Supplemental Materials

Table S1. All-cause dementia was defined by a narrow Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) of "dementia" including 21 preferred terms.

Table S2. Basic characteristics of 21 cardiovascular and renal outcome trials.

Table S3. Begg's test and Egger's test for the effects of DPP-4 inhibitors, GLP-1RAs, and SGLT2 inhibitors on risk of dementia.

Figure S1. The flowchart of the study selection. CENTRAL, Cochrane Central Register of Controlled Trials; DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; GLP-1RAs, glucagon-like peptide-1 receptor agonists; SGLT2 inhibitors, sodium-glucose co-transporter-2 inhibitors.

Figure S2. Sensitivity analysis of the effects of novel glucose-lowering drugs on the risk of allcause dementia (A) and vascular dementia (B) in participants with or without type 2 diabetes. OR, odds ratio; CI, confidence interval; DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; GLP-1RAs, glucagon-like peptide-1 receptor agonists; SGLT2 inhibitors, sodium-glucose co-transporter-2 inhibitors.

Figure S3. The funnel plot for the effects of DPP-4 inhibitors, GLP-1RAs, and SGLT2 inhibitors on risk of dementia. DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; GLP-1RAs, glucagon-like peptide-1 receptor agonists; SGLT2 inhibitors, sodium-glucose co-transporter-2 inhibitors.

Table S1. All-cause dementia was defined by a narrow Standardized Medical Dictionary forRegulatory Activities (MedDRA) Query (SMQ) of "dementia" including 21 preferred terms

Outcome	Preferred Terms
All cause	Clinical dementia rating scale score abnormal
dementia	Corticobasal degeneration
	Creutzfeldt-Jakob disease
	Dementia
	Dementia Alzheimer's type
	Dementia of the Alzheimer's type, uncomplicated
	Dementia of the Alzheimer's type, with delirium
	Dementia of the Alzheimer's type, with delusions
	Dementia of the Alzheimer's type, with depressed mood
	Dementia with Lewy bodies
	Early onset familial Alzheimer's disease
	Frontotemporal dementia
	Hippocampal sclerosis
	Korsakoff's syndrome
	Mini mental status examination abnormal
	Mixed dementia
	Presenile dementia
	Prion disease
	Progressive supranuclear palsy
	Scatolia
	Senile dementia
	Variant Creutzfeldt-Jakob disease
	Vascular dementia
Vascular	Vascular dementia
dementia	

Study	NCT	Trial name	No. of patients	Population	Patients with T2D (%)	Mean age (years)	Male (%)	White (%)	Mean duratio n of diabete s (years)	Comparisons	Median follow-up (years)
Scirica 2013 ¹	NCT0110 7886	SAVOR-TIMI 53	16,492	T2D patients with a history of, or were at risk for cardiovascular events	100	65	67	75	10	Saxagliptin vs Placebo	2.1
White 2013 ²	NCT0096 8708	EXAMINE	5,380	T2D patients with either an acute myocardial infarction or unstable angina requiring hospitalization within the previous 15 to 90 days	100	61	68	73	7	Alogliptin vs Placebo	1.5
Green 2015 ³	NCT0079 0205	TECOS	14,671	T2D patients with established cardiovascular disease	100	66	71	68	12	Sitagliptin vs Placebo	3
Gantz 2017 ⁴	NCT0170 3208	OMNEON	4,192	T2D patients with established cardiovascular disease	100	64	70	81	12	Omarigliptin vs Placebo	1.8
Rosenstock 2019 ⁵	NCT0189 7532	CARMELINA	6,979	T2D patients with high cardiovascular risk	100	66	63	80	15	Linagliptin vs Placebo	2.2
Pfeffer 2015 ⁶	NCT0114 7250	ELIXA	6,068	T2D patients who had had a myocardial infarction or who had been hospitalized for unstable angina within the previous 180 day	100	60	70	75	9	Lixisenatide vs Placebo	2.1
Marso 2016 ⁷	NCT0117 9048	LEADER	9,340	T2D patients with high cardiovascular risk	100	64	64	78	13	Liraglutide vs Placebo	3.8
Marso 2016 ⁸	NCT0172 0446	SUSTAIN-6	3,297	T2D patients with established cardiovascular disease or chronic kidney	100	65	61	83	14	Semaglutide vs Placebo	2.1

Table S2. Basic characteristics of 21 cardiovascular and renal outcome trials

				disease of stage 3 or higher or an age of 60 years or more with at least one cardiovascular risk factor							
Holman 2017 ⁹	NCT0114 4338	EXSCEL	14,752	T2D patients with or without previous cardiovascular disease	100	62	62	76	12	Exenatide vs Placebo	3.2
Hernandez 2018 ¹⁰	NCT0246 5515	HARMONY	9,432	T2D patients aged at least 40 years with cardiovascular disease	100	64	70	70	14	Albiglutide vs Placebo	1.6
Gerstein 2019 ¹¹	NCT0139 4952	REWIND	9,901	T2D patients aged at least 50 years with either a previous cardiovascular event or cardiovascular risk factors	100	66	54	76	11	Dulaglutide vs Placebo	5.4
Husain 2019 ¹²	NCT0269 2716	PIONEER-6	3,183	T2D patients at high cardiovascular risk	100	66	68	72	15	Oral semaglutide vs Placebo	1.3
Gerstein 2021 ¹³	NCT0349 6298	AMPLITUDE- O	4,076	T2D patients with either a history of cardiovascular disease or current kidney disease plus at least one other cardiovascular risk factor	100	72	55	76	NR	Efpeglenatide vs Placebo	2.2
Zinman 2015 ¹⁴	NCT0113 1676	EMPA-REG OUTCOME	7,020	T2D patients with established cardiovascular disease	100	63	72	72	NR	Empagliflozin vs Placebo	3.1
Neal 2017 ¹⁵	NCT0103 2629/ NCT0198 9754	CANVAS Program	10,142	T2D patients with high cardiovascular risk	100	63	64	78	14	Canagliflozin vs Placebo	2.4
Wiviott 2018 ¹⁶	NCT0173 0534	DECLARE– TIMI 58	17,161	T2D patients had or were at risk for atherosclerotic cardiovascular disease	100	64	63	80	11	Dapagliflozin vs Placebo	4.2

Perkovic	NCT0206	CREDENCE	4,401	T2D patients with	100	63	66	67	16	Canagliflozin	2.6
2019 ¹⁷	5791			albuminuric chronic						VS	
				kidney disease						Placebo	
Cannon	NCT0198	VERTIS-CV	8,246	T2D patients with	100	64	70	88	13	Ertugliflozin vs	3.5
2020 ¹⁸	6881			atherosclerotic						Placebo	
				cardiovascular disease							
McMurray	NCT0303	DAPA-HF	4,744	Patients with	41.8	66	77	70	NR	Dapagliflozin	1.5
2019 ¹⁹	6124			established heart failure						vs Placebo	
				and a reduced ejection							
				fraction, regardless of							
				the presence or							
				absence of T2D							
Heerspink	NCT0303	DAPA-CKD	4,304	Patients with chronic	67.5	62	67	53	NR	Dapagliflozin	2.4
2020 20	6150			kidney disease						vs Placebo	
Packer	NCT0305	EMPEROR-	3,730	Patients with class II, III,	49.8	67	76	70	NR	Empagliflozin	1.3
2020 ²¹	7977	Reduced		or IV heart failure and						vs Placebo	
				an ejection fraction of							
				40% or less							

T2D, Type 2 diabetes; CVD, cardiovascular disease; CKD, chronic kidney disease; NR, not reported

Table S3. Begg's test and Egger's test for the effects of DPP-4 inhibitors, GLP-1RAs, and SGLT2 inhibitors on risk of dementia.

