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ORIGINAL ARTICLE

Blood glucose reduction by diabetic drugs with minimal hypoglycaemia risk for cardiovascular outcomes: Evidence from meta-regression analysis of randomized controlled trials

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Aims: To investigate the effects of blood glucose control with antihyperglycaemic agents with minimal hypoglycaemia 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 hypoglycaemia risk were comprehensively researched 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 92 400 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 (range, 0.27%-0.86%) for participants given antihyperglycaemic 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 possible confounding factors including age, sex, baseline HbA1c, duration of follow-up, difference in achieved systolic blood pressure, difference in achieved body weight, and risk difference in hypoglycaemia. Lowering HbA1c by 1% conferred a significant risk reduction of 30% (95% confidence interval, 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 hypoglycaemic hazard significantly reduced the risk of MACE. The MACE reduction appears to be associated with HbA1c reduction in a linear relationship.

KEYWORDS

dipeptidyl peptidase-4 inhibitor, glucagon-like peptide-1 agonist, major adverse cardiovascular events, sodium-glucose cotransporter-2 inhibitor, thiazolidinedione, type 2 diabetes

1 | 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

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29 million people in the United States and 420 million people worldwide have T2D, with a projected global prevalence of 642 million by 2040.[2,3]

Conventional T2D drugs in randomized controlled trials (RCTs), in contrast with the benefits on microvascular outcomes, have failed to show consistent beneficial effects on major adverse cardiovascular events (MACE).[4–11] The inconsistency of 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 glycaemic control on cardiovascular disease.[12]

Due to concerns regarding increased adverse CV events incurred by new diabetic drugs,[13] the US 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, it was shown that hypoglycaemia 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 hypoglycaemia, their benefit-harm profiles on cardiovascular outcomes might be considerably different from those of conventional antihyperglycaemic 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. It was therefore hypothesized that the relative risk of MACE associated with the use of new T2D drugs is proportional to the reduction of blood glucose, estimated with haemoglobin A1c concentration (HbA1c).

To test this hypothesis, a meta-analysis and meta-regression analysis were conducted 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 CV events in the large endpoint-adjudicated RCTs for new T2D drugs with minimal hypoglycaemia risk.

2 | 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 (Table S1).

2.1 | Data sources and literature searches

MEDLINE, Embase and the Cochrane Library were systematically searched to identify all relevant studies from database inception to January 27, 2018 using keywords and the following Medical Subject Headings (MeSH) terms: type 2 diabetes mellitus, hypoglycaemic agents, diabetes treatment, blood sugar lowering, glucose reduction, glycaemic control, cardiovascular diseases, myocardial infarction, stroke, and cardiovascular mortality (Table S2). The search was limited to RCTs, 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 to any of these searches.

2.2 | Study selection

The inclusion criteria for eligible studies were: (1) RCTs comparing the effects of using intensive glucose-lowering drugs with a minimal hypoglycaemia hazard versus placebo or standard care, or comparison of one type of antihyperglycaemic agent with another type in patients with T2D, (2) those reporting major adverse cardiovascular events as the primary outcome and adjudicated by an independent committee, (3) those enrolling a total number of patients >1000[22] to avoid overestimation of the effect sizes from small trials[23], and (4) those with a follow-up of more than 1 year. Trials using mainly insulin, sulfonylureas (SUs) or glinides in blood glucose management were excluded, as were trials investigating antidiabetic drugs withdrawn from the market.

Two researchers (C.-J. H. and W.-T. W.) performed the study selection procedure, and the selected studies were checked by a third researcher (H.-M. C.) for accuracy.

2.3 | Data extraction and quality assessment

Relevant data extracted from each eligible trial were collected in a spreadsheet containing 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. The methodological quality of the included trials was judged 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 (W.-T. W. and C.-J. H.) independently performed the data extraction and quality appraisal, and any discrepancies were resolved through discussion with a third researcher (H.-M. C.).

