	
Henriksen 2011	-1.22	0.24	105	106	6.8%	-1.22 [-1.69, -0.75]		-	
Home 2015	-1.13	0.0987	277	115	9.4%	-1.13 [-1.32, -0.94]		•	
Kaku 2009A	-0.92	0.1325	83	86	8.8%	-0.92 [-1.18, -0.66]		-	
Mattoo 2005	-0.55	0.1203	142	147	9.0%	-0.55 [-0.79, -0.31]		•	
Punthakee 2012	-0.5	0.0656	392	541	9.8%	-0.50 [-0.63, -0.37]		•	
Sridhar 2013	0	0.1281	25	25	8.9%	0.00 [-0.25, 0.25]		†	
Tripathy 2013	-1.2	0.5381	11	9	2.9%	-1.20 [-2.25, -0.15]			
Total (95% CI)			1384	1373	100.0%	-0.70 [-0.91, -0.48]		•	
Heterogeneity: Tau ² =	: 0.12; Chi² = 103.89	l, df = 11	(P < 0.00001);	I ² = 89%			140	<u> </u>	4.0
Test for overall effect:	Z = 6.35 (P < 0.000)	01)					-10	Favours Pioglitazone Favours Placebo	10

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

Figure 342: Weight change (kg, lower values are better, change scores and final values) at end of follow up

-	,			-						
			Pioglitazone	Placebo		Mean Difference		Mean Diffe	rence	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI		IV, Random,	95% CI	
DePaoli 2014	3.83	0.7214	44	41	18.1%	3.83 [2.42, 5.24]		-		
Genovese 2013	2.2	2.1992	110	103	4.5%	2.20 [-2.11, 6.51]		+		
Grey 2014	1.44	0.7824	43	43	17.0%	1.44 [-0.09, 2.97]		•		
Henriksen 2011	4.5	0.6	105	106	20.4%	4.50 [3.32, 5.68]		-		
Home 2015	4.8	0.4472	277	115	23.3%	4.80 [3.92, 5.68]		-		
Mattoo 2005	3.85	4.9767	142	147	1.0%	3.85 [-5.90, 13.60]		+-	_	
Punthakee 2012	2.9	1.1692	392	541	11.4%	2.90 [0.61, 5.19]		-		
Sridhar 2013	2.4	2.4087	25	125	3.9%	2.40 [-2.32, 7.12]		+		
Tripathy 2013	3.1	8.4629	11	9	0.4%	3.10 [-13.49, 19.69]		+	_	
Total (95% CI)			1149	1230	100.0%	3.55 [2.54, 4.55]				
Heterogeneity: Tau ² =			= 0.03); I² = 52°	%			-100 -50		50	100
Test for overall effect	. ∠= 0.93 (P < 0.000	01)					Favours P	ioglitazone F	avours Placebo	

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

Figure 343: BMI change (kg/m², lower values are better, final values) at end of follow

u	·Ρ								
	Piogl	litazone		Pla	icebo			Mean Difference	Mean Difference
Study or Subgroup	Mean [kg/m2]	SD [kg/m2]	Total	Mean [kg/m2]	SD [kg/m2]	Total	Weight	IV, Fixed, 95% CI [kg/m2]	IV, Fixed, 95% CI [kg/m2]
Genovese 2013	32.5	5.6	110	31.9	5.3	103	17.7%	0.60 [-0.86, 2.06]	
Punthakee 2012	31.6	6	392	30.4	5.3	541	68.8%	1.20 [0.46, 1.94]	
Sridhar 2013	26	2.9	25	25.3	3.5	25	12.0%	0.70 [-1.08, 2.48]	
Tripathy 2013	34.2	6.3	11	33	5.4	9	1.4%	1.20 [-3.93, 6.33]	
Total (95% CI)			538			678	100.0%	1.03 [0.42, 1.65]	•
Heterogeneity: Chi ² = Test for overall effect:									-10 -5 0 5 10
restroi overan enect.	2 - 3.23 (1 - 0.0	01)							Favours Pioglitazone Favours Placebo

K.1.7.2 Adding pioglitazone compared to adding metformin

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

				-,			
	Pioglita	zone	Metfor	min		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Hanefeld 2004	1	319	2	320	74.9%	0.51 [0.05, 4.96]	
Morikawa 2011	0	32	1	31	25.1%	0.13 [0.00, 6.61]	-
Total (95% CI)		351		351	100.0%	0.36 [0.05, 2.60]	
Total events	1		3				
Heterogeneity: Chi²=	0.35, df =	1 (P = 0)	0.55); l ^z =	0%			0.001 0.1 1 10 1000
Test for overall effect:	Z = 1.01 (P = 0.31	I)				0.001 0.1 1 10 1000 Pioglitazone Metformin

Figure 345: Hypoglycaemia episodes at end of follow up

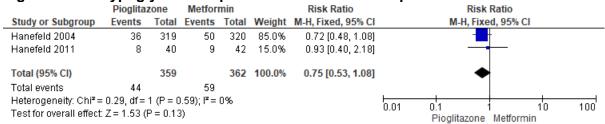


Figure 346: HbA1c change (%, lower values are better, change scores and final values) at end of follow up

7 (4)	acc, at one		oo up	•						
			Pioglitazone	Metformin		Mean Difference		Mean Difference	e	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% (CI	
Hanefeld 2004	0.13	0.09	315	313	45.5%	0.13 [-0.05, 0.31]		•		
Hanefeld 2011	-0.04	0.9841	37	39	0.4%	-0.04 [-1.97, 1.89]				
Kanazawa 2010	0	0.3436	22	23	3.1%	0.00 [-0.67, 0.67]		+		
Morikawa 2011	-0.32	0.234	32	31	6.7%	-0.32 [-0.78, 0.14]		-		
Park 2011	0.1	0.1242	34	33	23.9%	0.10 [-0.14, 0.34]		•		
van der Meer 2009	0.2	0.1404	39	39	18.7%	0.20 [-0.08, 0.48]		•		
Wu 2014	0.1	0.4669	46	47	1.7%	0.10 [-0.82, 1.02]		+		
Total (95% CI)			525	525	100.0%	0.10 [-0.02, 0.22]		•		
Heterogeneity: Chi ² =	3.94, df = 6 (P = 0.6	$(8); I^2 = 0$	%				<u> </u>	<u> </u>	<u> </u>	
Test for overall effect:							-10	-5 U Pioglitazone Metfor	min	10

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

7 4	, .				чP							
	Piogl	litazone		Met	formin			Mean Difference		Mean Diffe	rence	
Study or Subgroup	Mean [kg]	SD [kg]	Total	Mean [kg]	SD [kg]	Total	Weight	IV, Random, 95% CI [kg]		IV, Random, 9	5% CI [kg]	
Kanazawa 2010	61.2	8.8	22	62.7	10.8	23	22.6%	-1.50 [-7.24, 4.24]	-	-		
Roden 2005 1.2	3.06	4.09	316	-1.02	4.11	320	60.4%	4.08 [3.44, 4.72]			-	
van der Meer 2009	94	12.49	39	92	18.73	39	17.0%	2.00 [-5.07, 9.07]			•	
Total (95% CI)			377			382	100.0%	2.47 [-0.96, 5.89]		-		
Heterogeneity: Tau² = Test for overall effect:			2 (P =	0.14); I ² = 49	1%				-10	-5 0 Pioglitazone M	5 letformin	10

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

_	٦.									
	Piog	litazone		Met	formin			Mean Difference	Mean Difference	
Study or Subgroup	Mean [kg/m2]	SD [kg/m2]	Total	Mean [kg/m2]	SD [kg/m2]	Total	Weight	IV, Random, 95% CI [kg/m2]	IV, Random, 95% CI [kg/m2]	
Kanazawa 2010	23.4	2.6	22	25.1	3.6	23	33.0%	-1.70 [-3.53, 0.13]		
Park 2011	26.3	3.2	82	24.8	2.9	33	37.1%	1.50 [0.29, 2.71]		
Wu 2014	24.8	5.6	46	22.1	5.5	47	29.9%	2.70 [0.44, 4.96]	_ -	
Total (95% CI)			150			103	100.0%	0.80 [-1.56, 3.17]		
Heterogeneity: Tau ² = Test for overall effect:			0.004)); I²= 82%					-10 -5 0 5	10
1 COLIOI OVOIGII CIICCL	. 2 - 0.01 (1 - 0.0								Pioglitazone Metformin	

