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Cardiovascular safety of therapies for Type 2 diabetes

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Abstract

Introduction—Dipeptidyl peptidase-4 (DPP4) inhibitors, glucagon-like peptide-1 (GLP-1) analogs and sodium-glucose cotransporter 2 (SGLT2) inhibitors are relatively new therapies for the treatment of type 2 diabetes mellitus. Given the high prevalence of cardiovascular complications in patients with type 2 diabetes and recent concerns questioning CV safety of newer antidiabetic medications, cardiovascular safety of these medications requires evaluation.

Areas covered—Cardiovascular effects of these drug classes from preclinical and clinical data as well as non-cardiovascular safety issues are delineated from literature searches covering the last decade and up to June 2016. Major clinical trials assessing the cardiovascular safety of GLP-1 agonists (ELIXA and LEADER), DPP-4 inhibitors (SAVOR-TIMI 53, EXAMINE, and TECOS) and SGLT2 inhibitors (EMPA-REG OUTCOME) are reviewed and interpreted.

Expert Opinion—Based on review of the present evidence, these 3 classes of antihyperglycemic therapies have acceptably safe CV safety profiles for patients with type 2 diabetes. The latest evidence from LEADER and EMPA-REG OUTCOME trials indicate that lixisenatide and empagliflozin have cardiovascular benefits that may prove to be of clinical importance in the management of type 2 DM.

Keywords

Cardiovascular safety; DPP-4 inhibitors; GLP-1 agonists; SGLT-2 inhibitors; type 2 diabetes mellitus

1. INTRODUCTION

The risk of cardiovascular (CV) disease is substantially greater in people with type 2 diabetes compared to those without diabetes [1]. Type 2 diabetes is known to be associated with both microvascular and macrovascular complications [2] and although improved glycemic control reduces the risk of many of the microvascular complications of type 2 diabetes [3], studies have not shown a favorable impact of intensive glycemic control in

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Declaration of Interest

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reducing macrovascular events in type 2 diabetes [4,5]. Concerns regarding adverse CV outcomes with certain therapies for the treatment of diabetes [6, 7] prompted the US Food and Drug Administration (FDA) to release guidelines in late 2008 outlining specific requirements for CV safety assessment before and/or after approval of new anti-hyperglycemic therapies [8].

Given that diabetes is a major risk factor for cardiovascular disease and is considered a coronary heart disease equivalent, CV effects of anti-diabetic medications have become relevant to current clinical practice. Since 2013, three major CV clinical trials have evaluated the DPP-4 inhibitors in patients with type 2 diabetes and elevated CV risk: SAVOR-TIMI-53 [9], EXAMINE [10], and TECOS [11]. The GLP-1 agonists lixisenatide (ELIXA) and liraglutide (LEADER); and the SGLT-2 inhibitor empagliflozin (EMPA-REG OUTCOME) have also been evaluated for their CV safety in randomized placebo controlled trials [12–14]. This review focuses on these new clinical safety findings and unexpected cardiovascular benefits that have emerged from 2 of these trials, which may ultimately impact the management of type 2 diabetes.

2. MECHANISM OF ACTION

2.1 Incretin based therapies

The insulin release triggered by eating is mediated, in part, by two incretin hormones in the gut: glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 [15]. Both GIP and GLP-1 have relatively short plasma half-lives and undergo rapid enzymatic inactivation, in part by DPP-4 to the GLP-1 metabolite [16]. Since the GLP-1 receptor agonists are resistant to DPP-4 enzymatic degradation, they improve glycemic control by increasing insulin secretion and suppressing glucagon levels (Table 1). This heterogeneous class can be subclassified into the exendin-4-based agents (exenatide, lixisenatide) and the human GLP-1-based agents (albiglutide, dulaglutide, liraglutide).

The DPP-4 inhibitors specifically target the enzyme responsible for the inactivation of incretin hormones, thus increasing the available pool of active GLP-1 and GIP [17]. The resultant pharmacologic actions for the DPP-4 inhibitors are similar to those of the GLP-1 agonists, with the exception that they have negligible effects on gastric emptying. The 5 FDA-approved agents are divided into peptidomimetics (saxagliptin, sitagliptin, vildagliptin) and non-peptidomimetics (alogliptin, linagliptin). (Table 2) [18].

2.2 Sodium Glucose Co-transporter 2 (SGLT2) Inhibitors

The kidneys play an important role in glucose homeostasis, facilitating both elimination and reabsorption of glucose. The proximal convoluted tubule actively reabsorbs glucose through the action of SGLT1 (sodium glucose co-transporter 1) and SGLT2 and passively through the action of glucose transporter 1 and 2 (GLUT1 and GLUT2). It has been demonstrated that there is an enhanced expression of SGLT2 in patients with type 2 diabetes [19], increasing the system's capacity to reabsorb filtered glucose by approximately 20% [20]. These agents act by selective inhibition of SGLT2, a high-capacity, low affinity transporter, located in the proximal convoluted tubule and responsible for >90% of glucose reabsorption

in the kidney [21]. Inhibition of SGLT2 therefore, results in enhanced glycosuria and reduction in hyperglycemia. Lack of activity against SGLT1 prevents gastrointestinal side effects, since this transporter is also responsible for glucose reabsorption in the small intestine [20]. With this unique mechanism of action independent of insulin secretion and resistance, these drugs can be used alone or in combination with other antihyperglycemic therapies in early or late stage type 2 diabetes. The comparative pharmacological characteristics of the SGLT2 inhibitors available in clinical practice are shown in Table 3.

3. CARDIOVASCULAR EFFECTS

3.1 GLP-1 receptor agonists

The clinical CV effects of native GLP-1 and GLP-1 receptor agonists have been extensively studied. Patients undergoing coronary angioplasty following an acute myocardial infarction (MI) showed improvements in LV ejection fraction and myocardial wall motion with a 72-hour infusion of GLP-1 [22]. Additional improvements in LV function, oxygen consumption, and 6-min walk distance times were seen following a five-week infusion of GLP-1 in 12 patients (8 with type 2 diabetes) with New York Heart Association (NYHA) class III/IV heart failure [23]. However, these effects have not been confirmed in studies of patients without diabetes [24].

On administration of a 6 hour infusion of exenatide or placebo to 172 patients undergoing percutaneous coronary intervention for an ST-elevation myocardial infarction, [25] the primary endpoint of myocardial salvage index assessed using cardiac magnetic resonance imaging, was significantly increased ($p=0.003$), and the infarct size relative to the myocardial area at risk was reduced ($p=0.003$), although this did not translate into improved LV function ($p=0.82$) or 30-days cardiac death ($p=0.91$). A greater reduction in infarct size was seen in patients who had shorter door-to-balloon times [26].

