Title: The cardiovascular safety trials of DPP-4 inhibitors, GLP-1 agonists, and SGLT2 inhibitors

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Order of Authors: Matthew H Secrest , MSc; Jacob A Udell, MD MPH; Kristian B Filion, PhD

Abstract: In this paper, we review the results of large, double-blind, placebo-controlled randomized trials mandated by the US Food and Drug Administration to examine the cardiovascular safety of newly-approved antihyperglycemic agents in patients with type 2 diabetes. The cardiovascular effects of dipeptidyl peptidase-4 (DPP-4) inhibitors remain controversial: while these drugs did not reduce or increase the risk of primary, pre-specified composite cardiovascular outcomes, one DPP-4 inhibitor (saxagliptin) increased the risk of hospitalization for heart failure in the overall population, another (alogliptin) demonstrated inconsistent effects on heart failure hospitalization across subgroups of patients, and a third (sitagliptin) demonstrated no effect on heart failure. Evidence for cardiovascular benefits of glucagon-like peptide-1 (GLP-1) agonists has been similarly heterogeneous, with liraglutide and semaglutide reducing the risk of composite cardiovascular outcomes, but lixisenatide having no reduction or increase in cardiovascular risk. The effect of GLP-1 agonists on retinopathy remains a potential concern. In the only completed trial to date to assess a sodium-glucose cotransporter-2 (SGLT2) inhibitor, empagliflozin reduced the risk of composite cardiovascular endpoints, predominantly through its impact on cardiovascular mortality and heart failure hospitalization.

Response to Reviewers: Response to Reviewers' Comments

We appreciate the thoughtful comments provided by the reviewers during the review process, and believe our manuscript has been improved through their consideration. In the following page, we provide a point-by-point response to the most recent comments.

Reviewer #1:
The authors have adequately addressed my concerns.

The authors would like to thank Reviewer #1 again for the helpful comments made on previous iterations of this manuscript.

Reviewer #2:
The authors have addressed all my questions and from my perspective, significantly improved the manuscript.

1)   One minor point of clarification on the sentence below is needed, though, as it does not make intuitive sense.

"Though SGLT2 is expressed outside of cardiac tissue in the proximal tubule epithelium, SGLT2 inhibition may elicit several ancillary cardiovascular..."

We thank Reviewer #2 for the input throughout the peer review process and agree that the sentence in question lacked clarity—specifically, the implied relationship between the location of SGLT2 transporters and cardiovascular effects was not made explicit. We've improved the passage in question. Please refer to page 11 of the revised manuscript, which now reads:

SGLT2 transporters are almost entirely found in kidney epithelial cells [30], making their modulation unlikely to impact cardiac and vascular tissue and promote downstream cardiovascular effects. SGLT2 inhibition may still elicit several ancillary cardiovascular benefits through glycosuria and natriuresis, including for example decreased plasma uric acid (which potentially lowers hypertension and CVD) and reduced blood pressure [30, 31].

References:

30.   Heerspink HJL, Perkins BA, Fitchett DH, Husain M, Cherney DZI. Sodium Glucose Cotransporter 2 Inhibitors in the Treatment of Diabetes Mellitus: Cardiovascular and Kidney Effects, Potential Mechanisms, and Clinical Applications. Circulation. 2016;134:752-72.
31.   Cherney DZ, Udell JA. Use of Sodium Glucose Cotransporter 2 Inhibitors in the Hands of Cardiologists. Circulation. 2016;134:1915-7.

Cover Letter

January 26th, 2017

Douglas P Zipes, MD
Editor-in-Chief
Trends in Cardiovascular Medicine

Subject: Resubmission to *Trends in Cardiovascular Medicine* (manuscript number TCM-D-16-00143)

Dear Dr. Zipes:

Enclosed please find our manuscript entitled "The cardiovascular safety trials of DPP-4 inhibitors, GLP-1 agonists, and SGLT2 inhibitors" (manuscript number TCM-D-16-00143), which we have edited in response to Reviewer #2's request for more clarity regarding the implications of the location of SGLT2 transporters within the body. The revised manuscript attached provides more information, claiming that the location of SGLT2 transporters outside of cardiac tissue makes direct effects of SGLT2 inhibitors on cardiovascular health unlikely. We have provided a response document that includes the updated passage in question and have uploaded a version of the manuscript with changes tracked as a supplementary file.

Again, we appreciate the input from the reviewers and are confident that our manuscript has been improved in consideration of their comments. We hope that the revised manuscript meets your approval and look forward to the next steps.

Sincerely,

Kristian B. Filion, PhD FAHA
Assistant Professor
Departments of Medicine and of Epidemiology, Biostatistics, and Occupational Health

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Enc.

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We the undersigned declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that all authors are responsible for the content and have read and approved the manuscript; and that the manuscript conforms to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals published in *Annals in Internal Medicine*.

We understand that the Corresponding Author is the sole contact for the Editorial process. He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

Signed by all authors as follows:

Matthew H Secrest, MSc

Jacob A Udell, MD MPH

Kristian B Filion, PhD

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The cardiovascular safety trials of DPP-4 inhibitors, GLP-1 agonists, and SGLT2 inhibitors

Short Title: Cardiovascular outcome trials of newer antihyperglycemic drugs

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Word Count (excluding tables, abstract)**:** 5,467; **Tables:** 2

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Keywords: diabetes; cardiovascular; randomized controlled trial; DPP-4 inhibitors; GLP-1 agonists; SGLT2 inhibitors

ABSTRACT

In this paper, we review the results of large, double-blind, placebo-controlled randomized trials mandated by the US Food and Drug Administration to examine the cardiovascular safety of newly-approved antihyperglycemic agents in patients with type 2 diabetes. The cardiovascular effects of dipeptidyl peptidase-4 (DPP-4) inhibitors remain controversial: while these drugs did not reduce or increase the risk of primary, pre-specified composite cardiovascular outcomes, one DPP-4 inhibitor (saxagliptin) increased the risk of hospitalization for heart failure in the overall population, another (alogliptin) demonstrated inconsistent effects on heart failure hospitalization across subgroups of patients, and a third (sitagliptin) demonstrated no effect on heart failure. Evidence for cardiovascular benefits of glucagon-like peptide-1 (GLP-1) agonists has been similarly heterogeneous, with liraglutide and semaglutide reducing the risk of composite cardiovascular outcomes, but lixisenatide having no reduction or increase in cardiovascular risk. The effect of GLP-1 agonists on retinopathy remains a potential concern. In the only completed trial to date to assess a sodium-glucose cotransporter-2 (SGLT2) inhibitor, empagliflozin reduced the risk of composite cardiovascular endpoints, predominantly through its impact on cardiovascular mortality and heart failure hospitalization.

INTRODUCTION

In 2007, Nissen and colleagues published a meta-analysis suggesting that rosiglitazone, an antihyperglycemic agent in the thiazolidinedione class, was associated with an increased risk of myocardial infarction (MI) among patients with type 2 diabetes mellitus (T2DM) [1]. The resulting concern that antihyperglycemic agents may provoke adverse cardiovascular events motivated the US Food and Drug Administration (FDA) to mandate the conduct of large, randomized, placebo-controlled cardiovascular safety trials for all new antihyperglycemic agents [2]. The FDA defines its standard for safety as non-inferiority of the study drug compared with placebo for a composite cardiovascular outcome (*i.e.,* cardiovascular mortality, non-fatal MI, non-fatal stroke, and other optional endpoints) using a non-inferiority margin of 1.8 for pre-marketed drugs and 1.3 for post-marketed drugs [2]. Several large randomized controlled trials (RCTs) have since been completed to assess the cardiovascular safety of antihyperglycemic agents as add-on therapies to the normal standard of care in T2DM. Much interest has been directed to the RCT results of three antihyperglycemic agent classes: dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, and sodium-glucose co-transporter 2 (SGLT2) inhibitors. Here, we present and discuss these drug classes and their respective cardiovascular safety trials, the results of which have important implications for the prevention of cardiovascular events in patients with T2DM.

DIPEPTIDYL PEPTIDASE-4 INHIBITORS

The enzyme DPP-4 is responsible for the degradation of GLP-1, an incretin that stimulates insulin secretion in pancreatic β cells [3]. In patients with T2DM, the effect of GLP-1 on insulin secretion is significantly diminished. By blocking the enzymatic degradation of GLP-1, DPP-4 inhibitors increase endogenous GLP-1 levels, stimulating insulin secretion [3]. Because

endogenous GLP-1 is expressed in myocardial tissue and vascular endothelium [4], it is biologically plausible that incretin-based therapies such as DPP-4 inhibitors elicit cardiovascular effects. Three large, double-blind, placebo-controlled non-inferiority RCTs have been completed to assess the cardiovascular safety of DPP-4 inhibitors: SAVOR-TIMI 53 [5-8], EXAMINE [9-11], and TECOS [12-15].

<u>SAVOR-TIMI 53 (Saxagliptin)</u>

The SAVOR-TIMI 53 trial examined saxagliptin for the primary endpoint of major adverse cardiovascular events (MACE), a composite of cardiovascular death, non-fatal MI, and non-fatal stroke (Table 1) [5-8]. A total of 16,496 patients with or at high risk of atherosclerotic cardiovascular disease (CVD) were randomized to saxagliptin (5 mg daily, 2.5 mg in patients with reduced kidney function) or matching placebo. During a median follow-up of 2.1 years, MACE occurred in 7.3% of patients randomized to saxagliptin and 7.2% of patients randomized to placebo (hazard ratio [HR]: 1.00; 95% confidence interval [CI]: 0.89-1.12; Table 2) [7], consistent with the pre-specified non-inferiority margin of 1.3. Similar results were obtained for the secondary composite endpoint that included MACE, hospitalization for unstable angina (UA), coronary revascularization, and hospitalization for heart failure (HF) [7]. Importantly, an unexpected increased risk of hospitalization for HF was observed among patients randomized to saxagliptin (3.5% vs 2.8%; HR: 1.27; 95% CI: 1.07-1.51) [7], with similar effects among patients with and without a history of HF at baseline (p-interaction=0.67; Table 2) [8]. Saxagliptin led to a greater number of renal abnormalities than placebo (5.8% vs 5.1%; p=0.04), but did not increase the risk of the pre-specified composite renal outcome (HR: 1.08; 95% CI: 0.88-1.32) [7].

