Glycemic Control, Preexisting Cardiovascular Disease, and Risk of Major Cardiovascular Events in Patients with Type 2 Diabetes Mellitus: Systematic Review With Meta-Analysis of Cardiovascular Outcome Trials and Intensive Glucose Control Trials

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Background—The value of glycemic control and preexisting cardiovascular disease in determining the risk of major cardiovascular events (MACE) in type 2 diabetes mellitus is uncertain. Intensive glucose control trials suggest that the 9% lower risk of MACE associated with intensive glycemic control, as compared with conventional glycemic control, is only driven by patients with type 2 diabetes mellitus without cardiovascular disease at baseline.

Methods and Results—We did a meta-analysis of cardiovascular outcome trials dividing patients with or without preexisting cardiovascular disease; we found that the lower risk of MACE is confined to patients with cardiovascular disease at baseline. Compared with placebo, the use of both glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors was associated with a significant 14% lower MACE risk in patients with preexisting cardiovascular disease and with a nonsignificant 2% higher MACE risk in those without preexisting cardiovascular disease (*P* for interaction=0.021). The meta-regression analysis of all 12 trials demonstrated a significant (*P*=0.002) association between reductions of glycated hemoglobin in glycated hemoglobin A_{1C}. Accordingly, the reduction of MACE expected if all cardiovascular outcome trials had achieved a 0.9% glycated hemoglobin reduction would have been 33%. Routine clinical care data complement the results of cardiovascular outcome trials but with some differences: the lower risk of MACE with sodium-glucose cotransporter-2 inhibitor use is evident in patients with type 2 diabetes mellitus with or without preexisting cardiovascular disease.

Conclusions—Sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists should be included in the therapeutic plan of patients with type 2 diabetes mellitus and overt cardiovascular disease, with due attention paid to improvement of glycemic control, which may amplify their benefit on MACE. (***J Am Heart Assoc***. 2019;8:e012356. DOI: 10.1161/JAHA.119. 012356.)

Key Words: cardiovascular events • cardiovascular outcome trial • intensive glucose control • type 2 diabetes mellitus

T he prognosis of patients with type 2 diabetes mellitus (T2DM) has improved in the past 20 years, with a substantial decrease of mortality[1] and also of cardiovascular and renal complications.[2] This has occurred in both primary and secondary prevention settings, mainly because of improved management of cardiovascular risk factors. In a real-world population of 12 544 Danish patients with T2DM without angiographically documented coronary artery disease, for example, a high level of preventive therapy with statins and aspirin may remove the diabetes mellitus–associated increased risk of myocardial and cardiac death for at least a 7-year period.[3] In the TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) trial population of 13 616 patients with T2DM and established cardiovascular disease (CVD), statin and aspirin users, as compared to nonusers, had improved cardiovascular outcome (25% and 21% reduction of major cardiovascular events, respectively).[4]

As far as glycemic control of diabetes mellitus is concerned, it did not improve substantially in the past 10 years: the proportion of diabetic patients achieving a hemoglobin A_{1c} (A1C) target <7% is still around 50%.[5] The situation may be

Clinical Perspective

What Is New?

- Compared with placebo, the use of newer glucose-lowering agents, such as glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors, is associated with a significant 14% lower risk of major cardiovascular events (MACE) in patients with type 2 diabetes mellitus and preexisting cardiovascular disease, and with a nonsignificant 2% higher MACE risk in those without preexisting cardiovascular disease.

What Are the Clinical Implications?

- Sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists should be included in the therapeutic plan of patients with type 2 diabetes mellitus and overt cardiovascular disease, with due attention paid to improvement of glycemic control, which may amplify their benefit on MACE.

worse in the real world,[6] with only ≈40% of patients in the Health Maintenance Organization population or 30% of patients in the Medicaid population consistently achieving A1C levels <7% over the time period spanning 2007-2014.

Recently, a significant reduction in the incidence of cardiovascular events has been observed with some newer glucose-lowering drugs, suggesting the possibility of cardioprotective actions beyond glycemia for some molecules. We assessed the current evidence regarding the relationship among glycemic control, preexisting CVD, and major cardiovascular events (MACE), as revealed by both intensive glucose control trials (IGCTs) and cardiovascular outcome trials (CVOTs) in T2DM. We did a meta-analysis of CVOTs by dividing patients with or without preexisting CVD; we also assessed, with a meta-regression analysis of all 12 CVOTs, the relationship between reductions of A1C and risk of MACE.

