Glucose-Lowering and the Risk of Cardiovascular Events with Novel Antidiabetic Therapies: A Systematic Review and Additive-effects Network Meta-Analysis

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Abstract

Background: Among individuals with type 2 diabetes mellitus (T2DM), RCTs designed to investigate the cardiovascular effects of achieving HbA1c ≤7.0% by using insulin and sulfonylureas were unable to prevent the incidence of major adverse cardiovascular events (MACE) defined as CV death, non-fatal myocardial infarction, and non-fatal stroke. Intense glucose-lowering with newer antidiabetic therapies (ADTs) including SGLT2i, GLP1-RA, pioglitazone and DPP4i show lower risk of hypoglycemia and could lead to additive effect in preventing MACE. In this context, this study was designed to assess the impact of the HbA1c levels achieved with newer ADTs on the risk of MACE.

Methods. We searched MEDLINE/PubMed, Cochrane and ClinicalTrials.gov. RCTs published up to January/2021 reporting the occurrence of MACE and all-cause mortality in individuals with T2DM, including a sample size ≥100 individuals in each study arm and follow-up ≥24 weeks, were selected. Data was extracted by four independent observers following PRISMA guidelines. We performed a systematic review and additive-effects network meta-analysis with random effects and a multivariate meta-regression to assess the impact of achieved HbA1c on incident MACE.

Results. A total of 122 RCTs were included with 139 treatment arms, 256,990 individuals, and 689,346 individuals-years who were randomized to an active treatment vs. control group. Therapy with SGLT2i, GLP1-RA, or pioglitazone similarly reduced the risk of MACE compared to placebo (HR 0.88 [95%CI 0.83, 0.94, p<0.001], 0.89 [95% CI 0.85, 0.94, p<0.0001], and 0.86 [95% CI 0.76, 0.98, p=0.025], respectively). The achievement of HbA1c≤7.0% in RCTs with SGLT2i, DPP4i, TZD, or GLP1-RA in the active arm was associated with an adjusted HR of 0.91 (95% CI 0.80, 0.97; p=0.039) compared with HbA1c>7.0%. All-cause mortality was not influenced by HbA1c thresholds.

Conclusions: Achieving lower glucose levels with newer ADTs is linearly associated with a reduced risk of MACEs, without affecting all-cause mortality. Targeting HbA1c between 6.5 and 7% with SGLT2i, GLP1A, pioglitazone or DPP4i brings cardiovascular benefits considering the available RCT evidence.

Study registration: PROSPERO CRD42020200649

Introduction

Among individuals with type 2 diabetes mellitus (T2DM), observational studies have shown an increased risk of both macrovascular and microvascular events with increasing blood glucose levels[1,2]. Consistently, randomized clinical trials (RCTs) involving subjects with new-onset[3] or long-lasting[4–6] T2DM showed that intensive glucose control, *i.e.* glycated hemoglobin (HbA1c) ≤7.0% (53 mmol/mol), reduces the incidence of microvascular complications. Nevertheless, the RCTs that were designed to investigate the cardiovascular effects of achieving HbA1c ≤7.0% were not able to identify a significant decrease in the incidence of macrovascular events[4–6]. Several factors may explain these negative results, including lower rates of major adverse cardiovascular events (MACE) in the standard arm than originally predicted and adverse effects of therapies such as insulin- and sulfonylurea-associated weight gain and,

particularly, hypoglycemia[7]. A meta-analysis suggested that these drugs could marginally attenuate the incidence of MACE by about 6%, but the statistical power was insufficient to verify this assumption[8]. Therefore, it remains unclear whether the lack of evidence of cardiovascular benefit with an Hba1c ≤7.0% is due to the inadequacy of the statistical power or due to the side effects of some older antidiabetic therapies (ADTs)[4–6].

ADTs such as sodium-glucose cotransporter inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP1A), and pioglitazone, reduce MACE[9–11] via a broad spectrum of mechanisms, which may or may not be additive to their glucose-lowering effect. Moreover, these new therapies, as well as dipeptidyl peptidase-4 inhibitors (DPP4i) have a low risk of hypoglycemia as a common advantage compared to the old drugs. A large number of RCTs have been performed to prove safety with the new ADTs, and in these studies, a wide variability of HbA1c change was observed; while in some active arms, the post-treatment HbA1c was >8.0%; in others, the post-therapy HbA1c was <7.0%[12]. This scenario enabled us to test the assumption that glucose *lowering* has an additive effect in preventing MACE when drugs not associated with hypoglycemia are used, *that is*, SGLT2i, DPP4i, GLP1A, or pioglitazone. Hence, this systematic review aimed to investigate the association between glucose lowering in T2DM and the incidence of MACE in two sets of data: (i) all available RCTs reporting MACE to achieve sufficient statistical power, and (ii) exclusively RCTs that used the new ADTs.

