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REVIEW ARTICLE

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Cardiovascular prevention with glucose-lowering drugs in type 2 diabetes: An evidence-based approach to the categories of primary and secondary prevention

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Abstract

Aims: Whether to recommend specifically the glucose-lowering therapies with cardiovascular benefit only in secondary prevention, or also in patients with multiple risk factors (MRF) but without established atherosclerotic cardiovascular disease (ASCVD), is controversial across the guidelines for diabetes.

Materials and Methods: We performed a meta-analysis of clinical trials with major adverse cardiovascular events (MACE) as an outcome.

Results: The definitions of ASCVD and MRF were heterogeneous across trials; nevertheless, the incidence of MACE was 2.8-fold higher in people with ASCVD in trials with sodium-glucose cotransporter 2 inhibitors (SGLT2is), and 3.9-fold in trials with glucagon-like peptide-1 receptor agonists (GLP-1 RA). Both SGLT2i and GLP-1 RA were associated with a significant reduction in the incidence of MACE in people with previous ASCVD [inverse variance-odds ratio 0.91, 95% confidence interval (0.86: 0.97) for SGLT2i, Mantel-Haenszel odds ratio 0.85, 95% confidence interval (0.81: 0.90) for GLP-1 RA], whereas no significant reduction was detected in those without; on the other hand, no significant difference in effect was found between the two groups as well. The sample of patients without ASCVD enrolled in clinical trials is insufficient to draw reliable conclusions in this population; however, even assuming the same benefit detected in people with ASCVD also in those with MRF, the number needed to treat would differ (35 for secondary, 99 for primary prevention of a MACE with a SGLT2i; 21 for secondary, 82 for primary prevention with a GLP-1 RA, respectively), given the difference in absolute cardiovascular risk at baseline.

Conclusion: The distinction between patients with ASCVD and those without ASCVD and MRF appears therefore justified by available evidence.

KEYWORDS
cardiovascular disease, complications of diabetes, GLP-1 receptor agonist, meta-analysis, SGLT2 inhibitor, type 2 diabetes

1 | INTRODUCTION

Evidence from randomized trials shows that different glucose-lowering agents have differential effects on cardiovascular morbidity and mortality in people with type 2 diabetes mellitus.[1] Patients at higher cardiovascular risk can have a greater benefit from the reduction of such risk; consequently, many guidelines recommend different drug algorithms for the treatment of type 2 diabetes, based on the cardiovascular risk of patients.[2–4] In particular, drugs with proven cardiovascular benefit, such as sodium-glucose cotransporter 2 inhibitors (SGLT2is) and/or glucagon-like peptide-1 receptor agonists (GLP-1 RAs), are usually recommended as first-line treatments in patients at highest risk.[2–5]

The definition of high-risk patients in guidelines is very heterogeneous. Some guidelines recommend the specific choice of glucose-lowering drugs with proven cardiovascular benefit only in patients with established cardiovascular disease (CVD), i.e. in secondary prevention,[4] whereas others recommend the same treatment also in patients without previous cardiovascular events, but at high risk,[2,3,5] albeit with a different strength of recommendation.[6] The definition of high-risk subjects in primary prevention is also variable across guidelines. The European Society of Cardiology (ESC) defines as high-risk or very high-risk subjects all those with either one additional risk factor other than diabetes, target organ damage (i.e. microvascular complications of diabetes), or a duration of diabetes greater than 10 years.[3] Conversely, the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) position statement defines as high-risk patients those aged over 55 years with at least two additional risk factors.[5]

2 | DRUGS FOR DIABETES IN PRIMARY AND SECONDARY PREVENTION OF CARDIOVASCULAR DISEASE

Most available evidence on the cardiovascular effects of glucose-lowering drugs is derived from cardiovascular safety studies, usually performed to comply with regulatory requirements. In fact, because the concern of an association between specific glucose-lowering drugs, such as thiazolidinediones, and adverse cardiovascular outcomes, in 2008 the US Food and Drug Administration (FDA) issued a guidance, requiring the demonstration that all new diabetes drugs do not increase the incidence of major cardiovascular events (MACE; defined as the composite endpoint of non-fatal myocardial infarction, non-fatal stroke and cardiovascular mortality, with the optional addition of unstable angina), with an upper limit of 95% confidence interval (CI) not greater than 1.3. Such a result could be obtained either through pooled analyses of phase II-III trials, or through specifically designed placebo-controlled cardiovascular safety trials performed in high-risk patients. Such trials could be performed after drug marketing in the case that phase II-III trials did not show an increase of cardiovascular events, with an upper limit of CI not exceeding 1.8.[7] An amendment of the FDA guidance in 2020 explicitly stated the need to enrol in phase II-III studies a relevant number of patients with either established CVD, renal disease, or advanced age.[8]