<u>EXAMINE (Alogliptin)</u>

The EXAMINE trial investigated alogliptin (6.25 to 25 mg daily, according to kidney function) for the primary outcome of MACE among 5,380 patients with T2DM and a recent acute coronary syndrome (Table 1) [9-11]. After a median of 1.5 years of follow-up, 11.3% of patients randomized to alogliptin and 11.8% of those randomized to placebo experienced a MACE (HR: 0.96; one-sided 95% CI ≤1.16; Table 2) [10], satisfying the pre-specified non-inferiority margin of 1.3. Alogliptin was also non-inferior for the secondary composite outcome of MACE and urgent revascularization after hospitalization for UA (HR: 0.95; one-sided 95% CI ≤1.14) [10]. In contrast to SAVOR-TIMI 53, there was no overall increased risk of hospitalization for HF from alogliptin (3.1% vs 2.9%; HR: 1.07; 95% CI: 0.79-1.46) [10]. However, in a *post hoc* subgroup analysis motivated partially by the results of the SAVOR-TIMI 53 trial [11], alogliptin was associated with an increased risk of hospitalization for HF among patients *without* a baseline history of HF (2.2% vs 1.3%; HR: 1.76; 95% CI: 1.07-2.90), although this risk was not present among patients *with* prior HF (8.2% for alogliptin vs 8.5% for placebo; HR: 1.00; 95% CI: 0.71-1.42; p-interaction=0.07) [11].

TECOS (Sitagliptin)

The TECOS trial examined sitagliptin (100 mg daily; 50 mg if kidney function was impaired) for the primary composite endpoint of MACE and hospitalization for UA (Table 1) [12-15]. The trial included 14,735 diabetic patients ≥50 years old with a history of coronary artery disease, ischemic cerebrovascular disease, or atherosclerotic peripheral arterial disease. During a median follow-up of 3.0 years, 9.6% of patients randomized to sitagliptin and 9.6% of those randomized to placebo experienced the primary endpoint in the main, per-protocol analysis (HR: 0.98; 95% CI: 0.88-1.09), satisfying the non-inferiority margin of 1.3 [14]. Sitagliptin was also non-inferior to placebo in the per-protocol analysis of the secondary endpoint (MACE) [14] and for both

primary and secondary composite endpoints according to intention-to-treat analyses (Table 2).

Sitagliptin was not associated with an increased risk of hospitalization for HF (3.1% vs 3.1%; intention-to-treat HR: 1.00; 95% CI: 0.83-1.20), nor was there any evidence of interaction between sitagliptin and baseline history of HF (p-interaction=0.67; Table 2) [14, 15].

SUMMARY OF CARDIOVASCULAR EFFECTS OF DPP-4 INHIBITORS

DPP-4 inhibitor trials all met the FDA's non-inferiority criteria for all primary and secondary outcomes, though these positive results have been overshadowed by the HF hospitalization safety signal raised by the SAVOR-TIMI 53 trial. This signal was not reproduced in EXAMINE, which found an adverse effect on HF only after *post hoc* analyses, or in TECOS, which observed no signal for harm (or benefit). Several meta-analyses [15-18] of RCTs and observational studies have assessed the HF risk of DPP-4 inhibitors since the SAVOR-TIMI 53 safety signal arose and concluded that there is no definitive class-wide increase in HF hospitalization risk (meta-analyzed HR across the 3 cardiovascular RCTs: 1.14; 95% CI: 0.97-1.34) [15] nor major heterogeneity across trials/drugs (I^2=44.9%; p-interaction=0.16) [15]. RCTs conducted in non-cardiovascular patients [16], and population-based retrospective observational studies [19], also detected no increased risk of HF with DPP-4 use.

What, then, might explain the potential increased risk for HF hospitalization seen in the SAVOR-TIMI 53 trial but not reproduced in either EXAMINE or TECOS? It is possible that the overall HF effect of SAVOR-TIMI 53, and the subgroup HF effect of EXAMINE, were chance findings due to random error given the presence of multiple testing without correction, as both SAVOR-TIMI 53 and EXAMINE did not correct for multiplicity in their presented effects estimates. It is also possible that DPP-4 inhibitors have drug-specific HF effects, possibly as a result of different non-incretin substrate affinities [18], though no specific mechanisms have been identified thus

far. Indirect effects of DPP-4 inhibitors may also be important. For example, some evidence suggests the existence of an antagonistic interaction between DPP-4 inhibitors and angiotensin-converting-enzyme inhibitors on HF risk [20].

GLUCAGON-LIKE PEPTIDE 1 AGONISTS

GLP-1 agonists modulate glucose levels by stimulating insulin release and inhibiting glucagon secretion [21]. These drugs may be short-acting (requiring >1 administration per day), or long-acting (requiring ≤1 daily dose), which achieve their sustained effects through reduced degradation by endogenous DPP-4 [3]. GLP-1 agonists are thought to be capable of reducing cardiovascular risk through several pathways supplementary to their effect on blood glucose: weight loss promotion, reduced blood pressure, decreased myocardial and vascular inflammation, lower platelet aggregation, and others [21]. The relative importance of these and other mechanisms is a subject of great interest in light of the three large, cardiovascular non-inferiority RCTs that have been conducted to date on GLP-1 agonists in T2DM: ELIXA [22, 23], LEADER [24, 25], and SUSTAIN-6 [26].

ELIXA (Lixisenatide)

The ELIXA trial included 6,068 patients with T2DM aged ≥30 years with a recent history of spontaneous acute coronary syndrome that were randomized to receive subcutaneous injections of lixisenatide (10-20 μg *once daily* at the investigator's discretion) or matched placebo (Table 1) [22, 23]. After a median follow-up of 2.1 years, lixisenatide demonstrated non-inferiority to placebo (pre-specified HR margin: 1.3) for the primary composite endpoint of MACE and hospitalization for UA (13.4% vs 13.2%; HR: 1.02; 95% CI: 0.89-1.17) [23]. There were no significant treatment-group differences observed for secondary composite outcomes (*i.e.,*

MACE, hospitalization for UA, and hospitalization for HF, with or without coronary revascularization; Table 2) or their individual components [23].

LEADER (Liraglutide)

The LEADER trial randomized 9,340 patients with T2DM aged ≥50 years with a prior history of CVD or aged ≥60 years with at least one investigator-determined cardiovascular risk factor to liraglutide (*once-daily* subcutaneous injections ≥1.8 mg) or matched placebo to evaluate their effects on the primary endpoint of MACE (Table 1) [24, 25]. The secondary composite endpoint consisted of MACE, coronary revascularization, hospitalization for UA, and hospitalization for HF. After a median follow-up of 3.8 years, liraglutide was shown to not only be non-inferior to placebo (pre-specified HR margin: 1.3), but superior in reducing MACE (13.0% vs 14.9%; HR: 0.87; 95% CI: 0.78-0.97) [24]. Similar benefits were observed for the secondary composite outcome, and some benefits were also observed for pre-specified (all-cause mortality, cardiovascular mortality, total microvascular events, and nephropathy) and *post hoc* (MI) endpoints (Table 2) [24]. Although each individual endpoint of the composite primary outcome was underpowered, the decreased cardiovascular mortality risk following liraglutide treatment is noteworthy (4.7% vs 6.0%; HR: 0.78; 95% CI: 0.66-0.93) [24]. With regards to liraglutide's impact on microvascular events, there was a reduction in new or worsening nephropathy (HR: 0.78; 95% CI: 0.67-0.92) but a non-significant signal suggesting a higher rate of diabetic retinopathy (HR: 1.15; 95% CI: 0.87-1.52) [24].

SUSTAIN-6 (Semaglutide)

In the SUSTAIN-6 trial [26], 3,297 patients with T2DM either ≥50 years old with established CVD, chronic HF, or chronic kidney disease, or ≥60 years old with at least one cardiovascular

risk factor, were randomized 1:1:1:1 to receive *once-weekly* semaglutide (0.5 mg or 1.0 mg) or

matching placebo subcutaneously and then followed for the primary outcome of MACE (Table

1). After a median of 2.1 years of follow-up, patients taking any dose of semaglutide had a

significantly lower risk of MACE than those taking placebo (6.6% vs 8.9%, HR: 0.74; 95% CI:

0.58-0.95) [26], greatly surpassing the pre-specified non-inferiority margin of 1.8 and meeting a

post hoc definition of superiority (unadjusted for multiplicity). Beneficial effects were also

observed for two secondary composite outcomes: 1) MACE, hospitalization for UA, coronary or

peripheral revascularization, and hospitalization for HF; and 2) all-cause mortality, nonfatal

stroke, and nonfatal MI (Table 2). The protective effect of semaglutide on composite endpoints

appeared to be driven by semaglutide's reduction of nonfatal stroke (1.6% vs 2.7%; HR: 0.61;

95% CI: 0.38-0.99) [26]. With regards to microvascular complications, semaglutide reduced new

or worsening nephropathy (HR: 0.64; 95% CI: 0.46-0.88) but significantly increased the risk of

retinopathy complications (3.0% vs 1.8%; HR: 1.76; 95% CI: 1.11-2.78) [26]. The SUSTAIN-6

trial authors suggested that rapid decreases in blood glucose may have led to worsening

retinopathy, as in previous reports from the Diabetes Control and Complications trial and the

Oslo study [26].

