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Blood Glucose Reduction by Diabetic Drugs with Minimal Hypoglycemia Risk for Cardiovascular Outcomes: Evidence from Meta-regression Analysis of Randomized Controlled Trials

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Running title: Prevention of the major adverse cardiovascular events in type 2 diabetes

ABSTRACT

Aim

To investigate the effects of blood glucose control with antihyperglycemic agents with minimal hypoglycemia risk on cardiovascular outcomes in patients with type 2 diabetes (T2D).

Materials and Methods

Randomized controlled trials (RCTs) comparing the relative efficacy and safety of antidiabetic drugs with less hypoglycemia risk were comprehensively searched in MEDLINE, Embase, and the Cochrane Library up to January 27, 2018. Mixed-effects meta-regression analysis was conducted to explore the relationship between haemoglobin A1c (HbA1c) reduction and the risk of major adverse cardiovascular events (MACE),

myocardial infarction, stroke, cardiovascular death, all-cause death, and hospitalization for heart failure.

Results

Ten RCTs comprising 92400 participants with T2D were included and provided information on 9773 MACE during a median follow-up of 2.6 years. The mean HbA1c concentration was 0.42% lower (median, 0.27-0.86%) for participants given antihyperglycemic agents than those given placebo. The meta-regression analysis demonstrated that HbA1c reduction was significantly associated with a decreased risk of MACE (β value, -0.39 to -0.55; $P<0.02$) even after adjusting for each of the following possible confounding factors including age, sex, baseline HbA1c, duration of follow-up, difference in achieved systolic blood pressure, difference in achieved body weight, or risk difference in hypoglycemia. Lowering HbA1c by 1% conferred a significant risk reduction of 30% (95% CI, 17-40%) for MACE. By contrast, the meta-regression analysis for trials using conventional agents failed to demonstrate a significant relationship between achieved HbA1c difference and MACE risk ($P>0.74$).

Conclusions

Compared with placebo, newer T2D agents with less hypoglycemic hazard significantly reduced the risk of MACE. The MACE reduction seems to be associated with HbA1c reduction in a linear relationship.

Keywords: Type 2 diabetes, Major adverse cardiovascular events, Thiazolidinedione, Dipeptidyl peptidase-4 inhibitor, Glucagon-like peptide-1 agonist, Sodium-glucose

cotransporter-2 inhibitor

INTRODUCTION

Type 2 diabetes (T2D) is associated with an increased risk of cardiovascular (CV) and microvascular complications, with a higher risk for all-cause mortality compared with the general population [1]. More than 29 million people in the United States and 420 million globally have T2D, with a projected global prevalence of 642 million by 2040 [2,3].

Conventional T2D drugs in randomized controlled trials, in contrast with the benefits on microvascular outcomes, have failed to show consistent beneficial effects on major adverse cardiovascular events (MACE) [4-11]. Such inconsistent evidence has led to the American Heart Association, the American College of Cardiology, and the American Diabetes Association providing a conservative class IIb recommendation with level of evidence A for the benefit of glycemic control on cardiovascular disease [12].

Due to concerns regarding increased adverse CV events incurred by new diabetic drugs [13], the U.S. Food and Drug Administration and European Medicines Agency mandated that new diabetic therapies had to demonstrate CV safety in prospective, randomized controlled outcome trials. Although designed to address the safety issue, results from recent "cardiovascular outcomes trials" (CVOTs) have confirmed CV safety, as well as reduced CV and all-cause mortality in some studies [14-16].

Recently, we demonstrated that hypoglycemia is associated with an increased risk of CV events, all-cause hospitalization, and all-cause mortality in a dose-response manner [17,18]. Another cohort study has also confirmed this positive relationship [19]. Given that new T2D drugs are less prone to hypoglycemia, their benefit-harm profiles on cardiovascular outcomes might be considerably different from that of conventional antihyperglycemic agents. Moreover, a previous meta-analysis suggested that there were no significant

differences in the associations between available classes of glucose-lowering drugs and the risk of cardiovascular or all-cause mortalities [20]. The meta-regression analysis in this study did not evaluate the effect of blood sugar reduction on cardiovascular mortality. We therefore hypothesized that the relative risk of MACE associated with the use of new T2D drugs is in proportional to the reduction of blood glucose, estimated with haemoglobin A1c concentration (HbA1c).

To test this hypothesis, we conducted a meta-analysis and meta-regression analysis to systematically synthesize and investigate the relationship between HbA1c reduction and the outcomes of stroke, coronary heart disease (CHD), hospitalization for heart failure (HF), cardiovascular death, all-cause mortality and any major adverse cardiovascular events in the large endpoint-adjudicated randomized controlled trials for new T2D drugs with minimal hypoglycemia risk.

MATERIALS AND METHODS

The pre-specified protocol for this review was registered with PROSPERO, number CRD42017071367, and the study report adhered to the PRISMA statement [21] recommended by the Enhancing the Quality and Transparency of Health Research (EQUATOR) Network (Supplementary Table 1).

