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Review

Update on Cardiovascular Safety of Incretin-Based Therapy in Adults With Type 2 Diabetes Mellitus: A Meta-Analysis of Cardiovascular Outcome Trials

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Key Messages

- The cardiovascular (CV) safety of antidiabetes medications has been the focus in recent years.
- Glucagon-like peptide 1 receptor agonists (GLP-1RAs) reduced major adverse CV events, death resulting from CV effects and death from any cause.
- In this meta-analysis, GLP-1RAs resulted in a significant 13% reduction in stroke events.
- Dipeptidyl peptidase 4 (DPP-4) inhibitors are comparable to placebo in reducing CV outcomes, including heart failure.

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ABSTRACT

Objectives: The authors of 2 large randomized trials have recently published their findings related to the effects of a glucagon-like peptide 1 receptor agonist (GLP-1RA) (the HARMONY trial) and a dipeptidyl peptidase 4 (DPP-4) inhibitor (the CARMELINA trial) on cardiovascular (CV) outcomes in patients with type 2 diabetes mellitus. In light of these new data, we conducted a systematic review and meta-analysis of GLP-1RAs and DPP-4 inhibitors in CV outcome trials to assess their CV safety in patients with type 2 diabetes.

Methods: We conducted a comprehensive literature search in the Embase and MEDLINE databases to identify trials involving GLP-1RAs and DPP-4 inhibitors with major CV-related outcomes reported, including major adverse CV events, CV death, myocardial infarction, stroke, death from any cause and hospitalization because of heart failure. A total of 9 CV outcome trials were included. Odds ratios and 95% confidence intervals were calculated based on the Mantel-Haenszel method.

Results: Relative to placebo, GLP-1RAs were associated with a statistically significant reduction in the odds of major adverse CV events (13%), CV death (12%), death from any cause (11%) and stroke (13%). DPP-4 inhibitors were comparable to placebo for all outcomes. Moreover, DPP-4 inhibitors were associated with a nonsignificant 5% increase in the odds of hospitalization from heart failure compared to placebo.

Conclusions: This meta-analysis demonstrated that GLP-1RAs were associated with a significant reduction in major adverse CV events, CV death, stroke and death from any cause, while DPP-4 inhibitors were comparable to placebo for all CV outcomes, including hospitalizations for heart failure.

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RÉSUMÉ

Objectifs : Les auteurs de deux grands essais randomisés ont récemment publié leurs conclusions concernant les effets d'un agoniste du récepteur au glucagon-like peptide-1 (A-GLP-1R) (essai HARMONY) et d'un inhibiteur de la dipeptidyl peptidase 4 (DPP-4) (essai CARMELINA) sur les bénéfices cardiovasculaires (CV) chez les patients atteints de diabète sucré de type 2. À la lumière de ces nouvelles données, nous avons effectué une revue systématique et une méta-analyse des A-GLP-1R et des inhibiteurs de la DPP-4 dans des essais sur les répercussions CV afin d'évaluer leur innocuité CV chez les patients atteints de diabète de type 2.

Méthodes : Nous avons effectué une recherche documentaire exhaustive dans les bases de données Embase et MEDLINE afin d'identifier les essais portant sur les A-GLP-1R et les inhibiteurs de la DPP-4 dont les principaux effets liés au CV ont été rapportés, y compris les événements CV indésirables majeurs, les décès CV, les infarctus du myocarde, les AVC, les décès de toutes causes et les hospitalisations pour insuffisance cardiaque. Un total de 9 essais avec des conséquences CV ont été inclus. Les risques relatifs rapprochés et les intervalles de confiance à 95 % ont été calculés selon la méthode de Mantel-Haenszel.

Résultats : Par rapport au placebo, les A-GLP-1R ont été associés à une réduction statistiquement significative des risques d'événements CV indésirables majeurs (13 %), de décès d'origine CV (12 %), de décès toutes causes confondues (11 %) et d'AVC (13 %), tandis que les inhibiteurs de la DPP-4 étaient comparables au placebo pour tous les résultats. Par ailleurs, les inhibiteurs de la DPP-4 ont été associés à une augmentation non significative de 5 % des risques d'hospitalisation pour insuffisance cardiaque comparativement au placebo.

Conclusions : Cette méta-analyse a démontré que les A-GLP-1R étaient associés à une réduction significative des événements CV indésirables majeurs, de la mortalité CV, des accidents vasculaires cérébraux, des accidents vasculaires cérébraux et des décès de toute cause, tandis que les inhibiteurs de la DPP-4 étaient comparables au placebo pour tous les effets CV, notamment les hospitalisations pour insuffisance cardiaque.

