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ORIGINAL RESEARCH ARTICLE

Comparison of the Effects of Glucagon-Like Peptide Receptor Agonists and Sodium-Glucose Cotransporter 2 Inhibitors for Prevention of Major Adverse Cardiovascular and Renal Outcomes in Type 2 Diabetes Mellitus

Systematic Review and Meta-Analysis of Cardiovascular Outcomes Trials

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BACKGROUND: Glucagon-like peptide 1 receptor agonists (GLP1-RA) and sodium-glucose cotransporter-2 inhibitors (SGLT2i) have emerged as 2 new classes of antihyperglycemic agents that also reduce cardiovascular risk. The relative benefits in patients with and without established atherosclerotic cardiovascular disease for different outcomes with these classes of drugs remain undefined.

METHODS: We performed a systematic review and trial-level meta-analysis of GLP1-RA and SGLT2i cardiovascular outcomes trials using the PubMed and EMBASE databases (Excerpta Medica Database). The primary outcomes were the composite of myocardial infarction, stroke, and cardiovascular death (MACE); hospitalization for heart failure; and progression of kidney disease.

RESULTS: In total, data from 8 trials and 77 242 patients, 42 920 (55.6%) in GLP1-RA trials, and 34 322 (44.4%) in SGLT2i trials, were included. Both drug classes reduced MACE in a similar magnitude with GLP1-RA reducing the risk by 12% (hazard ratio [HR], 0.88; 95% CI, 0.84–0.94; $P<0.001$) and SGLT2i by 11% (HR, 0.89; 95% CI, 0.83–0.96; $P=0.001$). For both drug classes, this treatment effect was restricted to a 14% reduction in those with established atherosclerotic cardiovascular disease (HR, 0.86; 95% CI, 0.80–0.93; $P=0.002$), whereas no effect was seen in patients without established atherosclerotic cardiovascular disease (HR, 1.01; 95% CI, 0.87–1.19; $P=0.81$; P interaction, 0.028). SGLT2i reduced hospitalization for heart failure by 31% (HR, 0.69; 95% CI, 0.61–0.79; $P<0.001$), whereas GLP1-RA did not have a significant effect (HR, 0.93; 95% CI, 0.83–1.04; $P=0.20$). Both GLP1-RA (HR, 0.82; 95% CI, 0.75–0.89; $P<0.001$) and SGLT2i (HR, 0.62; 95% CI, 0.58–0.67; $P<0.001$) reduced the risk of progression of kidney disease including macroalbuminuria, but only SGLT2i reduced the risk of worsening estimated glomerular filtration rate, end-stage kidney disease, or renal death (HR, 0.55; 95% CI, 0.48–0.64; $P<0.001$).

CONCLUSIONS: In trials reported to date, GLP1-RA and SGLT2i reduce atherosclerotic MACE to a similar degree in patients with established atherosclerotic cardiovascular disease, whereas SGLT2i have a more marked effect on preventing hospitalization for heart failure and progression of kidney disease. Their distinct clinical benefit profiles should be considered in the decision-making process when treating patients with type 2 diabetes mellitus.

Key Words: glucagon-like peptide 1 receptor agonists ■ meta-analysis ■ sodium-glucose cotransporter-2 inhibitors ■ diabetes mellitus, type 2

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Clinical Perspective

What Is New?

- Sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide 1 receptor agonists (GLP1-RA) reduce atherosclerotic myocardial infarction, stroke, and cardiovascular death (MACE) to a similar degree in patients with established atherosclerotic cardiovascular but have no appreciable effect on MACE over the time frame studied in patients without established disease.
- SGLT2i but not GLP1-RA reduce the risk of heart failure.
- In terms of renal outcomes, GLP1-RA primarily reduce the risk of macroalbuminuria, whereas SGLT2i reduce the risk of worsening estimated glomerular filtration rate.

What Are the Clinical Implications?

- GLP1-RA and SGLT2i reduce atherosclerotic MACE in patients with established atherosclerotic cardiovascular disease, whereas SGLT2i also have effects on preventing hospitalization for heart failure and reduction in estimated glomerular filtration rate in a broad spectrum of patients.
- These considerations should be included in the decision-making process when treating patients with type 2 diabetes mellitus.