Data Sources and Literature Searches

We systematically searched MEDLINE, Embase and the Cochrane Library to identify all relevant studies from database inception to Jan 27, 2018, using keywords and the Medical Subject Headings (MeSH) terms as the following: type 2 diabetes mellitus, hypoglycemic agents, diabetes treatment, blood sugar lowering, glucose reduction, glycemic control, cardiovascular diseases, myocardial infarction, stroke, and cardiovascular mortality (Supplementary Table 2). We limited our search to randomized controlled trials, clinical trials or controlled clinical trials. Additional studies were retrieved by manually checking the reference lists of reviews, meta-analyses, and original publications. No language restrictions were applied on any of these searches.

Study Selection

The inclusion criteria for eligible studies required each of the following: (i) randomized controlled clinical trials (RCTs) comparing the effects of intensive glucose lowering using drugs with a minimal hypoglycemia hazard versus placebo or standard care, or comparing one type of antihyperglycemic agent with another type in patients with T2D; (ii) reporting major adverse cardiovascular events as the primary outcome and adjudicated by an independent committee; (iii) enrolling total number of patients more than 1000 [22] to avoid the overestimation of the effect sizes from small trials [23]; and (iv)

with a follow-up of more than one year. We excluded trials using mainly insulin, sulfonylureas (SUs), or glinides in blood glucose management. The trials investigating antidiabetic drugs withdrawn from market were also excluded.

Two researchers (CJH and WTW) performed the procedure of selecting the studies, which were further rechecked by a third researcher (HMC) for accuracy.

Data Extraction and Quality Assessment

Relevant data extracted from each eligible trial were collected using a spreadsheet. We collected information regarding study and participant characteristics, baseline and achieved HbA1c levels, mean difference in HbA1c between intervention and control groups, the antidiabetic regimens used, and outcome events. We judged the methodological quality of the included trials using the Cochrane Collaboration's tool for assessing the risk of bias [24] and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for rating the quality of evidence [25]. Two researchers (WTW and CJH) independently performed the data extraction and quality appraisal, and any discrepancies were resolved through discussion with a third researcher (HMC).

Outcomes

Our primary outcome of interest was major adverse cardiovascular events (MACE), a composite endpoint consisted of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Secondary outcomes were myocardial infarction, stroke, death from cardiovascular causes, death from any cause, and hospitalization for heart failure according to the definition of each study. Safety outcomes including hypoglycemia (any type of event) and severe hypoglycemia (requiring third-party

assistance) were also evaluated. Although patients on placebo may still receive conventional antidiabetic agents, given all other balanced baseline characteristics, the relative effects between treatment and control arms on cardiovascular outcomes were mainly rendered by the effects of the testing strategies.

Data Synthesis and Analysis

In this meta-analysis, we used aggregated data and performed a quantitative synthesis of the findings from the included studies. Because all adverse outcomes were binary indicators, the relative risk (RR) with 95% confidence interval (CI) was used as the measure of the effect of the intervention. For CANVAS program, we calculated a time-adjusted risk ratio, given the reported incidence rate (events per 1000 patient-year) in each group and the estimated total person-time of the control group, to get an approximate estimate of the hazard ratio for every outcome. We obtained the pooled estimates of effect measures by using the DerSimonian and Laird random-effects model as the primary analysis under consideration of the population variance across studies [26], supplement with the analysis of a fixed-effects model. The weighting scheme of the Mantel-Haenszel method was applied to both models. Heterogeneity of treatment effects among studies was assessed using both Cochran's Q and Higgins's I^2 statistics [24]. Publication bias was detected using funnel plots and Egger's regression asymmetry test [27].

Univariable analysis of mixed-effects meta-regression was performed to explore the relationships between the difference in achieved HbA1c and the absolute risk reduction (ARR) as well as the relative risk. These relationships were further examined by using multivariable meta-regression analysis adjusted for various confounding factors such as mean age, proportion of male patients, mean HbA1c at baseline, difference in achieved

systolic blood pressure (SBP), difference in achieved body weight, median length of follow-up, and risk difference in hypoglycemia. Data on mean difference in achieved SBP or achieved body weight were not available in SAVOR-TIMI 53 or TECOS trials [28,29], therefore in meta-regression analysis we replaced the missing data with a value of zero according to the findings of neutral effect of SBP or body weight on cardiovascular events with DPP4 inhibitor treatment from previous studies [30]. To verify our hypothesis, we conducted an additional analysis with the data from four large RCTs on cardiovascular outcomes, UKPDS [4,5], ADVANCE [7], VADT [9] and ACCORD [31], which compared intensive blood glucose reduction versus standard care using conventional antihyperglycemic treatment in patients with T2D [32].