2.4 | Outcomes

The primary outcome of interest was major adverse cardiovascular events (MACE), a composite endpoint which consisted of death from CV causes, non-fatal myocardial infarction or non-fatal stroke. Secondary outcomes were myocardial infarction, stroke, death from CV causes, death from any cause, and hospitalization for heart failure according to the definition of each study. Safety outcomes including hypoglycaemia (any type of event) and severe hypoglycaemia (requiring third-party assistance) were also evaluated. Although patients on placebo may still receive conventional antidiabetic agents, taking into consideration the other balanced baseline characteristics, the relative effects between treatment and control arms on CV outcomes were mainly rendered by the effects of the testing strategies.

2.5 | Data synthesis and analysis

In this meta-analysis, aggregated data were used and a quantitative synthesis of the findings from the included studies was performed. 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 the Canagliflozin Cardiovascular Assessment Study (CANVAS) program, a time-adjusted risk ratio was calculated using the reported incidence rate (events per 1000 patient-years) in each group and the estimated total person-time of the control group, to produce an estimate of the hazard ratio for every outcome. Pooled estimates of effect measures were obtained by using the DerSimonian and Laird random-effects model as the primary analysis considering population variance across studies,[26] supplemented with the analysis of a fixed-effects model. The weighting scheme of the Mantel-Haenszel method was applied to both models. The 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 differences in achieved HbA1c and the absolute risk reduction (ARR) and RR. These relationships were further examined 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 hypoglycaemia. 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, missing data were replaced with a value of zero according to findings of neutral effect of SBP or body weight on cardiovascular events with dipeptidyl peptidase-4 (DPP4) inhibitor treatment from previous studies.[30] To verify the hypothesis, additional analysis was conducted with the data from four large RCTs on cardiovascular outcomes, UKPDS,[4,5] ADVANCE,[7] VADT[9] and ACCORD,[8] which compared intensive blood glucose reduction versus standard care using conventional antihyperglycaemic treatment in patients with T2D.[31]

Subgroup analyses by the extent of HbA1c reduction and type of antihyperglycaemic agent were conducted to evaluate the difference between the estimates of treatment effect from the subsets of studies. A 2-tailed *P*-value of <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).

3 | RESULTS

Of the 4443 articles initially identified, 69 were further reviewed in full-text versions for assessing eligibility. Ten studies met the inclusion criteria and were chosen for this analysis (Figure S1).

3.1 | Study characteristics and quality assessment

The 10 selected RCTs enrolled a total of 92 400 type 2 diabetic patients with either established or high risk for CV disease and a mean age of 63.5 years, of whom 48 106 were assigned to receive antihyperglycaemic treatment with one of four classes of antidiabetic agents (DPP-4 inhibitors, glucagon-like peptide-1 [GLP-1] receptor agonists, sodium-glucose cotransporter-2 [SGLT-2] inhibitors, and thiazolidinedione) and 44 294 placebo (Table 1). These trials followed patients for a median of 1.5-3.8 years and > 60% were men. Most patients had T2D duration >10 years.

The included trials had similar baseline HbA1c between treatment and placebo groups, and the mean difference in achieved HbA1c varied from 0.27%-0.86% (mean 0.42%). All these studies had a low or an unclear risk of bias for seven domains of potential risk of bias (Figures S2 and S3). No clear evidence of publication bias was noted for all outcomes by funnel plot and/or Egger's test (all $P > 0.09$) (Figure S4).

3.2 | 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 Figure S5). 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 Figure S6). 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 antihyperglycaemic agents, the results of meta-regression analysis (Figures 1C and D) failed to demonstrate a significant relationship between achieved HbA1c difference and MACE risk ($P > 0.74$).

Further multiple meta-regression analyses were performed for MACE and stroke. The trend relationships from the estimates of absolute or relative effect of intervention were found in MACE after adjusting for possible confounders including age, sex, baseline HbA1c, duration of follow-up, difference in achieved SBP, difference in achieved body weight, or risk difference in hypoglycaemia ($P < 0.05$ for all models) (Table 2 and Table S3).

