Glucose-lowering drugs or strategies, atherosclerotic cardiovascular events, and heart failure in people with or at risk of type 2 diabetes: an updated systematic review and meta-analysis of randomised cardiovascular outcome trials

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See Comment page 353

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Summary

Background In our 2015 systematic review and meta-analysis of cardiovascular outcome trials for glucose-lowering drugs or strategies in people with or at risk of type 2 diabetes, we reported a modest reduction in atherosclerotic cardiovascular events and an increased risk of heart failure, but with heterogeneous effects by drug or intervention type. In view of the completion of many large cardiovascular outcome trials since our previous analysis, including trials of novel drugs that have shown beneficial effects on cardiovascular outcomes, we aimed to update our analysis to incorporate these findings.

Methods We did an updated systematic review and meta-analysis of large cardiovascular outcome trials of glucose-lowering drugs or strategies in people with or at risk of type 2 diabetes. We searched Ovid MEDLINE, PubMed, and the Cochrane Central Register of Controlled Trials databases for reports of trials published from Nov 15, 2013 to Nov 20, 2019. We included randomised controlled trials with a minimum of 1000 adults (aged ≥19 years) with or at risk of type 2 diabetes, with major adverse cardiovascular events (MACE) as an outcome, and with follow-up of at least 12 months. We excluded trials with patients enrolled with an acute cardiovascular event. The main outcomes of interest were MACE (generally defined as a composite of cardiovascular death, myocardial infarction, or stroke) and heart failure. We calculated pooled risk ratios (RRs) and 95% CIs with inverse-variance random-effects models, did meta-regression to analyse treatment effects per difference in bodyweight achieved, and explored results stratified by baseline subgroups.

Findings Our updated search yielded 30 eligible trials (n=225 305). The mean age of participants was 63·0 years (SD 8·4) and mean duration of diabetes was 9·4 years (6·6). After a mean follow-up of 3·8 years (1·8), 23 016 (10·2%) participants had MACE and 8169 (3·6%) had a heart failure event. Glucose-lowering drugs or strategies lowered the risk of MACE compared with standard care or placebo (RR 0·92, 95% CI 0·89–0·95, p<0·0001), with no overall effect on the risk of heart failure (0·98, 0·90–1·08, p=0·71). However, across drug classes or strategies, the magnitude and directionality of RR for heart failure varied ($p_{interaction}$<0·0001), with meta-regression showing that a decrease in bodyweight of 1 kg was associated with a 5·9% (3·9–8·0) relative decrease in the risk of heart failure (p<0·0001). Among trials that assessed drug classes or strategies associated with weight loss (intensive lifestyle changes, GLP-1 receptor agonists, or SGLT2 inhibitors), the risk reduction for MACE was consistent among participants with (0·87, 0·83–0·92) and without (0·92, 0·83–1·02) established cardiovascular disease at baseline ($p_{interaction}$=0·33). For heart failure, the RR for drug classes or strategies associated with weight loss was consistent among participants with (0·80, 0·73–0·89) and without (0·84, 0·74–0·95) cardiovascular disease at baseline ($p_{interaction}$=0·63).

Interpretation Glucose-lowering drugs or strategies overall reduced the risk of fatal and non-fatal atherosclerotic events. The effect on heart failure was neutral overall but varied substantially by intervention type, with interventions associated with weight loss showing a beneficial effect. The cardiovascular and heart failure benefits of interventions associated with weight loss might extend to patients without established cardiovascular disease.

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Introduction

Two classes of diabetes drugs, GLP-1 receptor agonists and SGLT2 inhibitors, have shown efficacy in reducing cardiovascular risk among patients with type 2 diabetes. Broadly considered to have varying effects, GLP-1 receptor agonists have mainly been shown to reduce atherosclerotic cardiovascular events, whereas SGLT2 inhibitors seem to affect the cardiorenal axis, reducing hospital admission for heart failure and showing renoprotection, with both drug classes having varying effects on cardiovascular death.[1,2] The mechanisms driving cardiovascular risk reduction for either drug class remain elusive without a clear understanding of whether the heterogeneity in observed effects is due to

Research in context

Evidence before this study

In 2015, we did a systematic review and meta-analysis of large cardiovascular outcome trials of glucose-lowering drugs or strategies among people with or at risk of type 2 diabetes. The net effect of any novel therapy compared with standard care was a 5% modest relative risk reduction in cardiovascular events, driven by an 8% reduction in non-fatal myocardial infarction, at the expense of an overall increase in the relative risk of heart failure. There was considerable heterogeneity in the risk of heart failure across various therapies, with peroxisome proliferation-activated receptor agonists increasing heart failure risk and no approach conclusively reducing risk. Several cardiovascular outcome trials have subsequently shown beneficial effects of some novel diabetes therapies (GLP-1 receptor agonists and SGLT2 inhibitors) on cardiovascular outcomes. For our updated systematic review and meta-analysis, we searched Ovid MEDLINE, PubMed, and the Cochrane Central Register of Controlled Trials for reports of randomised controlled trials published from Nov 15, 2013, to Nov 20, 2019, using the key search terms "hyperglycemic agents", "glucose control", "type 2 diabetes", "cardiovascular disease", and "heart failure", with no language restrictions. We included large cardiovascular outcome trials (≥1000 participants) that investigated glucose-lowering therapies for at least 12 months in people with or at risk of type 2 diabetes. Trials were considered if the intervention therapy was compared with standard care or placebo and resulted in an improvement in glycaemic control.

Added value of this study

Compared with our previous meta-analysis, 16 additional trials were incorporated into this updated analysis, to give a total of 30 trials and 225 305 participants. Overall, glucose-lowering drugs or strategies decreased the risk of a composite outcome of major adverse cardiovascular events (generally consisting of cardiovascular death, myocardial infarction, and stroke), each of the components of this composite outcome, and all-cause mortality, with no overall effect on heart failure. However, the risk for heart failure varied substantially by drug class or strategy, with meta-regression showing a potential association between the risk of heart failure and difference in bodyweight achieved between treatments. Novel glucose-lowering drugs or strategies that lower bodyweight (ie, GLP-1 receptor agonists, SGLT2 inhibitors, or intensive lifestyle changes) resulted in significant risk reductions in atherosclerotic cardiovascular events and heart failure events among people with and without established atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease.

Implications of all the available evidence

Overall, glucose-lowering drugs or strategies reduced the risk of fatal and non-fatal atherosclerotic cardiovascular events and all-cause mortality. Despite no overall effect on heart failure, risk varied by drug class or strategy, with a potential beneficial effect related to the extent of weight loss achieved. Among people with type 2 diabetes and established cardiovascular disease, clinicians can select among either class of newer diabetes therapies that lower weight (GLP-1 receptor agonists and SGLT2 inhibitors) to reduce atherosclerotic and heart failure events. The cardiovascular benefits of these therapies might extend to people with or without established atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease.

differences between specific drugs, duration of study follow-up, the extent of established atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease among the populations studied, or varying effects on cardiometabolic factors (eg, blood pressure, heart rate, circulating plasma volume). Clarification of this heterogeneity could further our understanding of which factors most affect cardiovascular risk in patients with type 2 diabetes, direct research towards other populations to study, and guide drug development.

In 2015, before the initial reports of GLP-1 receptor agonist and SGLT2 inhibitor cardiovascular outcome trials, we did a systematic review and meta-analysis of all of the large cardiovascular outcome trials that studied a variety of glucose-lowering drugs or strategies among people with or at risk of type 2 diabetes.[3] At that time, the net effect of any novel therapy compared with standard care was a modest 5% relative risk reduction in cardiovascular events, driven by an 8% reduction in non-fatal myocardial infarction, at the expense of an overall increase in relative risk of heart failure.[3] There was considerable heterogeneity in the risk of heart failure across various therapies, with the peroxisome proliferation-activated receptor (PPAR) agonists increasing risk and no approach conclusively reducing risk.[3] We hypothesised that the relative risk of heart failure could be partly associated with a therapy's effect on total bodyweight. In view of the substantial number of large cardiovascular outcome trials that have subsequently been reported testing various glucose-lowering drugs or strategies, we aimed to update our systematic review and meta-analysis to incorporate these new findings. Additionally, we aimed to explore which factors might affect the cardiovascular effects of newer diabetes therapies, via meta-regression and subgroup analyses.

