10.1161/CIRCULATIONAHA.118.038868

Comparison of the Effects of Glucagon-Like Peptide Receptor Agonists and Sodium-Glucose Co-Transporter 2 Inhibitors for Prevention of Major Adverse Cardiovascular and Renal Outcomes in Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Cardiovascular Outcomes Trials

Running Title: *Zelniker et al.; Meta-Analysis of GLP1-RA and SGLT2i in T2DM*

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10.1161/CIRCULATIONAHA.118.038868

Abstract

Background: Glucagon-like peptide 1 receptor agonists (GLP1-RA) and sodium-glucose contransporter-2 inhibitors (SGLT2i) have emerged as two new classes of antihyperglycemic agents that also reduce cardiovascular risk. The relative benefits in patients with and without established atherosclerotic cardiovascular disease (ASCVD) 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. The primary outcomes were: the composite of myocardial infarction, stroke, and cardiovascular death (MACE); hospitalization for heart failure (HHF); 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 GLP1RA reducing the risk by 12% (HR 0.88, 95%-CI 0.84 to 0.94; p<0.001) and SGLT2i by 11% (HR 0.89, 95%-CI 0.83 to 0.96; p=0.001). For both drug classes, this treatment effect was restricted to a 14% reduction in those with established ASCVD (HR 0.86, 95%-CI 0.80 to 0.93, P=0.002) whereas no effect was seen in patients without established ASCVD (HR 1.01, 95%-CI 0.87 to 1.16, P=0.81; p-interaction 0.028). SGLT2i reduced HHF 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 to 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 eGFR, 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 ASCVD, whereas SGLT2i have a more marked effect on preventing HHF and progression of kidney disease. Their distinct clinical benefit profiles should be considered in the decision-making process when treating patients with T2DM.

Key Words: Sodium-glucose contransporter-2 inhibitors; Glucagon-like peptide 1 receptor agonists; Type 2 diabetes; Meta-analysis

Clinical Perspective

What is new?

- SGLT2i and GLP1-RA reduce atherosclerotic MACE to a similar degree in patients with established atherosclerotic cardiovascular, but have no appreciable effect on MACE over the timeframe 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 eGFR.

What are the clinical implications?

- GLP1-RA and SGLT2i reduce atherosclerotic MACE in patients with established ASCVD, whereas SGLT2i also have effects on preventing HHF and reduction in eGFR in a broad spectrum of patients.
- These considerations should be included in the decision-making process when treating patients with T2DM.

Introduction

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 (T2DM) 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 and caused a shift in therapeutic focus from reducing glycated hemoglobin (HbA1c) in order to prevent microvascular complications to also reducing risk of cardiovascular outcomes. To date, only members of two drug classes, glucagon-like peptide 1 receptor agonists (GLP1-RA)[3-5] and sodium-glucose co-transporter-2 inhibitors (SGLT2i),[6, 7] have been shown to reduce significantly the risk of major cardiovascular events (MACE), the composite of myocardial infarction, stroke, and cardiovascular death. 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 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, 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, as primary prevention patients represent only a relatively small proportion of the patient population in each of the trials yielding much fewer events 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 supplementary files].

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 (PRISMA-P) statement.[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 Supplemental material. Data search and extraction was performed by two independent reviewers (TAZ, RHMF) using a standardized data form and any discrepancies were resolved by consensus or by consulting a third reviewer (MSS). 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 Supplemental Table 1).

Patient Subtypes & Outcomes

Patients were stratified into those with established ASCVD versus patients with multiple risk factors (MRF) for ASCVD (see Supplementary Table 2 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 due 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 for which 40% worsening GFR, end-stage kidney disease, or death due to renal causes was available),[4, 5, 16-18] whereas a composite of doubling of serum creatinine or a ≥40% worsening GFR, end-stage kidney disease, or death due to renal causes was available for the SGLT2i trials,[19-21] but the latter two elements constituted only 0.002% of the events (see Supplementary Table 3 for details).