The FDA guidance prompted a substantial number of cardiovascular safety trials with new drugs for type 2 diabetes, with MACE as the principal endpoint, often designed as non-inferiority studies versus placebo. The enrolment of very high-risk subjects, required by regulatory authorities to obtain a more reliable assessment of safety, was also functional to contain the number of patients enrolled and the duration of trials, while preserving a sufficient statistical power because of the high number of observed events. As a strategy for selecting patients at very high cardiovascular risk, many trials enrolled only subjects with established CVD.[9–12] Other trials also included a subgroup of patients without previous cardiovascular events, but with multiple risk factors; however, those subgroups in primary prevention accounted only for a minority (and sometimes only for a small fraction) of events in each trial.[13–21]

In all available trials, subgroup analyses, performed either as prespecified or as post-hoc analyses, did not show significant reductions of MACE with either GLP-1 RA or SGLT2-i in patients without established CVD,[11,13–19,21] whereas a significant reduction was often detected in patients with established CVD.[11,13,14,16,19,21] Notably, the sample size of a trial is calculated based on the principal endpoint in the whole sample; any subgroup analysis is therefore inherently under-powered, having only exploratory purposes. In this specific case, the small number of events recorded in primary prevention subgroups is far from reaching an adequate statistical power. On the other hand, analyses exploring differences in risk for MACE between subjects in primary or secondary prevention failed to detect statistically significant differences in effect across subgroups.[16,18] However, the lack of evidence on differences between subgroups is not evidence of the absence of such differences: the small number of events in primary prevention subgroups, while insufficient for establishing the difference between drug and placebo in the subgroup, is also insufficient to assess the differences in effects between subgroups reliably.

When the samples enrolled in individual trials are insufficient for drawing a clear conclusion, the combination of all available trials in a meta-analysis can increase the statistical power, and therefore the reliability of results.

3 | EVIDENCE OF CARDIOVASCULAR EFFECTS OF GLUCOSE-LOWERING DRUGS IN PRIMARY AND SECONDARY PREVENTION

To this purpose, we performed a meta-analysis, as a part of a broader systematic review, which was registered on the PROSPERO[22] website (CRD42022310017). The search string was updated to 5 April 2023, and limited to classes of anti-hyperglycaemic drugs of proven CVD benefit (i.e. GLP-1 RA, SGLT2i, pioglitazone and metformin[1]). The endpoint was the incidence of MACE. We included all randomized controlled trials with a duration of follow-up of at least 52 weeks, in which any SGLT2i or GLP-1 RA, or metformin or pioglitazone, was