K.1.7.3 Adding pioglitazone compared to adding insulin

Figure 349: Hypoglycaemia episodes at end of follow up

	Pioglita:	zone	Insul	in		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Hartemann-Heurtier 2009	6	14	10	13	71.8%	0.56 [0.28, 1.09]	
Meneghini 2010	1	126	4	121	28.2%	0.24 [0.03, 2.12]	
Total (95% CI)		140		134	100.0%	0.47 [0.24, 0.93]	•
Total events	7		14				
Heterogeneity: Chi² = 0.62, o			= 0%				0.01 0.1 1 10 100
Test for overall effect: Z = 2.1	17 (P = 0.0	3)					Favours Pioglitazone Favours Insulin

Figure 350: Severe hypoglycaemic episodes at end of follow up

	Pioglita	zone	Insul	in		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Hartemann-Heurtier 2009	0	14	0	13	9.8%	0.00 [-0.13, 0.13]	
Meneghini 2010	1	126	4	121	90.2%	-0.03 [-0.06, 0.01]	•
Total (95% CI)		140		134	100.0%	-0.02 [-0.06, 0.01]	•
Total events	1		4				
Heterogeneity: Chi² = 0.13, o	df=1 (P=	0.72); l²	= 0%				-1 -0.5 0 0.5 1
Test for overall effect: Z = 1.2	27 (P = 0.2	(0)					Favours Pioglitazone Favours Insulin

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

			Pioglitazone	Insulin		Mean Difference		Me	ean Differen	ce	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Fixed, 95% CI		IV	, Fixed, 95%	CI	
Dorkhan 2009	0.7	0.3587	15	15	11.9%	0.70 [-0.00, 1.40]			+		
Hartemann-Heurtier 2009	0.4	0.2329	14	13	28.2%	0.40 [-0.06, 0.86]			•		
Meneghini 2010	0.62	0.16	126	121	59.8%	0.62 [0.31, 0.93]			•		
Total (95% CI)			155	149	100.0%	0.57 [0.32, 0.81]					
Heterogeneity: Chi² = 0.76, Test for overall effect: Z = 4.	, ,,	0%					-100 Fav	-50 ours Pioglita	0 azone Favou	50 Irs Insulin	100

K.1.7.4 Adding pioglitazone compared to adding dapagliflozin

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

K.1.7.5 Adding pioglitazone compared to adding empagliflozin

Figure 352: Hypoglycaemia episodes at end of follow up

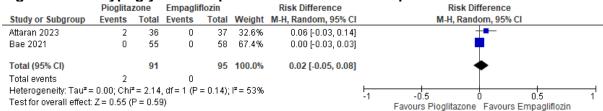


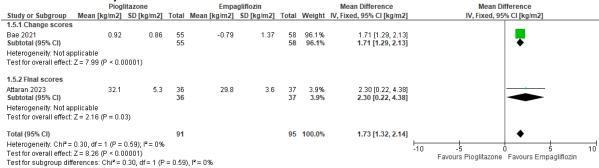
Figure 353: Severe hypoglycaemic episodes at end of follow up

	Pioglita	zone	Empaglif	lozin		Risk Difference		R	isk Difference	:	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-	H, Fixed, 95% (CI	
Attaran 2023	0	36	0	37	39.3%	0.00 [-0.05, 0.05]			+		
Bae 2021	0	55	0	58	60.7%	0.00 [-0.03, 0.03]			•		
Total (95% CI)		91		95	100.0%	0.00 [-0.03, 0.03]			•		
Total events	0		0								
Heterogeneity: Chi²=	0.00, df=	1 (P = 1	$.00); I^{z} = 0$	1%			-1	-0.5	- 	0.5	
Test for overall effect:	Z = 0.00 (1	P = 1.00	0)						azone Favour	s Empagliflozin	'

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

٧u	iucsji	ut Ci	ıu o		W up	,			
	Piogl	litazone		Empa	gliflozin			Mean Difference	Mean Difference
Study or Subgroup	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV, Fixed, 95% CI [%]	IV, Fixed, 95% CI [%]
1.4.1 Change scores									
Bae 2021	-0.87	0.99	55	-0.98	0.81	58	67.5%	0.11 [-0.22, 0.44]	·
Subtotal (95% CI)			55			58	67.5%	0.11 [-0.22, 0.44]	*
Heterogeneity: Not app	plicable								
Test for overall effect.	Z= 0.64 (P	= 0.52)							
1.4.2 Final scores									
Attaran 2023	7	1.1	36	7.2	1	37	32.5%	-0.20 [-0.68, 0.28]	+
Subtotal (95% CI)			36			37	32.5%	-0.20 [-0.68, 0.28]	◆
Heterogeneity: Not ap-	plicable								
Test for overall effect:	Z= 0.81 (P	= 0.42)							
Total (95% CI)			91			95	100.0%	0.01 [-0.27, 0.28]	•
Heterogeneity: Chi ² =	1.07, df = 1	(P = 0.31)	$0); I^2 = 0$	7%					-10 -5 0 5 10
Test for overall effect:	Z = 0.07 (P)	= 0.95)							-10 -5 0 5 10 Favours Pioglitazone Favours Empagliflozin
Test for subgroup diffe	erences: Ch	$ni^2 = 1.07$, df = 1	(P = 0.30)	$I^2 = 6.6\%$				Favours Floginazone Favours Empagnilozin

Figure 355: BMI change (kg/m², lower values are better, change scores and final values) at end of follow



K.1.7.6 Adding pioglitazone compared to adding exenatide

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

K.1.7.7 Adding pioglitazone compared to adding gliclazide

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

K.1.7.8 Adding pioglitazone compared to adding glimepiride

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

_	Pioglita	zone	Glimepi	ride		Peto Odds Ratio		Peto Ode	ds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI		Peto, Fixe	d, 95% CI	
Koyama 2014	1	31	0	32	50.0%	7.63 [0.15, 384.78]			_	_
Mazzone 2006	0	230	1	228	50.0%	0.13 [0.00, 6.76]	_	•		
Total (95% CI)		261		260	100.0%	1.01 [0.06, 16.18]				
Total events	1		1							
Heterogeneity: Chi²=	2.04, df =	1 (P = 0)	0.15); l² = :	51%			0.001	01	10	1000
Test for overall effect:	Z = 0.01 (8	P = 0.99	3)				0.001	Favours Pioglitazone		1000

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

	Pioglita	zone	Glimepi	ride		Peto Odds Ratio	Peto Od	lds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fix	ed, 95% CI	
Koyama 2014	0	31	1	32	50.0%	0.14 [0.00, 7.04]			
Mazzone 2006	0	230	1	228	50.0%	0.13 [0.00, 6.76]	-		
Total (95% CI)		261		260	100.0%	0.14 [0.01, 2.19]			
Total events	0		2						
Heterogeneity: Chi² = Test for overall effect:		,		0%			0.001 0.1	10	1000
			,				Favours Pioglitazone	Favours Glimepiride	

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

	Pioglita	zone	Glimepi	iride		Risk Difference		Risk Difference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Langenfeld 2005	2	89	0	84	13.4%	0.02 [-0.02, 0.06]		 -	
Mazzone 2006	1	230	0	228	35.4%	0.00 [-0.01, 0.02]		•	
Pfützner 2005	2	89	0	84	13.4%	0.02 [-0.02, 0.06]		 -	
Pfützner 2011B	0	142	2	146	22.3%	-0.01 [-0.04, 0.01]		-	
Umpierrez 2006	0	107	0	96	15.6%	0.00 [-0.02, 0.02]		†	
Total (95% CI)		657		638	100.0%	0.00 [-0.01, 0.01]			
Total events	5		2						
Heterogeneity: Chi ² =	4.36, df=	4 (P = 0)).36); I ^z =	8%			1	-0.5 0 0.5	
Test for overall effect:	Z = 0.86 (P = 0.39	3)				-1	-0.5 0 0.5 Favours Pioglitazone Favours Glimepiride	1