Statistical analysis

Hazard ratios with 95% confidence intervals 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 one 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 (REML) and Hartung-Knapp adjustment.[22] When combining the two 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 GLP-1 analogues vs exendin-based therapy) and ACS vs no ACS population (Acute coronary syndrome), duration of study follow-up period and absolute difference in HbA1c level reduction (see Supplemental Methods) were also examined in meta-regression models to understand between trial differences for GLP1-RA class. Heterogeneity was assessed using Cochrane Q statistic, and Higgins' and Thompsons 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 two-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 1). Supplemental Figure 1 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 28-40%) 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/min/1.73 m^2 ranged from 20% to 29% across the trials, with the exception of DECLARE-TIMI 58 that had a substantially smaller proportion (7.4%).

Composite of myocardial infarction, stroke, and cardiovascular death (MACE)

In total, 8,213 of 77,242 patients (10.6%) experienced a MACE event (4,871 patients in the GLP1-RA trials and 3,342 patients in the SGLT2i trials). A total of 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 to 0.94; p<0.001; Supplemental Figure

2) and SGLT2i by 11% (HR 0.89, 95% CI 0.83 to 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 to 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 to 1.19) (Figure 1, P-interaction=0.028; Supplemental Figure 3). The observed heterogeneity between GLP1-RA (p-interaction 0.06) and SGLT2i (p-interaction 0.05)[10] was similarly 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 non-significant trend towards greater benefit for the human GLP-1 analogues (HR 0.82, 95% CI 0.76 to 0.89, P<0.001) than for the exendin-based therapies (HR 0.94, 95% CI 0.87 to 1.02, P=0.14) but the difference was not statistically significant (p-interaction 0.12). However, one of the trials using the exendin-based GLP1-RA lixisenatide was in the post-acute coronary syndrome (ACS) setting, in which MACE risk may be less acutely modifiable by a metabolic agent. Examining all of the non-ACS trials, the overall HR was 0.86 (95% CI 0.81 to 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 modify significantly 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 (p-interaction overall 0.28, ASCVD subgroup only 0.22).

Treatment effect on the individual components of MACE

There were 4,274 patients who experienced a myocardial infarction (2,670 patients in GLP1-RA trials and 1,604 patients in SGLT2i trials), 2,237 a stroke (1,177 patients in GLP1-RA trials,

1,060 patients in SGLT2i trials), and 3,132 a cardiovascular death (1,876 in GLP1-RA trials, 1,256 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 to 0.98, p=0.012) and by 11% with SGLT2i (HR 0.89, 95% CI 0.80 to 0.98, p=0.018; p for heterogeneity 0.87; Supplemental Figure 4). In contrast, GLP1-RA reduced the relative risk of stroke significantly by 14% (HR 0.86, 95% CI 0.77 to 0.97, p=0.012), whereas SGLT2i had no effect (HR 0.97, 95% CI 0.86 to 1.10) (p for heterogeneity 0.25; Supplemental Figure 5). Both drug classes significantly reduced the relative risk of cardiovascular death: by 12% with GLP1-RA (HR 0.88, 95% CI 0.80 to 0.96, p=0.004) and by 16% with SGLT2i (HR 0.84, 95% CI 0.75 to 0.94, p=0.002; p for heterogeneity 0.51; Supplemental Figure 6).

Hospitalization for heart failure

In total, HHF occurred in 2,240 individuals, 1,278 in the GLP1-RA trials (not including data from the HARMONY trial that did not directly report that outcome) and 962 patients in the SGLT2i trials. Overall, GLP1-RA did not statistically significantly reduce the relative risk of HHF (HR 0.93, 95% CI 0.83 to 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 Supplementary Results).

Treatment Effects on Kidney Function

Overall, the broad composite kidney endpoint occurred in 5,071 patients. GLP-1RA reduced the relative risk of the broad composite kidney outcome significantly by 18% (HR 0.82, 95% CI 0.75

to 0.89, p<0.001), whereas there was a 38% reduction with SGLT2i (HR 0.62, 95% CI 0.58 to 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 non-significant effect of GLP1-RA on the risk of doubling serum creatinine (HR 0.92, 95% CI 0.80 to 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 to 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).

