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Heart Failure End Points in Cardiovascular Outcome Trials of Sodium Glucose Cotransporter 2 Inhibitors in Patients With Type 2 Diabetes Mellitus

A Critical Evaluation of Clinical and Regulatory Issues

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ABSTRACT: Following regulatory guidance set forth in 2008 by the US Food and Drug Administration for new drugs for type 2 diabetes mellitus, many large randomized, controlled trials have been conducted with the primary goal of assessing the safety of antihyperglycemic medications on the primary end point of major adverse cardiovascular events, defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Heart failure (HF) was not specifically mentioned in the US Food and Drug Administration guidance and therefore it was not a focus of these studies when planned. Several trials subsequently showed the impact of antihyperglycemic drugs on HF outcomes, which were not originally specified as the primary end point of the trials. The most impressive finding has been the substantial and consistent risk reduction in HF hospitalization seen across 4 trials of sodium glucose cotransporter 2 inhibitors. However, to date, these results have not led to regulatory approval of any of these drugs for a HF indication or a recommendation for use by US HF guidelines. It is therefore important to explore to what extent persuasive treatment effects on nonprimary end points can be used to support regulatory claims and guideline recommendations. This topic was discussed by researchers, clinicians, industry sponsors, regulators, and representatives from professional societies, who convened on the US Food and Drug Administration campus on March 6, 2019. This report summarizes these discussions and the key takeaway messages from this meeting.

In 2008, the US Food and Drug Administration (FDA) issued an industry guidance recommending that all emerging antihyperglycemic therapies for patients with type 2 diabetes mellitus (T2DM) undergo formal assessment of cardiovascular (CV) safety.[1] This guidance was largely in response to a meta-analysis of 42 trials of rosiglitazone, which highlighted the possibility that an agent with well-established glycemic benefits could potentially cause an increased risk of myocardial infarction (MI).[2] This observation with rosiglitazone occurred on the backdrop of decades of uncertainty regarding the CV safety of drugs for T2DM. For example, tolbutamide increased CV mortality (a warning that persists in every sulfonylurea product label to date in the United States),[3] thiazolidinediones increased the risk of heart failure (HF),[4] and muraglitazar increased a composite of CV outcomes, ultimately leading to discontinuation of the drug development program.[5]

The key FDA recommendation was for sponsors of new antihyperglycemic drugs to perform large-scale randomized trials to rule out unacceptable CV risk.

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Preapproval trials were specifically required to demonstrate an upper bound <1.8 for the 2-sided 95% CI of the hazard ratio of composite end point of major adverse cardiac events (MACE), consisting of CV death, nonfatal MI, and nonfatal stroke.[1] The choice of this end point was based on the CV safety concerns with rosiglitazone, tolbutamide, and muraglitazar, and the belief that glycemic control primarily had an impact on atherothrombotic pathways.[1]

These recommendations prompted the conduct of many global CV outcome trials (CVOTs). Although these were designed primarily to confirm CV safety, the trials for 2 classes of antihyperglycemic medications (glucagon-like peptide-1 receptor agonists and sodium glucose cotransporter 2 [SGLT2] inhibitors) showed superiority for the primary MACE end point. These findings led to FDA-approved product labeling with indications for CV risk mitigation, and guideline recommendations, as well, for reducing the risk of CV death or atherosclerotic CV disease outcomes among patients with T2DM.[6–11]

There was no specific mention of HF in the FDA guidance, and HF was neither an inclusion nor an exclusion criterion for these trials; furthermore, HF-related outcomes were not included in hierarchical analyses of primary CV outcomes when these trials were originally designed. In most of the trials, the evaluation of a treatment effect on HF events was relegated to a secondary or exploratory end point. However, results from these trials have shown that antihyperglycemic therapies can increase, decrease, or have a neutral effect on the risk of HF events.[6,8,12–14] Of particular note, 3 CVOTs and one renal outcomes trial with SGLT2 inhibitors have reported a consistent decrease in the risk of HF hospitalizations, thus generating enthusiasm for these medications as potential therapies to reduce these HF events in both patients with and without history of HF.[6,8,12,15,16]