Methods

Search Strategy and Study Eligibility

This systematic review was carried out in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses for Network Meta-analysis (PRISMA-NMA)[13]. A detailed description of all the procedures is provided in the Supplemental Material. Briefly, the review was performed by searching keywords in the following databases: Medline (PubMed), ClinicalTrials.gov, Cochrane Central Register of Controlled Trials, Embase, European Union Clinical Trials Register, and World Health Organization (WHO) International Clinical Trials Registry Platform electronic database entries until January 2021. Briefly, studies were included in the meta-analysis if they met all of the following criteria: (1) randomized double-blinded controlled study design; (2) sample size ≥100 individuals in each study arm; (3) follow-up ≥ 24 weeks; and (4) report of major adverse cardiovascular events (MACE) and CV mortality in both control and intervention groups. We excluded phase 1 or 2 RCTs, studies in type 1 diabetes, and studies without adequate information on outcomes or without a control group. The meta-analysis was registered in the International Prospective Register of Systematic Reviews (CRD42020200649) and detailed search terms, data sources are available in Supplementary Material.

Data extraction and quality assessment

Data were extracted by four authors (A.C.C.N., R.M.R.C., I.B., and B.L.), and any inconsistencies were resolved after debate with the senior researchers (A.C.S. and L.S.F.C.). Extracted data included the name

of first author, year of publication, sample size, duration of follow-up, patient characteristics (sex, age, race), duration of diabetes, active (or experimental) and comparative drug, history of cardiovascular events and heart failure, average systolic and diastolic blood pressure, weight, body mass index (BMI), glycated hemoglobin values (HbA1c), estimated glomerular filtration rate (eGFR), clinical outcomes, and adverse events.

Data synthesis and statistical analyses

The primary endpoint was defined as 3-point MACE according to the definition of the study, representing a combination of nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death. Secondary endpoints were defined as (i) nonfatal myocardial infarction and (ii) all-cause death. We used an additive component network meta-analysis (CNMA) framework to perform an indirect comparison between the drugs. This model is based on the premise that the effect of a treatment combination is the sum of the effects of its components, which implies that the common components cancel each other out in comparisons. An additive CNMA model can be used to evaluate the influence of individual components and their combinations, in contrast to standard network meta-analyses (NMA), which considers that all existing (single or combined) treatments are different nodes in the network. The advantage of employing CNMA here is to identify potential sources of bias related to drug combinations.

Dichotomous variables are reported as percentages, while continuous variables are reported as mean±SD or median (interquartile range). To identify the potential effects of therapies on clinical outcomes, we calculated the hazard ratios (HRs) with random-effects CNMA. We assessed statistical heterogeneity between trials using the I^2 statistic (with 95% CIs), which is derived from Cochran's Q [100×(Q−df÷Q)] and provides a measure of the proportion of overall variation attributable to between-trial heterogeneity. We investigated potential sources of heterogeneity between the RCTs through meta-regression analyses using the restricted maximum-likelihood estimator and the method by Knapp and Hartung [14] for adjusting test statistics and confidence intervals.

We performed prespecified multivariate meta-regressions to address the anticipated heterogeneity among RCTs in meta-regressions and to address the imbalance between RCTs that achieved HbA1c < 7.0% vs. HbA1c>7.0% at the study end in the active arm. The adjusting variables were defined after data collection and were chosen if imbalance was identified between achieved HbA1c subgroups, namely: (i) the time since the diagnosis of T2DM, (ii) type of ADT in the active arm, and (iii) the length of follow-up time. To test for publication bias, we created funnel charts and performed the Egger test.

Sensitivity analyses were carried out to evaluate the stability of meta-regression models after: (i) to address whether largest trials are critical to results presented as main analyses, we sequentially excluded trials with the largest exposures (sample size * follow-up time); (ii) exclusion of the ACCORD, VADT, and ADVANCE trials[4–6], RCTs that did not compare drug classes, but specific HbA1c targets. To estimate the effect of the treatment, a two-tailed p-value less than 0.05, was considered statistically significant. Post-hoc statistical power estimation was carried out using the method described by Jackson et al[15]. The

extracted data were analyzed using R v4.0.1 (2020, Auckland, New Zealand) and *discomb*, *metaviz*, and *metafor* packages.

Results

We identified 3878 citations using the search terms and platforms mentioned above. After excluding duplicates, 3308 articles remained. We further excluded 623 articles that were unsuitable according to the title and abstract. An additional 2572 studies were excluded after full-text evaluation, with no results reported, open-label studies, post-hoc analyses, comparisons of the same drug classes, n<100 per group and/or treatment duration <24 weeks (details on Supplement data and Figure 1). We ended this extraction with 228 trials to be included for qualitative synthesis and meta-analysis, but among them, only 122 RCTs reported MACE. The flow diagram of the selection process and study network is shown in Figure 1 and in the Supplementary material, Figure S1, respectively.

