The Innovation Medicine

Supplemental Information

Effect of anti-diabetic drugs in primary prevention of cardiovascular disease in type 2 diabetes and prediabetes: a systematic review and meta-analysis of randomized trials

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Supplemental Methods

This systematic review was reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[1] The research protocol was registered on the PROSPERO registry (CRD42020196192, 30 July 2020).

Study eligibility

Eligible studies included those where diet, exercise, lifestyle advice, or any other non-pharmacological intervention was used alongside drug therapy, providing the only difference between comparison arms was the presence or absence of anti-diabetic drug treatment. Trials were included if at least one of the following macrovascular outcomes were reported: fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, cardiovascular death, unstable angina, heart failure, and revascularization.

Search strategy

Relevant RCTs reporting management of diabetes and prediabetes were sought from database inception up to 20 September 2022 from Medline, Embase, the Cochrane library, Clinicaltrials.gov registry, and International Clinical Trials Registry Platform (ICTRP) of RCTs. Searches included keywords and MeSH terms for type 2 diabetes mellitus, impaired fasting glucose, impaired glucose tolerance, non-insulin anti-diabetes drugs and filters for RCTs (see Supplement Table 1 for search details). Hand-searching of the bibliographies of review articles and eligible trials was also conducted.

Screening

Initial screening of identified citations was undertaken by a member of the research group. Any potentially eligible trial was retained and further independently assessed by two researchers. Disagreements were resolved through discussion or consultation with a third experienced researcher.

Data extraction

Data were extracted independently by two researchers and entered into a structured extraction form. The following data were extracted from each eligible trial: 1) details of the citation (author, publication year, trial registration number); 2) study design, treatment details, and outcome measures; 3) patients' characteristics (age, body mass index [BMI], baseline glucose

measures, etc.); 4) main results about treatment effect. Discrepancy in extracted data was resolved through discussion or by consulting a third researcher, if necessary. Data not reported in original publications were sought from the online appendices, clinical trials registry websites, or other publications derived from the same trial.

Risk of bias assessment

The risk of bias was assessed independently by two reviewers with disagreements settled through discussions. The Cochrane Collaboration's tool for assessing risk of bias was used to assess six domains: sequence generation, concealment of allocation, blinding, incomplete outcome data, and selective reporting.[2]

Statistical analysis

Heterogeneity was assessed using the I^2 statistic, which describes the percentage of variability in effect estimates that was due to clinical and/or methodological factors rather than sampling error.[3] Heterogeneity was considered substantial if I^2 was greater than 50%. Publication bias was examined using the funnel plot and Egger's test.[3] All statistical analyses were conducted by using R (R version 4.3.1, R Foundation for Statistical Computing, Vienna, Austria, 2023, https://www.R-project.org/). A two-sided significance level of 0.05 was adopted for all analyses except for the statistical test for publication bias, in which a two-sided P value less than 0.1 was indicative of statistical significance.

Supplemental Results

Flow-diagram for literature search and screening is shown in Supplement Figure 1. Full citations of eligible trials are listed in the Supplement List. Characteristics of eligible trials are summarized in Supplement Table 2. The majority of patients (99.2%) were over-weight or obese. All-cause mortality, myocardial infarction, stroke, and the broader composite cardiovascular outcome were reported in 68, 90, 83, and 129 trials, respectively.

Overall, 40 trials evaluated the effects of various dipeptidyl peptidase 4 (DPP4) inhibitors, 6 evaluated metformin, 6 evaluated thiazolidinediones, 29 evaluated sodium glucose co-transporter 2 (SGLT2) inhibitors, 31 evaluated glucagon-like peptide 1 (GLP1) receptor agonists, and the other 20 trials evaluated alpha-glucosidase inhibitors, sulfonylureas, meglitinides, or combination of different drugs. In 98 trials (74.2%), some participants were already on certain anti-diabetic medications (background treatments) at baseline. Intervention treatment details are shown in Supplement Table 2.

Detailed results regarding risk of bias of eligible trials are shown in Supplement Table 3. All studies mentioned that they had allocated patients randomly to groups, although 33.3% of eligible trials did not report the details of randomization methods. A placebo was used in 94.7% of eligible trials. More than 80% of eligible trials had low risk of bias in the domains of "incomplete outcome data" and "selective reporting". No obvious evidence for publication bias was identified through visual inspection of the funnel plot (Supplement Figure 2) or Egger's test (P = 0.630).

Supplemental List List of citations of all eligible trials. Two eligible trials, NCT00121966 and NCT02273050, reported the results by different anti-diabetic drugs. These 2 trials were divided as separate studies in the quantitative synthesis.

1. Coniff RF, Shapiro JA, Seaton TB, Bray GA. Multicenter, placebo-controlled trial comparing acarbose (BAY g 5421) with placebo, tolbutamide, and tolbutamide-plus-acarbose in non-insulin-dependent diabetes mellitus. *American Journal of Medicine* 1995; **98 (5)**: 443-51.
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Supplemental Table S1 Search strategy on Medline (Ovid).

#	**Searches**
1	exp diabetes mellitus, type 2/
2	diabet*.ab.
3	non-insulin dependent.ab.
4	type-2.ab.
5	type II.ab.
6	type 2.ab.
7	4 or 5 or 6
8	2 and 7
9	1 or 8
10	exp thiazolidinediones/
11	exp glipizide/
12	exp glyburide/
13	exp metformin/
14	exp acarbose/
15	thiazolidinedione*.ab.
16	pioglitazone.ab.
17	rosiglitazone.ab.
18	sulfonylurea*.ab.
19	sulphonylurea*.ab.
20	glipizide.ab.
21	glyburide.ab.
22	glimepiride.ab.
23	biguanide*.ab.
24	metformin.ab.
25	insulin secretagogues.ab.
26	meglitinide*.ab.
27	repaglinide.ab.
28	nateglinide.ab.

#	**Searches**
29	alpha-glucosidase inhibitors.ab.
30	alpha-glucosidase inhibitor.ab.
31	acarbose.ab.
32	exp Dipeptidyl-Peptidase IV Inhibitors/
33	sitagliptin*.ab.
34	saxagliptin*.ab.
35	dpp-4.ab.
36	dpp-iv.ab.
37	exp bromocriptine/
38	bromocriptine.ab.
39	colesevelam.ab.
40	exp Glucagon-Like Peptide 1/
41	liraglutide.ab.
42	exenatide.ab.
43	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42
44	clinical trial.pt.
45	randomized.ab.
46	placebo.ab.
47	randomly.ab.
48	trial.ti.
49	exp Clinical Trial/
50	44 or 45 or 46 or 47 or 48 or 49
51	Animals/
52	Humans/
53	51 and 52
54	51 not 53
55	50 not 54
56	50 not 54
57	9 and 43

#	**Searches**
58	56 and 57
59	letter.pt.
60	comment.pt.
61	editorial.pt.
62	59 or 60 or 61
63	58 not 62

Supplemental Table S2 Characteristics of included trials.