These data have sparked questions and debate regarding the appropriate interpretation of findings on nonprimary end points in a trial and the reliance on such analyses in regulatory decisions and clinical guidelines. Both T2DM and HF are growing public health epidemics, with a high degree of overlap in pathophysiology and epidemiology, thus highlighting a need to develop therapies capable of reducing morbidity and mortality in these high-risk populations.[17–19] HF occurs earlier than many other macrovascular and microvascular complications, and negatively impacts prognosis to a comparable or greater degree than atherosclerotic CV events.[20,21] The existing HF data from recent CVOTs of SGLT2 inhibitors represent an opportunity for a critical reappraisal of the relevance of nonprimary clinical trial end points in regulatory and clinical decision making. Our reassessment is based on discussions between stakeholders across scientific disciplines, including clinical trialists, industry sponsors, regulators, representatives from professional societies, and practicing cardiologists and endocrinologists, that took place at the FDA campus on March 6, 2019.

GAPS IN CHARACTERIZATION OF HF

The characterization of HF events in CVOTs of antihyperglycemic therapies for T2DM has been limited, both at baseline and during the course of follow-up in these trials.

HF at Entry Into the Trial

Although the majority of CVOTs of antihyperglycemic therapies completed to date report baseline prevalence of HF, review of trials published through June 2017 found that only one trial provided a specific definition for the identification of HF at baseline.[22] In all other trials, the presence of HF was based on the judgment of local investigators. Similarly, the baseline left ventricular ejection fraction (LVEF) was assessed in only 3 programs, and no trial systematically collected values for LVEF among participants who experienced HF events.[22] More recently, the DECLARE-TIMI 58 trial (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58) investigators published LVEF data captured from records before trial entry among patients with and without HF at baseline.[23] Values for LVEF were available for ≈75% of patients with HF and ≈30% of the overall trial cohort, although the investigators did not specify a time window for the acquisition of LVEF data before trial enrollment.

Because of incomplete identification and characterization of HF, CVOTs cannot fully determine if observed HF treatment effects reflect the prevention of new-onset HF or the reduction in the risk of worsening of preexisting HF. Although it is tempting to make this distinction based on investigator identification of clinical HF at baseline, an accurate assessment typically requires echocardiography, measurement of natriuretic peptides, and documentation of the use of medications for the treatment of HF. Nonetheless, the investigator-based assessment does show certain validity, because observed event rates were substantially higher among patients with a diagnosis of HF at baseline in comparison with those without a diagnosis of HF at baseline.[24,25]

However, the effects of drugs to reduce the risk of HF events in T2DM trials may or may not be relevant to their use in patients with established HF with reduced LVEF. For example, statins and antihypertensive drugs prevent the development of HF in trials of patients at increased CV risk but without HF, but they do not reduce morbidity and mortality in those with established HF. This discordance may be explained by the possibility that statins and antihypertensive drugs selectively prevented the development of HF with a preserved

LVEF.[26] Given this uncertainty, dedicated trials with SGLT2 inhibitors among patients with established HF are ongoing, including those with and without T2DM and those with HF with reduced LVEF or HF with a preserved LVEF (NCT03036124, NCT03619213, NCT03057977, NCT03057951, and NCT03521934).[15,16] Nonetheless, even in patients in whom the identification of HF at baseline is incomplete,[22,27,28] any treatment that prevents HF hospitalization is valuable, because it is a clinically meaningful event that reflects disease progression and results in significant healthcare expenditure.[29–31]

Worsening and Incident HF Events

In addition to limited characterization of HF at trial entry, the analysis and interpretation of the HF outcomes in CVOTs in T2DM are further complicated by limited characterization of HF events that occurred after randomization. Data regarding clinical severity, administered treatments, and HF phenotype at the time of these events were collected only in some trials.[12,22,32] The CANVAS program (Canagliflozin Cardiovascular Assessment Study) specifically undertook a retrospective secondary review of medical record data to report the LVEF measured at the time of postrandomization HF events, but such data are not available from other CVOTs.[33]

