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# Prevalent and Incident Heart Failure in Cardiovascular Outcome Trials of Patients with Type 2 Diabetes

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## Abstract

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Despite multiple examples of glucose lowering therapies affecting heart failure (HF) risk, ascertainment of HF data in cardiovascular outcome trials of these medications has not been systematically characterized. In this review, large (N >1,000) published phase III/IV cardiovascular outcome trials evaluating glucose lowering therapies through June 2017 were identified. Data were abstracted from publications, Food and Drug Administration (FDA) Advisory Committee records, and FDA labeling documents. Overall, 21 trials including 152,737 patients were evaluated. Rates and definitions of baseline HF and incident HF were inconsistently provided. Baseline ejection fraction data were provided in 3 studies but not specific to patients with HF. No trial reported functional class, ejection fraction, or HF therapy at time of incident HF diagnosis. HF hospitalization data were available in 15 trials, but only 2 included a HF-related event within the primary composite endpoint. This systematic review highlights gaps in HF data capture within cardiovascular outcome trials of glucose lowering therapies and outlines rationale and strategies for improving HF characterization.

**Keywords**

heart failure; diabetes mellitus; clinical trial; medication; outcomes

Cardiovascular (CV) death is the leading cause of death among patients with type 2 diabetes mellitus (DM) (1–4). While several studies show an association between hemoglobin A1c lowering and reduction in microvascular events, including retinopathy and nephropathy, benefits for macrovascular disease risk and CV mortality had not been seen until recently (1,5,6). Based partly on a meta-analysis of 42 clinical trials that showed elevated risk of myocardial infarction with rosiglitazone, in 2008, the United States (U.S.) Food and Drug Administration (FDA) issued an industry guidance regarding the routine evaluation of CV risk for new therapies to treat type 2 DM (7,8). This guidance recommended establishment of independent CV endpoints committees for DM trials to prospectively adjudicate all CV events occurring across the phase II and phase III registration program, which should encompass major adverse CV events (MACE), including CV death, non-fatal myocardial infarction, and non-fatal stroke.(7) Additional endpoints for consideration included hospitalization for acute coronary syndrome and urgent revascularization procedures.

The FDA guidance document did not specifically mention heart failure (HF) as a condition or endpoint in DM trials. In recent years, a close relationship between DM and HF has become increasingly apparent. In a large observational study of patients with DM, HF was the second most common initial presentation of CV disease, after peripheral arterial disease. (9) Among older patients with DM, >20% have HF with a high proportion experiencing HF-related death (10). Likewise, among patients hospitalized for HF, the prevalence of DM may exceed 40% (11,12). Concomitant presence of both conditions worsens prognosis and complicates treatment. Moreover, data suggest strict glycemic control may not meaningfully change risk of HF in patients with DM and multiple trials of glucose lowering therapies have now been associated with increased or decreased risk of HF events, compared with placebo (13–18).

Despite these findings confirming important pathophysiologic and clinical interactions between DM and HF, compared to atherothrombotic cardiovascular events, the rigor with which HF data are ascertained within DM trials remains modest. Although recent publications have emphasized the need for improved description of HF events in DM trials, HF data capture within such trials has not been systematically characterized (18–20). We present a systematic review of the ascertainment of baseline HF, incident HF, and reporting of HF-related clinical events within published clinical trials of glucose lowering therapies.

## METHODS

**Data Sources and Search Strategy—**An extensive literature search was conducted using Cochrane library, EMBASE, PubMed, Scopus and ClinicalTrials.gov from the inception of these databases through June 2017 to identify publications from large (N >1,000) phase III or IV randomized clinical trials with primary clinical event endpoints evaluating glucose lowering therapies in adults >18 years of age. Medical subject headings and keywords used in the query included diabetes mellitus, glucose, sulfonylurea, metformin, glyburide, rosiglitazone, pioglitazone, glucose control, insulin, alogliptin, saxagliptin, sitagliptin, aleglitazar, sodium-glucose co-transporter 2 (SGLT-2) inhibitors, empagliflozin, canagliflozin, glucagon-like peptide 1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, liraglutide, semaglutide, lixisenatide, exenatide, and a combination of all these terms. Other data sources such as references of pertinent reviews and editorials from major medical journals were also searched. All publications indexed to a particular trial were screened, including the trial's dedicated design papers, when available. The search strategy did not include language limits. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram summarizing the search strategy and selected studies is presented in Figure 1.