Recent large-scale cardiovascular outcomes trials that have been mandated by regulatory authorities[1,2] to prove cardiovascular safety for the approval of new antihyperglycemic agents in patients with type 2 diabetes mellitus have contributed to a better understanding of the disease over the last decade. Their large sample sizes and robust results have dramatically changed the landscape of clinical trials in the field of diabetes mellitus and caused a shift in therapeutic focus from reducing glycohemoglobin (HbA1c) to prevent microvascular complications to also reducing risk of cardiovascular outcomes. To date, only members of 2 drug classes, glucagon-like peptide 1 receptor agonists (GLP1-RA)[3–5] and sodium-glucose cotransporter-2 inhibitors (SGLT2i),[6,7] have been shown to reduce significantly the risk of major cardiovascular events, such as the composite of myocardial infarction, stroke, and cardiovascular death (MACE). For that reason, recent guidelines focus on initiation of these 2 classes of medications.[8,9] A recent meta-analysis from our group showed that the favorable effects of SGLT2i on reducing atherosclerotic cardiovascular events are confined to patients with established atherosclerotic cardiovascular disease (ASCVD), but their salutary effects preventing hospitalization for heart failure (HHF) and the progression of kidney disease were seen in all patients.[10] A recent meta-analysis of GLP1-RA cardiovascular outcomes trials, which did not include the HARMONY Outcomes trial (Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus), showed a 10% reduction in MACE,[11] but differences in the treatment effect of GLP1-RA on MACE between patients with and without ASCVD have not been confirmed, because primary prevention patients represent only a relatively small proportion of the patient population in each of the trials, yielding much fewer events and thereby resulting in underpowered analyses. As such, the present meta-analysis of cardiovascular outcomes trials was designed to compare and contrast the clinical benefit of GLP1-RA and SGLT2i in patients with and without established ASCVD.

METHODS

The authors declare that all supporting data are available within the article and its online-only Data Supplement.

Data Search and Study Selection

The present meta-analysis was performed using the methods proposed in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (PRISMA-P).[12–14] A data search of all randomized, placebo-controlled, cardiovascular outcomes trials of GLP1-RA and SGLT2i was performed using PubMed and EMBASE until November 11, 2018, and complemented by results presented at the congress of the American Heart Association 2018. The search algorithm is presented in detail in the online-only Data Supplement. Data search and extraction were performed by 2 independent reviewers (T.A.Z., R.H.M.F.) using a standardized data form, and any discrepancies were resolved by consensus or by consulting a third reviewer (M.S.S.). No patients were involved in the conduction of this meta-analysis and thus no informed consent and institutional review board approval was required. All trials met criteria for being well conducted and had low risk of bias using the Cochrane tool for assessing risk of bias in randomized clinical trials[15] (see Table I in the online-only Data Supplement).

Patient Subtypes and Outcomes

Patients were stratified into those with established ASCVD versus patients with multiple risk factors (MRFs) for ASCVD (see Table II in the online-only Data Supplement for details). Efficacy outcomes of interest included MACE (and its individual components), HHF, and progression of kidney disease. The latter included both a broad composite consisting of new onset of macroalbuminuria, worsening of estimated glomerular filtration rate (eGFR), end-stage kidney disease, or death attributable to renal causes and a narrower kidney outcome excluding macroalbuminuria. For this latter outcome, sustained doubling of serum creatinine was available for the GLP1-RA trials (except for EXSCEL [Exenatide Study of Cardiovascular Event Lowering], for which 40% worsening glomerular filtration rate, end-stage kidney disease, or death attributable to renal causes were available),[4,5,16–18] whereas a composite of doubling of serum creatinine or a ≥40% worsening glomerular

Table 1. Summary of GLP1-RA and SGLT2i Cardiovascular Outcomes Trials

	GLP1-RA					SGLT2i		
Trial	ELIXA	LEADER	SUSTAIN-6	EXSCEL	HARMONY	EMPA-REG OUTCOME	CANVAS Program	DECLARE-TIMI 58
Drug	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Albiglutide	Empagliflozin	Canagliflozin	Dapagliflozin
Median follow-up time, y	2.1	3.8	2.1	3.2	1.6	3.1	2.4	4.2
Trial participants, n	6068	9340	3297	14 752	9463	7020	10 142	17 160
Age, y, mean	60.3	64.3	64.6	62.0	64.1	63.1	63.3	63.9
Female sex, n (%)	2894 (30.7)	3337 (35.7)	1295 (39.3)	5603 (38.0)	2894 (30.6)	2004 (28.5)	3633 (35.8)	6422 (37.4)
Proportion of patients with established atherosclerotic cardiovascular disease, n (%)	6068 (100)	6775 (72.5)	2735 (83.0)	10 782 (73.1)	9463 (100)	7020 (100)	6656 (66)	6974 (41)
History of heart failure, n (%)	1922 (20.3)	1667 (17.8)	777 (23.6)	2389 (16.2)	1922 (20.3)	706 (10.1)	1461 (14.4)	1724 (10.0)
eGFR <60 ml/min per 1.73 m^2, n (%)	1407 (23.2)	2158 (23.1)	939 (28.5)	3191 (21.6)	NA	1819 (25.9)	2039 (20.1)	1265 (7.4)

