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MACROVASCULAR COMPLICATIONS IN DIABETES (VR ARODA AND A GETANEH, SECTION EDITORS)

Assessment of Heart Failure in Diabetes Cardiovascular Outcomes Trials: Is What We Are Currently Capturing Adequate?

Christa D. Bowes[1] · Lillian F. Lien[1] · Javed Butler[2]

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Abstract

Purpose of Review Since the 2008 FDA guidance restructuring the design of trials for the approval of novel glucose-lowering agents, 13 medications have now been evaluated by dedicated cardiovascular outcome trials. All of the completed trials have included data (though with varying definitions) on rates of hospitalization for heart failure. This review is aimed at summarizing current heart failure outcome data available from cardiovascular safety trials for novel glucose-lowering agents in patients with type 2 diabetes mellitus.

Recent Findings There appears to be growing evidence for the benefit of sodium–glucose cotransporter-2 inhibitors, and there are still not enough data to fully support the safety of glucagon-like peptide 1 receptor agonists in heart failure. Increased rates of hospitalization for heart failure were seen with both saxagliptin and alogliptin, and this has led to a class warning for all dipeptidyl peptidase-4 inhibitors.

Summary Future studies should have a standardized definition of "hospitalization for heart failure," should consider including hospitalization for heart failure as a component of the primary composite endpoint, and should provide a more detailed description of the baseline characteristics of enrolled study participants with heart failure.

Keywords Heart failure · Cardiovascular outcomes · Diabetes mellitus

Introduction

Ten years ago, the US Food and Drug Administration (FDA) published ground-breaking guidance regarding the design of future trials for novel glucose-lowering agents to be evaluated for approval [1]. Since then, there are 13 novel agents with completed dedicated cardiovascular outcome (CVO) trials. These trials have significantly advanced our knowledge of critical aspects of cardiovascular safety and have even led to novel indications including reduction in risk of cardiovascular death with empagliflozin [2] and reduction in cardiovascular events with liraglutide [3]. Although these data significantly contribute to our knowledge of these agents and their effects on combined cardiovascular endpoints, specific information about safety and efficacy in the subset of patients with heart failure (HF) remains not fully defined.

It is essential to understand the various cardiovascular risks and benefits of current pharmacologic treatment options for diabetes, especially in light of the latest guidelines, which suggest that some of these novel glucose-lowering agents should be considered as second-line therapy options for many patients with diabetes [4••, 5]. To date, these contemporary CVO trials have selected "Hospitalization for Heart Failure" (HHF) as the endpoint to evaluate safety in patients with HF [6, 7, 8••, 9–17]. This choice has left an unmet need for further data collection regarding HF risks and benefits. In this review, we will discuss inclusion of participants with HF as well as

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✉ Javed Butler
Jbutler4@umc.edu

Christa D. Bowes
cbowes@umc.edu

Lillian F. Lien
llien@umc.edu

[1] Division of Endocrinology, University of Mississippi, Jackson, MS, USA

[2] Department of Medicine, University of Mississippi, 2500 North State Street, Jackson, MS 39216, USA

specific outcomes measured to evaluate safety and efficacy in HF. We will then discuss the evidence available for the safety of novel glucose-lowering agents in HF and recommendation to further achieve adequate data collection for patients with HF.

Design of Dedicated Cardiovascular Safety Trials for Novel Glucose-Lowering Agents

The dedicated restructuring of the design of trials for the approval of novel glucose-lowering agents began a new, bold era with the FDA "Guidance for Industry" [1]. This effort resulted, in large part, from public concerns regarding the cardiovascular safety of rosiglitazone [18]. It has long been recognized that cardiovascular disease is the leading cause of mortality in patients with diabetes. Nonetheless, prior to this guidance, cardiovascular outcomes were not formally evaluated, and the focus of most studies was primarily on drug-specific glycemic efficacy. The FDA guidance revolutionized the approach by recommending all phase 2 and phase 3 clinical trials to include cardiovascular endpoints including cardiovascular mortality, myocardial infarction (MI), and stroke (CVA). Other recommended endpoints included hospitalization for acute coronary syndrome, or urgent revascularization procedures, but, of particular note, there was no specific requirement or recommendation to compile HF data [1].