### Study Selection

Studies identified through the search strategy were transferred to Endnote X8 (Clarivate Analytics, Philadelphia, Pennsylvania) where duplicates were removed. All remaining articles underwent a rigorous manual screen by two independent reviewers. Large studies (N >1,000) including primary data from randomized clinical trials of glucose lowering therapies among patients with type 2 DM were included. Review articles and non-randomized studies were excluded. Discrepancies in study selection were resolved by consensus or, when necessary, by a third reviewer.

**FDA Advisory Committee and Labeling Document Review 1996 to 2016—**To best ensure inclusion of any available but unpublished data from any given clinical trial included in this review, for each study therapy, FDA Advisory Committee documents and FDA medical review documents were reviewed for relevant HF trial data. Specifically, we identified all Endocrinologic and Metabolic Drugs Advisory Committee meetings related to glucose lowering therapies from 1996 to 2016 available on the FDA website. We then systematically reviewed each published meeting transcript for the following terms: "heart failure", "cardiomyopathy", "pulmonary edema", and "natriuretic peptide" (NP). Relevant meeting slides and minutes were also reviewed for corroborating information.

**Data Extraction—**All pertinent data were extracted from main manuscript texts, manuscript supplementary appendices and the aforementioned relevant FDA documents. All data were collected on a standardized form by two reviewers. The main outcome variables were the ascertainment and definitions of HF at baseline and during follow up. Specific data regarding the following elements were extracted:

1. *Baseline HF assessment:* Reporting of HF prevalence, definition for pre-existing HF, ejection fraction (EF), New York Heart Association (NYHA) class (data provided for patients or referenced in study selection criteria), NP level, and baseline HF therapy (including diuretic therapy).
2. *Incident HF during follow-up:* Ascertainment of new-onset HF, definition for new-onset HF, adjudication of new-onset HF, reporting of information at the time of new HF diagnosis (care setting of diagnosis, EF, NP level, HF therapies received), and clinical event reporting subsequent to new HF diagnosis.
3. *Resource utilization and outcomes:* Reporting of fatal HF events, HF hospitalizations, emergency department visits for HF, outpatient worsening HF, inclusion of a HF event within the primary composite trial outcome, and adjudication of reported HF events.

**Data Analysis—**As appropriate, descriptive analyses were performed, ranges were presented, and proportions were assessed. In circumstances where rates of baseline or incident HF for the overall study population were not provided, these rates were manually calculated from the raw trial data, when available. Analyses were performed using STATA version 14.0 (Stata Corporation, College Station, TX).

## RESULTS

### Studies

The initial query yielded a total of 8,447 potentially relevant abstracts, of which 4,478 remained after removing duplicates. Based on manual screen of each of the remaining articles, 4,457 articles did not meet the systematic review eligibility criteria and were excluded. The remaining 21 articles were included in the systematic review which included a total of 152,737 patients. Figure 1 shows a PRISMA flow chart outlining the search strategy. SGLT-2 inhibitors and DPP- 4 inhibitors were studied by 3 trials each, while peroxisome proliferator-activated receptor modulators and GLP-1 receptor agonists were studied by 4 trials each. Remaining trials evaluated other drug therapies (including insulin regimens) or the role of intensive glycemic control.

### Baseline Heart Failure

Of the 21 trials, prevalence of baseline HF was reported in 14 (67%) studies (Table 1). One study, the ORIGIN (Outcome Reduction with an Initial Glargine Intervention) trial, listed HF as an exclusion criterion. LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) and SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes) included NYHA class II–III HF as trial eligibility criteria in patients above the age

of 50 years.(21,22) Excluding ORIGIN, all trials not providing baseline HF prevalence were published prior to 2010. Among studies reporting baseline HF, prevalence ranged from 0.5% in the RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Combination Therapy for Type 2 Diabetes) trial to 27.9% in the EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care) trial (15,23).