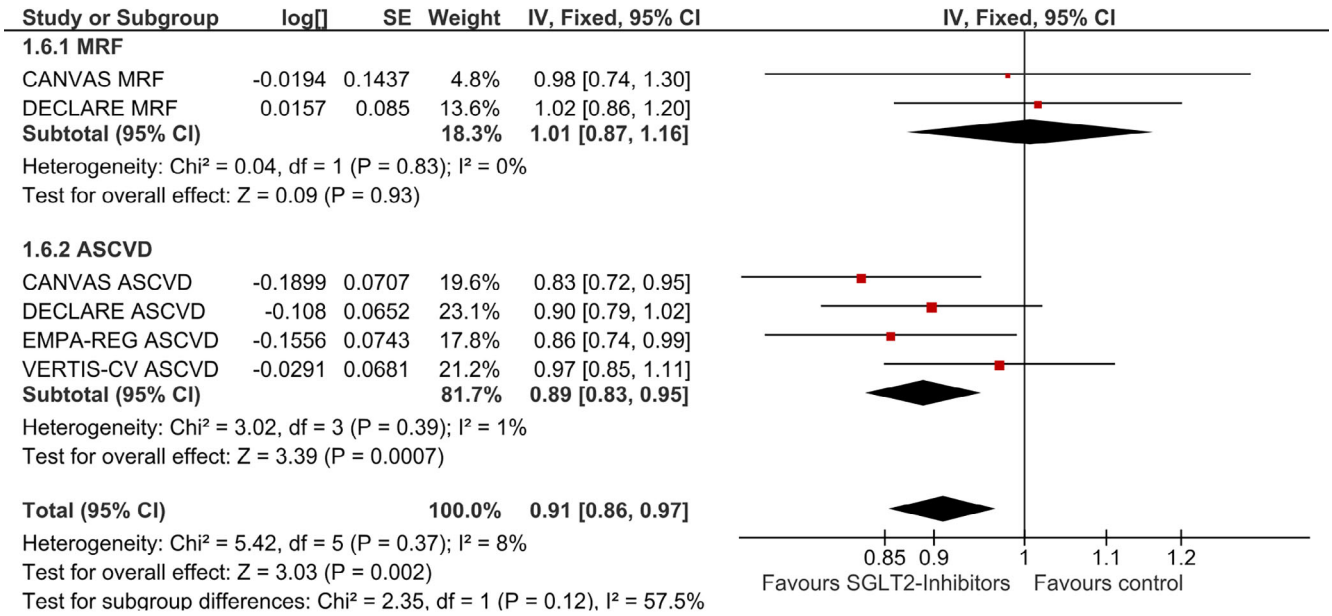

FIGURE 1 Incidence of major adverse cardiovascular events in randomized controlled trials performed on SGLT2 inhibitors in people with MRFs for cardiovascular disease or in people with established ASCVD; IV odds ratios with 95% CI. ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; IV, inverse-variance; MRF, multiple risk factors; SGLT, sodium-glucose cotransporter 2 inhibitor.

compared with either placebo or active comparators in adults with established T2DM, provided that they reported the formal external adjudication of events, and that they reported separate results for people with and without atherosclerotic CVD (ASCVD). Mantel-Haenszel odds ratios (MH-ORs) with 95% CIs were calculated for all outcomes defined above, on an intention-to-treat basis, when the number of events were available; when only ORs were available, inverse variance odds ratios (IV-ORs) were used. Heterogeneity was assessed using I^2 statistics. A fixed-effects model was applied and a random-effects analysis was used a sensitivity analysis. All analyses specified above were performed using Review Manager 5.4.1 (The Cochrane Collaboration) and SPSS 28.0.1.0 (IBM SPSS Statistics).

The four available trials performed in patients with ASCVD for SGLT2i, enrolling 29 564 subjects, showed a significant reduction in the incidence of MACE [IV-OR 0.91, 95% CI (0.86, 0.97)]. Only two trials reported the incidence of MACE in people without ASCVD (N = 10 186), with no significant effect of SGLT2i [IV-OR 1.01, 95% CI (0.87, 1.16)]. The difference in effects of SGLT2i between subgroups was not statistically significant ($p = .12$; Figure 1). Identical results were obtained with a random-effects model [IV-OR 0.89 (0.83, 0.95) and 1.01 (0.87, 1.16) in patients with and without ASVCD, respectively; $p = .88$ for subgroup difference].

For GLP-1 RA, 10 and eight trials were available for people with and without ASCVD, respectively. The number of patients enrolled was 49 587 and 19 102 with and without ASCVD, respectively. GLP-1 RA treatment was associated with a significant reduction of MACE in people with ASCVD [MH-OR 0.85, 95% CI (0.81, 0.90)], but not in those without ASCVD [MH-OR 0.94, 95% CI (0.83, 1.06)]. However, the difference in the effects of GLP-1 RA between the two subgroups was not statistically significant, with $p = .17$ (Figure 2). Similar results were obtained using a random-effects analysis, with MH-OR 0.85, 95% CI (0.77, 0.93) in those with ASCVD, and MH-OR 0.94, 95% CI (0.83, 1.06) in those without.

For pioglitazone, the only trial separately reporting data on MACE in patients without ASCVD is the TOSCA study[23]; a post-hoc analysis on patients without ASCVD did not show any difference in MACE between pioglitazone and sulphonylurea [OR 0.99 (0.73-1.34)] in 2693 patients. Conversely, in the only available trial reporting data on patients with ASCVD, the PROACTIVE study,[24] pioglitazone was associated with a significant reduction of MACE [hazard ratio 0.84 (0.72-0.98)]. Similar results [MH-OR: 0.84 (0.72, 0.99)] were obtained when a further study enrolling patients with mild coronary disease[25] was combined with the PROACTIVE study.