These published cardiovascular safety trials have now led to innovations in practice for the routine treatment of diabetes mellitus (DM). They have allowed the creation of new treatment algorithms that are individualized, with focus on patient-specific comorbidities. Yet, despite all these genuine advances, there has not yet been a specific focus on patients with HF partly due to the inadequate inclusion of these patients in trial designs as summarized in Table 1.

Baseline Heart Failure Characteristics Reporting of baseline HF characteristics across the CVO trials has been inconsistent. At a minimum, the CVO trials discussed here have reported the prevalence of HF at the time of enrollment. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) defined HF using a query for "cardiac failure" through the Medical Dictionary for Regulatory Activities [6]; no other trial provided how heart failure was defined at baseline. Four studies listed NYHA class IV HF as an exclusion criteria [8••, 10, 11, 15]. Both Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) and Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) included NYHA classes II–III as inclusion criteria for those participants 50 years or older [10, 11]. In a recent systematic review, these gaps in baseline HF data capture were well highlighted [22].

Heart Failure Requiring Hospitalization as an Outcome Since heart failure is the second most common initial presentation of cardiovascular disease (peripheral vascular disease being the most common) in patients with diabetes [23], this large growing cohort of patients cannot be adequately evaluated without a standardized approach. The FDA guidance did not mention heart failure as a specified outcome; therefore, there is no clear recommendation on which data to objectively collect in patients with HF. However, some data regarding HHF were collected in all of the cardiovascular trials [6–17], and all except one have included HHF as a secondary endpoint. Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction (DECLARE-TIMI 58) was the first trial to include HHF as a primary composite endpoint [6, 8••].

Though there were some similarities, inconsistent definitions for HHF were used across the CVO trials. Hospitalization was defined as an admission to an inpatient unit or a visit to an emergency department, but minimum length of stay required varied amongst the trials. DECLARE-TIMI 58 was the only study to also include outpatient urgent visits for HF [8••]. A combination of symptoms and/or objective evidence, including physical examination, labs, or diagnostic testing, was a required component of HF definition in all of the CVO trials. Each trial also had variable numbers and lists of what fell into these categories. Another requirement was the initiation or intensification of treatment for HF, although Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) was the only study that did not require this to define HHF [9].

Current Understanding of Benefits and Risks of Novel Glucose-Lowering Therapies on Heart Failure

All of the completed CVO trials to date have used a primary composite endpoint of MACE. Although HF was not consistently included as part of the composite MACE endpoint, DECLARE-TIMI 58, published in 2018, was the first CVO trial to include HHF as a primary composite endpoint [8••].

Sodium–Glucose Cotransporter-2 Inhibitors Sodium–glucose cotransporter-2 (SGLT-2) inhibitors contribute to both weight loss and reductions in both systolic and diastolic blood pressures primarily through inhibition of glucose and sodium reabsorption in the kidney leading to natriuresis [24]. There are three completed cardiovascular safety trials in this class, EMPA-REG [6, 19], Canagliflozin Cardiovascular Assessment (CANVAS/CANVAS-R) [7], and the most