These 122 RCTs provided data of 256,990 patients within 139 active arms, mean 1.48±1.16 years of follow-up and total 689,346 patient-years that were randomized to an active treatment vs. control (full description of study arms is available in Supplements). The baseline characteristics of the enrolled individuals within the trials are shown in Supplementary Table S1. All studies presented a low risk of bias as assessed by the Cochrane Collaboration tool for assessing risk of bias[16] (see Supplementary material, Table S2) and were deemed high quality by the GRADE system[17], except for two RCTs: the CONFIDENCE trial and Abdul-ghani (2017). As shown in Supplementary Table S3 and Figure S2, there was no significant publication bias in the funnel plots, and there was no significant small study bias in the Egger tests.

The mean age was 57.3±9.6 years (45% female). Individuals had the diagnosis of diabetes for 7.5±5.7 years, 80% were on metformin at baseline, 22% were on insulin, 50.4% were enrolled in trials with individuals with prior MI or stroke at baseline and 13% of the enrolled individuals had heart failure at baseline. The mean baseline body mass index (BMI) across trials was 31.2±5.4 kg/m^2, body weight was 86.5±18.7 kg, systolic blood pressure (SBP) was 131.1± 6 mmHg, diastolic blood pressure (DBP) was 78.1± 5 mmHg, estimated glomerular filtration rate was 81.09.3 ml/min/1.73 m^2 and HbA1c 8.1±0.9%.

Primary outcome

The primary outcome (MACE) occurred in 9,457 individuals assigned to active treatment (median across trials of 13.26/1,000 patient-years [interquartile range (IQR) 15.5]) and 9,721 individuals assigned to the control group (median of 16.02/1,000 patient-years [IQR 16.2]). In an additive model network meta-analysis with random effects, DPP4i alone (p=0.82), insulin (p=0.23), sulfonylurea alone (p=0.25), and metformin alone (p= 0.20) showed a neutral effect on the risk of MACE compared to placebo with no heterogeneity (Q=94.5; I^2=0%, p=0.9884). Contrarily, SGLT2i alone, GLP1A alone, and pioglitazone alone

reduced the risk of MACE compared to placebo with an HR of 0.88 [95%CI 0.83, 0.94, p<0.001, 0.89 [95% CI 0.85, 0.94, p<0.0001] and 0.86 [95% CI 0.76, 0.98, p=0.025], respectively) (Supplemental Figure S3). The meta-analysis with and without additive effects yielded similar results (p for difference 0.71).

Secondary outcomes

In order to evaluate the specificity of the findings, as secondary outcomes, we evaluated the relationship between HbA1c change and levels and secondary outcomes: (i) the HR for all-cause deaths and (ii) the HR for myocardial infarction. In meta-regression analyses, no relationship was found between the two secondary outcomes and achieved HbA1c at the study end (Supplementary Figures S5a and S5b), nor with the differential change in HbA1c between the active and control arms. Again, both the meta-analysis with and without additive effects showed similar effect (p for difference 0.91 for all-cause death and 0.56 for myocardial infarction).

Meta-regression analyses

As predicted during the study design, we observed that the RCTs contrasted largely in terms of glucose-lowering efficacy, with absolute reductions in HbA1c varying between -2.2% and 0 in the active arms compared to their respective control arms. We performed a prespecified bivariate meta-regression analysis with all 139 study arms, including DPP4i, pioglitazone, GLP1A, insulin, metformin, sulfonylurea, and SGLT2i in the active arms. RCTs reporting post-treatment HbA1c ≤7.0% were not associated (p for difference=0.39; I^2=3.3%) with the risk of MACE compared to those with HbA1c >7.0% (Table 1). As a continuous variable, each 1% decrease in HbA1c was also not associated (p for difference=0.12; I^2=2.1%) with the incidence of MACE (Table 1, Figure 2b). The achieved (post hoc) statistical power (1 – β) for comparing post-treatment HbA1c ≤7.0% vs >7.0% was 87%, considering the random-effect model, a two-tailed test and summary effect size of 0.0117.

A second analysis was performed including only RCTs with SGLT2i, DPP4i, pioglitazone, or GLP1A in the active arm (Table 1). In this subgroup of RCTs, we found associations between MACE incidence and both HbA1c values achieved after therapy and the absolute change in HbA1c; post-treatment HbA1c ≤7.0% was associated with 9% (95% CI 3, 19%, p=0.039) decrease in the risk of MACE compared with those achieving HbA1c >7.0% (Figure 2a); for every 1% reduction in HbA1c, there was an 18% reduction (95% CI 7%, 29%, p<0.001) in the risk of MACE (Figure 2b).