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 MI and CV 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 non-significant 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 risk for 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, reductions in eGFR has emerged as the more meaningful endpoint of greater importance and is used in ongoing diabetes trials for kidney outcomes.[31] When excluding macroalbuminuria, we found a non-significant 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 due to renal causes.[10]

The exact pathobiological explanations how these two 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 GLP-1 analogues compared with the exendin-based GLP1-RAs. Recently, a press release has been issued stating that the REWIND trial, 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 endpoint 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 endpoints 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 two drug classes in specific patient populations. However, trials with head to head comparison would be necessary to demonstrate possible superiority of one 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 two treatment regimens. As noted above, the REWIND data were not included, as this trial has not been 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 GLP1RA may reduce the risk of MACE in patients without established ASCVD.[37]

Conclusion

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 T2DM.

Acknowledgments

TAZ contributed to study design, data collection, statistical analysis, data interpretation, and drafting of the manuscript. **SDW** contributed to study design, data collection, data interpretation, and critical review of the manuscript. **IR** contributed to data interpretation, and critical review of the manuscript. **KI** contributed to statistical analysis, and critical review of the manuscript. **ELG** contributed to statistical analysis, and critical review of the manuscript. **MPB** contributed to data collection, data interpretation, and critical review of the manuscript. **OM** contributed to data interpretation, and critical review of the manuscript. **EK** contributed to data interpretation, and critical review of the manuscript. **AC** contributed to data interpretation, and critical review of the manuscript. **RHMF** contributed to data interpretation, data collection, and critical review of the manuscript. **DLB** contributed to data interpretation, and critical review of the manuscript. **LAL** contributed to data interpretation, and critical review of the manuscript. **DKM** data interpretation, and critical review of the manuscript. **JPHW** data interpretation, and critical review of the manuscript. **MSS** contributed to study design, data collection, statistical analysis, data interpretation, and critical review of the manuscript. MSS is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Sources of Funding

TAZ was supported by the German Research Foundation (Deutsche Forschungsgemeinschaft ZE 1109/1-1 to TAZ). RHMF was supported by the Lemann Foundation Cardiovascular Research Postdoctoral Fellowship – Harvard University/Brigham and Women´s Hospital. The funding sources had no role in data collection, analysis, writing of the manuscript or the decision to submit for publication. All authors had full access to all the data. All statistical analyses were performed at the TIMI Study Group. MSS is the guarantor of this work and all authors take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosures

TAZ reports a research grant from Deutsche Forschungsgemeinschaft (ZE 1109/1-1), and grants to his institution from Astra Zeneca, grants from Bristol-Myers Squibb, during the conduct of the study. **SDW** reports grants and personal fees from AstraZeneca, grants and personal fees from Bristol Myers Squibb, during the conduct of the study; grants from AMGEN, grants and personal fees from Arena, grants and personal fees from Daiichi Sankyo, grants and personal fees from Eisai, grants and personal fees from EliLilly, grants and personal fees from Janssen, grants, personal fees and other from Merck, grants from Sanofi Aventis, personal fees from Aegerion, personal fees from Allergan, personal fees from Angelmed, personal fees from Boehringer Ingelheim, personal fees from Boston Clinical Research Institute, personal fees from Icon Clinical, personal fees from Lexicon, personal fees from St Jude Medical, personal fees from Xoma, outside the submitted work. **IR** reports personal fees from AstraZeneca, personal fees from Bristol-Myers Squibb, during the conduct of the study; personal fees from Boehringer Ingelheim, personal fees from Concenter BioPharma/Silkim Ltd, personal fees from Eli Lilly and

Company, personal fees from Merck Sharp & Dohme Limited, personal fees from Novo Nordisk, Inc, personal fees from Orgenesis, personal fees from Pfizer, personal fees from Sanofi, personal fees from SmartZyme Innovation Ltd, personal fees from Panaxia, personal fees from FuturRx Ltd, personal fees from Insuline Medical, personal fees from Medial EarlySign Ltd, personal fees from CameraEyes, personal fees from Exscopia, personal fees from Dermal Biomics Inc, personal fees from Johnson & Johnson, personal fees from Novartis Pharma AG, personal fees from Teva, personal fees from Glucome Ltd, personal fees from DarioHealth, outside the submitted work.