Table 1 Baseline heart failure characteristics

Medication	Trial	Year	% of HF	Excluded HF	HF outcome
Sodium–glucose cotransporter-2 inhibitors					
Empagliflozin [6, 19]	EMPA-REG OUTCOME	2015	10.1	No	Secondary endpoint: HHF
Canagliflozin [7]	CANVAS/CANVAS-R	2017	14.4	No	Secondary endpoint: HHF
Dapagliflozin [8••]	DECLARE-TIMI 58	2018	10	NYHA class IV	Primary efficacy outcome: CVD + HHF
Glucagon-like peptide 1 receptor agonists					
Lixisenatide [9]	ELIXA	2015	22.4	No	Secondary endpoint: HHF
Liraglutide [10]	LEADER	2016	17.8	NYHA class IV	Secondary endpoint: HHF
Semaglutide [11]	SUSTAIN-6	2016	23.6	NYHA class IV	Secondary endpoint: HHF
Exenatide [12]	EXSCEL	2017	16.2	No	Secondary endpoint: HHF
Albiglutide [13]	HARMONY	2018	20	No	Secondary endpoint: HHF
Dipeptidyl peptidase-4 inhibitors					
Saxagliptin [14, 20]	SAVOR-TIMI 53	2013	12.8	No	Secondary endpoint: HHF
Alogliptin [15, 21]	EXAMINE	2013	27.9	NYHA class IV	Secondary endpoint: HHF
Sitagliptin [16]	TECOS	2015	18.3	No	Secondary endpoint: HHF
Linagliptin [17]	CARMELINA	2018	26.8	No	Tertiary endpoint: HHF

recently published DECLARE-TIMI 58 trial [8••]. Heart failure outcomes are summarized in Table 2.

The first of these CVO trials for SGLT-2 inhibitors evaluated empagliflozin [6], with 7020 patients randomized to receive 10 or 25 mg of empagliflozin or placebo. The population had established cardiovascular disease, with an average Hgb A1c of 8%, and 10.1% had HF at baseline. There was a significant decrease in the primary endpoint of MACE that was driven by a reduction in cardiovascular death. This result was especially intriguing at the time of release, as the CVO trials up to that point had only showed neutral effects on MACE. A closer look at the causes of cardiovascular death showed that the second most common cause after sudden death was worsening of heart failure in the placebo arm. Signs of worsening HF included initiation of new therapy for HF or increases in doses of current therapy, oxygen requirement, and confinement to bed, pulmonary edema, or cardiogenic shock. Although not part of the key secondary endpoint, HHF was shown to be significantly lower in both the 10 (2.6% vs 4.1%, $p = 0.004$) and 25 mg (2.8% vs 4.1%, $p = 0.02$) treatment arms compared with placebo.

CANVAS/CANVAS-R focused on the SGLT-2 inhibitor canagliflozin [7]. This study involved 10,142 participants at high cardiovascular risk with a baseline HF rate of 14.4%. There was a reduction in the primary composite endpoint of MACE with canagliflozin compared with placebo (26.9 vs 31.5 per 1000 patient years; HR 0.86; 95% CI 0.75–0.98; $p = 0.001$ for noninferiority; $p = 0.02$ for superiority) and rate of HHF (HR 0.67; 95% CI 0.52–0.87). Of note, CANVAS/CANVAS-R results have generated quite a bit of interest given that a reduction in the progression of renal disease was demonstrated.

The most recent CVO trial results published for an SGLT-2 inhibitor, DECLARE-TIMI 58 [8••], were unique in having two primary efficacy outcomes, MACE, as well as a composite of HHF or cardiovascular death. The DECLARE-TIMI 58 study was also unique in its results: it demonstrated noninferiority to placebo with regard to the primary endpoint of MACE, whereas the previous CVO trials for SGLT-2 have shown statistically significant reduction in MACE. However, there was a significantly lower rate of the composite primary efficacy outcome of cardiovascular death or HHF (4.9% vs 5.8%; HR 0.83; 95% CI 0.73–0.95; $p = 0.005$). This population of 17,160 participants, with a baseline HF rate of 10%, also differed from previous studies; in that, it included a larger population without any known atherosclerotic cardiovascular disease [8••].