The pattern of the association between HbA1c and MACE was investigated to estimate the existence of a threshold for the loss of benefit. Through polynomial meta-regression, we identified linear regression as the best fit for the association between MACE and the level of HbA1c or the magnitude of the change in

HbA1c after therapy, which does not suggest the existence of U or J curves for this association up to HbA1c levels between 6.5% and 7.0%. HbA1c levels ≤6.5% were not found in the RCTs.

Among all included RCTs, among those that reported post-treatment values of HbA1c ≤7.0%, we found more frequently studies that included patients with shorter T2DM duration (p=0.03), with longer follow-up (p=0.01) and with GLP1A as their active arm (p=0.03). These three variables were independently associated with the risk of developing MACEs. To circumvent these limitations, we performed multivariate meta-regressions for the risk of MACE adjusting for these covariates and, as shown in Table 1, each 1% decrease in HbA1c was associated with an HR for MACE of 0.90 (95% CI 0.75, 0.98, p=0.017, I2=0%) among RCTs with SGLT2i, DPP4i, pioglitazone, or GLP1A in the active arm. Likewise, the association between HbA1c ≤7.0% after treatment was also associated with an HR for MACE of 0.82 (95% CI 0.70, 0.96, p=0.013, I2=0%) in the adjusted analysis.

Sensitivity analyses

Sensitivity analyses were conducted using three approaches: (i) the exclusion of one study with the largest exposures (sample size * follow-up time) per drug in the active arm, (ii) the exclusion of two studies per drug group with the largest exposures, and (iii) the exclusion of ACCORD, ADVANCE, and VADT trials. The first two approaches address the impact of potential class-related mechanisms on the relationship between achieved HbA1c and the risk of MACE, and the third approach addresses the potential influence of the use of the old therapies with a higher risk of hypoglycemia.

To exclude that largest trials are critical to results presented as main analyses, in the first sensitivity analyses we excluded the trials TECOS, REWIND, DECLARE, and Dormandy (2005). As shown in Supplementary Figure S4a, in an additive model network meta-analysis with random-effects, only SGLT2i alone and GLP1A alone and the associations SGLT2i + GLP1A and SGLT2i + DPP4i were associated with reduced risk of MACE compared to placebo with HRs of 0.85 (95% CI 0.79, 0.92, p<0.0001), 0.89 (95% CI 0.85, 0.94, p<0.0001), 0.76 (95% CI 0.69, 0.83, p<0.0001) and 0.84 (95% CI 0.76, 0.93, p=0.001), respectively, and no heterogeneity (I^2=0%).

In the second sensitivity analysis, we excluded the TECOS, CAROLINA, REWIND, EXCEL, DECLARE, CANVAS, and Dormandy (2005), and the results were unchanged compared to the first sensitivity analysis, and no heterogeneity was found (I^2=0%) (Supplementary Figure S4b). A meta-regression based on this second approach yielded similar results when compared with the pre-exclusion dataset. There were significant relationships between the risk of MACE and the achieved HbA1c levels in the active arm or the differential change in HbA1c in the active arm compared to the control (Table 2).

In the third sensitivity analysis, we found no significant changes in the relationship between the risk of MACE and the achieved HbA1c levels in the active arm or the differential change in HbA1c when we excluded the ACCORD, ADVANCE, and VADT trials (data not shown).

Discussion

The present systematic review and meta-analysis evaluated 122 RCTs with over 689,000 individuals-years and showed that the absolute change in HbA1c and the target ≤7.0% were associated with reduced risk of MACE in therapies based on SGLT2i, DPP4i, pioglitazone, or GLP1A, with no evidence of increasing all-cause mortality.

Our results are in line with previous meta-analyses[8 12,18] and showed that the absolute change in HbA1c and an achieved HbA1c ≤7.0% in patients with T2DM is associated with mild reductions in MACE risk. In disagreement with our findings, Wang et al[18] pooled 15 studies with 88,266 type 2 diabetes individuals and reported that an HbA1c <7.0% did not improve cardiovascular outcomes. It is worth mentioning that their meta-analysis yielded high heterogeneity and pooled various study designs, including trials with post-acute coronary syndromes such as DIGAMI-1[19]. Our differential approach in this meta-analysis was to carry out a more comprehensive literature search and, therefore, with greater statistical power and evaluated the newer ADTs independently.

Notably, although our meta-analysis did not capture significant heterogeneity among RCTs regarding the risk of MACE within ADT classes, there was a marked imbalance in baseline characteristics of individuals enrolled in RCTs with HbA1c ≤7.0% compared to RCTs that achieved HbA1c >7.0%. RCTs achieving HbA1c >7.0% were shorter in duration and more frequently enrolled individuals with long-term T2D (> 8-10 years of disease). Although this is expected, no prior meta-analysis adjusted the regressions for these important cofactors [12,18]. Hence, in this study, we performed a step forward using multivariate meta-regression analyses adjusting for T2DM duration, follow-up duration, and the effect of treatment in the active arm, and confirmed that achieving HbA1c≤7.0% with SGLT2i, GLP1A, DPP4i, or pioglitazone was associated with a decreased risk of MACE compared to >7.0%.