KI: None. **ELG:** None. **MPB** reports grants from Amgen, AstraZeneca, Merck, Pfizer, personal fees from Aralez, Amgen, AstraZeneca, Bayer, Janssen, Pfizer, Sanofi, during the conduct of the study. **OM** reports grants and personal fees from AstraZeneca, grants and personal fees from Bristol-Myers Squibb, during the conduct of the study; grants and personal fees from NovoNordisk, personal fees from Eli Lilly, personal fees from sanofi, personal fees from Merck Sharp & Dohme, personal fees from Boehringer Ingelheim, personal fees from Jansen and Jansen, personal fees from Novartis, outside the submitted work. **ETK** reports personal fees from AstraZeneca, personal fees from Ono Pharmaceutical, personal fees from Daiichi Sankyo , personal fees from Bristol-Myers Squibb, personal fees from Tanabe-Mitsubishi Pharma, outside the submitted work. **AC** reports personal fees from Novonordisk, personal fees from Elli Lilly, personal fees from Sanofi, grants and personal fees from AstraZeneca, personal fees from Boeehringer Ingelheim, personal fees from Merck Sharp & Dohme, personal fees from Glucome, outside the submitted work. **RHMF** reports the following: Honoraria; Modest; AstraZeneca; Research Grant; Modest; AstraZeneca, DalCor, Boehinger, Pfizer, Bayer, Sanofi. **DLB** discloses the following relationships - Advisory Board: Cardax, Elsevier Practice Update Cardiology,

Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic, Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Amarin, Amgen, AstraZeneca, (including for the DECLARE-TIMI 58 Executive Committee), Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Idorsia, Ironwood, Ischemix, Lilly, Medtronic, PhaseBio, Pfizer, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-

Investigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Novo Nordisk, PLx Pharma, Takeda.

LAL reports grants and personal fees from AstraZeneca, grants and personal fees from Boehringer Ingelheim, grants and personal fees from Eli Lilly, grants and personal fees from Janssen, grants and personal fees from Merck, grants and personal fees from Novo Nordisk, grants and personal fees from Sanofi, personal fees from Servier, grants from GSK, outside the submitted work. **DKM** reports personal fees from AstraZeneca, during the conduct of the study; personal fees from Boehringer Ingelheim, personal fees from Janssen Research and Development LLC, personal fees from Sanofi US, personal fees from Merck Sharp and Dohme Corp., personal fees from Eli Lilly and Company, personal fees from Novo Nordisk, personal fees from GlaxoSmithKline, personal fees from AstraZeneca, personal fees from Lexicon, personal fees from Eisai Inc., personal fees from Esperion, personal fees from Metavant, personal fees from Pfizer, personal fees from Applied Therapeutics, outside the submitted work. **JW** reports personal fees and other from Brigham and Women's Hospital, during the conduct of the study; grants, personal fees and consultancy fees (paid to his institution) from AstraZeneca, personal fees and consultancy fees (paid to his institution) from Boehringer Ingelheim, personal fees and consultancy fees (paid to his institution) from Lilly, grants, personal fees and consultancy fees (paid to his institution) from Novo Nordisk, personal fees and consultancy fees (paid to his institution) from Janssen, personal fees and consultancy fees (paid to his institution) from Napp, personal fees and consultancy fees (paid to his institution) Mundipharma, personal fees, consultancy fees (paid to his institution) from Sanofi, grants, personal fees and consultancy fees (paid to his institution) from Takeda, consultancy fees (paid to his institution) from Wilmington

Healthcare, outside the submitted work. **MSS** reports grants from AstraZeneca, during the conduct of the study; grants and personal fees from Amgen, grants and personal fees from AstraZeneca, grants from Daiichi-Sankyo, grants from Eisai, grants from GlaxoSmithKline, grants and personal fees from Intarcia, grants and personal fees from Janssen Research and Development, grants and personal fees from Medicines Company, grants and personal fees from Medimmune, grants and personal fees from Merck, grants and personal fees from Novartis, grants from Pfizer, grants from Poxel, grants from Takeda, personal fees from Bristol-Myers Squibb, personal fees from CVS Caremark, personal fees from Dyrnamix, personal fees from Esperion, grants from Abbott Laboratories, grants from Critical Diagnostics, grants from Genzyme, grants from Gilead, grants from Roche Diagnostics, personal fees from Alnylam, personal fees from Ionis, personal fees from MyoKardia, outside the submitted work.

