Title

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

Journal

Circulation, 140(25)

ISSN

0009-7322

Authors

Butler, Javed
Packer, Milton
Greene, Stephen J
et al.

Publication Date

2019-12-17

DOI

10.1161/circulationaha.119.042155

Peer reviewed

Published in final edited form as:

Circulation. 2019 December 17; 140(25): 2108–2118. doi:10.1161/CIRCULATIONAHA.119.042155.

Heart Failure Endpoints in Cardiovascular Outcome Trials of SGLT2 inhibitors in Patients with Type 2 Diabetes: A Critical Evaluation of Clinical and Regulatory Issues

Javed Butler, MD MPH MBA

University of Mississippi Medical Center, Department of Medicine (L650), 2500 N. State Street, Jackson, MS 39216

Milton Packer, MD[2], **Stephen J. Greene, MD**[3,4], **Mona Fiuzat, PharmD**[3], **Stefan D. Anker, MD PhD**[5,6], **Kevin J. Anstrom, PhD**[3], **Peter E. Carson, MD**[7], **Lauren B. Cooper, MD MHS**[8], **Gregg C. Fonarow, MD**[9], **Adrian F. Hernandez, MD MHS**[3,4], **James L. Januzzi Jr., MD**[10], **Mariell Jessup, MD**[11], **Rita R. Kalyani, MD MHS**[12], **Sanjay Kaul, MD**[13], **Mikhail Kosiborod, MD**[14], **JoAnn Lindenfeld, MD**[15], **Darren K. McGuire, MD MHSc**[16], **Marc S. Sabatine, MD MPH**[17], **Scott D. Solomon, MD**[18], **John R. Teerlink, MD**[19,20], **Muthiah Vaduganathan, MD MPH**[18], **Clyde W. Yancy, MD MSc**[21], **Norman Stockbridge, MD, PhD**[22], **Christopher M. O'Connor, MD**[8]

[2]Baylor University Medical Center, Dallas, TX;

[3]Duke Clinical Research Institute, Durham, NC;

[4]Division of Cardiology, Duke University School of Medicine, Durham, NC;

[5]Berlin-Brandenburg Center for Regenerative Therapies, Berlin, Germany;

[6]Department of Cardiology, German Center for Cardiovascular Research partner site Berlin, Charite Universitatsmedizin Berlin, Berlin, Germany;

[7]Cardiovascular Division, Department of Cardiology, Washington Veterans Affairs Medical Center, Washington, DC;

[8]Inova Heart and Vascular Institute, Falls Church, VA;

[9]Ahmanson-UCLA Cardiomyopathy Center, University of California Los Angeles, Los Angeles, CA;

[10]Cardiology Division, Massachusetts General Hospital and Baim Institute for Clinical Research, Boston, MA;

[11]American Heart Association, Dallas, TX;

[12]Division of Endocrinology, Diabetes, and Metabolism, Johns Hopkins University School of Medicine, Baltimore, MD;

Address for Correspondence: Javed Butler, MD MPH MBA, University of Mississippi Medical Center, Department of Medicine (L650), 2500 N. State Street, Jackson, MS 39216. Telephone: 601-984-5600; Fax: 601-984-5608; jbutler4@umc.edu.
Tweet: How should we view #heartfailure results from SGLT2i trials of patients with diabetes? Assessing regulatory and clinical issues with non-primary endpoints.
Twitter handle: @JavedButler1, @UMMCMedicine

[13]Cedars-Sinai Medical Center, Los Angeles, CA;

[14]Saint Luke's Mid America Heart Institute, University of Missouri-Kansas City, Kansas City, MO and The George Institute for Global Health, University of New South Wales, Sydney, Australia;

[15]Vanderbilt Heart and Vascular Institute, Nashville, TN;

[16]Division of Cardiology, University of Texas Southwestern Medical Center, Dallas, TX;

[17]TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA;

[18]Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA;

[19]Section of Cardiology, San Francisco Veterans Affairs Medical Center, San Francisco, CA;

[20]School of Medicine, University of California, San Francisco, CA;

[21]Division of Cardiology, Northwestern University Feinberg School of Medicine;

[22]Division of Cardiovascular and Renal Products, United States Food and Drug Administration, Silver Spring, MD.

Abstract

Following regulatory guidance set forth in 2008 by the United States Food and Drug Administration (FDA) 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 endpoint of major adverse cardiovascular events, defined as cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. Heart failure (HF) was not specifically mentioned in the FDA guidance and therefore it was not a focus of these studies when planned. Several trials subsequently showed impact of antihyperglycemic drugs on HF outcomes, which were not originally specified as the primary endpoint of the trials. The most impressive finding has been the substantial and consistent risk-reduction in HF hospitalization seen across four 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 United States HF guidelines. It is therefore important to explore to what extent persuasive treatment effects on non-primary endpoints can be utilized 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 FDA campus on March 6, 2019. This report summarizes these discussions and key takeaway messages from this meeting.