SUMMARY OF CARDIOVASCULAR EFFECTS OF GLP-1 AGONISTS

ELIXA [22, 23], LEADER [24, 25], and SUSTAIN-6 [26] all demonstrated non-inferiority with

respect to their primary and secondary cardiovascular outcomes. LEADER and SUSTAIN-6

further generated optimism that GLP-1 agonists may improve cardiovascular morbidity in

patients with T2DM. Results from a meta-analysis of only the smaller phase II RCTs of GLP-1

agonists, which found a 72% relative reduction in mortality risk, support the benefits of this drug

class [27]; however, this finding was greater in magnitude than the effects observed in the major

GLP-1 agonist RCTs and reinforces that circumspection is necessary when interpreting meta-analyses of small trials, as publication bias is more likely. A number of retrospective cohort studies found no association between initiation of GLP-1 agonists and risk of HF [19] or MACE [28] when compared to other oral antihyperglycemic agents.

An important question remains: why was no cardiovascular benefit observed in ELIXA, while GLP-1 agonists reduced MACE (though with varying effects on individual endpoints) in LEADER and SUSTAIN-6? Chance is unlikely to explain the benefits of liraglutide and semaglutide on MACE because the relevant trials considered MACE to be the primary, pre-specified study result. Further, the superiority test in the LEADER trial was pre-specified in the study's hierarchical testing scheme. Though SUSTAIN-6 was not powered for a superiority test and did not correct for multiple testing, the use of two doses of semaglutide with consistent results makes random effects less likely. Instead, variations in drug specific effects or patient populations are likely responsible for the heterogeneity between trials. While no currently-known mechanism supports the differential effects of semaglutide and liraglutide compared with lixisenatide, considerable pharmacodynamic and pharmacokinetic differences between medications of the GLP-1 agonist class exist with respect to peak serum concentration, time to peak serum concentration, effect on HbA1c, route of elimination and, in particular, half-life [29]. In reported RCTs, the study drugs affected risk factors for CVD differently, with liraglutide and semaglutide reducing body weight and systolic blood pressure by more than lixisenatide (though still by minor amounts). Whether such mechanistic effects, or others yet to be determined, explain the variation in impact of these medications on individual cardiovascular outcomes seen between the LEADER and SUSTAIN-6 trials, remains unknown. Irrespective of drug properties, treatment effect differences may also originate in part from studying different types of patients

with T2DM in regards to proximity from an acute coronary event and presence or absence of other risk factors.

It is noteworthy and of concern that liraglutide and semaglutide trended towards increased retinopathy risk, a complication of T2DM that greatly reduces quality of life. Given the magnitude and significance of semaglutide's effect on the risk of diabetic retinopathy complications (a 1.2% absolute increase) and the potential for liraglutide to similarly increase retinopathy risk, more research is needed on the safety of GLP-1 receptor agonists as a class with respect to microvascular complications.

SODIUM-GLUCOSE CO-TRANSPORTER 2 INHIBITORS

SLGT2 is a glucose cotransporter that aids the reabsorption of glucose and sodium in the kidneys [29]. In response to hyperglycemic conditions, SGLT2 activity increases, raising the capacity of the kidneys to reabsorb glucose and lowering glucose secretion in the urine [30]. SGLT2 inhibitors lower the threshold for renal reabsorption of glucose and sodium, thereby increasing urinary glucose and sodium concentrations and decreasing plasma glucose and sodium concentrations. As a class of antihyperglycemic agents, SGLT2 inhibitors are thought to be safe with respect to hypoglycemia (because of their inherent loss of efficacy as HbA1c levels decrease) and body weight (because they improved caloric balance) [30]. SGLT2 transporters are almost entirely found in kidney epithelial cells [30], making their modulation unlikely to impact cardiac and vascular tissue and promote downstream cardiovascular effects. SGLT2 inhibition may still elicit several ancillary cardiovascular benefits through glycosuria and natriuresis, including for example decreased plasma uric acid (which potentially lowers hypertension and CVD) and reduced blood pressure [30, 31]. A single major cardiovascular safety trial (EMPA-REG OUTCOME) has been conducted for SGLT-2 inhibitors to date.

EMPA-REG OUTCOME (Empagliflozin)

EMPA-REG OUTCOME was a non-inferiority trial of empagliflozin among patients with

T2DM (n=7,028) and established CVD [32-34]. Patients were randomized 1:1:1 to daily low-

dose empagliflozin (10 mg), high-dose empagliflozin (25 mg), or placebo, and followed for the

primary outcome of MACE. After a median treatment duration of 2.6 years, MACE occurred in

10.5% of participants in the pooled empagliflozin group and 12.1% in the placebo group (HR:

0.85; 95% CI: 0.74-0.99; Table 2) [34], satisfying the pre-specified non-inferiority margin of 1.3

and demonstrating superiority according to a hierarchical testing strategy. The MACE results

were driven by a substantial reduction in cardiovascular mortality (3.7% vs 5.9%; HR: 0.62; 95%

CI: 0.49-0.77) rather than by reductions in non-fatal MI (HR: 0.87; 95% CI: 0.70-1.09; excludes

silent MI) or non-fatal stroke, for which a signal was present (HR: 1.24; 95% CI: 0.92-1.67).

Empagliflozin also demonstrated a 32% relative reduction in all-cause mortality, consistent with

the high proportion of cardiovascular deaths. In addition, empagliflozin substantially reduced the

risk of hospitalization for HF (2.7% vs 4.1%; HR: 0.65; 95% CI: 0.50-0.85) [34], an effect which

was robust to different subgroup analyses, including by baseline history of HF (Table 2) [32]. It

is important to note that baseline HF status and HF events were determined without ejection

fraction information; consequently, the effect of empagliflozin on ejection fraction in HF is

unclear [32]. Despite concern over its renal safety, empagliflozin significantly lowered the risk

of acute renal failure (5.2% vs 6.6%, p<0.01). Related to its pro-glycosuria effect, empagliflozin

increased the risk of genital infections (6.4% vs 1.8%, p<0.001) [34].

SUMMARY OF CARDIOVASCULAR EFFECTS OF SGLT2 INHIBITORS

Consistent with the EMPA-REG OUTCOME trial, the results of published meta-analyses of

smaller phase II/III RCTs of SGLT2 inhibitors [35, 36], and data presented to the FDA for initial

approval of dapagliflozin and canagliflozin have identified no cardiovascular safety signals for SGLT2 inhibitors [37, 38]. Some meta-analyses of clinical trials, such as that presented by Savarese and colleagues [35] have reported that SGLT2 inhibitors elicit cardiovascular benefits (*e.g.,* on MI and HF), though these results should be interpreted with caution given the size and duration of the included trials.

Potential mechanisms of benefit remain under active investigation, but leading pathways likely contributing to the reduction in the risk of HF and cardiovascular mortality include weight loss promotion and beneficial hemodynamic effects through a mix of glycosuria and natriuresis. The EMPA-REG OUTCOME trial showed that empagliflozin decreased weight (by ~2 kg), systolic blood pressure (by ~4-6 mm Hg), and plasma volume (measured as an increased concentration of hemoglobin of ~0.8 g/dL) [34]. And, while these effects were modest, their combination may have produced clinically important results. Other mechanisms, such as improvements in inflammation, arrhythmia, and arterial stiffness, are also thought to be relevant [39]. Whether these mechanisms play a role via hemoconcentration or hypotension to increase the risk of stroke remains unknown.

SUMMARY OF CARDIOVASCULAR SAFETY TRIALS

In the seven large, placebo-controlled RCTs reported upon to date, all studied antihyperglycemic agents were observed to be non-inferior to placebo for their primary, composite outcomes. Credible systematic reviews and meta-analyses support the cardiovascular safety of these drugs, as do their general pharmacologic properties, which include weight loss and hemodynamic effects [4, 30]. Though an increase in HF risk may follow treatment with saxagliptin or alogliptin, these effects also plausibly derive from chance or from indirect effects unrelated to the study drugs. Substantial benefits on CVD endpoints were observed for GLP-1 agonists

liraglutide (on primary and secondary MACE-based outcomes, MI, cardiovascular mortality, and all-cause mortality) and semaglutide (on primary and secondary MACE-based outcomes, and non-fatal stroke). The SGLT2 inhibitor empagliflozin reduced the risk of MACE, HF, cardiovascular mortality, and all-cause mortality, though its potential effects on stroke should not be ignored.

While adverse cardiovascular events are a major concern for patients with T2DM, the abovementioned drugs may elicit other adverse health effects that should be considered in clinical practice. Saxagliptin significantly increased the risk of renal abnormalities in the SAVOR-TIMI 53 trial [7]. Although semaglutide decreased new or worsened nephropathy in the SUSTAIN-6 trial, it increased retinopathy rates [26]. Liraglutide also non-significantly increased retinopathy rates, though this potential effect deserves further scrutiny given the results of the SUSTAIN-6 trial [24] and the potential for a class effect. Higher rates of gastrointestinal events were also reported for both semaglutide and liraglutide [24, 26]. Finally, empagliflozin led to increased rates of genital infection, though it appeared to prevent acute kidney failure [34].

To address lingering questions surrounding these antihyperglycemic agents, future research is needed. Information on pharmacologic mechanisms should examine the discrepant cardiovascular effects of drugs within the same class. It is also important that investigators quantify the mediating effects of background antihyperglycemic agents (including sulfonylureas and thiazolidinediones, which have been implicated in adverse cardiovascular events [1, 40]), among patients who were poorly controlled. All included placebo-controlled trials had important differences in the use of medications during follow-up, and these may have greatly impacted observed results. Similarly, the effect of hypoglycemia on CVD deserves further inquiry since this potential risk factor for CVD [41] often differed between treatment groups. Also, the

mediating effect of blood glucose may have contributed in part to the empirical benefits of study drugs, as treatment groups often differed in post-baseline HbA1c levels. Yet the effect of blood glucose alone is unlikely to drive the observed benefits, or else trials demonstrating lowered blood glucose would have been more consistent with respect to cardioprotection. In addition, the generalizability of the results of the cardiovascular outcome trials to patients with T2DM seen in everyday clinical practice should be further researched, as patients meeting inclusion criteria for these RCTs are different from many T2DM patients seen as part of routine practice. Finally, trials are needed to assess the use of combination therapies that include antihyperglycemic drugs with potentially complimentary mechanisms.