HF events in CVOTs have largely focused on HF hospitalizations, but new-onset or worsening HF is often diagnosed and treated as an outpatient.[22,34] Nonclinical factors (eg, healthcare system infrastructure, country, and caregiver support) are prominent drivers of the site of HF care.[34,35] Patients treated with outpatient intravenous diuretic therapy have a prognosis similar to those who are hospitalized.[36–38] Recognition of the clinical significance of these nonhospitalization HF events continues to evolve, and some trials now include them within end point definitions for a HF event.[32] Although such events may be relatively uncommon in the United States, rates of nonhospitalization HF events may be higher in global trials and may have an impact on the power of CVOTs to detect benefit or harm with respect to HF.[37,39,40]

Lack of data on HF-related nonhospitalization events makes it difficult to precisely identify the time of onset of HF among patients not previously diagnosed with HF. Only about one-third of published CVOTs have described rates of new-onset HF during follow-up, typically defined as a HF hospitalization event among patients without HF at baseline.[22] With administrative databases suggesting that nearly 50% of incident HF is diagnosed as an outpatient, HF hospitalization may not be an appropriate marker for new-onset HF.[41] In conjunction with a compatible clinical presentation, initiation of oral loop diuretic therapy may be a reasonable and practical marker of incident HF in the outpatient setting.

HF OUTCOMES IN LARGE-SCALE TRIALS IN DIABETES MELLITUS

To date, 4 large randomized trials among patients with diabetes mellitus at high CV risk have shown that SGLT2 inhibitors reduce the risk of HF hospitalization (Table 1).[6,8,12] The aggregate information is robust and includes the randomization of 38 733 patients and the analysis of 1192 total HF hospitalization events. The relative risk reduction for HF hospitalization has been large, ranging from 27% with dapagliflozin in the DECLARE-TIMI 58 trial to 39% in canagliflozin in CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation).[12,42] Moreover, the finding of a reduction in the risk of HF hospitalization has been consistent across all participants, including those with and without preexisting atherosclerotic cardiovascular disease and with and without preexisting HF.[23,43–46]

Most patients in CVOTs of SGLT2 inhibitors were reported as not having HF at baseline.[27,43] The reported prevalence of HF at trial entry ranged from 10.0% in the DECLARE-TIMI 58 trial to 14.8% in CREDENCE, suggesting that patients with HF were underrepresented in these programs relative to the prevalence of HF in patients with T2DM in clinical practice (ie, 20%–30%).[12,42,47] Nonetheless, it has been proposed that these randomized trials provide robust evidence for the use of SGLT2 inhibitors for reducing the risk of HF hospitalization among patients with T2DM, at least for those without a history of HF.[27] However, none of the agents within this drug class currently carries a regulatory indication related to the prevention of HF events (although the evidence from DECLARE-TIMI 58 has not yet completed regulatory review). Empagliflozin received an FDA indication for reducing CV death, and canagliflozin was approved for reducing the risk of atherosclerotic ischemic events. The absence of a HF-related labeled indication is related to the fact that HF was not included as part of the primary end point in these studies; yet, SGLT2 inhibitors exert greater benefits on HF outcomes in comparison with atherosclerotic ischemic outcomes.[43] In EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) and CANVAS, HF hospitalization was an exploratory analysis.[6,8] In DECLARE-TIMI 58, based on favorable findings from EMPA-REG OUTCOME, the protocol was amended in December 2016 to include the composite of CV death or HF hospitalization as a coprimary efficacy outcome together with MACE.[12,48] In this trial, dapagliflozin did not meet superiority for MACE but met superiority for CV death or HF hospitalization, a finding driven by a reduction in the risk of HF hospitalization.[12]

Table 1. Data From Cardiovascular Outcome Trials of SGLT2 Inhibitors in Patients With Type 2 Diabetes Mellitus