Some findings from this meta-analysis indicate a potential contribution of blood glucose lowering in the reduction of macrovascular events. With the new ADTs, RCTs with post-therapy HbA1c ≤7.0% were consistently associated with a 9% lower risk of MACE compared with RCTs that achieved HbA1c >7.0%, regardless of the therapies used. A linear trend was found between MACE and HbA1c in the range of 6.5–8.0%, with no evidence of U- or J-shaped curves and in a magnitude of association that is similar to that reported between hyperglycemia and MACE in observational studies[1,2]. We plan to verify this association by a meta-regression exclusively based on DPP4i, whose RCTs demonstrated a low risk of hypoglycemia, no weight gain, and no direct cardiovascular benefit. However, the sample size with the combination of these RCTs did not provide sufficient statistical power for this analysis. We found a very similar effect of SGLT2i, GLP1RA, and pioglitazone in the decrease of MACE risk. As commented above, these effects result from a wide range of mechanisms, which are concomitant and difficult to dissociate from their glucose-lowering effects. Thus, although this meta-analysis indicates the existence of a direct effect of lowering blood glucose levels on the incidence of MACE, our data do not allow us to determine the exact size of this effect.

Our study had limitations. First, our results were obtained by meta-regression analysis from RCTs, which is inferior to analyses at the patient level. Nevertheless, in sensitivity analyses, when we evaluated different scenarios, excluding trials with larger exposures, we noticed similar results. Second, as mentioned above, the new ADTs have demonstrated MACE risk-reduction mechanisms that are independent of glycemic control or hypoglycemia. Therefore, the available data do not allow us to accurately estimate the magnitude of the effect of lowering blood glucose levels in reducing MACE.

In summary, more intense reductions in HbA1c and lower levels of HbA1c achieved with newer ADTs are associated with a reduced risk of MACE. Targeting HbA1c between 6.5% and 7% with SGLT2i, GLP1A, pioglitazone, or DPP4i may be associated with cardiovascular risk reduction in light of the available RCT evidence.

Abbreviations

MACE
major acute cardiovascular events
T2DM
type 2 diabetes mellitus
RCT, randomized clinical trials
HbA1c
glycated hemoglobin A1c
CV, cardiovascular
ADT, antidiabetic therapies
SGLT2i, sodium-glucose cotransporter inhibitors
GLP1A, glucagon-like peptide-1 receptor agonists
DPP4i, dipeptidyl peptidase-4 (DPP4) inhibitors
HR, hazard ratio
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses for Network Meta-analysis
BMI, body mass index
eGFR, estimated glomerular filtration rate
CNMA, additive component network meta-analysis
NMA, network meta-analysis
IQR, interquartile range.

Declarations

Ethics approval and consent to participate. Not applicable.

Consent for publication. Not applicable.

Availability of data and materials. The data that support the findings of this study are available on request from the corresponding author, ACS.

Competing Interest: The authors have declared that no conflict of interest exists.

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Author Contributions: Professor Carvalho had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Benchimol, Couri, Borges, Sposito and Carvalho. Acquisition, analysis, or interpretation of data: Bonilha, Luchiari, Cintra, Barreto, Nogueira, Benchimol, Couri, Borges, Sposito, and Carvalho. Drafting of the manuscript: Sposito, Carvalho. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Carvalho. Supervision: Sposito, Carvalho.

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Tables

Table 1. Bivariate and multivariate meta-regression models with the hazard ratio for major adverse cardiovascular events (MACE) as dependent variable

Bivariate analyses	HR	95% CI		p
		Lower bound	Upper bound	
Achieved HbA1c at study end in the active arm (HbA1c ≤ 7.0% vs HbA1c > 7.0%) vs MACE				
All trials (139 study arms; n=256,990; 19,178 events)	0,9531	0,8001	1,1366	0.392
I^2 (residual heterogeneity / unaccounted variability): 3.28%, QE = 81.3 (p = 0.97); tau2 (estimated amount of residual heterogeneity): 0.010 (SE = 0.022)				
SGLT2i, DPP4i, TZD or GLP1A in the active arm (69 study arms*; n=185,344; 15,528 events)	0,9130	0,8098	0,9704	0.039
I^2 (residual heterogeneity / unaccounted variability): 10.39%, QE = 51.14 (p = 0.95); tau2 (estimated amount of residual heterogeneity): 0.010 (SE = 0.022)				
Change in HbA1c in the active arm compared to control (each reduction of 1%) vs MACE				
All trials (139 study arms; n=256,990; 19,178 events)	0,8926	0,7414	1,0257	0.116
I^2 (residual heterogeneity / unaccounted variability): 2.08%, QE = 91.3 (p = 0.99); tau2 (estimated amount of residual heterogeneity): 0.010 (SE = 0.022)				
SGLT2i, DPP4i, TZD or GLP1A in the active arm (69 study arms*; n=185,344; 15,528 events)	0,8241	0,7057	0,9318	<0.001
I^2 (residual heterogeneity / unaccounted variability): 5.8%, QE = 65.68 (p = 0.99); tau2 (estimated amount of residual heterogeneity): 0.008 (SE = 0.023)				