Methods

Search strategy and selection criteria

In this updated systematic review and study-level meta-analysis, we included large cardiovascular outcome randomised controlled trials that investigated a glucose-lowering drug therapy or strategy focused on a single risk factor (ie, blood glucose or bodyweight) with a minimum

of 1000 adult (aged ≥19 year) participants enrolled who had or were at risk of type 2 diabetes. Randomised controlled trials were considered if the glucose-lowering drug or strategy was compared with standard care or placebo and resulted in an improvement of glycaemic control between treatment groups. Trials must have considered major adverse cardiovascular events (MACE) as an outcome of interest and have had a follow-up of at least 12 months. We excluded trials with fewer than 1000 participants and those that enrolled patients with an acute cardiovascular event. Additionally, trials were excluded if a multifactorial risk-factor intervention or non-glycaemic drug were tested or if the intervention resulted in a mean difference of 0·01% or less in HbA_{1c} between treatment groups. Trials with fewer than 20 cardiovascular events were excluded.

We did an updated literature search of Ovid MEDLINE, PubMed, and the Cochrane Central Register of Controlled Trials databases for trials published from Nov 15, 2013, to Nov 20, 2019, with no language restrictions. Key search terms were "hyperglycemic agents", "glucose control", "type 2 diabetes", "adults", "cardiovascular disease", "heart failure", and "risk" (appendix p 2). To ensure accurate identification of relevant published and unpublished studies, we reviewed reference lists, appendices, and supplementary material of eligible publications and conference abstracts between Nov 15, 2013, and Nov 20, 2019, and we used ClinicalTrials.gov to find updated data or the primary or secondary report over the same time period. If study data were unavailable, we contacted the study principal investigator for input to harmonise outcomes. Two reviewers (ORG-S and JAU) independently collected and analysed information about outcomes and baseline characteristics. Results were compared and any discrepancies were resolved by consensus. This study was done in accordance with the recommendations of the Cochrane Collaboration and PRISMA guidelines.

See Online for appendix

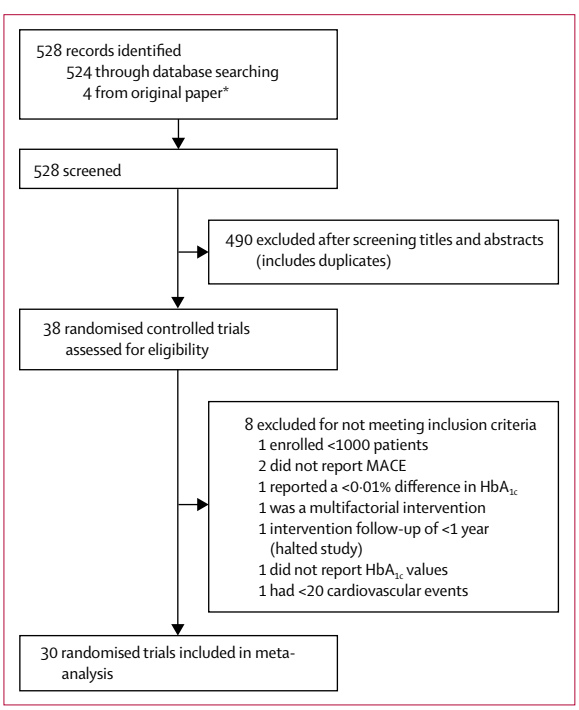

Figure 1: **Study selection**
MACE=major adverse cardiovascular events. *These studies (UKPDS, DREAM, ADOPT, and RECORD) did not appear in our search because they were published before Nov 15, 2013.

Data analysis

The primary outcomes of interest were heart failure and MACE (defined as a composite of cardiovascular death, myocardial infarction, or stroke). If trials did not report MACE as an outcome according to this definition, the following alternative definitions were used in preferential order: cardiovascular death, myocardial infarction, or ischaemic stroke; all-cause death, myocardial infarction, or stroke; an expanded MACE endpoint that included other atherothrombotic events (excluding heart failure), fatal and non-fatal myocardial infarction, or stroke; or fatal and non-fatal myocardial infarction. Secondary outcomes included all-cause mortality, individual components of MACE, and occurrence of new or worsening heart failure. All cardiovascular endpoints were adjudicated and defined within the individual trials according to standard criteria (appendix p 9). The definition of cardiovascular endpoints was in accordance with standard diagnostic criteria across all trials, which allowed for trial comparisons.

A review of quality metrics was done, including rating each trial according to their rigour of masking, participant attrition, therapeutic adherence, and adjudication of endpoints. From each study, data on baseline characteristics were collected and pooled, weighted results are presented as means (SDs), medians (IQRs), or proportions. We collected available risk ratios (RRs) as originally reported in each study or secondary analysis; otherwise, RRs and 95% CIs were derived from the reported number of events accrued and participants at risk per study group overall or in selected subgroups. Data from each trial were considered as per the intention-to-treat principle and pooled RRs and 95% CIs were calculated with inverse-variance random-effects models. Trials with unavailable data on a specific endpoint were excluded from the pooled analysis for that endpoint.

We assessed potential heterogeneity of treatment effects across studies with the use of the Cochrane Q statistic and the I^2 measure, with an I^2 of 75% or higher considered to represent high heterogeneity. Heterogeneity among subgroups was assessed according to the type of therapy studied, with an interaction term representing treatment effect by therapy category introduced into the models. Via random-effects meta-regression, we analysed the treatment effects per difference in bodyweight reached between study groups. Absolute differences in bodyweight between treatment groups were preferentially reported from a time-weighted least-square mean difference over the course of follow-up, at the end of follow-up, or at 1 year

	Population	n	Intervention	Control	Age, years	Women, n (%)	BMI, kg/m²	Follow-up, years, median (range)	Baseline athero-sclerotic CVD, n (%)	Baseline HF, n (%)	Baseline eGFR ≤60 mL/min, n (%)	Baseline weight, kg	Duration of diabetes, years	Change in HBA_{1c}, %; mmol/mol*	Change in weight, kg*
UKPDS 33 (1998)[25]	Outpatients with newly diagnosed type 2 diabetes with no history of MI in the previous year, no current angina or HF, not more than one vascular event, and no kidney failure	3867	Intensive treatment with sulfonylurea or insulin (target fasting blood glucose <6 mmol/L)	Standard care (diet; target fasting blood glucose <15 mmol/L)	53·3 (8·6)	920 (23·8%)	31·4 (4·6)	10·0 (7·7–12·4)	NR	NR	0	86·0 (15·0)	0 (NR)	–0·90% (NR); –9·84 (NR)	3·10 (2·02)
PROactive (2005)[4]	Outpatients with established type 2 diabetes and atherosclerotic CVD; excluded patients with recent ACS (<3 months), MI (<6 months), stroke (<6 months), or coronary revascularisation (<6 months), or with symptomatic HF (NYHA class ≥II)	5238	Pioglitazone	Placebo	61·7 (7·7)	1775 (33·9%)	30·8 (0·5)	2·9 (NR)	5238 (100·0%)	NR	597/5154 (11·6%)	NR	8·0 (4·0–13·0)†	–0·50% (NR); –5·46 (NR)	4·00 (NR)
ADOPT (2006)[7]	Outpatients with recently diagnosed type 2 diabetes receiving lifestyle management alone; excluded patients with unstable or severe angina or known HF	4351	Rosiglitazone (group 1)	Metformin (group 2); glyburide (group 3)	56·9 (10·1)	1840 (42·3%)	32·2 (6·4)	4·0 (NR)	NR	0	110 (2·5%)	92·0 (20·0)	1·5 (NR)	–0·13% (0·04) *vs* metformin; –1·42 (0·44); –0·42% (0·04) *vs* glyburide –4·59 (0·44)	6·90 (0·28) *vs* metformin; 2·50 (0·28) *vs* glyburide
DREAM (2006)[11]	Outpatients with newly diagnosed type 2 diabetes or prediabetes; excluded patients with previous CVD (including HF)	5269	Rosiglitazone	Placebo	54·7 (10·9)	3120 (59·2%)	30·9 (5·6)	3·0 (2·5–4·7)	0	0	0	NR	0 (0)	–0·50 (NR)‡	2·20 (NR)
ACCORD (2008)[26]	Outpatients with type 2 diabetes and either atherosclerotic CVD or multiple cardiovascular risk factors	10 251	Intensive treatment (target HbA_{1c} <6·0%)	Standard care (target HbA_{1c} 7·0–7·9%)	62·2 (6·8)	3952 (38·6%)	32·2 (5·5)	3·4 (NR)	3608 (35·2%)	497 (4·8%)	0	93·6 (NR)	10 (NR)	–1·10% (NR); –12·02 (NR)	3·10 (NR)
ADVANCE (2008)[27]	Outpatients with type 2 diabetes and either atherothrombosis, microvascular disease, or multiple cardiovascular risk factors	11140	Intensive treatment with gliclazide and other drugs as required (target HbA_{1c} <6·0%)	Standard care (target HbA_{1c} 7·0–7·9%)	66·0 (6·0)	4735 (42·5%)	28·0 (5·0)	5·0 (NR)	3590 (32·2%)	NR	2148 (19·3%)	NR	7·9 (6·4)	–0·67% (0·15); –7·32 (1·64)	0·70 (NR)