Keywords

clinical trial; endpoint; heart failure; type 2 diabetes mellitus

In 2008, the United States (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 cardiovascular safety of drugs for T2DM. For example, tolbutamide increased cardiovascular mortality (a warning that persists in every sulfonylurea product label to date in the US)[3], thiazolidinediones increased the risk of heart failure (HF)[4], and muraglitazar increased a composite of cardiovascular 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. Specifically, pre-approval trials were required to demonstrate an upper bound < 1.8 for the two-sided 95% confidence interval of the hazard ratio of composite end point of major adverse cardiac events (MACE), consisting of CV death, nonfatal MI, and non-fatal stroke.[1] The choice of this endpoint 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 cardiovascular safety, the trials for two classes of antihyperglycemic medications (glucagon-like peptide-1 [GLP1] receptor agonists and sodium glucose cotransporter 2 [SGLT2] inhibitors) showed superiority for the primary MACE endpoint. These findings led to FDA-approved product labeling with indications for CV risk mitigation as well as guideline recommendations for reducing the risk of cardiovascular 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 endpoint. 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, three 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 non-primary endpoints 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 non-primary

clinical trial endpoints 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, which took place at the FDA campus on March 6, 2019.

GAPS IN CHARACTERIZATION OF HEART FAILURE

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.

Heart Failure 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 only 1 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 (Dapagliflozin Effect on CardiovascularEvents–Thrombolysis in Myocardial Infarction 58) investigators published LVEF data captured from records prior to trial entry among patients with and without HF at baseline.[23] Values for LVEF were available for approximately 75% of HF patients and approximately 30% of the overall trial cohort, although the investigators did not specify a time window for the acquisition of LVEF data prior to 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 pre-existing HF. Although it is tempting to make this distinction based on investigator identification of clinical HF at baseline, an accurate assessment typically requires echocardiography, the measurement of natriuretic peptides, and documentation of the use of medications for the treatment of heart failure. Nonetheless, the investigator-based assessment does show certain validity, since observed event rates were substantially higher among patients with as compared 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 (HFrEF). For example, statins and antihypertensive drugs prevent the development of HF in trials of patients at increased cardiovascular 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 (HFpEF).[26] Given this uncertainty, dedicated trials with SGLT2 inhibitors among patients with established HF are ongoing, including those with and without T2DM and including those with HFrEF or HFpEF (; ; ; ; and).[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, since it is a clinically meaningful event that reflects disease progression and results in significant healthcare expenditure.[29–31]

Worsening and Incident Heart Failure Events

In addition to limited characterization of HF at trial entry, the analysis and interpretation of the HF outcomes in CVOTs in type 2 diabetes are further complicated by limited characterization of HF events that occurred following 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] Specifically, the CANVAS (Canagliflozin Cardiovascular Assessment Study) program undertook a retrospective secondary review of medical record data to report the LVEF measured at the time of post-randomization 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] Non-clinical factors (e.g., healthcare system infrastructure, country, caregiver support) are prominent drivers of the site of HF care.[34, 35] Interestingly, 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 non-hospitalization HF events continues to evolve, and some trials now include them within endpoint definitions for a HF event.[32] Although such events may be relatively uncommon in the US, rates of non-hospitalization 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 non-hospitalization events makes it difficult to precisely identify the time of onset of HF among patients not previously diagnosed with HF. Only ~1/3 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.

HEART FAILURE OUTCOMES IN LARGE-SCALE TRIALS IN DIABETES

To date, four large randomized trials among patients with diabetes 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 1,192 total HF hospitalization events. The relative risk reduction for HF hospitalization has been large, ranging from 27% with dapagliflozin in DECLARE-TIMI 58 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 pre-existing ASCVD and with and without pre-existing HF.[23, 43–46]

The vast majority of 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 DECLARE TIMI-58 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 (i.e., 20–30%).[12, 42, 47] Nonetheless, it has been proposed that these randomized trials provide robust evidence for use of SGLT2 inhibitors for reducing the risk of HF hospitalization among patients with T2DM, at least for those without history of HF.[27] However, currently none of the agents within this drug class 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 endpoint in these studies; yet, SGLT2 inhibitors exert greater benefits on HF outcomes as compared 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 co-primary 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]

REGULATORY INTERPRETATION OF NON-PRIMARY ENDPOINTS 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 non-primary trial outcomes is warranted.

The Emergence of the Primary Endpoint

The most readily interpretable finding in a prospective randomized controlled clinical trial is the effect of the study intervention on the pre-specified primary endpoint(s). Typically, a trial is designed to fully evaluate the effect of the treatment on the primary endpoint, 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 endpoint.