The CANVAS Program consisted of 2 trials, the CANVAS and CANVAS-R trials, but they are presented combined. CANVAS Program indicates Canagliflozin Cardiovascular Assessment Study Program; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; eGFR, estimated glomerular filtration rate; ELIXA, Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 (Lixisenatide); EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; GLP1-RA, glucagon-like peptide 1 receptor agonist; HARMONY, Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; NA, not applicable; SGLT2i, sodium-glucose contransporter-2 inhibitor; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes.

filtration rate, end-stage kidney disease, or death attributable to renal causes was available for the SGLT2i trials,[19–21] but the latter 2 elements constituted only 0.002% of the events (see Table III in the online-only Data Supplement for details).

Statistical Analysis

Hazard ratios with 95% CIs for the effect of randomized treatment allocation on the aforementioned outcomes were pooled across trials overall by drug class and within patients with ASCVD and MRF. Whenever data are summarized within a single drug class, fixed-effects models were considered to estimate the overall treatment effect under the hypothesis that there is 1 common treatment effect within the same drug class. When testing for treatment effect modification by drug class, random-effects models were considered with drug class as the moderator to make an inference by applying the method of residual maximum likelihood and Hartung-Knapp adjustment.[22] When combining the 2 drug classes and patient types to examine the treatment difference between patients with ASCVD and MRF, a mixed-effects model was considered to account for heterogeneity of the drug class level and at the trial level with an ASCVD and MRF patient type as a fixed effects moderator. Additional trial level covariates such as pharmacological subclass (human GLP1 analogues versus exendin-based therapy) and acute coronary syndrome versus no–acute coronary syndrome population, duration of study follow-up period, and absolute difference in HbA1c level reduction (see Methods in the online-only Data Supplement) were also examined in meta-regression models to understand between trial differences for GLP1-RA class. Heterogeneity was assessed using the Cochrane Q statistic and Higgins and Thompson's I^2. Heterogeneity was considered to be low, moderate, or high if I^2 was 25%, 50%, or 75%, respectively.[23] All reported P values are 2-sided, and no adjustments for multiple testing were performed. Statistical analyses were performed using R version 3.5.1 (R Core Team, Vienna, Austria) and the R package "metafor" (version 2.0-0).[24]

RESULTS

Study Characteristics

We identified a total of 8 trials, 5 GLP1-RA[3–5,25,26] trials and 3 SGLT2i[6,7,21] trials, that were eligible for inclusion (Table). Figure I in the online-only Data Supplement shows an overview of the search and the selection process. In total, data from 77 242 patients, 42 920 (55.6%) patients in GLP1-RA trials and 34 322 (44.4%) patients in SGLT2i trials, were included. The mean age of patients (range, 60–65 years) and the proportion of women (range, 28% to 40%) were similar across the trials. A total of 56,473 patients (73.1%) had established ASCVD, but this proportion ranged from 41% to 100% across the trials. A total of 12,568 patients (16.3%) had a history of heart failure, and this proportion ranged from 10% to 24% across the trials. The proportion of patients with eGFR <60 $mL{\cdot}min^{-1}{\cdot}1.73{\cdot}m^{-2}$ ranged from 20% to 29% across the trials, with the exception of DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58), which had a substantially smaller proportion (7.4%).

MACE

In total, 8213 of 77 242 patients (10.6%) experienced a MACE event (4871 patients in the GLP1-RA trials and 3342 patients in the SGLT2i trials). A total of