Beneficial effects of GLP-1 receptor agonists on ventricular function in heart failure models have also been observed. In an obesity-associated cardiomyopathy mouse model, once-weekly treatment with liraglutide improved markers of hypertrophy and fibrosis as well as improved cardiac function [27].

Reductions in blood pressure of patients with type 2 diabetes or obesity have also been seen with GLP-1 receptor agonist use. A meta-analysis of randomized controlled trials has shown that GLP-1 receptor agonists reduce systolic and diastolic blood pressure by 5.2 mmHg ($p<0.00001$) and 5.9 mm Hg ($p<0.00001$), respectively, compared with placebo [28]. These blood-pressure-lowering effects appear to be independent of glycemic or body-weight changes [29].

3.2 DPP-4 inhibitors

Data are available on the cardiovascular effects of DPP-4 inhibitors in both preclinical and clinical settings. Animal models analyzing administration of DPP-4 inhibitors have shown improvement in LV recovery from ischemic/reperfusion injury and reductions in infarct size [30, 31]. Short-term human studies of myocardial ischemia have confirmed these findings: Four weeks of sitagliptin attenuated dobutamine-stress-stimulated myocardial stunning in

patients with type 2 diabetes and coronary disease [32]. A rat model of ablation-induced cardiac dysfunction showed significant attenuation in heart failure–related LV end-diastolic pressure, systolic performance, and chamber stiffness following six weeks of sitagliptin [33]. Similar results were seen in a pacing-induced heart failure pig model [34] and improvements in survival rates in other animal studies have also been seen [35]. Taken together, these preclinical data suggested that DPP-4 inhibitors might have had potential efficacy in conditions of cardiac dysfunction and advanced cardiomyopathies.

3.3 SGLT2 inhibitors

Cardiovascular benefits of SGLT2 inhibitors have also been observed in some preclinical studies. Therapy with SGLT2 inhibitors has shown attenuation of cluster of differentiation (CD 36) and Lectin-like OX- low-density lipoprotein receptor-1 (LOX-1) scavenger receptor expression on macrophages which, in turn, reduces scavenging of oxidized LDL by macrophages. This effect has been shown to prevent development of atherosclerotic lesions in diabetic mice [36]. Similarly, another study in diabetic mice showed significant reduction in cardiac interstitial fibrosis, coronary arterial thickening, coronary arterial remodeling, vascular dysfunction, cardiac interstitial macrophage infiltration and cardiac superoxide levels after 10 weeks of empagliflozin treatment [37]. Improvement in endothelial function was also noted. Further studies in this direction are needed to elaborate the potential cardiovascular benefits of SGLT2 inhibitors.

Therapy with the SGLT2 inhibitors is associated with other beneficial clinical effects in patients with type 2 diabetes. Data from a number of trials have consistently demonstrated weight loss varying from 2 to 5 kg and >5% of body weight [38–41]. In a study of 3300 patients randomized to empagliflozin versus placebo, empagliflozin produced a weight loss as compared to baseline of 1.7 to 1.9 kg along with reduction in waist circumference of 1.3 cm, 0.2–0.3% reduction in total body fat and significant reductions in central and visceral obesity [42].

Reductions in systolic BP of 3 to 5 mmHg and in diastolic BP of 1 to 3 mmHg have been observed with most SGLT2 inhibitors in clinical trials [38–40,43–45]. Therapy with SGLT2 inhibitors is also associated with reductions in serum uric acid and triglyceride levels as well as increases in serum LDL and HDL cholesterol levels – the clinical significance of these findings is not fully understood. Significant improvements in the albumin:creatinine ratio has been noted with dapagliflozin and canagliflozin in clinical trials [46,47] and recent results from the EMPA-REG outcome trial showed a 39% reduction in new onset or worsening nephropathy in patients treated with empagliflozin [48].

4. Cardiovascular Outcome Trials for the GLP-1 Agonists (Table 4)

4.1 ELIXA (LIXISENATIDE)

The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) evaluated the CV safety of lixisenatide in 6,068 patients with type 2 diabetes who had had an acute coronary event within 180 days before enrollment [12]. Lixisenatide met the pre-specified criterion of non-inferiority versus placebo for the composite primary endpoint of CV death, nonfatal MI,

nonfatal stroke, and hospitalization for unstable angina [406/3,034 patients on lixisenatide and 399/3,034 on placebo for a hazard ratio (HR) of 1.02, 95% confidence interval (CI) 0.89–1.17]. No signal for increased risk of heart failure was observed (HR=0.96, 95% CI 0.75–1.23), and there were no significant changes in blood pressure or heart rate on lixisenatide versus placebo during the trial. The ELIXA study provided the first CV outcome results with a GLP-1 receptor agonist in patients with type 2 diabetes and high CV risk.

4.2 LEADER TRIAL (LIRAGLUTIDE)

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial [13] evaluated the cardiovascular effects of the GLP-1 receptor agonist liraglutide in patients with type 2 diabetes and high CV risk in a randomized, double-blind placebo controlled design. The primary endpoint of LEADER was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction and nonfatal stroke. Pre-specified exploratory outcomes included an expanded composite cardiovascular outcome (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina pectoris or heart failure), death from any cause, a composite renal and retinal microvascular outcome (nephropathy and retinopathy), neoplasms and pancreatitis. At 410 sites in 32 countries, a total of 9340 type 2 diabetic patients with a glycated hemoglobin level of $\geq 7\%$ were randomized to liraglutide (n=4668) or placebo (n=4672). Of note, 96.8% patients completed a final visit, died or had a primary outcome. The median follow-up was 3.8 years in each group.

Liraglutide was associated with a significant reduction in the occurrence of the composite primary outcome (hazard ratio = 0.87; 95% CI 0.78–0.97, $P<0.001$ for non-inferiority and $P<0.01$ for superiority) versus placebo. A 15% reduction in death from any cause (hazard ratio = 0.85; 95% CI, 0.74–0.97; $P<0.02$) and 22% reduction in death from cardiovascular causes (hazard ratio = 0.78; 95% CI, 0.66–0.93; $P<0.007$) was also noted (Table 5). The expanded composite outcome (primary outcome plus hospitalization for unstable angina pectoris and heart failure) was also less frequent with liraglutide group (hazard ratio = 0.88; 95% CI 0.81–0.96; $P<0.005$). However, when analyzed separately, nonfatal MI, nonfatal stroke and hospitalization from heart failure were not significantly different in comparison to placebo. Liraglutide showed a benefit in the reduction of nephropathy (defined as new-onset macroalbuminuria, doubling of serum creatinine and eGFR <45 ml/min/1.73m², need for continuous renal replacement therapy or death from renal disease) by 22% (hazard ratio 0.78; 95% CI 0.67–0.92; $P<0.003$). Modest reductions in systolic BP (–1.2 mm Hg) and weight (–2.3 kg) were also seen.