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	Population	n	Intervention	Control	Age, years	Women, n (%)	BMI, kg/m²	Follow-up, years, median (range)	Baseline athero-sclerotic CVD, n (%)	Baseline HF, n (%)	Baseline eGFR ≤60 mL/min, n (%)	Baseline weight, kg	Duration of diabetes, years	Change in HBA_{1c}, %; mmol/mol*	Change in weight, kg*
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BARI 2D (2009)[9]	Outpatients with type 2 diabetes and coronary heart disease identified as candidates for revascularisation (angina or ischaemia); excluded patients with symptomatic HF (NYHA class III–IV) or recent coronary revascularisation (<12 months)	2368	Insulin sensitisation with oral treatment	Insulin	62·4 (8·9)	701 (29·6%)	31·7 (5·4)	5·3 (NR)	2368 (100·0%)	156 (6·6%)	443/2146 (20·6%)	NR	10·4 (8·7)	–0·50% (NR); –5·46 (NR)	–1·80 (8·6)
RECORD (2009)[10]	Outpatients with type 2 diabetes receiving metformin or sulfonylurea; excluded patients with recent admission to hospital for a cardiovascular event (<3 months) or known HF	4447	Rosiglitazone	Metformin and sulfonylurea	58·4 (8·3)	2154 (48·4%)	31·5 (4·8)	5·5 (NR)	772 (17·4%)	21 (0·5%)	NR	89 (15·4)	7·1 (4·9)	–0·27% (0·05); –3·01 (0·55)	4·70 (0·45)
VADT (2009)[28]	Outpatients with type 2 diabetes; excluded patients with a recent cardiovascular event (<6 months), severe angina, or advanced HF	1791	Intensive therapy (treatment absolute difference in HbA_{1c} ≤1·5%)	Standard care	60·4 (9·0)	52 (2·9%)	31·2 (3·5)	5·6 (NR)	723 (40·4%)	NR	NR	97·3 (16·4)	11·5 (7·5)	–1·50% (NR); –16·39 (NR)	4·05 (NR)
ORIGIN (2012)[37]	Outpatients with type 2 diabetes or prediabetes and atherosclerotic CVD; excluded patients with HF	12 537	Insulin glargine	Standard care	63·5 (7·9)	4386 (35·0%)	29·9 (5·3)	6·2 (5·8–6·7)	7378 (58·8%)	0	1680/12 174 (13·8%)	NR	5·4 (6·0)	–0·30% (NR); –3·28 (NR)	2·10 (NR)
EXAMINE (2013)[21]	Outpatients with type 2 diabetes and stabilised within 15–90 days of an ACS; excluded patients with unstable cardiac disorders, including NYHA class IV HF	5380	Alogliptin	Placebo	61·0 (10)	1729 (32·1%)	28·3 (NR)§	1·5 (0·77–2·06)	5380 (100·0%)	1501 (27·9%)	1565 (29·1%)	NR	7·2 (NR)	–0·36% (0·04); –3·93 (0·44)	0·06 (0·16)

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	Population	n	Intervention	Control	Age, years	Women, n (%)	BMI, kg/m²	Follow-up, years, median (range)	Baseline athero-sclerotic CVD, n (%)	Baseline HF, n (%)	Baseline eGFR ≤60 mL/min, n (%)	Baseline weight, kg	Duration of diabetes, years	Change in HBA_{1c}, %; mmol/mol*	Change in weight, kg*
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Look AHEAD (2013)[38]	Outpatients with type 2 diabetes; excluded patients with a recent cardiovascular event (<3 months) or unstable cardiac disorders, including symptomatic HF (NYHA class ≥III)	5145	Intensive lifestyle intervention for weight loss (caloric restriction and exercise)	Standard care	58·8 (6·9)	3063 (59·5%)	35·9 (5·9)	9·6 (8·6–10·3)	714 (13·9%)	NR	238/4857 (4·9%)	101 (20·5)	5 (2–10)†	−0·22% (0·03); −2·40 (0·33)	−4·0 (1·0)
SAVOR-TIMI 53 (2013)[22]	Outpatients with type 2 diabetes and either atherosclerotic CVD or multiple cardiovascular risk factors; excluded patients with a recent or unstable cardiovascular event (<2 months)	16 492	Saxagliptin	Placebo	65·1 (8·5)	5452 (33·1%)	31·2 (5·6)	2·1 (1·8–2·3)	12 959 (78·6%)	2105 (12·8%)	2576 (15·6%)	87·9 (19·1)	10·3 (5·3–16·7)†	−0·20% (0·01); −2·19 (0·11)	−0·10 (0·15)
AleCardio (2014)[5]	Outpatients with type 2 diabetes and stabilised within 8 weeks of an ACS (mean 29 days); excluded patients with symptomatic HF (NYHA class ≥II) or recent hospital admission for HF (<12 months)	7226	Aleglitazar	Placebo	61·0 (10·0)	1966 (27·2%)	28·7 (NR)§	2·0 (1·6–2·2)	7226 (100·0%)	759 (10·5%)	1379 (19·1%)	83·1 (19·0)	8·6 (NR)	−0·60 (0·03); −6·56 (0·33)	3·50 (NR)
ELIXA (2015)[12]	Outpatients with type 2 diabetes and an acute coronary event within 180 days; excluded patients with planned (within 90 days) or recent (within 15 days) percutaneous coronary revascularisation or coronary artery bypass graft surgery for the qualifying event	6068	Lixisenatide	Placebo	60·2 (9·7)	1861 (30·7%)	30·2 (5·7)	2·1 (NR)	6068 (100·0%)	1358 (22·4%)	1407 (23·2%)	85·2 (19·4)	9·3 (8·3)	−0·27% (0·89); −2·95 (9·73)	−0·70 (3·97)

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	Population	n	Intervention	Control	Age, years	Women, n (%)	BMI, kg/m²	Follow-up, years, median (range)	Baseline atherosclerotic CVD, n (%)	Baseline HF, n (%)	Baseline eGFR ≤60 mL/min, n (%)	Baseline weight, kg	Duration of diabetes, years	Change in HBA_{1c}, %; mmol/mol*	Change in weight, kg*
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EMPA-REG OUTCOME (2015)[29,30]	Outpatients with type 2 diabetes and established atherosclerotic CVD; excluded patients with a recent ACS, stroke, or TIA (<2 months)	7020	Empagliflozin 25 mg or 10 mg	Placebo	63·1 (8·7)	2004 (28·5%)	30·6 (5·3)	3 (2·2–3·6)	7020 (100·0%)	706 (10·1%)	1819 (25·9%)	86·3 (19·0)	10 (NR)	−0·57% (NR); −6·23 (NR)	−2·00 (NR)
TECOS (2015)[23]	Outpatients with type 2 diabetes and atherosclerotic CVD; excluded patients with a planned revascularisation	14 671	Sitagliptin	Placebo	65·5 (8·0)	4297 (29·3%)	30·2 (5·6)	3·0 (2·3–3·8)	10 863 (74·0%)	2643 (18·0%)	3324 (22·7%)	85·1 (19·0)	11·6 (8·1)	−0·29% (0·77); −3·17 (8·42)	−0·05 (NR)
IRIS (2016)[6]	Outpatients with insulin resistance but no established diabetes and with a qualifying ischemic stroke or TIA during the 6 months before randomisation; excluded patients with HF (NYHA class III–IV, or II with reduced left ventricular ejection fraction)	3876	Pioglitazone	Placebo	63·5 (10·6)	1338 (34·5%)	29·9 (5·5)	4·8 (NR)	3876 (100·0%)	0	NR	NR	0 (NR)	−0·24% (NR); −2·62 (NR)	3·10 (NR)
LEADER (2016)[13,14]	Outpatients with type 2 diabetes and either atherosclerotic CVD, CKD, or HF (NYHA class II–III) or multiple cardiovascular risk factors; excluded patients with a recent acute coronary or cerebrovascular event (within 14 days)	9340	Liraglutide	Placebo	64·3 (7·2)	3337 (35·7%)	32·5 (6·3)	3·8 (NR)	7598 (81·3%)	1305 (14·0%)	2158 (23·1%)	91·8 (21·0)	12·8 (8·1)	−0·40% (1·36); −4·37 (14·86)	−2·30 (6·16)