Multivariate analyses**	HR	95% CI		p
		Lower bound	Upper bound	
Achieved HbA1c at study end in the active arm (HbA1c ≤ 7.0% vs HbA1c > 7.0%) vs MACE				
All trials (118 study arms[§]; n=231,071; 14,180 events)	0,8685	0,6263	1,0964	0.186
I^2 (residual heterogeneity / unaccounted variability): 0%, QE = 71.4 (p = 0.97); tau2 (estimated amount of residual heterogeneity): 0.014 (SE = 0.012)				
SGLT2i, DPP4i, TZD or GLP1A in the active arm (56 study arms*[§]; n=181,489; 14,876 events)	0,8204	0,7019	0,9579	0.013
I^2 (residual heterogeneity / unaccounted variability): 0%, QE = 6.4 (p = 0.21); tau2				

(estimated amount of residual heterogeneity): 0.010 (SE = 0.021)				
Change in HbA1c in the active arm compared to control (each reduction of 1%) vs MACE				
All trials (116 study arms[§]; n=228,852; 14,017 events	0,8762	0,6992	1,0020	0.052
I^2 (residual heterogeneity / unaccounted variability): 0%, QE = 84.1 (p = 0.99); tau2 (estimated amount of residual heterogeneity): 0.018 (SE = 0.027)				
SGLT2i, DPP4i, TZD or GLP1A in the active arm (56 study arms*[§]; n=181,489; 14,876 events)	0,9047	0,7514	0,9798	0.017
I^2 (residual heterogeneity / unaccounted variability): 0%, QE = 76.83 (p = 0.98); tau2 (estimated amount of residual heterogeneity): 0.008 (SE = 0.028)				

* Excluding RCTs with outlier HRs for MACE, defined as HR ≥ 2.0 or HR ≤ 0.5

** Adjusted for Time since the diagnosis of T2DM, follow-up time and type of ADT in the active arm. Adjusting variables were selected for their association with HR for MACE in bivariate analyses

[§] Some RCTs had missing data for covariates

Table 2. Sensitivity analyses[¥] using meta-regression models for the hazard ratio of MACE as dependent variable

Bivariate analyses	HR	95% CI		p
		Lower bound	Upper bound	
Achieved HbA1c at study end in the active arm (HbA1c ≤ 7.0% vs HbA1c > 7.0%) vs MACE				
All trials (132 study arms)	0,9560	0,7703	1,1865	0.680
I^2 (residual heterogeneity / unaccounted variability): 3.87%, QE = 90.0 (p = 0.99); tau2 (estimated amount of residual heterogeneity): 0.010 (SE = 0.022)				
SGLT2i, DPP4i, TZD or GLP1A in the active arm (62 study arms*)	0,8033	0,6338	0,9773	0.031
I^2 (residual heterogeneity / unaccounted variability): 5.31%, QE = 8.7 (p = 0.37); tau2 (estimated amount of residual heterogeneity): 0.010 (SE = 0.022)				
Change in HbA1c in the active arm compared to control (each reduction of 1%) vs MACE				
All trials (132 study arms)	0,9036	0,7300	1,0526	0.215
I^2 (residual heterogeneity / unaccounted variability): 22.08%, QE = 91.3 (p = 0.99); tau2 (estimated amount of residual heterogeneity): 0.010 (SE = 0.022)				
SGLT2i, DPP4i, TZD or GLP1A in the active arm (62 study arms*)	0,8265	0,6769	0,9581	0.009
I^2 (residual heterogeneity / unaccounted variability): 5.31%, QE = 8.4 (p = 0.35); tau2 (estimated amount of residual heterogeneity): 0.010 (SE = 0.022)				