	Begg's test	Egger's test
DPP-4 inhibitors	0.81	0.27
GLP-1RAs	0.71	0.53
SGLT2 inhibitors	0.76	0.91

DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; GLP-1RAs, glucagon-like peptide-1 receptor agonists; SGLT2 inhibitors, sodium-glucose co-transporter-2 inhibitors

Figure S1. The flowchart of the study selection. CENTRAL, Cochrane Central Register of Controlled Trials; DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; GLP-1RAs, glucagon-like peptide-1 receptor agonists; SGLT2 inhibitors, sodium-glucose co-transporter-2 inhibitors.

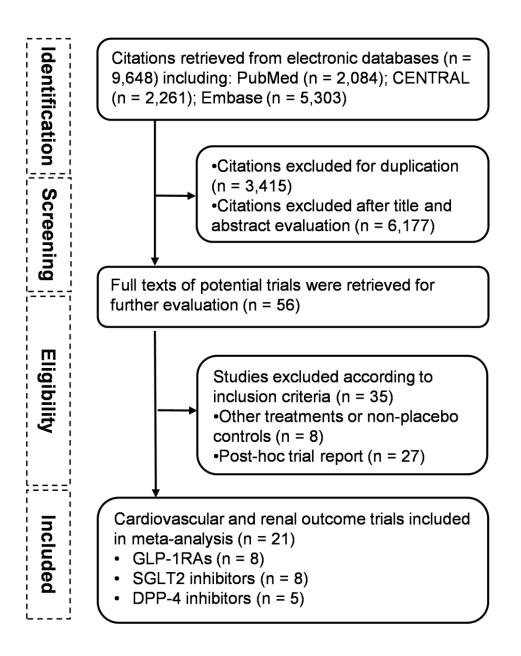
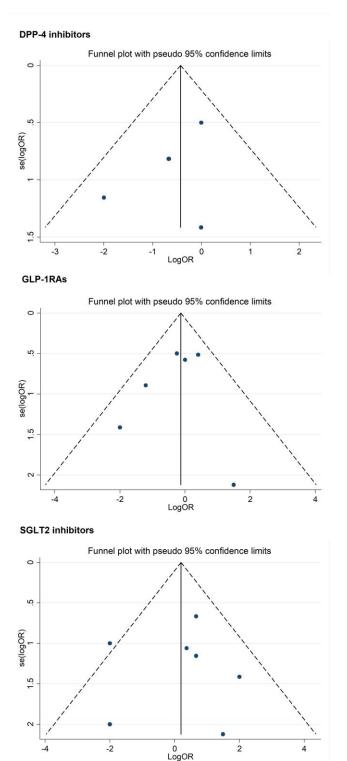


Figure S2. Sensitivity analysis of the effects of novel glucose-lowering drugs on the risk of allcause dementia (A) and vascular dementia (B) in patients with or without type 2 diabetes. OR, odds ratio; CI, confidence interval; DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; GLP-1RAs, glucagon-like peptide-1 receptor agonists; SGLT2 inhibitors, sodium-glucose co-transporter-2 inhibitors.