When clinical outcome trials first emerged as an important methodology in the 1960s, it was common to specify 3–5 primary endpoints of interest, and these were often described in the study protocol in a non-hierarchical manner.[49] When the trial was complete, hypothesis testing was performed on each endpoint, 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 endpoints are 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 endpoints achieved a 0.05 threshold. It was generally agreed that such an approach was unacceptably lenient, since many treatment effects that met such a threshold represented non-replicable findings. To rectify this, investigators began to distinguish amongst measures that mattered most (i.e., primary endpoints) from measures

that were less important (i.e., secondary endpoints). Using this framework, if the null hypothesis on primary endpoint was not rejected, any effect on secondary or exploratory endpoints was considered hypothesis-generating.

The Emergence of Hierarchical Testing of Secondary Endpoints

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

Although the hierarchical testing of trial endpoints 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 endpoint would be neutral. For example, in the Digitalis Investigation Group (DIG) Trial, the primary endpoint 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 pre-specified secondary endpoint. Could investigators interpret this positive secondary endpoint result if the null hypothesis on the primary endpoint 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 non-definitiveness. It should be noted that the DIG trial could have proposed a non-inferiority hypothesis for its primary endpoint, thus allowing for the analysis of secondary endpoints, 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 pre-specified endpoints, it was tempting to rank the endpoints of interest, not based on clinical importance, but on achievability. Since the stepwise testing procedure depended on success on testing of a predefined sequence of endpoints, it was strategically wise to place endpoints 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 (Comparison of Sacubitril–Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode) trial with sacubitril/valsartan, the primary endpoint was N-terminal-pro-B-type natriuretic peptide (NT-proBNP), 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 non-clinical primary endpoints may be reasonable in the setting of modestly-sized phase II studies, hierarchically testing a series of endpoints nonetheless introduces incentives to rank endpoints 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 endpoints 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 endpoint for the EMPA-REG OUTCOME and CANVAS trials, and the original primary endpoint in the DECLARE-TIMI 58 trial, was the occurrence of MACE, defined as the composite of CV death, non-fatal MI and non-fatal 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 endpoint, and indeed, this goal was uniformly achieved. However, the effect of treatment on the primary endpoints of these 3 trials did not adequately summarize the most clinically important findings, i.e., each trial reported a meaningful benefit of these drugs to reduce the risk of HF hospitalization.[43]

Interestingly, prompted by the results of EMPA-REG OUTCOME, the DECLARE-TIMI58 investigators added a second co-primary endpoint 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] Not surprisingly, the DECLARE-TIMI58 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-TIMI58 trial had designated this effect within a primary endpoint. 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 Alpha Spending?

Although regulatory agencies currently support hierarchical testing of endpoints as a decision-making tool, the US FDA and the European Medicines Agency have long made regulatory decisions that have not been entirely consistent with this statistical principle, particularly with respect to the evaluation of evidence for drugs for heart failure (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 US to reduce the risk of HF hospitalizations, even though this indication is based on a trial that did not meet its primary endpoint.

Similarly, the SOLVD (Studies of Left Ventricular Dysfunction) Prevention trial reported no benefit of enalapril on all-cause mortality, the primary endpoint 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 carried out 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 endpoint.

Perhaps most strikingly, the FDA approved carvedilol for use in patients with left ventricular dysfunction following an acute MI. The labeling notes a statistically significant decrease in all-cause mortality as well as in the risk of re-infarction. These indications are based on the results of the CAPRICORN (Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction Study) trial, which had two primary endpoints, with a prospectively distributed alpha, and two secondary endpoints (with no designated false positive error rates); the alpha distribution for the primary endpoints 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 endpoints. Nevertheless, an FDA advisory committee was persuaded by the totality of evidence with carvedilol and other beta-blockers from trials in patients with HF or post-infarction left ventricular dysfunction. The FDA provided an indication for use of carvedilol in post-MI patients to reduce the risk of death and re-infarction.

There are also instances when the finding of an effect on the trial's primary endpoint did not make it into labeling. The FDA provided an indication to captopril to reduce all-cause mortality for patients with left ventricular dysfunction following an acute MI, even though all-cause mortality was not the primary pre-specified endpoint of the SAVE (Survival and Ventricular Enlargement Trial) trial.[60] The effect of captopril on the primary endpoint, which was largely driven by a change in EF, 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 African-American patients with chronic HF, even though all-cause mortality was not the primary endpoint of the A-HeFT (African-American Heart Failure Trial) trial, and the study was stopped early based on a relatively sparse number of fatal events, in the absence of pre-specified 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 pre-specified 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 endpoints. Although rigorous statistical examination of new trial results must be performed, prior 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).