3.3 | Effects of antihyperglycaemic treatment on major adverse cardiovascular events

When the effectiveness of different extents of lowering HbA1c was evaluated (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%-

TABLE 1 Characteristics of the selected studies

Trial	Year	Participants, n (Int/Cont)	Comparison		Median follow-up, y	Mean age, y	Male, %	Duration of diabetes, y	Comorbidities, %	HbA1c, %			Mean achieved SBP reduction, mm Hg	Mean achieved body weight reduction, kg
			Intervention	Control						Baseline	Achieved (Int/Cont)	Mean reduction in achieved level		
PROactive[44]	2005	5238 (2605/2633)	TZD (pioglitazone)	Placebo	2.875[j]	61.7	66.1	8[a]	MI, 46.7; CVA, 18.8; HTN, 75.4	7.85[a]	7/7.6[b]	0.60[g]	0.4[g]	4 kg raises[g]
EXAMINE[45]	2013	5380 (2701/2679)	DPP-4 inhibitor (Alogliptin)	Placebo	1.5	61[a]	67.9	7.2[a]	MI, 88.0; HF, 27.9; CVA, 7.2; HTN, 83.1; CKD, 29.1	8.03	7.7/8.06[c]	0.36	0.8[i]	0.06 kg raises
SAVOR-TIMI 53 [29]	2013	16 492 (8280/8212)	DPP-4 inhibitor (Saxagliptin)	Placebo	2.1	65.1	66.9	10.3[a]	MI, 37.8; HF, 12.8; HTN, 81.8; CKD, 15.6	8	7.6/7.87[d]	0.27[g]	NR	0.53[g]
ELIXA[46]	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[d]	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[d]	0.45[g]	3.43[g]	1.79[g]
TECOS[28]	2015	14 671 (7332/7339)	DPP-4 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[d]	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[e]	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[f]	0.86[h]	1.93[h]	3.61[h]
CANVAS program[47]	2017	10 142 (5795/4347)	SGLT2 inhibitor (Canagliflozin)	Placebo	2.42[j]	63.3	64.2	13.5	CAD, 56.4; HF, 14.4; CVA, 19.3; HTN, 90.0	8.2	7.73/8.17[d]	0.58	3.93	1.6
EXSCEL[48]	2017	14 752 (7356/7396)	GLP-1 receptor agonist (Exenatide)	Placebo	3.2	62[a]	62	12[a]	CAD, 52.8; HF, 16.2; CVA, 17.0; CKD, 21.7	8.1	7.55/8.01[d]	0.53	1.57	1.27

Abbreviations: CAD, coronary artery disease; CANVAS, Canagliflozin Cardiovascular Assessment Study; CKD, chronic kidney disease; Cont, control; CVA, cerebrovascular accident; 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; HF, heart failure; HTN, hypertension; Int, intervention; 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; 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.

[a] Median value.

[b] Calculated by median change from baseline to final visit.

[c] Calculated by mean change from baseline to the end of the study period.

[d] Average of mean HbA1c across all visits.

[e] Estimated from the HbA1c level at 36 months.

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

[g] Difference of estimated achieved HbA1c/SBP/body weight between intervention and control groups.

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

[i] Estimated from the data reported in 2016.[49]

[j] Mean value.