Study	OR (95% CI)	Events, Treatment	Events, Placebo	% We
DPP-4 inhibitors				
Scirica 2013	0.56 (0.13, 2.46)	2 5/8280 5	4.5/8212.5	18.
White 2013		1.5/2701.5	1.5/2679.5	7.9
Green 2015	0.57 (0.13, 2.49)		4.5/7339.5	18.
Gantz 2017	0.22 (0.03, 1.59)	.5/2092.5	3.5/2100.5	10.
Rosenstock 2019	1.00 (0.39, 2.58)		8.5/3485.5	44.
Subtotal (I-squared = 0.0%, p = 0.720)	0.69 (0.36, 1.30)	15.5/23901.5	22.5/23817.5	5 100
GLP-1RAs				
Pfeffer 2015	1.00 (0.02, 50.40)	.5/3034.5	.5/3034.5	1.70
Marso 2016	1.00 (0.34, 2.97)		6.5/4672.5	22.1
Marso 2016	1.00 (0.02, 50.43)		.5/1649.5	1.70
Holman 2017	1.46 (0.55, 3.90)		6.5/7396.5	27.2
Hernandez 2018	0.37 (0.07, 1.82)		4.5/4715.5	10.2
Gerstein 2019	0.79 (0.31, 2.05)		9.5/4952.5	28.9
Husain 2019	0.26 (0.03, 2.54)		2.5/1592.5	5.11
Gerstein 2021	1.46 (0.08, 27.54)		.5/1359.5	3.03
Subtotal (I-squared = 0.0%, p = 0.836)	0.88 (0.53, 1.47)	28/30684	31/29373	100
SGLT2 inhibitors				
Zinman 2015	1.45 (0.08, 27.48)	1.5/4687.5	.5/2333.5	5.69
Neal 2017	0.75 (0.01, 39.21)		.5/4347.5	3.14
Wiviott 2018	1.82 (0.53, 6.30)		3.5/8579.5	32.0
Perkovic 2019	1.65 (0.23, 11.70)		1.5/2199.5	12.8
McMurray 2019	0.37 (0.02, 5.88)			6.41
· · ·	,		1.5/2371.5	
Cannon 2020	1.16 (0.18, 7.46)		1.5/2747.5	14.2
Heerspink 2020	3.80 (0.39, 36.51)		.5/2152.5	9.62
Packer 2020	0.20 (0.03, 1.17)	.5/1863.5	4.5/1867.5	16.0
Subtotal (I-squared = 0.0%, p = 0.515)	1.10 (0.55, 2.22)	18/33157	14/26599	100
.1 1 10				
	OR (95% CI)	Events, Treatment	Events, Placebo	% Weig
Study DPP-4 inhibitors	OR (95% CI)			
Study DPP-4 inhibitors	OR (95% CI)	Treatment		Weig
Study DPP-4 inhibitors Scirica 2013	0.99 (0.10, 9.54)	Treatment 1.5/8280.5	Placebo 1.5/8212.5	Weig 30.00
Study DPP-4 inhibitors Scrica 2013 White 2013	0.99 (0.10, 9.54) 2.70 (0.17, 43.13	Treatment 1.5/8280.5 3) 1.5/2701.5	Placebo 1.5/8212.5 .5/2679.5	Weig 30.00 20.00
Study DPP-4 inhibitors Scirica 2013 Green 2013 Green 2015	0.99 (0.10, 9.54) 2.70 (0.17, 43.13 0.37 (0.02, 5.89)	Treatment 1.5/8280.5) 1.5/2701.5 .5/7332.5	Placebo 1.5/8212.5 .5/2679.5 1.5/7339.5	Weig 30.00 20.00 20.00
Study DPP-4 inhibitors Scirica 2013 White 2013 Green 2015 Gantz 2017	0.99 (0.10, 9.54) 2.70 (0.17, 43.13 0.37 (0.02, 5.89) 0.37 (0.02, 5.90)	Treatment 1.5/8280.5 3) 1.5/2701.5 .5/7332.5 .5/2092.5	Placebo 1.5/8212.5 .5/2679.5 1.5/7339.5 1.5/2100.5	Weig 30.00 20.00 20.00 20.00
Study DPP-4 inhibitors Cerica 2013 White 2013 Green 2015 Green 2015 Rosenstock 2019	0.99 (0.10, 9.54) 2.70 (0.17, 43.13 0.37 (0.02, 5.89) 0.37 (0.02, 5.90) 1.00 (0.02, 50.27	Treatment 1.5/8280.5 3) 1.5/2701.5 .5/7332.5 .5/2092.5 r) .5/3494.5	Placebo 1.5/8212.5 .5/2679.5 1.5/7339.5 1.5/2100.5 .5/3485.5	Weig 30.00 20.00 20.00 10.00
Study DPP-4 inhibitors Scirica 2013 White 2013 Green 2015 Gantz 2017 Rosenstock 2019 Subtotal (I-squared = 0.0%, p = 0.847)	0.99 (0.10, 9.54) 2.70 (0.17, 43.13 0.37 (0.02, 5.89) 0.37 (0.02, 5.90)	Treatment 1.5/8280.5 3) 1.5/2701.5 .5/7332.5 .5/2092.5 r) .5/3494.5	Placebo 1.5/8212.5 .5/2679.5 1.5/7339.5 1.5/2100.5 .5/3485.5	Weig 30.00 20.00 20.00 10.00
Study DPP-4 inhibitors Cerica 2013 White 2013 Green 2015 Gantz 2017 Rosenstock 2019 GLP-1RAs	0.99 (0.10, 9.54) 2.70 (0.17, 43.13 0.37 (0.02, 5.89) 0.37 (0.02, 5.90) 1.00 (0.02, 50.27 0.82 (0.24, 2.82)	Treatment 1.5/8280.5 3) 1.5/2701.5 .5/7332.5 .5/2092.5 1) .5/3494.5 4.5/23901.5	Placebo 1.5/8212.5 .5/2679.5 1.5/7339.5 1.5/2100.5 .5/3485.5 5.5/23817.5	Weig 30.00 20.00 20.00 10.00 100.0
Study DPP-4 inhibitors Scrica 2013 White 2013 Green 2015 Gantz 2017 Rosenstock 2019 Subtotal (I-squared = 0.0%, p = 0.847) . GIP-1RAs Pfeffer 2015	0.99 (0.10, 9.54) 2.70 (0.17, 43.13 0.37 (0.02, 5.89) 0.37 (0.02, 5.90) 1.00 (0.02, 50.27 0.82 (0.24, 2.82) 1.00 (0.02, 50.40	Treatment 1.5/8280.5 5) 1.5/2701.5 5/7332.5 5/2092.5) .5/3494.5 4.5/23901.5) .5/3034.5	Placebo 1.5/8212.5 .5/2679.5 1.5/7339.5 1.5/2100.5 .5/3485.5 5.5/23817.5 .5/3034.5	Weig 30.00 20.00 20.00 10.00 100.0 5.03
Study DPP-4 inhibitors Scirica 2013 White 2013 Green 2015 Gantz 2017 Rosenstock 2019 Subtotal (I-squared = 0.0%, p = 0.847) GLP-1RAs Pfeffer 2015 Marso 2016	0.99 (0.10, 9.54) 2.70 (0.17, 43.12 0.37 (0.02, 5.89) 0.37 (0.02, 5.92) 1.00 (0.02, 50.27 0.82 (0.24, 2.82) 1.00 (0.02, 50.40 0.61 (0.09, 4.31)	Treatment 1.5/8280.5 1.5/2701.5 .5/2092.5).5/3494.5 4.5/23901.5).5/3034.5 1.5/4668.5	Placebo 1.5/8212.5 .5/2679.5 1.5/7339.5 1.5/2100.5 .5/3485.5 5.5/23817.5 .5/3034.5 2.5/4672.5	Weig 30.00 20.00 20.00 10.00 100.00 5.03 20.1
Study DPP-4 inhibitors Scirica 2013 White 2013 Green 2015 Gantz 2017 Rosenstock 2019 Subtotal (I-squared = 0.0%, p = 0.847) GLP-1RAs Pleffer 2015 Marso 2016	0.99 (0.10, 9.54) 2.70 (0.17, 43.13 0.37 (0.02, 5.89) 0.37 (0.02, 5.90) 1.00 (0.02, 50.27 0.82 (0.24, 2.82) 1.00 (0.02, 50.40 0.61 (0.09, 4.31) 1.00 (0.02, 50.43	Treatment 1.5/8280.5 1.5/2701.5 .5/7332.5 .5/2092.5 1.5/3494.5 4.5/23901.5 1.5/368.5 1.5/4688.5 3.5/1648.5	Placebo 1.5/8212.5 .5/2679.5 1.5/7339.5 1.5/2100.5 5.5/23817.5 5.5/23817.5 5.5/3034.5 2.5/4672.5 .5/1649.5	Weig 30.00 20.00 20.00 10.00 100.0 5.03 20.1 5.03