Of trials with baseline HF documentation, only 1 provided a definition of baseline HF (17). The EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose) trial defined HF through a query of the Medical Dictionary for Regulatory Activities (17,24). No trial reported individual prevalence of HF with reduced versus preserved EF, incorporated NP data, or described therapy (and degree of optimization) among patients with baseline HF. Three studies provided EF data for the overall trial population (25–27). Baseline NP levels for the overall population were reported within the primary publication for 1 trial and secondary publications for 2 trials.(28–30) Data for NYHA class were inconsistently provided. Of publications where NYHA class was mentioned, most included only in the context of study selection criteria (e.g., exclusion of patents with NYHA class IV symptoms) and did not provide specific data on functional class of patients who were enrolled.

**Incident Heart Failure—**Of the 20 trials with published study results, 6 (30%) trials ascertained incident HF during study follow-up (Table 2). Rates of incident HF over follow-up ranged from 1.7% in the EXAMINE trial to 17.9% in the BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial.(23,27,29) In BARI 2D, new onset HF was an adjudicated adverse event, but the exact definition used was not published (27). Aside from BARI 2D, incident HF was either not directly adjudicated or the adjudication status was unclear. Additionally, these 5 other studies included non-specific definitions of new onset HF with 4 studies providing data for hospitalization for HF among patients without prior history of HF (28,29,31,32). The remaining study (EMPA-REG OUTCOME) reported data on introduction of loop diuretics during follow-up (24). No trial reported data on clinical characteristics at the time of incident HF diagnosis, including EF, NP level, or HF therapy received. Two trials provided data on longitudinal NP levels during follow-up, but not at the time of new HF diagnosis (28,29). No trial accounted for potential new HF diagnoses made in the ambulatory setting or during urgent care or emergency department visits. No trial reported outcome data subsequent to an incident HF event.

**Heart Failure Outcomes—**Table 3 summarizes data on HF events reported during follow-up. Among trials reporting HF events, all utilized a blinded adjudication procedure. The RECORD trial used a separate prospective and post hoc adjudication committee for HF events (15,33,34). In the PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events) trial, serious HF events were retrospectively reviewed in blinded fashion (35).

Data were most frequently reported for hospitalizations for HF, with such information published for 15 (75%) trials. Six trials provided rates of HF death for both study arms (14–17,36,37). A single trial, the PROactive trial, provided data regarding outpatient worsening HF.(37) The EMPA-REG OUTCOME trial expanded the hospitalization for HF event

definition to include emergency room visits and worsening HF (defined as presence of signs and symptoms of congestion requiring initiation or uptitration of HF therapies) after interim data unblinding to an independent monitoring team (17,24). No other trial had available data on rates of emergency department visits for HF. Three trials provided non-specific data on HF episodes during follow-up without detailing associated death, hospitalization, or need for escalated HF treatment (25,38,39). The ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trial reported a composite of HF events, including HF death, hospitalization for HF, or worsening NYHA class, but did not publish data on specific components.(13) Two studies, the VADT (Veterans Affairs Diabetes Trial) trial and the ORIGIN (Outcome Reduction with an Initial Glargine Intervention) trial, included a HF-related event within a primary composite endpoint.(32,36)

## DISCUSSION

This systematic review of 21 large CV outcomes trials testing a broad range of glucose lowering therapies highlights several key points:

1. There is limited characterization of the baseline prevalence, severity, or treatment optimization of HF.
2. Even in trials reporting baseline information, HF representation is variable and low, accounting for <15% of the total enrolled sample.
3. Only 30% of trials describe new-onset HF among patients without baseline HF and definitions of incident HF events were generally non-specific.
4. Only two trials include HF in a primary composite endpoint and few trials report adjudicated HF events outside of HF hospitalizations.