Multivariate analyses**	HR	95% CI		P
		Lower bound	Upper bound	
Achieved HbA1c at study end in the active arm (HbA1c ≤ 7.0% vs HbA1c > 7.0%) vs MACE				
All trials (109 study arms[§])	0,8598	0,7082	1,0439	0.073
I^2 (residual heterogeneity / unaccounted variability): 0%, QE = 70.1 (p = 0.94); tau2 (estimated amount of residual heterogeneity): 0.014 (SE = 0.012)				
SGLT2i, DPP4i, TZD or GLP1A in the active arm (49 study arms*[§])	0,8328	0,7168	0,8755	0.004
I^2 (residual heterogeneity / unaccounted variability): 0%, QE = 5.6 (p = 0.21); tau2 (estimated amount of residual heterogeneity): 0.010 (SE = 0.021)				
Change in HbA1c in the active arm compared to control (each reduction of 1%) vs MACE				
All trials (109 study arms[§])	0,8837	0,6765	1,0402	0.107
I^2 (residual heterogeneity / unaccounted variability): 0%, QE = 83.7 (p = 0.97); tau2 (estimated amount of residual heterogeneity): 0.018 (SE = 0.027)				
SGLT2i, DPP4i, TZD or GLP1A in the active arm (49	0,8194	0,6887	0,9695	0.028

study arms*§)
I^2 (residual heterogeneity / unaccounted variability): 0%, QE = 6.1 (p = 0.28); tau2 (estimated amount of residual heterogeneity): 0.008 (SE = 0.028)

* Excluding RCTs with outlier HRs for MACE, defined as HR ≥ 2.0 or HR ≤ 0.5

** Adjusted for Time since the diagnosis of T2DM, follow-up time and type of ADT in the active arm. Adjusting variables were selected for their association with HR for MACE in bivariate analyses

§ Some RCTs had missing data for covariates

¥ Data corresponds to sensitivity analysis 2, which excluded the following RCTs: TECOS, CAROLINA, REWIND, EXCEL, DECLARE, CANVAS, and Dormandy (2005)

