

Cardiovascular safety outcomes of new antidiabetic therapies

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Purpose. The cardiovascular safety outcomes of newer antidiabetic agents were reviewed.

Summary. Seven randomized, placebo-controlled trials involving patients with type 2 diabetes mellitus with or at risk for cardiovascular disease were reviewed. The trials examined the cardiovascular safety outcomes of the following agents: alogliptin, saxagliptin, and sitagliptin (dipeptidyl peptidase-4 [DPP-4] inhibitors); liraglutide, lixisenatide, and semaglutide (glucagon-like peptide-1 agonists); and empagliflozin (a sodium glucose cotransport-2 inhibitor). The DPP-4 inhibitor and lixisenatide trials showed a neutral effect on cardiovascular events (composite of cardiovascular death, myocardial infarction, or stroke, with or without unstable angina). Empagliflozin showed a significant reduction in cardiovascular events, cardiovascular death, all-cause death, and hospitalization due to heart failure (HF); liraglutide reduced cardiovascular events, cardiovascular death, and all-cause death, and semaglutide reduced cardiovascular events and nonfatal stroke. Most studies showed a neutral effect of the drug on hospitalization for HF; however, saxagliptin and alogliptin (in the subgroups of patients without a history of HF) showed a significant increase while empagliflozin showed a significant reduction in hospitalizations for HF. The data for empagliflozin, liraglutide, and semaglutide are compelling; however, further studies are necessary to confirm observed benefits and better characterize long-term safety and their use as a strategy to reduce cardiovascular events.

Conclusion. A review of cardiovascular safety outcomes for new antidiabetic agents found that saxagliptin and alogliptin were associated with an increase in hospitalization for HF. The data for empagliflozin, liraglutide, and semaglutide showed a reduction in cardiovascular events and death or a neutral effect on cardiovascular endpoints.

Keywords: antidiabetic agent, cardiovascular disease, heart failure, pharmacotherapy, type 2 diabetes mellitus

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Type 2 diabetes mellitus is a common medical problem, affecting approximately 12.9% of adult North Americans as of 2015.¹ The estimated total economic burden of type 2 diabetes in the United States was \$245 billion in 2012, roughly 70% of which was attributable to direct medical costs.² An elevated glycosylated hemoglobin (HbA_{1c}) level and a diagnosis of type 2 diabetes are associated with an increased risk of cardiovascular disease

(CVD), including coronary heart disease, stroke, and peripheral arterial disease, which are the leading causes of death in these patients.^{3,4} While the majority of the therapies approved for the treatment of type 2 diabetes mellitus reduce HbA_{1c} levels, few have demonstrated a reduction in cardiovascular events. Furthermore, the use of some of these agents has resulted in increased cardiovascular risk, such as the higher rate of myocardial infarction (MI) ob-

served with rosiglitazone.^{5,6} These results led to the imposition of prescribing restrictions for rosiglitazone by the Food and Drug Administration (FDA) and Health Canada and withdrawal of the drug from the European market.

Based on the experience with rosiglitazone, in 2008 FDA issued guidance for drug manufacturers to establish cardiovascular safety for all new antidiabetic drugs in randomized controlled trials involving high cardiovascular risk patients (e.g., advanced disease, renal impairment, elderly).⁷ The new FDA requirements mandate that these postmarketing trials be at least 2 years in duration and show a 1-sided upper boundary of the 95% confidence interval (CI) of ≤ 1.3 for major adverse cardiovascular events versus a control. In other words, to establish cardiovascular safety, new drugs for type 2 diabetes mellitus cannot show a rate of risk greater than 30% compared to a control, which is often a placebo. While Phase III studies are designed to establish efficacy, most provide incomplete safety data due to limited follow-up, statistical power, and generalizability.⁸ The purpose of this review was to evaluate the cardiovascular safety outcomes of new antidiabetic agents for the treatment of type 2 diabetes mellitus since the release of the FDA guidance document.