Table 2 Heart failure outcomes in cardiovascular outcome trials for SGLT-2 inhibitors

Drug	Empagliflozin	Canagliflozin	Dapagliflozin
Trial	EMPA-REG OUTCOME [6, 19]	CANVAS/ CANVAS-R [7]	DECLARE-TIMI 58 [8••]
Baseline characteristics	$n =$ 7020 Mean Hgb A1c 8.07%	$n =$ 10,142 Mean Hgb A1c 8.2%	$n =$ 17,160 Mean Hgb A1c 8.3%
Endpoint HHF	9.4 vs 14.5 per 1000 patient years (HR 0.65; 95% CI 0.50–0.85)	5.5 vs 8.68 per 1000 patient years (HR 0.67; 95% CI 0.52–0.87)	6.2 vs 8.5 per 1000 patient years (HR 0.73; 95% CI 0.61–0.88)

Glucagon-like Peptide 1 Receptor Agonists Glucagon-like peptide 1 (GLP-1) receptor agonists are incretin-based therapies that stimulate postprandial insulin release but also affect glucagon, thereby improving glycemic control with a minimal risk of hypoglycemia. Several CVO trials have been completed evaluating cardiovascular safety and HHF of this class of glucose-lowering drugs. Results are summarized in Table 3.

ELIXA was the first of the CVO trials for GLP-1 receptor agonists [9]. It was unique in assessing those patients with a recent acute coronary event (within 180 days of presentation). In the 6068 patients who were randomized to either lixisenatide or placebo, 22% had baseline HF. There was no difference found in 4-point MACE that included hospitalization for unstable angina and no increased risk of HHF in the treatment arm when compared with placebo (4.0% vs 4.2%; HR 0.96; 95% CI 0.75–1.23). Subgroup analyses of those patients that required HHF demonstrated no difference between those with and without a prior diagnosis of HF [9].

The next GLP-1 agonist CVO trial reported was LEADER [10], which randomized high cardiovascular risk patients to receive liraglutide or placebo. A total of 9340 patients were included with a baseline HF rate of 17.8% and 14% with NYHA class II and III HF. However, those patients with NYHA class IV were excluded from enrollment. There was a statistically significant decrease in the rate of MACE (608 vs 694 patients; HR 0.87; 95% CI 0.78–0.97) in the treatment arm that was driven primarily by cardiovascular death. Liraglutide had a neutral effect on the rate of HHF when compared with placebo (4.7% vs 5.3%; HR 0.87; 95% CI 0.73–1.05) [10]. Hospitalization for HF was defined, in this trial, as a visit to the ER for at least 12 h with clinical manifestations of HF requiring addition or escalation of therapy for HF.

The SUSTAIN-6 study evaluated semaglutide vs placebo in 3290 patients with type 2 diabetes with established cardiovascular disease or high risk of cardiovascular disease, and 23.6% had HF at baseline [11]. One of the inclusion criteria, similar to the LEADER trial, was NYHA class II and III HF and age greater than 50 years. Again, similar to LEADER, patients with NYHA class IV HF were excluded. A description of blood pressure and heart failure treatment was available at the time of enrolment. The primary endpoint of MACE was decreased in the treatment arm (6.6% vs 8.9%; HR 0.74; 95% CI 0.58–0.95). There was no significant difference in the two groups in rates of HHF (3.6% vs 3.3%; HR 1.11; 95% CI 0.77–1.61).

The Exenatide Study of Cardiovascular Event Lowering (EXSCEL) [12] assessed the effects of exenatide vs placebo in patients with type 2 DM and high risk for cardiovascular disease. This was a large randomized trial, with a total of 14,752 patients with a baseline HF rate of 16.2%. This study did not exclude patients with HF. From the 16.2% of patients with HF, ~ 31% had NYHA class I, ~ 56% NYHA class II, ~ 13% NYHA class III, and 0.5% NYHA class IV heart failure [12]. This study demonstrated that exenatide was noninferior to placebo in regard to MACE (839 vs 905 patients; HR 0.91; 95% CI 0.83–1.00; $p < 0.001$), the primary endpoint. There was also no demonstrated effect on the rate of HHF (3% vs 3.1%; HR 0.94; 95% CI 0.78–1.13) [12].