Trial (first author, publication, name of trial, registration)	Sample size	Follow-up (week)*	Age (years, mean or median)	BMI (kg/m2, mean or median)	Baseline HbA_{1c} (%, mean)	Reduction in HbA_{1c} (%, mean)	One-year baseline CVD risk (%)	Drug used in the intervention group(s)
Type 2 diabetes								
Coniff 1995	255	24	55.9	29.9	6.9	1.0	Not reported	Acarbose and tolbutamide
Johnston 1998	364	56	67.8	29.7	8.4	0.6	Not reported	Miglitol and glyburide
UK Prospective Diabetes Study (UKPDS) Group 1998, UKPDS 34	753	558	53.0	31.7	7.2	0.6	2.3%	Metformin
Buse 2004, Exenatide-113	377	30	55.3	33.3	8.6	0.8	1.4%	Exenatide
Bosi 2007, NCT00099892	544	24	54.2	32.7	8.4	0.9	0.0%	Vildagliptin
Goldstein 2007, SITAGLIPTIN 036, NCT00103857	1091	24	53.5	32.1	8.8	1.4	1.2%	Sitagliptin and metformin
Hermansen 2007, NCT00106704	441	52	56.0	31.0	8.3	0.7	0.9%	Sitagliptin
Mita 2007	78	52	61.6	23.6	6.0	0.3	Not reported	Nateglinide
DeFronzo 2009, SAXAGLIPTIN 014, NCT00121667	743	24	54.6	31.4	8.1	0.8	3.6%	Saxagliptin
Hollander 2009, CV181-013, NCT00295633	565	24	54.1	30.0	8.3	0.5	1.2%	Saxagliptin
Kooy 2009, HOME, NCT00375388	390	224	61.5	30.0	7.9	0.4	4.1%	Metformin
Pratley 2009, Alogliptin Study 009, NCT00286494	493	26	55.4	32.8	8.0	0.5	0.0%	Alogliptin
Pratley 2009, NCT00286468	500	26	56.6	30.1	8.1	0.5	0.0%	Alogliptin
Rosenstock 2009, NCT00121641	401	24	53.5	31.7	7.9	0.7	2.3%	Saxagliptin
Rosenstock 2009, NCT00286429	390	26	55.4	32.5	9.3	0.5	1.5%	Alogliptin
Bailey 2010, NCT00528879	546	24	53.9	31.5	8.1	0.4	6.3%	Dapagliflozin
Liutkus 2010, NCT00603239	165	26	54.7	33.7	8.2	0.7	0.0%	Exenatide
Truitt 2010, NCT00143520	441	26	55.7	32.8	8.1	0.8	Not reported	Rivoglitazone and pioglitazone
Vilsboll 2010, NCT00395343	641	24	57.8	31.0	8.7	0.6	1.4%	Sitagliptin
Barzilai 2011, NCT00305604	206	24	71.9	31.0	7.7	0.7	Not reported	Sitagliptin
Chacra 2011, CV181040, NCT00313313	768	24	55.1	29.1	8.4	0.7	4.9%	Saxagliptin

Trial (first author, publication, name of trial, registration)	Sample size	Follow-up (week)*	Age (years, mean or median)	BMI (kg/m2, mean or median)	Baseline HbA_{1c} (%, mean)	Reduction in HbA_{1c} (%, mean)	One-year baseline CVD risk (%)	Drug used in the intervention group(s)
Del Prato 2011, NCT00621140	503	24	55.7	29.0	8.0	0.7	Not reported	Linagliptin
Gomis 2011, NCT00641043	389	24	57.5	29.0	8.6	0.5	Not reported	Linagliptin
Gram 2011, South Danish (metformin), NCT00121966	371	104	56.3	33.9	8.6	0.6	0.5%	Metformin
Gram 2011, South Danish (rosiglitazone), NCT00121966	371	104	56.3	33.9	8.6	0.6	0.3%	Rosiglitazone
Nowicki 2011, D1680C00007, NCT00614939	170	52	66.5	30.7	8.3	0.7	2.4%	Saxagliptin
Olansky 2011, NCT00482729	1246	44	49.7	33.3	9.9	0.5	0.4%	Sitagliptin
Owens 2011, NCT00602472	1055	24	58.1	28.3	8.1	0.6	0.0%	Linagliptin
Strojek 2011, NCT00680745	596	24	59.8	29.8	8.1	0.5	1.5%	Dapagliflozin
Taskinen 2011, NCT00601250	700	24	56.5	29.9	8.1	0.6	0.0%	Linagliptin
Chou 2012, NCT00484198	1912	26	55.1	29.8	7.7	0.8	0.0%	Rivoglitazone and pioglitazone
DeFronzo 2012, NCT00328627	1554	26	54.4	31.2	8.5	1.3	1.6%	Alogliptin
Haak 2012, NCT00798161	791	24	55.3	29.1	8.7	1.1	0.0%	Metformin and linagliptin
Pan 2012, NCT00698932	568	24	51.4	25.9	8.1	0.5	0.0%	Saxagliptin
Rosenstock 2012, NCT00683878	420	24	53.5	Not reported	8.4	0.5	0.0%	Dapagliflozin
Wilding 2012, Dapagliflozin 006, NCT00673231	807	24	59.3	33.1	8.5	0.5	1.1%	Dapagliflozin
Ahren 2013, GetGoal-M, NCT00712673	680	24	54.7	32.9	8.1	0.5	2.6%	Lixisenatide
Barnett 2013, NCT00757588	455	54	57.2	32.3	8.7	0.4	0.6%	Saxagliptin
Barnett 2013, NCT01084005	241	24	74.9	29.7	7.8	0.6	0.0%	Linagliptin
Dobs 2013, NCT00350779	278	54	54.5	30.3	8.8	0.8	0.0%	Sitagliptin
Haring 2013, EMPA-REG METSU, NCT01159600	666	24	57.1	28.2	8.1	0.6	1.9%	Empagliflozin
Lavalle-Gonzalez 2013, CANTATA-D, NCT01106677	1284	26	55.4	31.8	7.9	0.7	0.0%	Canagliflozin and sitagliptin
McGill 2013	133	52	64.4	32.0	8.2	0.7	4.6%	Linagliptin
Pinget 2013, GetGoal-P, NCT00763815	484	132	55.8	33.9	8.1	0.6	0.2%	Lixisenatide

Trial (first author, publication, name of trial, registration)	Sample size	Follow-up (week)*	Age (years, mean or median)	BMI (kg/m2, mean or median)	Baseline HbA_{1c} (%, mean)	Reduction in HbA_{1c} (%, mean)	One-year baseline CVD risk (%)	Drug used in the intervention group(s)
Riddle 2013, GetGoal-Duo 1 and GetGoal-L, NCT00975286	446	24	56.0	31.8	7.6	0.3	1.9%	Lixisenatide
Riddle 2013, GetGoal-L, NCT00715624	495	24	57.0	32.1	8.4	0.4	3.9%	Lixisenatide
Roden 2013, EMPA-REG MONO, NCT01177813	899	24	55.0	28.4	7.9	0.8	9.5%	Empagliflozin and sitagliptin
Stenlof 2013, CANTATA-M, NCT01081834	584	26	55.4	31.6	8.0	1.0	Not reported	Canagliflozin
Wildling 2013, CANTATA-MSU, NCT01106625	469	52	56.8	33.1	8.1	0.9	0.6%	Canagliflozin
Yki-Jarvinen 2013, NCT00954447	1261	54	60.0	31.0	8.3	0.7	0.6%	Linagliptin
Ahren 2014, HARMONY 3, NCT00838903	1012	164	54.5	32.6	8.1	0.5	0.9%	Albiglutide, sitagliptin, and glimepiride
Bajaj 2014, NCT00996658	272	24	53.8	28.2	8.4	0.6	2.4%	Linagliptin
Barnett 2014, EMPA-REG RENAL, NCT01164501	738	52	63.9	30.6	8.1	0.2	0.9%	Empagliflozin
Bolli 2014, GetGoal-F1, NCT00763451	482	112	56.1	32.5	8.0	0.5	0.9%	Lixisenatide
Buse 2014, NCT00765817	259	30	59.0	33.5	8.4	0.7	1.4%	Exenatide
Ferdinand 2014, NCT01149421	755	26	56.5	33.0	7.9	0.9	0.8%	Dulaglutide
Forst 2014, CANTATA-MP, NCT01106690	342	26	57.4	32.5	7.9	0.7	Not reported	Canagliflozin
Ji 2014, NCT01095653	393	24	51.4	25.6	8.3	0.8	1.6%	Dapagliflozin
Kohan 2014, NCT00663260	252	104	67.0	Not reported	8.4	0.1	3.0%	Dapagliflozin
McGill 2014, NCT00800683	133	52	64.4	32.0	8.2	0.7	9.2%	Linagliptin
Pan 2014, GetGoal-M-Asia, NCT01169779	390	24	54.8	26.9	7.9	0.4	0.0%	Lixisenatide
Pratley 2014, NCT01023581	784	26	45.7	30.7	8.4	1.0	0.0%	Metformin and alogliptin
Reusch 2014, HARMONY 1, NCT00849056	301	156	55.0	34.1	8.1	0.8	0.2%	Albiglutide
Rosenstock 2014, EMPA-REG MDI, NCT01306214	563	52	56.7	34.8	8.3	0.4	0.5%	Empagliflozin
Rosenstock 2014, GetGoal-S, NCT00713830	859	52	57.3	30.2	8.3	0.7	1.1%	Lixisenatide
Thrasher 2014, NCT01194830	226	24	53.9	32.7	8.7	0.6	1.8%	Linagliptin
Weir 2014, NCT01064414	269	26	68.5	Not reported	Not reported	0.4	2.2%	Canagliflozin