Methods

MEDLINE (January 2008–June 2016), Embase (January 2008–June 2016), and Google Scholar (to June 2016) were searched using the following terms: *hypoglycemic agent, cardiovascular outcome, and randomized controlled trial*. The references of included articles were manually searched to further identify relevant articles. Adequately powered randomized controlled trials (RCTs) that investigated an antihyperglycemic drug, reported clinically meaningful cardiovascular outcomes (i.e., cardiovascular death, MI, and stroke), and were at least 2 years in duration were included. The search strategy yielded 14 records from MEDLINE, 4 from Embase, and 5 from

KEY POINTS

- To date, 7 adequately powered cardiovascular outcomes trials have been completed that satisfy Food and Drug Administration requirements to establish cardiovascular safety outcomes of new antidiabetic agents.
- A review of cardiovascular safety outcomes for new antidiabetic agents found that saxagliptin and alogliptin were associated with an increase in hospitalization for heart failure.
- The data for empagliflozin, liraglutide, and semaglutide showed a neutral effect on cardiovascular endpoints or a reduction in cardiovascular events and death.

Google Scholar. One author reviewed the title and abstracts of these 23 articles for eligibility; 5 duplicate articles were removed. Of the remaining 18 articles, 11 were excluded, primarily due to a lack of cardiovascular outcomes reporting. All 3 authors reviewed the final 7 trials in full. Additional trials investigating the cardiovascular safety of other new antidiabetic drugs remain ongoing.⁹ Results from the SUSTAIN 6 trial were released before their online publication in September 2016.

Results

Dipeptidyl peptidase-4 inhibitors. Three published trials assessed the cardiovascular safety outcomes of dipeptidyl peptidase-4 (DPP-4) inhibitors alogliptin, saxagliptin, and sitagliptin.¹⁰⁻¹²

The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus—Thrombolysis in Myocardial Infarction (SAVOR-TIMI 53) trial evaluated the use of saxagliptin in 16,492 adult patients with

type 2 diabetes mellitus and either a history of stable CVD or cardiovascular risk factors (dyslipidemia, hypertension, or smoking).¹⁰ Patients receiving dialysis or with a serum creatinine concentration of >6 mg/dL were excluded. Patients were randomized to receive either saxagliptin 5 mg orally daily (2.5 mg orally daily if their estimated glomerular filtration rate [eGFR] did not exceed 50 mL/min) or placebo, in addition to usual care, for a median of 2.1 years. Patients had a mean age of 65 years and a mean HbA_{1c} level of 8%, and 79% ($n = 12,959$) had established CVD. At baseline, 82% ($n = 13,535$) were taking an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB), 78% ($n = 12,917$) a statin, 75% ($n = 12,404$) aspirin, and 62% ($n = 10,162$) a β -blocker. In terms of antidiabetic therapies, 70% ($n = 11,473$) were taking metformin, 41% ($n = 6,832$) an insulin, 40% ($n = 6,633$) a sulfonylurea, and 6% ($n = 978$) a thiazolidinedione. Saxagliptin was determined to be noninferior to placebo for the primary composite endpoint of cardiovascular death, nonfatal MI, or nonfatal ischemic stroke (7.3% versus 7.2%; intention-to-treat [ITT] analysis hazard ratio [HR], 1.00; 95% CI, 0.89–1.12; $p < 0.001$ for noninferiority; $p = 0.99$ for superiority). There was no significant difference between groups in the secondary composite endpoint of cardiovascular death, nonfatal MI, nonfatal ischemic stroke, hospitalization for unstable angina (UA), coronary revascularization, or heart failure (HF) (HR, 1.02; 95% CI, 0.94–1.11). Hospitalization for HF, a prespecified, blindly adjudicated outcome, was defined as (1) an event requiring hospitalization or an emergency department visit, (2) at least 1 new or worsening sign or symptom of HF; and (3) the initiation or a dosage increase of intravenous therapy or mechanical or surgical intervention. The rate of hospitalization for HF was significantly higher with saxagliptin versus placebo (3.5% versus 2.8%; HR, 1.27; 95% CI, 1.07–1.51). However, in a post hoc subgroup analysis of patients with HF at baseline ($n = 2,105$ [13%]),