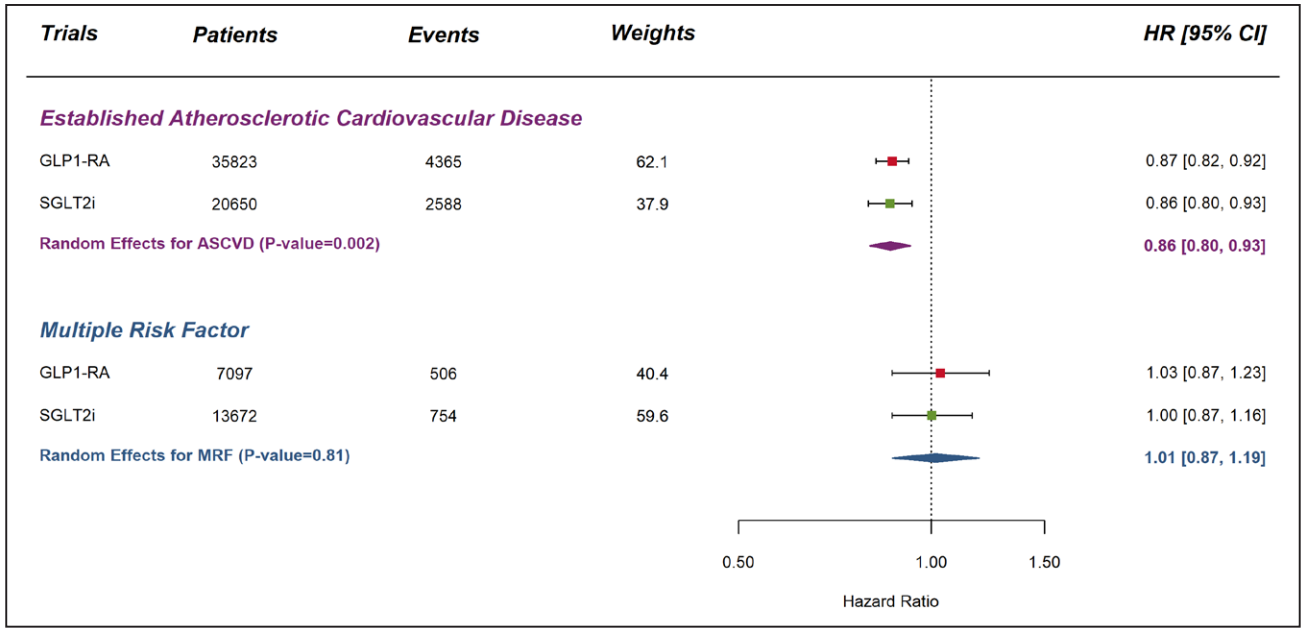

Figure 1. Meta-analysis of glucagon-like peptide 1 receptor agonist (GLP1-RA) and sodium-glucose cotransporter-2 inhibitor (SGLT2i) trials on the composite of myocardial infarction, stroke, and cardiovascular death stratified by the presence of atherosclerotic cardiovascular disease.
Forest plot showing the treatment estimates of each drug class in each subgroup using fixed effects. The summary estimates for each subgroup were modeled using random effects accounting for heterogeneity of the different drug classes. The test for subgroup differences was based on a F-test in a random effect metaregression using mixed effects accounting heterogeneity for drug class and patient population. The *P* value for subgroup differences was 0.028. For established atherosclerotic cardiovascular disease (ASCVD): GLP1-RA, Q statistic=10.89, *P*=0.028, I^2=63.3%; SGLT2i, Q statistic=0.94, *P*=0.63, I^2= 0%; total: Q statistic=11.85, *P*=0.11; and for multiple risk factor (MRF): GLP1-RA, Q statistic=0.24, *P*=0.89, I^2=0%; SGLT2i, Q statistic=0.033, *P*=0.86, I^2=0%; and total, Q statistic=0.34, *P*=0.99. HR indicates hazard ratio.

84.7% of these events occurred in the group with established ASCVD.

Overall, both drug classes reduced MACE by a similar magnitude, with GLP1-RA reducing the relative risk by 12% (HR, 0.88; 95% CI, 0.84–0.94; *P*<0.001; Figure II in the online-only Data Supplement) and SGLT2i by 11% (HR, 0.89; 95% CI, 0.83–0.96; *P*=0.001; *P* for heterogeneity, 0.86). For both drug classes, this effect was restricted to a 14% reduction in those with established ASCVD (HR, 0.86; 95% CI, 0.80–0.93), with nearly identical effects for GLP1-RA (HR, 0.87; 95% CI, 0.82–0.92) and SGLT2i (HR, 0.86; 95% CI, 0.80–0.93), whereas no treatment effect was seen in patients with MRF (HR, 1.01; 95% CI, 0.87–1.19; Figure 1; *P* interaction, 0.028; Figure III in the online-only Data Supplement). The observed heterogeneity between GLP1-RA (*P* interaction, 0.06) and SGLT2i (*P* interaction, 0.05)[10] was similar in both drug classes. There was borderline evidence of heterogeneity among the GLP1-RA trials (Q=9.72, *P*=0.046, I^2=58.8%) for the effect estimate on MACE. Stratifying the drug class by pharmacological subclass showed a nonsignificant trend toward greater benefit for the human GLP1 analogues (HR, 0.82; 95% CI, 0.76–0.89; *P*<0.001) than for the exendin-based therapies (HR, 0.94; 95% CI, 0.87–1.02; *P*=0.14), but the difference was not statistically significant (*P* interaction, 0.12). However, 1 of the trials using the exendin-based GLP1-RA lixisenatide was in the postacute coronary syndrome setting, in which MACE risk may be less acutely modifiable by a metabolic agent. Examining all of the non–acute coronary syndrome trials, the overall HR was 0.86 (95% CI, 0.81–0.91; *P*<0.001) with no significant heterogeneity (Q=4.75; *P*=0.19; I^2=36.8%). Furthermore, the median trial duration (*P* interaction, 0.69) did not significantly modify the treatment effect of GLP1-RA. There was a trend for greater risk reduction with greater HbA1c lowering (*P* interaction overall, 0.055; ASCVD subgroup only, 0.032), but this was not significant after the removal of the ELIXA trial (Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 [Lixisenatide]) (*P* interaction overall, 0.28; ASCVD subgroup only, 0.22).