Some of this information will come from ongoing cardiovascular RCTs with upcoming completion dates. The CARMELINA trial of linagliptin (NCT01897532) will provide evidence for or against a HF class effect of DPP-4 inhibitors, while the EXCSEL trial of exenatide (NCT01144338) will further elucidate the potential benefits of GLP-1 agonist therapy. Evidence supporting the cardiovascular safety, and potential benefit for cardiovascular mortality and HF hospitalization, of SGLT2 inhibitors beyond empagliflozin will be determined in the upcoming CANVAS (canagliflozin; NCT01032629) and DECLARE-TIMI 58 (dapagliflozin; NCT01730534) trials. RCTs in progress should also provide insight into any potential adverse effects on stroke, retinopathy, and other safety concerns. Finally, the ongoing CAROLINA trial (NCT01243424), which will randomize approximately 6,000 patients to either linagliptin or glimepiride, is the only ongoing large cardiovascular outcome trial with an active control and will help elucidate the role of background medications in already completed cardiovascular outcome trials of antihyperglycemic agents.

CLINICAL RECOMMENDATIONS

For diabetic patients at high cardiovascular risk, American, Canadian, and international guidelines recommend metformin monotherapy until treatment failure as the primary pharmacological approach, at which point combination therapy should be commenced. Because there are insufficient data on cardiovascular benefit of these agents as monotherapies, current guidelines do not recommend their use in such fashion.

Until further data are available on DPP-4 inhibitors, physicians should follow the label warnings added by the FDA in 2016, which recommend caution when prescribing saxagliptin or alogliptin, particularly in patients with T2DM who already have established heart disease or renal impairment. Many practitioners may consider avoiding the DPP-4 inhibitor class overall given the availability of alternative classes of therapies, which may have a marked impact on current treatment patterns. The FDA safety announcement nevertheless emphasized that patients currently treated with DPP-4 inhibitors should not stop taking their medications without first talking with their primary care, diabetes, or cardiology practitioners. Practitioners should monitor for signs (weight gain, edema) and symptoms (exertional dyspnea, orthopnea, fatigue) for HF after starting DPP-4 inhibitors and consider transitioning away from these drugs if HF develops.

We recommend GLP-1 agonists (especially liraglutide) and SGLT2 inhibitors (especially empagliflozin) as second-line treatments of T2DM given their proven reductions in cardiovascular events in patients at high risk of CVD. Empagliflozin has recently been approved by the FDA and Health Canada for the prevention of cardiovascular death, making it the only oral antihyperglycemic agent approved for this indication. We note that the GLP-1 agonist semaglutide is not available for clinical use anywhere at the time of writing. Though physicians should have limited concern that lixisenatide, liraglutide, or semaglutide increase cardiovascular risk when used as add-on therapies to metformin, further data on retinopathy risk and

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effectiveness in routine clinical practice are awaited. Similar data may inform the risk of stroke among SGLT2 inhibitor users, which remains a potential concern.

For patients with low cardiovascular risk, no clinical evidence supports the preferential use of DPP-4 inhibitors, GLP-1 agonists, or SGLT2 inhibitors to improve cardiovascular risk profiles. Physician and patient preference considering the efficacy and potential side effects of different treatments should determine therapy choice in this low-risk group.

ACKNOWLEDGEMENTS

DISCLOSURES

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Table 1. Design characteristics and baseline statistics of all major, cardiovascular safety trials of DPP-4 inhibitors, GLP-1 agonists, and SGLT2 inhibitors.

	Treatment groups	Primary endpoint	Secondary endpoint(s)	Selected major inclusion criteria	Number randomized	Mean age in years (SD)	Men %	Mean diabetes duration (years)	Mean HbA1c %
DPP-4 inhibitors									
SAVOR-TIMI 53 [5-8]	1) saxagliptin 2) placebo	MACE	MACE + HUA + coronary revascularization + HF	• Not taking DPP-4 inhibitors or GLP-1 agonists • EITHER ≥40 years old with history of atherosclerosis OR ≥55 (men) or ≥60 (women) years old with >1 CV risk factor • HbA1c ≥6.5% and ≤12.0% • No acute vascular event <2 months before randomization	16,496	65.0 (8.6)	67%	11.9	8.0%
EXAMINE [9-11]	1) alogliptin 2) placebo	MACE	MACE + urgent revascularization after HUA	• Taking antihyperglycemic agents other than DPP-4 inhibitors or GLP-1 agonists • ≥18 years old • History of ACS 15 - 90 days prior to randomization • HbA1c ≥6.5% (≥7.0% if taking insulin) and ≤11.0% • No unstable cardiac disorder • No ACE event <15 days before randomization	5,380	60.9 (10.0)	70%	7.1	8.0%
TECOS [12-15]	1) sitagliptin 2) placebo	MACE + HUA	MACE	• EITHER taking pioglitazone, metformin and/or sulfonylurea OR taking insulin with or without metformin • ≥50 years old • HbA1c ≥6.5% and ≤8.0% • History of CAD, ICD, or atherosclerotic peripheral arterial disease • No history of ≥2 hypoglycemic episodes in the year prior to enrollment	14,735*	66.0 (8.0)	71%	9.4+	7.3%
GLP-1 agonists									
ELIXA [22, 23]	1) lixisenatide 2) placebo	MACE + HUA	1) MACE + HUA + HHF 2) MACE + HUA + HHF + coronary revascularization	• Not taking DPP-4 inhibitors or GLP-1 agonists • ≥30 years old • ACS within 180 before screening without bypass graft surgery • HbA1c ≥5.5% and ≤11.0% • No percutaneous coronary intervention ≤15 days prior to screening	6,068	60.3 (9.7)	69%	9.3	7.7%
LEADER [24, 25]	1) liraglutide 2) placebo	MACE	MACE + coronary revascularization + HUA + HHF	• Not taking DPP-4 inhibitors or GLP-1 agonists • EITHER ≥50 years old with ≥1 prior incidence of CVD OR ≥60 years old with ≥1 CV risk factor • HbA1c ≥7.0% • No acute coronary or cerebrovascular event <15 days prior to screening	9,340	64.3 (7.2)	64%	12.7	8.7%
SUSTAIN-6 [26]	1) semaglutide 0.5 mg 2) semaglutide 1.0 mg 3) placebo 4) placebo	MACE	1) MACE + HUA + coronary revascularization 2) all-cause mortality + nonfatal stroke + nonfatal MI	• On ≤2 antihyperglycemic agents other than DPP-4 inhibitors or GLP-1 agonists with or without basal or premixed insulin • EITHER ≥50 years old with CVD, chronic heart failure, or chronic kidney disease OR ≥60 years old with ≥1 CV risk factor • HbA1c ≥7.0% • Acute coronary or cerebrovascular event ≤90 days prior to randomization	3,297	64.6 (7.4)	61%	13.9	8.7%
SGLT2 inhibitors									
EMPA-REG OUTCOME [32-34]	1) empagliflozin 10 mg 2) empagliflozin 25 mg 3) placebo	MACE	MACE + HUA	• ≥18 years old • HbA1c ≥7.0% and ≤10.0% (or ≤9.0% if no recent history of antihyperglycemic agent use) • Established CVD as determined by history of MI, stroke, UA, or evidence of CAD or PAD • ACS, stroke, or transient ischemic attack ≤2 months prior to informed consent	7,028†	63.1 (8.6)	71%	57% patients > 10 years	8.1%

Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; CV, cardiovascular; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; HF, heart failure; HHF, hospitalization for heart failure; HUA, hospitalization for unstable angina; ICD, ischemic cerebrovascular disease; MACE, major adverse cardiovascular events (composite endpoint that includes cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke); MI, myocardial infarction; PAD, peripheral arterial disease; SD, standard deviation; SGLT2, sodium-glucose co-transporter 2.

* Data provided for the 14,724 patients who consented to the trial protocol.

† Data for the 7,034 patients originally reported as treated [33], unless otherwise specified

‡ Median

Table 2. Adjusted HRs and 95% CIs for the intention-to-treat† analyses of select trial endpoints of major, cardiovascular safety trials of DPP-4 inhibitors, GLP-1 agonists, and SGLT2 inhibitors.*