Trial Name	Therapy	N	Follow-Up (Median)	Primary End Point	Effect on Primary End Point(s) HR (95% CI)	Effect on Fatal or Nonfatal MI; Effect on Fatal or Nonfatal Stroke HR (95% CI)	Effect on Composite CVD or HF Hosp HR (95% CI)	Effect on HF Hosp HR (95% CI)
Overall trial population								
EMPA-REG OUTCOME (2015)[6]	Empagliflozin	7020	3.1 y	Composite of CVD, nonfatal MI, or nonfatal stroke	0.86 (0.74–0.99), *P*<0.001 for noninferiority; *P*=0.04 for superiority	0.87 (0.70–1.09), *P*=0.23 1.18 (0.89–1.56), *P*=0.26	0.66 (0.55–0.79), *P*<0.001 [CVD excluding fatal stroke]	0.65 (0.50–0.85), *P*=0.002
CANVAS (2017)[8]	Canagliflozin	10 142	2.4 y	Composite of CVD, nonfatal MI, or nonfatal stroke	0.86 (0.75–0.97)	0.89 (0.73–1.09) 0.87 (0.69–1.09)	0.78 (0.67–0.91)	0.67 (0.52–0.87)
DECLARE-TIMI 58 (2019)[12]	Dapagliflozin	17 160	4.2 y	(1) Composite of CVD, nonfatal MI, or nonfatal stroke; (2) CVD or HF hospitalization	(1) 0.93 (0.84–1.03), *P*=0.17 (2) 0.83 (0.73–0.95), *P*=0.005	0.89 (0.77–1.01) 1.01 (0.84–1.21) [ischemic stroke]	0.83 (0.73–0.95), *P*=0.005	0.73 (0.61–0.88)
CREDENCE (2019)[42]	Canagliflozin	4401	2.6 y	Composite of end-stage renal disease, doubling of serum creatinine, or death from renal or CV causes	0.70 (0.59–0.82), *P*<0.001	–	0.69 (0.57–0.83), *P*<0.001	0.61 (0.47–0.80), *P*<0.001
Subset of patients with heart failure at baseline								
EMPA-REG OUTCOME (2015)[6]	Empagliflozin	706	3.1 y	Composite of CVD, nonfatal MI, or nonfatal stroke	–	–	0.72 (0.50–1.04) [CVD excluding fatal stroke]	0.75 (0.48–1.19)
CANVAS (2017)[8]	Canagliflozin	1461	2.4 y	Composite of CVD, nonfatal MI, or nonfatal stroke	0.80 (0.61–1.05)	1.11 (0.65–1.89) 0.84 (0.51–1.39)	0.61 (0.46–0.80)	0.51 (0.33–0.78)
DECLARE-TIMI 58 (2019)[12]	Dapagliflozin	1724	4.2 y	(1) Composite of CVD, nonfatal MI, or nonfatal stroke; (2) CVD or HF hospitalization	(1) 1.01 (0.81–1.27) (2) 0.79 (0.63–0.99)	0.85 (0.61–1.18) 1.21 (0.77–1.91) [ischemic stroke]	0.79 (0.63–0.99)	0.73 (0.55–0.96)
Subset of patients without heart failure at baseline								
EMPA-REG OUTCOME (2015)[6]	Empagliflozin	6314	3.1 y	Composite of CVD, nonfatal MI, or nonfatal stroke	–	–	0.63 (0.51–0.78) [CVD excluding fatal stroke]	0.59 (0.43–0.82)
CANVAS (2017)[8]	Canagliflozin	8681	2.4 y	Composite of CVD, nonfatal MI, or nonfatal stroke	0.87 (0.76–1.01)	0.86 (0.69–1.06) 0.88 (0.68–1.14)	0.87 (0.72–1.06)	0.79 (0.57–1.09)
DECLARE-TIMI 58 (2019)[12]	Dapagliflozin	15 436	4.2 y	(1) Composite of CVD, nonfatal MI, or nonfatal stroke; (2) CVD or HF hospitalization	(1) 0.92 (0.82–1.02) (2) 0.84 (0.72–0.99)	0.89 (0.77–1.04) 0.98 (0.80–1.20) [ischemic stroke]	0.84 (0.72–0.99)	0.73 (0.58–0.92)

CV indicates cardiovascular; CVD, cardiovascular disease; HF, heart failure; hosp, hospitalization; HR, hazard ratio; MI, myocardial infarction; and SGLT2, sodium glucose cotransporter 2.

REGULATORY INTERPRETATION OF NONPRIMARY END POINTS IN CLINICAL TRIALS

With the substantial and reproducible benefits on HF hospitalization seen in CVOTs of SGLT2 inhibitors, a critical reappraisal of the analysis and interpretation of primary versus nonprimary trial outcomes is warranted.