Methods

We conducted this systematic review and meta-analysis based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[7] The PRISMA checklist is provided (Table S1). Neither ethics approval nor patient consent was required for this analysis. The authors are experienced in meta-analyses.[8,9]

Literature Search

Databases for our search included PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and ClinicalTrials.gov. (http://

www.clinicaltrials.gov). The last search was performed on January 15, 2019. The search terms used were "dipeptidyl-peptidase inhibitor," "saxagliptin," "alogliptin," "sitagliptin," "linagliptin," "glucagon-like peptide-1 receptor agonist," "exenatide," "lixisenatide," "liraglutide," "semaglutide," "dulaglutide," "albiglutide," "sodium-glucose cotransporter-2 inhibitor," "empagliflozin," "canagliflozin," "dapagliflozin," "cardiovascular outcome trials," "intensive glucose control trials," "cardiovascular outcome trials," and "major cardiovascular events."

Selection Criteria

We included CVOTs if they were randomized controlled trials performed in adults with T2DM, compared add-on therapy with any dipeptidyl peptidase-4 (DPP-4) inhibitor, glucagon-like peptide-1 (GLP-1) receptor agonists, or sodium-glucose cotransporter-2 (SGLT-2) inhibitor with placebo, and had MACE as the primary outcome. We excluded trials if they were completed before the FDA guidance of 2008.[10] We included IGCTs if they were randomized controlled trials designed to assess the impact of achieving lower versus higher levels of glycemia on MACE in adults with T2DM and had large size (at least 1000 person-years of follow-up in each treatment arm) and a minimum of 2 years median postrandomization follow-up. Two investigators (D.G., M.I.M.) used a standardized tool to independently abstract all data, and disagreements were resolved by consensus.

Statistical Analyses

Findings are given as both hazard ratios (HRs) with 95% CIs and HR reduction. We did de novo meta-analyses to assess the effect of both GLP-1 agonists and SGLT-2 inhibitors on MACE risk in T2DM patients with or without a history of CVD at baseline. Heterogeneity between studies was assessed by using the Q statistic and I^2, which is the proportion of total variance observed between the trials attributed to the differences between trials rather than to sampling error. $I^2 < 25\%$ was considered as low in heterogeneity, and a Q statistic P value of <0.10 was considered significant.[11] In a conservative way we calculated the summary estimates and 95% CIs for cardiovascular efficacy outcomes using a random-effects model meta-analysis. However, we used a fixed-effects model in the case that heterogeneity was not significant. Publication bias was assessed with the Egger test[12]; a P value of <0.10 was considered significant.

We also did a meta-regression analysis including all CVOTs in order to describe the relationship between the differences in achieved A1C at the end of CVOTs and the corresponding HR reduction for MACE. The meta-regression relates the treatment effect to study-level covariates while assuming additivity of within-study and between-studies components of

variance.[13] Restricted maximum-likelihood estimators were used to estimate model parameters. A permutation test (using 1000 reallocations) was used for assessing the true statistical significance of an observed meta-regression finding. In the meta-regression model, as recommended by Higgins and Thompson,[13] *P*-values were calculated by using a Monte Carlo permutation test. This test is implemented in the *meta-reg* function of Stata statistical software (Statacorp, College Station, TX) using the option *permute*. Permutation tests are well established as a means of calculating significance levels. A permutation test may be constructed in the same way as in standard linear regression, that is, by randomly shuffling the rows of the design matrix and reassigning them to the response vector. We used the meta-regression analysis to calculate the expected decrease of MACE risk at any A1C reduction.

The data that support the findings of this study are available from the corresponding author on reasonable request.

IGCTs and MACE

Intensive glycemic control (IGC) has an imperfect role in reducing the cardiovascular complications associated with T2DM. The CONTROL (Collaborators on Trials of Glucose Lowering) meta-analysis[14] included 4 large IGCTs (UKPDS (United Kingdom Prospective Diabetes Study), ACCORD (Action to Control Cardiovascular Risk in Diabetes), ADVANCE (Action in Diabetes and Vascular Disease), and VADT (Veterans Administration Diabetes Trial))[15-18] with 27 049 patients: IGC led to a mean 0.9% A1C reduction and was associated with a significant 9% reduction of MACE (Table 1), although the reduction was not significant in any single trial. Moreover, compared with less intensive glycemic control, IGC was associated with a clear risk of serious hypoglycemia (HR=2.48, 95% CI 1.91-3.21).[14] There is some evidence favoring a delayed cardiovascular benefit of early IGC, as suggested by the 10-year follow-up of UKPDS,[19] which enrolled newly diagnosed T2DM patients, most without preexisting CVD. On the other hand, the attainment of IGC in long-established and poorly controlled T2DM was associated with 22% excess cardiovascular mortality, prompting early termination of the intensive arm of the ACCORD trial.[16] This evidence has generated the concept of "residual vascular risk," the risk of macrovascular event that persists high to very high after IGC despite the attainment of prespecified and near-to-normal A1C targets.[20,21]

CVOTs and MACE

The leading IGCTs that have been the object of the CONTROL meta-analysis used glucose-lowering drugs that were on the market when they were planned. In particular, the use of sulfonylureas was as high as 90% in ADVANCE participants, the use of insulin 87% in VADT participants, and the use of thiazolidinediones 55% in ACCORD participants. In 2008 the US Food and Drug Administration issued a guidance to pharmaceutical companies requiring the proof of cardiovascular safety as a necessary condition for the approval of new glucose-lowering drugs.[7] The guidance has led to dedicated CVOTs with the aim of ruling out unacceptable MACE risk (maximum hazard of 1.30, upper 95% CI) of any licensed glucose-lowering medications.