Study DPP-4 inhibitors Scirica 2013 White 2013 Green 2015 Gantz 2017 Rosenstock 2019 Subtotal (I-squared = 0.0%, p = 0.847) GLP-1RAs Pleffer 2015 Marso 2016	0.99 (0.10, 9.54) 2.70 (0.17, 43.12 0.37 (0.02, 5.89) 0.37 (0.02, 5.92) 1.00 (0.02, 50.27 0.82 (0.24, 2.82) 1.00 (0.02, 50.40 0.61 (0.09, 4.31)	Treatment 1.5/8280.5 1.5/2701.5 .5/7332.5 .5/2092.5 1.5/3494.5 4.5/23901.5 1.5/368.5 1.5/4688.5 3.5/1648.5	Placebo 1.5/8212.5 .5/2679.5 1.5/7339.5 1.5/2100.5 .5/3485.5 5.5/23817.5 .5/3034.5 2.5/4672.5	Weig 30.00 20.00 20.00 10.00 100.0 5.03 20.1 5.03
Study DPP-4 inhibitors Scrica 2013 White 2013 Green 2015 Gantz 2017 Rosenstock 2019 Subtotal (I-squared = 0.0%, p = 0.847) GP-1RAs Pfeffer 2015 Marso 2016 Holman 2017	0.99 (0.10, 9.54) 2.70 (0.17, 43.13 0.37 (0.02, 5.89) 0.37 (0.02, 5.90) 1.00 (0.02, 50.27 0.82 (0.24, 2.82) 1.00 (0.02, 50.40 0.61 (0.09, 4.31) 1.00 (0.02, 50.43	Treatment 1.5/8280.5 3) 1.5/2701.5 .5/7332.5 .5/2092.5 1.5/3494.5 4.5/23901.5 3) .5/3034.5 1.5/4688.5 1.5/4648.5 1.5/7356.5	Placebo 1.5/8212.5 .5/2679.5 1.5/7339.5 1.5/2100.5 5.5/23817.5 5.5/23817.5 5.5/3034.5 2.5/4672.5 .5/1649.5	Weig 30.00 20.00 20.00 10.00 100.0 5.03 20.1 5.03
Study DPP-4 inhibitors Scirica 2013 White 2013 Green 2015 Gantz 2017 Rosenstock 2019 Subtotal (I-squared = 0.0%, p = 0.847) GLP-1RAs Pfeffer 2015 Marso 2016 Marso 2016 Holman 2017 Hernandez 2018	0.99 (0.10, 9.54) 2.70 (0.17, 43.13 0.37 (0.02, 5.89) 1.00 (0.02, 5.027) 0.82 (0.24, 2.82) 1.00 (0.02, 50.40 0.61 (0.09, 4.31) 1.00 (0.02, 50.43	Treatment 1.5/8280.5 b) 1.5/2701.5 5/7332.5 5/2092.5 c) 5/3494.5 4.5/23901.5 1.5/3034.5 1.5/468.5 b) 5/1648.5 c) 5/1648.5 c) 5/1756.5 c) 5/4717.5 c)	Placebo 1.5/8212.5 .5/2679.5 1.5/7339.5 1.5/2100.5 .5/3485.5 5.5/23817.5 .5/3034.5 2.5/4672.5 .5/1649.5 2.5/7396.5	Weig 30.00 20.00 20.00 10.00 10.00 5.03 20.11 5.03 20.11 5.03
Study DPP-4 inhibitors Scirica 2013 White 2013 Green 2015 Gantz 2017 Rosenstock 2019 Subtatal (I-squared = 0.0%, p = 0.847) GLP-1RAs Pfeffer 2015 Marso 2016	0.99 (0.10, 9.54) 2.70 (0.17, 43.13 0.37 (0.02, 5.89) 0.37 (0.02, 5.90) 1.00 (0.02, 50.27 0.82 (0.24, 2.82) 1.00 (0.02, 50.42 0.61 (0.09, 4.31) 1.00 (0.02, 50.43 0.61 (0.09, 4.33) 1.00 (0.02, 50.38 0.37 (0.07, 1.82)	Treatment 1.5/8280.5 1.5/2701.5 5/7332.5 5/2092.5 1.5/3494.5 4.5/23901.5 1.5/4668.5 1.5/4668.5 1.5/4668.5 1.5/1648.5 1.5/7356.5 1.5/4949.5	Placebo 1.5/8212.5 .5/2679.5 1.5/2100.5 1.5/2100.5 .5/3485.5 5.5/23817.5 .5/3034.5 2.5/4672.5 .5/1649.5 2.5/7396.5 .5/4715.5	30.00 20.00 20.00 20.00 10.00 100.0 5.03 20.11 5.03 20.11 5.03 30.16
Study DPP-4 inhibitors Scrica 2013 White 2013 Green 2015 Gantz 2017 CDP-1RAs Pleffer 2015 Holman 2017 Hernandez 2018 Gerstein 2019 Husain 2019	0.99 (0.10, 9.54) 2.70 (0.17, 43.13 0.37 (0.02, 5.89) 1.00 (0.02, 50.27 0.82 (0.24, 2.82) 1.00 (0.02, 50.47 0.61 (0.09, 4.31) 1.00 (0.02, 50.43 0.61 (0.09, 4.33) 1.00 (0.02, 50.38 0.37 (0.07, 1.82) 0.37 (0.02, 5.89)	Treatment 1.5/8280.5 1) 1.5/2701.5 .5/7332.5 .5/2092.5 1) .5/3094.5 4.5/23901.5 1) .5/3094.5 1.5/468.5 1.5/7565.5 1) .5/494.9 .5/1591.5	Placebo 1.5/8212.5 .5/2679.5 1.5/7339.5 1.5/7339.5 1.5/2100.5 .5/3485.5 5.5/23817.5 .5/3034.5 2.5/7396.5 .5/1649.5 1.5/1592.5	Weig 30.00 20.00 20.00 10.00 5.03 20.11 5.03 20.11 5.03 30.16 10.06
Study DPP-4 inhibitors Scirica 2013 White 2013 Green 2015 Gantz 2017 Rosenstock 2019 Subtotal (I-squared = 0.0%, p = 0.847) GLP-1RAs Peffer 2015 Marso 2016 Holman 2017 Gerstein 2019	0.99 (0.10, 9.54) 2.70 (0.17, 43.13 0.37 (0.02, 5.89) 0.37 (0.02, 5.90) 1.00 (0.02, 50.27 0.82 (0.24, 2.82) 1.00 (0.02, 50.42 0.61 (0.09, 4.31) 1.00 (0.02, 50.43 0.61 (0.09, 4.33) 1.00 (0.02, 50.38 0.37 (0.07, 1.82)	Treatment 1.5/8280.5 1) 1.5/2701.5 5/732.5 5/2092.5 1.5/2494.5 4.5/23901.5 1.5/4668.5 1) 5/744.5 1.5/4648.5 1.5/4648.5 1.5/4949.5 5) 5/5717.5	Placebo 1.5/8212.5 .5/2679.5 1.5/239.5 1.5/2100.5 .5/3485.5 5.5/23817.5 5.5/3034.5 2.5/4672.5 .5/1649.5 2.5/7396.5 .5/7415.5 4.5/4952.5	Weig 30.00 20.00 20.00 10.00 100.0 5.03 20.1 5.03 20.1 5.03 30.1 10.00 4.47
Study DPP-4 inhibitors Scrica 2013 White 2013 Green 2015 Gant 2017 CDP-1RAs Pleffer 2015 Marso 2016 Holman 2017 Hernandez 2018 Gerstein 2019 Gerstein 2021 Subtotal (I-squared = 0.0%, p = 0.999)	0.99 (0.10, 9.54) 2.70 (0.17, 43.13 0.37 (0.02, 5.89) 1.00 (0.02, 50.27) 0.82 (0.24, 2.82) 1.00 (0.02, 50.27 0.82 (0.24, 2.82) 1.00 (0.02, 50.42 0.61 (0.09, 4.33) 1.00 (0.02, 50.38 0.87 (0.07, 1.82) 0.37 (0.02, 5.89) 0.47 (0.01, 30.21	Treatment 1.5/8280.5 1) 1.5/2701.5 5/732.5 5/2092.5 1.5/2494.5 4.5/23901.5 1.5/4668.5 1) 5/744.5 1.5/4648.5 1.5/4648.5 1.5/4949.5 5) 5/4717.5 1.5/4949.5 5) 5/2717.5	Placebo 1.5/8212.5 .5/2679.5 1.5/730.5 1.5/2100.5 .5/3034.5 2.5/4672.5 .5/1649.5 2.5/4672.5 .5/14715.5 4.5/4852.5 .5/1359.5	Weig 30.00 20.00 20.00 10.00 100.0 5.03 20.1 5.03 20.1 5.03 30.1 10.00 4.47