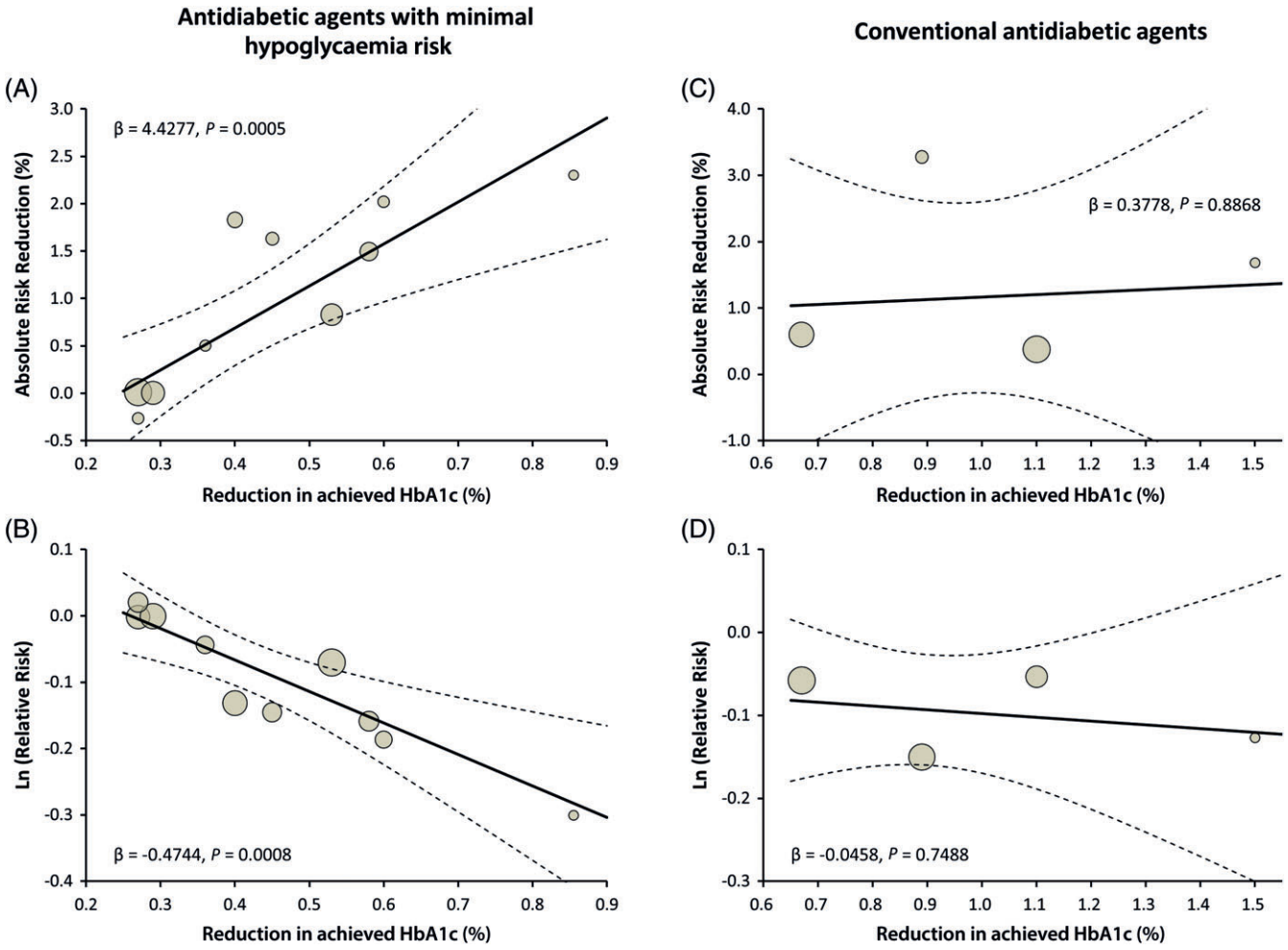

FIGURE 1 Univariable meta-regression for the relationship of achieved HbA1c difference between intervention and control groups with absolute risk reduction (A, C) and the natural logarithm of a relative risk (B, D) for MACE in patients with type 2 diabetes, according to trials using antidiabetic agents with minimal hypoglycaemia risk or conventional drugs as the option of intensive glycaemic management. The regression fit (solid line) and 95% CI (dashed line) are shown. The size of the circle represents the weighting 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 antihyperglycaemic treatment for each 1% difference in achieved HbA1c between intervention and control groups

6%; $P = 0.90$). Overall, antihyperglycaemic treatment significantly reduced the risk of MACE by 8% (95% CI, 3%-13%; $P = 0.002$) compared to placebo.

The efficacy of four classes of oral antidiabetic agents in the prevention of MACE in patients with T2D was also assessed. The results showed that the effects of antihyperglycaemic treatment differed

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

	ARR (%)		LnRR	
	β (95% CI)	*P* value	β (95% CI)	*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 hypoglycaemia	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 hypoglycaemia[a]	5.104 (1.349 to 8.859)	0.0077	−0.477 (−0.839 to −0.116)	0.0097

Abbreviations: ARR, absolute risk reduction; LnRR, natural logarithm of relative risk.

[a] Model 8 was performed on the data from eight trials with reports of severe hypoglycaemia.

between drug classes (P = 0.03; I^2 = 65.3%) (Figure S7). 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 DPP-4 inhibitors was not found.