Twelve CVOTs[22–33] have been completed and published to date, with the following classes of glucose-lowering medications: DPP-4 inhibitors saxagliptin, alogliptin, sitagliptin, and linagliptin; GLP-1 receptor agonists lixisenatide, liraglutide, semaglutide, once-weekly exenatide, and albiglutide; and SGLT-2 inhibitors empagliflozin, canagliflozin, and dapagliflozin (Table 2). The total number of T2D patients evaluated in the 12 CVOTs was 120 765. Table 1 shows the effects of the newer glucose-lowering medications on the mean A1C reduction at the end of treatment and the risk of MACE. The overall analysis of the 12 CVOTs showed a highly significant (*P*=0.001) 8% reduction of MACE risk associated with no publication bias (Egger test, *P*=0.210) and significant heterogeneity (I^2=45.8%, *P*=0.041), indicating the lack of homogeneity in the whole analysis that grouped 3 different classes of glucose-lowering drugs. Use of DPP-4 inhibitors in 4 CVOTs (SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction (TIMI) 53), EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care), TECOS, CARMELINA (Cardiovascular and Renal Microvascular Outcome Study With Linagliptin)) was associated with a negligible and not significant 1% reduction of MACE risk (HR=0.99, 95% CI 0.94-1.05), as compared with placebo; in contrast, the use of both SGLT-2 inhibitors (3 CVOTs: EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 diabetes Mellitus Patients), CANVAS (Canagliflozin Cardiovascular Assessment Study), DECLARE

Table 1. IGCTs, CVOTs, and Risk of MACE in Patients With T2DM

Trials	ΔA1C (%)	Hazard Ratio for MACE
IGCTs	−0.90 (−1.30 to −0.50)	0.91 (0.84 to 0.99)
N=27 049		
CVOTs	−0.42 (−0.53 to −0.30)	0.92 (0.87 to 0.96)
N=120 765		
CVOTs	−0.90	0.67 (0.49 to 0.93)
meta-regression		

CVOTs indicates cardiovascular outcome trials; ΔA1C, change in glycated hemoglobin; IGCTs, intensive glucose control trials; MACE, major cardiovascular events; T2DM, type 2 diabetes mellitus.

Table 2. Summary of CVOTs and IGCTs Evaluating the HR of MACE in T2DM patients with Pre-existing CVD

Trial/year of publication	Study drug/ Mean follow up (years)	Participants (n)	Participants with prior CVD	Type of prior CVD	HR fo MACE (whole population) and 95% CI	HR for MACE (prior CVD) and 95% CI
CVOTs						
DPP-4i						
SAVOR-TIMI 53	Saxagliptin	16 492	12,963	History of CVD	1.0	NR
2013	2.1 yr		78.6%	(CHD, CeVD, PVD)	0.91-1.10	
EXAMINE	Alogliptin	5380	5380	Acute coronary	0.96	0.96
2013	1.5 yr		100%	syndrome	0.79-1.16	0.79-1.16
TECOS	Sitagliptin	14,671	10,857	Established CVD	0.98	NR
2015			74%	(CHD, CeVD, PVD)	0.89-1.08	
CARMELINA	Linagliptin	6979	6979	History of CVD	1.02	1.02
2018	2.2 yr		100%	(CHD, CeVD, PVD)	0.89-1.17	0.89-1.17
GLP-1RAs						
ELIXA	Lixisenatide	6068	6068	Acute coronary	1.02	1.02
2015	2.1 yr		100%	syndrome	0.89-1.17	0.89-1.17
LEADER	Liraglutide	9340	7598	CVD or CKD or CV	0.83	1.20
2016	3.8 yr		81.3%	risk factors	0.74-0.93	0.86-1.67
SUSTAIN-6	Semaglutide	3297	2735	CVD or CKD or CV	0.74	0.72
2016	3.1 yr		83%	risk factors	0.58-0.95	0.55-0.93
EXSCEL	Exenatide OW	14,752	10 792	History of CVD	0.91	0.90
2017	3.2 yr		73.1%	(CHD, CeVD, PVD)	0.83-1.00	0.82-1.00
HARMONY	Albiglutide	9463	9463	History of CVD	0.78	0.78
2018	1.6 yr		100%	(CHD, CeVD, PVD)	0.68-0.90	0.68-0.90
SGLT-2i						
EMPA-REG	Empagliflozin	7020	7020	History of CVD	0.86	0.86
OUTCOME 2015	3.1 yr		100%	(CHD, CeVD, PVD)	0.74-0.99	0.74-0.99
CANVAS	Canagliflozin	10 142	6656	CVD or CV	0.86	0.82
2017	2.4 yr		72.2%	risk factors	0.76-0.98	0.72-0.95
DECLARE	Dapagliflozin	17,160	6974	Established CVD	0.93	0.90
2019	4.2 yr		40.6%		0.84-1.03	0.79-1.02
IGCTs						
UKPDS	Sulfonylurea	3867	116	Previous CVD	0.80	0.98
1998	or insulin (10 yr)		3%		0.62-1.04	0.64-1.51
ACCORD	Any (A1C <6%)	10 251	3609	Previous CV events	0.90	1.02
2008	3.5 yr		35%		0.78-1.04	0.85-1.21
ADVANCE	Gliclazide + any	11 140	3590	Previous CVD	0.94	0.99
2008	(A1C ≤6.5%) 5.0 yr		32%		0.84-1.06	0.85-1.15
VADT	Any (A1C <6%)	1791	723	Previous CVD	0.90	1.01
2009	5.6 yr		40%		0.70-1-16	0.87-1-18