Heart Failure Characterization and Endpoint

The occurrence of serious fatal and non-fatal 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 non-fatal HF events should be included as the primary endpoint or a component of a composite primary endpoint. A similar approach is warranted for trials that seek to evaluate the effects of an intervention in those with an established diagnosis of HF. Additionally, it would be useful for a meaningful proportion of eligible participants to have HF at the start of the trial (i.e., 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. The representation of HF patients in current CVOTs in T2DM was generally 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]

The Role of SGLT2 Inhibitors in Heart Failure 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 for the clinical use of these drugs for this purpose. This consideration is warranted, even though HF hospitalization was not a primary endpoint 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 precedent set by previous regulatory decisions for CV medications (particularly 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) at trial entry are expected to provide additional important insights.[15, 16]

DISCLOSURES

Dr. Butler has received research support from the National Institutes of Health (NIH), Patient-Centered Outcomes Research Institute, and the European Union; and serves as a consultant for Amgen, Array, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squib, CVRx, G3 Pharmacautical, Innolife, Janssen, Luitpold, Medtronic, Merck, Novartis, Relypsa, StealthPeptide, SC Pharma, Vifor, and ZS Pharma. Dr. Packer has consulted for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cardiorentis, Celyad, Daiichi Sankyo, Gilead, NovoNordisk, Novartis, Relypsa, Sanofi, Takeda, and ZS Pharma. Dr. Greene is supported by a Heart Failure Society of America/ Emergency Medicine Foundation Acute Heart Failure Young Investigator Award funded by Novartis, has received research support from Amgen, Bristol-Myers Squibb, and Novartis, and serves on an advisory board for Amgen. Dr. Fiuzat has received grant support from the NIH and Roche Diagnostics. Dr. Anker reports personal fees from Servier, Vifor, Bayer, Boehringer Ingelheim, and Novartis. Dr. Anstrom reports receiving grants from the NIH. Dr. Cooper has received research support from Abbott Laboratories, and has consulted for AstraZeneca. Dr. Fonarow has served as a consultant for Abbott, Amgen, Bayer, Janssen, Medtronic, and Novartis. Dr. Hernandez reports consulting fees from AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Merck, Novartis, Sanofi, and research support from American Regent, AstraZeneca, GlaxoSmithKline, Merck, Novartis and Verily. Dr. Januzzi has received grant support from Roche Diagnostics, Abbott Diagnostics, Singulex, Prevencio, and Cleveland Heart Labs; has received consulting income from Roche Diagnostics and Critical Diagnostics; and participates in Clinical Endpoint Committees/Data Safety Monitoring Boards for Siemens Diagnostics. Dr. Kosiborod has received research grant support from AstraZeneca, Boehringer Ingelheim, and has consulted for AstraZeneca, Boehringer Ingelheim, Amgen, GSK, Novo Nordisk, Sanofi, Merck, Eisai, Janssen, Glytec, Intarcia, Novartis, Bayer, Applied Therapeutics, Amarin. Dr. Lindenfeld has received grant research support from Novartis; and consultant support from St. Jude, Abbott, Relypsa, RESMED, Cardiokinetix, Edwards, and CVRx. Dr. McGuire has received personal fees from Boehringer-Ingelheim, Janssen Research and Development, Sanofi-Aventis, Merck Sharp & Dohme, Merck & Co, Eli Lilly, Novo Nordisk, GlaxoSmithKline, AstraZeneca, Lexicon, Eisai, Pfizer, Metavant, Applied Therapeutics, and Esperion. Dr. Sabatine has received research grant support through Brigham and Women's Hospital from Amgen, AstraZeneca, Bayer, Daiichi-Sankyo, Eisai, GlaxoSmithKline, Intarcia, Medicines Company, MedImmune, Merck, Novartis, Pfizer, Quark Pharmaceuticals, Takeda (All >$10,000 per year), and has consulted for Amgen, AstraZeneca, Bristol-Myers Squibb, CVS Caremark, Dyrnamix, IFM Therapeutics, Medicines Company, MedImmune, Merck (all ≤$10,000 per year except Amgen). Dr. Solomon has received research grants from Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, BMS, Celladon, Cytokinetics, Eidos, Gilead, GSK, Ionis, Lone Star Heart, Mesoblast, MyoKardia, NIH/NHLBI, Novartis, Sanofi Pasteur, Theracos, and has consulted for Akros, Alnylam, Amgen, AstraZeneca, Bayer, BMS, Cardior, Corvia, Cytokinetics, Gilead, GSK, Ironwood, Merck, Novartis, Roche, Takeda, Theracos, Quantum Genetics, Cardurion, AoBiome, Janssen, Cardiac Dimensions, Tenaya. Dr. Teerlink is a consultant for Abbott, Amgen, Bayer, Bristol-Myers Squibb, Cytokinetics, Medtronic, Merck, Novartis, Stealth Health, and St. Jude Medical; has received funding from Abbott, Amgen, Bayer, Bristol-Myers Squibb, Novartis, and scPharma; has received research grants and personal fees from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cytokinetics, Medtronic, and St. Jude; Dr. Vaduganathan is supported by the KL2/Catalyst Medical Research Investigator Training award from Harvard Catalyst (NIH/NCATS Award UL 1TR002541), and has served on advisory boards or received research funding from Amgen, AstraZeneca, Bayer AG, and Baxter Healthcare. Dr. O'Connor has received grant support from the NIH and Roche Diagnostics; has served as a consultant for Bayer, Bristol Myers Squib, and Merck. All other authors report no disclosures.