Study DPP-4 inhibitors Scirica 2013 White 2013 Green 2015 Gantz 2017 Rosenstock 2019 Subtotal (I-squared = 0.0%, p = 0.847) GLP-1RAs Pfeffer 2015 Marso 2016 Marso 2016 Gerstein 2019 Gerstein 2019 Gerstein 2019 Gerstein 201 Subtotal (I-squared = 0.0%, p = 0.999) . GLT2 inhibitors	0.99 (0.10, 9.54) 2.70 (0.17, 43.13 0.37 (0.02, 5.89) 1.00 (0.02, 50.27) 0.82 (0.24, 2.82) 1.00 (0.02, 50.40 0.61 (0.09, 4.31) 1.00 (0.02, 50.43 0.61 (0.09, 4.33) 1.00 (0.02, 50.83 0.61 (0.09, 4.33) 1.00 (0.02, 50.89) 0.37 (0.02, 5.89) 0.47 (0.01, 30.21 0.53 (0.22, 1.28)	Treatment 1.5/8280.5 1) 1.5/2701.5 5/732.5 5/2092.5 1) 5/3034.5 1.5/464.5 1.5/4668.5 1) 5/144.5 1.5/4648.5 1.5/4541.5 5) 5/1471.7 5) 5/1591.5 5) 5/12717.5 7/30684	Placebo 1.5/8212.5 .5/2679.5 1.5/730.5 1.5/2100.5 .5/3034.5 2.5/4672.5 .5/1649.5 2.5/4672.5 .5/1649.5 2.5/46715.5 .5/14715.5 .5/1359.5 13/29373	Weig 30.00 20.00 20.00 10.00 10.00 5.03 20.11 5.03 20.11 5.03 30.16 10.06 4.47
Study DPP-4 inhibitors Scirica 2013 White 2013 Green 2015 Gantz 2017 Rosenstock 2019 Subtotal (I-squared = 0.0%, p = 0.847) GLP-1RAs Pfeffer 2015 Marso 2016 Homand 2017 Gerstein 2019 Gerstein 2019 Subtotal (I-squared = 0.0%, p = 0.999) SGLT2 inhibitors Zinman 2015	0.99 (0.10, 9.54) 2.70 (0.17, 43.13 0.37 (0.02, 5.89) 0.37 (0.02, 5.90) 1.00 (0.02, 50.27 0.82 (0.24, 2.82) 1.00 (0.02, 50.43 0.61 (0.09, 4.31) 1.00 (0.02, 50.43 0.61 (0.09, 4.33) 1.00 (0.02, 50.38 0.37 (0.07, 1.82) 0.37 (0.07, 1.82) 0.37 (0.01, 30.21 0.53 (0.22, 1.28)	Treatment 1.5/8280.5) 1.5/2701.5 .5/7332.5 .5/2092.5) 5/3034.5 1.5/468.5 1.5/3668.5) 5/5444.5 1.5/468.5 1.5/7356.5) 5/6471.5 1.5/4949.5 .5/1591.5) 5/2717.5 2.5/271.5 .5/271.5 .5/2735.5) 5/271.5 .5/2735.5) 5/271.5 .5/2735.5 .5/2755.5	Placebo 1.5/8212.5 .5/2679.5 1.5/739.5 1.5/2100.5 .5/3034.5 2.5/4672.5 .5/1649.5 2.5/7396.5 .5/1475.5 4.5/4952.5 1.5/1952.5 .5/1359.5 .5/1359.3 .5/1359	Weig 30.00 20.00 20.00 10.00 10.00 5.03 20.11 5.03 30.16 4.47 100.0 7.02
Study DPP-4 inhibitors Scrica 2013 White 2013 Green 2015 Gant 2017 CSLP-1RAs Peffer 2015 Marso 2016 Holman 2017 Hernandez 2016 Gerstein 2019 Gerstein 201 Schutz (I-squared = 0.0%, p = 0.999) CSLT2 inhibitors Schutz (I-squared = 0.0%, p = 0.999) CSLT2 inhibitors Schutz (I-squared = 0.0%, p = 0.999) CSLT2 inhibitors Schutz (I-squared = 0.0%, p = 0.999) CSLT2 inhibitors Schutz (I-squared = 0.0%, p = 0.999) CSLT2 inhibitors Schutz (I-squared = 0.0%, p = 0.999) CSLT2 inhibitors Schutz (I-squared = 0.0%, p = 0.999) CSLT2 inhibitors Schutz (I-squared = 0.0%, p = 0.999) CSLT2 inhibitors Schutz (I-squared = 0.0%, p = 0.999) CSLT2 inhibitors Schutz (I-squared = 0.0%, p = 0.999) CSLT2 inhibitors Schutz (I-squared = 0.0%, p = 0.999) CSLT2 inhibitors Schutz (I-squared = 0.0%, p = 0.999) CSLT2 inhibitors Schutz (I-squared = 0.0%, p = 0.999) CSLT2 inhibitors Schutz (I-squared = 0.0%, p = 0.999) CSLT2 inhibitors Schutz (I-squared = 0.0%, p = 0.999) CSLT2 inhibitors Schutz (I-squared = 0.0%, p = 0.999) CSLT2 inhibitors Schutz (I-squared = 0.0%, p = 0.999) CSLT2 inhibitors Schutz (I-squared = 0.0%, p = 0.999) CSLT2 (I-squa	0.99 (0.10, 9.54) 2.70 (0.17, 43.13 0.37 (0.02, 5.89) 0.37 (0.02, 5.90) 1.00 (0.02, 50.27 0.82 (0.24, 2.82) 1.00 (0.02, 50.47 0.61 (0.09, 4.31) 1.00 (0.02, 50.42 0.61 (0.09, 4.33) 1.00 (0.02, 50.33 0.67 (0.07, 1.82) 0.37 (0.02, 5.89) 0.47 (0.01, 30.21 0.53 (0.22, 1.28) 0.47 (0.01, 30.12 0.75 (0.01, 39.21	Treatment 1.5/8280.5) 1.5/2701.5 .5/7332.5 .5/2092.5) 5/3034.5 1.5/464.5 1.5/7356.5)) 5/1648.5 1.5/7356.5)) 5/1648.5 1.5/4591.5).5/4591.5) 5/2717.5 1.5/4597.5) 5/4687.5).5/4687.5	Placebo 1.5/8212.5 .5/2679.5 1.5/7339.5 1.5/7339.5 1.5/210.5 .5/3034.5 2.5/3034.5 2.5/308.5 .5/1649.5 2.5/1986.5 .5/4715.5 4.5/452.5 1.5/159.5 1.3/299.5 .5/1329.5 .5/1329.5 .5/233.5 .5/233.5 .5/233.5	Weig 30.00 20.00 20.00 10.00 100.00 5.03 20.11 5.03 20.11 5.03 30.16 10.06 4.47 100.0 7.02 7.75