### An Unmet and Compelling Need

Accumulating data support an increasingly greater need to clearly appraise the potential benefits and harms of novel glucose lowering therapies in patients with or at risk for HF (Central Illustration). First, comorbid DM is present in a significant subset of patients with prevalent HF and is associated with heightened CV risk (10–12). The prevalence of HF is poised to increase given population trends towards increasing age, worsening comorbidity burden, and improved survival following myocardial infarction. Second, risk profiles of individuals with and without baseline HF may be markedly different. Judicious accounting and profiling of this HF subset in CV outcome trials of glucose lowering therapies will substantially influence the background risk of the trial cohort and the planned number of enrolled patients. Third, some glucose lowering therapies that improve overall CV outcomes in high-risk populations may not benefit patients with prevalent HF.(40) Fourth, HF-related events are frequently encountered in DM trials, and are perhaps more common than certain components of MACE, depending on the population studied. These events may preferentially drive treatment-related safety or efficacy. Unlike atherothrombotic events that may take time to accrue, mechanisms linking glucose lowering therapies with HF risk or benefit may operate on a shorter timescale (e.g., therapy induced changes in volume status influencing HF hospitalization risk), and may be more readily detectable during the course

of typical CV outcome trials. Fifth, there is convincing CV benefit with select agents from at least 2 major glucose lowering therapeutic classes, one of which (i.e., SGLT-2 inhibitors) appears to have profound effects on risk of HF hospitalization.(17,21,22) Finally, the US FDA has broadened the indications for use of empagliflozin and liraglutide to specifically reduce CV risk, the first clinical outcomes indications for any glucose lowering therapy for type 2 DM. Indeed, there is growing appreciation and interest within the cardiology community for utilization of novel DM therapies to mitigate CV risk (41).

## Heart Failure Risks and Benefits of Novel Diabetes Therapies

Although designed to detect risk of MACE, CV outcome trials for glucose lowering therapies have found certain agents to increase HF risk.(37,42–44) Most recently, DPP-4 inhibitors have been shown to heighten risk of HF, but this does not appear to be a class effect, and may be specific to saxagliptin.(28,29,45,46) In the SAVOR-TIMI (Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus–Thrombolysis In Myocardial Infarction) 53 trial, the risk of HF appeared to drive the safety hazard associated with the drug, and was more frequently observed than certain components of the primary endpoint (i.e., stroke) (47). As such, regulatory warnings have been issued and U.S. product labels modified to acknowledge potential HF risks with use of saxagliptin. The U.S. FDA now suggests judicious use of the DPP-4 inhibitor class in patients at risk for HF.

Despite the original purpose for confirming safety, outcome data from large, phase IV outcome trials has led to efficacy indications within 2 classes of glucose lowering therapies; GLP-1 receptor agonists and SGLT-2 inhibitors. However, although 2 large clinical trials studying the GLP-1 receptor agonists liraglutide and semaglutide showed reductions in the primary composite CV endpoint, no clear effects on risk of HF hospitalization were demonstrated.(21,22) Indeed, in 2 phase II studies, liraglutide did not improve clinical outcomes in patients with reduced EF and some have speculated that the GLP-1 receptor agonist mechanism may not be consistent with HF benefits (40,48,49).

Although the mechanism of therapeutic effects of SGLT-2 inhibitors requires further study, benefits appear at least partly mediated by effects on hemodynamic and congestive status. (50,51) The EMPA-REG OUTCOME trial found empagliflozin therapy to result in a pronounced and early lowering of risk of MACE, driven by reductions in CV death, along with reductions in HF events in patients with type 2 DM and established CV disease (10% of whom carried a history of HF at enrollment)(17,24). Similarly, the benefits of empagliflozin on CV death and HF hospitalization were consistent across the spectrum of low to high incident HF risk.(52) In the paired CANVAS (Canagliflozin Cardiovascular Assessment Study) trials of patients with type 2 DM at high CV risk (14% of whom had a baseline HF diagnosis), canagliflozin reduced the primary composite CV endpoint at the expense of heightened risk of lower extremity amputations.(53) In addition, canagliflozin demonstrated marked reductions in the risk of HF hospitalization and progression of renal disease (53).