Trial (first author, publication, name of trial, registration)	Sample size	Follow-up (week)*	Age (years, mean or median)	BMI (kg/m2, mean or median)	Baseline HbA_{1c} (%, mean)	Reduction in HbA_{1c} (%, mean)	One-year baseline CVD risk (%)	Drug used in the intervention group(s)
Wysham 2014, AWARD-1, NCT01064687	976	26	55.6	33.3	8.1	0.8	0.0%	Dulaglutide and exenatide
Ahmann 2015, NN2211-3917, NCT01617434	450	26	58.4	32.3	8.3	1.2	0.0%	Liraglutide
Chen 2015, NCT01214239	300	24	54.4	25.4	8.0	0.5	2.2%	Linagliptin
Davies 2015, SCALE Diabetes, NCT01272232	846	56	54.9	37.2	7.9	0.9	0.9%	Liraglutide
Haering 2015, EMPA-REG EXTEND METSU, NCT01289990	666	76	57.1	28.2	8.1	0.7	0.9%	Empagliflozin
Home 2015, HARMONY 5, NCT00839527	663	56	55.2	32.2	8.2	1.0	2.4%	Albiglutide and pioglitazone
Mathieu 2015, NCT01462266	658	24	58.8	32.1	8.8	0.4	1.3%	Sitagliptin
Matthaei 2015, NCT01619059	315	52	54.6	31.4	7.9	0.4	0.6%	Saxagliptin
Rosenstock 2015, NCT01011868	494	82	58.8	32.2	8.2	0.5	0.4%	Empagliflozin
Yang 2015	109	24	56.2	25.0	7.1	0.7	Not reported	Anagliptin
Aroda 2016, LixiLan-L, NCT02058160	736	30	60.0	31.1	8.1	0.5	0.0%	Lixisenatide
Davies 2016, LIRA-RENAL, NCT01620489	277	26	67.2	33.9	8.0	0.7	1.5%	Liraglutide
Dungan 2016, AWARD-8, NCT01769378	299	24	57.8	31.2	8.4	1.3	0.0%	Dulaglutide
Ji 2016, NCT01076088	744	24	52.7	25.8	8.7	0.9	Not reported	Metformin and sitagliptin
Nauck 2016, HARMONY 2, NCT00849017	309	52	52.9	33.5	8.1	0.9	2.9%	Albiglutide
Oyama 2016, PROLOGUE, UMIN000004490	463	104	69.3	25.1	7.0	0.2	0.4%	Sitagliptin
Rodbard 2016, SUSTAIN-5, NCT02305381	397	30	58.8	Not reported	8.4	1.6	0.0%	Semaglutide
Seino 2016, NCT01572740	257	36	60.5	25.6	8.8	0.8	2.2%	Liraglutide
Takeda 2016, NCT01890122	647	28	53.6	26.3	Not reported	-0.9	Not reported	Alogliptin and metformin
Chacra 2017, NCT01698775	213	24	65.2	30.1	8.3	0.3	2.0%	Omarigliptin
Gadde 2017, DURATION-NEO-2, NCT01652729	364	28	53.7	31.8	8.5	0.6	3.1%	Exenatide and sitagliptin
Groop 2017, MARLINA-T2D, NCT01792518	360	24	60.6	28.4	7.8	0.6	0.0%	Linagliptin
Januzzi 2017, NCT01106651	666	104	63.7	31.6	7.7	0.6	0.7%	Canagliflozin

Trial (first author, publication, name of trial, registration)	Sample size	Follow-up (week)*	Age (years, mean or median)	BMI (kg/m2, mean or median)	Baseline HbA_{1c} (%, mean)	Reduction in HbA_{1c} (%, mean)	One-year baseline CVD risk (%)	Drug used in the intervention group(s)
Neal 2017, CANVAS (primary prevention), NCT01989754	3486	126	62.7	32.3	8.3	0.6	1.5%	Canagliflozin
Shankar 2017, NCT01755156	402	24	57.2	32.5	8.1	0.6	Not reported	Omarigliptin
Softeland 2017, NCT01734785	327	24	55.2	30.2	8.0	0.7	Not reported	Empagliflozin
Sorli 2017, SUSTAIN-1, NCT02054897	387	35	53.7	32.9	8.1	1.5	0.0%	Semaglutide
Chen 2018, SUPER, NCT02104804	462	24	59.1	26.2	8.5	0.6	0.0%	Saxagliptin
Dagogo-Jack 2018, VERTIS SITA2, NCT02036515	462	54	59.1	30.8	8.0	0.8	0.6%	Ertugliflozin
Dou 2018, START (Metformin), NCT02273050	423	24	50.1	26.6	9.4	0.9	1.0%	Metformin
Dou 2018, START (Saxagliptin), NCT02273050	417	24	50.1	26.6	9.4	0.2	2.1%	Saxagliptin
Grunberger 2018, VERTIS RENAL, NCT01986855	467	54	67.3	32.5	8.2	0.1	1.3%	Ertugliflozin
Guja 2018, DURATION-7, NCT02229383	461	28	57.7	33.7	8.5	0.7	0.8%	Exenatide
Miller 2018, VERTIS SITA, NCT02226003	291	28	55.6	32.2	8.9	1.2	1.9%	Ertugliflozin and sitagliptin
Yang 2018, NCT02096705	272	24	57.5	26.5	8.5	0.9	3.3%	Dapagliflozin
Aroda 2019, PIONEER 1, NCT02906930	703	31	55.0	31.8	8.0	0.9	0.9%	Semaglutide
Pratley 2019, PIONEER 4, NCT02863419	711	57	56.0	33.0	8.0	0.9	1.3%	Semaglutide and liraglutide
Wiviott 2019, DECLARE-TIMI 58 (primary prevention), NCT01730534	10186	219	64.7	32.0	8.3	0.2	1.2%	Dapagliflozin
Zinman 2019, PIONEER 8, NCT03021187	731	57	61.0	31.0	8.2	0.9	2.0%	Semaglutide
Zinman 2019, SUSTAIN 9, NCT03086330	302	30	57.0	31.9	8.0	1.4	Not reported	Semaglutide
Blonde 2020, LIRA-ADD2SGLT2i, NCT02964247	303	27	55.2	32.2	8.0	0.7	Not reported	Liraglutide
Cho 2020, ZEUS II, NCT02831361	283	24	60.4	26.7	8.4	0.7	0.0%	Gemigliptin
Halvorsen 2020, NCT03259789	317	26	55.8	29.8	Not reported	0.5	0.0%	Bexagliflozin
Sone 2020, NCT02589639	266	52	58.7	26.9	8.8	0.9	0.0%	Empagliflozin
Cherney 2021, SOTA-CKD4, NCT03242018	277	56	67.4	31.6	8.3	0.5	11.0%	Sotagliflozin
Cioffi 2021, DYDA 2, NCT02851745	188	48	69.0	30.0	6.4	0.2	1.1%	Linagliptin