Using the GRADE system, the overall quality of the body of evidence was high for MACE when comparing antidiabetic drugs to placebo for patients with T2D (Table S4). Nine fewer MACE (from three to 14 fewer) could be prevented per 1000 patients with T2D receiving antidiabetic drugs compared to placebo.

3.4 | Antihyperglycaemic treatment and hypoglycaemia risk

The risk of hypoglycaemia had no linear relationship with achieved HbA1c difference between treatment and control groups (Figure S8A). Antihyperglycaemic treatment conferred a significantly higher risk for hypoglycaemia than placebo (RR, 1.09; 95% CI, 1.01-1.18; P = 0.03), with the excess risk contributed by the use of DPP-4 inhibitors or thiazolidinediones (Figure S9). No increased risk for severe hypoglycaemia with antihyperglycaemic therapy was detected (Figures S8B and S10). The quality of evidence was moderate for hypoglycaemia and low for severe hypoglycaemia (Table S4), and no publication bias was found (Egger's test P = 0.1583 for hypoglycaemia and 0.6741 for severe hypoglycaemia; data not shown).

4 | DISCUSSION

The present meta-analysis and meta-regression analysis of the CVOTs (10 trials, 92 400 patients) for antihyperglycaemic agents with less hypoglycaemia risk, including pioglitazone, DPP-4 inhibitors, GLP-1 receptor agonists and SGLT2 inhibitors, have clearly shown 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 hypoglycaemia,[17,18] demonstrates for the first time that risk reduction of the T2D population in MACE was proportional to the magnitude of HbA1c decrease conferred by antihyperglycaemic agents without hypoglycaemia hazard. In other words, rather than the extra-glycaemic 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 antihyperglycaemic agents without hypoglycaemia hazard.

During median treatment of 2.6 years, reduction of HbA1c concentration by 1% resulted in significant reduction in the risk of MACE by 30%. This positive correlation was consistent with the result of a previous meta-regression analysis.[32] Similarly, in trials using conventional antihyperglycaemic agents, there has been no significant association between CV events and HbA1c reduction. The information obtained in the current study will be useful for clinicians when selecting the optimal antihyperglycaemic agents to avoid or reduce the huge health burden resulting from the high MACE rate in patients with T2D.

These results were consistent with the 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 result achieved in subgroup analysis by different categories of antihyperglycaemic agents. With different benefit-harm profiles to traditional medication, new antihyperglycaemic agents, similar to antihypertensive[33] and anti-hypercholesterolemia drugs,[34] 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 the extra-glycaemic 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 to haemodynamic 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 possible alternative mechanisms of benefit.[35]

In currently available trials, the control group is not simply represented 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 RCTs, the use of SUs is associated with increased mortality and a higher risk of stroke.[36] Moreover, SUs did increase the risk of hypoglycaemic episodes when compared with DPP-4 inhibitors[37,38] or metformin, regardless of the individual sulfonylurea.[39] Therefore, it is possible that part of the differences in outcome is determined by the detrimental effects of conventional therapies on some cardiovascular outcomes.

During the UK Prospective Diabetes Study,[40] risk reductions for myocardial infarction and death from any cause emerged in the 10 years of follow-up. However, the ADVANCE[7] and ACCORD[41] trials suggested that significant differences in HbA1c concentration might not confer benefits to macrovascular events, and may even cause an excess risk of all-cause mortality, possibly associated with the higher drug-related adverse events of the hypoglycaemia. A meta-analysis of data from 13 RCTs suggested intensive glucose-lowering treatment resulted in a 19% increase in all-cause mortality and a 43% increase in CV death.[42] By contrast, one meta-analysis using pooled data from ACCORD, ADVANCE and UKPDS showed an overall reduction in the risk of major CV events by 9%, and a 15% reduction in myocardial infarction.[6] Another meta-analysis from five RCTs of 33 040 participants provides reassurance about the effectiveness of intensive glycaemic control for cardiovascular risk reduction (17% reduction in events of non-fatal myocardial infarction and 15% reduction of coronary heart disease).[31]

Possible explanations of such differing results may be (1) that treatment duration was shorter than necessary to reveal a clinical benefit,[40] thus event rates were lower than expected due to improved control of risk factors, (2) differences in glycaemic control between patients' groups were too small to show benefit, and (3) the prevalent