CVOTs, cardiovascular outcome trials; IGCTs, intensive glucose control trials; HR, hazard ratio; TD2M, type 2 diabetes mellitus; MACE, major cardiovascular events; DPP-4i, dipeptidyl-peptidase 4 inhibitors; GLP-1RAs, glucagon-like peptide-1 receptor agonists; SGLT-2i, sodium-glucose co-transporter-2 inhibitors; CVD, cardiovascular disease; CDH, coronary heart disease; CKD, chronic kidney disease; CeVD, cerebrovascular disease; CV, cardiovascular; OW, once weekly exenatide; PVD, peripheral artery disease; NR, not reported

(Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58)) and GLP-1 agonists (5 CVOTs: ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome), LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes), EXSCEL (Exenatide Study of Cardiovascular Event Lowering), HARMONY (Albiglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Cardiovascular Disease) OUTCOME) was associated with 11% (*P*=0.005) and 12% (*P*=0.001) MACE risk reductions, respectively. The interaction between subgroups was significant (*P*=0.021), indicating the differences of the MACE risk reduction obtained with the 3 classes of drugs were not due to chance.

GLP-1 receptor agonists reduce glycemia in T2DM patients by augmenting insulin secretion and suppressing glucagon release via the stimulation of GLP-1 receptors; they also exert beneficial effects on an array of cardiovascular risk factors (decreased weight and appetite, reduced blood pressure, amelioration of the lipid profile, amelioration of endothelial dysfunction and inflammation) that may improve the poor cardiovascular outlook of the diabetic patient.[34] SGLT-2 inhibitors exert their glucose-lowering effects by promoting glycosuria, which also results in body-weight and fat-mass reductions; moreover, they increase natriuresis, thereby lowering extracellular volume and arterial blood pressure, as well as uricosuria, which may result in better cardiovascular and renal outcomes and rates of mortality.[35]

CVOTs, IGCTs, and Glycemic Control

All the CVOTs were designed to promote "glycemic equipoise" in order to reduce the influence of different glucose levels between treatment and placebo groups. Even then, some difference between treatment and placebo groups in A1C levels was observed at the end of CVOTs: compared with placebo, the range of A1C reduction in CVOTs was 0.27% to 0.86%. The mean weighted A1C reduction was the least with DPP-4 inhibitors (0.30%) and the highest with GLP-1 receptor agonists (0.47%), with intermediate values for SGLT-2 inhibitors (0.44%). Because of the principle of "glycemic equipoise," the weighted mean A1C reduction in all 12 CVOTs was more than halved (−0.42%) as compared with that obtained in IGCTs (−0.9%) (Table 1). In spite of this difference in the attained A1C levels at the end of respective treatments, the HR for MACE was almost identical in CVOTs (0.92) and IGCTs (0.91), as were their respective 95% CIs (0.84-0.99 and 0.87-0.96). Heterogeneity was moderate and significant in CVOTs (I^2=46%, *P*=0.041) and was null (I^2=0%) and nonsignificant (*P*=0.72) in IGCTs.

This evidence has led to the suggestion that newer glucose-lowering drugs may have additional beneficial effects on MACE that are not dependent on the amelioration of the glycemic control they produce. Table 1 also shows the extrapolation of MACE risk reduction if the A1C decrease in the CVOTs had equaled that obtained in IGCTs. This was obtained by fitting the desired A1C reduction (0.9%) in the meta-regression analysis. Figure 1 shows the results of the meta-regression analysis of all 12 trials demonstrating a significant (*P*=0.002) association between reductions of A1C and risk of MACE. Accordingly, the reduction of MACE expected if all CVOTs had achieved a 0.9% A1C reduction would have been 33% (expected β=0.67, 95% CI 0.49-0.93). SUSTAIN-6 was the only CVOT that succeeded in obtaining an A1C reduction (0.86%) closer to those obtained in IGTs; in fact, the reduction of MACE risk in SUSTAIN-6 was 26% less than that with placebo (HR 0.74, CI 0.58-0.95). This evidence suggests that (1) A1C reduction may also play a role in the mediation of benefit on MACE risk observed with the newer glucose-lowering drugs, in particular GLP-1 agonists and SGLT-2 inhibitors, and (2) at the same level of glycemic control, the use of these newer glucose-lowering drugs is associated with more benefit on MACE risk than the use of older ones.