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	Population	n	Intervention	Control	Age, years	Women, n (%)	BMI, kg/m²	Follow-up, years, median (range)	Baseline athero-sclerotic CVD, n (%)	Baseline HF, n (%)	Baseline eGFR ≤60 mL/min, n (%)	Baseline weight, kg	Duration of diabetes, years	Change in HBA_{1c}, %; mmol/mol*	Change in weight, kg*
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SUSTAIN-6 (2016)[15]	Outpatients with type 2 diabetes and either atherosclerotic CVD, CKD, or HF (NYHA class II–III), or multiple cardiovascular risk factors; excluded patients with a recent acute coronary or cerebrovascular event (within 90 days) or planned coronary, carotid, or peripheral artery revascularisation	3297	Semaglutide 0·5 mg or 1·0 mg	Placebo	64·6 (7·4)	1295 (39·3%)	32·8 (6·2)	2·1 (NR)	2735 (83·0%)	777 (23·6%)	939 (28·5%)	92·1 (20·6)	13·9 (8·1)	−0·85% (1·46); −9·29 (15·96)	−3·61 (6·21)
CANVAS (2017)[31–33]	Outpatients with type 2 diabetes and either symptomatic atherosclerotic CVD or multiple cardiovascular risk factors; excluded patients with a recent ACS, revascularisation, stroke, or TIA (<3 months), planned revascularisation, or NYHA class IV HF	10 142	Canagliflozin	Placebo	63·3 (8·3)	3633 (35·8%)	32·0 (5·9)	3·6 (2·0)¶	6656 (65·6%)	1461 (14·4%)	2039 (20·1%)	90·2 (NR)	13·5 (7·8)	−0·58% (0·64); −6·34 (6·99)	−1·60 (2·42)
EXSCEL (2017)[16,20]	Outpatients with type 2 diabetes either with or without a previous atherosclerotic CVD event	14 752	Exenatide	Placebo	62·0 (NR)	5603 (38·0%)	31·8 (28·2–36·2)§	3·2 (2·2–4·4)	10 782 (73·1%)	2389 (16·2%)	3191 (21·6%)	93 (NR)	12·0 (NR)	−0·53% (1·08); −5·79 (11·80)	−1·27 (4·18)
ACE (2017)[39]	Outpatients with impaired glucose tolerance and established coronary heart disease	6522	Acarbose	Placebo	64·3 (8·1)	1762 (27·0%)	25·4 (3·1)	5·0 (3·4–6·0)	6522 (100·0%)	69 (1·1%)	438 (6·7%)	70·2 (10·8)	0 (0)	−0·07% (0·62); −0·77 (6·78)	−0·64 (2·26)
TOSCA.IT (2017)[8]	Outpatients with type 2 diabetes on metformin; excluded patients with acute cardiovascular events (≤6 months) or HF (NYHA I–IV)	3028	Pioglitazone	Sulfonylurea	62·3 (6·5)	1254 (41·4%)	30·3 (4·5)	4·8 (3·5–5·0)	335 (11·1%)	0	107 (3·5%)	82·5 (NR)	8·5 (5·7)	−0·06% (0·20); −0·66 (2·19)	0·0 (9·8)

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	Population	n	Intervention	Control	Age, years	Women, n (%)	BMI, kg/m²	Follow-up, years, median (range)	Baseline athero-sclerotic CVD, n (%)	Baseline HF, n (%)	Baseline eGFR ≤60 mL/min, n (%)	Baseline weight, kg	Duration of diabetes, years	Change in HBA_{1c}, %; mmol/mol*	Change in weight, kg*
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DECLARE–TIMI 58 (2018)[34]	Outpatients with type 2 diabetes and either atherosclerotic CVD or multiple cardiovascular risk factors; excluded patients with a recent acute cardiovascular event (<2 months)	17 160	Dapagliflozin	Placebo	64·0 (6·8)	6422 (37·4%)	32·1 (6·0)	4·2 (3·9–4·4)	6974 (40·6%)	1724 (10·0%)	1265 (7·4%)	91·0 (NR)	10·5 (6·0–1·6)†	−0·42% (0·84); −4·59 (9·18)	−1·8 (5·0)
Harmony Outcomes (2018)[19]	Outpatients who had type 2 diabetes and atherosclerotic CVD	9463	Albiglutide	Placebo	64·2 (8·7)	2894 (30·6%)	32·3 (5·9)	1·6 (1·3–2·0)	9463 (100·0%)	1922 (20·3%)	2222 (23·5%)	92·5 (NR)	14·1 (8·8)	−0·52% (1·61); −5·68 (17·60)	−0·83 (5·71)
CARMELINA (2018)[24]	Outpatients with type 2 diabetes and albuminuria with atherosclerotic CVD or CKD; excluded patients with ESKD, a recent acute cardiovascular event (ACS ≤2 months, TIA or stroke ≤3 months), or planned revascularisation (≤2 months)	6979	Linagliptin	Placebo	65·9 (9·1)	2589 (37·1%)	31·4 (5·4)	2·2 (NR)	4081 (58·5%)	1873 (26·8%)	4348 (62·3%)	86 (NR)	14·7 (9·5)	−0·36% (1·39); −3·93 (15·19)	−0·15 (5·86)
CREDENCE (2019)[35,36]	Outpatients with type 2 diabetes and CKD and albuminuria; excluded patients with a recent ACS, revascularisation, stroke, or TIA (<3 months), planned revascularisation, NYHA class IV HF, or ESKD	4401	Canagliflozin	Placebo	63·0 (9·2)	1494 (33·9%)	31·3 (6·2)	2·6 (0·02–4·53)	2220 (50·4%)	652 (14·8%)	2631 (59·8%)	87·1 (NR)	15·8 (8·6)	−0·25% (0·93); −2·73 (10·16)	−0·80 (1·95)

(Table continues on next page)

	Population	n	Intervention	Control	Age, years	Women, n (%)	BMI, kg/m²	Follow-up, years, median (range)	Baseline atherosclerotic CVD, n (%)	Baseline HF, n (%)	Baseline eGFR ≤60 mL/min, n (%)	Baseline weight, kg	Duration of diabetes, years	Change in HBA_{1c}, %; mmol/mol*	Change in weight, kg*
(Continued from previous page)															
REWIND (2019)[17]	Outpatients with type 2 diabetes and either atherosclerotic CVD, left ventricular hypertrophy, CKD, albuminuria, or multiple cardiovascular risk factors; excluded patients with a recent coronary event, stroke, or TIA (≤2 months) or planned revascularisation	9901	Dulaglutide	Placebo	66·2 (6·5)	4589 (46·3%)	32·3 (5·8)	5·4 (5·1–5·9)	3114 (31·5%)	853 (8·6%)	2199 (22·2%)	NR	9·5 (NR)	–0·61% (0·89); –6·67 (9·73)	–1·46 (5·33)
PIONEER 6 (2019)[18]	Outpatients with type 2 diabetes and either atherosclerotic CVD, CKD, or multiple cardiovascular risk factors; excluded patients with planned coronary, carotid, or peripheral artery revascularisation, recent unstable angina or TIA (≤2 months), or NYHA class IV HF	3183	Semaglutide	Placebo	66·0 (7·0)	1007 (31·6%)	32·3 (6·5)	1·3 (0·03–1·67)	2695 (84·7%)	NR	856 (26·9%)	90·9 (21·2)	14·9 (8·5)	–0·7% (NR); –7·65 (NR)	–3·4 (NR)
Total	..	225 305	..	..	63·0 (8·4)	81 224 (36·1%)	31·1 (5·6)	3·8 (1·8)¶	140 958/217 087 (64·9%)	22 771/194 941 (11·7%)	39 679/214 234 (18·5%)	88·7 (15·1)	9·4 (6·6)	–0·46% (0·78); –5·01 (8·52)	0·09 (4·13)