	Primary outcome	Secondary outcome(s)	Heart Failure			MI	Stroke	HUA	Mortality	
			Total	History of HF	No history of HF				Cardiovascular	All-cause
DPP-4 inhibitors										
SAVOR-TIMI 53 [5-8]	1.00 (0.89-1.12)	1.02 (0.94-1.11)	1.27 (1.07-1.51)	1.21 (0.93-1.58)	1.32 (1.04-1.66)	0.95 (0.80-1.12)	1.11 (0.88-1.39)	1.19 (0.89-1.60)	1.03 (0.87-1.22)	1.11 (0.96-1.27)
EXAMINE [9-11]	0.96 (≤1.16)‡	0.95 (≤1.14)‡	1.07 (0.79-1.46)	1.00 (0.71-1.42)	1.76 (1.07-2.90)	1.08 (0.88-1.33)§	0.91 (0.55-1.50)§	0.90 (0.60-1.37)¶	0.79 (0.60-1.04)	0.88 (0.71-1.09)
TECOS [12-15]	0.98 (0.89-1.08)	0.99 (0.89-1.10)	1.00 (0.83-1.20)	1.05 (0.79-1.39)	0.96 (0.76-1.23)	0.95 (0.81-1.11)	0.97 (0.79-1.19)	0.90 (0.70-1.16)	1.03 (0.89-1.19)	1.01 (0.90-1.14)
GLP-1 agonists										
ELIXA [22, 23]	1.02 (0.89-1.17)	1) 0.97 (0.85-1.10) 2) 1.00 (0.90-1.11)	0.96 (0.75-1.23)	0.93 (0.66-1.30)	0.97 (0.67-1.40)	1.03 (0.87-1.22)	1.12 (0.79-1.58)	1.11 (0.47-2.62)	0.98 (0.78-1.22)	0.94 (0.78-1.13)
LEADER [24, 25]	0.87 (0.78-0.97)	0.88 (0.81-0.96)	0.87 (0.73-1.05)	Not reported	Not reported	0.86 (0.73-1.00)	0.86 (0.71-1.06)	0.98 (0.76-1.26)	0.78 (0.66-0.93)	0.85 (0.74-0.97)
SUSTAIN-6 [26]	0.74 (0.58-0.95)	1) 0.74 (0.62-0.89) 2) 0.77 (0.61-0.97)	1.11 (0.77-1.61)	Not reported	Not reported	0.74 (0.51-1.08)§	0.61 (0.38-0.99)§	0.82 (0.47-1.44)	0.98 (0.65-1.48)	1.05 (0.74-1.50)
SGLT2 inhibitors										
EMPA-REG OUTCOME [32-34]	0.86 (0.74-0.99)	0.89 (0.78-1.01)	0.65 (0.50-0.85)	0.75 (0.48-1.19)	0.59 (0.43-0.82)	0.87 (0.70-1.09)**	1.18 (0.89-1.56)	0.99 (0.74-1.34)	0.62 (0.49-0.77)	0.68 (0.57-0.82)

Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; HF, heart failure; HR, hazard ratio; HUA, hospitalization for unstable angina; MI, myocardial infarction; SGLT2, sodium-glucose co-transporter 2.

*The primary outcome was major adverse cardiovascular events (MACE, a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke) for all trials except TECOS and ELIXA, where it was MACE + hospitalization for unstable angina (Table 1). Secondary outcomes are described in Table 1. All dose categories were pooled for each study drug.

† EMPA-REG used a modified intention-to-treat protocol restricted to patients who received at least one dose of a study drug.

‡ One-tailed test

§ Non-fatal events only

¶ Requiring revascularization

** Excluding silent myocardial infarction

The cardiovascular safety trials of DPP-4 inhibitors, GLP-1 agonists, and SGLT2 inhibitors

Short Title: Cardiovascular outcome trials of newer antihyperglycemic drugs

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Word Count (excluding tables, abstract)**:** 5,467~~61~~; **Tables:** 2

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Keywords: diabetes; cardiovascular; randomized controlled trial; DPP-4 inhibitors; GLP-1 agonists; SGLT2 inhibitors

ABSTRACT

In this paper, we review the results of large, double-blind, placebo-controlled randomized trials mandated by the US Food and Drug Administration to examine the cardiovascular safety of newly-approved antihyperglycemic agents in patients with type 2 diabetes. The cardiovascular effects of dipeptidyl peptidase-4 (DPP-4) inhibitors remain controversial: while these drugs did not reduce or increase the risk of primary, pre-specified composite cardiovascular outcomes, one DPP-4 inhibitor (saxagliptin) increased the risk of hospitalization for heart failure in the overall population, another (alogliptin) demonstrated inconsistent effects on heart failure hospitalization across subgroups of patients, and a third (sitagliptin) demonstrated no effect on heart failure. Evidence for cardiovascular benefits of glucagon-like peptide-1 (GLP-1) agonists has been similarly heterogeneous, with liraglutide and semaglutide reducing the risk of composite cardiovascular outcomes, but lixisenatide having no reduction or increase in cardiovascular risk. The effect of GLP-1 agonists on retinopathy remains a potential concern. In the only completed trial to date to assess a sodium-glucose cotransporter-2 (SGLT2) inhibitor, empagliflozin reduced the risk of composite cardiovascular endpoints, predominantly through its impact on cardiovascular mortality and heart failure hospitalization.

INTRODUCTION

In 2007, Nissen and colleagues published a meta-analysis suggesting that rosiglitazone, an antihyperglycemic agent in the thiazolidinedione class, was associated with an increased risk of myocardial infarction (MI) among patients with type 2 diabetes mellitus (T2DM) [1]. The resulting concern that antihyperglycemic agents may provoke adverse cardiovascular events motivated the US Food and Drug Administration (FDA) to mandate the conduct of large, randomized, placebo-controlled cardiovascular safety trials for all new antihyperglycemic agents [2]. The FDA defines its standard for safety as non-inferiority of the study drug compared with placebo for a composite cardiovascular outcome (*i.e.,* cardiovascular mortality, non-fatal MI, non-fatal stroke, and other optional endpoints) using a non-inferiority margin of 1.8 for pre-marketed drugs and 1.3 for post-marketed drugs [2]. Several large randomized controlled trials (RCTs) have since been completed to assess the cardiovascular safety of antihyperglycemic agents as add-on therapies to the normal standard of care in T2DM. Much interest has been directed to the RCT results of three antihyperglycemic agent classes: dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, and sodium-glucose co-transporter 2 (SGLT2) inhibitors. Here, we present and discuss these drug classes and their respective cardiovascular safety trials, the results of which have important implications for the prevention of cardiovascular events in patients with T2DM.

DIPEPTIDYL PEPTIDASE-4 INHIBITORS

The enzyme DPP-4 is responsible for the degradation of GLP-1, an incretin that stimulates insulin secretion in pancreatic β cells [3]. In patients with T2DM, the effect of GLP-1 on insulin secretion is significantly diminished. By blocking the enzymatic degradation of GLP-1, DPP-4 inhibitors increase endogenous GLP-1 levels, stimulating insulin secretion [3]. Because

endogenous GLP-1 is expressed in myocardial tissue and vascular endothelium [4], it is biologically plausible that incretin-based therapies such as DPP-4 inhibitors elicit cardiovascular effects. Three large, double-blind, placebo-controlled non-inferiority RCTs have been completed to assess the cardiovascular safety of DPP-4 inhibitors: SAVOR-TIMI 53 [5-8], EXAMINE [9-11], and TECOS [12-15].

SAVOR-TIMI 53 (Saxagliptin)

The SAVOR-TIMI 53 trial examined saxagliptin for the primary endpoint of major adverse cardiovascular events (MACE), a composite of cardiovascular death, non-fatal MI, and non-fatal stroke (Table 1) [5-8]. A total of 16,496 patients with or at high risk of atherosclerotic cardiovascular disease (CVD) were randomized to saxagliptin (5 mg daily, 2.5 mg in patients with reduced kidney function) or matching placebo. During a median follow-up of 2.1 years, MACE occurred in 7.3% of patients randomized to saxagliptin and 7.2% of patients randomized to placebo (hazard ratio [HR]: 1.00; 95% confidence interval [CI]: 0.89-1.12; Table 2) [7], consistent with the pre-specified non-inferiority margin of 1.3. Similar results were obtained for the secondary composite endpoint that included MACE, hospitalization for unstable angina (UA), coronary revascularization, and hospitalization for heart failure (HF) [7]. Importantly, an unexpected increased risk of hospitalization for HF was observed among patients randomized to saxagliptin (3.5% vs 2.8%; HR: 1.27; 95% CI: 1.07-1.51) [7], with similar effects among patients with and without a history of HF at baseline (p-interaction=0.67; Table 2) [8]. Saxagliptin led to a greater number of renal abnormalities than placebo (5.8% vs 5.1%; p=0.04), but did not increase the risk of the pre-specified composite renal outcome (HR: 1.08; 95% CI: 0.88-1.32) [7].

EXAMINE (Alogliptin)

The EXAMINE trial investigated alogliptin (6.25 to 25 mg daily, according to kidney function) for the primary outcome of MACE among 5,380 patients with T2DM and a recent acute coronary syndrome (Table 1) [9-11]. After a median of 1.5 years of follow-up, 11.3% of patients randomized to alogliptin and 11.8% of those randomized to placebo experienced a MACE (HR: 0.96; one-sided 95% CI ≤1.16; Table 2) [10], satisfying the pre-specified non-inferiority margin of 1.3. Alogliptin was also non-inferior for the secondary composite outcome of MACE and urgent revascularization after hospitalization for UA (HR: 0.95; one-sided 95% CI ≤1.14) [10]. In contrast to SAVOR-TIMI 53, there was no overall increased risk of hospitalization for HF from alogliptin (3.1% vs 2.9%; HR: 1.07; 95% CI: 0.79-1.46) [10]. However, in a *post hoc* subgroup analysis motivated partially by the results of the SAVOR-TIMI 53 trial [11], alogliptin was associated with an increased risk of hospitalization for HF among patients *without* a baseline history of HF (2.2% vs 1.3%; HR: 1.76; 95% CI: 1.07-2.90), although this risk was not present among patients *with* prior HF (8.2% for alogliptin vs 8.5% for placebo; HR: 1.00; 95% CI: 0.71-1.42; p-interaction=0.07) [11].

TECOS (Sitagliptin)

The TECOS trial examined sitagliptin (100 mg daily; 50 mg if kidney function was impaired) for the primary composite endpoint of MACE and hospitalization for UA (Table 1) [12-15]. The trial included 14,735 diabetic patients ≥50 years old with a history of coronary artery disease, ischemic cerebrovascular disease, or atherosclerotic peripheral arterial disease. During a median follow-up of 3.0 years, 9.6% of patients randomized to sitagliptin and 9.6% of those randomized to placebo experienced the primary endpoint in the main, per-protocol analysis (HR: 0.98; 95% CI: 0.88-1.09), satisfying the non-inferiority margin of 1.3 [14]. Sitagliptin was also non-inferior to placebo in the per-protocol analysis of the secondary endpoint (MACE) [14] and for both

primary and secondary composite endpoints according to intention-to-treat analyses (Table 2).