Trial (first author, publication, name of trial, registration)	Sample size	Follow-up (week)*	Age (years, mean or median)	BMI (kg/m2, mean or median)	Baseline HbA_{1c} (%, mean)	Reduction in HbA_{1c} (%, mean)	One-year baseline CVD risk (%)	Drug used in the intervention group(s)
Davies 2021, STEP 2, NCT03552757	1210	75	55.0	35.7	8.1	1.2	0.5%	Semaglutide
Ji 2021, NCT02924064	246	24	55.3	26.1	7.9	0.7	1.8%	Teneligliptin
Kaku 2021, MK-0431J-843, NCT02577003	143	26	60.5	25.8	8.1	0.8	0.0%	Ipragliflozin
Nahra 2021, NCT03235050	834	54	56.8	35.0	8.1	0.7	0.9%	Cotadutide and liraglutide
Rosenstock 2021, SURPASS-1, NCT03954834	478	44	54.1	31.9	7.9	2.0	1.0%	Tirzepatide
Weng 2021, NCT04390295	483	24	54.8	25.5	8.5	0.8	0.0%	Henagliflozin
Akasaka 2022, EXCEED, UMIN000027095	68	24	71.1	25.3	8.0	0.1	6.8%	Ipragliflozin
Dahl 2022, SURPASS-5, NCT04039503	475	74	60.7	33.4	8.3	1.4	0.6%	Tirzepatide
Wada 2022, NCT03436693	308	104	62.5	26.9	7.8	0.2	1.0%	Canagliflozin
Intermediate hyperglycemia								
Chiasson 2003, STOP-NIDDM	1429	170	54.5	30.9	Not reported	Not reported	0.8%	Acarbose
DPP Research Group 2005, DPP	2155	155	50.6	34.1	5.9	-0.1	Not reported	Metformin
DREAM Trial Investigators 2006, DREAM, NCT00095654	5269	156	54.7	30.9	Not reported	Not reported	0.3%	Rosiglitazone
Ramachandran 2006, IDPP-1	398	129	45.9	25.8	6.2	Not reported	Not reported	Metformin
Kawamori 2009, Voglibose Ph-3 Study, UMIN000001109	1780	207	55.7	25.8	Not reported	Not reported	Not reported	Voglibose
Ramachandran 2009, IDPP-2, NCT00276497	407	155	45.3	26.1	5.8	0.1	Not reported	Pioglitazone
Zinman 2010, CANOE, NCT00116932	207	201	52.5	31.7	Not reported	Not reported	Not reported	Metformin and rosiglitazone
DeFronzo 2011, ACT NOW, NCT00220961	602	125	52.3	34.5	5.5	0.2	0.1%	Pioglitazone
Lindblad 2011, NANSY	274	191	60.0	29.7	4.9	Not reported	Not reported	Glimepiride
Pi-Sunyer 2015, SCALE Obesity and Prediabetes, NCT01272219	3731	56	45.1	38.3	5.6	0.2	0.1%	Liraglutide

Abbreviations: CVD, cardiovascular disease; BMI, body mass index; HbA_{1c}, hemoglobin A_{1c}.

*In studies reporting ≤56 weeks of follow-up, this value represents the planned duration of treatment. In studies reporting >56 weeks of follow-up this value represents the mean or median duration.

Supplemental Table S3 Risk of bias of included trials.

Trial (first author, publication, name of trial, registration)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Type 2 diabetes						
Coniff 1995	Unclear	Low	Low	Low	Unclear	Unclear
Johnston 1998	High	Low	Low	Low	Unclear	Unclear
UK Prospective Diabetes Study (UKPDS) Group 1998, UKPDS 34	Low	Low	Low	Unclear	Unclear	Unclear
Buse 2004, Exenatide-113	Unclear	Unclear	Unclear	Unclear	High	Unclear
Bosi 2007, NCT00099892	Unclear	Unclear	Unclear	Unclear	High	Unclear
Goldstein 2007, SITAGLIPTIN 036, NCT00103857	Unclear	Low	Low	Low	Low	Low
Hermansen 2007, NCT00106704	Low	Low	Low	Unclear	Low	Low
Mita 2007	Low	Unclear	Unclear	Low	Low	Unclear
DeFronzo 2009, SAXAGLIPTIN 014, NCT00121667	Low	Low	Unclear	Unclear	High	Low
Hollander 2009, CV181-013, NCT00295633	Low	Low	Unclear	Low	Unclear	Low
Kooy 2009, HOME, NCT00375388	Unclear	Unclear	Unclear	Unclear	Low	Low
Pratley 2009, Alogliptin Study 009, NCT00286494	Low	Low	Unclear	Unclear	Low	Low
Pratley 2009, NCT00286468	Unclear	Unclear	Low	High	High	Low
Rosenstock 2009, NCT00121641	Unclear	Low	Low	Low	Low	Low
Rosenstock 2009, NCT00286429	Low	Low	Unclear	Unclear	High	Low
Bailey 2010, NCT00528879	Low	Low	Low	Low	Low	Low
Liutkus 2010, NCT00603239	Unclear	Unclear	Unclear	Unclear	Low	Low
Truitt 2010, NCT00143520	Unclear	Low	Low	Low	Low	Low
Vilsboll 2010, NCT00395343	Low	Unclear	Unclear	Unclear	Low	Low
Barzilai 2011, NCT00305604	Low	Low	Low	Low	Low	Low

Trial (first author, publication, name of trial, registration)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Chacra 2011, CV181040, NCT00313313	Low	Low	Low	Unclear	Low	Low
Del Prato 2011, NCT00621140	Low	Low	Low	Low	Low	Low
Gomis 2011, NCT00641043	Low	Low	Unclear	Unclear	Low	Low
Gram 2011, South Danish (metformin), NCT00121966	Unclear	Unclear	Unclear	Unclear	Low	Low
Gram 2011, South Danish (rosiglitazone), NCT00121966	Unclear	Unclear	Unclear	Unclear	Low	Low
Nowicki 2011, D1680C00007, NCT00614939	Low	Low	Unclear	Unclear	High	Low
Olansky 2011, NCT00482729	Unclear	Unclear	Low	Unclear	High	Low
Owens 2011, NCT00602472	Unclear	Unclear	Unclear	Unclear	Low	Low
Strojek 2011, NCT00680745	Low	Unclear	Low	Low	Low	Low
Taskinen 2011, NCT00601250	Unclear	Unclear	Unclear	Unclear	Low	Low
Chou 2012, NCT00484198	Unclear	Low	Low	Low	Low	Low
DeFronzo 2012, NCT00328627	Unclear	Unclear	Low	Unclear	Unclear	Low
Haak 2012, NCT00798161	Unclear	Low	Low	Low	Low	Low
Pan 2012, NCT00698932	Low	Low	Low	Low	Low	Low
Rosenstock 2012, NCT00683878	Unclear	Unclear	Unclear	Unclear	Low	Low
Wilding 2012, Dapagliflozin 006, NCT00673231	Low	Low	Low	Low	Low	Low
Ahren 2013, GetGoal-M, NCT00712673	Unclear	Unclear	Unclear	Unclear	Low	Low
Barnett 2013, NCT00757588	Low	Low	High	Low	Low	Low
Barnett 2013, NCT01084005	Low	Low	Low	Low	Low	Low
Dobs 2013, NCT00350779	Low	Unclear	Low	Low	High	Low
Haring 2013, EMPA-REG METSU, NCT01159600	Low	Low	Unclear	Unclear	Low	Low
Lavalle-Gonzalez 2013, CANTATA-D, NCT01106677	Low	Unclear	Low	Low	Low	Low