5. CARDIOVASCULAR OUTCOMES OF the DPP-4 INHIBITORS

5.1 SAVOR-TIMI 53 (Saxagliptin)

The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR) – Thrombolysis in Myocardial Infarction (TIMI) 53 trial [9] compared the DPP-4 inhibitor saxagliptin with placebo in 16,492 patients with type 2 diabetes who had a history of CV disease (~80% of the study population) or who were older and had elevated risk factors (~20%). The analysis plan for SAVOR-TIMI 53 included hypotheses for both

superiority and non-inferiority for saxagliptin versus placebo, with a primary composite endpoint of death from CV causes, nonfatal MI, and nonfatal ischemic stroke. The major secondary endpoint of SAVOR-TIMI 53 was a composite of CV death, nonfatal MI, ischemic stroke, hospitalization for heart failure, unstable angina, or coronary revascularization. There were 95% in each treatment group available for assessment for the primary endpoint, and 0.2% of study participants were lost to follow-up.

At baseline, patients in SAVOR-TIMI 53 were 65 years old on average and 79% had established CV disease (n=12,959) while 21% had multiple risk factors (n=3,553) such as dyslipidemia and hypertension in addition to the type 2 diabetes. The majority of patients were taking aspirin (75%), statins (78%), and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) (82 and 83%, respectively). In addition, at baseline, 41–42% of SAVOR-TIMI 53 participants were taking insulin, 40% were taking sulfonylureas, and ~70% were taking metformin. The change from baseline in the HbA1c for saxagliptin versus placebo was –0.3%, and the degree of HbA1c reduction was related to the baseline HbA1c. Of note, a small number of participants developed hypoglycemia on saxagliptin compared to placebo, and this occurrence was most likely in patients whose baseline HbA1c values were <7.0% and who were taking long-acting sulfonylureas during the trial.

Following 2.1 years median duration of follow-up, saxagliptin had no effect on the primary endpoint compared to placebo (7.3% versus 7.2%, HR=1.00, 95% CI 0.89–1.12, p <0.001 for noninferiority) (Table 5). Similarly, the expanded secondary endpoint occurred in 12.8% of patients assigned to saxagliptin versus 12.4% of those on placebo (HR=1.02, 95% CI 0.94–1.11). Patients in the saxagliptin group were more likely to be admitted to the hospital for heart failure than were those in the placebo group (3.5% versus 2.8%, HR=1.27, 95% CI 1.07–1.51, p=0.007). In a post hoc analysis presented to the FDA in 2015, the composite endpoint of CV death and hospitalized heart failure was greater on saxagliptin than on placebo (6.0% versus 5.3%, HR=1.14, 95% CI 1.00–1.30). Similarly, the composite of hospitalized heart failure and all-cause mortality was marginally greater for saxagliptin than placebo (7.6% versus 6.7%; HR=1.16; 95% CI 1.03–1.30).

Clinical factors at baseline that were associated with hospitalized heart failure in SAVOR-TIMI 53 included a history of heart failure (13% of the study population), elevation of N-terminal pro-B-type natriuretic peptide (NT-proBNP), and reduced kidney function [9, 49]. In addition, patients in the highest quartile for NT-proBNP were those at greatest risk of heart failure hospitalization on saxagliptin versus placebo (11.0% versus 8.9% on saxagliptin and placebo, respectively, with an absolute risk difference of 2.1%; HR=1.31, p=0.02). Of note, the primary study endpoint was not different for patients randomized to saxagliptin versus placebo in the NT-proBNP quartile 4 group (16.9% versus 16.7%, HR=1.01, p=0.90), nor in those patients with a baseline history of heart failure.

There are no obvious causal mechanisms for heart failure with saxagliptin, and, as noted above, the DPP-4 inhibitors have shown favorable mechanistic effects in animal models of CV disease. Theoretical concerns, such as increased rates of hypoglycemia [4,9] and stimulation of the sympathetic nervous system in patients on both ACE inhibitors and DPP-4

inhibitors [50,51], have been proposed but are unlikely to be attributable because no interactions with ACE inhibitors and the DPP-4 inhibitors were seen in SAVOR-TIMI 53 or EXAMINE [49, 52]. Due to the unexpected finding of heart failure in this trial, mechanistic research that evaluates changes in cardiac function in patients on saxagliptin with type 2 diabetes may be useful.

5.2 EXAMINE (Alogliptin)

The EXAMINE study (Examination of Cardiovascular Outcomes: Alogliptin versus Standard of Care in Patients with T2DM) [10] compared the DPP-4 inhibitor alogliptin with placebo in patients with type 2 diabetes who had had an acute coronary syndrome 15–90 days before randomization into the trial. The primary analysis plan for EXAMINE was to prove non-inferiority for alogliptin versus placebo on a primary endpoint of death from CV causes, nonfatal MI and nonfatal stroke. The major secondary endpoint included CV death, nonfatal MI and stroke, and urgent revascularization for unstable angina. EXAMINE enrolled 5,380 participants; 95–96% of the patients in each treatment group were available for assessment for the primary endpoint, and the lost-to-follow-up rate was low (9 in the alogliptin arm and 16 in the placebo arm; 0.4% of the overall study population).

At baseline, patients in EXAMINE were on average 61 years old, and 100% had established CV disease in addition to the type 2 diabetes. The majority of participants were taking antiplatelet therapies (97%), statins (91%), beta-blockers (82%) and ACE inhibitors or ARBs (82%). In addition, at baseline, 29–30% were taking insulin, 47% were taking sulfonylureas, and 65% were taking metformin. The change from baseline in the HbA1c for alogliptin versus placebo was –0.4%, and, as in SAVOR-TIMI-53, the degree of HbA1c reduction was related to the baseline HbA1c. Of note, there were no differences in the rates of hypoglycemia on alogliptin compared to placebo in any category (mild, requiring assistance, or severe and requiring hospitalization).