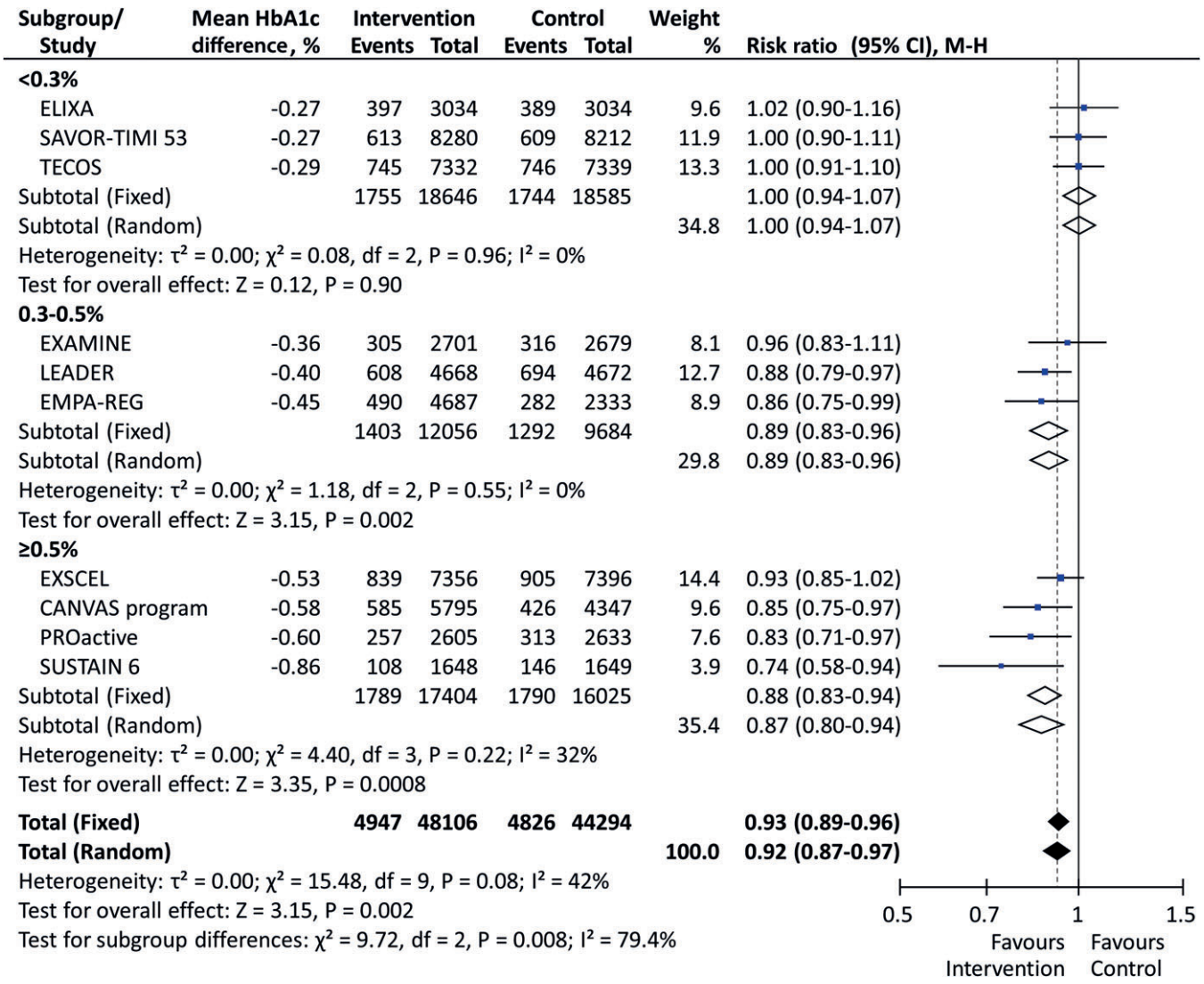

FIGURE 2 Effects of antihyperglycaemic treatment on MACE in patients with type 2 diabetes, stratified by achieved HbA1c difference between intervention and control groups. Mean HbA1c difference indicates the difference in achieved HbA1c between intervention and control groups. Diamonds denote the pooled estimate of relative risks and 95% CI