Subgroup analyses by the extents of HbA1c reduction and type of antihyperglycemic agents were conducted to evaluate the difference between the estimates of treatment effect from subsets of studies. A 2-tailed P value of less than 0.05 was considered statistically significant. All analyses were performed using R software (version 3.1.3, R Foundation for Statistical Computing), Review Manager (version 5.3, Cochrane Collaboration), and the Comprehensive Meta-Analysis software package (version 2.2.064, Biostat, Englewood, NJ).

RESULTS

Of the 4443 articles identified initially, 69 were further reviewed in full-text for assessing eligibility. Finally, 10 studies met our inclusion criteria and were chosen for this analysis (see Supplementary Figure 1).

Study Characteristics and Quality Assessment [Table 1]

All 10 RCTs enrolled a total of 92400 type 2 diabetic patients with established or at high risk for cardiovascular disease, with a mean age of 63.5 years, in whom 48106 were assigned to receive antihyperglycemic treatment with one of four classes of antidiabetic agents (dipeptidyl peptidase 4 inhibitor, glucagon-like peptide 1 receptor agonists, sodium-glucose cotransporter inhibitor, and thiazolidinedione) and 44294 to receive placebo. These trials followed patients for a median of 1.5 to 3.8 years and recruited more than 60% of the men. Most patients had T2D of >10-years duration.

The included trials had similar baseline HbA1c between treatment and placebo groups, and the mean difference in achieved HbA1c varied from 0.27 to 0.86% (mean 0.42%). All these studies had a low or an unclear risk of bias for 7 domains of potential risk of bias (see Supplementary Figure 2 and 3). No clear evidence of publication bias was noted for all outcomes by funnel plot and or Egger's test (all P>0.09) (Supplementary Figure 4).

Achieved HbA1c Difference and Risk of Adverse Events

Univariable meta-regression analyses showed that the absolute risk reduction for MACE (P=0.0005) and stroke (P=0.0044) was proportional to the reduction in achieved HbA1c. With an increment of 1% in achieved HbA1c difference, the magnitude of risk reduction increased 4.43% for MACE (95% CI, 1.92-6.94%) and 1.92% for stroke (95%

CI, 0.60-3.23%) (Figure 1A and Supplementary Figure 5). Similarly, a larger reduction in achieved HbA1c was significantly associated with a lower relative risk of MACE (P=0.0008) and stroke (P=0.0092) (Figure 1B and Supplementary Figure 6). Lowering HbA1c by 1% conferred a significant risk reduction of 30% (95% CI, 17-40%) for MACE and 40% (95% CI, 15-57%) for stroke. By contrast, using conventional antihyperglycemic agents, the results of meta-regression analysis (Figure 1C and D) failed to demonstrate a significant relationship between achieved HbA1c difference and MACE risk (P>0.74).

We further performed the multiple meta-regression analyses for MACE and stroke. The trend relationships from the estimates of absolute or relative effect of intervention were found in MACE after adjusting for each of the following possible confounders including age, sex, baseline HbA1c, duration of follow-up, difference in achieved SBP, difference in achieved body weight, or risk difference in hypoglycemia (P<0.05 for all models) (Table 2 and Supplementary Table 3).

Effects of Antihyperglycemic Treatment on Major Adverse Cardiovascular Events

When we evaluated the effectiveness of different extents of lowering HbA1c (Figure 2), there was significant heterogeneity in the treatment effects across strata (P=0.008; I^2=79.4%), with greater risk reductions in trials with a ≥0.5% difference in achieved HbA1c (relative risk reduction [RRR], 13%; 95% CI, 6-20%; P=0.0008) than in trials with a 0.3-0.5% difference (11%; 95% CI, 4%-17%; P=0.002), but no benefits were found in trials with a <0.3% difference in achieved HbA1c (0%; 95% CI, -7 to 6%; P=0.90). Overall, antihyperglycemic treatment significantly reduced the risk of MACE by 8% (95% CI, 3-13%; P=0.002) compared to placebo.

We also assessed the efficacy of four classes of oral antidiabetic agents in the prevention of MACE in patients with T2D. The results showed the effects of antihyperglycemic treatment differed between drug classes (P=0.03; I^2=65.3%) (Supplementary Figure 7). Compared to placebo, GLP-1 receptor agonists (RRR, 9%; 95% CI, 0-17%; P=0.048), SGLT2 inhibitors (14%; 95% CI, 6-22%; P=0.002), and thiazolidinediones (17%; 95% CI, 3-29%; P=0.02) were significantly associated with a decreased risk of MACE. A significant treatment effect with DPP4 inhibitors was not found.

Using the GRADE system, the overall quality of the body of evidence was high for MACE in comparing antidiabetic drugs to placebo for patients with T2D (Supplementary Table 4). Nine fewer MACE (from 3 fewer to 14 fewer) could be prevented per 1000 patients with T2D receiving antidiabetic drugs compared to placebo.