Introduction

Incretin-based antidiabetes agents have been used for the management of type 2 diabetes for several years as a second- or third-line option after metformin. The dipeptidyl peptidase-4 (DPP-4) inhibitor class works by inactivating natural incretin hormones (glucose-dependent insulinotropic polypeptides), which increases the half-life of glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (1,2). On the other hand, the glucoregulatory properties of GLP-1 receptors are achieved through stimulation of GLP-1 receptors localized in the pancreas, where they stimulate insulin secretion and inhibit glucagon secretion in a glucose-dependent manner (1,3). As such, both DPP-4 inhibitors and GLP-1 receptor agonists (GLP-1RAs) operate by increasing insulin secretion and suppressing glucagon secretion (1).

Cardiovascular (CV) disease is a major complication associated with type 2 diabetes (4). Previous reports have estimated the prevalence of CV disease in people with type 2 diabetes at approximately 30% (5). Of those, 21.2% had coronary heart disease, 14.9% had heart failure, and CV disease was the cause of death in 50% of all deaths. The cost of treating CV disease was found to be up to 49% of the total cost of treating patients with type 2 diabetes, and the cost of treating CV events is much higher for those with type 2 diabetes than for patients without diabetes (6).

In recent years, there has been increased focus on the CV safety of antidiabetes medications. In 2008, the United States Food and Drug Administration directed drug companies to conduct CV outcome trials (CVOTs) to ensure that antidiabetes drugs are proven to be CV safe (7). To date, several CVOTs have been published, including 3 DPP-4 inhibitor trials, the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction (SAVOR-TIMI 53) trial (saxagliptin), the EXamination of cArdiovascular outcoMes with alogliptIN (EXAMINE trial) (alogliptin) and the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) (sitagliptin), all of which have shown CV safety, with adverse events occurring at rates comparable to those for placebo (8–10). However, an increase in the rate of hospitalizations because of heart failure (HF) associated with saxagliptin resulted in a Food and Drug Administration warning suggesting the discontinuation of saxagliptin in patients with HF (11). A secondary analysis of the EXAMINE trial data has also shown possible unfavourable results regarding death among HF patients, which resulted in a similar alert by the Food and Drug Administration for alogliptin (11,12).

CVOTs of GLP-1Ras, including the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) (lixisenatide) trial; the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) (liraglutide) trial; the Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6) (semaglutide) trial and the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) (exenatide) trial, have shown that among their respective study populations, these 4 medications were not associated with excess CV risk (13–16). Moreover, liraglutide and semaglutide have shown some CV benefits. Recently, the results of the Efficacy and safety of once-weekly glucagon-like peptide 1 receptor agonist albiglutide (HARMONY) (albiglutide) (17) and the CArdiovascular safety and Renal Microvascular outcomE with LINAgliptin in patients with type 2 diabetes at high vascular risk (CARMELINA) (linagliptin) trials were published (18), adding to the literature regarding the CV safety profiles of antidiabetes medications. Thus, we conducted a systematic review and meta-analysis of CVOTs involving DPP-4 inhibitors and GLP-1RAs to assess their CV safety in patients with type 2 diabetes. To our knowledge, this is the first meta-analysis that includes the results of the HARMONY (albiglutide) and CARMELINA (linagliptin) trials.

Table 1
Comparison of glucagon like peptide-1 receptor agonist and dipeptidyl peptidase IV inhibitor cardiovascular outcome trials

Study	Design	Medications	Sample size, N	Male sex, N (%)	Age, years, mean (SD)	Median follow up, years	Duration of diabetes, years, mean (SD)	A1C, %, mean (SD)	Existence of CVD at enrollment, N (%)
Glucagon-like peptide-1 receptor agonist									
ELIXA	Randomized, double-blind, placebo-controlled trial	Lixisenatide once daily vs placebo	6,068	4,207 (69)	59.9 (9.7)*	2.1	9.2 (8.2)*	7.7 (1.3)*	6068 (100)
LEADER	Randomized, double-blind, placebo-controlled trial	Liraglutide once daily vs placebo	9,340	6,003 (64)	64.2 (7.2)*	3.8	12.8 (8.0)*	8.7 (1.6)*	7598 (81)
SUSTAIN-6	Randomized, double-blind, placebo-controlled trial	Semaglutide once weekly vs placebo	3,297	2,002 (61)	64.6 (7.4)	2.1	13.9 (8.1)	8.7 (1.5)	2735 (83)
EXSCEL	Randomized, double-blind, placebo-controlled trial	Exenatide once weekly vs placebo	14,752	9,149 (62)	61.9 (9.4)	3.2	13.1 (8.3)	8.1 (1.0)	10 782 (73)
HARMONY	Randomized, double-blind, placebo-controlled trial	Albiglutide once weekly vs placebo	9,463	6,569 (69)	64.1 (8.7)	1.6	14.1 (8.6)*	8.7 (1.5)	6,678 (71)
Dipeptidyl peptidase IV inhibitor									
EXAMINE	Randomized, double-blind, placebo-controlled trial	Alogliptin once daily vs placebo	5,380	3,651 (68)	61 (median)	1.5	7.3* (median)	8.0 (1.1)*	5,366 (100)
TECOS	Randomized, double-blind, placebo-controlled trial	Sitagliptin once daily vs placebo	14,671	10,374 (71)	65.5 (8)	3	11.6 (8.1)	7.2 (0.5)	10,863 (74.)
SAVOR/TIMI 53	Randomized, double-blind, placebo-controlled trial	Saxagliptin once daily vs placebo	16,492	11,037 (70)	65.1 (8.6)*	2.1	10.3 (median)	8.0 (1.4)	12,959 (79)
CARMELINA	Randomized, double-blind, placebo-controlled trial	Linagliptin once daily vs placebo	6,980	4,390 (63)	65.8 (9.1)	2.2	14.7 (9.5)	7.9 (1.0)	6,258 (90)