those in the saxagliptin group had a higher but nonsignificant rate of hospitalization for HF when compared with placebo (11.7% versus 10.2%; HR, 1.23; 95% CI, 0.94–1.59).¹³ On the contrary, patients without a history of HF had an unanticipated increase in the rate of hospitalization for HF with saxagliptin versus placebo (2.3% versus 1.7%; HR, 1.30; 95% CI, 1.03–1.65). Overall, while saxagliptin was deemed noninferior to placebo with respect to cardiovascular safety, an unexpected increase in hospitalizations for HF was observed with saxagliptin use.

The Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care in Patients with Type 2 Diabetes Mellitus and Acute Coronary Syndrome (EXAMINE) evaluated alogliptin in 5,380 adult patients with type 2 diabetes and a recent (within 15–90 days) acute coronary syndrome (ACS) event (MI or UA requiring hospitalization).¹¹ Patients receiving dialysis or with unstable cardiac disorders (e.g., refractory angina, uncontrolled arrhythmia) were excluded. Patients were randomized a median of 46 days post-ACS event to receive either oral alogliptin 25 mg daily (12.5 mg daily if their eGFR was 30–59 mL/min/1.73 m² and 6.25 mg daily if their eGFR was less than 30 mL/min/1.73 m²) or placebo, in addition to usual care, for a median of 18 months. Patients' median age was 61 years and mean HbA_{1c} level was 8.0%, and 77% (*n* = 4,152) of patients' index ACS event was MI. At baseline, 91% (*n* = 4,881) were taking aspirin, 90% (*n* = 4,866) a statin, 82% (*n* = 4,411) an ACEI or ARB, and 82% (*n* = 4,411) a β -blocker. In terms of antidiabetic therapies, 66% (*n* = 3,562) were taking metformin, 47% (*n* = 2,503) a sulfonylurea, 30% (*n* = 1,605) an insulin, and 2% (*n* = 131) a thiazolidinedione. Alogliptin was deemed noninferior to placebo for the primary composite endpoint of cardiovascular death, nonfatal MI, or nonfatal ischemic stroke (11.3% versus 11.8%; ITT HR, 0.96; upper boundary of 1-sided repeated CI, 1.16; *p* < 0.001 for noninferiority; *p* = 0.32 for superiority). There was no statistically

significant difference in the secondary composite endpoint of cardiovascular death, nonfatal MI, nonfatal stroke, or urgent revascularization attributable to UA within 24 hours of hospital admission (HR, 0.95; upper boundary of 1-sided repeated CI, 1.14). Due to concerns regarding increased rates of hospitalization for HF with saxagliptin, a post hoc analysis of EXAMINE data was conducted.¹⁴ Hospitalization for HF was defined similarly to that in the SAVOR-TIMI 53 trial, and events were adjudicated prospectively by a blinded committee. The rate of hospitalization for HF in the entire study population was similar between groups (3.1% versus 2.9%; HR, 1.07; 95% CI, 0.79–1.46). Based on a post hoc subgroup analysis, patients without a history of HF at baseline (*n* = 3,847 [72%]) had an increased rate of HF hospital admissions (HR, 1.76; 95% CI, 1.07–2.90), which was not observed in patients with a history of HF at baseline (HR, 1.00; 95% CI, 0.71–1.42). Consistent with the results found with saxagliptin, the rate of hospitalization for HF increased among patients without a history of HF at baseline; however, in contrast to the study of saxagliptin, there was no overall increase in rates of hospitalization for HF.

The Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS) was conducted to investigate the cardiovascular safety of sitagliptin in patients over age 50 years with type 2 diabetes with established CVD.¹² Patients were excluded if their eGFR was less than 30 mL/min/1.73 m² or if they experienced at least 2 episodes of severe hypoglycemia. In total, 14,671 patients were randomized to receive oral sitagliptin 100 mg daily (50 mg daily if their eGFR was 30–49 mL/min/1.73 m²) or placebo, in addition to usual care, for a median of 3 years. Patients' mean age was 66 years and mean HbA_{1c} level was 7.2%. Forty-three percent of patients (*n* = 6,255) had a previous MI, 39% (*n* = 5,714) a previous percutaneous coronary intervention, and 25% (*n* = 3,664) a previous coronary artery bypass graft surgery. At baseline, 80% (*n* = 11,719)

were taking a statin, 79% (*n* = 11,518) aspirin, 79% (*n* = 11,555) an ACEI or ARB, and 64% (*n* = 9,322) a β -blocker. In terms of antidiabetic therapy, 82% (*n* = 11,966) were taking metformin, 45% (*n* = 6,645) a sulfonylurea, 23% (*n* = 3,408) an insulin, and 3% (*n* = 396) a thiazolidinedione. Sitagliptin was observed to be noninferior to placebo for the primary composite endpoint of cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalization for UA (9.6% versus 9.6%; per-protocol analysis HR, 0.98; 95% CI, 0.88–1.09; *p* < 0.001 for noninferiority), as well as the secondary composite endpoint of cardiovascular death, nonfatal MI, or nonfatal stroke (per-protocol analysis HR, 0.99; 95% CI, 0.89–1.11; *p* < 0.001 for noninferiority). Neither outcome demonstrated superiority with sitagliptin in the ITT analysis. In a predefined analysis, a blinded committee adjudicated hospitalization for HF (defined similarly to that in SAVOR-TIMI 53 and EXAMINE trials), which did not significantly differ between sitagliptin and placebo (HR, 1.00; 95% CI, 0.83–1.20). A predefined analysis demonstrated no significant difference in hospitalization for HF when adjusted for baseline HF (*n* = 2,643 [18%]).¹⁵ Based on these data, sitagliptin demonstrated an overall neutral effect on cardiovascular events and hospitalization for HF, even when adjusted for a history of HF at baseline.

Sodium glucose cotransport-2 inhibitors. To date, just 1 published trial assessed the cardiovascular safety of a sodium glucose cotransport-2 inhibitor. The Empagliflozin Cardiovascular Outcomes and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) trial evaluated empagliflozin in 7,028 adult patients with established CVD.¹⁶ Patients with an eGFR of \leq 30 mL/min/1.73 m² were excluded. Patients were randomized in a 1:1:1 fashion to oral empagliflozin 10 or 25 mg daily or placebo, in addition to standard therapy. The mean age was 63 years, the mean HbA_{1c} level was 8.1%, 76% (*n* = 5,308) of patients had coronary artery disease, 23% (*n* = 1,637) had a previous stroke, and 21% (*n* = 1,461) had

peripheral arterial disease. At baseline, 83% ($n = 5,803$) were taking aspirin, 81% ($n = 5,666$) an ACEI or ARB, 77% ($n = 5,403$) a statin, and 65% ($n = 4,554$) a β -blocker. In terms of antidiabetic therapies, 74% ($n = 5,193$) were taking metformin, 48% ($n = 3,387$) an insulin, 43% ($n = 3,006$) a sulfonylurea, 11% ($n = 796$) a DPP-4 inhibitor, 4% ($n = 299$) a thiazolidinedione, and 3% ($n = 196$) a glucagon-like peptide-1 (GLP-1) agonist. After a median follow-up of 3.1 years, empagliflozin (pooled analysis of both 10- and 25-mg doses) demonstrated superiority over placebo for the primary composite endpoint of cardiovascular death, nonfatal MI, or nonfatal stroke (10.5% versus 12.1%; modified ITT analysis HR, 0.86; 95% CI, 0.74–0.99; $p < 0.001$ for noninferiority; $p = 0.04$ for superiority). This outcome was primarily driven by a reduction in cardiovascular death (3.7% versus 5.9%; HR, 0.62; 95% CI, 0.49–0.77). Of note, the primary outcome was not significantly reduced with either dose of empagliflozin when analyzed separately against placebo. Other components of the primary composite endpoint did not significantly differ; however, the all-cause mortality rate was lower with treatment (5.7% versus 8.3%; HR, 0.68; 95% CI, 0.57–0.82). For the secondary composite endpoint of cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalization for UA, empagliflozin was noninferior to placebo but did not demonstrate superiority (modified ITT analysis HR, 0.89; 95% CI, 0.78–1.01; $p < 0.001$ for noninferiority). Hospitalization for HF was a prespecified endpoint adjudicated by an independent committee, though blinding was not explicitly stated. In contrast to the data for DPP-4 inhibitors, the rate of hospitalization for HF was lower in the treatment group versus patients receiving placebo (2.7% versus 4.1%; HR, 0.65; 95% CI, 0.50–0.85). A post hoc subgroup analysis demonstrated a decrease in hospitalization rates for HF among patients with no history of HF at baseline (HR, 0.59; 95% CI, 0.43–0.82) but not in patients with HF at baseline (HR, 0.75; 95% CI, 0.48–1.19),