Antihyperglycemic Treatment and Hypoglycemia Risk

The risk of hypoglycemia had no linear relationship with the between-group difference in achieved HbA1c (Supplementary Figure 8A), antihyperglycemic treatment conferred a significantly higher risk for hypoglycemia than placebo (RR, 1.09; 95% CI, 1.01-1.18; P=0.03), with the excess risk contributed by DPP4 inhibitors or thiazolidinediones use (Supplementary Figure 9). We did not detect an increased risk for severe hypoglycemia with antihyperglycemic therapy (Supplementary Figure 8B and 10). The quality of evidence was moderate for hypoglycemia and low for severe hypoglycemia (Supplementary Table 4), and no publication bias was found (Egger's test P=0.1583 for hypoglycemia and 0.6741 for severe hypoglycemia, data not shown).

DISCUSSION

The present meta-analysis and meta-regression analysis of the CVOTs (10 trials, 92400 patients) for antihyperglycemic agents with less hypoglycemia risk, including pioglitazone, DPP-4 inhibitors, GLP-1 receptor agonist, and SGLT2 inhibitor, have demonstrated clearly that the magnitude of risk reduction of MACE was proportional to the differences of HbA1c between treatment and control groups, even after accounting for potential confounding factors. The present analysis, without the potential noise of the adverse impacts resulting from hypoglycemia [17,18], demonstrates for the first time that risk reduction of T2D population in the MACE was proportional to the magnitude of HbA1c decrease conferred by antihyperglycemic agents without hypoglycemia hazard. In other words, rather than the extra-glycemic actions of individual drugs or classes of drugs, the blood glucose reduction may play a more important role than previously expected in reducing the risk of MACE by using the antihyperglycemic agents without hypoglycemia hazard.

During about median treatment of 2.6 years, reduction of HbA1c concentration by 1% resulted in a significant reduction in the risk of MACE by 30%. This positive correlation was consistent with the result of a previous meta-regression analysis [33]. Similarly, in trials with the use of conventional antihyperglycemic agents, there have been no significant association between cardiovascular events and HbA1c reduction. The information obtained in our study will be useful for clinicians for selecting the optimal antihyperglycemic agents to avoid or reduce the huge health burden resulting from the high MACE rate in patients with T2D.

These results were consistent with our subgroup analysis (Figure 2), whereby the higher HbA1c reduction between the treatment and control groups was associated with a

larger risk reduction in MACE with the same protective result in subgroup analysis by different categories of antihyperglycemic agents. With the different benefit-harm profiles from the traditional medication, new antihyperglycemic agents, similar to antihypertensive [34] and anti-hypercholesterolemia drugs [35], can bring about a predictable risk reduction in MACE, which is proportional to the reduction of these risk factors. Nevertheless, we cannot exclude the possibility that the benefits observed with GLP-1 receptor agonists, SGLT2 inhibitors, and thiazolidinediones are at least partly due to extra-glycemic actions of these drugs. For example, the SGLT2 inhibitor, empagliflozin, markedly and rapidly reduced CV mortality and heart failure hospitalization,[14] which may be related with hemodynamic or metabolic-associated mechanisms. The GLP-1 receptor agonists, liraglutide[16] and semaglutide,[15] reduced CV death and MACE with beneficial effects appearing more slowly, and did not influence heart failure risks, suggesting the possible alternative mechanisms of benefit.[36]

In currently available trials, the control group is not represented simply by "placebo": study protocols recommend the adjustment of concurrent therapies for reaching an optimal glucose control in all patients; as a result, T2D patients in placebo groups are more often treated with insulin and SUs than those on active treatment. As shown in a previous meta-analysis of 115 randomized trial, the use of the sulfonylurea is associated with increased mortality and a higher risk of stroke.[37] Moreover, the sulfonylurea did increase the risk of hypoglycemic episodes when compared with DPP4 inhibitors [38,39] or metformin regardless of the individual sulfonylurea.[40] Therefore, it is possible that part of the differences in outcome is determined by detrimental effects of conventional therapies on some cardiovascular outcomes.

During the United Kingdom Prospective Diabetes Study,[41] risk reductions for myocardial infarction and death from any cause emerged in the 10 years follow-up. However, the ADVANCE [7] and ACCORD [42] trials suggested that significant differences in HbA1c concentration might not confer benefits to macrovascular events and even cause an excess risk of all-cause mortality possibly associated with the higher drug-related adverse events of the hypoglycemia. A meta-analysis of data from 13 randomized controlled trials suggested intensive glucose lowering treatment resulted in a 19% increase in all-cause mortality and a 43% increase in cardiovascular death [43]. By contrast, one meta-analysis using pooled data from ACCORD, ADVANCE, and UKPDS showed an overall reduction in the risk of major cardiovascular events by 9% and a 15% reduction in myocardial infarction [6]. Another meta-analysis from 5 randomized controlled trials of 33040 participants provide reassurance about the effectiveness of intensive glycemic control for cardiovascular risk reduction (17% reduction in events of non-fatal myocardial infarction and 15% reduction of coronary heart disease) [32].