Data are mean (SD) unless otherwise indicated. CVD=cardiovascular disease. HF=heart failure. eGFR=estimated glomerular filtration rate. MI=myocardial infarction. NR=not reported. ACS=acute coronary syndrome. NYHA=New York Heart Association. TIA=transient ischaemic attack. CKD=chronic kidney disease. ESKD=end-stage kidney disease. *Absolute differences in fasting blood glucose, HbA_{1c}, or bodyweight between treatment groups was preferentially reported as a time-weighted least-square mean difference over the course of follow-up, at end of follow-up, or at 1 year of follow-up, as per the original study report; if none of these data were reported, the first available follow-up values were used. †Data are median (range). ‡Reported as fasting plasma glucose (mmol/L) measurement. §Data are median (IQR). ¶Data are mean (SD).

Table: **Summary of included studies**

of follow-up, as per the original study report. If none of these data were reported, the first available follow-up values were used.

Studies of intensive weight loss, GLP-1 receptor agonists, or SGLT2 inhibitors (herein referred to as diabetes therapies with effective weight reduction) were also assessed for consistency of treatment effects among key subgroups for the endpoints of heart failure and MACE. Subgroups included participants with and without baseline atherosclerotic cardiovascular disease, heart failure, and chronic kidney disease as defined in each trial, apart from chronic kidney disease for which we used an estimated glomerular filtration rate or creatinine clearance threshold of less than 60 mL/min.

We assessed publication bias and other small study effects by visual inspection of funnel plots, with the ascertainment for potential asymmetry of published results by Egger's regression test and Duval and Tweedie's trim-and-fill method.

Two-sided p values were calculated, with $p<0·05$ considered significant for pooled RR results. $p<0·01$ was considered significant for subgroup interactions to compensate for the effects of multiple testing. Statistical analyses were done with Review Manager version 5.3.4 and Comprehensive Meta-Analysis version 3.1.

The study is registered with PROSPERO, number CRD42018045806.

Role of the funding source

There was no funding source for this study. All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

Our search for trial reports published from Nov 15, 2013 to Nov 20, 2019, yielded 38 randomised controlled trials of glucose-lowering drugs or strategies in people with or at risk of type 2 diabetes,[4–48] of which eight trials were excluded (figure 1; appendix p 10).[40–47] We included 14 cardiovascular outcome trials from our previous analysis,[3] in addition to 16 new trials reported subsequently.[6,8,12–20,23,24,29–36,39] In total, 30 trials and 225 305 participants were included (table).[4–39] The mean duration of diabetes was 9·4 years (SD 6·6). The mean age of participants was 63·0 years (8·4), 81 224 (36·1%) were women, and 140 958 (64·9%) of 217 087 assessable participants had a history of atherosclerotic cardiovascular disease. 22 771 (11·7%) of 194 941 assessable participants had a history of heart failure, and 39 679 (18·5%) of 214 234 assessable participants had a history of moderate to severe chronic kidney disease (estimated glomerular filtration rate ≤60 mL/min). Mean BMI was 31·1 kg/m² (5·6) and mean bodyweight was 88·7 kg (15·1). Regarding baseline background medical therapy, more than 65% of participants were treated with metformin, lipid-lowering, and antiplatelet therapies; 80 756 (42·0%) were treated with a sulfonylurea; and 69 263 (38·2%) were treated with insulin (appendix p 11).

Among the 30 included trials, eight (n=35 803) assessed PPAR agonist treatment strategies;[4–11] seven (n=56 004) assessed GLP-1 receptor agonists;[12–20] four (n=43 522) assessed DPP-4 inhibitors;[21–24] four (n=27 049) assessed a strategy of intensive glycaemic control;[25–28] four (n=38 723) assessed SGLT2 inhibitors;[28–36] one (n=12 537) assessed insulin glargine;[37] one (n=5145) assessed a strategy of intensive weight loss;[38] and one (n=6522) assessed acarbose.[39] Available endpoints across all 30 trials included a composite of MACE (typically cardiovascular death or all-cause mortality, non-fatal myocardial infarction, and non-fatal stroke), hospital admission for heart failure, and all-cause mortality. All trials apart from two included cardiovascular death as an outcome.[6,9] The trial quality metrics and assessment of risk of bias are shown in the appendix (p 13). Visual inspection of funnel plots and quantitative assessment suggested no indication of publication bias (appendix pp 7, 8, 14).

During a mean follow-up of 3·8 years (SD 1·8), 23 016 (10·2%) participants had a MACE outcome event, 8169 (3·6%) participants had a heart failure event, 10 633 (4·9%) had a myocardial infarction, 6159 (2·9%) had a stroke, 16 330 (7·3%) had died from any cause, and 10 013 (4·5%) had died from a cardiovascular cause. Among surrogate metabolic endpoints, overall there was a pooled, weighted reduction in HbA_{1c} of 0·46% (SD 0·78; 5·0 mmol/mol [8·5]) and a gain in bodyweight of 0·09 kg (4·13) in the intervention group compared with the control group.

Overall, glucose-lowering drugs or strategies significantly decreased the risk of atherosclerotic MACE (RR 0·92, 95% CI 0·89–0·95, $p<0·0001$; figure 2). There were also significant reductions in risk for cardiovascular death (0·92, 0·87–0·97, p=0·004), all-cause mortality (0·94, 0·90–0·98, p=0·004), fatal and non-fatal myocardial infarction (0·92, 0·88–0·96, p=0·0002), and fatal and non-fatal stroke (0·93, 0·89–0·98, p=0·006; figure 3). By contrast with the findings of our previous meta-analysis,[3] glucose-lowering drugs or strategies had no overall significant effect on the risk of heart failure (0·98, 0·90–1·08, p=0·71; figure 4).

Despite these overall results, the magnitude and directionality of the risk varied modestly for MACE ($p_{interaction}=0·02$; figure 2) and substantially for heart failure ($p_{interaction}<0·00001$; figure 4) depending on the class of drug or strategy tested. Moreover, in a meta-regression, observed effects for heart failure within each trial aligned well with what was predicted on the basis of the extent of mean bodyweight loss across diabetes drug classes or strategies (figure 5). Updating the meta-regression analysis to incorporate these results showed that a 1 kg difference in weight between treatment groups was associated with a 5·9% (3·9–8·0%) difference in the RR of heart failure; $p<0·0001$; figure 5). The association