Following 18–19 months median duration of follow up, there was no overall effect of alogliptin versus placebo on the primary endpoint (11.8% versus 11.3%, HR=0.96, upper 99% CI 1.16, $p < 0.001$ for noninferiority) (Table 5). Similarly, the expanded secondary endpoint occurred in 12.7% of patients assigned to alogliptin versus 13.4% on placebo (HR=0.95, one-sided upper 99% CI boundary 1.14). In a post hoc exploratory analysis (53), the rate of the composite of CV death and hospitalized heart failure was higher in EXAMINE than in the SAVOR study, but similar for alogliptin compared to placebo (7.4% versus 7.5%, HR=0.97, 95% CI 0.82–1.12) (Table 5). Clinical factors at baseline that were significantly associated with hospitalized heart failure in EXAMINE included a history of heart failure (28% of the study population), elevations in NT-pro-BNP, a history of MI, baseline insulin use, and severe kidney impairment. In this multivariate model adjusting for baseline risk factors in the EXAMINE trial, hospitalization for heart failure alone was not significantly different for alogliptin versus placebo (HR=1.097, 95% CI 0.82–1.47, $p=0.54$) (Table 6) (53).

The levels of NT-pro BNP fell in patients in both treatment groups in EXAMINE, and initiation of loop diuretic use was virtually the same in patients randomized to alogliptin and placebo. Taken together, these findings showed no evidence that alogliptin induced heart

failure in patients with type 2 diabetes and coronary disease, including those with a history of compensated heart failure entering the trial (53,54). A *post hoc* analysis in patients taking low and high doses of ACE inhibitors was performed in the EXAMINE trial population [52]. ACE inhibitors were being taken by about two-thirds of EXAMINE patients, and in this large subgroup there was no evidence that patients on alogliptin had different outcomes from those on placebo. Similar findings were observed in SAVOR-TIMI 53 [49].

5.3 TECOS (Sitagliptin)

The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) (11) assessed long-term CV safety of the DPP-4 inhibitor sitagliptin versus placebo in addition to usual care in patients with type 2 diabetes and established CV disease (defined as a history of major coronary artery disease, ischemic cerebrovascular disease, or atherosclerotic peripheral arterial disease). The analysis plan for TECOS included a primary non-inferiority hypothesis for sitagliptin versus placebo on a primary end point of death from CV causes, MI, ischemic stroke, and hospitalization for unstable angina. Superiority of the primary composite endpoint was tested following non-inferiority testing for the primary and secondary endpoints. Hence, this trial was larger and longer than the two trials discussed above, since assuming a true underlying HR of 0.85 required 1,300 endpoints to achieve a power of 81%. Other secondary outcomes in TECOS included the individual components of CV death, fatal and nonfatal MI, fatal and nonfatal stroke, all-cause mortality, and time to hospitalization for heart failure. The study population included 14,735 participants; 94–95% of them completed the study, and vital status was known in 97.5%.

At baseline, patients in TECOS were on average 66 years old, and all had established CV disease in addition to the T2DM. The mean HbA1c was 7.2% and the mean duration of diabetes 11.6 years. The change from baseline in HbA1c for sitagliptin versus placebo was –0.3%, and sitagliptin-assigned patients received fewer oral antihyperglycemic agents and insulin during the course of the trial. A greater number of patients assigned to sitagliptin developed pancreatitis (n=23, 0.3%) compared to placebo (n=14, 0.2%), but this did not achieve statistical significance (p=0.065).

Following 3.0 years median duration, no overall effect of sitagliptin versus placebo occurred on the primary endpoint (9.6% versus 9.6%, HR=0.98, 95% CI 0.88–1.09, p <0.001 for noninferiority) (Table 5). Similarly, the secondary endpoint that excluded hospitalization for unstable angina occurred in 8.4% of patients assigned to sitagliptin versus 8.3% on placebo (HR=0.99, 95% CI 0.89–1.11). Rates of hospitalization for heart failure in the sitagliptin group were similar to those in the placebo group (3.1% versus 3.1%, HR=1.00, 95% CI 0.90–1.20, p=0.983). Furthermore, the composite of CV death and hospitalized heart failure was the same on sitagliptin and placebo (7.3% versus 7.2%, HR=1.01, p=0.813) (Table 5). The TECOS investigators concluded that the addition of sitagliptin to usual care of type 2 diabetes did not impact risk for major adverse CV events or hospitalization for heart failure.

6. INCRETIN BASED THERAPIES AND RISK OF HEART FAILURE

The finding of increased risk of heart failure hospitalization with saxagliptin in SAVOR-TIMI 53 trial has prompted further evaluation of this risk in newer studies. In a recent

population based retrospective cohort study involving 78,553 saxagliptin users and 298,124 sitagliptin users [55] with type 2 diabetes who were newly started on various oral antidiabetic medications and long acting insulin products, a higher risk of hospitalized heart failure was not seen in users of saxagliptin and sitagliptin on separate head-to-head comparisons with different agents. In another large observational study from Italy [56], the use of DPP-4 inhibitors was associated with a reduced risk of heart failure hospitalization as compared to sulfonylureas. Another large multinational observational study with patients from Canada, US and UK showed no increase in the risk of heart failure hospitalization with the use of incretin-based drugs as compared with oral antidiabetic drug combinations among patients with or without a history of heart failure [57]. The results were similar for DPP-4 inhibitors and GLP-1 analogues. A recent meta-analysis by Li et al [58] suggests that the jury is still out for the heart failure safety of DPP-4 inhibitors based on the duration of the trials and the inconclusive evidence from observational studies. However, the totality of observational data support the safety of incretin-based therapies in patients with heart failure.

7. Cardiovascular Outcomes of SGLT2 inhibitors

7.1 EMPA-REG OUTCOME (Empagliflozin)

The EMPA-REG OUTCOME trial [14] was a randomized, double blind, placebo-controlled trial aimed at evaluating the effects of empagliflozin, an inhibitor of sodium-glucose cotransporter 2, in addition to standard care on cardiovascular morbidity and mortality in patients with type 2 diabetes with established CV disease. Patients were randomly assigned in a 1:1:1 ratio to receive either 10 mg or 25 mg of empagliflozin or placebo once daily. The primary outcome was a composite of death from cardiovascular causes, nonfatal MI or nonfatal stroke. The secondary outcome was a composite of primary outcome plus hospitalization for unstable angina. The median duration of treatment was 2.6 years and the median observation time was 3.1 years.

A total of 7020 patients at 590 sites in 42 countries were treated and included in the primary analysis. As compared with placebo (n=2333), empagliflozin (n=4687); pooled data from groups receiving 10 mg and 25 mg empagliflozin resulted in a significantly lower risk of death from cardiovascular causes (hazard ratio, 0.62; 95% CI, 0.49–0.77; P<0.001), death from any cause (hazard ratio, 0.68; 95% CI, 0.57–0.82, P<0.001), and hospitalization from heart failure (hazard ratio, 0.68; 95% CI, 0.50–0.85; P<0.002). This translated into a significantly lower rate of primary outcome in patients treated with empagliflozin. Of interest, there was no significant between-group difference in the occurrence of MI, stroke or key secondary outcome. When 10 mg and 25 mg doses of empagliflozin were separately compared with placebo, hazard ratios for primary and key secondary outcome were similar to those in pooled analysis of the 2 drug doses but did not meet criteria for significance.