Possible explanation of such different results may include that treatment duration was shorter than was needed to reveal a clinical benefit [41], thus event rates were lower than expected due to improved control of risk factors, differences in glycemic control between patients groups were too small to show benefit, and the prevalent side effects of hypoglycemia, which may counteract the benefit from intensive glucose control with insulin and sulfonylurea [17,18]. The last one hypothesis helps explain why the beneficial effects of glucose lowering in previous diabetic trials using insulin and sulfonylurea only appeared with a longer follow-up duration. It may be because that the risk associated with hypoglycemia resulting from conventional antihyperglycemic agents may “dilute” the

protective effects of blood sugar control. Such "dilution" needs longer follow-up duration and a larger event number to counterbalance. Overall, these discrepancies indicate that the role of glucose control in patients with T2D who receive glycemic therapy has yet to be determined until now.

Our findings are in agreement with the results of a systematic review which investigated the impact of incretin based treatment, including both GLP-1 agonists and DPP-4 inhibitors on all-cause mortality in patients with T2D [44]. Although no meta-regression analysis was conducted in that study, by enrolling few large and several small RCTs and registry reports, the results suggested a probable mortality benefit with GLP-1 agonists [44].

In addition to the risk conferred from hyperglycemia, cardiovascular risk may also be modulated by various mechanisms; First of all, baseline characteristics, such as duration since T2D diagnosis at baseline (≥10 years), the baseline HbA1c concentration, and adverse side effects of T2D drugs. In the ACCORD trial, for example, HbA1c fell rapidly by around 1.5% within half years and the average HbA1c was less than 6% by 1 year in intensively treated individuals through aggressive use of bolus insulin dose when necessary and receiving greater proportion of rosiglitazone at the end of follow-up compared with those receiving standard treatment (92% vs 58%) [42]. Adverse effects of a 2.5 kg difference in weight gain and nearly double severe hypoglycemic episodes compared with standard treatment were found. More importantly, our meta-regression analysis, accounts for these possible confounding effects and still demonstrated a strong significant linear relationship between HbA1c difference and the risk reduction in MACE.

Despite Dipeptidyl peptidase 4 inhibitor is associated with a low risk of hypoglycemia [28], it failed to demonstrate a significant risk reduction in MACE (Supplement Figure 7). As suggested by our meta-regression analysis in Figure 1 and subgroup analysis by the magnitude of HbA1c reduction in Figure 2, its small benefit on MACE in these CV safety trials is probably related to its small magnitude of HbA1c differences.

Antidiabetic drugs with a low hypoglycemic potential can increase the risk of hypoglycemia when added to insulin or SUs. If hypoglycemia is detrimental for the cardiovascular system, this could reduce an underestimation of the potential benefits of the reduction of HbA1c. In order to have a reliable assessment of the effects of the improvement of glycemic control on CV events, we would need a large trial on intensification of therapy in which insulin and SUs are not allowed or allowed only as rescue therapy.

Study Limitations

Our study has several potential limitations. First, similar to other meta-analyses, the absence of primary data to analyze the effects of intensive glycemic control within various patient subgroups by gender, prevalence of cardiovascular disease at baseline, comorbidity, duration of T2D, and the selective reporting of primary studies might confound our study results. Second, these results should be interpreted carefully because of the significant heterogeneity with respect to the demographic characteristics of participants, duration of follow-up, and medication for intensive glucose control. Third, we cannot provide evidence of superiority or harm of a specific glucose-lowering regimen without access to individual participant data. Finally, despite the comprehensive

literature search, we may have failed to locate some eligible published or unpublished studies even we tried to keep the probability of bias to a minimum by developing a detailed protocol and using explicit criteria for study selection, data collection, and data analysis. Similar to trends reported in previous meta-analysis,[6] we believe that we have been robust in out methodology and that the results and conclusions would not likely be altered substantially and provide reliable recommendation for clinical practice.

Conclusions

Compared with placebo, newer T2D agents with less hypoglycemic hazard significantly reduced the risk of MACE. The MACE reduction seems to be associated with HbA1c reduction in a linear relationship.

Author Contributions

All authors conceived the concept and design of the study. CJH and WTW contributed to the acquisition of data. CJH did the statistical analyses. All authors were involved in the analysis and interpretation of data. CJH, WTW and HMC drafted the manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content. All authors have read and approved the final version. CJH, WTW, HMC, and CEC take responsibility for the integrity of the data and the accuracy of the analyses. HMC and CEC was the study supervision.

Conflict of Interest

All authors declare no competing interests.

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Role of the Funding/Sponsor

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. CJH, WTW, and HMC had full access to all the data in the study, and HMC and CEC had final responsibility for the decision to submit for publication.