which constituted 10% of patients ($n = 706$).¹⁷ Empagliflozin was the first new antidiabetic drug that demonstrated a reduction in cardiovascular events and mortality in a contemporary RCT.

GLP-1 agonists. Three trials have been completed assessing the GLP-1 agonists lixisenatide, liraglutide, and semaglutide.^{18–20}

The first published trial of a GLP-1 agonist, Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA), assessed the cardiovascular safety outcomes of lixisenatide in 6,068 adults with type 2 diabetes who had a recent (within the previous 180 days) ACS event.¹⁸ Patients with an eGFR of <30 mL/min/1.73 m², a coronary artery bypass graft surgery after their qualifying ACS event, a percutaneous coronary intervention within the previous 15 days, or a planned revascularization procedure within 90 days were excluded. Patients were randomized after a median of 72 days post-ACS event to receive lixisenatide 10 μ g subcutaneously daily (increased after 2 weeks to a maximum dose of 20 μ g at the investigator's discretion) or a volume-matched placebo, in addition to standard care, for a median of 25 months. Patients' mean age was 60 years and mean HbA_{1c} level was 7.7%. Forty-four percent of patients ($n = 2,666$) had an ST segment elevation myocardial infarction (STEMI), 39% ($n = 2,348$) a non-STEMI, and 17% ($n = 1,042$) UA as their index ACS event. At baseline, 98% of patients ($n = 5,917$) were taking an antiplatelet agent, 93% ($n = 5,627$) a statin, 85% ($n = 5,156$) an ACEI or ARB, and 84% ($n = 5,124$) a β -blocker. In terms of diabetes therapy, 66% ($n = 4,021$) were taking metformin, 39% ($n = 2,374$) an insulin, 33% ($n = 2,004$) a sulfonylurea, and 2% ($n = 95$) a thiazolidinedione. Lixisenatide was deemed to be noninferior to placebo for the primary composite endpoint of cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalization for UA (13.4% versus 13.2%; ITT analysis HR, 1.02; 95% CI, 0.89–1.17; $p < 0.001$ for noninferiority; $p = 0.81$ for superiority). There was no significant difference in either secondary composite end-

point of cardiovascular death, nonfatal MI, nonfatal stroke, hospitalization for UA or HF (HR, 0.97; 95% CI, 0.85–1.10), or cardiovascular death, nonfatal MI, nonfatal stroke, hospitalization for HF, or coronary revascularization (HR, 1.00; 95% CI, 0.90–1.11). Hospitalization for HF was a prespecified, blinded endpoint that did not significantly differ between groups (4.0% versus 4.2%; HR, 0.96; 95% CI, 0.75–1.23). A post hoc subgroup analysis demonstrated no difference in the rate of hospitalization for HF by baseline presence of HF ($n = 1,358$ [22%]). Overall, lixisenatide, which was approved by FDA in July 2016, demonstrated neutral effects on both cardiovascular events and hospitalization for HF in patients with diabetes.