Treatment Effect on the Individual Components of MACE

There were 4274 patients who experienced a myocardial infarction (2670 patients in GLP1-RA trials and 1604 patients in SGLT2i trials), 2237 who experienced a stroke (1177 patients in GLP1-RA trials and 1060 patients in SGLT2i trials), and 3132 who experienced a cardiovascular death (1876 in GLP1-RA trials and 1256 patients in SGLT2i trials).

Both GLP1-RA and SGLT2i reduced the relative risk of myocardial infarction: by 9% with GLP1-RA (HR, 0.91; 95% CI, 0.84–0.98; *P*=0.012) and by 11% with SGLT2i (HR, 0.89; 95% CI, 0.80–0.98; *P*=0.018; *P* for

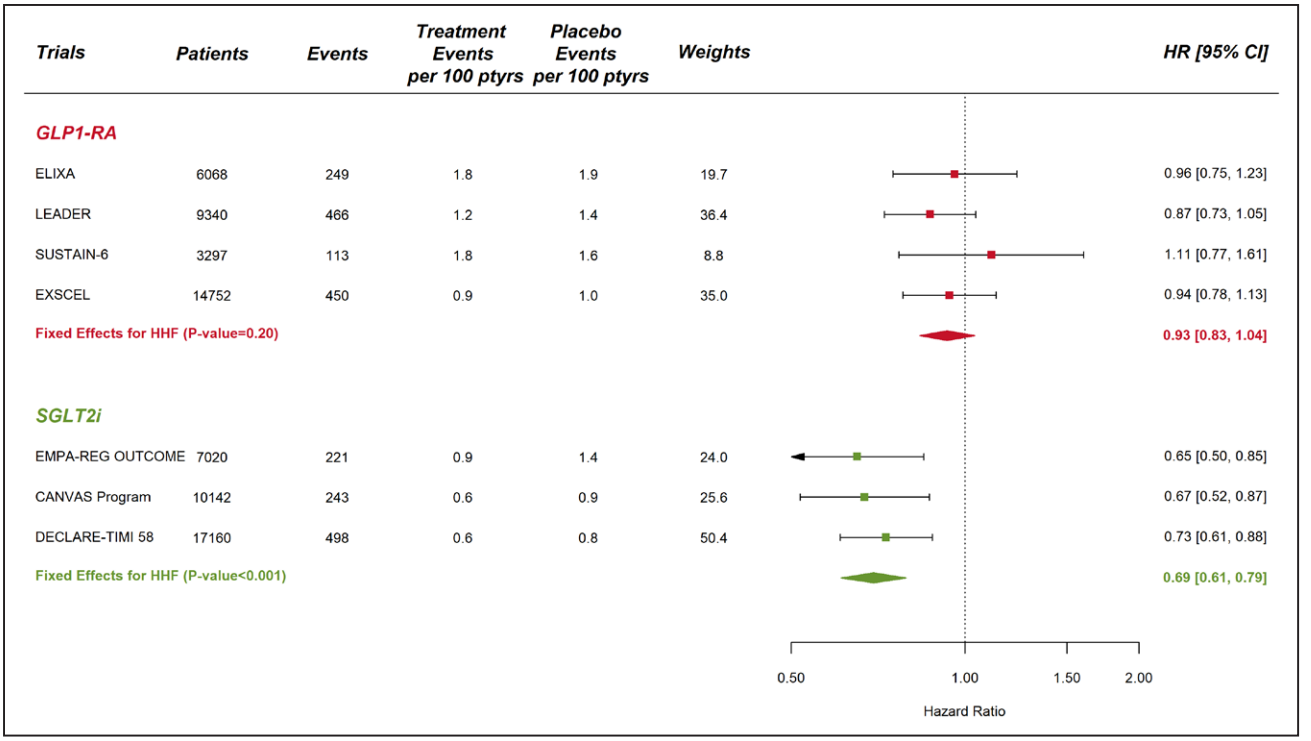

Figure 2. Meta-analysis of glucagon-like peptide 1 receptor agonist (GLP1-RA) and sodium-glucose cotransporter-2 inhibitor (SGLT2i) trials on hospitalization for heart failure (HHF) stratified by drug class.