Study DPP-4 inhibitors Scirica 2013 White 2013 Green 2015 Gantz 2017 Rosenstock 2019 Subtotal (I-squared = 0.0%, p = 0.847) GLP-1RAs Pfeffer 2015 Marso 2016 Marso 2016 Hernandez 2018 Gerstein 2019 Gerstein 2019 Subtotal (I-squared = 0.0%, p = 0.999) SGL72 inhibitors Zinman 2015 Wixiott 2018	0.99 (0.10, 9.54) 2.70 (0.17, 43.13 0.37 (0.02, 5.89) 1.00 (0.02, 50.27 0.82 (0.24, 2.82) 1.00 (0.02, 50.47 0.61 (0.09, 4.31) 1.00 (0.02, 50.43 0.61 (0.09, 4.33) 1.00 (0.02, 50.83 0.37 (0.07, 1.82) 0.37 (0.02, 5.89) 0.47 (0.01, 30.21 0.53 (0.22, 1.28) 0.47 (0.01, 30.12 0.75 (0.01, 39.21 0.76 (0.01, 30.25)	Treatment 1.5/8280.5 1) 1.5/2701.5 5/732.5 5/2092.5) 5/3034.5 1.5/4645.5 1) 5/3034.5 1.5/4645.5 1) 5/1471.7 5/1591.5 2) 5/1591.5 2) 5/1591.5 2) 5/4687.5 5/5695.5 .5/8582.5	Placebo 1.5/8212.5 .5/2679.5 1.5/730.5 1.5/2100.5 .5/3485.5 .5/3487.5 .5/4672.5 .5/4672.5 .5/4674.5 .5/44715.5 .5/1359.5 13/29373 .5/233.5 .5/233.5 .5/233.5 .5/2347.5	Weig 30.00 20.00 20.00 20.00 10.00 100.00 5.03 20.11 5.03 20.11 5.03 30.16 10.06 4.47 100.0 7.02 7.75 23.73
Study DPP-4 inhibitors Scirica 2013 Mite 2013 Green 2015 Santz 2017 Rosenstock 2019 Subtotal (I-squared = 0.0%, p = 0.847) GLP-1RAs Preffer 2015 Marso 2016 Howarso 2016 Gerstein 2019 Serstein 2019 Subtotal (I-squared = 0.0%, p = 0.999) SGLT2 inhibitors Zinman 2017 Wriviott 2018 Perkovic 2019	0.99 (0.10, 9.54) 2.70 (0.17, 43.13 0.37 (0.02, 5.89) 0.37 (0.02, 5.90) 1.00 (0.02, 50.27 0.82 (0.24, 2.82) 1.00 (0.02, 50.43 0.61 (0.09, 4.31) 1.00 (0.02, 50.43 0.61 (0.09, 4.33) 1.00 (0.02, 50.38 0.37 (0.07, 1.82) 0.37 (0.07, 1.82) 0.37 (0.07, 1.82) 0.37 (0.01, 30.21 0.53 (0.22, 1.28) 0.47 (0.01, 30.12 0.75 (0.01, 30.21 0.76 (0.01, 30.21 0.76 (0.01, 32, 53) 1.00 (0.02, 50.33	Treatment 1.5/8280.5) 1.5/2701.5 .5/7332.5 .5/2092.5) 5/3034.5 1.5/4668.5 1.5/3668.5 1.5/7356.5) 5/444.5 1.5/4668.5 1.5/7356.5) 5/2717.5 1.5/291.5) 5/2717.5 1.5/2684 2) 5/4667.5) 5/5785.5 .5/5785.5) 5/5785.5) 5/5785.5) 5/5785.5	Placebo 1.5/8212.5 .5/2679.5 1.5/730.5 1.5/2100.5 .5/3034.5 2.5/4672.5 .5/1649.5 2.5/7396.5 .5/14715.5 1.5/1592.5 .5/1399.5 13/2937.3 .5/2333.5 .5/2439.5 .5/2447.5 .5/247	Weig 30.00 20.00 20.00 10.00 10.00 5.03 20.11 5.03 30.16 10.06 4.47 100.6 7.02 7.75 23.73 7.91
Study DPP-4 inhibitors Scirica 2013 White 2013 Green 2015 Gantz 2017 Rosenstock 2019 Subtotal (I-squared = 0.0%, p = 0.847) GLP-1RAs Preffer 2015 Marso 2016 Marso 2016 Gerstein 2019 Subtotal (I-squared = 0.0%, p = 0.999) SCLT2 inhibitors Zinman 2017 Wiviott 2018 Persource 2019	0.99 (0.10, 9.54) 2.70 (0.17, 43.13 0.37 (0.02, 5.89) 1.00 (0.02, 50.27 0.82 (0.24, 2.82) 1.00 (0.02, 50.47 0.61 (0.09, 4.31) 1.00 (0.02, 50.43 0.61 (0.09, 4.33) 1.00 (0.02, 50.83 0.37 (0.07, 1.82) 0.37 (0.02, 5.89) 0.47 (0.01, 30.21 0.53 (0.22, 1.28) 0.47 (0.01, 30.12 0.75 (0.01, 39.21 0.76 (0.01, 30.25)	Treatment 1.5/8280.5) 1.5/2701.5 .5/7332.5 .5/2092.5) 5/3034.5 1.5/4668.5 1.5/3668.5 1.5/7356.5) 5/444.5 1.5/4668.5 1.5/7356.5) 5/2717.5 1.5/291.5) 5/2717.5 1.5/2684 2) 5/4667.5) 5/5785.5 .5/5785.5) 5/5785.5) 5/5785.5) 5/5785.5	Placebo 1.5/8212.5 .5/2679.5 1.5/730.5 1.5/2100.5 .5/3485.5 .5/3487.5 .5/4672.5 .5/4672.5 .5/4674.5 .5/44715.5 .5/1359.5 13/29373 .5/233.5 .5/233.5 .5/233.5 .5/2347.5	Weig 30.00 20.00 20.00 10.00 10.00 5.03 20.11 5.03 30.16 10.06 4.47 100.6 7.02 7.75 23.73 7.91
Study DPP-4 inhibitors Scirica 2013 White 2013 Green 2015 Gantz 2017 Rosenstock 2019 Subtotal (I-squared = 0.0%, p = 0.847) GLP-1RAs Pfeffer 2015 Marso 2016 Marso 2016 Gerstein 2019 Gerstein 2019 Gerstein 2019 Gerstein 201 Subtotal (I-squared = 0.0%, p = 0.999) . GLT2 inhibitors	0.99 (0.10, 9.54) 2.70 (0.17, 43.13 0.37 (0.02, 5.89) 0.37 (0.02, 5.90) 1.00 (0.02, 50.27 0.82 (0.24, 2.82) 1.00 (0.02, 50.43 0.61 (0.09, 4.31) 1.00 (0.02, 50.43 0.61 (0.09, 4.33) 1.00 (0.02, 50.38 0.37 (0.07, 1.82) 0.37 (0.07, 1.82) 0.37 (0.07, 1.82) 0.37 (0.01, 30.21 0.53 (0.22, 1.28) 0.47 (0.01, 30.12 0.75 (0.01, 30.21 0.76 (0.01, 30.21 0.76 (0.01, 32, 53) 1.00 (0.02, 50.33	Treatment 1.5/6280.5 1) 1.5/2701.5 5/7332.5 5/7302.5 1.5/3494.5 4.5/23901.5 1.5/4668.5 1.5/4668.5 1.5/16468.5 1.5/16468.5 1.5/1649.5 5/1591.5 1.5/4687.5 1.5/4687.5 5/56795.5 5/6595.5 5/6520.5 1.5/2717.5 1.5/2620.5 5/273.5 1.5/2795.5 5/2795.5	Placebo 1.5/8212.5 .5/2679.5 1.5/730.5 1.5/2100.5 .5/3034.5 2.5/4672.5 .5/1649.5 2.5/7396.5 .5/14715.5 1.5/1592.5 .5/1399.5 13/2937.3 .5/2333.5 .5/2439.5 .5/2447.5 .5/247	Weig 30.00 20.00 20.00 10.00 10.00 5.03 20.11 5.03 20.11 5.03 30.16 10.06 4.47 100.0 7.02 7.75 23.73 7.91
Study DPP-4 inhibitors Scirica 2013 White 2013 Green 2015 Gantz 2017 Rosenstock 2019 Subtatl (I-squared = 0.0%, p = 0.847) GLP-1RAs Peffer 2015 Marso 2016 Homan 2017 Gerstein 2019 Gerstein 2019 Gerstein 2019 Subtotal (I-squared = 0.0%, p = 0.999) Status SGLT2 inhibitors Xinman 2015 Verkovic 2019 Mixed 2019	0.99 (0.10, 9.54) 2.70 (0.17, 43.13 0.37 (0.02, 5.89) 0.37 (0.02, 5.90) 1.00 (0.02, 50.27 0.82 (0.24, 2.82) 1.00 (0.02, 50.42 0.61 (0.09, 4.31) 1.00 (0.02, 50.43 0.61 (0.09, 4.33) 1.00 (0.02, 50.33 0.37 (0.07, 1.82) 0.37 (0.07, 1.82) 0.37 (0.07, 1.82) 0.37 (0.02, 5.89) 0.47 (0.01, 30.21 0.53 (0.22, 1.28) 0.47 (0.01, 30.12 0.75 (0.01, 39.21 0.25 (0.01, 39.21 0.26 (0.03, 2.53) 1.00 (0.02, 5.88)	Treatment 1.5/8280.5 1) 1.5/2701.5 5/732.5 5/2092.5) 5/3034.5 1.5/4645.5 1) 5/47417.5 1.5/4645.5 1) 5/14717.5 1.5/4949.5 5/1591.5 2) 5/12717.5 7/30684 2) 5/4687.5) 5/6795.5 5/6862.5) 5/2733.5 5/5233.5	Placebo 1.5/8212.5 .5/2679.5 1.5/7339.5 1.5/7339.5 1.5/2100.5 .5/3034.5 2.5/3034.5 2.5/475.5 .5/1649.5 2.5/475.5 .5/1592.5 .5/475.5 .5/475.5 .5/475.5 .5/475.5 .5/439.5 1.3/2937.3 .5/233.5 .5/2497.5 1.5/2371.5	Weig 30.00 20.00 20.00 10.00 10.00 5.03 20.11 5.03 20.11 5.03 30.16 10.06 4.47 100.0 7.02 7.75 23.73 7.91