The most recent published CVO trial for GLP-1 agonists is the albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (HARMONY Outcomes) evaluating the effects of albiglutide vs placebo in 9463 patients with known cardiovascular disease [13]. Albiglutide was found to be superior to placebo in the primary endpoint of MACE (7% vs 9%; HR 0.78; 95% CI 0.68–0.90) [13]. The secondary endpoint assessing heart failure safety is a composite of death from cardiovascular causes or HHF, which demonstrated that albiglutide had a neutral effect when compared with placebo (4% vs 5%; HR 0.85; 95% CI 0.70–1.04).

Recently completed was the Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial, designed to determine the effects of dulaglutide vs placebo in 9901 patients, on the primary outcome of MACE and HHF as a secondary endpoint [25]. Eli Lilly and Company has released a statement that dulaglutide did demonstrate superiority in MACE, but the full trial results are yet to be published.

SUSTAIN-6, LEADER, and HARMONY have all shown superiority to placebo with regard to MACE. The not-yet-published results of REWIND are of interest, as it would be the first study of the GLP-1 agonists that could demonstrate superiority in cardiovascular safety compared with placebo in a population of patients that do not have established cardiovascular disease.

Table 3 Heart failure outcomes in cardiovascular outcome trials for GLP-1 agonists

Drug	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Albiglutide
Trial	ELIXA [9]	LEADER [10]	SUSTAIN-6 [11]	EXSCEL [12]	HARMONY [13]
Baseline characteristics	$n =$ 6068 Mean Hgb A1c 7.65%	$n =$ 9340 Mean Hgb A1c 8.7%	$n =$ 3297 Mean Hgb A1c 8.7%	$n =$ 14,752 Mean Hgb A1c 8.0%	$n =$ 9463 Mean Hgb A1c 8.74%
Endpoint HHF	4% vs 4.2% (HR 0.96; 95% CI 0.75–1.23)	4.7% vs 5.3% (HR 0.87; 95% CI 0.73–1.05)	3.6% vs 3.3% (HR 1.11; 95% CI 0.77–1.61)	3% vs 3.1% (HR 0.94; 95% CI 0.78–1.13)	Composite of CV death or HHF 4% vs 5% (HR 0.85; 95% CI 0.70–1.04)

Despite these intriguing findings and absence of demonstrated increased risk in HHF, there are still not enough data to fully describe GLP-1 agonist safety in heart failure. Both LEADER and SUSTAIN-6 excluded patients with NYHA class IV heart failure, a population often more susceptible to arrhythmias and adverse events due to elevations in heart rate. This is relevant due to concerns about the safety of liraglutide in HF with reduced EF (HFrEF). The effect of liraglutide on left ventricular function in stable chronic heart failure patients with and without diabetes (LIVE trial) compared liraglutide to placebo, 37% of the patients had diabetes, average EF was 35%, and NYHA was broken down as follows: class I (36%), class II (65%), and class III (17%). Note those patients with NYHA class IV were excluded from this trial. A statistically significant increase in heart rate was demonstrated in the liraglutide group. The treatment arm was also associated with an increased rate of serious cardiac events when compared with placebo (10% vs 3% of pts.; $p = 0.04$) including ventricular tachycardia (3% vs 1%), atrial fibrillation (4% vs 2%), and acute coronary syndrome (3% vs 0%) [26]. The field will benefit from more comprehensive data collected to ensure the safety of novel agents in patients with HF, with a focus on outcomes in addition to just rates of HHF.

Dipeptidyl Peptidase-4 Inhibitors Dipeptidyl peptidase-4 (DPP-4) inhibitors are incretin-based therapies. DPP-4 is responsible for the degradation of GLP-1, and this class of medications leads to inhibition of that enzyme. This results in increased fasting and postprandial levels of GLP-1. In comparison with GLP-1 agonists, these agents are associated with decreased rates of nausea but are weight neutral. There are four medications with completed CVO trials, and summarized results of the HHF outcomes are in Table 4.