Trial (first author, publication, name of trial, registration)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
McGill 2013	Unclear	Unclear	Low	Low	Low	Unclear
Pinget 2013, GetGoal-P, NCT00763815	Low	Low	Low	Low	Low	Low
Riddle 2013, GetGoal-Duo 1 and GetGoal-L, NCT00975286	Low	Low	Unclear	Low	Low	Low
Riddle 2013, GetGoal-L, NCT00715624	Low	Low	Low	Low	Unclear	Low
Roden 2013, EMPA-REG MONO, NCT01177813	Low	Low	Low	Low	Low	Low
Stenlof 2013, CANTATA-M, NCT01081834	Unclear	Low	Low	Low	Low	Low
Wildling 2013, CANTATA-MSU, NCT01106625	Low	Low	Low	Low	Low	Low
Yki-Jarvinen 2013, NCT00954447	Low	Low	Unclear	Low	Low	Low
Ahren 2014, HARMONY 3, NCT00838903	Unclear	Unclear	Low	Low	Low	Low
Bajaj 2014, NCT00996658	Low	Low	Unclear	Low	High	Low
Barnett 2014, EMPA-REG RENAL, NCT01164501	Low	Low	Low	Low	Low	Low
Bolli 2014, GetGoal-F1, NCT00763451	Unclear	Unclear	Low	Low	Low	Low
Buse 2014, NCT00765817	Low	Low	Low	Low	Low	Low
Ferdinand 2014, NCT01149421	Low	Unclear	Unclear	High	Low	Low
Forst 2014, CANTATA-MP, NCT01106690	Low	Low	Low	Low	Low	Low
Ji 2014, NCT01095653	Low	Low	Low	Low	Low	Low
Kohan 2014, NCT00663260	Unclear	Unclear	Unclear	Unclear	High	Low
McGill 2014, NCT00800683	Unclear	Unclear	Low	Low	Low	Low
Pan 2014, GetGoal-M-Asia, NCT01169779	Low	Low	Unclear	Unclear	Low	Low
Pratley 2014, NCT01023581	Unclear	Low	Low	Low	Low	Low
Reusch 2014, HARMONY 1, NCT00849056	Low	Low	Low	Low	High	Low
Rosenstock 2014, EMPA-REG MDI, NCT01306214	Low	Low	Unclear	Unclear	Low	Low

Trial (first author, publication, name of trial, registration)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Rosenstock 2014, GetGoal-S, NCT00713830	Unclear	Unclear	Unclear	Unclear	Low	Low
Thrasher 2014, NCT01194830	Low	Unclear	Unclear	Unclear	Low	High
Weir 2014, NCT01064414	Unclear	Unclear	Low	Low	Unclear	Low
Wysham 2014, AWARD-1, NCT01064687	Low	Low	Low	Unclear	Low	Low
Ahmann 2015, NN2211-3917, NCT01617434	Unclear	Unclear	Low	Low	Unclear	Low
Chen 2015, NCT01214239	Low	Low	Low	Low	Low	Low
Davies 2015, SCALE Diabetes, NCT01272232	Low	Low	Low	Unclear	Low	Low
Haering 2015, EMPA-REG EXTEND METSU, NCT01289990	Unclear	Unclear	Unclear	Unclear	Low	Low
Home 2015, HARMONY 5, NCT00839527	Low	Low	Unclear	Low	Low	Low
Mathieu 2015, NCT01462266	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Matthaei 2015, NCT01619059	Low	Low	Unclear	Unclear	Low	Low
Rosenstock 2015, NCT01011868	Low	Low	Unclear	Unclear	Low	Low
Yang 2015	Unclear	Low	Low	Low	Low	Unclear
Aroda 2016, LixiLan-L, NCT02058160	Low	Low	High	High	Low	Low
Davies 2016, LIRA-RENAL, NCT01620489	Low	Low	Low	Low	High	Low
Dungan 2016, AWARD-8, NCT01769378	Unclear	Unclear	Unclear	Unclear	Low	Low
Ji 2016, NCT01076088	Low	Low	Low	Low	Low	Low
Nauck 2016, HARMONY 2, NCT00849017	Unclear	Low	Low	Low	Low	Low
Oyama 2016, PROLOGUE, UMIN000004490	Low	Low	High	Low	Low	Low
Rodbard 2016, SUSTAIN-5, NCT02305381	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Seino 2016, NCT01572740	Low	Low	Unclear	Unclear	Low	Low
Takeda 2016, NCT01890122	Unclear	Unclear	Unclear	Unclear	Low	Low
Chacra 2017, NCT01698775	Low	Low	Unclear	Unclear	Low	Low

Trial (first author, publication, name of trial, registration)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Gadde 2017, DURATION-NEO-2, NCT01652729	Low	Low	Low	Low	High	Low
Groop 2017, MARLINA-T2D, NCT01792518	Low	Low	Low	Low	Low	Low
Januzzi 2017, NCT01106651	Low	Low	Low	Low	Low	Low
Neal 2017, CANVAS (primary prevention), NCT01989754	Low	Low	Low	Low	Low	Low
Shankar 2017, NCT01755156	Unclear	Unclear	Unclear	Unclear	Low	Low
Softeland 2017, NCT01734785	Low	Low	Low	Low	Low	Low
Sorli 2017, SUSTAIN-1, NCT02054897	Low	Low	Low	Low	Low	Low
Chen 2018, SUPER, NCT02104804	Unclear	Unclear	Unclear	Unclear	Low	Low
Dagogo-Jack 2018, VERTIS SITA2, NCT02036515	Low	Unclear	Low	Low	Low	Low
Dou 2018, START (Metformin), NCT02273050	Low	Low	Unclear	Unclear	Low	Low
Dou 2018, START (Saxagliptin), NCT02273050	Low	Low	Unclear	Unclear	Low	Low
Grunberger 2018, VERTIS RENAL, NCT01986855	Low	Low	Low	Low	Unclear	Low
Guja 2018, DURATION-7, NCT02229383	Low	Low	Low	Low	Low	Low
Miller 2018, VERTIS SITA, NCT02226003	Low	Low	Low	Low	Low	Low
Yang 2018, NCT02096705	Low	Low	Unclear	Unclear	Low	Low
Aroda 2019, PIONEER 1, NCT02906930	Low	Low	Low	Low	Low	Low
Pratley 2019, PIONEER 4, NCT02863419	Low	Low	Low	Low	Low	Low
Wiviott 2019, DECLARE-TIMI 58 (primary prevention), NCT01730534	Low	Low	Low	Low	Low	Low
Zinman 2019, PIONEER 8, NCT03021187	Low	Low	Low	Low	Low	Low
Zinman 2019, SUSTAIN 9, NCT03086330	Low	Low	Low	Low	Low	Low
Blonde 2020, LIRA-ADD2SGLT2i, NCT02964247	Low	Low	Low	Low	Low	Low
Cho 2020, ZEUS II, NCT02831361	Low	Low	Low	Low	Low	Low