Study DPP-4 inhibitors Scirica 2013 White 2013 Green 2015 Gantz 2017 Rosenstock 2019 Subtotal (I-squared = 0.0%, p = 0.847) GLP-1RAs Preffer 2015 Marso 2016 Marso 2016 Gerstein 2019 Subtotal (I-squared = 0.0%, p = 0.999) SCLT2 inhibitors Zinman 2017 Wiviott 2018 Perkovic 2019 Memory 2019 Cannon 2020 Heerspink 2020	0.99 (0.10, 9.54) 2.70 (0.17, 43.13 0.37 (0.02, 5.89) 0.37 (0.02, 5.90) 1.00 (0.02, 50.27 0.82 (0.24, 2.82) 1.00 (0.02, 50.43 0.61 (0.09, 4.31) 1.00 (0.02, 50.43 0.61 (0.09, 4.33) 1.00 (0.02, 50.34 0.37 (0.07, 1.82) 0.37 (0.01, 30.21 0.53 (0.22, 1.28) 0.47 (0.01, 30.21 0.53 (0.22, 5.83) 0.47 (0.01, 2.503) 1.00 (0.02, 5.64)	Treatment 1.5/8280.5) 1.5/2701.5 .5/7332.5 .5/2092.5) .5/3034.5 1.5/4668.5) .5/3034.5 1.5/4668.5) .5/1648.5 1.5/7356.5) .5/449.5 .5/1591.5) .5/2715.5 .5/5785.5 .5/5785.5 .5/5785.5) .5/2202.5 .5/5785.5 .5/5	Placebo 1.5/8212.5 .5/2679.5 1.5/739.5 1.5/2100.5 .5/3034.5 2.5/4672.5 .5/1649.5 2.5/7396.5 .5/14715.5 1.5/139.5 1.3/12937.3 .5/139.5 .5/219.5 .5/219.5 .5/219.5 .5/219.5 .5/217.5 .5/219.5 .5/219.5 .5/217.5 .5/219.5 .5/219.5 .5/215.5 .5/215.5 .5/219.5 .5/219.5 .5/215.5 .5/219.5 .5/219.5 .5/215.5 .5/219.5 .5/219.5 .5/215.5 .5/219.5 .5/219.5 .5/219.5 .5/219.5 .5/215.5 .5/219.5 .5/219.5 .5/215.5 .5/219.5 .5/219.5 .5/219.5 .5/215.5 .5/219.5 .5/219.5 .5/215.5 .5/215.5 .5/219.5 .5/215.5	30.00 20.00 20.00 20.00 20.00 10.00 10.00 5.03 20.11 5.03 20.12 5.03 20.10 20.10 20.1
Study DPP-4 inhibitors Scirica 2013 White 2013 Green 2015 Santz 2017 Rosenstock 2019 Subtotal (I-squared = 0.0%, p = 0.847) GLP-1RAs Pleffer 2015 Warso 2016 Howarso 2016 Howarso 2016 Serstein 2019 Subtotal (I-squared = 0.0%, p = 0.999) GGLT2 inhibitors Summa 2015 Verkovic 2019 Mixer 2019 Serktorin 2021 Subtotal (I-squared = 0.0%, p = 0.999) GGLT2 inhibitors Simma 2015 Verkovic 2019 Mixer 2019 Heerspink 2020 Parkovic 2019 Mixer 2020	0.99 (0.10, 9.54) 2.70 (0.17, 43, 13) 0.37 (0.02, 5.89) 0.37 (0.02, 5.90) 1.00 (0.02, 50.27) 0.82 (0.24, 2.82) 1.00 (0.02, 50.42) 0.61 (0.09, 4.33) 1.00 (0.02, 50.38) 0.37 (0.02, 50.38) 0.37 (0.02, 5.89) 0.47 (0.01, 30.21) 0.53 (0.22, 1.28) 0.47 (0.01, 30.21) 0.53 (0.22, 1.28) 0.47 (0.01, 30.21) 0.53 (0.22, 1.28) 0.47 (0.01, 30.21) 0.53 (0.02, 5.88) 0.47 (0.02, 5.88) 0.55 (0.01, 2.90)	Treatment 1.5/6280.5 1) 1.5/2701.5 5/7332.5 5/7392.5 1.5/4668.5 1.5/4668.5 1.5/4668.5 1.5/4668.5 1.5/16468.5 1.5/1640.5 1.5/1649.5 5/5191.5 1.5/4687.5 1.5/4687.5 1.5/4687.5 1.5/4687.5 1.5/4687.5 1.5/4687.5 1.5/4687.5 1.5/4687.5 1.5/2717.5 5/569.5 5/579.5 5/5	Placebo 1.5/8212.5 .5/2679.5 1.5/730.5 1.5/2100.5 .5/3455.5 .5/24672.5 .5/1649.5 .5/4672.5 .5/14715.5 .5/14715.5 .5/1359.5 13/29373 .5/2333.5 .5/2333.5 .5/24347.5 2.5/24347.5 1.5/2371.5	Weig 30.00 20.00 20.00 10.00 10.00 5.03 20.11 5.03 20.11 5.03 30.16 10.06 7.02 7.75 23.73 7.91 15.82 14.06
Study DPP-4 inhibitors Scirica 2013 White 2013 Green 2015 Gantz 2017 Rosenstock 2019 Subtotal (I-squared = 0.0%, p = 0.847) GLP-1RAs Pfeffer 2015 Marso 2016 Holman 2017 Hernandez 2018 Gerstein 2019 Gerstein 2019 Subtotal (I-squared = 0.0%, p = 0.999) Subtotal (I-squared = 0.0%, p = 0.999) GLZ inhibitors Zinman 2015 Wiviott 2018 Perkovic 2019 Gartarian 2017 McMurray 2019 Gartarian 2017	0.99 (0.10, 9.54) 2.70 (0.17, 43.13 0.37 (0.02, 5.89) 0.37 (0.02, 5.90) 1.00 (0.02, 50.27 0.82 (0.24, 2.82) 1.00 (0.02, 50.42 0.61 (0.09, 4.31) 1.00 (0.02, 50.43 0.61 (0.09, 4.33) 1.00 (0.02, 50.36 0.37 (0.02, 5.83) 0.47 (0.01, 30.21 0.53 (0.22, 1.28) 0.47 (0.01, 30.21 0.75 (0.01, 39.21 0.75 (0.01, 39.21 0.75 (0.01, 39.21 0.75 (0.01, 39.21 0.75 (0.01, 39.21 0.75 (0.01, 39.21 0.75 (0.01, 2.58) 0.15 (0.01, 2.50) 1.00 (0.02, 5.88)	Treatment 1.5/6280.5 1) 1.5/2701.5 5/7332.5 5/7392.5 1.5/4668.5 1.5/4668.5 1.5/4668.5 1.5/4668.5 1.5/16468.5 1.5/1640.5 1.5/1649.5 5/5191.5 1.5/4687.5 1.5/4687.5 1.5/4687.5 1.5/4687.5 1.5/4687.5 1.5/4687.5 1.5/4687.5 1.5/4687.5 1.5/2717.5 5/569.5 5/579.5 5/5	Placebo 1.5/8212.5 .5/2679.5 1.5/2309.5 1.5/2308.5 .5/3485.5 .5/3485.5 .5/3485.5 .5/34872.5 .5/1649.5 2.5/4715.5 .5/1649.5 .5/1359.5 .5/1359.5 .5/2333.5 .5/2333.5 .5/2331.5 .5/24347.5 1.5/2271.5 1.5/2271.5 1.5/2371.5	Weig 30.00 20.00 20.00 20.00 20.00 10.00 10.00 5.03 20.11 5.03 20.11 5.03 30.16 10.00 4.47 100.0 7.02 7.75 23.73 7.91 15.83 14.00 7.91 15.83