The greater benefit on MACE risk might be due to the beneficial effects of the newer glucose-lowering drugs, the detrimental effects of the older glucose-lowering drugs, or both. However, the use of older drugs was fully permitted in the CVOTs just to compensate the different potencies of the added newer drug versus placebo. For example, the use of sulfonylureas in CVOT participants ranged from 31% in CARMELINA to 50% in LEADER, the use of insulin from 23% in TECOS to 60% in HARMONY, and the use of metformin from 54% in CARMELINA to 82% in both DECLARE and TECOS. So,
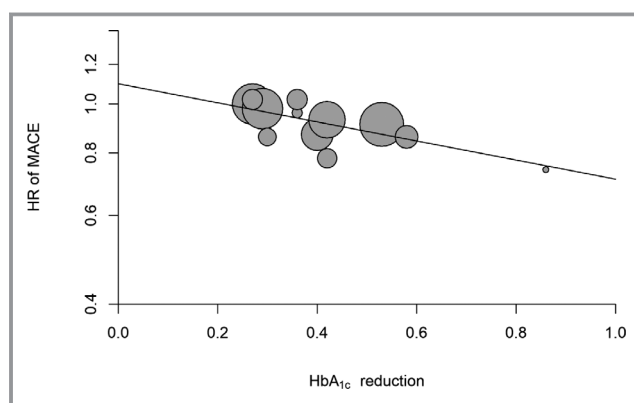
Figure 1. Meta-regression analysis between reduction of HbA_{1c} and MACE risk in the 12 CVOTs. CVOT indicates cardiovascular outcome trial; HbA_{1c}, glycated hemoglobin; HR, hazard ratio; MACE, major cardiovascular events.

in CVOTs, the newer glucose-lowering drugs were added to older glucose-lowering drugs, formerly assessed in IGCTs, without too much emphasis on the glycemic control as being the reason for "glycemic equipoise." In contrast to IGCTs, this may have reduced the occurrence of hypoglycemia, especially severe hypoglycemia, with a possible better cardiovascular outlook, as happened in the LEADER trial.[36] This post hoc analysis has demonstrated an association between the occurrence of severe hypoglycemia and an increased risk of cardiovascular events and mortality in the overall LEADER trial population (irrespective of randomized treatment). It seems that both GLP-1 agonists and SGLT-2 inhibitors may allow near normoglycemia to exert its full potential to improve MACE risk in patients with T2DM.

Diabetic Population

In CVOTs, many patients had established CVD, which ranged from 41% in DECLARE to 100% in EXAMINE, ELIXA, EMPA-REG OUTCOME, and HARMONY (Table 2). The main reason underlying the inclusion of participants with established CVD was to ensure sufficient events in the shortest possible time. This choice has limited generalizability of the results to other diabetic populations, prevented the assessment of primary prevention, as well as the identification of longer-term safety issues, and the identification of slowly evolving benefits; on the other hand, it has allowed a distinction of the T2DM population in high-risk patients (with established CVD) and lower-risk patients (without established CVD), where such distinction was possible.

Table 3. HR and 95% CI of MACE in Trials Divided According to Presence of CVD at Baseline

| Trials	HR	95% CI	I^2 (%)	*P* Value Q Test
IGCTs				
All	0.91	0.84 to 0.99	0.0	0.94
With CVD	1.00	0.91 to 1.10	0.0	0.47
SGLT-2i				
All	0.89	0.83 to 0.96	0.0	0.55
With CVD	0.86	0.79 to 0.95	0.0	0.423
Without CVD	1.00	0.87 to 1.16	0.0	0.900
GLP-1 RAs				
All	0.88	0.80 to 0.96	58.8	0.045
With CVD	0.86	0.80 to 0.92	31.7	0.231
Without CVD	1.06	0.87 to 1.29	0.0	0.660

CVD indicates cardiovascular disease; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; HR, hazard ratio; IGCTs, intensive glycemic control trials; MACE, major adverse cardiovascular events; SGLT-2i, sodium-glucose cotransporter-2 inhibitor.

Table 3 shows the effect of IGCTs and CVOTs on MACE risk divided according to the presence/absence of CVD at baseline. In IGCTs, 8038 participants had CVD at baseline, representing 30% of the whole diabetic population (27 049) in the trials: 3% in UKPDS, 40% in VADT, 35% in ACCORD, and 32% in ADVANCE (Table 2). In this subset of diabetic population the cardiovascular benefit of the IGC was completely absent (HR=1.00, 95% CI 0.91-1.10), indicating that the reduction of MACE risk observed in the whole population was driven by patients without cardiovascular disease at baseline.[37] Although these data diminish previous alerts about the cardiovascular safety of IGC in the subgroup of individuals with preexisting CVD, they also admit that IGC cannot reduce MACE risk in this population.