Figure 359: Hypoglycaemia episodes at end of follow up

	Pioglita	zone	Glimepi	ride		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Derosa 2010A	0	83	4	85	4.8%	0.11 [0.01, 2.08]	
Kim 2020	4	69	30	66	16.5%	0.13 [0.05, 0.34]	
Kinoshita 2020	0	33	2	33	4.6%	0.20 [0.01, 4.01]	
Langenfeld 2005	17	89	17	84	20.6%	0.94 [0.52, 1.72]	-
Mazzone 2006	45	230	53	228	22.8%	0.84 [0.59, 1.20]	
Pfützner 2011B	5	142	2	146	10.7%	2.57 [0.51, 13.03]	 •
Umpierrez 2006	10	107	32	96	20.0%	0.28 [0.15, 0.54]	
Total (95% CI)		753		738	100.0%	0.49 [0.24, 0.99]	•
Total events	81		140				
Heterogeneity: Tau ² =	= 0.55; Chi	z= 25.9	1, df = 6 (l	P = 0.00	002); I *= 1	77%	0.001 0.1 1 10 1000
Test for overall effect	Z = 1.99 (P = 0.06	5)				0.001 0.1 1 10 1000 Favours Pioglitazone Favours Glimepiride

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



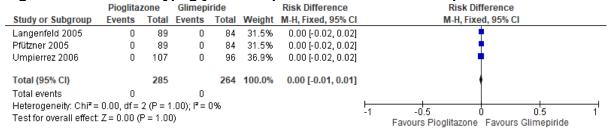


Figure 361: HbA1c change (%, lower values are better, change scores and final values) at end of follow up

Pioglitazone				Oli-				11 Diff	M Diff
044	_		T-4-1		epiride	T-4-1	187-1-1-4	Mean Difference	Mean Difference
Study or Subgroup	Mean [%]	SD [%]	rotai	mean [%]	SD [%]	Total	weignt	IV, Random, 95% CI [%]	IV, Random, 95% CI [%]
1.12.1 Change scores									
Kim 2020	-0.81	1.1	69	-1.05	0.87	66	7.4%	0.24 [-0.09, 0.57]	-
Kinoshita 2020	-0.48	1.03	33	-0.3	1.03	33	4.4%	-0.18 [-0.68, 0.32]	-
Koyama 2014	-0.28	0.78	27	0.1	0.77	30	5.9%	-0.38 [-0.78, 0.02]	
Ohira 2014A	-0.82	1.07	30	-0.44	1.23	30	3.4%	-0.38 [-0.96, 0.20]	
Pfützner 2005	-0.8	0.9	89	-0.6	0.8	84	9.9%	-0.20 [-0.45, 0.05]	*
Pfützner 2011B	-1	0.9	142	-0.8	0.9	146	11.5%	-0.20 [-0.41, 0.01]	•
Umpierrez 2006	-1.23	0.76	107	-1.3	0.75	96	11.5%	0.07 [-0.14, 0.28]	<u>†</u>
Subtotal (95% CI)			497			485	54.0%	-0.11 [-0.27, 0.05]	•
Test for overall effect: Z = 1.12.2 Final scores	1.36 (P = 0	.17)							
Derosa 2010A	6.9	0.2	78	6.8	0.1	77	17.2%	0.10 [0.05, 0.15]	•
Forst 2005	6.71	0.89	89	6.83	0.85	84	9.7%	-0.12 [-0.38, 0.14]	+
Langenfeld 2005	6.71	0.89	89	6.83	0.85	84	9.7%	-0.12 [-0.38, 0.14]	+
Papathanassiou 2009	7.1	0.8	14	6.9	0.5	14	4.4%	0.20 [-0.29, 0.69]	-
Petrica 2011	6.85	0.73	34	7.19	1.12	34	5.1%	-0.34 [-0.79, 0.11]	-
Subtotal (95% CI)			304			293	46.0%	-0.03 [-0.19, 0.14]	•
Heterogeneity: Tau² = 0.0 Test for overall effect: Z =			1 (P = 0	.07); I² = 54	%				
Total (95% CI)			801			778	100.0%	-0.07 [-0.19, 0.05]	•
Heterogeneity: Tau ² = 0.0	02; Chi² = 28	3.28, df=	11 (P :	= 0.003); 2=	= 61%				-10 -5 0 5 1
Test for overall effect: Z=	1.22 (P = 0)	.22)							Favours Pioglitazone Favours Glimepiride
Test for subgroup differe	nces: Chi²=	= 0.52, dt	= 1 (P	= 0.47), l2=	0%				ravours rioginazone ravours Gilliepinue

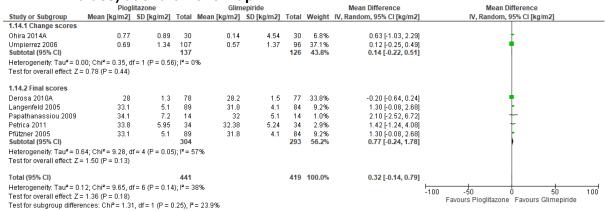
Note: Heterogeneity was not explained by sensitivity analysis nor subgroup analysis.

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

					-					
	Pioglitazone				Glimepiride			Mean Difference	Mean Difference	
Study or Subgroup	Mean [kg]	SD [kg]	Total	Mean [kg]	SD [kg]	Total	Weight	IV, Random, 95% CI [kg]	IV, Random, 95% CI [kg]	
1.13.1 Change scores										
Kinoshita 2020	2.5	2.3	33	1.4	2.3	33	16.6%	1.10 [-0.01, 2.21]	•	
Koyama 2014	1.49	1.61	27	0.21	2.9	30	15.8%	1.28 [0.08, 2.48]	•	
Mazzone 2006	3.2	5.4	232	1	3.7	230	18.8%	2.20 [1.36, 3.04]	<u> </u>	
Ohira 2014A	1.98	2.34	30	0.37	1.86	30	16.9%	1.61 [0.54, 2.68]	•	
Umpierrez 2006	1.85	3.93	107	1.74	4.02	96	16.7%	0.11 [-0.99, 1.21]	<u> </u>	
Subtotal (95% CI)			429			419	84.9%	1.30 [0.59, 2.02])	
Heterogeneity: Tau2 = 0.	.38; $Chi^2 = 9.2$	24, df = 4	P = 0.0	6); I ² = 57%						
Test for overall effect: Z	= 3.56 (P = 0.	0004)								
1.13.2 Final scores										
Derosa 2010A	77.2	5.4	78	78.6	6.4	77	11.0%	-1.40 [-3.27, 0.47]	+	
Papathanassiou 2009	86.4	19.2	14	82	15.4	14	0.4%	4.40 [-8.49, 17.29]		
Pfützner 2011B	94.8	18.2	142	96.9	17.8	146	3.6%	-2.10 [-6.26, 2.06]		
Subtotal (95% CI)			234			237	15.1%	-1.42 [-3.10, 0.27]	•	
Heterogeneity: Tau ² = 0.	.00; Chi ² = 0.8	39, df = 2 (P = 0.6	4); $I^2 = 0\%$						
Test for overall effect: Z	= 1.64 (P = 0.	10)								
Total (95% CI)			663			656	100.0%	0.88 [0.02, 1.74]		
Heterogeneity: Tau ² = 0.	.83: Chi ² = 19	.92. df = 7	(P = 0.	006): P= 65	%				L	
Test for overall effect: Z = 2.01 (P = 0.04)								-100 -50 0 50 100		
Test for subgroup differen			1 (P=	0.004), $I^2 = 8$	8.2%				Favours Pioglitazone Favours Glimepiride	
				2.1						

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

Figure 363: BMI change (kg/m², lower values are better, change scores and final values) at end of follow up



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

K.1.7.9 Adding pioglitazone compared to adding glipizide

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

K.1.7.10 Adding pioglitazone compared to adding sitagliptin

Figure 364: Hypoglycaemia episodes at end of follow up

	Pioglita	zone	Sitagli	ptin		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Bergenstal 2010	1	165	5	166	38.4%	0.20 [0.02, 1.70]	
Liu 2013	5	60	6	60	46.2%	0.83 [0.27, 2.58]	
Takihata 2013	2	65	2	65	15.4%	1.00 [0.15, 6.89]	
Total (95% CI)		290		291	100.0%	0.62 [0.26, 1.45]	-
Total events	8		13				
Heterogeneity: Chi²=	1.57, df=	2(P = 0)	1.46); I ^z =	0%			0.01 0.1 1 10 100
Test for overall effect:	Z=1.11 (P = 0.27	7)				0.01 0.1 1 10 100 Favours Pioglitazone Favours Sitagliptin