Forest plot showing the treatment estimates of each drug class using fixed effects. The test for subgroup differences between the 2 drug classes was based on a F-test in a random effect metaregression using mixed effects accounting heterogeneity for drug class. The *P* value for subgroup differences was 0.003. For GLP1-RA: Q statistic=1.48, *P*=0.69, I^2=0%; and for SGLT2i: Q statistic=0.60, *P*=0.74, I^2=0%. CANVAS Program indicates Canagliflozin Cardiovascular Assessment Study Program; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; ELIXA, Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 (Lixisenatide); EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; HR, hazard ratio; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; ptyrs, patient years; and SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes.

heterogeneity, 0.87; Figure IV in the online-only Data Supplement). In contrast, GLP1-RA reduced the relative risk of stroke significantly by 14% (HR, 0.86; 95% CI, 0.77–0.97; *P*=0.012), whereas SGLT2i had no effect (HR, 0.97; 95% CI, 0.86–1.10; *P* for heterogeneity, 0.25; Figure V in the online-only Data Supplement). Both drug classes significantly reduced the relative risk of cardiovascular death: by 12% with GLP1-RA (HR, 0.88; 95% CI, 0.80–0.96; *P*=0.004) and by 16% with SGLT2i (HR, 0.84; 95% CI, 0.75–0.94; *P*=0.002; *P* for heterogeneity, 0.51; Figure VI in the online-only Data Supplement).

HHF

In total, HHF occurred in 2240 individuals, 1278 in the GLP1-RA trials (not including data from the HARMONY trial that did not directly report that outcome) and 962 in the SGLT2i trials. Overall, GLP1-RA did not statistically significantly reduce the relative risk of HHF (HR, 0.93; 95% CI, 0.83–1.04; *P*=0.20), whereas SGLT2i did reduce the relative risk for HHF by 31% (HR, 0.69; 95% CI, 0.61–0.79; *P*<0.001; *P* for heterogeneity, 0.003; Figure 2). These findings, including the significant interaction, remained similar in a sensitivity analysis after including estimated treatment effect data from the HARMONY trial (see Results in the online-only Data Supplement).

Treatment Effects on Kidney Function

Overall, the broad composite kidney end point occurred in 5071 patients. GLP1-RA reduced the relative risk of the broad composite kidney outcome significantly by 18% (HR, 0.82; 95% CI, 0.75–0.89; *P*<0.001), whereas there was a 38% reduction with SGLT2i (HR, 0.62; 95% CI, 0.58–0.67; *P*<0.001; *P* for heterogeneity, 0.010; Figure 3A). Moreover, the relative risk reduction of the kidney composite with GLP1-RA appeared to be mainly driven by a reduction in macroalbuminuria. Excluding that particular outcome, there was a nonsignificant effect of GLP1-RA on the risk of doubling serum creatinine (HR, 0.92; 95% CI, 0.80–1.06; *P*=0.24). Conversely, SGLT2i significantly reduced the relative risk of worsening eGFR, end-stage kidney disease, or renal death by 45% (HR, 0.55; 95% CI, 0.48–0.64; *P*<0.001; *P* for heterogeneity, 0.001; Figure 3B). A sensitivity analysis using doubling of serum creatinine alone yielded an almost identical effect estimate (HR, 0.56; 95% CI, 0.44–0.71; *P*<0.001).