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Figure legends

Figure 1. Univariable meta-regression for the relationship of achieved HbA1c difference between intervention and control groups with absolute risk reduction (A) (C) and the natural logarithm of a relative risk (B) (D) for MACE in patients with type 2 diabetes, according to the trials using antidiabetic agents with minimal hypoglycemia risk or conventional drugs as the option of intensive glycemic management. The regression fit (solid line) and 95% confidence interval (dash line) are shown. The size of the circle represents the weight of each trial and is inversely proportional to the standard error of the effect estimate. Beta coefficient depicts a change in absolute or relative effect of antihyperglycemic treatment for each 1% difference in achieved HbA1c between intervention and control groups. HbA1c = haemoglobin A1c; MACE = major adverse cardiovascular event.

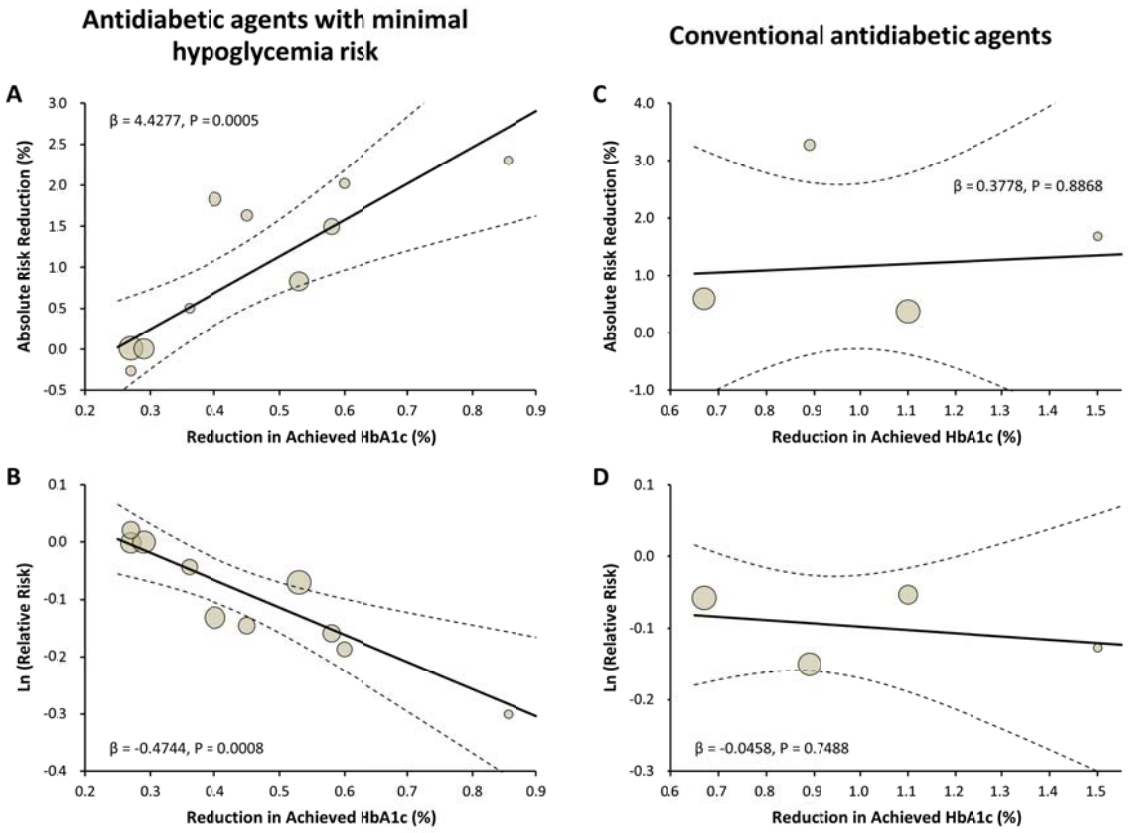

Figure 2. Effects of antihyperglycemic treatment on MACE in patients with type 2 diabetes, stratified by achieved HbA1c difference between intervention and control groups. Mean HbA1c difference indicates the difference in achieved HbA1c between intervention and control groups. Diamond denotes the pooled estimate of relative risks and its 95% confidence interval. HbA1c = haemoglobin A1c; MACE = major adverse cardiovascular event.