A1C, glycated hemoglobin level; *CARMELINA,* cardiovascular safety and renal microvascular outcome study with linagliptin; *CVD,* cardiovascular disease; *ELIXA,* the evaluation of lixisenatide in acute coronary syndrome trial; *EXAMINE,* an examination of cardiovascular outcomes with alogliptin vs standard-of-care trial; *EXSCEL,* the exenatide study of cardiovascular event lowering; *HARMONY,* a long-term, randomized, double blind, placebo-controlled study to determine the effect of albiglutide, when added to standard blood-glucose-lowering therapies, on major cardiovascular events in patients with type 2 diabetes mellitus; *LEADER,* the liraglutide effect and action in diabetes evaluation of cardiovascular outcome results trial; *SAVOR-TIMI 53,* saxagliptin assessment of vascular outcomes recorded in patients with diabetes mellitus thrombolysis in myocardial infarction trial; *SD,* standard deviation; *SUSTAIN-6,* the preapproval trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes; *TECOS,* trial evaluating cardiovascular outcomes with sitagliptin.

* Data for the treatment arm.

Methods

This systematic review and meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (19).

Literature search

We conducted a comprehensive literature search in the Embase and MEDLINE databases from January to October 2018, with the most recent update conducted on October 15, 2018. Our search keywords were: glucagon like peptide-1 receptor agonist, GLP-1 agonist, liraglutide, lixisenatide, albiglutide, exenatide, semaglutide, dipeptidyl peptidase IV inhibitor, DPP-4 inhibitor, sitagliptin, saxagliptin, linagliptin, randomized controlled trials, diabetes mellitus and type 2 diabetes. We also checked the references of previously published reviews for additional citations.

Inclusion and exclusion criteria

We included double-blind, placebo-controlled, randomized trials that evaluated the effects of GLP-1RAs and/or DPP-4 inhibitors on CV outcomes in adults with type 2 diabetes. Studies were excluded if they were not published in English or if they reported CV outcomes as secondary endpoints only.

Data extraction and bias assessment

Two independent reviewers (OA, MA) completed the initial screening based on the titles and abstracts of all potentially relevant citations, followed by a review of the full texts, based on the inclusion and exclusion criteria described above (Supplementary Figure 1). Disagreement between the reviewers was resolved by consensus or consultation with a third reviewer (AA). Data from the included studies were retrieved and cross-checked for completeness and accuracy. Two reviewers evaluated the potential for bias in the included studies using the Cochrane collaboration tool for assessing risk of bias in randomized trials (Supplementary Table 1) (20).

Outcome measures

The primary outcome of this meta-analysis was major adverse CV events (MACE), defined as the composite endpoint of death from CV causes, nonfatal myocardial infarction (MI) and nonfatal stroke. Other outcomes of interest included death from any cause and hospitalization for heart failure (HF).

Data synthesis and analysis

The pooled odds ratio (OR) for each outcome was estimated for GLP-1RAs, DPP-4 inhibitors and both classes vs the control group, using the random-effects meta-analysis model. The estimated ORs and 95% confidence intervals (CIs) were calculated based on the Mantel-Haenszel method. The degree of heterogeneity between studies was estimated using I^2 statistics, where I^2 >50% represented significant heterogeneity.

Results

Search results

A total of 9 CVOTs were included in the analysis, as summarized in Table 1. GLP-1RA trials included a total of 42,920 patients, with the EXSCEL trial having the largest sample size (14,752 patients) and the SUSTAIN-6 trial having the smallest (3,297 patients). All included studies were randomized, double-blind, placebo-controlled trials. The median follow up was the longest in the LEADER trial (3.8 years) and the shortest in the HARMONY trial (1.5 years). The mean duration of diabetes at baseline was