Non-standard Abbreviations and Acronyms

A-HeFT	African-American Heart Failure Trial
CANVAS	Canagliflozin Cardiovascular Assessment Study

CAPRICORN	Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction Study
CVOT	cardiovascular outcome trial
DECLARE-TIMI 58	Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58
EMPA-REG	Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients
FDA	Food and Drug Administration
SAVE	Survival and Ventricular Enlargement Trial
SGLT2	sodium glucose cotransporter 2
SOLVD	Studies of Left Ventricular Dysfunction

REFERENCES

1. Food and Drug Administration. Guidance for industry: diabetes mellitus—evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 mellitus. 2008 http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf. Accessed June 1, 2017
2. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007;356:2457–2471 [PubMed: 17517853]
3. Goldner MG, Knatterud GL, Prout TE. Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. 3. Clinical implications of ugdp results. JAMA. 1971;218:1400–1410 [PubMed: 4941698]
4. Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: A meta-analysis of randomised clinical trials. Lancet. 2007;370:1129–1136 [PubMed: 17905165]
5. Nissen SE, Wolski K, Topol EJ. Effect of muraglitazar on death and major adverse cardiovascular events in patients with type 2 diabetes mellitus. JAMA. 2005;294:2581–2586 [PubMed: 16239637]
6. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE, Investigators E-RO. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117–2128 [PubMed: 26378978]
7. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB, Committee LS, Investigators LT. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375:311–322 [PubMed: 27295427]
8. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR, Group CPC. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377:644–657 [PubMed: 28605608]
9. Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, Rossing P, Tsapas A, Wexler DJ, Buse JB. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the american diabetes association (ada) and the european association for the study of diabetes (easd). Diabetes Care. 2018;41:2669–2701 [PubMed: 30291106]
10. American Diabetes A. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2019. Diabetes Care. 2019;42(Suppl 1):S90–S102. [PubMed: 30559235]
11. Das SR, Everett BM, Birtcher KK, Brown JM, Cefalu WT, Januzzi JL Jr, Kalyani RR, Kosiborod M, Magwire ML, Morris PB, Sperling LS. 2018 acc expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes and atherosclerotic

cardiovascular disease: A report of the american college of cardiology task force on expert consensus decision pathways. J Am Coll Cardiol. 2018;72:3200–3223 [PubMed: 30497881]

12. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde AM, Sabatine MS, Investigators D-T. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380:347–357 [PubMed: 30415602]
13. Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, Jones NP, Komajda M, McMurray JJ, Team RS. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (record): A multicentre, randomised, open-label trial. Lancet. 2009;373:2125–2135 [PubMed: 19501900]
14. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mosenzon O, McGuire DK, Ray KK, Leiter LA, Raz I, Committee S-TS, Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013;369:1317–1326 [PubMed: 23992601]
15. Butler J, Hamo CE, Filippatos G, Pocock SJ, Bernstein RA, Brueckmann M, Cheung AK, George JT, Green JB, Januzzi JL, Kaul S, Lam CSP, Lip GYH, Marx N, McCullough PA, Mehta CR, Ponikowski P, Rosenstock J, Sattar N, Salsali A, Scirica BM, Shah SJ, Tsutsui H, Verma S, Wanner C, Woerle HJ, Zannad F, Anker SD, Program ET. The potential role and rationale for treatment of heart failure with sodium-glucose co-transporter 2 inhibitors. Eur J Heart Fail. 2017;19:1390–1400 [PubMed: 28836359]
16. McMurray JJV, DeMets DL, Inzucchi SE, Kober L, Kosiborod MN, Langkilde AM, Martinez FA, Bengtsson O, Ponikowski P, Sabatine MS, Sjostrand M, Solomon SD, Committees D-H, Investigators. A trial to evaluate the effect of the sodium-glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (dapa-hf). Eur J Heart Fail. 2019;21:665–675 [PubMed: 30895697]
17. Ziaeian B, Hernandez AF, DeVore AD, Wu J, Xu H, Heidenreich PA, Matsouaka RA, Bhatt DL, Yancy CW, Fonarow GC. Long-term outcomes for heart failure patients with and without diabetes: From the get with the guidelines-heart failure registry. Am Heart J. 2019;211:1–10 [PubMed: 30818060]
18. Bertoni AG, Hundley WG, Massing MW, Bonds DE, Burke GL, Goff DC Jr. Heart failure prevalence, incidence, and mortality in the elderly with diabetes. Diabetes Care. 2004;27:699–703 [PubMed: 14988288]
19. Khan SS, Butler J, Gheorghiade M. Management of comorbid diabetes mellitus and worsening heart failure. JAMA. 2014;311:2379–2380 [PubMed: 24938559]
20. Packer M Heart failure: The most important, preventable, and treatable cardiovascular complication of type 2 diabetes. Diabetes Care. 2018;41:11–13 [PubMed: 29263193]
21. McMurray JJ, Gerstein HC, Holman RR, Pfeffer MA. Heart failure: A cardiovascular outcome in diabetes that can no longer be ignored. Lancet Diabetes Endocrinol. 2014;2:843–851 [PubMed: 24731668]
22. Greene SJ, Vaduganathan M, Khan MS, Bakris GL, Weir MR, Seltzer JH, Sattar N, McGuire DK, Januzzi JL, Stockbridge N, Butler J. Prevalent and incident heart failure in cardiovascular outcome trials of patients with type 2 diabetes. J Am Coll Cardiol. 2018;71:1379–1390 [PubMed: 29534825]
23. Kato ET, Silverman MG, Mosenzon O, Zelniker TA, Cahn A, Furtado RHM, Kuder J, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Bonaca MP, Ruff CT, Desai AS, Goto S, Johansson PA, Gause-Nilsson I, Johanson P, Langkilde AM, Raz I, Sabatine MS, Wiviott SD. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. Circulation. 2019;139:2528–2536 [PubMed: 30882238]
24. Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE, investigators E-ROt. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: Results of the empa-reg outcome(r) trial. Eur Heart J. 2016;37:1526–1534 [PubMed: 26819227]