Emergence of the Primary End Point

The most readily interpretable finding in a prospective randomized, controlled clinical trial is the effect of the study intervention on the prespecified primary end point(s). Typically, a trial is designed to fully evaluate the effect of the treatment on the primary end point, and all efforts are made to minimize the likelihood of false-positive or false-negative errors by designating

acceptable rates of error in advance. The sample size of the trial is usually determined by projections that are based on the expected event rate in the comparator group and the anticipated effect size of the intervention on the primary end point.

When clinical outcome trials first emerged as an important methodology in the 1960s, it was common to specify 3 to 5 primary end points of interest, and these were often described in the study protocol in a nonhierarchical manner.[49] When the trial was complete, hypothesis testing was performed on each end point, using a false-positive error rate of 0.05. However, such an approach could inflate the false-positive error rate beyond acceptable limits.[50,51] When multiple primary end points were specified without adjustment for multiplicity of comparisons, it was possible for investigators to conclude that a treatment effect had been found, if only 1 of 5 end points achieved a 0.05 threshold. In general, it was agreed that such an approach was unacceptably lenient, because many treatment effects that met such a threshold represented nonreplicable findings. To rectify this, investigators began to distinguish among measures that mattered most (ie, primary end points) from measures that were less important (ie, secondary end points). With the use of this framework, if the null hypothesis on primary end point was not rejected, any effect on secondary or exploratory end points was considered hypothesis generating.

Emergence of Hierarchical Testing of Secondary End Points

Subsequently, many statisticians and certain regulatory agencies proposed that acceptable false-positive error rates needed to be prospectively identified for entire sets of end points.[52,53] One approach was to create a sequence of hierarchical testing of prespecified hypotheses for all prespecified end points.[52,53] With the use of this framework, one or more end points are allocated a share of the studywide acceptable false-positive error rate (usually 5%), making these primary end points. If the null hypothesis is rejected, its allocated α is passed to successive secondary end points, thus allowing the overall studywise error rate to be preserved for declared findings. Any assessment outside this planned sequence is considered exploratory, and its *P* value is considered to be nominal.

Although the hierarchical testing of trial end points minimized the likelihood of a false-positive finding, it led to certain difficulties in the design and interpretation of clinical trials. First, it undermined the ability of investigators to fully evaluate the effects of a new treatment if they expected that the effect on the primary end point would be neutral. For example, in the DIG trial (Digitalis Investigation Group), the primary end point of the trial was all-cause mortality.[54] The investigators feared that digoxin might increase mortality, and thus were reassured that no adverse effect on the risk of death was detected in the trial. The trial also reported a specific benefit of digoxin to reduce the risk of HF hospitalization, a prespecified secondary end point. Could investigators interpret this positive secondary end point result if the null hypothesis on the primary end point had not been rejected? In the case of the DIG trial, the investigators believed that the trial actually had achieved its principal objective; yet, hierarchical testing would not have allowed conclusions based on other analyses of the trial data. Such an approach would have assigned the vast majority of the data collected in the DIG trial to a state of nondefinitiveness. It should be noted that the DIG trial could have proposed a noninferiority hypothesis for its primary end point, thus allowing for the analysis of secondary end points, but this was not the approach used for the trial.

Second, when investigators and sponsors realized that regulatory agencies would require hierarchical testing of all prespecified end points, it was tempting to rank the end points of interest, not based on clinical importance, but on achievability. Because the stepwise testing procedure depended on the success on testing of a predefined sequence of end points, it was strategically wise to place end points that were deemed easy to achieve higher in rank, even if they were less clinically important. As a result, the enthusiasm for hierarchical testing created potential perverse incentives in the design of clinical trials, which could undermine their ability to answer clinically relevant questions. For example, in the PIONEER-HF trial (Comparison of Sacubitril–Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode) with sacubitril/valsartan, the primary end point was N-terminal pro-B-type natriuretic peptide, a biomarker expected to be favorably influenced by angiotensin-receptor neprilysin inhibition.[55] Yet, the most important clinically relevant measure of efficacy in this 8-week trial was the effect of treatment on HF hospitalizations. However, because the trial was underpowered to assess this measure of efficacy, it was placed at the bottom of hierarchical testing procedure, and thus, the *P* value for the treatment effect was nominal. Although nonclinical primary end points may be reasonable in the setting of modestly sized phase II studies, hierarchically testing a series of end points nonetheless introduces incentives to rank end points by achievability rather than clinical meaning.