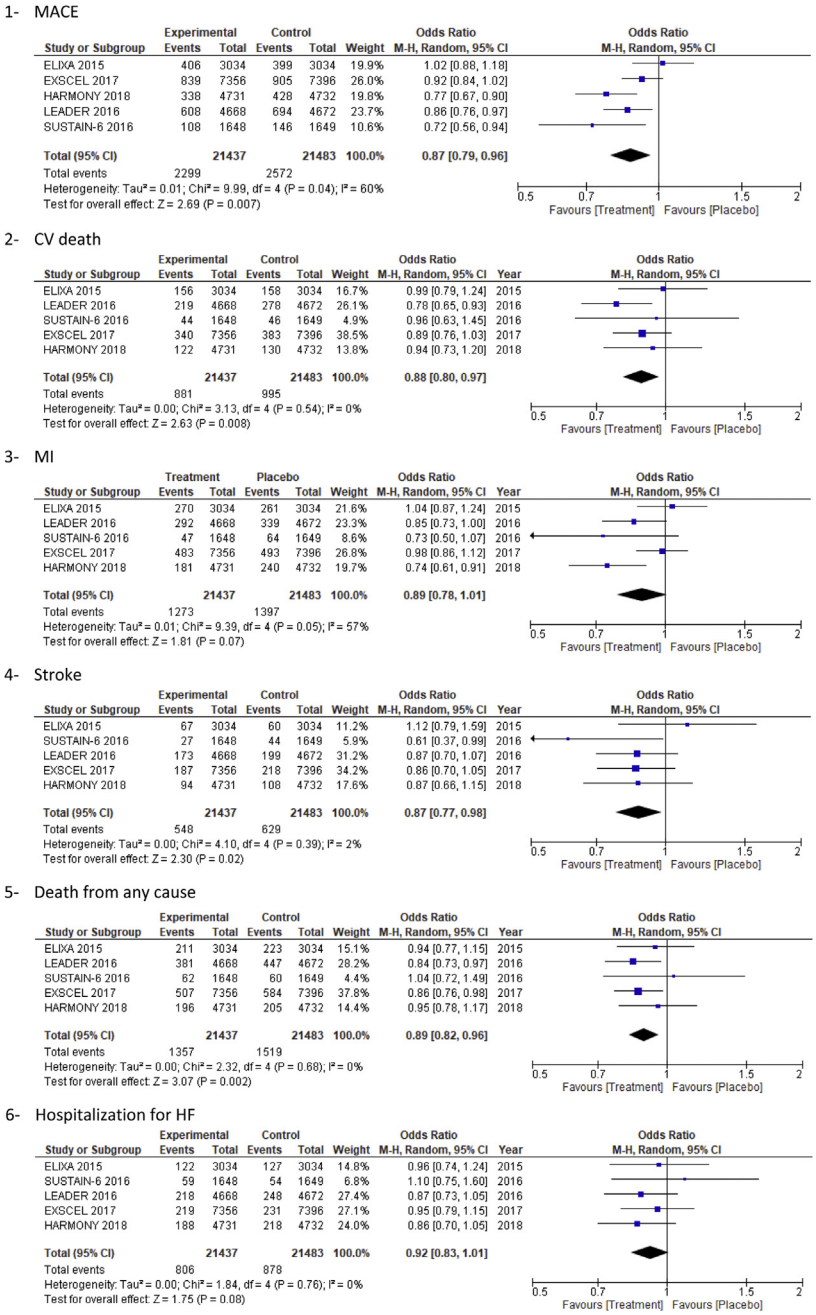

Figure 1. Meta-analysis results of GLP-1 receptor agonists cardiovascular outcome trials. *CV*, cardiovascular; *ELIXA*, the evaluation of lixisenatide in acute coronary syndrome trial; *EXSCEL*, the exenatide study of cardiovascular event lowering; *GLP-1*, glucagon-like peptide-1; *HARMONY*, a long-term, randomized, double blind, placebo-controlled study to determine the effect of albiglutide, when added to standard blood-glucose-lowering therapies, on major cardiovascular events in patients with type 2 diabetes mellitus; *HF*, heart failure; *LEADER*, the liraglutide effect and action in diabetes evaluation of cardiovascular outcome results trial; *MACE*, major adverse CV events; *MI*, myocardial infarction; *SUSTAIN-6*, the preapproval trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes.

shortest in the ELIXA and LEADER trials (9.3 years) and longest in the EXSCEL and HARMONY trials (approximately 14 years). There were differences in major inclusion criteria among the trials. However, all included patients had type 2 diabetes and established or potential risks for CV disease.

Of the DPP-4 inhibitor trials, SAVOR/TIMI 53 was the largest, followed by TECOS. The median follow up was longest in TECOS (3 years) and shortest in EXAMINE (1.5 years). The mean glycated hemoglobin (A1C) level was 8.0% except for the TECOS trial, for which it was 7.2%. All patients in the EXAMINE trial had had a recent acute coronary syndrome, and the CARMELINA trial was the only trial that included a large portion of patients with established kidney disease (74% of the study population).

Composite endpoint

GLP-1RAs were associated with a statistically significant 13% reduction in the odds of MACE compared to placebo (OR=0.87; 95% CI 0.79 to 0.96; I^2=60%; p=0.04) (Figure 1). Patients receiving DPP-4 inhibitors, on the other hand, experienced MACE at a level comparable to those taking the placebo (OR=0.99; 95% CI 0.93 to 1.06) (Figure 2).