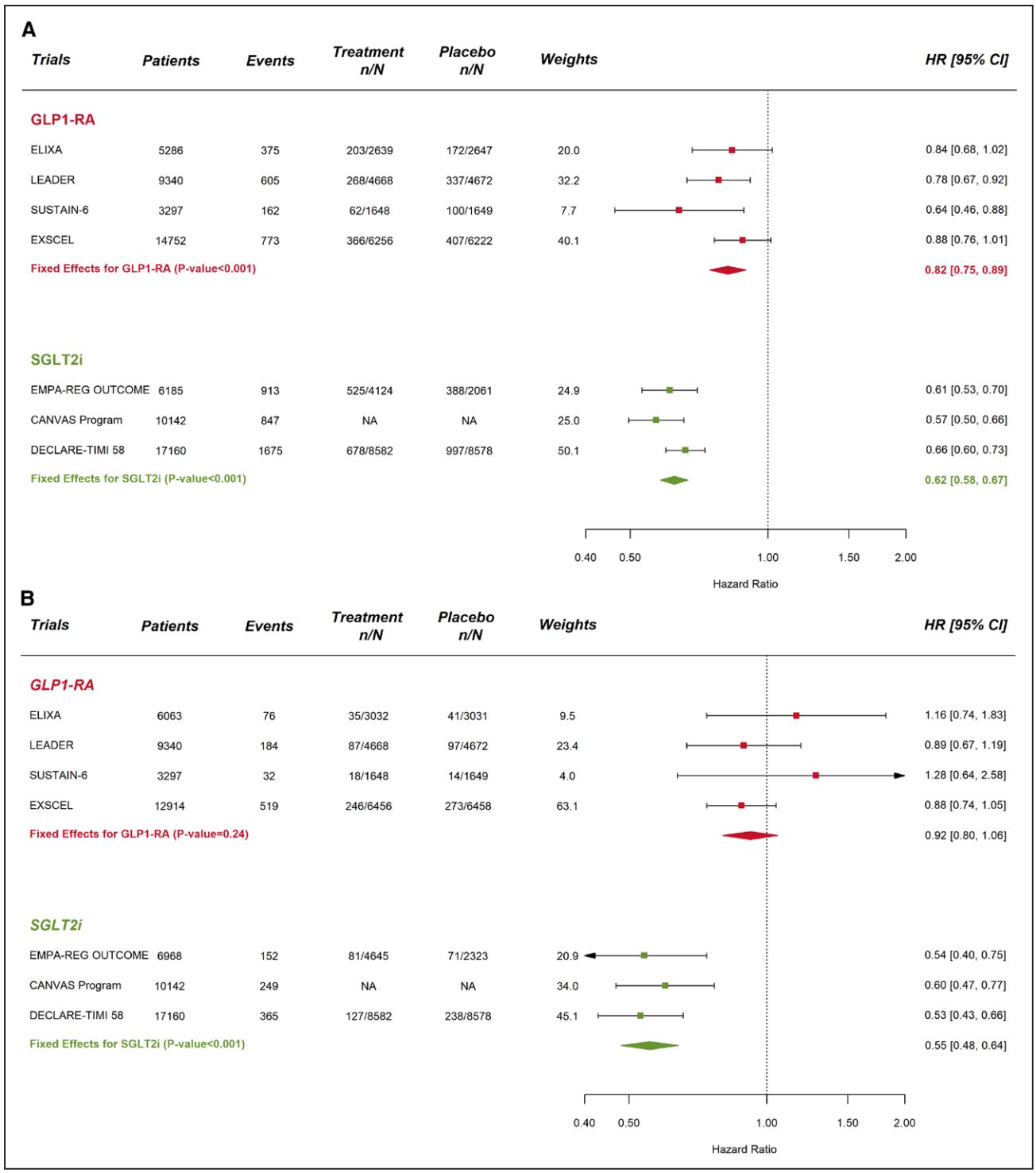

Figure 3. Meta-analysis of glucagon-like peptide 1 receptor agonist (GLP1-RA) and sodium-glucose cotransporter-2 inhibitor (SGLT2i) trials on renal end points. **A**, Meta-analysis of GLP1-RA and SGLT2i trials on hospitalization for a broad kidney end point (new-onset macroalbuminuria sustained doubling of serum creatinine or a 40% decline in estimated glomerular filtration rate, end-stage kidney disease, or death of renal cause) stratified by drug class. Forest plot showing the treatment estimates of each drug class using fixed effects. The test for subgroup differences between the 2 drug classes was based on a F-test in a random effect metaregression using mixed effects accounting heterogeneity for drug class. The *P* value for subgroup differences was 0.010. For GLP1-RA: Q statistic=3.60, *P*=0.31, I^2=16.6%; and for SGLT2i: Q statistic=2.99, *P*=0.22, I^2=33.2%. **B**, Meta-analysis of GLP1-RA and SGLT2i trials on a kidney outcome excluding macroalbuminuria stratified by drug class. Forest plot showing the treatment estimates of each drug class using fixed effects. The test for subgroup differences between the 2 drug classes was based on a F-test in a random effect metaregression using mixed effects accounting heterogeneity for drug class. The *P* value for subgroup differences was <0.001. For GLP1-RA: Q statistic= 2.18, *P*=0.54, I^2=0%; and for SGLT2i: Q statistic=0.59, *P*=0.74. I^2=0%. CANVAS Program indicates Canagliflozin Cardiovascular Assessment Study Program; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; ELIXA, Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 (Lixisenatide); EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; HR, hazard ratio; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; NA, not available; and SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes.