Was Evidence Collected From Other Trials Informative?

The most important limitation of the hierarchical designation of primary and secondary end points was that the approach restricted the evaluation of evidence for

efficacy to that collected in a single trial. In a frequentist framework, evidence from other trials with the same drug or with drugs of the same class could not be considered in the formal statistical evaluation of the findings of an individual trial. Such a philosophy was at odds with the pervasive belief that the true effects of a drug or device can be most validly assessed by examining and integrating all relevant evidence.

The large and consistent benefit of SGLT2 inhibitors on HF hospitalization was not anticipated when these trials were first designed (Table 1). The primary end point for the EMPA-REG OUTCOME and CANVAS trials, and the original primary end point in the DECLARE-TIMI 58 trial, was the occurrence of MACE, defined as the composite of CV death, nonfatal MI, and nonfatal stroke. The sponsors funded these trials with the expectation and hope that each SGLT2 inhibitor would at least demonstrate a neutral effect on the primary end point, and, indeed, this goal was uniformly achieved. However, the effect of treatment on the primary end points of these 3 trials did not adequately summarize the most clinically important findings, ie, each trial reported a meaningful benefit of these drugs to reduce the risk of HF hospitalization.[43]

Prompted by the results of EMPA-REG OUTCOME, the DECLARE-TIMI 58 investigators added a second coprimary end point that included HF hospitalizations while the trial was in progress.[6,48] This decision was reinforced when the results of CANVAS were subsequently reported.[8] It is not surprising that the DECLARE-TIMI 58 trial demonstrated an effect on HF events that was highly concordant with that seen in the EMPA-REG OUTCOME and CANVAS trials; yet, only the DECLARE-TIMI 58 trial had designated this effect within a primary end point. This intriguing sequence of events could allow dapagliflozin to gain approval to reduce the risk of HF hospitalizations in T2DM, even though the mid-study change in protocol was entirely motivated by the results of trials of empagliflozin and canagliflozin. At the same time, the labeling for empagliflozin and canagliflozin might not include any mention of a benefit on HF hospitalizations, even though the EMPA-REG OUTCOME and CANVAS trials were the first to report the benefit and demonstrated treatment effects that were as impressive as those for dapagliflozin. This example illustrates the conundrum created by our current reliance on hierarchical testing for clinical and regulatory decision making.

How Have Regulatory Agencies Made Decisions in an Era of α Spending?

Although regulatory agencies currently support the hierarchical testing of end points as a decision-making tool, the FDA and the European Medicines Agency have long made regulatory decisions that have not been entirely consistent with this statistical principle, in particular, with respect to the evaluation of evidence for drugs for HF (Table 2).[52,53] As noted above, the DIG trial reported no benefit of digoxin on all-cause mortality, but observed a benefit on HF hospitalizations,[54] which was consistent with that seen in other trials with digoxin in patients with HF.[56] As a result, digoxin is approved in the United States to reduce the risk of HF hospitalizations, even though this indication is based on a trial that did not meet its primary end point.

Similarly, the SOLVD Prevention trial (Studies of Left Ventricular Dysfunction) reported no benefit of enalapril on all-cause mortality, the primary end point of the trial[57]; yet, the trial observed a meaningful decrease in the risk of HF hospitalizations, a finding that was highly consistent with a similar result in a sister trial that was performed in patients with symptomatic HF, the SOLVD Treatment trial.[58] The FDA provided enalapril with an indication to reduce the risk of HF hospitalizations in patients with asymptomatic left ventricular dysfunction, even though this indication was based on a trial that did not meet its primary end point.