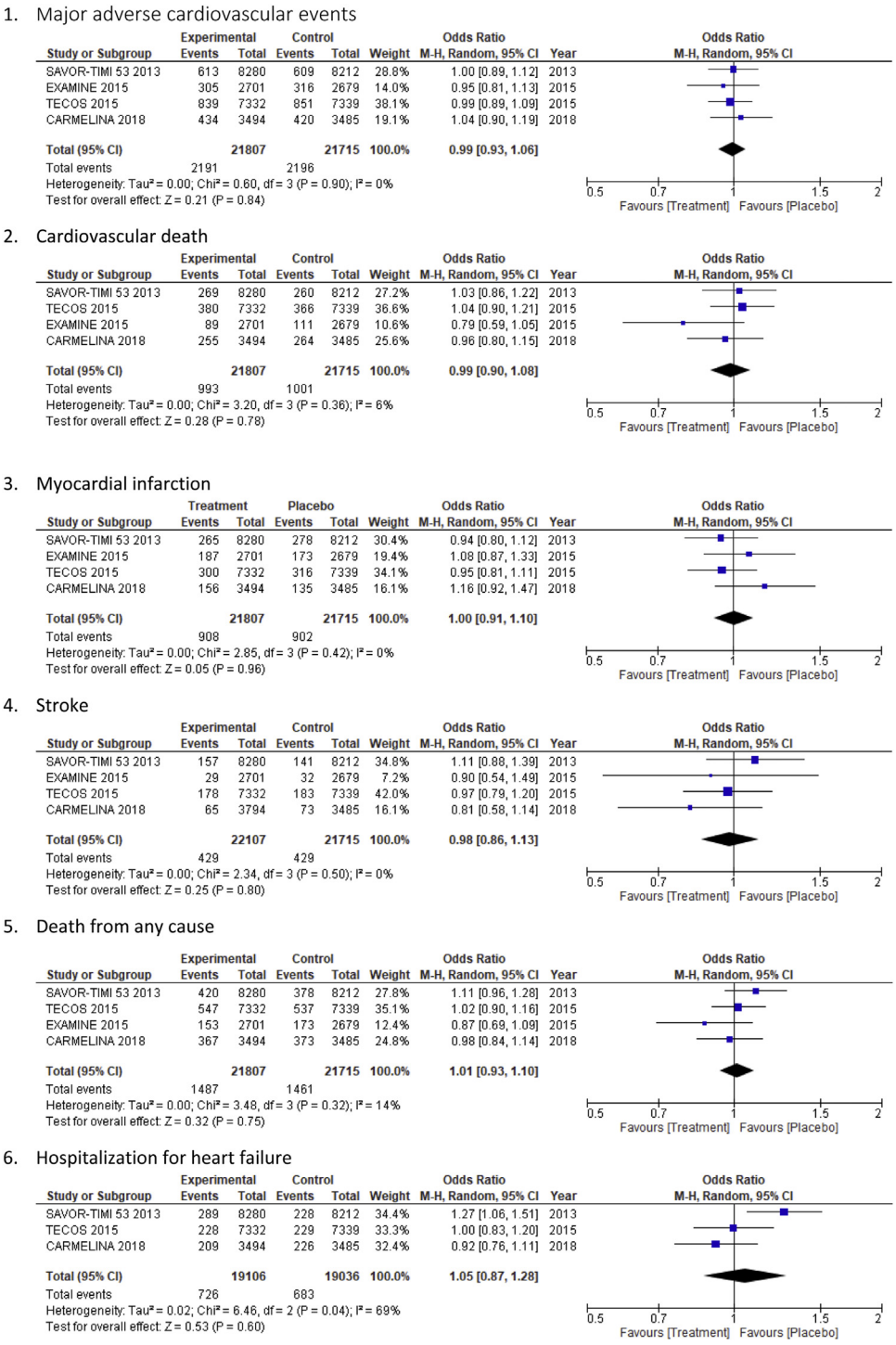

Figure 2. Metanalysis results of dipeptidyl peptidase-4 inhibitors cardiovascular outcome trials. *CARMELINA*, cardiovascular safety and renal microvascular outcome study with linagliptin; *EXAMINE*, an examination of cardiovascular outcomes with alogliptin vs standard-of-care trial; *SAVOR-TIMI 53*, saxagliptin assessment of vascular outcomes recorded in patients with diabetes mellitus thrombolysis in myocardial infarction trial; *TECOS*, trial evaluating cardiovascular outcomes with sitagliptin.

Death from CV causes

GLP-1RA use was associated with a significant 12% reduction in the odds of CV death relative to placebo (OR=0.88; 95% CI 0.8 to 0.97; I^2=0%; p=0.008) (Figure 1). DPP-4 inhibitors were not associated with a change in CV mortality compared to placebo (Figure 2).

Death from any cause

The results for death from any cause were similar to those observed for CV death. GLP-1RAs were associated with a significant reduction in the odds of death from any cause compared to placebo (OR=0.89, 95% CI 0.82 to 0.96; I^2=0%; p=0.002). DPP-4 inhibitors did not show a significant reduction in deaths when compared to placebo.