The retrieval of data on metformin was more problematic. The UKPDS enrolled a small fraction of patients with ASCVD, but did not report separate analyses for patients with or without ASCVD.[26] The SPREAD-DIMCAD[27] trial, which randomized people with diabetes and ASCVD to metformin or glipizide, detected a non-significant trend toward a reduction of MACE in metformin arm [OR M-H, 0.45, 95% CI (0.18, 1.15)].

Overall, available evidence is insufficient to show a significant reduction in the incidence of MACE in patients without ASCVD with any class of drugs for diabetes. However, this could depend on the insufficient size of samples enrolled in clinical trials. Even for GLP-1 RA, which were studied in relatively larger samples of patients in primary prevention, the total number of events reported in subjects without ASCVD (i.e. 1235) had a power of 18.8% to detect as statistically significant a 10% reduction of cardiovascular events; this post-hoc power calculation was performed using a one-sample z-test.[28] Based on the observed incidence of MACE in placebo arms of primary

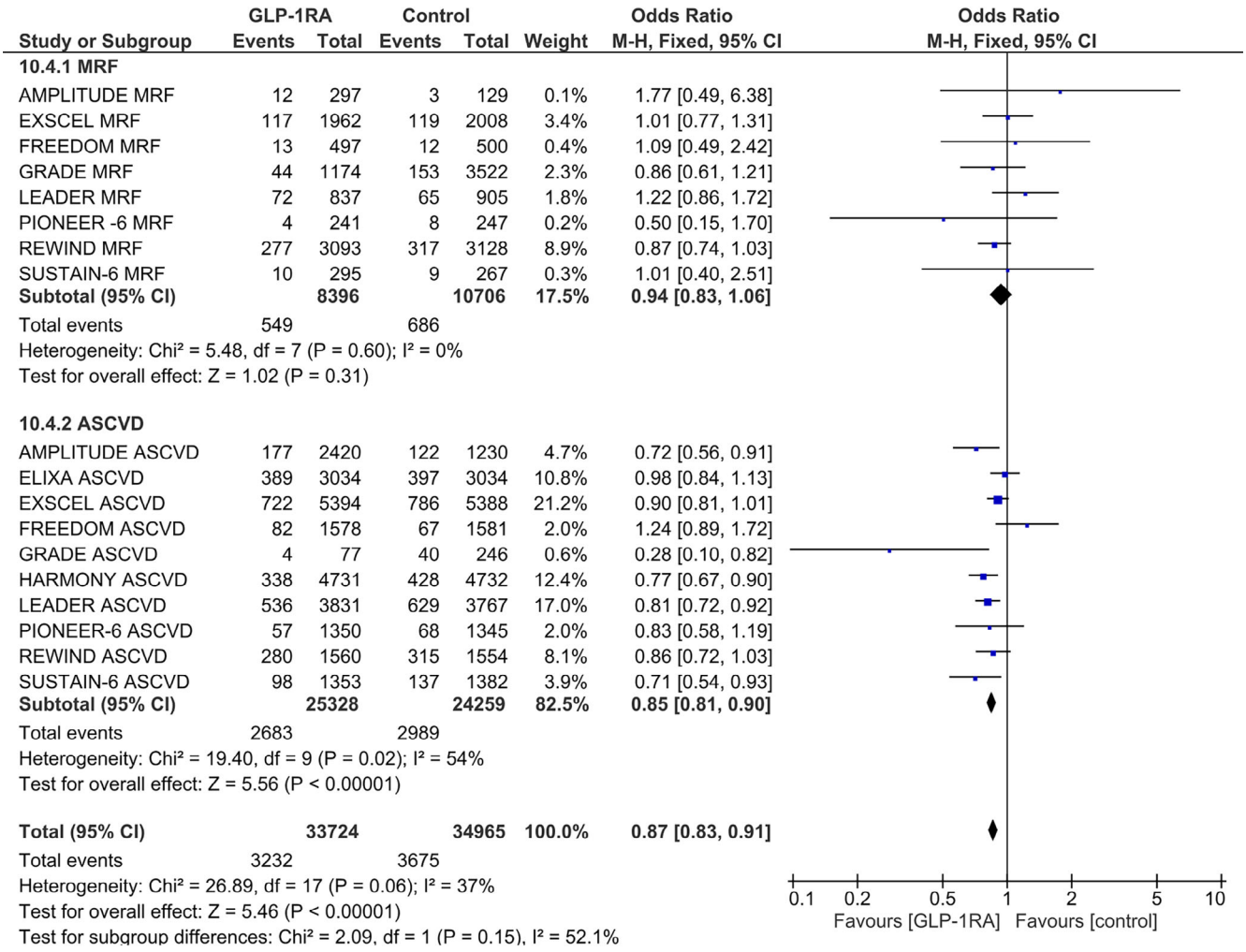

FIGURE 2 Incidence of major adverse cardiovascular events in randomized controlled trials performed on GLP-1 RA in people with MRF for cardiovascular disease or in people with established ASCVD; MH odds ratios with 95% CIs. ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist; M-H, Mantel-Haenzel; MRF, multiple risk factors.