Trial (first author, publication, name of trial, registration)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Halvorsen 2020, NCT03259789	Low	Low	Low	Low	Low	Low
Sone 2020, NCT02589639	Low	Low	Unclear	Unclear	Low	Low
Cherney 2021, SOTA-CKD4, NCT03242018	Unclear	Unclear	Low	Low	Low	Low
Cioffi 2021, DYDA 2, NCT02851745	Low	Low	Low	Low	Low	Low
Davies 2021, STEP 2, NCT03552757	Low	Low	Low	Low	Low	Low
Ji 2021, NCT02924064	Low	Low	Low	Low	Low	Low
Kaku 2021, MK-0431J-843, NCT02577003	Low	Low	Low	Unclear	Low	Low
Nahra 2021, NCT03235050	Low	Low	Low	Low	Low	Low
Rosenstock 2021, SURPASS-1, NCT03954834	Low	Low	Low	Low	Low	Low
Weng 2021, NCT04390295	Low	Low	Low	Low	Low	Low
Akasaka 2022, EXCEED, UMIN000027095	Low	Unclear	Low	Low	Low	Low
Dahl 2022, SURPASS-5, NCT04039503	Low	Low	Low	Low	Low	Low
Wada 2022, NCT03436693	Unclear	Unclear	Unclear	Unclear	Low	Low
Intermediate hyperglycemia						
Chiasson 2003, STOP-NIDDM	Low	Low	Low	Low	Low	Low
DPP Research Group 2005, DPP	Unclear	Low	Low	Low	Unclear	Low
DREAM Trial Investigators 2006, DREAM, NCT00095654	Low	Low	Low	Low	Low	Low
Ramachandran 2006, IDPP-1	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Kawamori 2009, Voglibose Ph-3 Study, UMIN000001109	Low	Low	Low	Low	Low	Low
Ramachandran 2009, IDPP-2, NCT00276497	High	Low	Low	Low	Low	Low
Zinman 2010, CANOE, NCT00116932	Low	Low	Low	Low	Low	Low
DeFronzo 2011, ACT NOW, NCT00220961	Low	Low	Low	Low	Low	Low

Trial (first author, publication, name of trial, registration)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Lindblad 2011, NANSY	Unclear	Low	Low	Low	Unclear	Unclear
Pi-Sunyer 2015, SCALE Obesity and Prediabetes, NCT01272219	Unclear	Low	Low	Low	Low	Low

Supplemental Table S4 Detailed results of meta-analysis of anti-diabetic drugs in preventing major cardiovascular events.

Trial (first author, publication, name of trial, registration)	Event number, intervention group	Total number, intervention group	Event number, control group	Total number, control group	Odds ratio	Lower bound of 95% CI	Upper bound of 95% CI	Weight (random-effects)
UK Prospective Diabetes Study (UKPDS) Group 1998, UKPDS 34	52	342	103	411	0.5	0.4	0.8	7.3%
Buse 2004, Exenatide-113	1	254	1	123	0.5	0.0	7.8	0.3%
Bosi 2007, NCT00099892	1	362	0	182	1.5	0.1	37.4	0.3%
Goldstein 2007, SITAGLIPTIN 036, NCT00103857	4	915	1	176	0.8	0.1	6.9	0.5%
Hermansen 2007, NCT00106704	2	222	2	219	1.0	0.1	7.1	0.7%
DeFronzo 2009, SAXAGLIPTIN 014, NCT00121667	5	564	3	179	0.5	0.1	2.2	1.2%
Hollander 2009, CV181-013, NCT00295633	4	381	1	184	1.9	0.2	17.5	0.5%
Kooy 2009, HOME, NCT00375388	37	196	34	194	1.1	0.7	1.8	5.4%
Pratley 2009, Alogliptin Study 009, NCT00286494	3	396	0	97	1.7	0.1	33.9	0.3%
Pratley 2009, NCT00286468	1	401	0	99	0.7	0.0	18.4	0.3%
Rosenstock 2009, NCT00121641	3	306	1	95	0.9	0.1	9.1	0.5%
Rosenstock 2009, NCT00286429	0	260	1	130	0.2	0.0	4.1	0.3%
Bailey 2010, NCT00528879	3	409	4	137	0.2	0.1	1.1	1.1%
Liutkus 2010, NCT00603239	1	111	0	54	1.5	0.1	36.9	0.3%
Vilsboll 2010, NCT00395343	1	322	2	319	0.5	0.0	5.5	0.5%
Chacra 2011, CV181040, NCT00313313	3	501	6	267	0.3	0.1	1.1	1.3%
Gram 2011, South Danish (metformin), NCT00121966	3	184	2	187	1.5	0.3	9.3	0.8%
Gram 2011, South Danish (rosiglitazone), NCT00121966	4	187	1	184	4.0	0.4	36.1	0.5%
Nowicki 2011, D1680C00007, NCT00614939	4	85	2	85	2.0	0.4	11.5	0.9%