side effects of hypoglycaemia, which may counteract the benefit from intensive glucose control with insulin and SUs.[17,18] The last of these helps explain why the beneficial effects of glucose-lowering in previous diabetic trials using insulin and SUs only emerged after a longer follow-up duration. This could be because the risk associated with hypoglycaemia resulting from conventional antihyperglycaemic agents may dilute the protective effects of blood sugar control. Such dilution requires a longer follow-up duration and a larger event number to counterbalance it. Overall, these discrepancies indicate that the role of glucose control in patients with T2D who receive glycaemic therapy has only now been determined.

These 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.[43] Although no meta-regression analysis was conducted, by including a few large and several small RCTs as well as registry reports, results suggested a probable mortality benefit with GLP-1 agonists.[43]

In addition to the risk conferred from hyperglycaemia, CV risk may also be modulated by various mechanisms including baseline characteristics such as duration since T2D diagnosis at baseline (≥10 years), the baseline HbA1c concentration, and the adverse side effects of T2D drugs. For example, in the ACCORD trial, HbA1c fell rapidly by around 1.5% within 6 months and the average HbA1c was less than 6% after 1 year in intensively treated individuals through the aggressive use of bolus insulin doses when necessary, and by them receiving a greater proportion of rosiglitazone at the end of follow-up compared with those receiving standard treatment (92% vs 58%).[41] The adverse effects of a 2.5 kg difference in weight gain and nearly double the number of severe hypoglycaemic episodes compared with standard treatment were recorded. More importantly, the meta-regression analysis accounts for these potentially confounding effects, and still shows a significant linear relationship between HbA1c difference and the risk reduction in MACE.

Despite DPP-4 inhibitor being associated with a low risk of hypoglycaemia,[28] it failed to show a corresponding significant risk

reduction in MACE (Figure S7). As suggested by the meta-regression analysis in Figure 1 and subgroup analysis by the magnitude of HbA1c reduction in Figure 2, the small benefit of DPP-4 inhibitor on MACE in these CV safety trials is probably related to its small amount of HbA1c differences.

Antidiabetic drugs with a low hypoglycaemic potential can increase the risk of hypoglycaemia when added to insulin or SUs. If hypoglycaemia is detrimental for the CV system, this could result in 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 glycaemic control on CV events, a large trial is needed on the intensification of therapy, in which insulin and SUs are not allowed, or allowed only as rescue therapy.

4.1 | Study limitations

This study has several potential limitations. First, similar to other meta-analyses, the absence of primary data to analyze the effects of intensive glycaemic control within various patient subgroups by gender, prevalence of CV disease at baseline, comorbidity, duration of T2D, and the selective reporting of primary studies might confound the 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, no evidence of superiority or harm of a specific glucose-lowering regimen can be provided without access to individual participant data. Finally, despite the comprehensive literature search, and by keeping the probability of bias to a minimum by developing a detailed protocol and using explicit criteria for study selection, data collection and data analysis, other eligible published or unpublished studies may have been excluded. However, similar to trends reported in previous meta-analyses,[6] due to robust methodology the results and conclusions would be unlikely to alter substantially, and therefore provide reliable recommendations for clinical practice.

In conclusion, compared with placebo, newer T2D agents with less hypoglycaemic hazard significantly reduced the risk of MACE. The MACE reduction appears to be associated with HbA1c reduction in a linear relationship.

4.2 | Author contributions

All authors conceived the concept and design of the study. C.-J. H. and W.-T. W. contributed to the acquisition of data. C.-J. H. did the statistical analyses. All authors were involved in the analysis and interpretation of data. C.-J. H., W.-T. W. and H.-M. C. 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. C.-J. H., W.-T. W., H.-M. C. and C.-E. C. take responsibility for the integrity of the data and the accuracy of the analyses. H.-M. C. and C.-E. C. were the study supervisors. C.-J. H., W.-T. W. and H.-M. C. had full access to all the data in the study, and H.-M. C. and C.-E. C. had final responsibility for the decision to submit the manuscript for publication.

Conflict of interest

All authors declare no competing interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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