Adjusted mean differences in the glycated hemoglobin levels between patients receiving empagliflozin and those receiving placebo at 12 weeks were –0.54% and –0.60% in the 10 mg and 25 mg group respectively. These differences persisted at –0.24% and –0.36% respectively at 206 weeks. Empagliflozin was also shown to exhibit a significant renoprotective effect [48]. New onset or worsening kidney disease were reduced by 39%,

new macroalbuminuria by 38%, doubling of serum creatinine by 44 %, and incidence of end-stage renal disease by 55%. Small but significant reductions in weight, waist circumference, uric acid level, systolic and diastolic blood pressure with no increase in heart rate and small increases in both LDL and HDL cholesterol were noted as compared to placebo.

The proportion of patients who had adverse events, serious adverse events, and adverse events leading to discontinuation of a study drug were similar in the empagliflozin group and the placebo group (14). Confirmed hypoglycemic events, diabetic ketoacidosis, thromboembolic events, bone fracture and events consistent with volume depletion were similar in the two study groups. Genital infection and urosepsis were reported in a higher proportion of patients in the pooled empagliflozin group, but there was no increase in the overall rate of urinary tract infection. Although concerns have been expressed regarding the renal safety of SGLT2 inhibitors, renal function was maintained with empagliflozin.

8. Non-cardiovascular safety issues

8.1 GLP-1 receptor agonists

An increased risk of hypoglycemia has been reported when GLP-1 agonists are added to sulfonylurea (SU) therapy. In the AMIGO II study comparing co-administration of exenatide versus placebo with SU, mild to moderate hypoglycemia episodes occurred in 14–36% of patients treated with exenatide compared to 3% in patients receiving placebo [59]. Increased risk of minor hypoglycemic events is also noted when GLP-1 receptor agonists are added to a combination of metformin and sulfonylurea [60], lower doses of sulfonylurea in this combination appear to decrease this risk to some extent [59]. Exenatide monotherapy also results in a higher risk of hypoglycemia (4–5% incidence versus 1%) compared to placebo alone [61]. When GLP-1 receptor agonists are added onto metformin therapy, the risk of hypoglycemia does not appear to be increased [62].

The formation of drug specific antibodies has been reported in a significant proportion of patients on GLP-1 agonists [63]. This appears to be more frequent with exenatide than liraglutide, and glycemic response to exenatide therapy may be attenuated by high-titer antibodies [63,64]. Local injection site reactions do not appear to be frequent and generally tend to improve with treatment duration [63]. Several cases of pancreatitis have been reported to the FDA in connection with GLP-1 agonist therapy, but a causal association has never been established (6). However, caution is warranted since some of these cases also noted recurrence of pancreatitis on reintroduction of the medication [63]. When patients present with abdominal pain, therapy should be promptly discontinued and evaluation for pancreatitis should be initiated.

Gastrointestinal (GI) side effects including nausea, vomiting and diarrhea are frequent with initiation of GLP-1 agonist therapy (61–65). Incidence is higher when GLP-1 agonists are used in combination therapy with metformin, sulfonylureas and insulin [60,66,67]. Studies demonstrate these symptoms to be dose dependent; and a tendency to improve after a few weeks of therapy. Although these symptoms appear to be minor, they can result in noncompliance. In a study of 124 patients with type 2 diabetes on exenatide combined with

insulin, 36% patients discontinued therapy within a year due to GI symptoms [67]. Clinicians may recommend initiation of the medication at lower dose to circumvent this problem, attempting to gradually up-titrate the medication to achieve optimal glycemic control. There is some evidence that extended dose titration of exenatide reduces the incidence of severe nausea and vomiting leading to treatment discontinuation [68].

There have been concerns of thyroid C-cell hyperplasia, adenomas and carcinomas on GLP-1 agonist therapy in studies in diabetic mice and rats. These changes were typically preceded by increased calcitonin levels in mice and rats, but similar increase in calcitonin was not identified in humans [69]. Rats appear to have a much higher density of GLP1 receptors on their C cells than humans and such receptors have not been identified to be functional in humans [70]. There has been no evidence in human clinical trials that showed GLP-1 receptor agonists to be related to thyroid c-cell hyperplasia or neoplasms.

8.2 DPP-4 inhibitors

As monotherapy, the DPP-4 inhibitors do not increase the overall risk of hypoglycemia when compared to placebo [71–73,10]. There may be an increase in the risk of hypoglycemia when DPP-4 inhibitors are combined with sulfonylureas [74]. Dose reduction for sulfonylureas is therefore recommended in combination therapy, although the effects on overall glycemic control must be weighed into management decisions. In a pooled analysis of 22 randomized placebo controlled trials, the incidence of investigator defined hypoglycemic adverse events were similar for linagliptin and placebo treated patients receiving insulin during treatment phase [73]. Another review reported increased risk of hypoglycemia in combination therapy of DPP4 inhibitors with insulin [71].

The DPP-4 inhibitors do not have a significant effect on body weight [71]. A meta-analysis of 29 randomized controlled trials involving sitagliptin and vildagliptin showed an increased risk of infection (risk ratio, 1.2 [95% CI, 1.0–1.4] for nasopharyngitis and 1.5 [95% CI, 1.0–2.2] for urinary tract infection) and headache [75]. Another meta-analysis of controlled trials published later showed no increased risk of infections on DPP4 inhibitor therapy (RR 0.98 [95% CI, 0.93–1.05]) compared to placebo, although a significantly increased risk of nasopharyngitis (attributed by authors to exacerbation of the inflammatory reaction in the nasal mucosa from DPP-4 inhibition) was noted in the sitagliptin subgroup [71].

As with GLP-1 receptor agonists, acute pancreatitis has been reported with DPP-4 inhibitors without an established cause-effect relationship. However, in meta-analyses [75,76] as well as pooled studies of randomized controlled trials [73], DPP-4 inhibitors did not increase the risk of pancreatitis. In contrast, a population based case control study with 1269 patients in both groups showed increased odds of hospitalization for acute pancreatitis among DPP-4 inhibitors [76]. Nevertheless, it is recommended that treatment with DPP-4 inhibitors be discontinued if pancreatitis occurs and should not be restarted.

Other less commonly reported side effects with DPP-4 inhibitors include arthralgias, hypersensitivity reactions including anaphylaxis, and liver function abnormalities [77,78].