25. Radholm K, Figtree G, Perkovic V, Solomon SD, Mahaffey KW, de Zeeuw D, Fulcher G, Barrett TD, Shaw W, Desai M, Matthews DR, Neal B. Canagliflozin and heart failure in type 2 diabetes mellitus. Circulation. 2018;138:458–468 [PubMed: 29526832]
26. Packer M Are the effects of drugs to prevent and to treat heart failure always concordant? The statin paradox and its implications for understanding the actions of antidiabetic medications. Eur J Heart Fail. 2018;20:1100–1105 [PubMed: 29566300]
27. Greene SJ, Butler J. Primary prevention of heart failure in patients with type 2 diabetes mellitus. Circulation. 2019;139:152–154 [PubMed: 30615507]
28. Vijayakumar S, Vaduganathan M, Butler J. Glucose-lowering therapies and heart failure in type 2 diabetes mellitus: Mechanistic links, clinical data, and future directions. Circulation. 2018;137:1060–1073 [PubMed: 29506996]
29. Gerber Y, Weston SA, Redfield MM, Chamberlain AM, Manemann SM, Jiang R, Killian JM, Roger VL. A contemporary appraisal of the heart failure epidemic in Olmsted County, minnesota, 2000 to 2010. JAMA Intern Med. 2015;175:996–1004 [PubMed: 25895156]
30. Shah KS, Xu H, Matsouaka RA, Bhatt DL, Heidenreich PA, Hernandez AF, Devore AD, Yancy CW, Fonarow GC. Heart failure with preserved, borderline, and reduced ejection fraction: 5-year outcomes. J Am Coll Cardiol. 2017;70:2476–2486 [PubMed: 29141781]
31. Greene SJ, O'Brien EC, Mentz RJ, Luo N, Hardy NC, Laskey WK, Heidenreich PA, Chang CL, Turner SJ, Yancy CW, Hernandez AF, Curtis LH, Peterson PN, Fonarow GC, Hammill BG. Home-time after discharge among patients hospitalized with heart failure. J Am Coll Cardiol. 2018;71:2643–2652 [PubMed: 29880124]
32. Hicks KA, Mahaffey KW, Mehran R, Nissen SE, Wiviott SD, Dunn B, Solomon SD, Marler JR, Teerlink JR, Farb A, Morrow DA, Targum SL, Sila CA, Hai MTT, Jaff MR, Joffe HV, Cutlip DE, Desai AS, Lewis EF, Gibson CM, Landray MJ, Lincoff AM, White CJ, Brooks SS, Rosenfield K, Domanski MJ, Lansky AJ, McMurray JJV, Tcheng JE, Steinhubl SR, Burton P, Mauri L, O'Connor CM, Pfeffer MA, Hung HMJ, Stockbridge NL, Chaitman BR, Temple RJ, Standardized Data Collection for Cardiovascular Trials I. 2017 cardiovascular and stroke endpoint definitions for clinical trials. Circulation. 2018;137:961–972 [PubMed: 29483172]
33. Figtree GA, Radholm K, Barrett TD, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Matthews DR, Shaw W, Neal B. Effects of canagliflozin on heart failure outcomes associated with preserved and reduced ejection fraction in type 2 diabetes: Results from the CANVAS program. Circulation. 2019;139:2591–2593 [PubMed: 30882240]
34. Greene SJ, Mentz RJ, Felker GM. Outpatient worsening heart failure as a target for therapy: A review. JAMA Cardiol. 2018;3:252–259 [PubMed: 29387880]
35. Greene SJ, Felker GM, Butler J. Outpatient versus inpatient worsening heart failure: Distinguishing biology and risk from location of care. Eur J Heart Fail. 2019;21:121–124 [PubMed: 30394644]
36. Skali H, Dwyer EM, Goldstein R, Haigney M, Krone R, Kukin M, Lichstein E, McNitt S, Moss AJ, Pfeffer MA, Solomon SD. Prognosis and response to therapy of first inpatient and outpatient heart failure event in a heart failure clinical trial: Madit-crt. Eur J Heart Fail. 2014;16:560–565 [PubMed: 24578164]
37. Okumura N, Jhund PS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Swedberg K, Zile MR, Solomon SD, Packer M, McMurray JJ, Investigators P-H, Committees*. Importance of clinical worsening of heart failure treated in the outpatient setting: Evidence from the prospective comparison of arni with acei to determine impact on global mortality and morbidity in heart failure trial (paradigm-hf). Circulation. 2016;133:2254–2262 [PubMed: 27143684]
38. Ferreira JP, Metra M, Mordi I, Gregson J, Ter Maaten JM, Tromp J, Anker SD, Dickstein K, Hillege HL, Ng LL, van Veldhuisen DJ, Lang CC, Voors AA, Zannad F. Heart failure in the outpatient versus inpatient setting: Findings from the biostat-chf study. Eur J Heart Fail. 2019;21:112–120 [PubMed: 30338883]
39. Greene SJ, Wilson LE, Abbasi SA, Yusuf AA, Hammill BG. Outpatient intravenous diuretic therapy for heart failure in the united states. J Am Coll Cardiol. 2019;73:1101–1103 [PubMed: 30846106]
40. Shen L, Jhund PS, Mogensen UM, Kober L, Claggett B, Rogers JK, McMurray JJV. Re-examination of the best trial using composite outcomes, including emergency department visits. JACC Heart Fail. 2017;5:591–599 [PubMed: 28774394]