prevention subgroups of available trials, a hypothetical placebo-controlled trial performed in patients with multiple risk factors, but without known ASCVD, designed to show a superiority of a GLP-1 RA with a 10% reduction of MACE (90% power, $p = .05$, 1:1 randomization) would need the enrolment of 46 670 patients, with a duration of treatment of 5 years. The need of very large samples for the assessment of cardiovascular effects of drugs for diabetes in patients without previous cardiovascular events, even when selecting only individuals with multiple risk factors, is a good reason for the preferential enrolment of subjects with ASCVD in cardiovascular trials.

On the other hand, we should be aware that most available evidence on the cardiovascular effects of glucose-lowering drugs is derived from trials originally designed for safety purposes, following regulatory requirements.[7] In fact, even for trials with superiority endpoints,[18] the main characteristics of the study had to comply with the FDA guidance.[7] As the original purpose of the study was the assessment of safety, trials included the patients at highest risk of adverse events, rather than those potentially receiving the greater benefit from therapy.[29] In addition, most of those studies enrolled a large number of participants, to reach the expected number of events in a relatively short time, thus confirming the safety of treatment as soon as possible; the duration of observation, however, could have been insufficient for the detection of longer-term effects.[29] In particular, anti-atherogenic effects of other drugs used for cardiovascular protection, such as statins, are scarcely evident in the first 2 years of treatment[30,31]; many cardiovascular trials in diabetes have a mean duration of follow-up ≤2 years,[16,17,20,21] potentially underestimating efficacy.

A further issue of cardiovascular trials in diabetes is the definition of the principal outcome. The FDA guidance recommends a composite endpoint of non-fatal myocardial infarction, non-fatal stroke and cardiovascular mortality, with the possible addition of unstable angina.[7] Such composite, although facilitating the collection of a relatively large number of incident events, combines heterogeneous pathological conditions, which could be differentially affected by treatments. In fact, the biology of cerebrovascular endothelium is partly different from that of coronary endothelial cells[32]; in addition, the peculiar haemodynamic condition of coronary arteries, with myocardial

TABLE 1 Inclusion criteria for enrolling subjects with atherosclerotic cardiovascular disease in randomized clinical trials assessing incidence of major cardiovascular events in people with type 2 diabetes mellitus

Study	Ischaemic stroke	Haemorrhagic stroke	TIA	Carotid PTA/ endarterectomy	Carotid stenosis	Peripheral PTA/ bypass	Peripheral stenosis	Claudication	ABI <90	Amputation	AMI	CABG/ PTCA	CHF NYHA I-III	Stable angina	≥2 Coronary stenosis	≥1 Coronary stenosis	Unstable angina	eGFR <60 ml/min	Age, years
SGLT2is																			
Empareg	✓					✓	✓		✓	✓	✓	✓			✓	✓			>18
Declare	✓			✓		✓		✓		✓	✓	✓			✓				>40
Vertis-CV	✓			✓		✓	✓	✓		✓	✓	✓							>40
Canvas	✓			✓		✓		✓		✓	✓	✓					✓		>30
GLP-1 RAs																			
Leader	✓	✓	✓	✓	✓	✓	✓				✓	✓	✓	✓	✓	✓	✓	✓	>50
Exscel	✓			✓	✓		✓	✓	✓	✓	✓	✓			✓	✓			>18
Rewind	✓			✓		✓					✓	✓		✓			✓		>50
Sustain-6	✓		✓	✓	✓	✓	✓				✓	✓	✓	✓	✓	✓	✓	✓	>50
Amplitude	✓	✓				✓	✓		✓	✓	✓	✓			✓	✓			>18
Elixa											✓						✓		>30
Pioneer 6	✓		✓	✓	✓	✓	✓				✓	✓	✓	✓	✓	✓	✓	✓	>50
Harmony	✓			✓	✓	✓	✓		✓	✓	✓	✓							>40
Freedom	✓			✓	✓	✓	✓	✓	✓		✓								>40
Pioglitazone																			
Proactive	✓						✓				✓			✓		✓			35-75
Metformin																			
Spread-dimcad											✓				✓	✓			<80