Figure 365: Severe hypoglycaemic episodes at end of follow up

	Pioglita	zone	Sitagli	ptin		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Bergenstal 2010	0	165	0	166	57.0%	0.00 [-0.01, 0.01]	•
Liu 2013	0	60	0	60	20.7%	0.00 [-0.03, 0.03]	+
Takihata 2013	0	65	0	65	22.4%	0.00 [-0.03, 0.03]	†
Total (95% CI)		290		291	100.0%	0.00 [-0.01, 0.01]	
Total events	0		0				
Heterogeneity: Chi²=	0.00, df =	2(P = 1)	.00); l²=	0%			-1 -05 0 05 1
Test for overall effect:	Z = 0.00 (P = 1.00	0)				Favours Pioglitazone Favours Sitagliptin

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

	Piogl	itazone		Sita	gliptin			Mean Difference		Mean Difference	
Study or Subgroup	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV, Random, 95% CI [%]		IV, Random, 95% CI [%]	
Bergenstal 2010	-1.2	1.3	165	-0.8	1.31	166	22.5%	-0.40 [-0.68, -0.12]		•	
Khaloo 2019	-1.9	1.2	110	-1.8	1	112	22.1%	-0.10 [-0.39, 0.19]		+	
Liu 2013	-0.94	0.12	59	-0.71	0.12	60	31.0%	-0.23 [-0.27, -0.19]		•	
Takihata 2013	-0.58	0.68	57	-0.86	0.63	58	24.4%	0.28 [0.04, 0.52]		•	
Total (95% CI)			391			396	100.0%	-0.12 [-0.37, 0.14]		•	
Heterogeneity: Tau ² =	0.05; Chi ² =	: 19.11, 0	df = 3 (F	e = 0.0003);	I ² = 84%	5			-10	1 1	10
Test for overall effect:	= 0.37)							-10	Favours Pioglitazone Favours Sitagliptin	10	

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

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

	Piogl	litazone		Sita	gliptin			Mean Difference		Me	ean Differenc	e	
Study or Subgroup	Mean [kg]	SD [kg]	Total	Mean [kg]	SD [kg]	Total	Weight	IV, Random, 95% CI [kg]		IV, Ra	ndom, 95% C	l [kg]	
Bergenstal 2010	2.8	3.9	165	-0.8	4.24	166	17.2%	3.60 [2.72, 4.48]					
Khaloo 2019	0.9	1.5	110	-0.5	1.1	112	28.3%	1.40 [1.05, 1.75]			•		
Liu 2013	1.34	0.32	59	-0.26	0.32	60	31.6%	1.60 [1.49, 1.71]			•		
Takihata 2013	1.7	1.82	57	-0.29	1.4	58	22.9%	1.99 [1.40, 2.58]			•		
Total (95% CI)			391			396	100.0%	1.98 [1.44, 2.51]					
Heterogeneity: Tau² = Test for overall effect:	-100 F:	-50 avours Pioglita	0 azone Favou	50 irs Sitagliptin	100								

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

K.1.7.11 Adding pioglitazone compared to adding vildagliptin

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

K.1.8 Insulin combinations

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

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

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

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

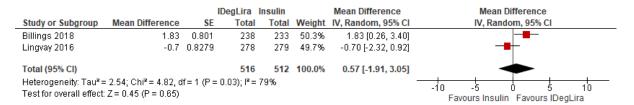


Figure 369: Health-related quality of life - subscale physical component (SF-36 v2, 0-100, higher scores are better, change scores and final values) at end of follow up

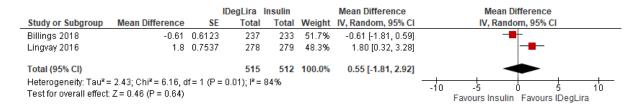


Figure 370: All-cause mortality at end of follow up

	IDegL	ira	Insul	in		Risk Difference		Risk Difference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Aroda 2019a	2	506	5	504	20.8%	-0.01 [-0.02, 0.00]		•	
Billings 2018	0	252	0	253	10.4%	0.00 [-0.01, 0.01]		+	
Gough 2014	2	833	0	413	22.7%	0.00 [-0.00, 0.01]		•	
Lingvay 2016	0	278	1	279	11.5%	-0.00 [-0.01, 0.01]		•	
Mathieu 2014	0	87	0	86	3.6%	0.00 [-0.02, 0.02]		+	
Pei 2021	0	301	0	151	8.3%	0.00 [-0.01, 0.01]		+	
Philis-Tsimikas 2019	0	209	1	210	8.6%	-0.00 [-0.02, 0.01]		+	
Wang 2022b	0	361	0	179	9.9%	0.00 [-0.01, 0.01]		+	
Watada 2019	0	105	0	105	4.3%	0.00 [-0.02, 0.02]		†	
Total (95% CI)		2932		2180	100.0%	-0.00 [-0.00, 0.00]			
Total events	4		7						
Heterogeneity: Chi ² = 3.	89, df = 8	(P = 0.	$87); I^2 = 0$	1%			<u> </u>		
Test for overall effect: Z	= 0.87 (P	= 0.39)					-1	-0.5 0 0.5 Favours IDegLira Favours Insulin	1

Figure 371: Cardiovascular mortality at end of follow up

	IDegL	ira	Insul	in		Risk Difference		Risk Difference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Aroda 2019a	0	506	3	504	20.8%	-0.01 [-0.01, 0.00]		•	
Billings 2018	0	252	0	253	10.4%	0.00 [-0.01, 0.01]		•	
Gough 2014	2	833	0	413	22.7%	0.00 [-0.00, 0.01]		•	
Lingvay 2016	0	278	1	279	11.5%	-0.00 [-0.01, 0.01]		•	
Mathieu 2014	0	87	0	86	3.6%	0.00 [-0.02, 0.02]		+	
Pei 2021	0	301	0	151	8.3%	0.00 [-0.01, 0.01]		+	
Philis-Tsimikas 2019	0	209	1	210	8.6%	-0.00 [-0.02, 0.01]		+	
Wang 2022b	0	361	0	179	9.9%	0.00 [-0.01, 0.01]		•	
Watada 2019	0	105	0	105	4.3%	0.00 [-0.02, 0.02]		†	
Total (95% CI)		2932		2180	100.0%	-0.00 [-0.00, 0.00]			
Total events	2		5						
Heterogeneity: Chi ² = 4.	42, df = 8	(P = 0.	82); $I^2 = 0$	1%			<u> </u>		—
Test for overall effect: Z	= 0.94 (P	= 0.34))				-1	-0.5 0 0.5 Favours IDegLira Favours Insulin	1

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

	IDegL	ira	Insul	in		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Gough 2014	4	833	1	413	34.5%	1.81 [0.28, 11.71]	- •
Pei 2021	3	301	2	151	34.5%	0.74 [0.11, 4.80]	
Philis-Tsimikas 2019	2	209	2	210	31.0%	1.00 [0.14, 7.18]	
Total (95% CI)		1343		774	100.0%	1.11 [0.37, 3.32]	-
Total events	9		5				
Heterogeneity: Chi² = 0	.46, df = 2	(P = 0.	$80); I^2 = 0$)%			0.01 0.1 10 100
Test for overall effect: Z	= 0.19 (P	= 0.85))				Favours IDegLira Favours Insulin

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

	IDegL	ira	Insul	in		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Aroda 2019a	2	506	0	504	19.4%	7.37 [0.46, 118.06]	-
Buse 2014	0	199	1	199	9.7%	0.14 [0.00, 6.82]	
Lingvay 2016	1	278	0	279	9.7%	7.42 [0.15, 373.73]	- •
Mathieu 2014	0	87	1	86	9.7%	0.13 [0.00, 6.74]	•
Pei 2021	2	301	2	151	34.3%	0.47 [0.06, 3.80]	
Wang 2022b	2	361	0	179	17.2%	4.48 [0.23, 85.24]	
Total (95% CI)		1732		1398	100.0%	1.21 [0.36, 4.11]	•
Total events	7		4				
Heterogeneity: Chi ² =	6.41, df=	5 (P=	0.27); l² :	= 22%			0.001 0.1 1 10 1000
Test for overall effect:	Z = 0.31	(P = 0.7)	'6)				Favours IDegLira Favours Insulin