41. Yeung DF, Boom NK, Guo H, Lee DS, Schultz SE, Tu JV. Trends in the incidence and outcomes of heart failure in ontario, canada: 1997 to 2007. CMAJ. 2012;184:E765–773 [PubMed: 22908143]
42. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu PL, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner BM, Mahaffey KW, Investigators CT. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019;380:2295–2306 [PubMed: 30990260]
43. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Furtado RHM, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Sabatine MS. Sglt2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: A systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019;393:31–39 [PubMed: 30424892]
44. Verma S, Juni P, Mazer CD. Pump, pipes, and filter: Do sglt2 inhibitors cover it all? Lancet. 2019;393:3–5 [PubMed: 30424891]
45. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Furtado RHM, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Sabatine MS. Comparison of the effects of glucagon-like peptide receptor agonists and sodium-glucose cotransporter 2 inhibitors for prevention of major adverse cardiovascular and renal outcomes in type 2 diabetes mellitus. Circulation. 2019;139:2022–2031 [PubMed: 30786725]
46. Furtado RHM, Bonaca MP, Raz I, Zelniker TA, Mosenzon O, Cahn A, Kuder J, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Nicolau JC, Gause-Nilsson IAM, Fredriksson M, Langkilde AM, Sabatine MS, Wiviott SD. Dapagliflozin and cardiovascular outcomes in patients with type 2 diabetes and prior myocardial infarction: A sub-analysis from declare timi-58 trial. Circulation. 2019
47. Arnold SV, Echouffo-Tcheugui JB, Lam CS, Inzucchi SE, Tang F, McGuire DK, Goyal A, Maddox TM, Sperling LS, Fonarow GC, Masoudi FA, Kosiborod M. Patterns of glucose-lowering medication use in patients with type 2 diabetes and heart failure. Insights from the diabetes collaborative registry (dcr). Am Heart J. 2018;203:25–29 [PubMed: 30015065]
48. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Bansilal S, Bhatt DL, Leiter LA, McGuire DK, Wilding JP, Gause-Nilsson IA, Langkilde AM, Johansson PA, Sabatine MS. The design and rationale for the dapagliflozin effect on cardiovascular events (declare)-timi 58 trial. Am Heart J. 2018;200:83–89 [PubMed: 29898853]
49. Junod S FDA and Clinical Drug Trials: A Short History In: Davies M, Kermani F, eds. A Quick Guide to Clinical Trials. 2nd ed. Rockville, MD: Bioplan, INc; 2016:25–55.
50. D'Agostino RB, Heeren TC. Multiple comparisons in over-the-counter drug clinical trials with both positive and placebo controls. Stat Med. 1991;10:1–6; discussion 7–31 [PubMed: 2006348]
51. Dmitrienko A, D'Agostino RB Sr. Multiplicity considerations in clinical trials. N Engl J Med. 2018;378:2115–2122 [PubMed: 29847757]
52. Food and Drug Administration. Multiple endpoints in clinical trials: guidance for industry. 2017 https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm536750.pdf. Accessed April 8, 2019.
53. European Medicines Agency. Points to consider on multiplicity issues in clinical trials. 2002 https://www.ema.europa.eu/en/documents/scientific-guideline/points-consider-multiplicity-issues-clinical-trials_en.pdf. Accessed April 9, 2019.
54. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med. 1997;336:525–533 [PubMed: 9036306]
55. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, Rocha R, Braunwald E, Investigators P-H. Angiotensin-neprilysin inhibition in acute decompensated heart failure. N Engl J Med. 2019;380:539–548 [PubMed: 30415601]
56. Packer M, Gheorghiade M, Young JB, Costantini PJ, Adams KF, Cody RJ, Smith LK, Van Voorhees L, Gourley LA, Jolly MK. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. Radiance study. N Engl J Med. 1993;329:1–7 [PubMed: 8505940]