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long Term Evaluation (LEADER) enrolled 9,340 patients age 50 years or older with type 2 diabetes and either a history of at least 1 cardiovascular condition (coronary heart disease, cerebrovascular disease, peripheral vascular disease, New York Heart Association class II–III HF, stage 3 or higher chronic kidney disease) or age 60 years or older with at least 1 cardiovascular risk factor (microalbuminuria or proteinuria, hypertension and left ventricular hypertrophy, left ventricular dysfunction, or ankle–brachial index of <0.9).¹⁹ Patients with an acute (<14 days) coronary or cerebrovascular event, a planned arterial revascularization, or New York Heart Association class IV HF were excluded. Patients were randomized to receive liraglutide 0.6 mg subcutaneously (increased after 2 weeks to a maximum of 1.8 mg based on tolerance) or placebo as an adjunct to standard care. The median follow-up time was 3.8 years. Patients' mean age was 64 years and mean HbA_{1c} level was 8.7%. Eighty-one percent ($n = 7,598$) had established CVD, 31% ($n = 2,864$) prior MI, 16% ($n = 1,507$) prior stroke or transient ischemic attack, 14% ($n = 1,305$) HF, and 25% ($n = 2,307$) chronic kidney disease. At baseline, 83% ($n = 7,731$) were taking an ACEI

or ARB, 72% ($n = 6,729$) a statin, 63% ($n = 5,874$) aspirin, 55% ($n = 5,173$) a β -blocker, and 16% ($n = 1,461$) a P2Y₁₂ inhibitor. Furthermore, 76% ($n = 7,136$) were taking metformin, 51% ($n = 4,721$) a sulfonylurea, 45% ($n = 4,159$) insulin, and 6% ($n = 573$) a thiazolidinedione. Liraglutide demonstrated superiority for the primary composite outcome of cardiovascular death, nonfatal MI, or nonfatal stroke (13.0% versus 14.9%; ITT analysis HR, 0.87; 95% CI, 0.78–0.97; $p < 0.001$ for noninferiority; $p = 0.01$ for superiority). Similar to empagliflozin results, these positive findings included a reduction in cardiovascular death (4.7% versus 6.0%; HR, 0.78; 95% CI, 0.66–0.93), as other components of the primary composite endpoint did not significantly differ. For the secondary composite endpoint of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for angina pectoris or HF, liraglutide was superior to placebo (HR, 0.88; 95% CI, 0.81–0.96). In addition, like empagliflozin, death from any cause was also lower with liraglutide (8.2% versus 9.6%; HR, 0.85; 95% CI, 0.74–0.97). Hospitalization for HF, a prespecified endpoint adjudicated by an independent external committee, did not significantly differ between groups (HR, 0.87; 95% CI, 0.73–1.05). No subgroup analysis of hospitalizations for HF for patients with HF at baseline ($n = 1,667$ [18%]) was performed. Liraglutide is the second newer antidiabetic drug that has demonstrated a reduction in cardiovascular events and mortality.

The results of a third GLP-1 agonist trial were published in 2016.²⁰ The Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN 6) assessed the cardiovascular safety outcomes of semaglutide in 3,297 patients with type 2 diabetes. SUSTAIN 6 used the same inclusion and exclusion criteria as LEADER; however, in SUSTAIN 6, patients with an acute coronary or cerebrovascular event within 90 days were excluded (versus 14 days with LEADER). Patients