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

	IDegL	ira	Insul	in		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Aroda 2019a	3	506	2	504	36.8%	1.49 [0.26, 8.62]	
Billings 2018	0	252	1	253	7.4%	0.14 [0.00, 6.85]	-
Buse 2014	1	199	1	199	14.8%	1.00 [0.06, 16.04]	
Gough 2014	2	833	1	413	19.6%	0.99 [0.09, 10.99]	
Pei 2021	1	301	0	151	6.6%	4.49 [0.07, 286.31]	
Philis-Tsimikas 2019	1	209	0	210	7.4%	7.42 [0.15, 374.18]	
Watada 2019	1	105	0	105	7.4%	7.39 [0.15, 372.38]	
Total (95% CI)		2405		1835	100.0%	1.48 [0.51, 4.30]	•
Total events	9		5				
Heterogeneity: Chi ² = 3.	18, df = 6	(P = 0.	$79); I^2 = 0$)%			0.001 0.1 1 10 1000
Test for overall effect: Z	= 0.72 (P	= 0.47))				0.001 0.1 1 10 1000 Favours IDegLira Favours Insulin

Figure 375: Unstable angina at end of follow up



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

	IDegL	ira	Insul	in		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Aroda 2019a	0	506	2	504	66.6%	0.13 [0.01, 2.15]	
Billings 2018	1	252	0	253	33.4%	7.42 [0.15, 373.87]	
Total (95% CI)		758		757	100.0%	0.51 [0.05, 4.93]	
Total events	1		2				
Heterogeneity: Chi²=	2.68, df=	1 (P=	0.10); l² =	63%			0.001 0.1 1 10 1000
Test for overall effect:	Z = 0.58 (P = 0.5	66)	Favours IDegLira Favours Insulin			

Figure 377: Cardiac arrhythmia at end of follow up

	IDegL	ira	Insul	in		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Aroda 2019a	0	506	2	504	50.0%	0.13 [0.01, 2.15]	
Billings 2018	2	252	0	253	50.0%	7.45 [0.46, 119.40]	
Total (95% CI)		758		757	100.0%	1.00 [0.14, 7.11]	
Total events	2		2				
Heterogeneity: Chi ² =	4.02, df=	1 (P =	0.04); l² =	= 75%			0.001 0.1 1 10 1000
Test for overall effect:	Z = 0.00 ((P = 1.0)	00)				Favours IDegLira Favours Insulin

Figure 378: Hypoglycaemia episodes at end of follow up

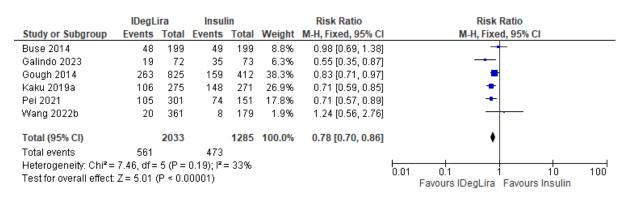


Figure 379: At night hypoglycaemic episodes

	IDegL	ira	Insul	lin		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Billings 2018	12	252	49	253	41.1%	0.25 [0.13, 0.45]	
Buse 2014	12	199	17	199	38.0%	0.71 [0.35, 1.44]	
Wang 2022b	5	361	3	179	20.9%	0.83 [0.20, 3.42]	
Total (95% CI)		812		631	100.0%	0.47 [0.20, 1.09]	•
Total events	29		69				
Heterogeneity: Tau² =	0.35; Ch	i² = 5.9	5, df = 2 (P = 0.0	5); I² = 66	%	0.01 0.1 1 10 100
Test for overall effect:	Z = 1.75	(P = 0.0)	18)				Favours IDegLira Favours Insulin



	IDegL	ira	Insul	in		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Billings 2018	3	252	4	254	24.5%	-0.00 [-0.02, 0.02]	•
Buse 2014	1	199	0	199	19.3%	0.01 [-0.01, 0.02]	•
Galindo 2023	7	72	14	73	7.0%	-0.09 [-0.21, 0.02]	
Gough 2014	3	151	2	413	21.4%	0.02 [-0.01, 0.04]	<u>†</u>
Mathieu 2014	0	87	0	86	8.4%	0.00 [-0.02, 0.02]	†
Pei 2021	2	301	0	151	19.5%	0.01 [-0.01, 0.02]	†
Total (95% CI)		1062		1176	100.0%	-0.00 [-0.01, 0.01]	(
Total events	16		20				
Heterogeneity: Chi²=	7.29, df=	5 (P=	0.20); l² =	= 31%			-1 -0.5 0 0.5 1
Test for overall effect:	Z = 0.36	(P = 0.7)	'2)				Favours IDegLira Favours Insulin

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

	•							
			IDegLira	Insulin		Mean Difference		Mean Difference
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI
Aroda 2019a	-0.47	0.0561	506	506	11.3%	-0.47 [-0.58, -0.36]		•
Billings 2018	-0.02	0.8572	252	254	0.9%	-0.02 [-1.70, 1.66]		
Buse 2014	-1.05	0.1276	199	199	9.4%	-1.05 [-1.30, -0.80]		•
Galindo 2023	-0.18	0.3417	72	73	4.1%	-0.18 [-0.85, 0.49]		-
Gough 2014	-0.5	0.0622	834	414	11.2%	-0.50 [-0.62, -0.38]		•
Kaku 2019a	-0.63	0.0612	275	271	11.2%	-0.63 [-0.75, -0.51]		•
Lingvay 2016	-0.68	0.0874	278	279	10.5%	-0.68 [-0.85, -0.51]		•
Mathieu 2014	-0.32	0.1071	88	89	10.0%	-0.32 [-0.53, -0.11]		•
Pei 2021	-0.9	0.0765	302	151	10.8%	-0.90 [-1.05, -0.75]		•
Philis-Tsimikas 2019	-0.36	0.0765	210	210	10.8%	-0.36 [-0.51, -0.21]		•
Watada 2019	-1.28	0.1122	105	105	9.8%	-1.28 [-1.50, -1.06]		•
Total (95% CI)			3121	2551	100.0%	-0.65 [-0.82, -0.48]		•
Heterogeneity: Tau ² = 0	i.06; Chi² = 92.09, df	= 10 (P ·	< 0.00001);	, l² = 89%)		10	+ + + +
Test for overall effect: Z							-10	-5 0 5 10 Favours IDegLira Favours Insulin

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

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

			IDegLira	Insulin		Mean Difference		Mean Difference	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI	
Aroda 2019a	-1.7	0.4243	506	506	8.2%	-1.70 [-2.53, -0.87]		•	
Billings 2018	-3.6	0.3061	506	506	9.0%	-3.60 [-4.20, -3.00]		•	
Buse 2014	-2.5	0.3571	199	199	8.7%	-2.50 [-3.20, -1.80]		•	
Galindo 2023	-4.6	1.2194	72	73	3.7%	-4.60 [-6.99, -2.21]		+	
Gough 2014	-2.1	0.2309	834	414	9.4%	-2.10 [-2.55, -1.65]		-	
Kaku 2019a	-1.19	0.3112	275	271	8.9%	-1.19 [-1.80, -0.58]		1	
Lingvay 2016	-3.2	0.2877	278	279	9.1%	-3.20 [-3.76, -2.64]		•	
Mathieu 2014	-3.7	0.4841	88	89	7.8%	-3.70 [-4.65, -2.75]		•	
Pei 2021	-1.05	0.2806	302	151	9.1%	-1.05 [-1.60, -0.50]		1	
Philis-Tsimikas 2019	-1.92	0.3674	210	210	8.6%	-1.92 [-2.64, -1.20]		•	
Wang 2022b	-1.08	0.2398	361	179	9.3%	-1.08 [-1.55, -0.61]		1	
Watada 2019	-1.41	0.4337	105	105	8.2%	-1.41 [-2.26, -0.56]		1	
Total (95% CI)			3736	2982	100.0%	-2.21 [-2.79, -1.63]			
Heterogeneity: Tau ² = 0		,	< 0.00001);	I² = 89%	5		-100	-50 0 50	100
Test for overall effect: Z	= 7.50 (P < 0.00001)						Favours IDegLira Favours Insulin	

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

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

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

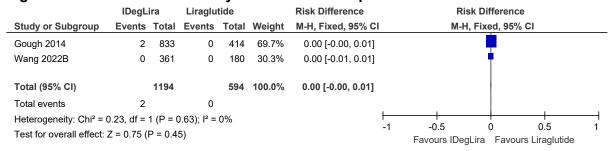


Figure 384: Hypoglycaemia episodes at end of follow up

	IDegL	ira	Liraglu	tide		Risk Ratio		Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		М-Н,	Random, 95	% CI		
Gough 2014	263	825	28	412	44.9%	4.69 [3.24, 6.80]			-	-		
Kaku 2019A	106	275	6	273	37.4%	17.54 [7.84, 39.24]				_	_	
Wang 2022B	20	361	1	180	17.7%	9.97 [1.35, 73.71]				•		
Total (95% CI)		1461		865	100.0%	8.77 [3.03, 25.43]			-	~		
Total events	389		35									
Heterogeneity: Tau ² =	0.62; Chi ²	= 9.05	, df = 2 (P	9 = 0.01); I ² = 78%	0	0.01	0.1	 	10	100	
Test for overall effect:	Z = 4.00 (P < 0.0	001)				0.01	Favours IDeg	ı JLira Favou	rs Liraglutid		