The first of the published DPP-4 inhibitor CVO trials was the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction (SAVOR-TIMI 53) [14] ($n = 16{,}392$; baseline HF 12.8%). Saxagliptin, when compared with placebo, demonstrated no difference in the primary endpoint of MACE (7.3% vs 7.2% patients; HR 1.00; 95% CI 0.89–1.12). Surprisingly, this was the first CVO trial to demonstrate deleterious effects on HHF (3.5% vs 2.8%; HR 1.27; 95% CI 1.07–1.51) [14]. The highest risk of HHF was in the first 12 months and in patients who had a history of HF, impaired renal function, and elevated baseline levels of N-terminal pro-B-type natriuretic peptide [20].

The next trial was the Examination of Cardiovascular Outcomes with Alogliptin versus Standard Care (EXAMINE), which randomized 5380 patients, 27.9% with baseline heart failure, to receive alogliptin or placebo [15]. The functional classes of those patients with HF at the time of enrollment were as follows: NYHA class I (22.6%), NYHA class II (55%), NYHA class III (19.2%), and NYHA class IV (1.3%) [21]. This was a unique population compared with previous trials, as these were patients with type 2 DM who had experienced either an acute myocardial infarction or unstable angina requiring hospitalization in the preceding 15–90 days. Alogliptin was found to be noninferior to placebo with regard to the primary endpoint of MACE (11.3% vs 11.8% patients; HR 0.96; upper limit of 95% CI 1.16; $p < 0.001$) [15]. However, the results for HHF were intriguing, demonstrating a slight increase in HHF without statistical significance (3.1% vs 2.9%; HR 1.07; 95% CI 0.79–1.46) [21].

The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) randomized 14,671 patients with diabetes and established cardiovascular disease to receive sitagliptin or placebo [16]. The baseline rate of HF was 18.3% in this study population. Sitagliptin, when compared with placebo, had a neutral effect on the primary endpoint of MACE (11.4% vs 11.6% patients; HR 0.98; 95% CI 0.89–1.08; $p < 0.001$). This study also showed no increased rate of HHF [16].

The most recent CVO trial for DPP-4 inhibitors was the Cardiovascular Safety and Renal Microvascular Outcome Study with Linagliptin (CARMELINA) [17]. The aim of this study was to evaluate not only cardiovascular safety but also renal outcomes. Patients with established cardiovascular disease and/or the presence of CKD were randomized to receive linagliptin or placebo ($n = 6979$, baseline HF 26.8%). Linagliptin demonstrated neutral effects on the primary endpoint of MACE (12.4% vs 12.1% patients; HR 1.02; 95% CI 0.89–1.17; $p < 0.001$) and the exploratory endpoint of HHF (6% vs 6.5% patients; HR 0.90; 95% CI 0.74–1.08; $p = 0.26$) [17].

After the results of SAVOR-TIMI 53 were published, there was a significant concern, so in 2014, the FDA added a warning to the label of saxagliptin detailing the increased risk of HHF [27]. In late 2017, the FDA went further and placed a HF warning label on all agents in this class. Despite this, the data

Table 4 Heart failure outcomes in cardiovascular outcome trials for DPP-4 inhibitors

Drug	Saxagliptin	Alogliptin	Sitagliptin	Linagliptin
Trial	SAVOR-TIMI 53 [14, 20]	EXAMINE [15, 21]	TECOS [16]	CARMELINA [17]
Baseline characteristics	$n =$ 16,492 Mean Hgb A1c 8%	$n =$ 5380 Mean Hgb A1c 8%	$n =$ 14,671 Mean Hgb A1c 7.2%	$n =$ 6979 Mean Hgb A1c 7.9%
Endpoint HHF	3.5% vs 2.8% (HR 1.27; 95% CI 1.07–1.51)	3.1% vs 2.9% (HR 1.07; 95% CI 0.79–1.46)	3.1% vs 3.1% (HR 1.0; 95% CI 0.83–1.20)	6% vs 6.5% (HR 0.9; 95% CI 0.74–1.08)

from the latest DPP-4 trials have been inconsistent and not conclusive of a true class effect [16, 17].