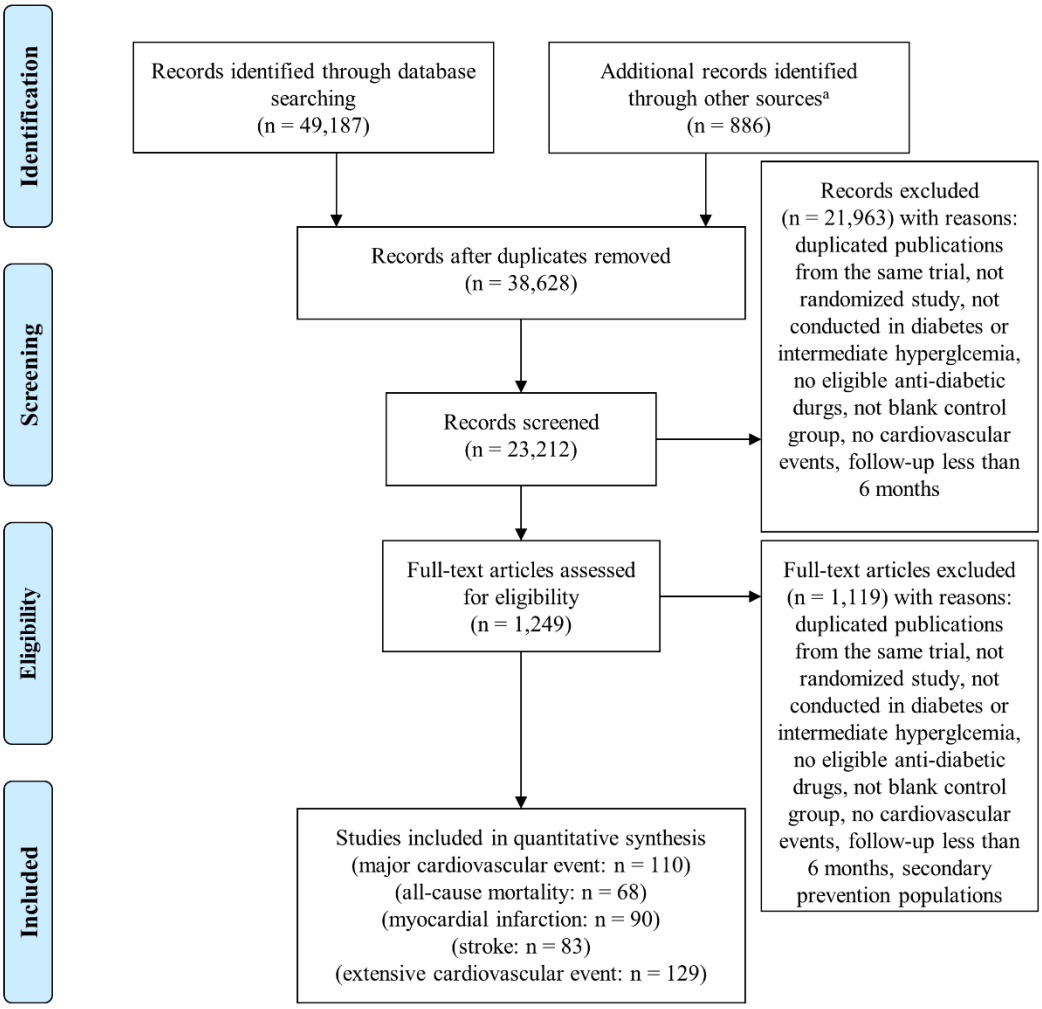
Trial (first author, publication, name of trial, registration)	Event number, intervention group	Total number, intervention group	Event number, control group	Total number, control group	Odds ratio	Lower bound of 95% CI	Upper bound of 95% CI	Weight (random-effects)
Olansky 2011, NCT00482729	2	625	2	621	1.0	0.1	7.1	0.7%
Owens 2011, NCT00602472	1	792	0	263	1.0	0.0	24.6	0.3%
Strojek 2011, NCT00680745	3	450	1	146	1.0	0.1	9.4	0.5%
Taskinen 2011, NCT00601250	1	523	0	177	1.0	0.0	25.1	0.3%
Chou 2012, NCT00484198	3	1775	0	137	0.5	0.0	10.6	0.3%
DeFronzo 2012, NCT00328627	3	1425	1	129	0.3	0.0	2.6	0.5%
Haak 2012, NCT00798161	2	719	0	72	0.5	0.0	10.6	0.3%
Pan 2012, NCT00698932	2	284	0	284	5.0	0.2	105.4	0.3%
Rosenstock 2012, NCT00683878	1	281	0	139	1.5	0.1	36.9	0.3%
Wilding 2012, Dapagliflozin 006, NCT00673231	4	610	1	197	1.3	0.1	11.6	0.5%
Ahren 2013, GetGoal-M, NCT00712673	2	510	2	170	0.3	0.0	2.4	0.7%
Barnett 2013, NCT00757588	2	304	1	151	1.0	0.1	11.0	0.5%
Barnett 2013, NCT01084005	2	162	0	79	2.5	0.1	52.2	0.3%
Dobs 2013, NCT00350779	3	181	0	97	3.8	0.2	74.8	0.3%
Haring 2013, EMPA-REG METSU, NCT01159600	2	441	2	225	0.5	0.1	3.6	0.7%
Lavalle-Gonzalez 2013, CANTATA-D, NCT01106677	1	1101	0	183	0.5	0.0	12.3	0.3%
McGill 2013	5	68	3	65	1.6	0.4	7.2	1.1%
Pi-Sunyer 2015, SCALE Obesity and Prediabetes, NCT01272219	2	2487	2	1244	0.5	0.1	3.6	0.7%
Riddle 2013, GetGoal-Duo 1 and GetGoal-L, NCT00975286	1	223	2	223	0.5	0.0	5.5	0.5%
Riddle 2013, GetGoal-L, NCT00715624	2	328	3	167	0.3	0.1	2.0	0.8%
Roden 2013, EMPA-REG MONO, NCT01177813	12	671	10	228	0.4	0.2	0.9	2.9%

Trial (first author, publication, name of trial, registration)	Event number, intervention group	Total number, intervention group	Event number, control group	Total number, control group	Odds ratio	Lower bound of 95% CI	Upper bound of 95% CI	Weight (random-effects)
Wildling 2013, CANTATA-MSU, NCT01106625	1	313	1	156	0.5	0.0	8.0	0.3%
Yki-Jarvinen 2013, NCT00954447	6	631	4	630	1.5	0.4	5.3	1.5%
Ahren 2014, HARMONY 3, NCT00838903	11	911	3	101	0.4	0.1	1.5	1.4%
Bajaj 2014, NCT00996658	0	183	1	89	0.2	0.0	4.0	0.3%
Barnett 2014, EMPA-REG RENAL, NCT01164501	3	419	3	319	0.8	0.2	3.8	1.0%
Bolli 2014, GetGoal-F1, NCT00763451	6	322	3	160	1.0	0.2	4.0	1.3%
Buse 2014, NCT00765817	0	137	1	122	0.3	0.0	7.3	0.3%
Ferdinand 2014, NCT01149421	1	505	1	250	0.5	0.0	7.9	0.3%
Ji 2014, NCT01095653	2	261	1	132	1.0	0.1	11.3	0.5%
Kohan 2014, NCT00663260	6	168	5	84	0.6	0.2	2.0	1.6%
McGill 2014, NCT00800683	5	68	6	65	0.8	0.2	2.7	1.6%
Pan 2014, GetGoal-M-Asia, NCT01169779	2	196	0	194	5.0	0.2	104.8	0.3%
Pratley 2014, NCT01023581	3	675	0	109	1.1	0.1	22.2	0.3%
Reusch 2014, HARMONY 1, NCT00849056	2	150	1	151	2.0	0.2	22.6	0.5%
Rosenstock 2014, EMPA-REG MDI, NCT01306214	2	375	1	188	1.0	0.1	11.1	0.5%
Rosenstock 2014, GetGoal-S, NCT00713830	7	574	3	285	1.2	0.3	4.5	1.3%
Thrasher 2014, NCT01194830	0	106	1	120	0.4	0.0	9.3	0.3%
Weir 2014, NCT01064414	0	179	1	90	0.2	0.0	4.1	0.3%
Wysham 2014, AWARD-1, NCT01064687	2	835	0	141	0.8	0.0	17.8	0.3%
Ahmann 2015, NN2211-3917, NCT01617434	1	225	0	225	3.0	0.1	74.4	0.3%
Chen 2015, NCT01214239	1	201	1	99	0.5	0.0	7.9	0.3%
Davies 2015, SCALE Diabetes, NCT01272232	5	634	2	212	0.8	0.2	4.3	0.9%