Abbreviations: ABI, ankle-brachial index; AMI, acute myocardial infarction; BMI, body mass index; CABG, coronary artery bypass graft; CHF, chronic heart failure; eGFR, estimated glomerular filtration rate; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; NYHA, New York Heart Association; PTA, peripheral transluminal angioplasty; PTCA, percutaneous coronary angioplasty; SGLT2is, sodium-glucose cotransporter 2 inhibitors; TIA, transient ischaemic attack.

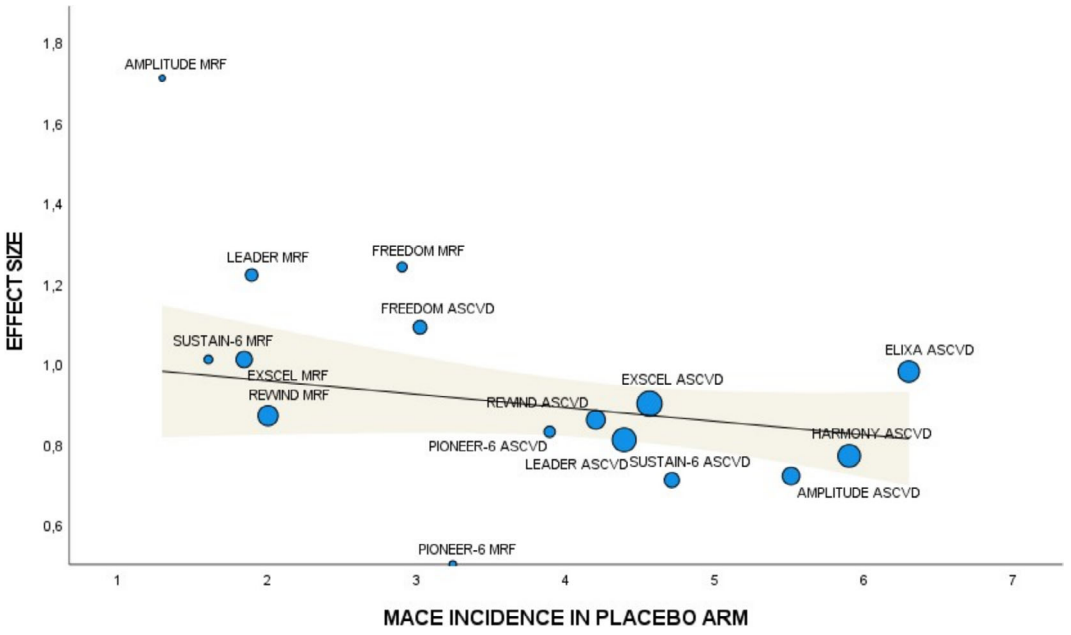

FIGURE 3 Meta regression for median effect size of glucagon-like peptide-1 receptor agonist on MACE and incidence of MACE in placebo group in randomized controlled trials performed on glucagon-like peptide-1 receptor agonist in people with MRF for cardiovascular disease or in people with established ASCVD. ASCVD, atherosclerotic cardiovascular diseaseMACE, major adverse cardiovascular events; MRF, multiple risk factors.

contraction affecting intravascular pressure, is very different from that of carotid and cerebral arteries. Furthermore, the incidence of myocardial ischaemia is moderated by myocardial oxygen consumption, which is much more variable than cerebral oxygen consumption.[33,34] Consequently, different agents could have differential effects on either coronary or cerebrovascular events, which are not discriminated in analyses on MACE, as defined above. In particular, pioglitazone could have greater beneficial effects on cerebrovascular events, with fewer benefits on ischaemic heart disease,[35] possibly for the increase of myocardial oxygen consumption determined by fluid retention and increase pre-load.[36] Conversely, SGLT2is seem to have greater effects on coronary, rather than cerebrovascular, events.[37]

4 | DEFINITION OF PRIMARY AND SECONDARY PREVENTION: AN OPEN ISSUE

The preferential or exclusive enrolment of patients with ASCVD in cardiovascular outcome trials in diabetes is justified for two reasons: first, as regulatory authorities require those trials for the assessment of safety, the enrolment of subjects with established CVD, who could be at higher risk of cardiovascular adverse events, appears logical. In addition, the selection of patients with ASCVD allows the identification of a population with a very high incidence of MACE, thus limiting the size of required samples.