were randomized to receive semaglutide 0.5 or 1 mg subcutaneously once weekly (increased every 4 weeks from starting dose of 0.25 mg until maintenance dose reached) or placebo as an adjunct to standard care for 104 weeks. The median follow-up time was 2.1 years. Patients' mean age was 65 years and mean HbA_{1c} was 8.7%. Eighty-three percent ($n = 2,735$) had established CVD and/or chronic kidney disease (33% [$n = 1,072$] prior MI, 15% [$n = 491$] prior stroke, 11% [$n = 353$] chronic kidney disease), and 24% ($n = 777$) HF. At baseline, 84% ($n = 2,753$) were taking an ACEI or ARB, 73% ($n = 2,399$) a statin, 64% ($n = 2,108$) aspirin, 57% ($n = 1,894$) a β -blocker, and 21% ($n = 696$) a P2Y₁₂ inhibitor. Furthermore, 73% ($n = 2,414$) were taking a biguanide, 43% ($n = 1,410$) a sulfonylurea, 58% ($n = 1,913$) insulin, and 2% ($n = 76$) a thiazolidinedione. Semaglutide (pooled analysis of both 0.5- and 1-mg doses) demonstrated both noninferiority and superiority for the primary composite outcome of cardiovascular death, nonfatal MI, or nonfatal stroke (6.6% versus 8.9%; ITT analysis HR, 0.74; 95% CI, 0.58–0.95; $p < 0.001$ for noninferiority; $p = 0.02$ for superiority). In contrast to the LEADER results, the primary outcome was driven by a reduction in nonfatal stroke (1.6% versus 2.7%; HR, 0.61; 95% CI, 0.38–0.99), as other components of the primary composite endpoint did not significantly differ. For the secondary composite endpoint of cardiovascular death, nonfatal MI, nonfatal stroke, revascularization (coronary or peripheral), or hospitalization for UA or HF, semaglutide was superior to placebo (HR, 0.74; 95% CI, 0.62–0.89). In contrast to the LEADER results, the rate of death from any cause or cardiovascular causes did not significantly differ between semaglutide and placebo (HR, 1.05; 95% CI, 0.74–1.50; and HR, 0.98; 95% CI, 0.65–1.48, respectively). Hospitalization for HF, a prespecified endpoint adjudicated by an independent external committee, did not significantly differ between groups (HR, 1.11; 95% CI, 0.77–1.61). A prespecified subgroup analysis of hospitalization for HF

among patients with New York Heart Association Class II–III HF at baseline ($n = 573$ [17%]) demonstrated no significant difference between semaglutide and placebo (HR, 1.03; 95% CI, 0.64–1.66). Currently, semaglutide is not approved by FDA; however, it is the third contemporary antidiabetic drug that has demonstrated a reduction in cardiovascular events among patients with diabetes.

Discussion

The accurate assessment of drug safety signals in clinical trials poses many challenges.⁸ In RCTs, patients are carefully selected, and there is no accepted threshold for determining whether a numerically higher rate of events with an intervention is representative of true harm, as RCTs are typically not powered to detect these differences. In addition, adverse events are usually not prespecified, which may lead to their misclassification. These limitations were mitigated in the aforementioned trials due to the requirements mandated by FDA. These RCTs included patients at high risk for adverse cardiovascular events, were adequately powered to detect a statistically significant difference between groups, and used prespecified and clinically relevant cardiovascular outcomes. The noninferiority margin of 1.3 was arbitrarily set by FDA and may not represent a clinically important difference to clinicians or patients; however, this margin does represent a small overall increase in cardiovascular risk due to the low event rate. It is generally accepted that concluding noninferiority between 2 therapies should be based on a per-protocol analysis, as an ITT analysis may result in an underestimation of the benefit of the standard treatment.²¹ Of the included studies, only TECOS and LEADER reported a per-protocol noninferiority analysis.^{12,19} Despite these limitations, the results of the trials reviewed herein provide clinicians with valuable insight regarding the safety and efficacy of these new antihyperglycemic agents.