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

			IDegLira	Liraglutide		Mean Difference		M	lean Differen	ce	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Fixed, 95% CI		IV	/, Fixed, 95%	CI	
Gough 2014	-0.6	0.0661	834	415	46.2%	-0.60 [-0.73, -0.47]					
Kaku 2019A	-0.48	0.0612	361	273	53.8%	-0.48 [-0.60, -0.36]					
Total (95% CI)			1195	688	100.0%	-0.54 [-0.62, -0.45]			+		
Heterogeneity: Chi ² = Test for overall effect:		,.	4%				- 10	-5 Favours IDe	0 egLira Favoi	5 urs Liraglutio	10 de

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

			IDegLira	Liraglutide		Mean Difference		Mean	Differe	nce	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Random, 95% C		IV, Rar	ndom, 9	5% CI	
Gough 2014	2.5	0.2104	834	414	34.8%	2.50 [2.09, 2.91]				•	
Kaku 2019A	3.89	0.3061	275	273	31.4%	3.89 [3.29, 4.49]				-	
Wang 2022B	2.57	0.2398	361	180	33.8%	2.57 [2.10, 3.04]				•	
Total (95% CI)			1470	867	100.0%	2.96 [2.17, 3.75]				•	
Heterogeneity: Tau ² =	0.42; Chi² = 15.62,	df = 2 (P	= 0.0004);	I ² = 87%			-10		-		10
Test for overall effect:	Z = 7.36 (P < 0.000	01)					-10	-o Favours IDegLir	•	ວ ours Liraglutide	

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

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

	Insulin glargine/Lixise	nsulin glargine/Lixisenatide Insulin		Risk Difference		Ris	sk Difference				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95%	CI	M-H	l, Fixed, 95% C	1	
Aroda 2016B	1	366	2	365	17.6%	-0.00 [-0.01, 0.0	1]		•		
Kaneto 2020	0	255	0	257	12.4%	0.00 [-0.01, 0.0	1]		+		
Rosenstock 2016B	2	469	3	467	22.6%	-0.00 [-0.01, 0.0	1]		•		
Rosenstock 2016C	0	161	0	162	7.8%	0.00 [-0.01, 0.0	1]		†		
Terauchi 2020	1	260	0	261	12.6%	0.00 [-0.01, 0.0	1]		•		
Yang 2022	0	348	0	349	16.8%	0.00 [-0.01, 0.0	1]		†		
Yuan 2022	0	211	0	212	10.2%	0.00 [-0.01, 0.0	1]		†		
Total (95% CI)		2070		2073	100.0%	-0.00 [-0.00, 0.0	0]				
Total events	4		5								
Heterogeneity: Chi ² =	: 1.06, df = 6 (P = 0.98); l ²	= 0%					1	1.5	_ 	0.5	
Test for overall effect	: Z = 0.27 (P = 0.79)						- I	-0.5	-#-d-	0.5	1
					ravours ins	ulin glargine/Lixisen	atide Favour:	s insulin			

Figure 388: Cardiovascular mortality at end of follow up

	Insulin glargine/Lixise	in glargine/Lixisenatide Insulin		in		Risk Difference	Risk Difference				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI				
Aroda 2016B	0	366	1	365	17.6%	-0.00 [-0.01, 0.00	•				
Kaneto 2020	48	255	43	257	12.4%	0.02 [-0.05, 0.09	<u>+</u> -				
Rosenstock 2016B	1	469	2	467	22.6%	-0.00 [-0.01, 0.01	•				
Rosenstock 2016C	0	161	0	162	7.8%	0.00 [-0.01, 0.01	l				
Terauchi 2020	1	260	0	261	12.6%	0.00 [-0.01, 0.01	†				
Yang 2022	0	348	0	349	16.8%	0.00 [-0.01, 0.01	†				
Yuan 2022	0	211	0	212	10.2%	0.00 [-0.01, 0.01	†				
Total (95% CI)		2070		2073	100.0%	0.00 [-0.01, 0.01	1				
Total events	50		46								
Heterogeneity: Chi²=	4.17, df = 6 (P = 0.65); P	²= 0%					-1 -0.5 0 0.5 1				
Test for overall effect:	Z = 0.47 (P = 0.64)					F	avours Insulin glargine/Lixisenatide Favours Insulin				

Figure 389: Hypoglycaemia episodes at end of follow up

	Insulin glargine/Lixise	enatide	Insul	in		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% (CI M-H, Fixed, 95% CI
Aroda 2016B	146	365	155	365	17.6%	-0.02 [-0.10, 0.0	05]
Kaneto 2020	0	255	0	257	12.4%	0.00 [-0.01, 0.01	01]
Rosenstock 2016B	120	469	110	467	22.6%	0.02 [-0.03, 0.08)8] *
Rosenstock 2016C	35	161	37	162	7.8%	-0.01 [-0.10, 0.08	D8] -
Terauchi 2020	1	260	0	261	12.6%	0.00 [-0.01, 0.01)1]
Yang 2022	0	348	0	349	16.8%	0.00 [-0.01, 0.01	o1]
Yuan 2022	97	211	95	212	10.2%	0.01 [-0.08, 0.11	1]
Total (95% CI)		2069		2073	100.0%	0.00 [-0.02, 0.02	2]
Total events	399		397				
Heterogeneity: Chi ² =	1.56, df = 6 (P = 0.96); P	= 0%					-1 -0.5 0 0.5 1
Test for overall effect:	Z = 0.10 (P = 0.92)						Favours Insulin glargine/Lixisenatide Favours Insulin

Figure 390: Severe hypoglycaemic episodes at end of follow up

	Insulin glargine/Lixise	enatide	Insul	in	Risk Difference			Risk Difference			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	1	M-H	, Fixed, 95% C	1	
Aroda 2016B	4	365	1	365	17.6%	0.01 [-0.00, 0.02	2]		+		
Kaneto 2020	0	255	1	257	12.4%	-0.00 [-0.01, 0.01]		+		
Rosenstock 2016B	0	469	1	467	22.6%	-0.00 [-0.01, 0.00	0]		•		
Rosenstock 2016C	0	161	0	162	7.8%	0.00 [-0.01, 0.01]		+		
Terauchi 2020	0	260	0	261	12.6%	0.00 [-0.01, 0.01]		+		
Yang 2022	1	348	1	349	16.8%	0.00 [-0.01, 0.01]		+		
Yuan 2022	2	211	2	212	10.2%	0.00 [-0.02, 0.02	2]		†		
Total (95% CI)		2069		2073	100.0%	0.00 [-0.00, 0.00)]				
Total events	7		6								
Heterogeneity: Chi ² =	= 3.05, df = 6 (P = 0.80); l ²	= 0%					1	0.5	_ 	0.5	
Test for overall effect	: Z = 0.25 (P = 0.81)						-1	-0.5 Ilin glargine/Lixisen:	U otido Fovour	0.5	1
						F	avours msu	iiiii giargiile/Lixiseli:	adde ravours	HISUIII	

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

	•		Insulin glargine/Lixisenatide	Insulin		Mean Difference	Mean Di	fference	
Study or Subgroup	Mean Difference	SE	Tota	I Total	Weight	IV, Random, 95% CI	IV, Rando	m, 95% CI	
Aroda 2016B	-0.5	0.06	366	365	14.4%	-0.50 [-0.62, -0.38]			
Kaneto 2020	-0.7405	0.0633	255	5 257	14.3%	-0.74 [-0.86, -0.62]	-		
Rosenstock 2016B	-0.3	0.0566	468	3 466	14.6%	-0.30 [-0.41, -0.19]			
Rosenstock 2016C	-0.17	0.0689	161	162	14.0%	-0.17 [-0.31, -0.03]	•		
Terauchi 2020	-0.631	0.06	260	260	14.4%	-0.63 [-0.75, -0.51]			
Yang 2022	-0.45	0.051	348	349	14.8%	-0.45 [-0.55, -0.35]	•		
Yuan 2022	-0.7	0.0765	210	211	13.6%	-0.70 [-0.85, -0.55]	•		
Total (95% CI)			2068	3 2070	100.0%	-0.50 [-0.64, -0.35]	•		
Heterogeneity: Tau² = Test for overall effect:		,	< 0.00001); I² = 90%			Fa	-10 -5 vours Insulin glargine/Lixisenatide) 5 Favours Insulin	10