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Table 1. Summary of GLP1-RA and SGLT2i cardiovascular outcomes trials

	GLP-1RA					**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 (years)	2.1	3.8	2.1	3.2	1.6	3.1	2.4	4.2
Trial participants (n)	6068	9340	3297	14752	9463	7020	10142	17160
Age (mean)	60.3	64.3	64.6	62.0	64.1	63.1	63.3	63.9
Female Sex	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%)	10782 (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/1.73m^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 are presented combined.

Figure Legends

Figure 1. Meta-Analysis of GLP1-RA and SGLT2i trials on the composite of myocardial infarction, stroke, and CV death (MACE) stratified by 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 meta-regression using mixed effects accounting heterogeneity for drug class and patient population.

P-value for subgroup differences: 0.028

Established ASCVD:

GLP-1RA: 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

MRF:

GLP-1RA: Q statistic=0.24, p=0.89; I^2=0%

SGLT2i: Q-statistic= 0.033, p=0.86; I^2=0%

Total: Q-statistic=0.34, p=0.99

Figure 2. Meta-Analysis of GLP1-RA and SGLT2i trials on hospitalization for heart failure 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 meta-regression using mixed effects accounting heterogeneity for drug class.

P-value for subgroup differences 0.003

GLP1-RA: Q-statistic= 1.48, p=0.69; I^2=0%

SGLT2i: Q statistic=0.60, p=0.74; I^2=0%

Figure 3. Meta-Analysis of GLP1-RA and SGLT2i trials on renal endpoints.

A. Meta-Analysis of GLP1-RA and SGLT2i trials on hospitalization for a broad kidney endpoint (new- onset macroalbuminuria sustained doubling of serum creatinine or a 40% decline in eGFR, ESRD, 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 meta-regression using mixed effects accounting heterogeneity for drug class.