57. SOLVD Investigators, Yusuf S, Pitt B, Davis CE, Hood WB Jr., Cohn JN Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med. 1992;327:685–691. [PubMed: 1463530]

58. SOLVD Investigators, Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med. 1991;325:293–302 [PubMed: 2057034]

59. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: The capricorn randomised trial. Lancet. 2001;357:1385–1390 [PubMed: 11356434]

60. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ Jr., Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The save investigators. N Engl J Med. 1992;327:669–677 [PubMed: 1386652]

61. Taylor AL, Ziesche S, Yancy C, Carson P, D'Agostino R Jr., Ferdinand K, Taylor M, Adams K, Sabolinski M, Worcel M, Cohn JN, African-American Heart Failure Trial I. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med. 2004;351:2049–2057 [PubMed: 15533851]

62. Bohm M, Borer J, Ford I, Gonzalez-Juanatey JR, Komajda M, Lopez-Sendon J, Reil JC, Swedberg K, Tavazzi L. Heart rate at baseline influences the effect of ivabradine on cardiovascular outcomes in chronic heart failure: Analysis from the shift study. Clin Res Cardiol. 2013;102:11–22 [PubMed: 22575988]

63. Patel RB, Vaduganathan M, Greene SJ, Butler J. Nomenclature in heart failure: A call for objective, reproducible, and biologically-driven terminology. Eur J Heart Fail. 2018;20:1379–1381 [PubMed: 29943879]

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 endpoint	Effect on primary endpoint(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	7,020	3.1 years	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 years	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 years	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	4,401	2.6 years	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 years	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	1,461	2.4 years	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	1,724	4.2 years	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	6,314	3.1 years	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	8,681	2.4 years	Composite of CVD, nonfatal MI, or nonfatal stroke	0.87 (0.76–1.01)	0.86 (0.69–1.06)	0.87 (0.72–1.06)	0.79 (0.57–1.09)

Trial Name	Therapy	N	Follow-up (median)	Primary endpoint	Effect on primary endpoint(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)
						0.88 (0.68–1.14)		
DECLARE-TIMI 58 (2019)[12]	Dapagliflozin	15,436	4.2 years	1) Composite of CVD, nonfatal MI, or nonfatal stroke. 2) CVD or HF hospitalization	1) 0.92 (0.82–1.02)	0.89 (0.77–1.04)	0.84 (0.72–0.99)	0.73 (0.58–0.92)
					2) 0.84 (0.72–0.99)	0.98 (0.80–1.20) [ischemic stroke]		

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HF, heart failure; hosp, hospitalization; HR, hazard ratio; MI, myocardial infarction; SGLT2, sodium glucose cotransporter 2

Table 2.

Select Past Examples of Use of Non-primary Endpoints and Regulatory Decisions for Heart Failure

DIG trial[54] • Digoxin did not meet the primary endpoint of all-cause mortality. • Digoxin showed a benefit for the non-primary endpoint 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 endpoint of all-cause mortality. • Enalapril showed a benefit for the non-primary endpoint 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 pre-specified primary endpoint, 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 co-primary endpoints 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 endpoints (sudden death, HF hospitalization). • Carvedilol was approved to reduce all-cause mortality and re-infarction in this patient population.

Abbreviations: HF, heart failure; HFrEF, heart failure with reduced ejection fraction

Table 3.

Summary Points and Recommendations

Characterization of Heart Failure in Cardiovascular Outcome Trials of Type 2 Diabetes Mellitus

- 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 endpoints reflect prevention of new-onset HF or treatment of pre-existing HF.
    - Lack of granular description of HF phenotype (e.g., 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 (e.g., 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.

Heart Failure Outcomes in Cardiovascular Outcome Trials of SGLT2 Inhibitors

- Four large trials (EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, CREDENCE) have consistently shown SGLT2 inhibitor therapy to decrease risk of HF hospitalization by 27–39%.
  - Trials include a combined 38,733 randomized patients and 1,192 HF hospitalization events.
  - Magnitude of benefit from SGLT2 inhibitor therapy on MACE was absent or modest relative to 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 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 Heart Failure and Non-primary Endpoints 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 co-morbid 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 endpoint or within a primary composite endpoint.

SGLT2 inhibitors and Heart Failure Hospitalization

- Based on consistent and clinically relevant benefits across four 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 T2DM patients similar to those enrolled in these trials.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CVOT, cardiovascular outcome trial; EF, ejection fraction; HF, heart failure; MACE, major adverse cardiovascular events; SGLT2, sodium glucose cotransporter 2