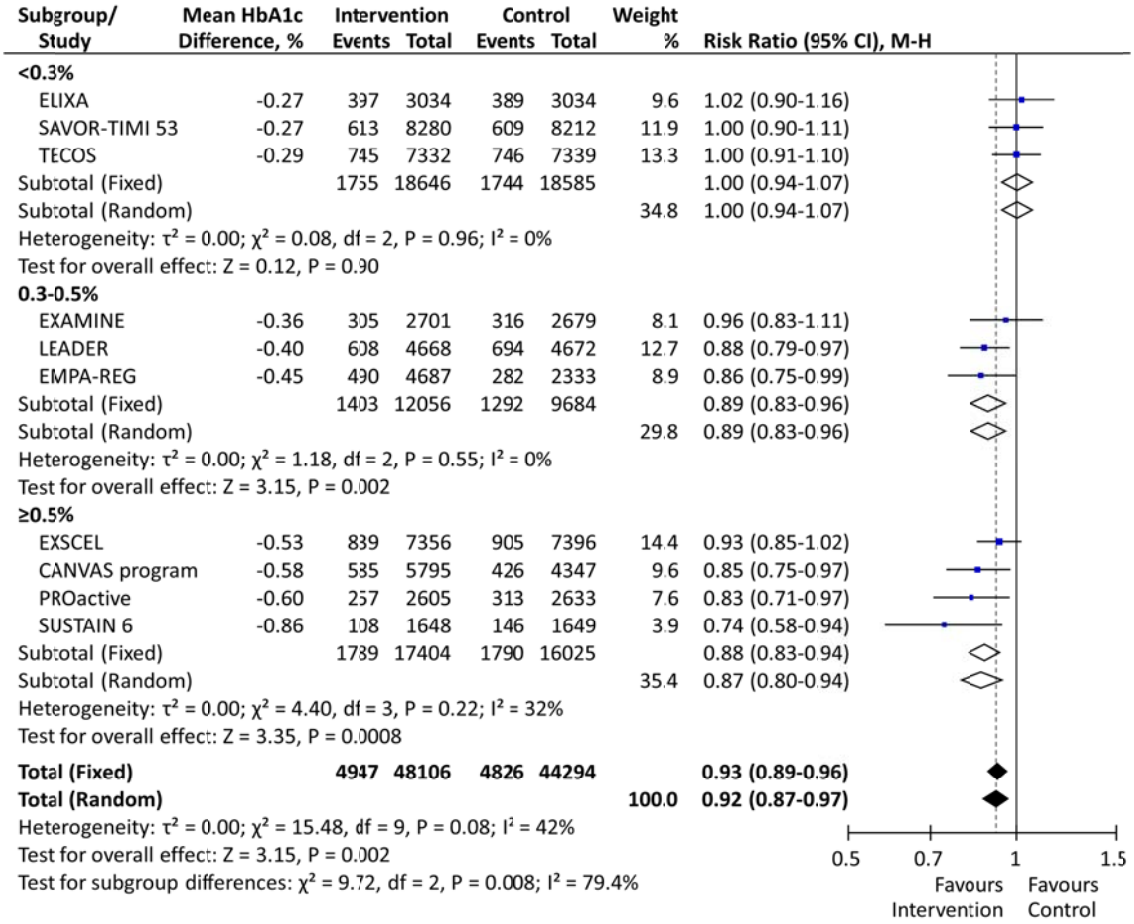

Table 1. Characteristics of the included studies

Trial	Year	Participants, n (Int/Cont)	Comparison		Median follow-up, years	Mean age, years	Male, %	Duration of diabetes, years	Comorbidities, %	HbA1c, %			Mean achieved SBP reduction, mmHg	Mean achieved body-weight reduction, kg
			Intervention	Control						Baseline	Achieved (Int/Cont)	Mean reduction in achieved level		
PROactive [45]	2005	5238 (2605/2633)	TZD (Pioglitazone)	Placebo	2.875*	61.7	66.1	8†	MI, 46.7; CVA, 18.8; HTN, 75.4	7.85†	7/7.6‡	0.60**	0.4**	4 kg raises**
EXAMINE [46]	2013	5380 (2701/2679)	DPP4 inhibitor (Alogliptin)	Placebo	1.5	61†	67.9	7.2†	MI, 88.0; HF, 27.9; CVA, 7.2; HTN, 83.1; CKD, 29.1	8.03	7.7/8.06§	0.36	0.8‡‡	0.06 kg raises
SAVOR-TIMI 53 [29]	2013	16492 (8280/8212)	DPP4 inhibitor (Saxagliptin)	Placebo	2.1	65.1	66.9	10.3†	MI, 37.8; HF, 12.8; HTN, 81.8; CKD, 15.6	8	7.6/7.87‖	0.27**	NR	0.53**
ELIXA [47]	2015	6068 (3034/3034)	GLP-1 receptor agonist (Lixisenatide)	Placebo	2.08	60.3	69.3	9.3	MI, 22.1; HF, 22.4; CVA, 5.5; HTN, 76.4; CKD, 23.2	7.7	7.32/7.53‖	0.27	0.8	0.7
EMPA-REG OUTCOME [14]	2015	7020 (4687/2333)	SGLT2 inhibitor (Empagliflozin)	Placebo	3.1	63.1	71.5	≤1 y: 2.6; >1-5 y: 15.4; >5-10 y: 24.9; >10 y: 57.1	MI, 46.6; HF, 10.1; CVA, 23.3; CKD, 25.9	8.07	7.55/8‖	0.45**	3.43**	1.79**
TECOS [28]	2015	14671 (7332/7339)	DPP4 inhibitor (Sitagliptin)	Placebo	3	65.5	70.7	11.6	MI, 42.6; HF, 18.0; CVA, 24.5; CKD, 9.3	7.2	7.09/7.37‖	0.29	NR	NR
LEADER [16]	2016	9340 (4668/4672)	GLP-1 receptor agonist (Liraglutide)	Placebo	3.8	64.3	64.3	12.9	MI, 30.7; HF, 17.8; CVA, 16.1; CKD, 24.7	8.7	7.54/7.93¶	0.40	1.2	2.3
SUSTAIN 6 [15]	2016	3297 (1648/1649)	GLP-1 receptor agonist (Semaglutide)	Placebo	2.1	64.6	60.7	13.9	MI, 32.5; HF, 23.6; CVA, 14.9; HTN, 92.8; CKD, 28.5	8.7	7.45/8.3#	0.86††	1.93††	3.61††
CANVAS program [48]	2017	10142 (5795/4347)	SGLT2 inhibitor (Canagliflozin)	Placebo	2.42*	63.3	64.2	13.5	CAD, 56.4; HF, 14.4; CVA, 19.3; HTN, 90.0	8.2	7.73/8.17‖	0.58	3.93	1.6
EXSCEL [49]	2017	14752 (7356/7396)	GLP-1 receptor agonist (Exenatide)	Placebo	3.2	62†	62	12†	CAD, 52.8; HF, 16.2; CVA, 17.0; CKD, 21.7	8.1	7.55/8.01‖	0.53	1.57	1.27