Sitagliptin was not associated with an increased risk of hospitalization for HF (3.1% vs 3.1%;

intention-to-treat HR: 1.00; 95% CI: 0.83-1.20), nor was there any evidence of interaction

between sitagliptin and baseline history of HF (p-interaction=0.67; Table 2) [14, 15].

SUMMARY OF CARDIOVASCULAR EFFECTS OF DPP-4 INHIBITORS

DPP-4 inhibitor trials all met the FDA's non-inferiority criteria for all primary and secondary

outcomes, though these positive results have been overshadowed by the HF hospitalization

safety signal raised by the SAVOR-TIMI 53 trial. This signal was not reproduced in EXAMINE,

which found an adverse effect on HF only after *post hoc* analyses, or in TECOS, which observed

no signal for harm (or benefit). Several meta-analyses [15-18] of RCTs and observational studies

have assessed the HF risk of DPP-4 inhibitors since the SAVOR-TIMI 53 safety signal arose and

concluded that there is no definitive class-wide increase in HF hospitalization risk (meta-

analyzed HR across the 3 cardiovascular RCTs: 1.14; 95% CI: 0.97-1.34) [15] nor major

heterogeneity across trials/drugs (I^2=44.9%; p-interaction=0.16) [15]. RCTs conducted in non-

cardiovascular patients [16], and population-based retrospective observational studies [19], also

detected no increased risk of HF with DPP-4 use.

What, then, might explain the potential increased risk for HF hospitalization seen in the SAVOR-

TIMI 53 trial but not reproduced in either EXAMINE or TECOS? It is possible that the overall

HF effect of SAVOR-TIMI 53, and the subgroup HF effect of EXAMINE, were chance findings

due to random error given the presence of multiple testing without correction, as both SAVOR-

TIMI 53 and EXAMINE did not correct for multiplicity in their presented effects estimates. It is

also possible that DPP-4 inhibitors have drug-specific HF effects, possibly as a result of different

non-incretin substrate affinities [18], though no specific mechanisms have been identified thus

far. Indirect effects of DPP-4 inhibitors may also be important. For example, some evidence suggests the existence of an antagonistic interaction between DPP-4 inhibitors and angiotensin-converting-enzyme inhibitors on HF risk [20].

GLUCAGON-LIKE PEPTIDE 1 AGONISTS

GLP-1 agonists modulate glucose levels by stimulating insulin release and inhibiting glucagon secretion [21]. These drugs may be short-acting (requiring >1 administration per day), or long-acting (requiring ≤1 daily dose), which achieve their sustained effects through reduced degradation by endogenous DPP-4 [3]. GLP-1 agonists are thought to be capable of reducing cardiovascular risk through several pathways supplementary to their effect on blood glucose: weight loss promotion, reduced blood pressure, decreased myocardial and vascular inflammation, lower platelet aggregation, and others [21]. The relative importance of these and other mechanisms is a subject of great interest in light of the three large, cardiovascular non-inferiority RCTs that have been conducted to date on GLP-1 agonists in T2DM: ELIXA [22, 23], LEADER [24, 25], and SUSTAIN-6 [26].

ELIXA (Lixisenatide)

The ELIXA trial included 6,068 patients with T2DM aged ≥30 years with a recent history of spontaneous acute coronary syndrome that were randomized to receive subcutaneous injections of lixisenatide (10-20 μg *once daily* at the investigator's discretion) or matched placebo (Table 1) [22, 23]. After a median follow-up of 2.1 years, lixisenatide demonstrated non-inferiority to placebo (pre-specified HR margin: 1.3) for the primary composite endpoint of MACE and hospitalization for UA (13.4% vs 13.2%; HR: 1.02; 95% CI: 0.89-1.17) [23]. There were no significant treatment-group differences observed for secondary composite outcomes (*i.e.,*

MACE, hospitalization for UA, and hospitalization for HF, with or without coronary revascularization; Table 2) or their individual components [23].

LEADER (Liraglutide)

The LEADER trial randomized 9,340 patients with T2DM aged ≥50 years with a prior history of CVD or aged ≥60 years with at least one investigator-determined cardiovascular risk factor to liraglutide (*once-daily* subcutaneous injections ≥1.8 mg) or matched placebo to evaluate their effects on the primary endpoint of MACE (Table 1) [24, 25]. The secondary composite endpoint consisted of MACE, coronary revascularization, hospitalization for UA, and hospitalization for HF. After a median follow-up of 3.8 years, liraglutide was shown to not only be non-inferior to placebo (pre-specified HR margin: 1.3), but superior in reducing MACE (13.0% vs 14.9%; HR: 0.87; 95% CI: 0.78-0.97) [24]. Similar benefits were observed for the secondary composite outcome, and some benefits were also observed for pre-specified (all-cause mortality, cardiovascular mortality, total microvascular events, and nephropathy) and *post hoc* (MI) endpoints (Table 2) [24]. Although each individual endpoint of the composite primary outcome was underpowered, the decreased cardiovascular mortality risk following liraglutide treatment is noteworthy (4.7% vs 6.0%; HR: 0.78; 95% CI: 0.66-0.93) [24]. With regards to liraglutide's impact on microvascular events, there was a reduction in new or worsening nephropathy (HR: 0.78; 95% CI: 0.67-0.92) but a non-significant signal suggesting a higher rate of diabetic retinopathy (HR: 1.15; 95% CI: 0.87-1.52) [24].

SUSTAIN-6 (Semaglutide)

In the SUSTAIN-6 trial [26], 3,297 patients with T2DM either ≥50 years old with established CVD, chronic HF, or chronic kidney disease, or ≥60 years old with at least one cardiovascular

risk factor, were randomized 1:1:1:1 to receive *once-weekly* semaglutide (0.5 mg or 1.0 mg) or

matching placebo subcutaneously and then followed for the primary outcome of MACE (Table

1). After a median of 2.1 years of follow-up, patients taking any dose of semaglutide had a

significantly lower risk of MACE than those taking placebo (6.6% vs 8.9%, HR: 0.74; 95% CI:

0.58-0.95) [26], greatly surpassing the pre-specified non-inferiority margin of 1.8 and meeting a

post hoc definition of superiority (unadjusted for multiplicity). Beneficial effects were also

observed for two secondary composite outcomes: 1) MACE, hospitalization for UA, coronary or

peripheral revascularization, and hospitalization for HF; and 2) all-cause mortality, nonfatal

stroke, and nonfatal MI (Table 2). The protective effect of semaglutide on composite endpoints

appeared to be driven by semaglutide's reduction of nonfatal stroke (1.6% vs 2.7%; HR: 0.61;

95% CI: 0.38-0.99) [26]. With regards to microvascular complications, semaglutide reduced new

or worsening nephropathy (HR: 0.64; 95% CI: 0.46-0.88) but significantly increased the risk of

retinopathy complications (3.0% vs 1.8%; HR: 1.76; 95% CI: 1.11-2.78) [26]. The SUSTAIN-6

trial authors suggested that rapid decreases in blood glucose may have led to worsening

retinopathy, as in previous reports from the Diabetes Control and Complications trial and the

Oslo study [26].

SUMMARY OF CARDIOVASCULAR EFFECTS OF GLP-1 AGONISTS

ELIXA [22, 23], LEADER [24, 25], and SUSTAIN-6 [26] all demonstrated non-inferiority with

respect to their primary and secondary cardiovascular outcomes. LEADER and SUSTAIN-6

further generated optimism that GLP-1 agonists may improve cardiovascular morbidity in

patients with T2DM. Results from a meta-analysis of only the smaller phase II RCTs of GLP-1

agonists, which found a 72% relative reduction in mortality risk, support the benefits of this drug

class [27]; however, this finding was greater in magnitude than the effects observed in the major

GLP-1 agonist RCTs and reinforces that circumspection is necessary when interpreting meta-analyses of small trials, as publication bias is more likely. A number of retrospective cohort studies found no association between initiation of GLP-1 agonists and risk of HF [19] or MACE [28] when compared to other oral antihyperglycemic agents.

An important question remains: why was no cardiovascular benefit observed in ELIXA, while GLP-1 agonists reduced MACE (though with varying effects on individual endpoints) in LEADER and SUSTAIN-6? Chance is unlikely to explain the benefits of liraglutide and semaglutide on MACE because the relevant trials considered MACE to be the primary, pre-specified study result. Further, the superiority test in the LEADER trial was pre-specified in the study's hierarchical testing scheme. Though SUSTAIN-6 was not powered for a superiority test and did not correct for multiple testing, the use of two doses of semaglutide with consistent results makes random effects less likely. Instead, variations in drug specific effects or patient populations are likely responsible for the heterogeneity between trials. While no currently-known mechanism supports the differential effects of semaglutide and liraglutide compared with lixisenatide, considerable pharmacodynamic and pharmacokinetic differences between medications of the GLP-1 agonist class exist with respect to peak serum concentration, time to peak serum concentration, effect on HbA1c, route of elimination and, in particular, half-life [29]. In reported RCTs, the study drugs affected risk factors for CVD differently, with liraglutide and semaglutide reducing body weight and systolic blood pressure by more than lixisenatide (though still by minor amounts). Whether such mechanistic effects, or others yet to be determined, explain the variation in impact of these medications on individual cardiovascular outcomes seen between the LEADER and SUSTAIN-6 trials, remains unknown. Irrespective of drug properties, treatment effect differences may also originate in part from studying different types of patients

with T2DM in regards to proximity from an acute coronary event and presence or absence of other risk factors.