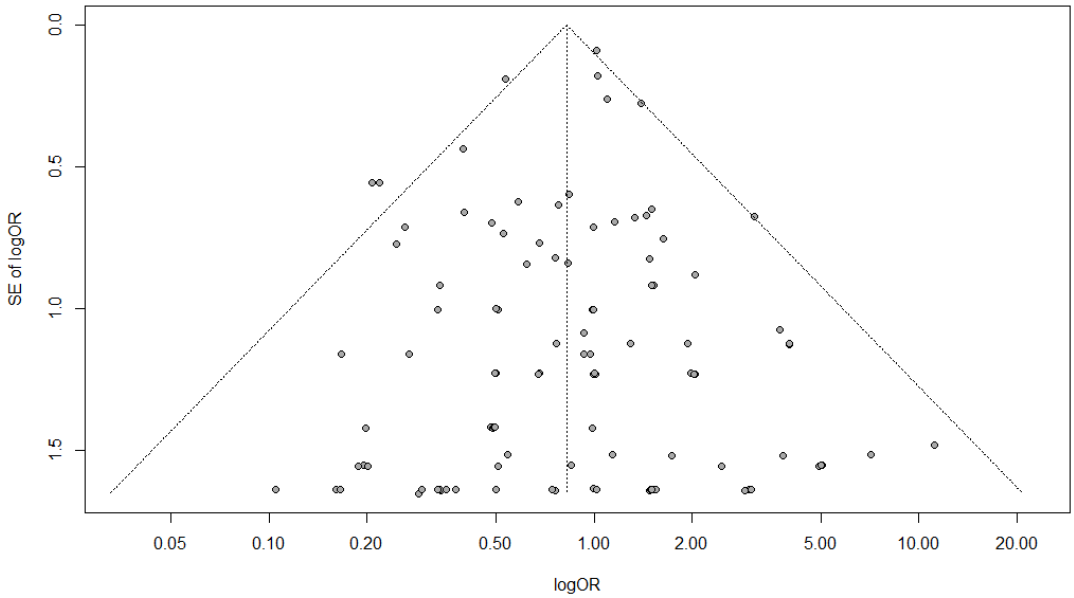
Trial (first author, publication, name of trial, registration)	Event number, intervention group	Total number, intervention group	Event number, control group	Total number, control group	Odds ratio	Lower bound of 95% CI	Upper bound of 95% CI	Weight (random-effects)
Haering 2015, EMPA-REG EXTEND METSU, NCT01289990	4	441	3	225	0.7	0.2	3.1	1.1%
Home 2015, HARMONY 5, NCT00839527	7	548	3	115	0.5	0.1	1.9	1.3%
Mathieu 2015, NCT01462266	1	329	2	329	0.5	0.0	5.5	0.5%
Matthaei 2015, NCT01619059	0	153	1	162	0.4	0.0	8.7	0.3%
Rosenstock 2015, NCT01011868	7	324	1	170	3.7	0.5	30.6	0.6%
Aroda 2016, LixiLan-L, NCT02058160	3	367	0	369	7.1	0.4	137.9	0.3%
Davies 2016, LIRA-RENAL, NCT01620489	4	140	1	137	4.0	0.4	36.3	0.5%
Dungan 2016, AWARD-8, NCT01769378	1	239	0	60	0.8	0.0	18.9	0.3%
Nauck 2016, HARMONY 2, NCT00849017	1	204	3	105	0.2	0.0	1.6	0.5%
Oyama 2016, PROLOGUE, UMIN000004490	3	232	2	231	1.5	0.2	9.1	0.8%
Rodbard 2016, SUSTAIN-5, NCT02305381	1	264	0	133	1.5	0.1	37.6	0.3%
Seino 2016, NCT01572740	0	127	2	130	0.2	0.0	4.2	0.3%
Chacra 2017, NCT01698775	1	107	1	106	1.0	0.1	16.0	0.3%
Gadde 2017, DURATION-NEO-2, NCT01652729	1	303	1	61	0.2	0.0	3.2	0.3%
Groop 2017, MARLINA-T2D, NCT01792518	2	182	0	178	4.9	0.2	103.7	0.3%
Januzzi 2017, NCT01106651	9	450	3	216	1.4	0.4	5.4	1.4%
Neal 2017, CANVAS (primary prevention), NCT01989754	78	2039	54	1447	1.0	0.7	1.5	7.5%
Sorli 2017, SUSTAIN-1, NCT02054897	1	258	0	129	1.5	0.1	37.3	0.3%
Chen 2018, SUPER, NCT02104804	5	232	0	230	11.1	0.6	202.7	0.3%
Dagogo-Jack 2018, VERTIS SITA2, NCT02036515	1	309	1	153	0.5	0.0	7.9	0.3%
Dou 2018, START (Metformin), NCT02273050	0	210	1	213	0.3	0.0	8.3	0.3%

Trial (first author, publication, name of trial, registration)	Event number, intervention group	Total number, intervention group	Event number, control group	Total number, control group	Odds ratio	Lower bound of 95% CI	Upper bound of 95% CI	Weight (random-effects)
Dou 2018, START (Saxagliptin), NCT02273050	0	210	2	207	0.2	0.0	4.1	0.3%
Grunberger 2018, VERTIS RENAL, NCT01986855	6	313	2	154	1.5	0.3	7.4	1.0%
Guja 2018, DURATION-7, NCT02229383	0	231	1	230	0.3	0.0	8.2	0.3%
Miller 2018, VERTIS SITA, NCT02226003	0	194	1	97	0.2	0.0	4.1	0.3%
Yang 2018, NCT02096705	0	139	2	133	0.2	0.0	4.0	0.3%
Aroda 2019, PIONEER 1, NCT02906930	2	525	1	178	0.7	0.1	7.5	0.5%
Pratley 2019, PIONEER 4, NCT02863419	5	569	2	142	0.6	0.1	3.2	0.9%
Wiviott 2019, DECLARE-TIMI 58 (primary prevention), NCT01730534	273	5108	266	5078	1.0	0.9	1.2	10.1%
Zinman 2019, PIONEER 8, NCT03021187	10	547	4	184	0.8	0.3	2.7	1.7%
Cho 2020, ZEUS II, NCT02831361	1	188	0	95	1.5	0.1	37.9	0.3%
Halvorsen 2020, NCT03259789	1	158	0	159	3.0	0.1	75.1	0.3%
Sone 2020, NCT02589639	1	176	0	90	1.5	0.1	38.4	0.3%
Cherney 2021, SOTA-CKD4, NCT03242018	5	184	11	93	0.2	0.1	0.6	1.9%
Cioffi 2021, DYDA 2, NCT02851745	0	93	1	95	0.3	0.0	8.4	0.3%
Davies 2021, STEP 2, NCT03552757	8	807	3	403	1.3	0.4	5.1	1.4%
Ji 2021, NCT02924064	2	122	1	124	2.1	0.2	22.9	0.5%
Kaku 2021, MK-0431J-843, NCT02577003	1	73	0	70	2.9	0.1	72.8	0.3%
Nahra 2021, NCT03235050	6	722	1	112	0.9	0.1	7.8	0.6%
Rosenstock 2021, SURPASS-1, NCT03954834	0	363	1	115	0.1	0.0	2.6	0.3%
Weng 2021, NCT04390295	1	322	0	161	1.5	0.1	37.2	0.3%
Akasaka 2022, EXCEED, UMIN000027095	0	36	1	32	0.3	0.0	7.3	0.3%
Dahl 2022, SURPASS-5, NCT04039503	2	355	1	120	0.7	0.1	7.5	0.5%
Wada 2022, NCT03436693	9	154	3	154	3.1	0.8	11.8	1.4%

Trial (first author, publication, name of trial, registration)	Event number, intervention group	Total number, intervention group	Event number, control group	Total number, control group	Odds ratio	Lower bound of 95% CI	Upper bound of 95% CI	Weight (random-effects)
Chiasson 2003, STOP-NIDDM	4	714	18	715	0.2	0.1	0.6	1.9%
DREAM Trial Investigators 2006, DREAM, NCT00095654	32	2635	23	2634	1.4	0.8	2.4	5.2%
DeFronzo 2011, ACT NOW, NCT00220961	2	303	1	299	2.0	0.2	22.0	0.5%
Pinget 2013, GetGoal-P, NCT00763815	1	323	1	161	0.5	0.0	8.0	0.3%



Supplemental Figure1 Flow-diagram for literature search and screening.



Supplemental Figure2 Funnel plot of anti-diabetic drugs in preventing major cardiovascular events.

Supplemental References

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3. Higgins, J. P., & Green, S. (Eds.). (2008). Cochrane handbook for systematic reviews of interventions.