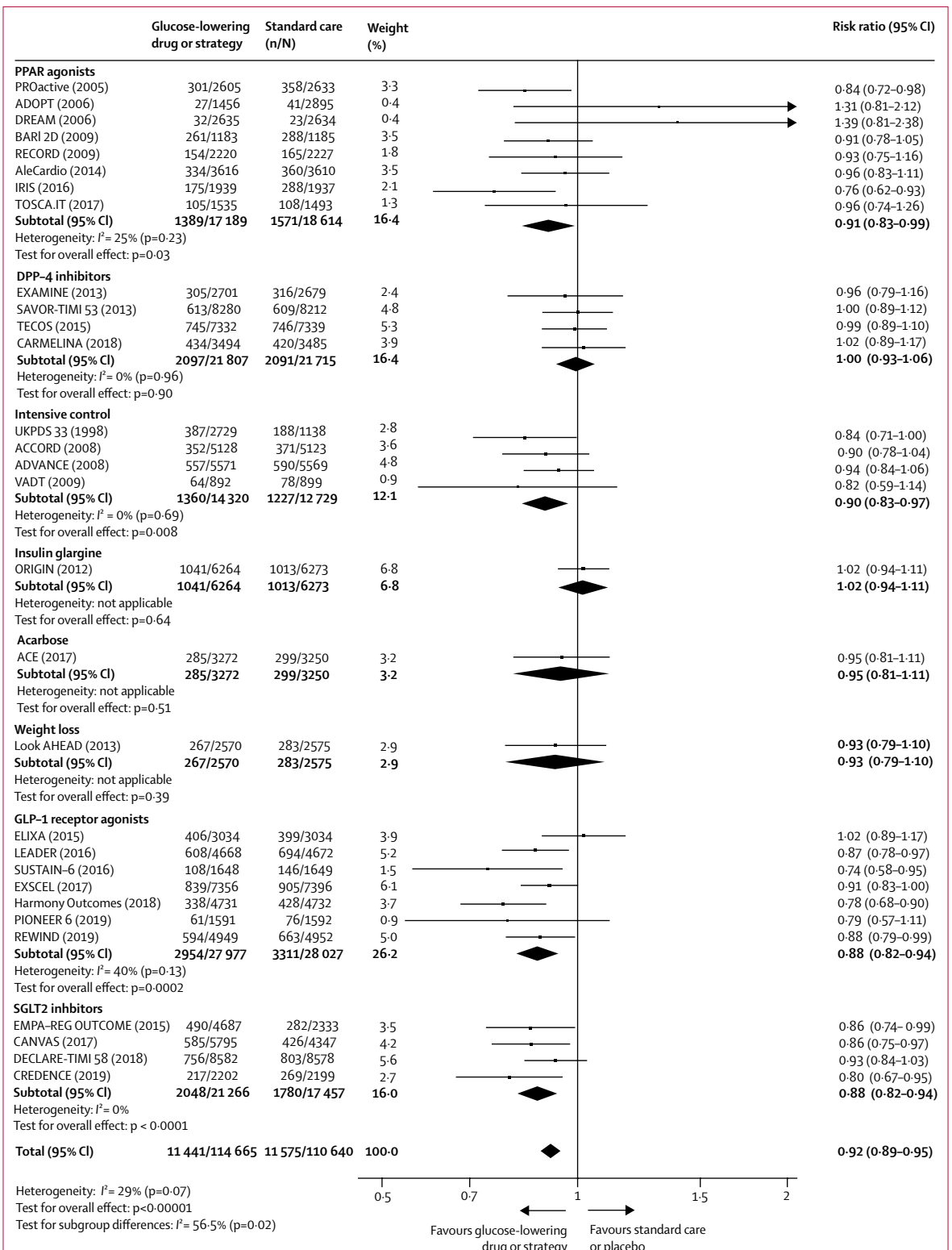

***Figure 2*: Risk of atherosclerotic major adverse cardiovascular events comparing glucose-lowering drugs or strategies with standard care or placebo, stratified by strategy or drug class**

Risk ratios were calculated from an inverse-variance random-effects model. Heterogeneity among diabetes drug class or strategy subgroups was assessed with an interaction term representing treatment effect by therapy category. PPAR=peroxisome proliferator-activated receptor.

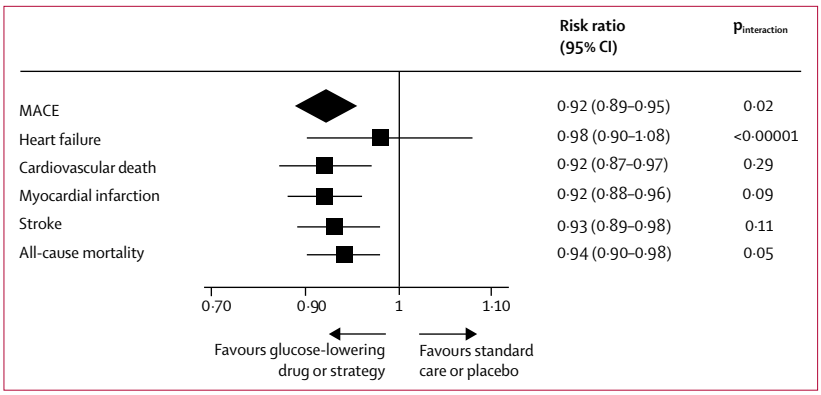

Figure 3: **MACE and individual cardiovascular events comparing glucose-lowering drugs or strategies versus standard care or placebo**

Risk ratios were calculated from an inverse-variance random-effects model. Heterogeneity among diabetes drug class or strategy subgroups was assessed with an interaction term representing treatment effect by therapy category. The findings for myocardial infarction and stroke represent all (fatal and non-fatal) events. MACE=major adverse cardiovascular events.

remained significant in a sensitivity analysis that removed the PPAR agonist trials (1 kg difference in weight resulted in a 3·7% [1·0–6·6%] difference in the RR of heart failure; p=0·0074; appendix p 3).

We subsequently focused our analyses on deriving summary effect estimates across glucose-lowering drugs or strategies that result in effective weight reduction (appendix p 12), specifically intensive weight loss via lifestyle modification, GLP-1 receptor agonists, and SGLT2 inhibitors.[12–20,29–36,38] When assessing therapies or strategies that lower bodyweight, the direction of risk reduction was consistent across these drugs or strategies (appendix p 4). The risk of MACE was significantly lower overall (RR 0·88, 95% CI 0·84–0·92, p<0·0001) with no significant heterogeneity ($p_{interaction}$=0·80). Similar findings were seen for cardiovascular death (0·85, 0·79–0·93, p=0·0002; $p_{interaction}$=0·74), all-cause mortality (0·87, 0·82–0·92, p<0·0001; $p_{interaction}$=0·68), myocardial infarction (0·90, 0·85–0·95, p=0·0001; $p_{interaction}$=0·78), and stroke (0·90, 0·82–0·98, p=0·014; $p_{interaction}$=0·19). There was also a reduced risk of heart failure overall with therapies or strategies that lower bodyweight (0·81, 0·74–0·89, p<0·0001; $p_{interaction}$=0·0004), with a greater reduction of risk with SGLT2 inhibitors (0·68, 0·60–0·76, p<0·0001) than with intensive lifestyle changes (0·80, 0·62–1·04, p=0·10) or GLP-1 receptor agonists (0·91, 0·84–0·999, p=0·049).

We explored the consistency of treatment effects for MACE and heart failure across therapies or strategies that lower bodyweight across key subgroups of participants with and without baseline atherosclerotic cardiovascular disease, heart failure, and chronic kidney disease (appendix pp 5, 6). Compared with standard care or placebo, MACE risk reduction with therapies or strategies that lower bodyweight was consistent among participants with established atherosclerotic cardiovascular disease (RR 0·87, 95% CI 0·83–0·92) and those without (0·92, 0·83–1·02; $p_{interaction}$=0·33). There was consistent risk reduction for MACE in subgroups with (0·89, 0·82–0·97) and without baseline heart failure (0·86, 0·82–0·91; $p_{interaction}$=0·50). Similarly, there was consistent risk reduction for MACE in participants with (0·83, 0·75–0·93) and without advanced chronic kidney disease at baseline (0·89, 0·83–0·94; $p_{interaction}$=0·32). Regarding heart failure outcomes, therapies or strategies that lower bodyweight showed consistent risk reduction in participants with atherosclerotic cardiovascular disease at baseline (0·80, 0·73–0·89) and those without (0·84, 0·74–0·95; $p_{interaction}$=0·63). Reductions in the risk of heart failure were consistent among participants with (0·85, 0·71–1·01) and without heart failure at baseline (0·81, 0·73–0·90; $p_{interaction}$=0·71). Heart failure risk was reduced in participants with (0·73, 0·63–0·84) and without (0·88, 0·78–0·99) advanced chronic kidney disease at baseline, although the risk was reduced further in those with chronic kidney disease at baseline than in those without ($p_{interaction}$=0·044).

Discussion

In this updated systematic review and meta-analysis of large cardiovascular outcome trials of glucose-lowering drugs or strategies in people with or at risk of type 2 diabetes, we found that, with data pooled across interventions, glucose-lowering drugs or strategies significantly reduced the risk of MACE (RR 0·92, 95% CI 0·89–0·95) and had no overall effect on the risk of heart failure (0·98, 0·90–1·08) compared with standard care or placebo.