In CVOTs the situation is inverted: the lower risk of MACE is confined to patients with CVD at baseline. Figures 2 and 3 show the meta-analysis of the 5 CVOTs that reported the evaluation of MACE risk as a subanalysis of T2DM people divided according to the presence or absence of CVD at baseline, respectively. In the 3 CVOTs with GLP-1 receptor agonists (LEADER, SUSTAIN-6, EXSCEL), the percentage of patients with CVD at baseline was 77%; compared with placebo, treatment with GLP-1 agonists was associated with a 14% lower risk of MACE (*P*<0.001) in T2DM patients with preexisting CVD and with a nonsignificant 6% higher risk of MACE (*P*=0.563) in those without preexisting CVD. In the 2 CVOTs with SGLT-2 inhibitors (CANVAS, DECLARE), the percentage of patients with CVD at baseline was 66%; compared with placebo, treatment with SGLT-2 inhibitor was associated with a 14% lower risk of MACE (*P*=0.002) in T2DM patients with preexisting CVD and with a null effect (*P*=0.977) in those without preexisting CVD. Two important conclusions emerge from these data: the equal reduction of MACE risk (14%) with both GL-1 agonists and SGLT-2 inhibitors and the absence of any heterogeneity in both evaluations (I^2=0%), indicating a robust and reproducible effect with no variation among studies.