Myocardial infarction

As shown in Figure 1, GLP-1RAs and DPP-4 inhibitors were comparable to placebo in reducing myocardial infarction (MI) events. GLP-1RAs resulted in an 11% reduction in the odds of MI events. However, this reduction was not statistically significant (OR=0.89; 95% CI 0.78 to 1.01; I^2=57%; p=0.07).

Stroke

A significant reduction in the odds of stroke was seen with GLP-1RAs compared to placebo (Figure 1). The magnitude of the reduction was 13% (OR=0.87; 95% CI 0.77 to 0.98; I^2=2%; p=0.02). DPP-4 inhibitors were not associated with a significant reduction in stroke events (Figure 2).

Hospitalization for heart failure

GLP-1RAs were associated with an 8% reduction in the odds of hospitalization because of HF relative to placebo. However, this reduction was not statistically significant (OR=0.92; 95% CI 0.83 to 1.01; I^2=0%; p=0.08). DPP-4 inhibitors resulted in a 5% increase in the odds of hospitalization resulting from HF compared to placebo, although this finding was also not statistically significant (OR=1.05; 95% CI 0.87 to 1.28; I^2=69%; p=0.6).

Discussion

Macrovascular complications are a major cause of death in patients with type 2 diabetes (4). The risk for CV events is known to be significantly higher in patients with diabetes, and it is crucial for glucose-lowering therapy to decrease, or at least not increase, CV risk. Several CVOTs involving DPP-4 inhibitors and GLP-1RAs have been published in the past few years, including the recently published HARMONY and CARMELINA trials. Thus, in this systematic review and meta-analysis, we provide an update on the CV safety of GLP-1RAs and DPP-4 inhibitors in the context of type 2 diabetes.

The results of GLP-1RA CVOTs have been inconsistent. Lixisenatide (a short-acting GLP-1RA) was studied in the ELIXA trial and found to be noninferior to placebo in reducing MACE, CV deaths and all-cause mortality. However, it is important to note that all patients enrolled in this trial had had recent coronary artery disease (13). Liraglutide was assessed in the LEADER trial. Compared to placebo, liraglutide showed significant reductions in MACE (13%), CV death (22%), death from any cause (15%) and MI (14%). This trial was the longest in terms of follow-up time (median 3.8 years) and included patients with type 2 diabetes, established CV disease or CV risk factors (14). Semaglutide (a once-weekly formulation) in the SUSTAIN-6 trial was noninferior to placebo. Significant reductions in the primary endpoint (hazard ratio [HR]= 0.74; 95% CI 0.58 to 0.95) and nonfatal stroke (HR=0.61; 95% CI 0.38 to 0.99) were also observed (15).

The EXSCEL trial allowed the addition of once-weekly exenatide to the standard of care. In that trial, exenatide for MACE was noninferior to placebo (HR=0.91; 95% CI 0.83 to 1.00) (16). The HARMONY trial demonstrated that the addition of once-weekly albiglutide was associated with a significant 22% reduction in MACE and a 25% reduction in MI compared to placebo. However, there was no significant reduction in the overall mortality rate. This trial was the shortest, at 1.5 years of median follow-up time, with 1.6 years' median exposure to the intervention (17).

GLP-1RAs have previously shown inconsistent associations with CV outcomes, and the CV benefit observed in this meta-analysis was seen only with some GLP-1RAs. This might be attributed to the differences in study design and population studied in the various trials. For example, the inclusion of patients with recent coronary artery disease, as in the case of the ELIXA trial, results in a population at higher risk for CV disease, and this may have masked the true benefit of the GLP-1RAs (13). It is also possible that differences in the mean duration of the studies may have played a role as well. The LEADER trial was the longest in terms of exposure to the intervention, which may have improved the likelihood of observing a significant difference between the treatment and placebo groups (14). The HARMONY trial, on the other hand, showed a significant reduction in MACE at a much shorter follow up and duration of exposure (1.5 years). However, unlike liraglutide, albiglutide was not associated with a significant reduction in CV death or death from any cause (17). Whether such an effect would appear with a longer exposure to the medication remains unknown.

In addition to differences among GLP-1RA CVOTs, there are also differences among the medications in terms of structure and duration. Lixisenatide and exenatide are both exendin-4-based GLP-1RAs. However, lixisenatide is a short-acting GLP-1RA administered once daily, whereas the exenatide formulation used in the EXSCEL trial was a once-weekly formulation. The exendin-4-based GLP-1RAs are more prone to inducing an immune responses in which antibodies could reduce their effects (1,2). Liraglutide, semaglutide and albiglutide are structurally similar to human GLP-1. However, liraglutide is administered once daily, whereas the rest were once-weekly formulations.