To the best of our knowledge, our study is the most comprehensive meta-analysis of large cardiovascular outcome trials in people with or at risk of type 2 diabetes. Our analysis integrated data from 30 trials and 225 305 participants, with about 10% of patients having an atherosclerotic cardiovascular event and about 4% having a heart failure event during follow-up. With the benefit of time, accrual of a large sample of participants and accumulation of sufficient endpoint events, it has become clear that glucose-lowering drugs or strategies reduce atherosclerotic cardiovascular events, with some drug classes or strategies modestly more beneficial than others. The significant reduction in MACE is no longer confined to myocardial infarction alone and includes fatal cardiovascular events and all-cause mortality, since most deaths in the trials were cardiovascular in nature.

Although there was no overall effect on the risk of heart failure, the directionality and magnitude of heart failure effect differed substantially depending on the drug class or strategy assessed; an increased risk was apparent with PPAR agonists, no effect was seen overall with DPP-4 inhibitors, and a reduced risk was apparent with SGLT2 inhibitors. Plotting the association between observed RRs for heart failure within each trial and the absolute difference in bodyweight achieved between treatment

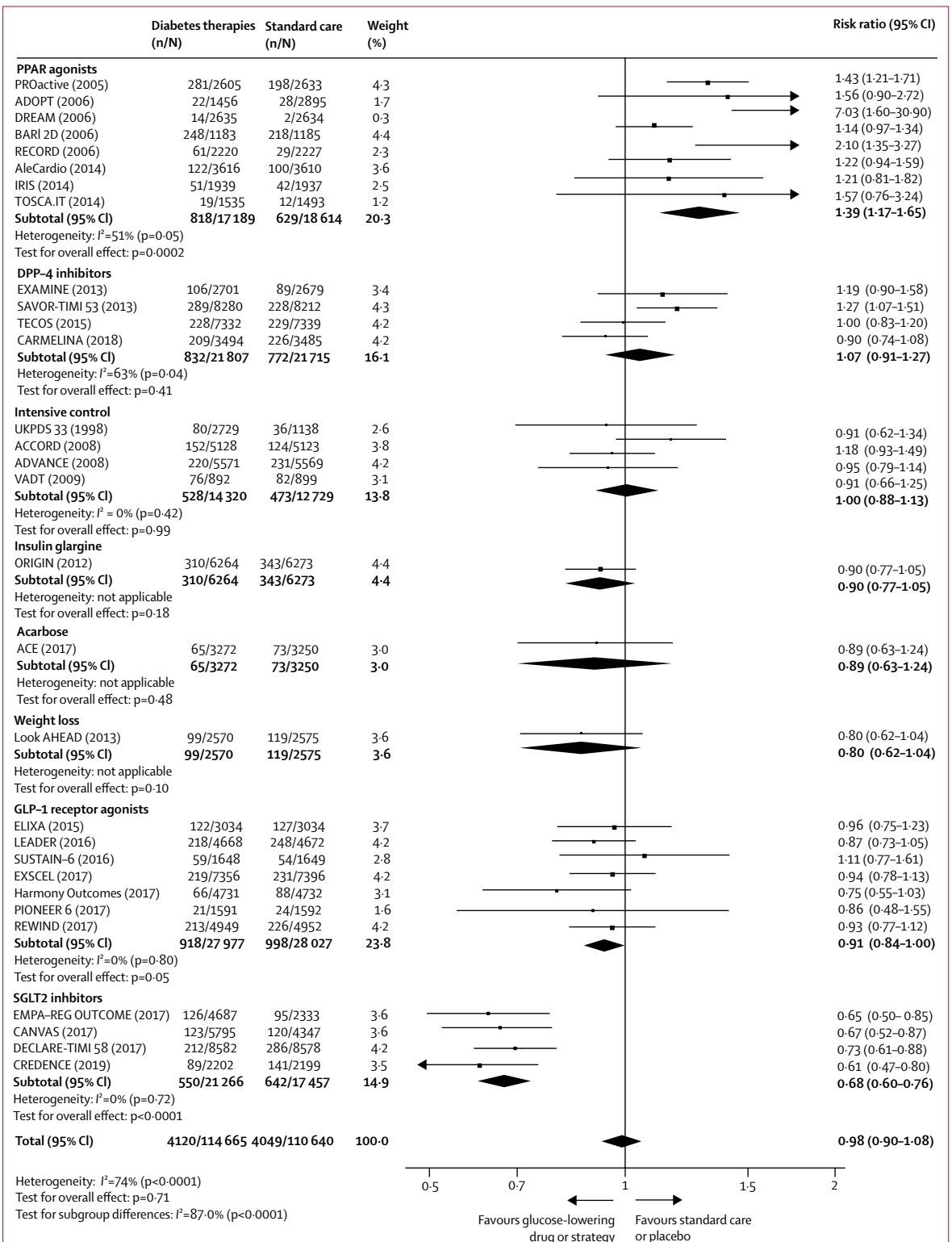

Figure 4: **Risk of heart failure events comparing glucose-lowering drugs or strategies with standard care or placebo, stratified by strategy or drug class**
Risk ratios were calculated from an inverse-variance random-effects model. Heterogeneity among diabetes drug class or strategy subgroups was assessed with an interaction term representing treatment effect by therapy category. PPAR=peroxisome proliferator-activated receptor.

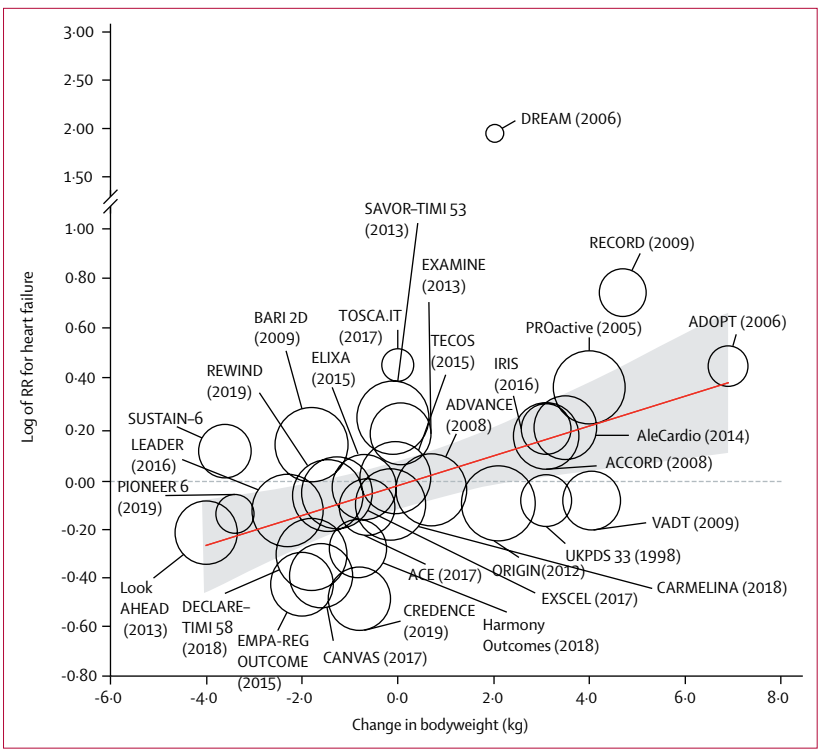

Figure 5: **Relation between change in bodyweight and risk of heart failure**
Red line shows meta-regression with 95% CI shown as shading. The size of the circles reflects the number of outcome events contributed. RR=risk ratio.

groups suggested potential effect modification via effects on bodyweight. Confining the analysis to therapies or strategies that lower bodyweight (intensive lifestyle change, SGLT2 inhibitors, and GLP-1 receptor agonists), we found significant risk reductions of between 10% and 15% for MACE, all-cause mortality, myocardial infarction, and stroke. Furthermore, we identified a 19% risk reduction in the risk of heart failure, which was most apparent with SGLT2 inhibitors. With the inclusion of two trials of GLP-1 receptor agonists reported in 2019, the REWIND trial of dulaglutide[17] and the PIONEER 6 trial of oral semaglutide,[18] our findings also support a reduction in heart failure risk with this drug class.[17,18] After incorporating the results of the CREDENCE trial from 2019,[35,36] which enrolled a very high-risk primary and secondary prevention population with diabetic nephropathy, there was no longer significant heterogeneity in the risk reduction for MACE among therapies or strategies that lower weight by presence or absence of atherosclerotic cardiovascular disease at baseline, in line with consistent effects observed among participants with or without heart failure or chronic kidney disease at baseline. Similarly, risk reduction for heart failure was consistent among participants with or without baseline atherosclerotic cardiovascular disease, heart failure, and chronic kidney disease.