Translation Into Routine Clinical Care

Although randomized controlled trials are the gold standard in assessing the effectiveness of medications, the restricted environment of CVOTs limits generalizability. Observational data from large international studies including a broad population of T2DM patients seen in clinical practice are largely consistent with the results observed in CVOTs. In the CVD-REAL,[38] for example, patients with T2DM (13% with preexisting CVD) receiving SGLT-2 inhibitors had a 51% lower risk of all-cause mortality compared with a propensity-matched cohort of patients receiving other oral glucose-lowering drugs, but the effect on MACE risk was not
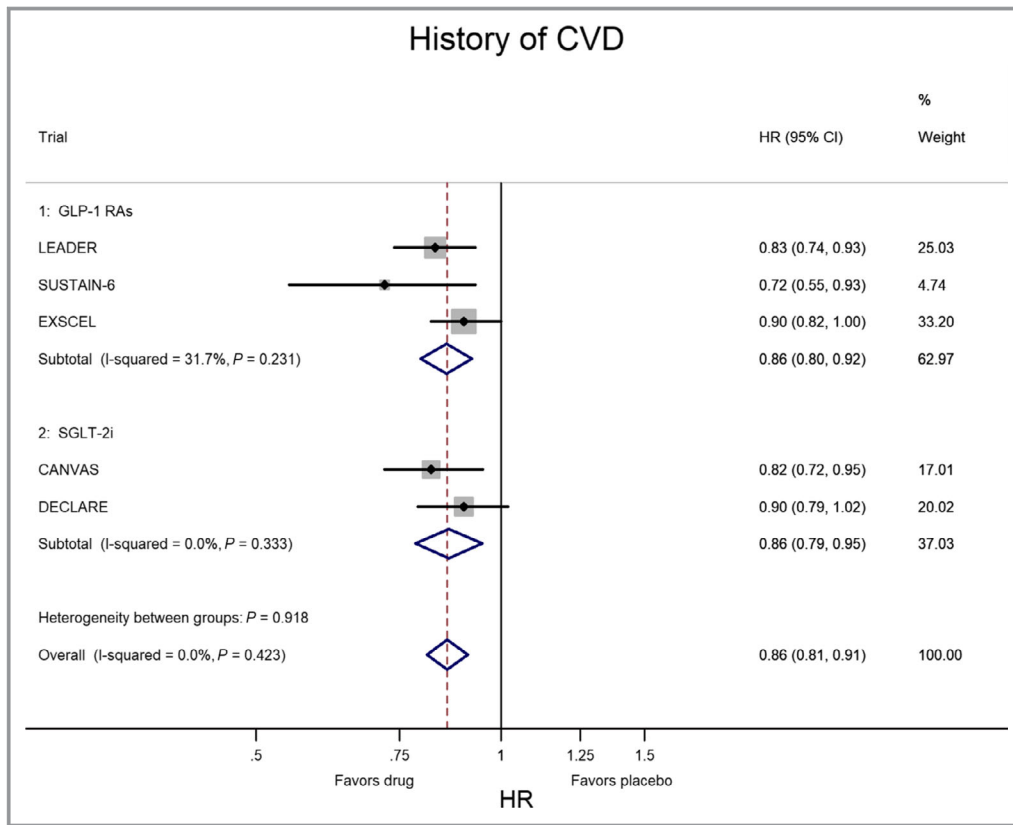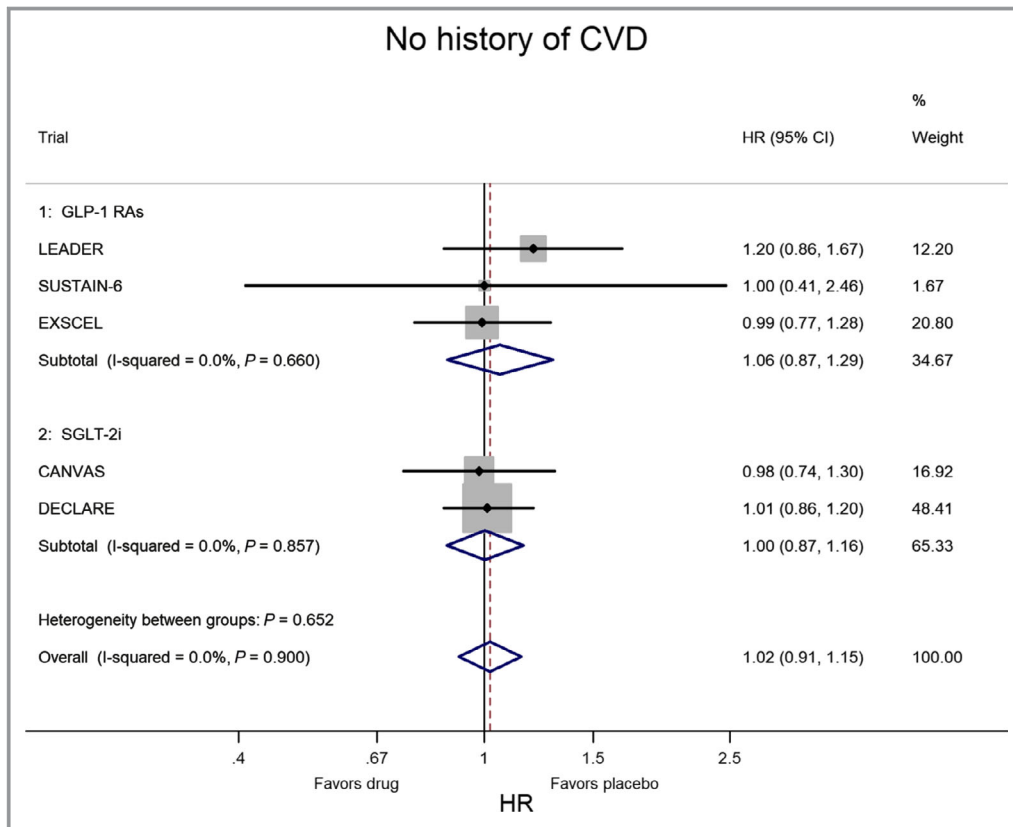
Figure 2. Meta-analysis of 5 CVOTs (3 with GLP-1 RAs and 2 with SGLT-2i) in patients with history of CVD at baseline. The results are highly homogeneous, as heterogeneity was almost nil and not significant. CVD indicates cardiovascular disease; CVOTs, cardiovascular outcome trials; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; HR, hazard ratio; SGLT-2i, sodium-glucose cotransporter 2 inhibitor.

reported. Among patients with T2DM and established CVD, compared with non-SGLT2 inhibitors, initiation of therapy with an SGLT-2 inhibitor was associated with a 33% lower risk of MACE.[39] The differences seen between CVOTs and routine clinical care data are the likely consequence of the overestimation of the effectiveness of these medications in the latter setting.

Two recent large-scale studies assessed the cardiovascular effects of liraglutide as compared with DPP-4 inhibitors[40] and SGLT-2 inhibitors as compared with sulfonylureas[41] in routine clinical practice. Both reported sensitivity analyses according to the presence/absence of CVD at baseline. Data from nationwide registers in Denmark and Sweden (2010-2016) indicate that 3-point MACE occurred significantly less frequently when liraglutide was used instead of a DPP-4 inhibitor (HR 0.90, 95% CI 0.83-0.98). The HRs were 0.81 (95% CI 0.71-0.92) for patients with a history of CVD (19%, n=4491) and 0.96 (0.86-1.06) for patients without such a history (81%, n=18 911), suggesting that patients with CVD might derive the largest absolute benefit from treatment with liraglutide.[40] In a retrospective cohort analysis, a total of 125 534 patients were included in the SGLT-2 inhibitor/