Since the FDA requirements were instituted in 2008, 3 antidiabetic agents have demonstrated a reduction in cardiovascular events. Empagliflozin was shown to be superior to placebo in terms of cardiovascular events and hospitalization for HF; however, the true magnitude of effect is unclear, as the EMPA-REG OUTCOME trial was a pooled analysis of 2 different doses.¹⁶ Furthermore, the apparent mechanism of action responsible for this cardiovascular benefit is not clear, but multiple theories were proposed by the authors of the EMPA-REG OUTCOME trial, including cardiorenal effects; changes in arterial stiffness, cardiac function, or cardiac demand; and a reduction in albuminuria, uric acid, hyperglycemia, weight, visceral adiposity, or blood pressure. The EMPA-REG OUTCOME trial investigators reported that patients treated with empagliflozin had a small reduction in blood pressure when compared with placebo, but the data were not reported.¹⁶ There are 2 ongoing cardiovascular outcome trials with SGLT-2 inhibitors: dapagliflozin (due to be completed in 2019)²² and ertugliflozin (due to be completed in 2020).²³ A third trial with canagliflozin has been completed but not published.²⁴

Liraglutide and semaglutide were found to be superior to placebo in terms of a composite cardiovascular outcome; however, the mechanism behind this benefit is also unknown.¹⁹ Interestingly, a neutral effect was demonstrated in a post hoc analysis of 15 Phase II and III studies of liraglutide versus a control, which included approximately 4,000 patients and 39 adjudicated major adverse cardiovascular events (incidence ratio, 0.73; 95% CI, 0.38–1.41).²⁵ Furthermore, lixisenatide, another GLP-1 agonist, was noninferior (but not superior) to placebo. While the results of the EMPA-REG OUTCOME trial, LEADER, and SUSTAIN 6 trial are intriguing, they remain the only published studies demonstrating this benefit in their respective classes. The long-term safety and real-world effectiveness of these agents remain unknown.

Alogliptin, saxagliptin, and sitagliptin were found to be noninferior to placebo with respect to cardiovascular events, which was somewhat unexpected based on findings from preliminary studies; initial in vitro and Phase I and II studies of DPP-4 inhibitors showed positive effects on endothelial function, inflammatory markers, prevention of left ventricular remodeling, blood pressure, and cholesterol.²⁶ It is unclear whether the increased risk of hospitalization for HF is a class effect of DPP-4 inhibitors or specific to saxagliptin, which was the only DPP-4 inhibitor that increased the risk of hospitalization for HF overall in all patients when compared with placebo (number needed to harm, 143 over 2 years).¹⁰ Unexpectedly, the subgroup of patients with HF at baseline did not have a higher risk of hospitalization for HF with saxagliptin, but this risk was increased in patients with no history of HF at baseline.¹³ However, this may be explained by the low number of patients with HF at baseline ($n = 2,105$ of 16,492).¹⁰ Furthermore, HF rates were significantly increased at 12 months but not thereafter. Alogliptin did not increase overall hospitalizations for HF; however, like saxagliptin, alogliptin was associated with an increased risk of hospitalization for HF in patients with no history of HF at baseline but not in those patients with a history of HF.¹⁴ Sitagliptin was not associated with an increased risk of HF hospitalization in any population.^{12,15} Still, observational data with sitagliptin have demonstrated inconsistent results; 2 studies demonstrated an association between sitagliptin and an increased risk of hospitalization for HF, while 1 study demonstrated a neutral effect.^{27–29} Misclassification of this outcome was unlikely, as the definition of HF hospitalization was similar among the included trials and reflective of the definition developed by FDA for cardiovascular trials.³⁰ Moreover, a theoretical mechanism for the association between DPP-4 inhibitors and HF exacerbation has not been identified. Nonetheless, the risk of HF hospitalization with saxagliptin and

possibly alogliptin is difficult to ignore, but it is unclear whether this was a true treatment effect or a chance finding. On April 5, 2016, FDA issued a warning that both saxagliptin and alogliptin may increase the risk of HF, particularly in patients with preexisting HF or renal impairment, based on the results of the SAVOR-TIMI 53 and EXAMINE trials.³¹

Conclusion

A review of cardiovascular safety outcomes for new antidiabetic agents found that saxagliptin and alogliptin were associated with an increase in hospitalization for HF. The data for empagliflozin, liraglutide, and semaglutide showed a reduction in cardiovascular events and death or a neutral effect on cardiovascular endpoints.

Disclosures

The authors have declared no potential conflicts of interest.

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