GLP-1 RAs also differ in terms of reducing A1C levels and body weights. In a head-to-head efficacy trial, liraglutide was associated with greater decreases in both A1C levels and body weights compared to albiglutide (21). In the CVOTs, albiglutide was associated with smaller reductions in body weight compared to both liraglutide and semaglutide. Regardless of its modest effect on body weight and A1C level, in the HARMONY trial, albiglutide was associated with a significant reduction in MACE with a shorter medication-exposure time (1.6 years) (17). Such a significant reduction in MACE is unlikely to be due to glycemic control, so this finding is suggestive of a nonglycemic mechanism for reducing CV events. It is possible that such differences might have contributed to the different CV benefits observed in the GLP-1RA trials. Until the advent of head-to-head trials, it had been very challenging to draw conclusions about whether any observed CV benefit could be attributed to the entire class rather than to individual medications.

A meta-analysis of GLP-1RA CVOTs by Bethel et al showed a significant 10% reduction in MACE with no heterogeneity (HR=0.87; 95% CI 0.79 to 0.96; I^2=0%; p=0.43) (22). Similar results were reported by Zhang et al (23), GLP-1RAs were also associated with significant reductions in CV death and all-cause mortality relative to placebo (22,23). The magnitude of the effect was a 13% reduction in CV mortality and a 12% reduction in all-cause mortality, with no observed heterogeneity. Moreover, GLP-1RAs were comparable to placebo with respect to rates of MI, stroke and hospitalizations for HF in previous meta-analyses (22,23).

To our knowledge, this is the first meta-analysis to include the results of the HARMONY trial. Our analysis is consistent with previous meta-analyses concerning a reduction in MACE, CV death and all-cause mortality. However, unlike previous meta-analyses, stroke events were reduced significantly by 13% (OR=0.87, 95% CI 0.77 to 0.98), with no observed between-trial heterogeneity. Moreover, no significant difference in MI or hospitalizations resulting from HF was seen in this meta-analysis.

DPP-4 inhibitor CVOT results were more consistent than the trials involving GLP-1RAs. The rates of MACE, CV death, MI, stroke and all-cause mortality with DPP-4 inhibitors were comparable to those with placebo (8–10). However, this was not the case with HF hospitalization events. Several previous meta-analyses have examined the association of DPP-4 inhibitors with risk for HF or HF hospitalization. These results were inconsistent, with only some suggesting a trend toward increased hospitalizations because of HF

(24–29). In the current meta-analysis of CVOTs, we found no increase in hospitalizations because of HF associated with DPP-4 inhibitors vs placebo (OR=1.05; 95% CI 0.87 to 1.28). However, there was significant heterogeneity associated with this finding (I^2=69%; p=0.04).

The results of the HARMONY (albiglutide) and CARMELINA (linagliptin) trials will contribute additional evidence to the CV-safety profile of incretin based therapy and may help to solidify their roles in the treatment of type 2 diabetes. This is particularly relevant now, as the American Diabetes Association recently updated its treatment algorithm to include patients with established CV disease (4,30). As such, the new data provided by these trials will be useful for assessing CV risk in individual patients, potentially providing the option to select diabetes treatments that are proven to reduce CV risk or overall mortality.

The CARMELINA trial demonstrated that linagliptin has a CV safety profile comparable to that of placebo in patients with type 2 diabetes and in those with chronic kidney disease (74% of the study population) (18). Such a result is significant because the existence of chronic kidney disease increases the risk for developing CV disease in patients with type 2 diabetes (31). Moreover, linagliptin was comparable to placebo in terms of long-term kidney safety. This is an understudied population, and this result might have an impact on future recommendations for patients with type 2 diabetes and chronic kidney disease (18).

An important limitation of our study was the heterogeneity of CVOTs in terms of design and inclusion criteria, which cannot be controlled by meta-analysis. In addition, data on stroke were reported only as nonfatal stroke in the SUSTAIN-6, SAVOR-TIMI 53, CARMELINA and EXAMINE trials. In addition, data on MI were reported as nonfatal MI in the SUSTAIN-6, CARMELINA and EXAMINE trials.

Conclusions

In conclusion, this meta-analysis showed that GLP-1RAs were associated with a significant reduction in MACE, CV death and all-cause mortality. The addition of the HARMONY trial data to this meta-analysis revealed a significant reduction in stroke events associated with GLP-1RAs compared to placebo. DPP-4 inhibitors were comparable to placebo in all CV outcomes, including hospitalizations for HF.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Diabetes* at https://www.canadianjournalofdiabetes.com.

Author Disclosures

Conflicts of interest: None.

Author Contributions

OA: Contributed to the conception, design, acquisition and interpretation. ARA: Contributed to the design, analysis and interpretation. AA and MSAY: Contributed to the acquisition and interpretation. All authors drafted sections of the manuscript, critically revised the manuscript and gave final approval.