8.3 SGLT-2 inhibitors

Significant increases in the incidence of genital mycotic infections have been reported with all SGLT2 inhibitors in multiple randomized studies [79,80]. In a pooled analysis from 17 randomized clinical trials and 6 extension studies with > 9000 patient-years exposure to empagliflozin, the incidence of genital mycotic infections was 4.7–5/100 patient years as compared to 1.3/100 patients years in placebo [20]. Almost all of these infections were mild to moderate in intensity and events requiring prolonged hospitalization were not significantly increased versus placebo. This has been attributed to increased urinary glucose excretion providing conditions conducive to yeast growth [20, 79]. Balanitis has also been reported in men [20]. The risk of urinary tract infections appears to be similar to placebo in multiple studies [80].

The incidence of hypoglycemia is not significantly increased with SGLT2 inhibitor monotherapy when compared to placebo [38,39,81,82]. Addition of SGLT2 inhibitors to metformin [83–85], pioglitazone [86] as well as linagliptin [87] also confers a low risk of hypoglycemic events (~1–5%). There is a significantly increased risk of hypoglycemia (11.5–23.7%) with add-on therapy to a combination of metformin and sulfonylurea [89–90]. Studies of empagliflozin combination with basal insulin and multiple daily injections of short-acting insulin [90] showed some evidence of increased risk of hypoglycemia in initial phase of treatment with fixed doses of insulin, but no significant differences were observed at the end of 78 and 52 weeks respectively when insulin doses were stabilized.

Enhanced glucosuria also results in greater incidence of osmotic diuresis-related events like pollakiuria and polyuria, but volume depletion events (hypotension, orthostasis) are infrequent and occurred at rates similar to placebo [20]. Risk of these events appear to be increased in patients >75 years of age, moderate renal impairment and concomitant loop diuretic therapy [82,91]. In the interim analysis of CANVAS trial, an increase in bone fractures was found with canagliflozin (4% vs 2.6% with placebo) [91]. However, no such increased risk was found in a pooled analysis of 8 randomized controlled trials [92]. In older patients (aged 55–80 years), modest reductions in total hip bone mineral density have been observed but without significant changes in the femoral neck, lumbar spine or distal forearm [91,92]. Some cases of euglycemic diabetic ketoacidosis (DKA) have been noted in type 1 diabetics (rarely in type 2 diabetics in special settings such as post-surgery) treated with SGLT2 inhibitors, a significant proportion of such cases being related to off-label use [20,93]. Clinicians should be aware of the possibility of the diagnosis of DKA being delayed due to normal blood sugars in patients treated with SGLT2 inhibitors.

9. Expert Opinion

The major CV outcome trials with the DPP-4 inhibitors, GLP-1 agonists and the SGLT2 inhibitors have clearly demonstrated that these newer therapies have acceptable CV safety profiles in patients with type 2 diabetes and moderate-to-high CV risk for major adverse CV events. The results of the EXAMINE and TECOS trials provide substantial evidence in favor of the cardiovascular safety of the DPP-4 inhibitors. In addition, the DPP-4 inhibitors provide a useful adjunct to metformin, sulfonylureas, SGLT inhibitors or insulin in the management of glycemic control for type 2 diabetes. The heart failure findings in SAVOR-

TIMI 53 were unexpected but do not appear be a class effect of the incretin-based therapies. Furthermore, large observational studies with DPP-4 inhibitors, including saxagliptin, have not shown increases in the risk of hospitalization for heart failure.

The unexpected cardiovascular benefits of the GLP-1 agonist liraglutide and the SGLT2 inhibitor empagliflozin found in LEADER and the EMPA-REG outcomes studies, respectively, should initiate an interesting new era in the management of type 2 diabetes. These 2 trials have provided placebo controlled evidence of significant reductions in all-cause and cardiovascular mortality with liraglutide and empagliflozin in large patient populations with established cardiovascular disease. In addition, empagliflozin has been shown to have a renoprotective effect by producing significant reductions in the incidence of new onset kidney disease, macro-albuminuria, progression of existing kidney disease and end stage renal failure. When combined with reductions in weight, systolic and diastolic blood pressure, waist circumference as well as better glycemic control, these medications provide a versatile tool for the physicians for modifying the risk factor profile of their diabetic patients. It is important to recognize that it is not possible to state that the GLP-1 agonists or the SGLT2 inhibitors have a beneficial class effect on the CV outcomes. First, the ELIXA trial showed non-inferiority but not benefit for lixisenatide – hence, not the benefit seen in LEADER with liraglutide. Additionally, there are no results with other SGLT2 inhibitors to corroborate the findings of EMPA-REG Outcome and empagliflozin - the CANVAS trial (for canagliflozin) and DECLARE TIMI-58 (dapagliflozin) will ultimately shed more light on whether these outcomes are a class effect of SGLT2 inhibitors.

One of the major limitations of the evidence presented thus far is that the high CV risk patients with type 2 diabetes in these trials have only been followed for 2 to 3 years. It may be possible that some cardiovascular beneficial effects as well as adverse events may take longer to become clinically evident. Although designing clinical studies with longer follow up times may have logistical and financial challenges, the importance of continued observational surveillance cannot be overstated. Since the patient populations evaluated in the CV outcome trials were high risk given the presence of established CV disease, the potential benefits of starting empagliflozin and liraglutide in patients with new onset diabetes with no evidence for CV disease remains unclear and could be of interest in future observational studies. The effects of specific combinations of antihyperglycemic therapies on cardiovascular outcomes are also not clear at this time. The major CV outcome trials add the ‘new’ therapy versus placebo to standard of care but the subgroups are underpowered to determine a benefit (or risk) of the combinations of therapies.

The consistency of evidence generated since the implementation of the 2008 FDA guidance on assessing CV safety of new antihyperglycemic therapies raises the question of whether large safety outcome studies should continue to be necessary for all new drugs for the treatment of type 2 diabetes that lack a signal of concern during drug development [94]. A more specific approach might now be appropriate, where the need for CV outcome studies would be determined by regulators for each individual agent based on its mechanism of action and its preclinical and phase I to III development safety data. Requiring CV outcome safety trials seems reasonable when there is a cardiovascular signal from early development data. Given the difficult logistics of continuing CV safety trials for a long duration, it may be

prudent to derive CV outcome data from observational studies, registries and ongoing surveillance through adverse event reporting systems.