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

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

	•		Insulin glargine/Lixisenatide	Insulin		Mean Difference	Mean D	ifference	
Study or Subgroup	Mean Difference	SE	Total	Total	Weight	IV, Fixed, 95% CI	IV, Fixe	d, 95% CI	
Aroda 2016B	-1.4	0.2	366	365	17.5%	-1.40 [-1.79, -1.01]			
Kaneto 2020	-1.052	0.1719	255	257	23.7%	-1.05 [-1.39, -0.72]	-		
Rosenstock 2016B	-1.4	0.2828	468	466	8.8%	-1.40 [-1.95, -0.85]	-		
Rosenstock 2016C	-1.44	0.3316	161	162	6.4%	-1.44 [-2.09, -0.79]			
Terauchi 2020	-1.064	0.2214	260	260	14.3%	-1.06 [-1.50, -0.63]	-		
Yang 2022	-1.09	0.2092	348	349	16.0%	-1.09 [-1.50, -0.68]	-		
Yuan 2022	-0.9	0.2296	210	211	13.3%	-0.90 [-1.35, -0.45]	-		
Total (95% CI)			2068	2070	100.0%	-1.16 [-1.32, -0.99]	•		
Heterogeneity: Chi ² =			%				-10 -5	1 5	10
Test for overall effect:	Z=13.81 (P < 0.00	001)				Fa	vours Insulin glargine/Lixisenatide	Favours Insulin	10

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

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



Figure 394: Cardiovascular mortality at end of follow up

li I	nsulin glargine/Lixise	natide	Lixisenatide			Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Rosenstock 2016B	1	469	1	233	100.0%	0.47 [0.02, 8.90]	
Yang 2022	0	348	0	176		Not estimable	_
Total (95% CI)		817		409	100.0%	0.47 [0.02, 8.90]	
Total events	1		1				
Heterogeneity: Not appli Test for overall effect: Z							0.01 0.1 1 10 100 Favours IGlarLixi Favours Lixisenatide

Figure 395: Hypoglycaemia episodes at end of follow up

	Insulin glargine/Lixise	natide	Lixisen	atide		Risk Ratio	F	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H,	Fixed, 95% CI		
Rosenstock 2016B	120	469	15	233	55.7%	3.97 [2.38, 6.64]		-		
Yang 2022	171	348	12	176	44.3%	7.21 [4.13, 12.57]		-		
Total (95% CI)		817		409	100.0%	5.41 [3.71, 7.87]		•		
Total events	291		27							
Heterogeneity: Chi² = Test for overall effect:					0.01 0.1 Favours IGlar	1 10 Lixi Favours Lixise	100 natide			

Figure 396: Severe hypoglycaemic episodes at end of follow up



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

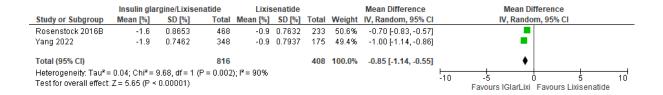
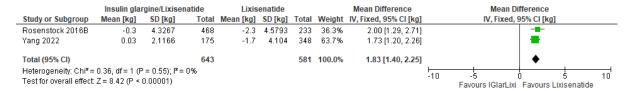


Figure 398: Weight change (kg, lower values are better, change scores) at end of follow up



K.1.9 Combinations

K.1.9.1 Adding dapagliflozin + exenatide compared to adding dapagliflozin

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

K.1.9.2 Adding dapagliflozin + exenatide compared to adding exenatide

K.1.9.3 Adding dapagliflozin + saxagliptin compared to adding dapagliflozin

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

	Dapagliflozin + Saxa	agliptin	Dapagli	flozin		Risk Difference	Risk Differ	ence	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 9	95% CI	
Rosenstock 2015A	0	179	0	179	37.9%	0.00 [-0.01, 0.01]	•		
Rosenstock 2019D	1	293	2	293	62.1%	-0.00 [-0.01, 0.01]	•		
Total (95% CI)		472		472	100.0%	-0.00 [-0.01, 0.01]	•		
Total events	1		2						
Heterogeneity: Chi ² =					-1 -0.5	0.5	1		
Test for overall effect					Favours Dapagliflozin + Saxagliptin Fa				

Figure 400: Cardiovascular mortality at end of follow up

	Dapagliflozin + Saxa	ıgliptin	Dapagli	flozin		Risk Difference		Risk Difference		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI		
Rosenstock 2015A	0	179	0	179	37.9%	0.00 [-0.01, 0.01]		•		
Rosenstock 2019D	0	293	2	293	62.1%	-0.01 [-0.02, 0.00]		•		
Total (95% CI)		472		472	100.0%	-0.00 [-0.01, 0.00]				
Total events	0		2							
Heterogeneity: Chi2=	0.78, df = 1 (P = 0.38);	$I^2 = 0\%$					1 05		0.5	
Test for overall effect: Z = 1.00 (P = 0.32)							Favours Dapagliflozin	+ Saxagliptin Favours		'

Figure 401: Hypoglycaemia episodes at end of follow up

	Dapagliflozin + Saxa	gliptin	Dapagliflozin		gliflozin Peto Odds Ratio		Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Muller-Wieland 2018	1	312	0	311	8.4%	7.37 [0.15, 371.20]	
Rosenstock 2015A	2	179	2	179	33.3%	1.00 [0.14, 7.16]	
Rosenstock 2019D	6	293	1	293	58.2%	4.23 [0.96, 18.78]	
Total (95% CI)		784		783	100.0%	2.74 [0.88, 8.54]	-
Total events	9		3				
Heterogeneity: Chi² = 1	= 0%					0.001 0.1 1 10 1000	
Test for overall effect: 2					0.001 0.1 1 10 1000 Favours Dapagliflozin + Saxagliptin Favours Dapagliflozin		

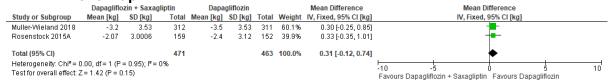
Figure 402: Severe hypoglycaemic episodes at end of follow up

	Dapagliflozin + Saxag	liptin	Dapaglif	lozin		Risk Difference	Risk Difference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
Muller-Wieland 2018	0	312	0	311	39.8%	0.00 [-0.01, 0.01]	•	
Rosenstock 2015A	0	179	0	179	22.8%	0.00 [-0.01, 0.01]	•	
Rosenstock 2019D	1	293	1	293	37.4%	0.00 [-0.01, 0.01]	•	
Total (95% CI)		784		783	100.0%	0.00 [-0.00, 0.00]		
Total events	1		1					
Heterogeneity: Chi² = 0 Test for overall effect: Z		= 0%					-1 -0.5 0.5 Favours Dapagliflozin + Saxagliptin Favours Dapagliflozin	T

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



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



K.1.9.4 Adding dapagliflozin + saxagliptin compared to adding glimepiride

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

_	Dapagliflozin + Saxa	agliptin	Glimep	iride		Risk Difference	Risk Difference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	I M-H, Fixed, 95% CI	
Frias 2020	0	227	0	216	41.5%	0.00 [-0.01, 0.01]	•	
Muller-Wieland 2018	0	312	1	312	58.5%	-0.00 [-0.01, 0.01]	1 📍	
Total (95% CI)		539		528	100.0%	-0.00 [-0.01, 0.00]	1	
Total events	0		1					
Heterogeneity: Chi² = 0	0.26, df = 1 (P = 0.61); I	² =0%					-1 -0.5 0 0.5	
Test for overall effect: 2					Favours Dapagliflozin + Saxagliptin Favours Glimepiride	'		

Figure 406: Hypoglycaemia episodes at end of follow up

_	Dapagliflozin + Sax	agliptin	Glimepi	iride		Risk Ratio	Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Rand	om, 95% CI	
Frias 2020	19	227	53	216	71.3%	0.34 [0.21, 0.56]	-		
Muller-Wieland 2018	1	312	13	309	28.7%	0.08 [0.01, 0.58]	-		
Total (95% CI)		539		525	100.0%	0.22 [0.06, 0.87]			
Total events	20		66						
Heterogeneity: Tau ² =		I (P = 0.15)	5); I² = 52°		0.01 0.1	1 10	100		
Test for overall effect: Z = 2.16 (P = 0.03)							Favours Dapagliflozin + Saxagliptin	Favours Glimepiride	