However, the definition of ASCVD is significantly heterogeneous across cardiovascular safety trials in diabetes (Table 1). Although some events (e.g. myocardial infarction) are listed among criteria for defining ASCVD in all studies, others, such as peripheral artery disease or heart failure, are included in the definition of ASCVD only in some cases. This means that some patients, which were included in the secondary prevention groups in a trial, would have been included in the primary prevention cohort if they had been enrolled in a different trial. This is not surprising, as the ASCVD category in trial protocols was created as an operational tool aimed at identifying patients at very high cardiovascular risk, more than at describing an actual nosological entity.

Whatever the definition used in each trial, the category of ASCVD appears to be very heterogeneous. First, it usually includes both patients with ischaemic heart disease and cerebrovascular disease, which are biologically different.[32] In addition, this category usually includes both patients with and without endovascular revascularization procedures. In patients who underwent a percutaneous angioplasty, a relevant fraction of new cardiovascular events will be represented by re-stenosis, which is often primarily a fibroproliferative phenomenon,[38] different from primary atherosclerosis. It is conceivable that, in patients in secondary prevention, different agents could have a differential efficacy in preventing cardiovascular events with diverse pathogenesis.

Despite these limitations, the use of ASCVD among inclusion criteria was a very effective means of selecting patients at high risk. Based on the reported number of events, the projected 5-year cumulative incidence of MACE in placebo arms of trials with GLP-1 RA was 8.2% and 31.9% in primary and secondary prevention cohorts, whereas the corresponding figures for SGLT2i were 7.8% and 21.9%, respectively. Therefore, when exploring potential differences in efficacy of drugs in primary or secondary prevention of CVD, we are comparing the effects of treatment in populations with widely different cardiovascular risk.

TABLE 2 Inclusion criteria for enrolling subjects without ASCVD in randomized clinical trials assessing incidence of major cardiovascular events in people with type 2 diabetes mellitus

Study	TIA	Previous stroke	Previous haemorrhagic stroke	Carotid stenosis	Peripheral stenosis	Peripheral PTA/ bypass	ABI <90	CHF NYHA I-III	Stable angina (stress test)	≥2, ≥50% Coronary stenosis	≥1, ≥50% Coronary stenosis	Unstable angina	eGFR <60 ml/min	Hypertension + LV hypertrophy	Systolic/ Diastolic dysfunction	Elevated UACR	Triglycerides >200 mg/dl	HDL-C <39 mg/dl	LDL-C >130 mg/dl	DBP >90 mmHg	SBP >140 mmHg	BP treatment	Current daily smoker	Diabetes duration ≥10 years	BMI ≥35 kg/m^2	Waist to hip ratio >0.8	Coronary calcium score >400	Family history of ASCVD	Age at baseline, years	Number of risk factors
SGLT2is																														
Declare																				✓			✓						>55 M, >60 F	1
Canvas														✓		✓		✓			✓	✓	✓	✓					>50	2
GLP-1 RAs																														
Leader							✓							✓	✓	✓													>60	1
Exscel	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	>18	1
Rewind				✓	✓		✓		✓	✓	✓		✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓				>55	2
Sustain-6							✓							✓	✓	✓													>60	1
Amplitude																✓		✓	✓	✓			✓		✓				>50 M, >55 F	1
Pioneer 6							✓							✓	✓	✓		✓	✓										>60	1
Freedom										✓						✓				✓	✓	✓	✓	✓			✓	✓	60	1

Abbreviations: ABI, ankle-brachial index; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; BP, blood pressure; CHF, chronic heart failure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; F, female; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LV, left ventricle; M, male; NYHA, New York Heart Association; PTA, peripheral transluminal angioplasty; SBP, systolic blood pressure; SGLT2is, sodium-glucose cotransporter 2 inhibitors; TIA, transient ischaemic attack; UACR, urinary albumin-creatinine ratio.

The class of drugs with the larger number of available trials is that of GLP-1 RAs. For this category, we performed a metaregression, considering separately the primary and secondary prevention cohorts, and plotting the effect of treatment on the incidence of MACE (expressed as relative risk reduction) versus yearly incidence of events in the placebo arm, which is an index of baseline cardiovascular risk (Figure 3). There is no evidence of differences in the efficacy of GLP-1 RA on MACE associated with differences in baseline risk ($p = .77$). However, there is also no indication of differences between patients with or without ASCVD in relative risk reductions obtained with GLP-1 RA, independent of baseline cardiovascular risk.