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** of considerable interest

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Article Highlights Box

- The paper focuses on the pharmacologic and clinical cardiovascular (CV) effects of drugs for the treatment of type 2 diabetes
- The clinical pharmacology of the newer classes of therapies for the treatment of type 2 diabetes are reviewed
- Several major clinical trials that have evaluated the CV safety of these agents (SAVOR TIMI 53, EXAMINE, ELIXA, TECOS, EMPA-REG OUTCOME, LEADER] have been described.
- The results of these major studies have shown either a non-inferior or in 2 cases, a beneficial effect on major CV outcomes. It is not yet clear if those studies showing a benefit could be considered a 'class effect'
- Heart failure safety has received a great deal of attention over the past 3 years and has become a pre-specified part of the more recent studies. Only 1 study showed a small but statistically significant increase in hospitalization for heart failure. The bulk of evidence does not suggest heart failure to be of major clinical concern with the newer drugs used for the treatment of type 2 diabetes.

Table 1

Pharmacologic characteristics of the GLP-1 agonists

Parameter	Short-acting GLP-1 receptor agonist	Long-acting GLP-1 receptor agonist
Agents	Exenatide Lixisenatide	Albiglutide Dulaglutide Exenatide-LAR Liraglutide
Half-life	2–5 h	12h – several days
Fasting insulin secretion	Modest or no stimulation	Strong stimulation
Postprandial insulin secretion	Reduction	Modest stimulation
Gastric emptying rate	Deceleration	No effect
Postprandial hyperglycemia	Strong reduction	Modest reduction
Fasting blood glucose levels	Modest reduction	Strong reduction

Abbreviations: GLP-1, glucagon-like peptide 1; LAR, long-acting release.

Table 2

Pharmacologic characteristics of the DPP-4 inhibitors

Agent	Structure	Bioavailability	Half-life	Primary elimination	DPP-4 selectivity
Alogliptin	Pyrimidine	63–70%	21 h	Renal	>14,000
Linagliptin	Pyrimidine	30%	120–142 h	Enterohepatic	>10,000
Saxagliptin	Methanoproline-nitrile	75%	3 h	Renal	100
Sitagliptin	Piperazine	87%	11–13 h	Renal	>2,600
Vildagliptin	Cyanopyrrolidine	84%	2–3 h	Renal	100

Abbreviation: DPP-4, dipeptidyl peptidase-4

Table 3

Pharmacologic properties of the SGLT-2 Inhibitors

	Canagliflozin	Dapagliflozin	Empagliflozin
Onset of action	Within 24 hours (dose-dependent)	Within 24 hours	Peak plasma: within 1.5 h Post-dose
Duration of action	24 hours	24 hours	24 hours
Absorption	Not affected by food; taking before first meal may decrease postprandial hyperglycemia	High-fat meal decreases peak plasma concentration by up to 50%	Lower absorption with high fat and high-calorie meal; AUC ↓16%, but not clinically significant
Distribution	Vd: 119 L	Vd: 118 L	Vd: 73.8L
Protein binding	99% mainly to albumin	91%	86.2%
Metabolism	O-glucuronidation by UGT1A9 & UGT2B4 to 2 inactive metabolites; minor CYP3A4 oxidation	UGT 1A9 to 1 inactive metabolite (Dapagliflozin 3-O-glucuronide), minor CYP	Glucuronidation by UGT2BT, UGT1A2, UGT1A3, UGT1A8, UGT1A9
Bioavailability	~ 65%	78%	N/A
Half-life elimination	100 mg: 10.6 hours 300 mg: 13.1 hours	12.9 hours	12.4 hours
Time to peak concentration	1–2 hours	2 hours	1.5 hours
Excretion	Feces (51.7%) Urine (~ 33%)	Urine (75%) Feces (21%)	Urine (54.4%) Feces (41.2%)
SGLT receptor selectivity	250:1	1200:1	2500:1

Vd – volume of distribution; CYP – cytochrome P450

Table 4
Cardiovascular outcome studies for the GLP-1 agonists, DPP-4 inhibitors and SGLT2 inhibitors

Key Inclusion Criteria	SAVOR-TIME 53 Trial	EXAMINE Trial	TECOS Trial	ELIXA Trial	LEADER Trial	EMPA-REG OUTCOME Trial
	Type 2 Diabetes Mellitus HbA1c 6.5% – 12.0% CVD for multiple risk factors for vascular disease	Type 2 Diabetes Mellitus receiving treatment HbA1c 6.5% – 11% (7.0% – 10.0% if on insulin ACS within 15–90 days	HbA1c 6.5% – 8.0% on 1 – 2 oral antihyperglycemic agent or on insulin Established CVD	Type 2 Diabetes Mellitus HbA1c 5.5% – 11.0% Acute coronary event within 180 days of screening	Type 2 Diabetes Mellitus HbA1c 7.0% Prior CVD or no prior CVD >60 yrs of age with > 1of the following criteria (Microalbuminuria or proteinuria, Hypertension, left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, ankle-brachial index <0.9)	Type 2 DM HbA1c 7.0% & 9% if not on glucose-lowering agents HbA1c 7.0% & 10% if on glucose-lowering therapy Established CVD
Duration	Median follow up of 2.1 years	Median follow up of 1.58 years	Median follow up of 3 years	Median follow up of 2.1 years	Median follow up of 3.8 years	Median observation time of 3.1 years Median duration of treatment 2.6 years
Sample Size	16,492	5,380	14,671	6,068	9,340	7,020
Design	Non-inferiority & superiority of Saxagliptin to placebo for primary outcome	Non-inferiority of Alogliptin to placebo for primary outcome	Non-inferiority of Sitagliptin to placebo for primary outcome	Non-inferiority of Lixisenatide to placebo for primary outcome	Non-inferiority & superiority of Liraglutide to placebo for primary outcome	Non-inferiority & superiority of Empagliflozin to placebo for primary outcome
Drug	Saxagliptin 5 mg daily Saxagliptin 2–5 mg daily in patients with eGFR 50 ml/min	Alogliptin 25 mg daily [eGFR >60 ml/min/1.73m ² BSA] 12.5 mg daily [eGFR 30–60 ml/min/1.73m ² BSA] 6.25 mg daily [eGFR <30 ml/min/m ² BSA]	Sitagliptin 100 mg daily Sitagliptin 50 mg daily if eGFR 30 & <50 ml/min/1.73m ²	Lixisenatide 10– 20 mg daily	Liraglutide 1.8 mg subcutaneously daily or the maximum tolerated dose of Liraglutide	Empagliflozin 10 mg daily Empagliflozin 25 mg daily
Primary outcome measure	Composite of death from Cardiovascular causes Nonfatal MI Nonfatal ischemic stroke	Composite of death from Cardiovascular causes Nonfatal MI Nonfatal stroke	Composite of death from Cardiovascular causes Nonfatal MI Nonfatal stroke Hospitalization for unstable angina	Composite of death from Cardiovascular causes Nonfatal MI Nonfatal stroke Hospitalization for unstable angina	Composite of death from Cardiovascular causes Nonfatal MI Nonfatal stroke	Composite of death from Cardiovascular causes Nonfatal MI Nonfatal stroke

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Abbreviations: SAVOR TIMI 53 Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus(SAVOR) – Thrombolysis in Myocardial Infarction (TIMI) 53; EXAMINE Examination of Cardiovascular Outcomes: Alogliptin versus Standard of Care in Patients with T2DM; TECOS Trial Evaluating Cardiovascular Outcomes with Sitagliptin; ELIXA Evaluation of Lixisenatide in Acute Coronary Syndrome; LEADER Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; EMPA-REG OUTCOME : Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; CVD=cardiovascular disease; eGFR=estimated glomerular filtration rate; BSA=body surface area; MI=myocardial infarction.