These findings build on our earlier work,[3] in which we hypothesised a potential clustering of risk reduction for heart failure in cardiovascular outcome trials of glucose-lowering drugs or strategies proportional to a demonstrable reduction in bodyweight. In our previous meta-analysis,[3] the risk of heart failure was predicted to increase with diabetes therapies, predominantly based on data from therapies associated with fluid retention and weight gain. There was a suggestion of potential heart failure benefit associated with weight loss from Look AHEAD,[38] but no large trials of diabetes therapies that substantially lower weight had been reported at the time.

The results from our updated analysis dispel perceptions that risk reduction for MACE is confined to GLP-1 receptor agonists and that for heart failure is confined to SGLT2 inhibitors. Of course, not all changes in bodyweight are equal and changes in adiposity, plasma volume, and bone mass could have varying effects on intramyocardial glucose metabolism, haemodynamics, and the vasculature.[48] As well as changes in bodyweight, the mechanism by which interventions achieve a change in weight (eg, glycosuria, natriuresis, change in circulating insulin and glucagon, satiety, caloric restriction) could have a varying impact on cardiovascular outcomes beyond simply lowering glucose concentration. Our findings with respect to the effects of GLP-1 receptor agonists and SGLT2 inhibitors might reassure clinicians having difficulty implementing guidance that suggests prioritising one drug class over the other depending on which type of cardiovascular risk is most relevant to reduce in a patient with type 2 diabetes and established cardiovascular disease. Our results also emphasise that intensive lifestyle changes still warrant consideration, since the findings in Look AHEAD were ascertained despite the trial being halted for presumed futility for a primary MACE endpoint.[38] However, problems with adherence to intensive lifestyle changes could mean that they are not as effective as drug classes that achieve early and persistent weight loss effects.

Our results also raise the possibility that risk reduction for MACE with therapies that lower weight might be consistent among patients with atherosclerotic cardiovascular disease (ie, secondary prevention) and high-risk primary prevention patients (eg, those with diabetic nephropathy). Consideration of risk level in primary prevention is not inconsequential; compared with the placebo group in the primary prevention cohort in DECLARE–TIMI 58,[34] who were followed up for a median of 4·2 years, primary prevention patients assigned to placebo in CREDENCE,[35,36] followed up for a mean of 2·6 years, had a 1·5–2·0-times higher rate of cardiovascular death or heart failure and MACE. Risk reduction for MACE in our updated meta-analysis was also consistent among participants with type 2 diabetes with and without established heart failure or chronic kidney disease, and risk reduction for heart failure was consistent among patients with type 2 diabetes with and without established atherosclerotic cardiovascular

disease, heart failure, or chronic kidney disease.[34–36] These hypothesis-generating findings are therefore encouraging for the ongoing trials of SGLT2 inhibitors in patients with heart failure (NCT03619213, NCT03057951, NCT03057977, and NCT03521934) or chronic kidney disease (NCT03036150 and NCT03594110) with or without established type 2 diabetes. Furthermore, testing glucose-lowering therapies that lower bodyweight among patients with or without type 2 diabetes who have had an acute or recent atherosclerotic cardiovascular event (ie, tertiary prevention) could also be useful. Such endeavours should be pursued cautiously, in view of the null results of the ELIXA trial with lixisenatide,[12] although this finding might have resulted because lixisenatide is a non-human GLP-1 analogue with a relatively short half-life.

Our study has strengths and limitations. We prospectively defined our study question, inclusion and exclusion criteria, outcomes, and subgroups of interest, and we used conservative assumptions with random-effects analyses for precision estimates in view of the inherent likelihood of heterogeneity between and within classes of diabetes therapy. Although we set a higher threshold than is conventional for declaring heterogeneity, in view of the potential for chance findings within a large dataset testing multiple hypotheses, the overall pooled treatment effect on MACE should be interpreted with caution, since modest heterogeneity was detected across drug classes or strategies (I^2=29%; $p_{interaction}$=0·02). The included trials varied in study design, intervention and controls, population studied, and definition of cardiovascular endpoints. However, the range of participants studied is representative of those with type 2 diabetes or prediabetes seen in routine practice. The evidence generated from these trials forms the basis for international clinical practice guideline recommendations, and the cardiovascular endpoints studied followed standard diagnostic criteria. Focusing on large cardiovascular outcome trials led to a low likelihood of detecting publication bias, because any small studies with large effects would be excluded and studies with negative effects are likely to have been published because of the large sample size. Individual participant-level data were unavailable, limiting our ability to control for potential confounding across studies, but it is unlikely that substantial changes to our primary results would be affected. However, individual participant-level data would be useful to further delineate the independent effect of effect-modifying variables such as bodyweight or left ventricular ejection fraction. For example, such data could show whether or not achieved weight loss by individual participants was associated with the cardioprotective effects of the interventions. Finally, our results for the effect of GLP-1 receptor agonists on heart failure and MACE stratified by subgroups of heart failure and chronic kidney disease were limited by these analyses being ongoing in the primary study teams of some trials. When further data are reported, these analyses should be updated.

To conclude, meta-analysis of 30 large cardiovascular outcome trials in people with or at risk of type 2 diabetes showed that glucose-lowering drugs or strategies overall reduced the risk of fatal and non-fatal atherosclerotic cardiovascular events and all-cause mortality. Although there was no overall effect on heart failure, risk varied by drug class or strategy, with a potential beneficial effect related to the extent of weight loss achieved. Therapies that lower bodyweight (SGLT2 inhibitors, GLP-1 receptor agonists, and intensive lifestyle changes) significantly reduced the risk of fatal and non-fatal atherosclerotic events and heart failure. Reductions in MACE and heart failure risk were consistent among participants with and without atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease at baseline. These data suggest a potential broad cardiovascular benefit of using diabetes therapies that reduce bodyweight in routine clinical practice.

Contributors

ORG-S did the literature search and created the figures. ORG-S and JAU did the data collection. All authors contributed to data analysis and interpretation of the findings. ORG-S and JAU wrote the first draft of the report and all authors provided critical input for important intellectual content.

Declaration of interests

SGG has received research grant support (steering committee or data monitoring committee) from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, CSL Behring, Daiichi Sankyo, Eli Lilly, Esperion, Ferring Pharmaceuticals, GlaxoSmithKline, Janssen/Johnson & Johnson, Matrizyme, Novartis, Novo Nordisk, Pfizer, Regeneron, Sanofi, and Tenax Therapeutics; speaker or consulting honoraria (advisory boards) from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, CSL Behring, Eli Lilly, Fenix Group International, Ferring Pharmaceuticals, HLS Therapeutics, Merck, Novartis, Pfizer, Regeneron, Sanofi, and Tenax Therapeutics; and salary support from the Heart and Stroke Foundation of Ontario and University of Toronto (Polo) Chair, Canadian Heart Research Centre and MD Primer, Canadian VIGOUR Centre, Duke Clinical Research Institute, New York University Clinical Coordinating Center, and PERFUSE. LAL has received honoraria for advisory board participation and provided continuing medical education on behalf of AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi, and Servier; and has received research grants from AstraZeneca, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Janssen, Novo Nordisk, and Sanofi. AC has received honoraria for advisory board participation from AstraZeneca, Abbott, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi, HLS Therapeutics, and Medtronic; and has received speaker honoraria from AstraZeneca, Abbott, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, and Sanofi. KAC is listed as an inventor on a patent application by Boehringer Ingelheim on the use of DPP-4 inhibitors in heart failure; has received research grants to his institution from AstraZeneca and Boehringer Ingelheim; has received support for travel to scientific meetings from Boehringer Ingelheim; and has received honoraria for speaking engagements and ad-hoc participation in advisory boards from AstraZeneca, Boehringer Ingelheim, Merck, Servier, and Janssen. DF has provided research CME on behalf of or has acted as an advisor to AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, and Sanofi; and has been chair of data and safety monitoring boards for Novo Nordisk. MEF has received research grants from Amgen, Novo Nordisk, and Novartis. JAU has received honoraria for advisory board participation from Janssen, Merck, Novartis, and Sanofi Pasteur; and research grants from Novartis. ORG-S and PJ declare no competing interests.

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