DISCUSSION

GLP1-RA and SGLT2i are antihyperglycemic agents that have now been demonstrated to reduce the risk of cardiovascular events in patients with type 2 diabetes mellitus.[11] The relative benefits of these drugs in different patient populations remains undefined. The present meta-analysis showed that both GLP1-RA and SGLT2i reduce the risk of MACE by approximately 14% in patients with known ASCVD, whereas in the trials published to date, neither reduces the risk of MACE in patients with only MRF but without established ASCVD.

In terms of the individual components of MACE, both classes reduced the risk of myocardial infarction and cardiovascular death, but only GLP1-RA reduced the risk of stroke. In contrast, SGLT2i robustly reduced the relative risk of HHF by 31%, whereas there was only a nonsignificant 7% relative risk reduction with GLP1-RA.

Members of GLP1-RA have been found to reduce kidney events mainly driven by a reduction in macroalbuminuria.[16] Although albuminuria is a well-established biomarker reflecting a risk of diabetic kidney disease and cardiovascular disease,[27,28] it represents a surrogate marker and may even be absent in patients with reduced eGFR.[29,30] As such, a reduction in eGFR has emerged as the more meaningful end point of greater importance and is used in ongoing diabetes mellitus trials for kidney outcomes.[31] When excluding macroalbuminuria, we found a nonsignificant relative reduction by 8%. This stands in contrast to a recent meta-analysis of SGLT2i that showed robust relative risk reductions by 45% for the composite of reductions in eGFR, end-stage kidney disease, and death attributable to renal causes.[10]

The exact pathobiological explanations of how these 2 drug classes exert their favorable effects are still unclear.[10,32–34] Both drug classes have modest and relatively similar reductions of HbA1c and therefore appear to exert their beneficial cardiovascular effects independent of glucose control through their individual pleiotropic properties. However, the natriuresis and inhibition of the tubuloglomerular feedback by SGLT2i may play a central role and explain the observed reduction in HHF and the delayed progression of diabetic kidney disease.[35] Potentially adding to the complexity, structural differences in the GLP1-RA group might explain somewhat more pronounced effects with the human GLP1 analogues compared with the exendin-based GLP1-RA. Recently, a press release has been issued stating that the REWIND trial (Researching Cardiovascular Events With a Weekly Incretin in Diabetes), a cardiovascular outcomes trial comparing the GLP1-RA dulaglutide in approximately 9900 patients (68.6% of whom did not have known ASCVD), has met its primary end point of reducing the risk of MACE.[36,37] Detailed results have not yet been presented or published, including any heterogeneity in benefit between patients with established ASCVD and those only with MRF for ASCVD. However, its uniquely long duration of 8 years raises the possibility that a reduction in MACE may require more time to become evident in patients with lower risk for MACE. It is biologically plausible that SGLT2i and GLP1-RA have the same benefit in both patient populations, but the treatment effect may require more time to become evident in patients at lower risk.

Limitations

There are several potential limitations to address. We have included aggregate trial-level data instead of patient-level data, and as such, observed differences in treatment effects between subgroups have been analyzed only based on a single factor of stratification. However, a more complex interplay involving multiple baseline characteristics may exist. In addition, the exact inclusion/exclusion criteria and definitions of end points differed slightly among the included trials. As such, a higher-risk patient cohort with a larger proportion of patients with ASCVD and lower eGFR baseline levels was included in the GLP1-RA trials. This meta-analysis aimed to provide clinical context and show their clinical efficacy of 2 drug classes in specific patient populations. However, trials with head-to-head comparison would be necessary to demonstrate possible superiority of 1 drug class over the other. Also, this meta-analysis is not able to evaluate potential incremental or additive treatment effects when both drug classes are combined. Further research is warranted to explore the cardiovascular and kidney effects of combining the 2 treatment regimens. As noted above, the REWIND data were not included, because this trial was not published at the time of submission. However, based on topline results of superiority reported by press release, they raise the possibility that very long-term treatment with a GLP1-RA may reduce the risk of MACE in patients without established ASCVD.[37]

CONCLUSIONS

In conclusion, GLP1-RA and SGLT-2i reduce the risk of MACE to a similar degree in patients with established ASCVD but have no effect in patients without established ASCVD over a short-term follow-up ranging from 2 to 4 years. The prevention of heart failure and progression of kidney disease by SGLT2i should be considered in the decision-making process when treating patients with type 2 diabetes mellitus.

ARTICLE INFORMATION

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