CAD = coronary artery disease; CANVAS = Canagliflozin Cardiovascular Assessment Study; CKD = chronic kidney disease; CVA = cerebrovascular accident; DPP4 = dipeptidyl peptidase 4; ELIXA =

Evaluation of Lixisenatide in Acute Coronary Syndrome; EMPA-REG OUTCOME = Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; EXAMINE = Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; EXSCEL = Exenatide Study of Cardiovascular Event Lowering; GLP-1 = glucagon-like peptide 1; HbA1c = haemoglobin A1c; HF = heart failure; HTN = hypertension; LEADER = Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MI = myocardial infarction; NR = not reported; PROactive = PROspective pioglitAzone Clinical Trial In macroVascular Events; SAVOR-TIMI 53 = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction (TIMI) 53; SBP = systolic blood pressure; SGLT2 = sodium-glucose cotransporter 2; SUSTAIN 6 = Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; TECOS = Trial Evaluating Cardiovascular Outcomes with Sitagliptin; TZD = thiazolidinedione

*Mean value

†Median value

‡Calculated by median change from baseline to final visit

§Calculated by mean change from baseline to the end of the study period

‖Average of mean HbA1c across all visits

¶Estimated from the HbA1c level at 36 months

#Estimated from the HbA1c level at week 104 in the group receiving doses of 0.5 mg and 1.0 mg.

**Difference of estimated achieved HbA1c/SBP/body-weight between intervention and control groups

††Meta-analysis of mean HbA1c/SBP/body-weight reduction at week 104 in the semaglutide group receiving 0.5 mg and 1.0 mg

‡‡Estimated from the data reported in 2016 [50].

Table 2. Meta-regression analysis for the relationship between achieved HbA1c difference and MACE risk

	ARR (%)		LnRR	
	β	P value	β	P value
Univariable	4.428 (1.920 to 6.935)	0.0005	-0.474 (-0.751 to -0.197)	0.0008
Model 1: adjusted for age	4.495 (1.825 to 7.165)	0.0010	-0.502 (-0.790 to -0.214)	0.0006
Model 2: adjusted for sex	4.945 (1.484 to 8.407)	0.0051	-0.550 (-0.923 to -0.178)	0.0038
Model 3: adjusted for baseline HbA1c	3.559 (0.576 to 6.542)	0.0194	-0.391 (-0.706 to -0.076)	0.0150
Model 4: adjusted for follow-up duration	4.212 (1.669 to 6.755)	0.0012	-0.458 (-0.740 to -0.175)	0.0015
Model 5: adjusted for achieved SBP difference	3.766 (0.467 to 7.066)	0.0253	-0.417 (-0.766 to -0.068)	0.0191
Model 6: adjusted for achieved body-weight difference	4.410 (1.811 to 7.009)	0.0009	-0.469 (-0.748 to -0.190)	0.0010
Model 7: adjusted for risk difference in hypoglycemia	4.494 (1.947 to 7.040)	0.0005	-0.487 (-0.772 to -0.201)	0.0008
Model 8: adjusted for risk difference in severe hypoglycemia*	5.104 (1.349 to 8.859)	0.0077	-0.477 (-0.839 to -0.116)	0.0097

ARR = absolute risk reduction; HbA1c = haemoglobin A1c; LnRR = natural logarithm of relative risk; MACE = major adverse cardiovascular event; SBP = systolic blood pressure

*The Model was performed on the data from 8 trials with reports of severe hypoglycemia.