5 | HIGH RISK MEANS HIGH BENEFIT: DEFINITION OF HIGH CARDIOVASCULAR RISK AS A GUIDE FOR THE SELECTION OF DRUGS WITH CARDIOVASCULAR BENEFITS

In summary, although there is no definitive demonstration of efficacy in reducing MACE in primary prevention for any class of drugs for diabetes, there is also no evidence that the effects of drugs on relative risk reduction are different between patients with or without ASCVD. In addition, the definition of ASCVD is widely heterogeneous across trials, indicating that the distinction between primary and secondary prevention could be an artificial tool to identify patients at very high risk, rather than the description of an actual biological dichotomy. Consequently, the position of Scientific Societies gathering in a single 'high-risk' category patients with ASCVD and those with additional risk factors[3,5,6] appears justified.

On the other hand, despite its heterogeneity, the ASCVD category is very effective in the discrimination of very high-risk subjects. Notably, patients without ASCVD included in cardiovascular trials with GLP-1 RA or SGLT2i were enrolled only when showing multiple risk factors, although with some differences across trials (Table 2). Inclusion criteria in primary prevention cohorts of those trials resemble the definition of high-risk patients suggested by the ADA/EASD Consensus,[5] while the ESC guideline provides a much wider definition, thus including a large number of patients at lower risk.[3] The reduction of absolute risk with any treatment depends on the relative risk reduction and on the absolute risk at baseline. Consequently, the use of a treatment with cardiovascular benefit in populations at lower risk produces a smaller absolute effect on the incidence of MACE. This can be easily highlighted by calculating the number needed to treat, i.e. the number of patients to be treated with a drug to prevent one major cardiovascular event. Here we perform such a calculation, applying the effect of GLP-1 RA and SGLT2i observed in clinical trials to the 5-year incidence of MACE, calculated based on the observed incidence of events in control groups of aforementioned randomized trials.

Assuming that the relative risk reduction with GLP-1 RA is the same (i.e. −15%) in patients with and without ASCVD, the 5-year number needed to treat in secondary prevention would be 21, whereas in primary prevention in patients with multiple risk

factors it would be 82. The corresponding figures for SGLT2i, considering the differences in baseline absolute risk in cohorts enrolled in available trials, and assuming a 9% relative risk reduction, would be 51 and 143 for secondary and primary prevention, respectively.

As the formulation of treatment guidelines requires an assessment of risk/benefit and cost/effectiveness ratios, which are based on absolute, rather than relative, risks, the distinction between patients with ASCVD and those without ASCVD and with MRF,[4] appears justified by available evidence. The choice of drugs recommended as first-line treatments in each one of those two categories may differ based on the available resources and on the relevance attributed to issues of equity in access.

6 | CONCLUSIONS

A methodologically rigorous assessment of available evidence leads to the conclusion that, at present, there is no clear demonstration of efficacy for the prevention of MACE in patients with diabetes and without established ASCVD with any class of glucose-lowering drugs. At the same time, available evidence suggests that, in people with diabetes, there is no major difference in relative risk reduction with GLP-1 RA and SGLT2i between patients with ASCVD and those without ASCVD and with MRF. On the other hand, baseline absolute risk in cohorts enrolled in clinical trials is much higher in the ASCVD than in the MRF subgroups; consequently, even in the case that relative risk reduction with drug treatment was independent of ASCVD, the expected effect of GLP-1 RA and SGLT2i on absolute risk would be considerably greater in patients with ASCVD. The distinction between primary and secondary prevention, although questionable, is a useful tool in the management of diabetes mellitus, to identify a very high-risk population, possibly deserving a specific therapeutic approach for cardiovascular risk reduction.

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EM and GAS were involved in the design, data collection, analysis and writing of the manuscript. The manuscript was drafted, revised and approved by both authors in accordance with ICJME standards for authorship. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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CONFLICT OF INTEREST STATEMENT

EM has received consultancy fees from Merck and Novartis speaking fees from Astra Zeneca, Bristol Myers Squibb, Boehringer-Ingelheim, Eli-Lilly, Merck, Novo Nordisk, Sanofi and Novartis and research grants from Merck, Novartis and Takeda outside the submitted work. GAS has received speaking fees from Astra Zeneca, Novonordisk and Eli Lilly outside the submitted work.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15226.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article.

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