It is noteworthy and of concern that liraglutide and semaglutide trended towards increased retinopathy risk, a complication of T2DM that greatly reduces quality of life. Given the magnitude and significance of semaglutide's effect on the risk of diabetic retinopathy complications (a 1.2% absolute increase) and the potential for liraglutide to similarly increase retinopathy risk, more research is needed on the safety of GLP-1 receptor agonists as a class with respect to microvascular complications.

SODIUM-GLUCOSE CO-TRANSPORTER 2 INHIBITORS

SLGT2 is a glucose cotransporter that aids the reabsorption of glucose and sodium in the kidneys [29]. In response to hyperglycemic conditions, SGLT2 activity increases, raising the capacity of the kidneys to reabsorb glucose and lowering glucose secretion in the urine [30]. SGLT2 inhibitors lower the threshold for renal reabsorption of glucose and sodium, thereby increasing urinary glucose and sodium concentrations and decreasing plasma glucose and sodium concentrations. As a class of antihyperglycemic agents, SGLT2 inhibitors are thought to be safe with respect to hypoglycemia (because of their inherent loss of efficacy as HbA1c levels decrease) and body weight (because they improved caloric balance) [30]. ~~Though~~ SGLT2 transporters are~~is expressed outside of cardiac tissue in the~~ almost entirely found in kidney epithelial cells [30], making their modulation unlikely to impact cardiac and vascular tissue and promote downstream cardiovascular effects~~proximal tubule epithelium[30].~~ ~~,~~ SGLT2 inhibition may still elicit several ancillary cardiovascular benefits through glycosuria and natriuresis, including for example decreased plasma uric acid (which potentially lowers hypertension and

CVD) and reduced blood pressure [30, 31]. A single major cardiovascular safety trial (EMPA-REG OUTCOME) has been conducted for SGLT-2 inhibitors to date.

EMPA-REG OUTCOME (Empagliflozin)

EMPA-REG OUTCOME was a non-inferiority trial of empagliflozin among patients with T2DM (n=7,028) and established CVD [32-34]. Patients were randomized 1:1:1 to daily low-dose empagliflozin (10 mg), high-dose empagliflozin (25 mg), or placebo, and followed for the primary outcome of MACE. After a median treatment duration of 2.6 years, MACE occurred in 10.5% of participants in the pooled empagliflozin group and 12.1% in the placebo group (HR: 0.85; 95% CI: 0.74-0.99; Table 2) [34], satisfying the pre-specified non-inferiority margin of 1.3 and demonstrating superiority according to a hierarchical testing strategy. The MACE results were driven by a substantial reduction in cardiovascular mortality (3.7% vs 5.9%; HR: 0.62; 95% CI: 0.49-0.77) rather than by reductions in non-fatal MI (HR: 0.87; 95% CI: 0.70-1.09; excludes silent MI) or non-fatal stroke, for which a signal was present (HR: 1.24; 95% CI: 0.92-1.67). Empagliflozin also demonstrated a 32% relative reduction in all-cause mortality, consistent with the high proportion of cardiovascular deaths. In addition, empagliflozin substantially reduced the risk of hospitalization for HF (2.7% vs 4.1%; HR: 0.65; 95% CI: 0.50-0.85) [34], an effect which was robust to different subgroup analyses, including by baseline history of HF (Table 2) [32]. It is important to note that baseline HF status and HF events were determined without ejection fraction information; consequently, the effect of empagliflozin on ejection fraction in HF is unclear [32]. Despite concern over its renal safety, empagliflozin significantly lowered the risk of acute renal failure (5.2% vs 6.6%, p<0.01). Related to its pro-glycosuria effect, empagliflozin increased the risk of genital infections (6.4% vs 1.8%, p<0.001) [34].

SUMMARY OF CARDIOVASCULAR EFFECTS OF SGLT2 INHIBITORS

Consistent with the EMPA-REG OUTCOME trial, the results of published meta-analyses of smaller phase II/III RCTs of SGLT2 inhibitors [35, 36], and data presented to the FDA for initial approval of dapagliflozin and canagliflozin have identified no cardiovascular safety signals for SGLT2 inhibitors [37, 38]. Some meta-analyses of clinical trials, such as that presented by Savarese and colleagues [35] have reported that SGLT2 inhibitors elicit cardiovascular benefits (*e.g.,* on MI and HF), though these results should be interpreted with caution given the size and duration of the included trials.

Potential mechanisms of benefit remain under active investigation, but leading pathways likely contributing to the reduction in the risk of HF and cardiovascular mortality include weight loss promotion and beneficial hemodynamic effects through a mix of glycosuria and natriuresis. The EMPA-REG OUTCOME trial showed that empagliflozin decreased weight (by ~2 kg), systolic blood pressure (by ~4-6 mm Hg), and plasma volume (measured as an increased concentration of hemoglobin of ~0.8 g/dL) [34]. And, while these effects were modest, their combination may have produced clinically important results. Other mechanisms, such as improvements in inflammation, arrhythmia, and arterial stiffness, are also thought to be relevant [39]. Whether these mechanisms play a role via hemoconcentration or hypotension to increase the risk of stroke remains unknown.

SUMMARY OF CARDIOVASCULAR SAFETY TRIALS

In the seven large, placebo-controlled RCTs reported upon to date, all studied antihyperglycemic agents were observed to be non-inferior to placebo for their primary, composite outcomes. Credible systematic reviews and meta-analyses support the cardiovascular safety of these drugs, as do their general pharmacologic properties, which include weight loss and hemodynamic effects [4, 30]. Though an increase in HF risk may follow treatment with saxagliptin or

alogliptin, these effects also plausibly derive from chance or from indirect effects unrelated to the study drugs. Substantial benefits on CVD endpoints were observed for GLP-1 agonists liraglutide (on primary and secondary MACE-based outcomes, MI, cardiovascular mortality, and all-cause mortality) and semaglutide (on primary and secondary MACE-based outcomes, and non-fatal stroke). The SGLT2 inhibitor empagliflozin reduced the risk of MACE, HF, cardiovascular mortality, and all-cause mortality, though its potential effects on stroke should not be ignored.

While adverse cardiovascular events are a major concern for patients with T2DM, the abovementioned drugs may elicit other adverse health effects that should be considered in clinical practice. Saxagliptin significantly increased the risk of renal abnormalities in the SAVOR-TIMI 53 trial [7]. Although semaglutide decreased new or worsened nephropathy in the SUSTAIN-6 trial, it increased retinopathy rates [26]. Liraglutide also non-significantly increased retinopathy rates, though this potential effect deserves further scrutiny given the results of the SUSTAIN-6 trial [24] and the potential for a class effect. Higher rates of gastrointestinal events were also reported for both semaglutide and liraglutide [24, 26]. Finally, empagliflozin led to increased rates of genital infection, though it appeared to prevent acute kidney failure [34].

To address lingering questions surrounding these antihyperglycemic agents, future research is needed. Information on pharmacologic mechanisms should examine the discrepant cardiovascular effects of drugs within the same class. It is also important that investigators quantify the mediating effects of background antihyperglycemic agents (including sulfonylureas and thiazolidinediones, which have been implicated in adverse cardiovascular events [1, 40]), among patients who were poorly controlled. All included placebo-controlled trials had important differences in the use of medications during follow-up, and these may have greatly impacted

observed results. Similarly, the effect of hypoglycemia on CVD deserves further inquiry since this potential risk factor for CVD [41] often differed between treatment groups. Also, the mediating effect of blood glucose may have contributed in part to the empirical benefits of study drugs, as treatment groups often differed in post-baseline HbA1c levels. Yet the effect of blood glucose alone is unlikely to drive the observed benefits, or else trials demonstrating lowered blood glucose would have been more consistent with respect to cardioprotection. In addition, the generalizability of the results of the cardiovascular outcome trials to patients with T2DM seen in everyday clinical practice should be further researched, as patients meeting inclusion criteria for these RCTs are different from many T2DM patients seen as part of routine practice. Finally, trials are needed to assess the use of combination therapies that include antihyperglycemic drugs with potentially complimentary mechanisms.

Some of this information will come from ongoing cardiovascular RCTs with upcoming completion dates. The CARMELINA trial of linagliptin (NCT01897532) will provide evidence for or against a HF class effect of DPP-4 inhibitors, while the EXCSEL trial of exenatide (NCT01144338) will further elucidate the potential benefits of GLP-1 agonist therapy. Evidence supporting the cardiovascular safety, and potential benefit for cardiovascular mortality and HF hospitalization, of SGLT2 inhibitors beyond empagliflozin will be determined in the upcoming CANVAS (canagliflozin; NCT01032629) and DECLARE-TIMI 58 (dapagliflozin; NCT01730534) trials. RCTs in progress should also provide insight into any potential adverse effects on stroke, retinopathy, and other safety concerns. Finally, the ongoing CAROLINA trial (NCT01243424), which will randomize approximately 6,000 patients to either linagliptin or glimepiride, is the only ongoing large cardiovascular outcome trial with an active control and

will help elucidate the role of background medications in already completed cardiovascular outcome trials of antihyperglycemic agents.

CLINICAL RECOMMENDATIONS

For diabetic patients at high cardiovascular risk, American, Canadian, and international guidelines recommend metformin monotherapy until treatment failure as the primary pharmacological approach, at which point combination therapy should be commenced. Because there are insufficient data on cardiovascular benefit of these agents as monotherapies, current guidelines do not recommend their use in such fashion.

Until further data are available on DPP-4 inhibitors, physicians should follow the label warnings added by the FDA in 2016, which recommend caution when prescribing saxagliptin or alogliptin, particularly in patients with T2DM who already have established heart disease or renal impairment. Many practitioners may consider avoiding the DPP-4 inhibitor class overall given the availability of alternative classes of therapies, which may have a marked impact on current treatment patterns. The FDA safety announcement nevertheless emphasized that patients currently treated with DPP-4 inhibitors should not stop taking their medications without first talking with their primary care, diabetes, or cardiology practitioners. Practitioners should monitor for signs (weight gain, edema) and symptoms (exertional dyspnea, orthopnea, fatigue) for HF after starting DPP-4 inhibitors and consider transitioning away from these drugs if HF develops.