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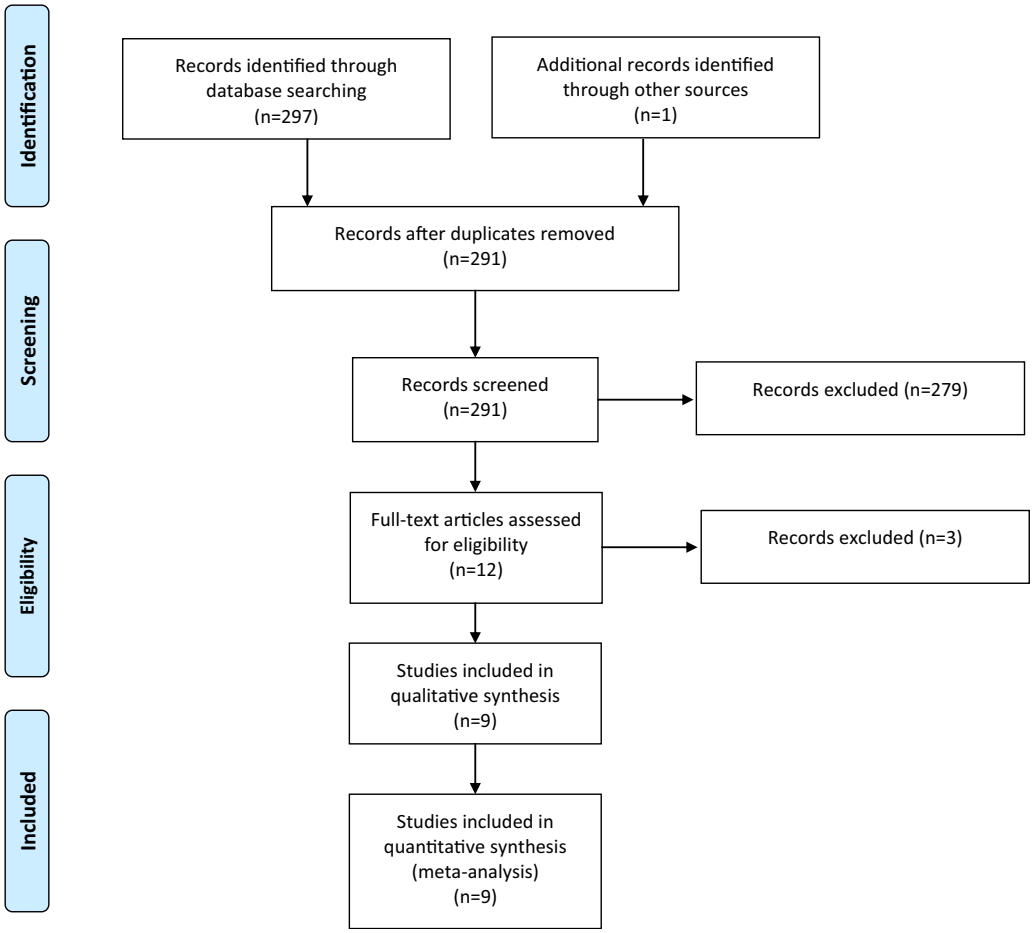

Supplementary Figure 1. Trial identification and inclusion.

Supplementary Table 1
Risk of bias assessment of cardiovascular outcome trials included in the study

Study	Publication year	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
		Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
ELIXA	2015	Low	Low	Low	Low	Low	Low	Unclear
LEADER	2016	Low	Low	Low	Low	Low	Low	Unclear
SUSTAIN-6	2016	Low	Low	Low	Low	Low	Low	Unclear
EXSCEL	2017	Low	Low	Low	Low	Low	Low	Unclear
HARMONY	2018	Low	Low	Low	Low	Low	Low	Unclear
SAVOR-TIMI 53	2013	Low	Low	Low	Low	Low	Low	Unclear
EXAMINE	2015	Low	Low	Low	Low	Low	Low	Unclear
TECOS	2015	Low	Low	Low	Low	Low	Low	Unclear
CARMELINA	2018	Low	Low	Low	Low	Low	Low	Unclear

CARMELINA, cardiovascular safety and renal microvascular outcome study with linagliptin; *ELIXA*, the evaluation of lixisenatide in acute coronary syndrome trial; *EXAMINE,* examination of cardiovascular outcomes with alogliptin versus standard of care trial; *EXSCEL*, the exenatide study of cardiovascular event lowering; *HARMONY*, A long-term, randomized, double blind, placebo-controlled study to determine the effect of albiglutide, when added to standard blood glucose lowering therapies, on major cardiovascular events in patients with type 2 diabetes mellitus; *LEADER*, the liraglutide effect and action in diabetes evaluation of cardiovascular outcome results trial; *SAVOR-TIMI 53*, saxagliptin assessment of vascular outcomes recorded in patients with diabetes mellitus–thrombolysis in myocardial infarction trial; *SUSTAIN-6*, the preapproval trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes; *TECOS*, trial evaluating cardiovascular outcomes with sitagliptin.
Note: Each domain of risk was assigned "Low" for low risk, "Unclear" for unclear risk and "High" for high risk.