P-value for subgroup differences 0.010

GLP1-RA: Q-statistic= 3.60, p=0.31; I^2=16.6%

SGLT2i: Q statistic=3.48, p=0.18; I^2=42.5%

B. Meta-Analysis of GLP1-RA and SGLT2i trials on a kidney outcome excluding macroalbuminuria stratified by drug class

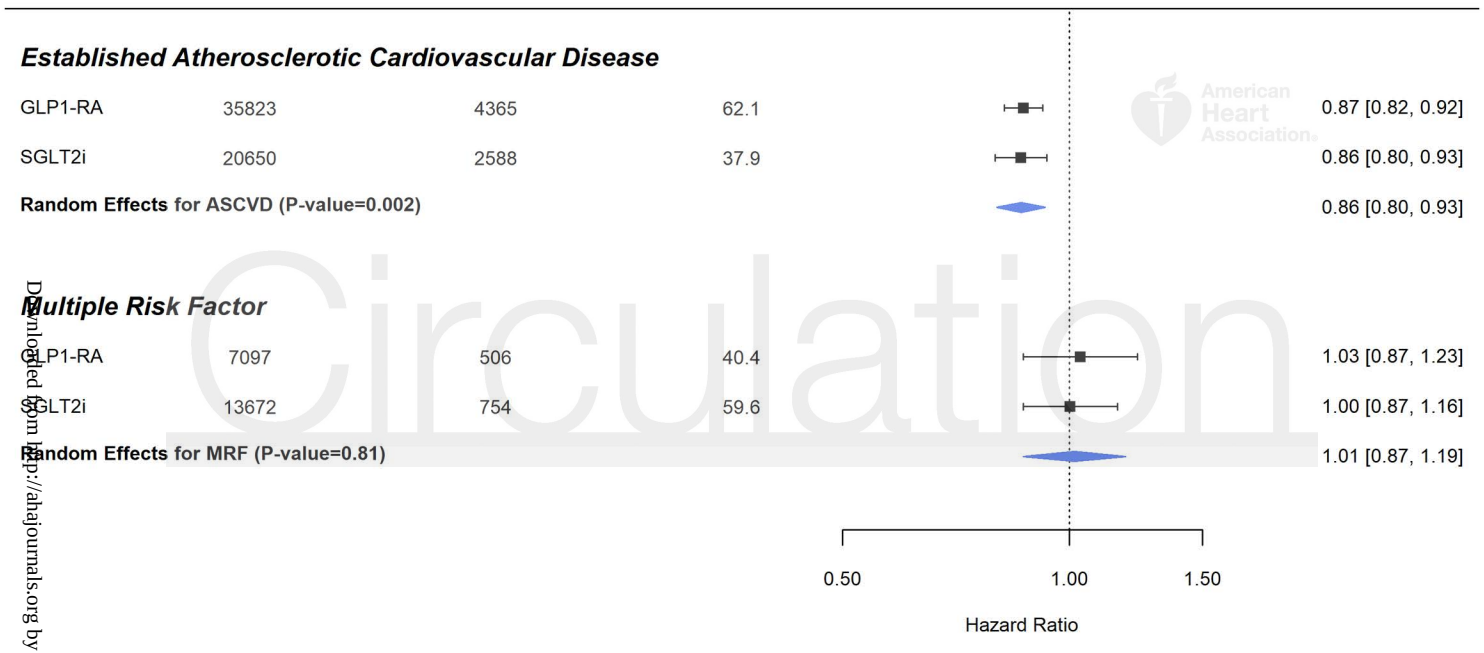
Forest plot showing the treatment estimates of each drug class using fixed effects. The test for

subgroup differences between the 2 drug classes was based on a F-test in a random effect meta-regression using mixed effects accounting heterogeneity for drug class.