Figure S3. The funnel plot for the effects of DPP-4 inhibitors, GLP-1RAs, and SGLT2 inhibitors on risk of dementia. OR, odds ratio; DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; GLP-1RAs, glucagon-like peptide-1 receptor agonists; SGLT2 inhibitors, sodium-glucose co-transporter-2 inhibitors



4

References

- 1. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med.* 2013;369:1317-1326.
- 2. White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med.* 2013;369:1327-1335.
- 3. Green JB, Bethel MA, Armstrong PW, et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med.* 2015;373:232-242.
- 4. Gantz I, Chen M, Suryawanshi S, et al. A randomized, placebo-controlled study of the cardiovascular safety of the once-weekly DPP-4 inhibitor omarigliptin in patients with type 2 diabetes mellitus. *Cardiovasc Diabetol.* 2017;16:112.
- 5. Rosenstock J, Perkovic V, Johansen OE, et al. Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial. *JAMA*. 2019;321:69-79.
- 6. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. *N Engl J Med.* 2015;373:2247-2257.
- 7. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med.* 2016;375:311-322.
- 8. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med.* 2016;375:1834-1844.
- 9. Holman RR, Bethel MA, Mentz RJ, et al. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med.* 2017;377:1228-1239.
- 10. Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet.* 2018;392:1519-1529.
- 11. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet*. 2019;394:121-130.
- 12. Husain M, Birkenfeld AL, Donsmark M, et al. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med.* 2019;381:841-851.
- 13. Gerstein HC, Sattar N, Rosenstock J, et al. Cardiovascular and Renal Outcomes with Efpeglenatide in Type 2 Diabetes. *N Engl J Med.* 2021;385:896-907.
- 14. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med.* 2015;373:2117-2128.
- 15. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med.* 2017;377:644-657.
- 16. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med.* 2019;380:347-357.
- 17. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med.* 2019;380:2295-2306.
- 18. Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. *N Engl J Med.* 2020;383:1425-1435.
- 19. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med.* 2019;381:1995-2008.
- 20. Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med.* 2020;383:1436-1446.
- 21. Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med.* 2020;383:1413-1424.