Table 5

Results of major cardiovascular outcomes trials of GLP-1 agonists, DPP-4 inhibitors and SGLT2 inhibitors.

ELIXA (12)	Lixisenatide (n=3,034)	Placebo (n=3,034)	Hazard ratio (95% CI)	p Value
Death from cardiovascular causes, nonfatal stroke, nonfatal MI, or hospitalization from unstable angina	406 (13.4%)	399 (13.2%)	1.02 (0.85–1.17)	0.81
Death from any cause	211 (7.0%)	223 (7.4%)	0.94 (0.78–1.13)	0.50
Death from cardiovascular causes	156 (5.1%)	158 (5.2)	0.98 (0.78–1.22)	0.85
Hospitalization for heart failure	122 (4.0%)	127 (4.2%)	0.96 (0.75–1.23)	0.75
LEADER (13)	Liraglutide (n=4668)	Placebo (n=4672)	Hazard ratio (95% CI)	p Value
Death from cardiovascular causes, nonfatal MI, and nonfatal stroke	608 (13%)	694 (14.3%)	0.87 (0.78–0.97)	0.01
Death from any cause	381 (8.2%)	447 (9.6%)	0.85 (0.74–0.97)	0.02
Death from cardiovascular causes	215 (4.7%)	278 (6.0%)	0.78 (0.66–0.93)	0.007
Hospitalization for heart failure	218 (4.7%)	248 (5.3%)	0.87 (0.73–1.05)	0.14
Microvascular event (Retinopathy & nephropathy)	355 (7.6%)	416 (8.9%)	0.84 (0.73–0.97)	0.02
EXAMINE (10)	Alogliptin (n=2,679)	Placebo (n=2,679)	Hazard ratio (95% CI)	p Value
Cardiovascular death, nonfatal MI, and nonfatal stroke	305 (11.3%)	316 (11.8%)	0.96 (<1.16) ^a	0.32
Death from any cause	153 (5.7%)	173 (6.5%)	0.88 (0.71–1.09)	0.23
Death from cardiovascular causes	112 (4.1%)	130 (4.9%)	0.85 (0.66–1.10)	0.21
Hospitalization for heart failure or cardiovascular death	201 (7.4%)	201 (7.5%)	1.00 (0.82–1.21)	0.98
SAVOR-TIMI 53 (9)	Saxagliptin (n=8,280)	Placebo (n=8,212)	Hazard ratio (95% CI)	p Value
Cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke	613 (7.3%)	609 (7.2%)	1.00 (0.89–1.12)	0.99
Death from any cause	420 (4.9%)	378 (4.2%)	1.11 (0.96–1.27)	0.15
Death from cardiovascular causes	269 (3.2%)	260 (2.9%)	1.03 (0.87–1.22)	0.72
Hospitalization for heart failure or cardiovascular death	493 (6.0%)	432 (5.3%)	1.14 (1.00–1.30)	Not reported
TECOS (11)	Sitagliptin (n=7,257)	Placebo (n=7,266)	Hazard ratio (95% CI)	p Value
Cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke	609 (8.4%)	602 (8.3%)	0.99 (0.89–1.11)	<0.001 (for noninferiority)
Death from any cause	547 (7.5%)	537 (7.3%)	1.01 (0.90–1.14)	0.88
Death from cardiovascular causes	380 (5.2%)	366 (5.0%)	1.03 (0.89–1.19)	0.71
Hospitalization for heart failure or cardiovascular death	538 (7.3%)	525 (7.2%)	1.02 (0.90–1.15)	0.74
EMPA-REG OUTCOME (14)	Empagliflozin (n=4687)	Placebo (n=2333)	Hazard ratio (95% CI)	p value

ELIXA (12)	Lixisenatide (n=3,034)	Placebo (n=3,034)	Hazard ratio (95% CI)	p Value
Death from cardiovascular causes, nonfatal MI and nonfatal stroke	480 (10.5%)	282 (12.1%)	0.86 (0.74–0.99)	<0.001 for noninferiority 0.04 for superiority
Death from any cause	269 (5.7%)	194 (8.3%)	0.68 (0.57–0.82)	<0.001
Death from cardiovascular causes	172 (3.7%)	137 (5.9%)	0.62 (0.43–0.77)	<0.001
Hospitalization for heart failure	126 (2.7%)	95 (4.1%)	0.65 (0.50–0.85)	0.002

* The parenthetical value is the upper boundary of the one-sided repeated confidence interval, at an alpha level of 0.01.

Table 6

Factors predicting subsequent hospitalized heart failure during the EXAMINE study [53]

Baseline factors adjusted	Hazard ratio (95% CI)	P Value ^a
Treatment (alogliptin versus placebo)	1.10 (0.82, 1.47)	0.538
History of heart failure	3.24 (2.31, 4.53)	<0.001
Baseline NT-proBNP (second quartile versus first quartile)	3.62 (1.21, 10.8)	0.022
Baseline NT-proBNP (third quartile versus first quartile)	7.52 (2.63, 21.3)	<0.001
Baseline NT-proBNP (fourth quartile versus first quartile)	24.70 (8.87, 68.77)	<0.001
Baseline insulin use	1.43 (1.06, 1.93)	0.020
History of myocardial infarction	1.78 (1.29, 2.46)	<0.001
Mild renal impairment at baseline	1.59 (0.72, 3.53)	0.256
Moderate renal impairment at baseline	1.92 (0.85, 4.34)	0.116
Severe renal impairment/ESRD at baseline	2.73 (1.07, 6.92)	0.035
Age (<65 years versus ≥65 years)	1.14 (0.83, 1.58)	0.417
Gender (female versus male)	0.79 (0.57, 1.08)	0.143
Time from index ACS to randomization (one-day increase)	0.99 (0.99, 1.02)	0.143

Abbreviations: ACS, acute coronary syndrome; ESRD, end-stage renal dysfunction; CI, confidence interval; NT-proBNP, N-terminal probrain natriuretic peptide.

^aBoldface indicates statistically significant values.