sulfonylurea cohort (n=62 767 per exposure group); use of SGLT-2 inhibitors was associated with a decreased risk of developing cardiovascular events as compared with use of sulfonylureas (HR, 0.50; 0.45-0.55), with no significant difference in effect when stratifying by baseline CVD presence (HR=0.51, 0.43-0.60) or absence (HR=0.56, 0.49-0.64).[41] These data confirm that liraglutide may produce the largest absolute cardiovascular benefit in patients with preexisting CVD; on the other hand, they add further emphasis to the disproportional increased cardiovascular benefit in clinical practice, as compared with CVOTs. Confirming previous observational data (CVD-REAL), most people taking SGLT-2 inhibitors in routine clinical care are those without CVD, and even in this population the drugs can lower MACE risk. According to 1 large-scale study with 803 836 patients,[42] the general T2DM population has less prevalent CVD (25% to 44%), and patients are slightly older than those included in the CVOTs. Although observational data have important limitations,[43] they are thought to be complementary to those from randomized controlled trials in supporting the beneficial cardiovascular effects of both GLP-1 receptor agonists and SGLT-2 inhibitors.[44]

Figure 3. Meta-analysis of the 5 CVOTs in patients without history of CVD at baseline. The results are highly homogeneous, as heterogeneity was almost nil and not significant. CVD indicates cardiovascular disease; CVOTs, cardiovascular outcome trials; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; HR, hazard ratio; SGLT-2i, sodium-glucose cotransporter 2 inhibitor.

Ideal Patient: T2DM With CVD

T2DM is a complex and heterogeneous disease, with CVD representing its main and often fatal complication. In high-risk patients with T2DM and CVD, the best possible glycemic control obtained with the older glucose-lowering medications (different combinations of metformin, sulfonylureas, thiazolidinediones, glinides, and insulin) is unlikely to improve their cardiovascular outlook, although it can improve kidney and eye vascular complications.[45] The newer glucose-lowering drugs, in particular SGLT-2 inhibitors and GLP-1 agonists, have demonstrated a consistent effect of reducing MACE risk in both CVOTs and in routine clinical care; therefore, they should be included in the therapeutic plan of these patients, for most in addition to the existing glucose-lowering therapy. In addition to their benefits on MACE risk, SGLT-2 inhibitors and, to a lesser extent, GLP-1 agonists display protective actions on the kidney that may be useful to delay diabetic nephropathy.[46] In patients with T2DM and kidney disease, for example, the risk of kidney failure and cardiovascular events was reduced by 30% with canagliflozin as compared to placebo at a median follow-up of 2.6 years.[47] Last, SGLT-2

inhibitors, but not GLP-1 receptor agonists, exert a robust and consistent reduction (≈30%) in the risk of heart failure regardless the presence of established atherosclerotic CVD.[21] Thus, there are many reasons for adding a newer glucose-lowering drug in people with T2DM and preexisting CVD: at present, this patient is the ideal, although not the exclusive one, in whom SGLT-2 inhibitors and GLP-1 agonists exert their best cardiorenal effects.

In patients with T2DM and no preexisting CVD, the best possible glycemic control can reduce MACE by 9%; this can be obtained with any combination of older glucose-lowering drugs. In consideration of the cardiorenal protective effect of SGLT-2 inhibitors on both nephropathy (reduced progression of kidney disease) and heart failure (demonstrated protection in primary prevention),[21] their use should also be taken into consideration by clinicians.

Areas of Uncertainty

The evidence for a MACE benefit of both SGLT-2 inhibitors and GLP-1 agonists in patients with well-controlled A1C (<7%) is limited, as the patients with both T2DM and preexisting

CVD in most CVOTs (LEADER, SUSTAIN-6, CANVAS) had a baseline A1C value ≥7%. It has been stated that the cardiovascular benefit of both GLP-1 agonists and SGLT-2 inhibitors appears to be unrelated to the direct glucose-lowering effects of these agents.[44] That statement does not take into account the evidence that part of their cardiovascular benefit, at least for MACE, is mediated by amelioration of glycemic control, as herein discussed. Moreover, acknowledging the contributive role for the blood glucose reduction in decreasing the risk of MACE during treatment with GLP-1 agonists and SGLT-2 inhibitors may overcome some residual reluctance of conservative specialists, who are still not ready to acknowledge that drugs might work in diabetes mellitus independently of blood glucose.

Conclusions

T2DM and CVD are so close to have merited the nickname of "deadly duo" (more than 1 million results in Google at the input "deadly duo for diabetes"). Because the prevalence of CVD in the T2DM population may range from 24% (real-world) to 100% (CVOTs),[42] at least one fourth of the average T2DM outpatients are possible candidates for the use of the newer glucose-lowering medications demonstrated to improve the MACE outcome. Liraglutide, semaglutide, and albiglutide for the GLP-1 agonist class and empagliflozin and canagliflozin for the SGLT-2 inhibitor class have been demonstrated to significantly reduce the risk of MACE in CVOTs, although this effect is limited to T2DM patients with preexisting CVD.

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Disclosures

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SUPPLEMENTAL MATERIAL

Table S1. PRISMA Check-list.

Section/topic	#	Checklist item	Reported on page #
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8,10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future	13,14

		research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14