Where Has This Taken Us?

These large multicenter cardiovascular outcome trials have already made a significant impact on the clinical management of type 2 DM. The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) published a position statement offering a comprehensive approach to the treatment of DM [4••]. This statement takes into account the current data from the CVO trials and recommends identifying the comorbidity of CVD early in the process of selection of medications. The statement offers an algorithmic approach to the selection of medications based on CVD risk, offering also a specific pathway for patients when HF predominates. Metformin remains first-line, but SGLT-2 inhibitors are identified as second-line therapy, and when not tolerated, GLP-1 agonists are offered as a supplemental second-line therapy [4••].

The results of the EMPA-REG OUTCOME and LEADER trials have been ground-breaking in that the FDA has responded by issuing novel indications for the efficacy of these particular medications in CVD risk reduction [2, 3]. Empagliflozin in 2016 was specifically approved for reducing the risk of cardiovascular death and cardiovascular disease in patients with type 2 DM. Liraglutide in 2017 received the indication for reduction in major adverse cardiovascular events in type 2 DM with established cardiovascular disease.

Where Do We Go from Here?

While continuing the commitment to assessing cardiovascular safety in novel glucose-lowering agents, data collected on heart failure outcomes still need to be further expanded to understand the risk of developing HF with novel glucose agents and to ensure efficacy in patients with established HF. To establish safety in HF patients, defining HF at baseline, specifically including EF and NYHA functional class, is essential. This will allow subanalyses of heart failure outcomes, potentially allowing more precise characterization of participants with baseline HF. Furthermore, since HF can often be managed in other settings (e.g., outpatient, urgent office visits, ED visits), HHF should not be accepted as the only outcome measured. A broader definition of HHF is necessary and should be applied uniformly, to better allow comparison between studies. Finally, further studies directed toward medications that show "neutral" effects on HHF (i.e., liraglutide in LEADER) could define potential risks and benefits, before recommendations for widespread use of these agents in the HF population.

At the time of this writing, there are three trials ongoing, assessing the role of HF treatment with SGLT-2 inhibitors, but it is important to note that DM is not identified as a necessary inclusion criterion. EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction) (NCT03057977) [28] and EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction) (NCT03057951) [29] will randomize patients to empagliflozin or placebo with CV death and HHF as the primary endpoint. Similarly, Dapa-HF (NCT03036124) [30] will randomize patients to dapagliflozin and placebo with the primary endpoint of CV death and HHF.

Conclusion

As demonstrated by available data to date, much effort needs to be devoted to standardizing patient characteristics and HHF definitions in trials. The importance of this effort cannot be over-emphasized: it is known that patients with diabetes have a 2.5 higher risk of developing HF than those without diabetes, and the incidence increases with age and known cardiovascular diseases [31]. It is fair to conclude that patients with baseline HF are still under-represented in the CVO trials compared with the population with established cardiovascular disease. Aside from the lack of standardization and under-representation of HF, another area which requires further study is the prevention of HF and improved outcomes in those already with established HF. Future glycemic-agent trials should account specifically for the above gaps.

The 2008 FDA guidance has provided us with a more thorough understanding of cardiovascular safety of the available and emerging glucose-lowering agents and has allowed us to highlight novel therapeutic effects. The ultimate goal, when focusing on treatment for type 2 DM, should always be improving long-term outcomes. It is well recognized that cardiovascular disease is the number one cause of death in this patient population. Our treatment approach for these patients can no longer be limited to glycemic control alone. It is a major leap forward that we now have evidence of medications providing cardiovascular risk reduction. However, it is also true that heart failure is the second most common presentation of cardiovascular disease. The focus of the CVO trials needs to broaden beyond assessing only cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke as a composite primary endpoint and include specific assessments of the safety and efficacy of these agents in heart failure.

Compliance with Ethical Standards

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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