Figure 407: Severe hypoglycaemic episodes at end of follow up

	Dapagliflozin + Saxa	gliptin	Glimepi	iride		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Frias 2020	0	227	3	216	40.4%	-0.01 [-0.03, 0.00]	
Muller-Wieland 2018	0	312	0	309	59.6%	0.00 [-0.01, 0.01]	•
Total (95% CI)		539		525	100.0%	-0.01 [-0.02, 0.01]	•
Total events	0		3				
Heterogeneity: Tau ² = 1	0.00; Chi² = 4.04, df = 1	(P = 0.04)	4); I ² = 75°		-1 -0.5 0 0.5 1		
Test for overall effect: Z = 0.59 (P = 0.56)							-1 -0.5 0 0.5 1 Favours Dapadiflozin + Saxadiptin Favours Glimepiride

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

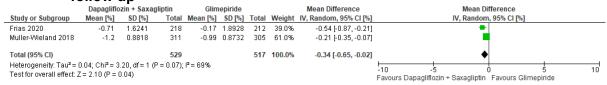


Figure 409: Weight change (kg, lower values are better, change scores) at end of follow up

-		-										
	Dapagliflo	zin + Saxag	liptin	Glim	epiride			Mean Difference	Mean D)ifference		
Study or Subgroup	Mean [kg]	SD [kg]	Total	Mean [kg]	SD [kg]	Total	Weight	IV, Random, 95% CI [kg]	IV, Randon	n, 95% CI [kg]		
Frias 2020	-2.64	7.7826	224	0.3	9.5087	214	42.8%	-2.94 [-4.57, -1.31]				
Muller-Wieland 2018	-3.2	3.5327	312	1.8	3.51	308	57.2%	-5.00 [-5.55, -4.45]	-			
Total (95% CI)			536			522	100.0%	-4.12 [-6.12, -2.12]				
Heterogeneity: Tau² =			= 0.02); I	l² = 82%					-10 -5	h .		10
Test for overall effect: 2	Z = 4.04 (P < 0)).0001)							Favours Dapagliflozin + Saxagliptin	Favours Glimepi	ide	

K.1.9.5 Adding dapagliflozin + saxagliptin compared to adding insulin

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

K.1.9.6 Adding dapagliflozin + saxagliptin compared to adding saxagliptin

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

	Dapagliflozin + Saxa	gliptin	Saxagl	iptin		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Rosenstock 2015A	0	179	0	176	37.6%	0.00 [-0.01, 0.01]	•
Rosenstock 2019D	1	293	0	295	62.4%	0.00 [-0.01, 0.01]	•
Total (95% CI)		472		471	100.0%	0.00 [-0.01, 0.01]	
Total events	1		0				
Heterogeneity: Chi²=					1 05 0 05		
Test for overall effect:					-1 -0.5 0 0.5 1 Favours Dapaqliflozin + Saxaqliptin Favours Saxaqliptin		

Figure 411: Cardiovascular mortality at end of follow up

_	Dapagliflozin + Saxa	agliptin	Saxagli	iptin	_	Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Rosenstock 2015A	0	179	0	176	37.6%	0.00 [-0.01, 0.01]	•
Rosenstock 2019D	0	293	0	295	62.4%	0.00 [-0.01, 0.01]	•
Total (95% CI)		472		471	100.0%	0.00 [-0.01, 0.01]	
Total events	0		0				
Heterogeneity: Chi² =	0.00, $df = 1 (P = 1.00)$;	$I^2 = 0\%$					-1 -0.5 0 0.5 1
Test for overall effect: $Z = 0.00$ (P = 1.00)							Favours Dapagliflozin + Saxagliptin Favours Saxagliptin



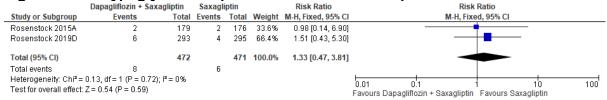


Figure 413: Severe hypoglycaemic episodes at end of follow up

	Dapagliflozin + Saxagliptin		Saxagliptin			Risk Difference	Risk Difference		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI		
Rosenstock 2015A	0	179	0	176	37.7%	0.00 [-0.01, 0.01]	•		
Rosenstock 2019D	1	293	0	293	62.3%	0.00 [-0.01, 0.01]]		
Total (95% CI)		472		469	100.0%	0.00 [-0.01, 0.01]	1		
Total events	1		0						
Heterogeneity: Chi ² = Test for overall effect:					-1 -0.5 0 0.5 1 Favours Dapadiflozin + Saxadliptin Favours Saxadliptin				
		Favours Dapagiilioziii + Saxagiipiiii Favours Saxagiipiiii							

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

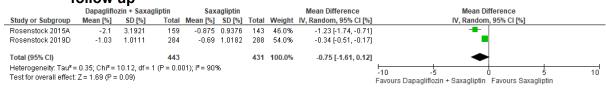


Figure 415: Weight change (kg, lower values are better, change scores) at end of follow up

	Dapagliflozin + Saxagliptin			Saxagliptin				Mean Difference	Mean D	Mean Difference		
Study or Subgroup	Mean [kg]	SD [kg]	Total	Mean [kg]	SD [kg]	Total	Weight	IV, Fixed, 95% CI [kg]	IV, Fixed,	95% CI [kg]		
Rosenstock 2015A	-2.07	3.0006	159	0	3.0461	145	39.9%	-2.07 [-2.75, -1.39]	-			
Rosenstock 2019D	-2	3.3705	284	-0.4	3.3941	288	60.1%	-1.60 [-2.15, -1.05]	-			
Total (95% CI)			443			433	100.0%	-1.79 [-2.22, -1.36]	•			
Heterogeneity: Chi ² = 1.10, df = 1 (P = 0.29); i ² = 9% Test for overall effect: Z = 8.15 (P < 0.00001) Favours Dapagliflozin + Saxagliptin Favours Saxagliptin											j 10	

K.1.9.7 Adding dapagliflozin + saxagliptin compared to adding sitagliptin

K.1.9.8 Adding empagliflozin + liraglutide compared to adding empagliflozin

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

K.1.9.9 Adding empagliflozin + liraglutide compared to adding insulin

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

K.1.9.10 Adding empagliflozin + liraglutide compared to adding liraglutide

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

K.1.9.11 Adding ertugliflozin + sitagliptin compared to adding ertugliflozin

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

K.1.9.12 Adding ertugliflozin + sitagliptin compared to adding sitagliptin

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

K.1.9.13 Adding glimepiride + metformin compared to adding glimepiride

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

K.1.9.14 Adding glimepiride + metformin compared to adding metformin

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

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

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

K.1.9.16 Adding liraglutide + metformin compared to adding metformin

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

K.1.9.17 Adding pioglitazone + alogliptin compared to adding pioglitazone

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

K.1.9.18 Adding pioglitazone + exenatide compared to adding insulin

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

K.1.9.19 Adding pioglitazone + exenatide compared to adding pioglitazone

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

K.1.9.20 Adding pioglitazone + metformin compared to adding metformin

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

K.1.9.21 Adding pioglitazone + metformin compared to adding pioglitazone

K.2 Switching

K.2.1 Metformin

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

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

K.2.2 DPP-4 inhibitors

K.2.2.1 Switching to sitagliptin compared to switching to placebo

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

K.2.2.2 Switching to vildagliptin compared to switching to alogliptin

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

K.2.3 GLP-1 receptor agonist

K.2.3.1 Switching to liraglutide compared to staying on sitagliptin

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

K.2.3.2 Switching to semaglutide compared to switching to dulaglutide

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

K.2.3.3 Switching to semaglutide compared to staying on sitagliptin

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

K.2.4 SGLT2 inhibitors

K.2.4.1 Switching to glimepiride compared to switching to liraglutide

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

K.2.4.2 Switching to canagliflozin compared to switching to liraglutide

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

K.2.1 Thiazolidinediones

K.2.1.1 Staying on pioglitazone compared to switching to dapagliflozin

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

K.2.1.2 Switching to pioglitazone compared to switching to glimepiride

K.2.2 Combinations

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