Perhaps most strikingly, the FDA approved carvedilol for use in patients with left ventricular dysfunction after an acute MI. The labeling notes a statistically significant decrease in all-cause mortality, and in the risk

Table 2. Select Past Examples of the Use of Nonprimary End Points and Regulatory Decisions for Heart Failure

DIG trial[54]
Digoxin did not meet the primary end point of all-cause mortality.
Digoxin showed a benefit for the nonprimary end point of HF hospitalization.
Digoxin was approved to reduce HF hospitalization.
SOLVD Prevention trial[57]
In patients with asymptomatic left ventricular dysfunction, enalapril did not show benefit on the primary end point of all-cause mortality.
Enalapril showed a benefit for the nonprimary end point of HF hospitalization.
Enalapril was approved to reduce HF hospitalization among patients with asymptomatic left ventricular dysfunction.
SAVE trial[60]
Among patients with left ventricular dysfunction following acute myocardial infarction, captopril reduced the risk of all-cause mortality.
Despite all-cause mortality not being the prespecified primary end point, captopril was approved to reduce all-cause mortality in this patient population.
CAPRICORN trial[59]
Among patients with left ventricular dysfunction following acute myocardial infarction, carvedilol did not have a beneficial effect on either of the coprimary end points of all-cause mortality, or the composite of all-cause mortality or cardiovascular hospitalization.
Carvedilol did not demonstrate benefit on either of the 2 secondary end points (sudden death, HF hospitalization).
Carvedilol was approved to reduce all-cause mortality and reinfarction in this patient population.

HF indicates heart failure.

of reinfarction, as well. These indications are based on the results of the CAPRICORN trial (Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction Study), which had 2 primary end points, with a prospectively distributed α, and 2 secondary end points (with no designated false-positive error rates); the α distribution for the primary end points had been revised during the course of the trial in a manner that placed less statistical weight on all-cause mortality.[59] As judged by the thresholds specified in the final statistical plan, the trial did not achieve either of its 2 primary or 2 secondary end points. Nevertheless, an FDA advisory committee was persuaded by the totality of evidence with carvedilol and β-blockers from trials in patients with HF or postinfarction left ventricular dysfunction. The FDA provided an indication for the use of carvedilol in patients after MI to reduce the risk of death and reinfarction.

There are also instances when the finding of an effect on the trial's primary end point did not make it into labeling. The FDA provided an indication to captopril to reduce all-cause mortality for patients with left ventricular dysfunction after an acute MI, even though all-cause mortality was not the primary prespecified end point of the SAVE trial (Survival and Ventricular Enlargement Trial).[60] The effect of captopril on the primary end point, which was largely driven by a change in ejection fraction, is not noted in the FDA labeling for the drug. Similarly, the FDA approved a combination of hydralazine and isosorbide dinitrate to reduce mortality in black patients with chronic HF, even though all-cause mortality was not the primary end point of the A-HeFT trial (African-American Heart Failure Trial), and the study was stopped early based on a relatively sparse number of fatal events, in the absence of prespecified boundaries for early termination.[61] Analogously, the European Medicines Agency granted an indication for ivabradine to reduce all-cause mortality in select patients with HF, even though the supporting evidence was based on a post hoc analysis that had been assigned no prespecified false-positive rate in the trial's statistical plan.[62]

These examples demonstrate that, for several decades, regulatory agencies have previously relied on the totality of evidence across clinical trials and across members of the same drug class in granting efficacy indications for clinical use. Decisions were not exclusively focused on specific statistical rules and some approved indications were based on the results, and analyses of clinical trials that did not fulfill current standards for the hierarchical testing of primary and secondary end points. Although rigorous statistical examination of new trial results must be performed, previous philosophy differs from the current more inflexible approach focused on formal statistical rules pertaining to a single clinical trial.

CONCLUSIONS AND FUTURE DIRECTION

These observations lead to several conclusions and recommendations for future direction (Table 3).

HF Characterization and End Point

The occurrence of serious fatal and nonfatal HF events has substantial clinical importance. It is therefore recommended that future large-scale CVOTs of antihyperglycemic therapies include a standardized characterization of the presence, phenotype, severity, recent clinical course, and treatment of HF at the time of enrollment. If the research question warrants a specific focus on HF outcomes, then dedicated trials should be conducted in patients at high risk for new HF events, and an assessment of the effect of treatment on nonfatal HF events should be included as the primary end point or a component of a composite primary end point. A similar approach is warranted for trials that seek to evaluate the effects of an intervention in those with an established diagnosis of HF. It would be useful for a meaningful proportion of eligible participants to have HF at the start of the trial (ie, a proportion representative of the proportion seen in routine clinical practice) and for the phenotype and treatment of HF to be adequately characterized from existing records to allow for post hoc analyses. In general, the representation of patients with HF in current CVOTs in T2DM was less than that reported in routine practice (10% vs 20%–30%, respectively).[22]