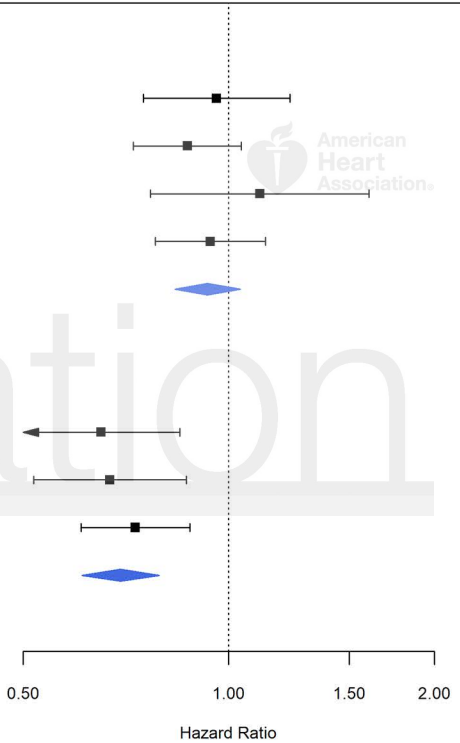
P-value for subgroup differences <0.001

GLP1-RA: Q-statistic= 2.18, p=0.54; I^2=0%

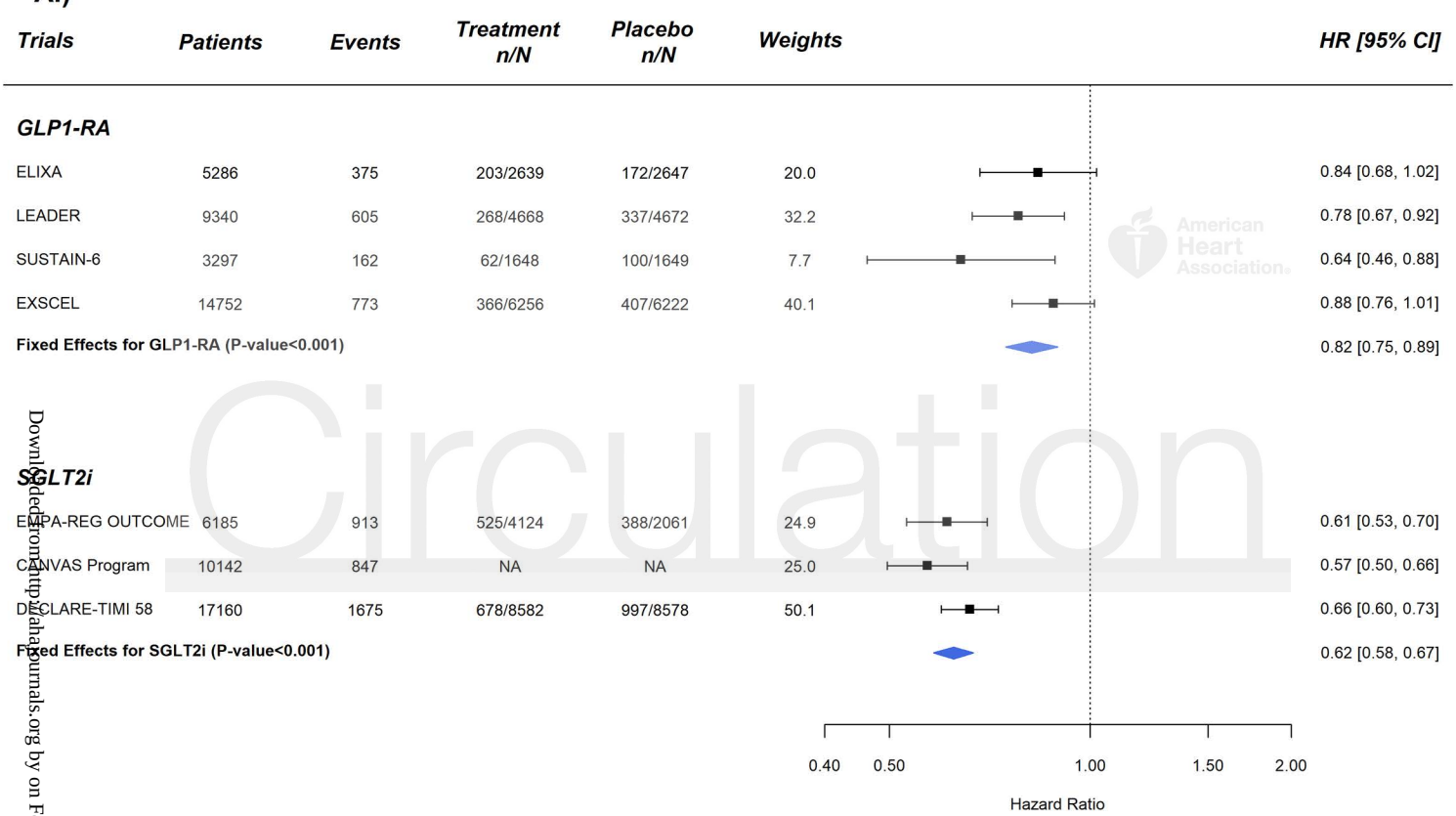
SGLT2i: Q statistic= 0.59, p=0.74; I^2=0%



Trials	Patients	Events	Treatment Events per 100 ptyrs	Placebo Events per 100 ptyrs	Weights	HR [95% CI]
GLP1-RA						
ELIXA	6068	249	1.8	1.9	19.7	0.96 [0.75, 1.23]
LEADER	9340	466	1.2	1.4	36.4	0.87 [0.73, 1.05]
SUSTAIN-6	3297	113	1.8	1.6	8.8	1.11 [0.77, 1.61]
EXSCEL	14752	450	0.9	1.0	35.0	0.94 [0.78, 1.13]
Fixed Effects for HHF (P-value=0.20)						0.93 [0.83, 1.04]
SGLT2i						
EMPA-REG OUTCOME	7020	221	0.9	1.4	24.0	0.65 [0.50, 0.85]
CANVAS Program	10142	243	0.6	0.9	25.6	0.67 [0.52, 0.87]
DECLARE-TIMI 58	17160	498	0.6	0.8	50.4	0.73 [0.61, 0.88]
Fixed Effects for HHF (P-value<0.001)						0.69 [0.61, 0.79]



A.)



B.)