We recommend GLP-1 agonists (especially liraglutide) and SGLT2 inhibitors (especially empagliflozin) as second-line treatments of T2DM given their proven reductions in cardiovascular events in patients at high risk of CVD. Empagliflozin has recently been approved by the FDA and Health Canada for the prevention of cardiovascular death, making it the only

oral antihyperglycemic agent approved for this indication. We note that the GLP-1 agonist semaglutide is not available for clinical use anywhere at the time of writing. Though physicians should have limited concern that lixisenatide, liraglutide, or semaglutide increase cardiovascular risk when used as add-on therapies to metformin, further data on retinopathy risk and effectiveness in routine clinical practice are awaited. Similar data may inform the risk of stroke among SGLT2 inhibitor users, which remains a potential concern.

For patients with low cardiovascular risk, no clinical evidence supports the preferential use of DPP-4 inhibitors, GLP-1 agonists, or SGLT2 inhibitors to improve cardiovascular risk profiles. Physician and patient preference considering the efficacy and potential side effects of different treatments should determine therapy choice in this low-risk group.

ACKNOWLEDGEMENTS

DISCLOSURES

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Table 1. Design characteristics and baseline statistics of all major, cardiovascular safety trials of DPP-4 inhibitors, GLP-1 agonists, and SGLT2 inhibitors.

	Treatment groups	Primary endpoint	Secondary endpoint(s)	Selected major inclusion criteria	Number randomized	Mean age in years (SD)	Men %	Mean diabetes duration (years)	Mean HbA1c %
DPP-4 inhibitors									
SAVOR-TIMI 53 [5-8]	1) saxagliptin 2) placebo	MACE	MACE + HUA + coronary revascularization + HF	• Not taking DPP-4 inhibitors or GLP-1 agonists • EITHER ≥40 years old with history of atherosclerosis OR ≥55 (men) or ≥60 (women) years old with >1 CV risk factor • HbA1c ≥6.5% and ≤12.0% • No acute vascular event <2 months before randomization	16,496	65.0 (8.6)	67%	11.9	8.0%
EXAMINE [9-11]	1) alogliptin 2) placebo	MACE	MACE + urgent revascularization after HUA	• Taking antihyperglycemic agents other than DPP-4 inhibitors or GLP-1 agonists • ≥18 years old • History of ACS 15 - 90 days prior to randomization • HbA1c ≥6.5% (≥7.0% if taking insulin) and ≤11.0% • No unstable cardiac disorder • No ACE event <15 days before randomization	5,380	60.9 (10.0)	70%	7.1	8.0%
TECOS [12-15]	1) sitagliptin 2) placebo	MACE + HUA	MACE	• EITHER taking pioglitazone, metformin and/or sulfonylurea OR taking insulin with or without metformin • ≥50 years old • HbA1c ≥6.5% and ≤8.0% • History of CAD, ICD, or atherosclerotic peripheral arterial disease • No history of ≥2 hypoglycemic episodes in the year prior to enrollment	14,735*	66.0 (8.0)	71%	9.4+	7.3%
GLP-1 agonists									
ELIXA [22, 23]	1) lixisenatide 2) placebo	MACE + HUA	1) MACE + HUA + HHF 2) MACE + HUA + HHF + coronary revascularization	• Not taking DPP-4 inhibitors or GLP-1 agonists • ≥30 years old • ACS within 180 before screening without bypass graft surgery • HbA1c ≥5.5% and ≤11.0% • No percutaneous coronary intervention ≤15 days prior to screening	6,068	60.3 (9.7)	69%	9.3	7.7%
LEADER [24, 25]	1) liraglutide 2) placebo	MACE	MACE + coronary revascularization + HUA + HHF	• Not taking DPP-4 inhibitors or GLP-1 agonists • EITHER ≥50 years old with ≥1 prior incidence of CVD OR ≥60 years old with ≥1 CV risk factor • HbA1c ≥7.0% • No acute coronary or cerebrovascular event <15 days prior to screening	9,340	64.3 (7.2)	64%	12.7	8.7%
SUSTAIN-6 [26]	1) semaglutide 0.5 mg 2) semaglutide 1.0 mg 3) placebo 4) placebo	MACE	1) MACE + HUA + coronary revascularization 2) all-cause mortality + nonfatal stroke + nonfatal MI	• On ≤2 antihyperglycemic agents other than DPP-4 inhibitors or GLP-1 agonists with or without basal or premixed insulin • EITHER ≥50 years old with CVD, chronic heart failure, or chronic kidney disease OR ≥60 years old with ≥1 CV risk factor • HbA1c ≥7.0% • Acute coronary or cerebrovascular event ≤90 days prior to randomization	3,297	64.6 (7.4)	61%	13.9	8.7%
SGLT2 inhibitors									
EMPA-REG OUTCOME [32-34]	1) empagliflozin 10 mg 2) empagliflozin 25 mg 3) placebo	MACE	MACE + HUA	• ≥18 years old • HbA1c ≥7.0% and ≤10.0% (or ≤9.0% if no recent history of antihyperglycemic agent use) • Established CVD as determined by history of MI, stroke, UA, or evidence of CAD or PAD • ACS, stroke, or transient ischemic attack ≤2 months prior to informed consent	7,028†	63.1 (8.6)	71%	57% patients > 10 years	8.1%

Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; CV, cardiovascular; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; HF, heart failure; HHF, hospitalization for heart failure; HUA, hospitalization for unstable angina; ICD, ischemic cerebrovascular disease; MACE, major adverse cardiovascular events (composite endpoint that includes cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke); MI, myocardial infarction; PAD, peripheral arterial disease; SD, standard deviation; SGLT2, sodium-glucose co-transporter 2.

* Data provided for the 14,724 patients who consented to the trial protocol.

† Data for the 7,034 patients originally reported as treated [33], unless otherwise specified

‡ Median

Table 2. Adjusted HRs and 95% CIs for the intention-to-treat† analyses of select trial endpoints of major, cardiovascular safety trials of DPP-4 inhibitors, GLP-1 agonists, and SGLT2 inhibitors.*

	Primary outcome	Secondary outcome(s)	Heart Failure			MI	Stroke	HUA	Mortality	
			Total	History of HF	No history of HF				Cardiovascular	All-cause
DPP-4 inhibitors										
SAVOR-TIMI 53 [5-8]	1.00 (0.89-1.12)	1.02 (0.94-1.11)	1.27 (1.07-1.51)	1.21 (0.93-1.58)	1.32 (1.04-1.66)	0.95 (0.80-1.12)	1.11 (0.88-1.39)	1.19 (0.89-1.60)	1.03 (0.87-1.22)	1.11 (0.96-1.27)
EXAMINE [9-11]	0.96 (≤1.16)‡	0.95 (≤1.14)‡	1.07 (0.79-1.46)	1.00 (0.71-1.42)	1.76 (1.07-2.90)	1.08 (0.88-1.33)§	0.91 (0.55-1.50)§	0.90 (0.60-1.37)¶	0.79 (0.60-1.04)	0.88 (0.71-1.09)
TECOS [12-15]	0.98 (0.89-1.08)	0.99 (0.89-1.10)	1.00 (0.83-1.20)	1.05 (0.79-1.39)	0.96 (0.76-1.23)	0.95 (0.81-1.11)	0.97 (0.79-1.19)	0.90 (0.70-1.16)	1.03 (0.89-1.19)	1.01 (0.90-1.14)
GLP-1 agonists										
ELIXA [22, 23]	1.02 (0.89-1.17)	1) 0.97 (0.85-1.10) 2) 1.00 (0.90-1.11)	0.96 (0.75-1.23)	0.93 (0.66-1.30)	0.97 (0.67-1.40)	1.03 (0.87-1.22)	1.12 (0.79-1.58)	1.11 (0.47-2.62)	0.98 (0.78-1.22)	0.94 (0.78-1.13)
LEADER [24, 25]	0.87 (0.78-0.97)	0.88 (0.81-0.96)	0.87 (0.73-1.05)	Not reported	Not reported	0.86 (0.73-1.00)	0.86 (0.71-1.06)	0.98 (0.76-1.26)	0.78 (0.66-0.93)	0.85 (0.74-0.97)
SUSTAIN-6 [26]	0.74 (0.58-0.95)	1) 0.74 (0.62-0.89) 2) 0.77 (0.61-0.97)	1.11 (0.77-1.61)	Not reported	Not reported	0.74 (0.51-1.08)§	0.61 (0.38-0.99)§	0.82 (0.47-1.44)	0.98 (0.65-1.48)	1.05 (0.74-1.50)
SGLT2 inhibitors										
EMPA-REG OUTCOME [32-34]	0.86 (0.74-0.99)	0.89 (0.78-1.01)	0.65 (0.50-0.85)	0.75 (0.48-1.19)	0.59 (0.43-0.82)	0.87 (0.70-1.09)**	1.18 (0.89-1.56)	0.99 (0.74-1.34)	0.62 (0.49-0.77)	0.68 (0.57-0.82)

Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; HF, heart failure; HR, hazard ratio; HUA, hospitalization for unstable angina; MI, myocardial infarction; SGLT2, sodium-glucose co-transporter 2.

*The primary outcome was major adverse cardiovascular events (MACE, a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke) for all trials except TECOS and ELIXA, where it was MACE + hospitalization for unstable angina (Table 1). Secondary outcomes are described in Table 1. All dose categories were pooled for each study drug.

† EMPA-REG used a modified intention-to-treat protocol restricted to patients who received at least one dose of a study drug.

‡ One-tailed test

§ Non-fatal events only

¶ Requiring revascularization

** Excluding silent myocardial infarction