These efforts can be substantially aided by consensus regarding the data that should be collected at baseline and during the progress of the trials pertinent to HF risk and outcomes. Further research is warranted to better understand the development and diagnosis of new-onset HF, especially in the outpatient setting. The characterization of HF stages (stage A, B, C, and D), although useful to understand the spectrum of risk, is not useful for regulatory and clinical decision making.[63]

Role of SGLT2 Inhibitors in HF Hospitalization Risk Reduction

Considering the consistent and clinically relevant risk reduction for HF hospitalization achieved by SGLT2 inhibitors across several large CVOTs, careful consideration should be given to the clinical use of these drugs for this purpose. This consideration is warranted, even though HF hospitalization was not a primary end point in these trials, and even though the benefit on HF hospitalization did not fulfill criteria for statistical significance according to the hierarchical testing procedure specified in these trials. Such a recommendation is consistent with the precedent set by previous regulatory decisions for CV

Table 3. Summary Points and Recommendations

Characterization of HF in cardiovascular outcome trials of T2DM
There are substantial gaps in the characterization of HF in contemporary CVOTs of patients with T2DM.
Challenges associated with characterization of baseline HF
Uncertainty regarding whether effects on HF end points reflect prevention of new-onset HF or treatment of preexisting HF.
Lack of granular description of HF phenotype (eg, functional class, EF, background HF therapy) hinders generalizability of trial data to clinical practice, regulatory decisions, and subsequent research.
Challenges associated with worsening and incident HF events during follow-up
HF events in CVOTs are largely limited to HF hospitalizations, ignoring outpatient worsening HF events (eg, emergency department visits, outpatient intravenous diuretic administration) that may carry comparable prognostic significance.
Focus on HF hospitalizations neglects a large proportion of new-onset HF diagnosed as outpatient.
HF outcomes in cardiovascular outcome trials of SGLT2 inhibitors
Four large trials (EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, and CREDENCE) have consistently shown that SGLT2 inhibitor therapy decreases the risk of HF hospitalization by 27%–39%.
Trials include a combined 38 733 randomly assigned patients and 1192 HF hospitalization events.
Magnitude of benefit from SGLT2 inhibitor therapy on MACE was absent or modest relative to the large magnitude of HF hospitalization benefit.
Whereas the effect of SGLT2 inhibitors on MACE was confined to patients with history of ASCVD, the finding of a reduction in HF hospitalization extended to all participants, including those with and without existing ASCVD and with and without existing HF.
Despite the size of the randomized sample and consistent benefits on HF hospitalization events, none of the tested SGLT2 inhibitor agents carry a regulatory indication for prevention of HF hospitalization in patients with T2DM.
Absence of HF label indication is largely due to HF not being a primary endpoint in the CVOTs of SGLT2 inhibitors.
Future directions for HF and nonprimary end points in cardiovascular outcome trials
When HF is present at baseline, standardize a comprehensive characterization of HF.
Ensure that the proportion of patients with baseline HF is reflective of the prevalence of comorbid HF in routine clinical practice.
When significant effects of the agent on HF are likely or anticipated, trials should be conducted among populations with high risk for HF events, and HF events should be included as a primary end point or within a primary composite end point.
SGLT2 inhibitors and HF hospitalization
Based on consistent and clinically relevant benefits across 4 large randomized trials, careful consideration should be given to regulatory approval, guideline recommendation, and clinical use of SGLT2 inhibitors to reduce HF hospitalization in a broad group of patients with T2DM similar to those enrolled in these trials.

ASCVD indicates atherosclerotic cardiovascular disease; CVOT, cardiovascular outcome trial; EF, ejection fraction; HF, heart failure; MACE, major adverse cardiovascular events; SGLT2, sodium glucose cotransporter 2; and T2DM, type 2 diabetes mellitus.

medications (in particular, drugs used in patients with HF or left ventricular dysfunction), which have been based on the totality of available evidence concerning the relation of benefit to risk. Ongoing clinical trials that are evaluating the effect of SGLT2 inhibitors in patients who have well-characterized HF (with or without diabetes mellitus) at trial entry are expected to provide additional important insights.[15,16]

ARTICLE INFORMATION

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