Figures

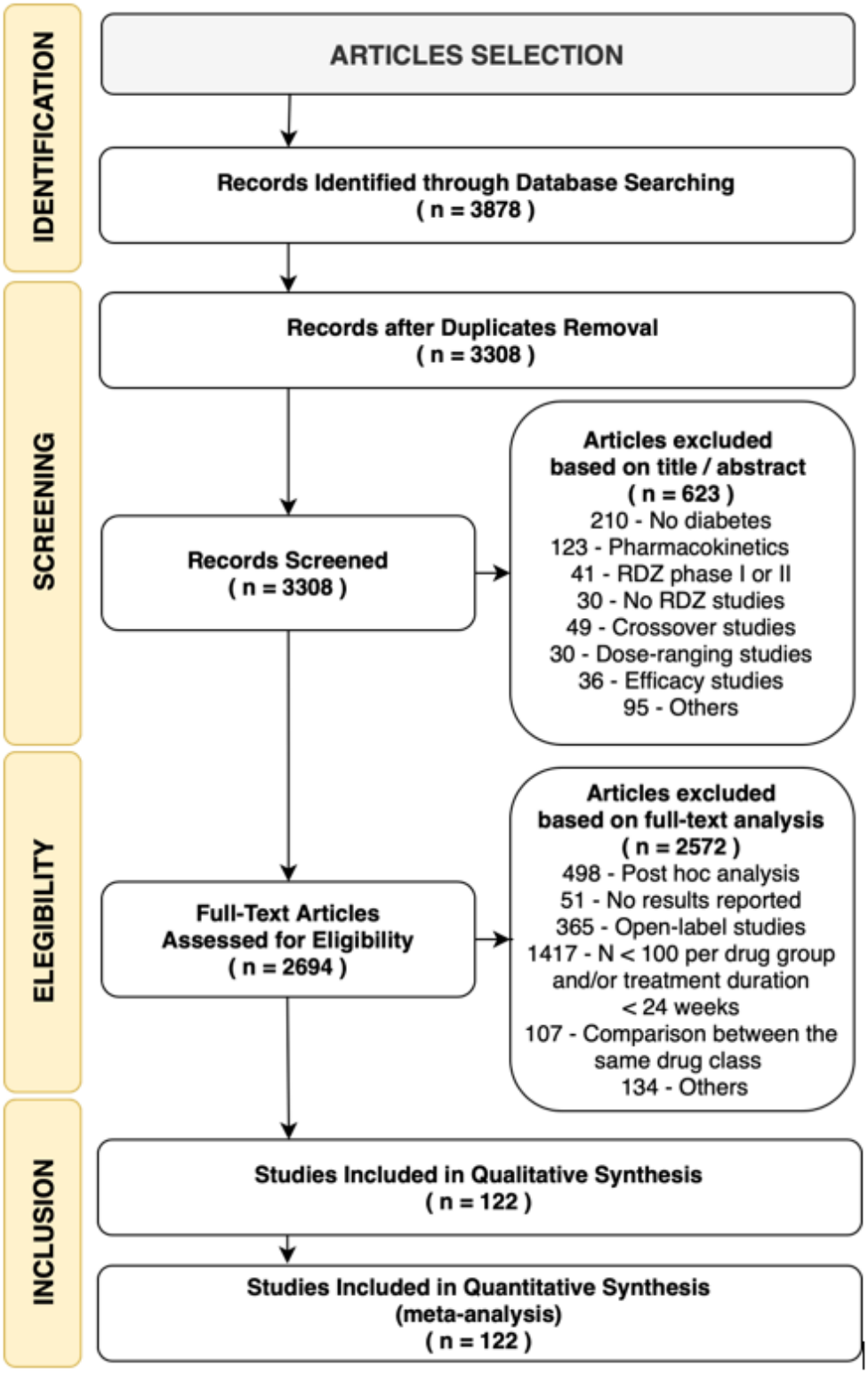

Figure 1

Flow diagram of the trials' selection process. RDZ: randomization.

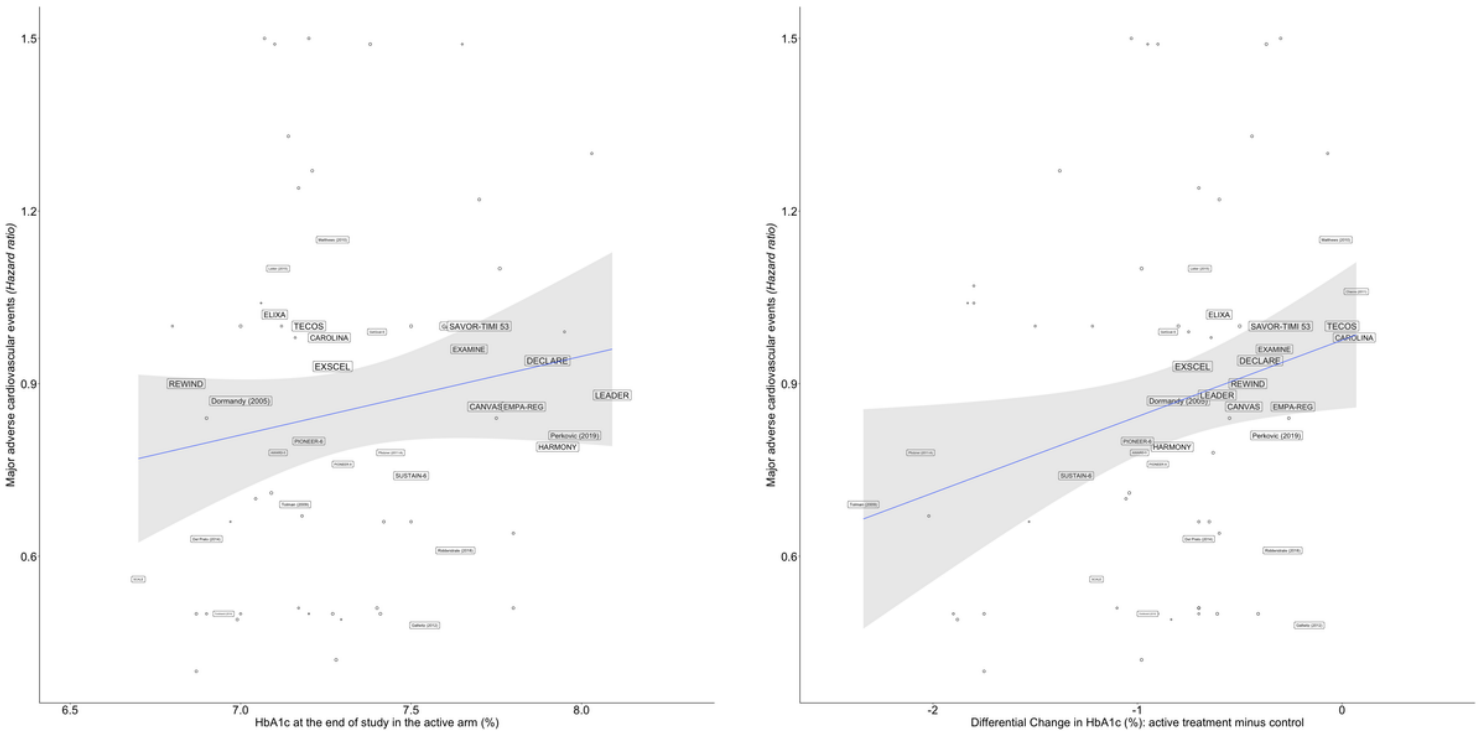

Figure 2

Meta-regression model for all drugs showing the relationship between the HR for MACE versus: (a) achieved HbA1c levels at study end in the active arms of each trial, and (b) differential change in HbA1c levels between active and control arms. The size of the trials' name corresponds to their proportional weight in the regression.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMA2020checklist1.pdf
- Suppl20092021copy.docx