## Future Trials of Novel Glucose Lowering Therapies

Despite recent progress and converging lines of evidence regarding the general CV effects of novel glucose lowering therapies, the specific risk-benefit profile of these therapies with respect to HF remains uncertain. As such, a number of phase III clinical trials of SGLT-2 inhibitors in HF patients are currently ongoing, including EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction; NCT03057977), EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction; NCT03057951), and Dapa-HF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure; NCT03036124).(50,54)

Moving forward, we strongly recommend that CV outcome trials of glucose lowering therapies are viewed in the context of 2 distinct but important goals for purposes of HF: a) evaluation of downstream incident HF among those *without* HF at baseline, and b) evaluation of safety and/or efficacy signals among those *with* prevalent HF at baseline. As such, subgroup analysis by presence or absence of baseline HF should be standard and adequate enrollment of both subgroups should be ensured to allow for meaningful analysis. Although dedicated trials of glucose lowering therapies among patients with established HF will likely remain necessary for purposes of drug labeling and changing HF guidelines, we believe that accurately defining and characterizing HF within CV outcome trials is critical for successful application of safety and efficacy findings to routine clinical practice. Moreover, and perhaps underappreciated, we believe that CV outcome trials may have the important potential to inform HF prevention strategies and potentially change prevention guidelines (although dedicated trials would likely be required for class I recommendations). Acknowledgement of these 2 discrete objectives sets a framework for specific strategies aimed at improving HF characterization in future CV outcome trials of glucose lowering therapies. To define the CV profile of these agents more comprehensively, we propose a modified approach in emerging CV outcome trials of glucose lowering therapies focused on the following elements:

1. **Population Enrolled:** CV outcome trials should routinely enroll sufficient number of patients with baseline HF to allow meaningful evaluation of therapeutic safety in this subgroup. The proportion of patients enrolled with manifest HF in EMPA-REG OUTCOME and CANVAS were <15%.(17,53) Likewise, despite specifying NYHA class II–III HF as a means of meeting trial inclusion criteria, LEADER only enrolled ~18% patients with HF at baseline. Given the substantial overlap between HF and DM in routine practice, robust representation of HF patients in CV outcome trials must be a priority to adequately evaluate safety. Moreover, although the threshold for declaring therapeutic efficacy must remain higher than that for raising safety concerns, improved enrollment of HF patients should be strongly considered to generate a subgroup with sample size sufficient for exploring potential HF efficacy signals worthy of further dedicated study.

2. **Improved Data Collection:** Routine assessment of cardiac imaging and biomarkers parameters would add significant additional cost and complexity to CV outcome trials. Thus, collection of these data should be guided largely by the presence or absence of baseline HF. For example, when assessing HF prevention in patients without baseline HF, prospective routine collection of these tests cannot be recommended for cost and logistical reasons. However, for such patients who develop new-onset HF during study follow-up, the majority likely undergo such testing locally as part of routine clinical care at the time of the suspected incident HF event (e.g., echocardiogram, NP level testing); acquisition of these data would be invaluable in characterizing potential treatment-related adverse HF effects (e.g., incident HF with reduced versus preserved EF, HF severity at diagnosis) and would carry only modest incremental cost to the trial. In contrast, for patients with an existing diagnosis of HF at trial enrollment, we believe added prospective data collection at baseline is imperative to best explore the impact of therapy in various HF subsets based on EF, baseline HF therapy, and severity of disease. More granular data from patients with prevalent HF would better inform a) the application of trial findings to the general DM population with concomitant HF, and b) design of dedicated HF trials should a therapeutic indication for the treatment of HF be pursued.

3. **Standardized Event Ascertainment:** HF events should be prospectively and clearly defined with objective criteria. Indeed, evolution in the definition of HF hospitalization (with liberalization to include emergency room visits and worsening HF) during the EMPA-REG OUTCOME trial, together with incomplete baseline HF profiling, contributed to the FDA considering the HF-based results exploratory and in need of further confirmation. In and of themselves, clinical signs and symptoms for HF may be non-specific and may therefore preclude accurate endpoint assessment. However, documentation of escalation of HF care for such signs and symptoms, such as treatment with intravenous diuretics, would more definitively confirm a HF event by linking a subjective clinician assessment with an objective therapeutic decision. The multidisciplinary Clinical Data Interchange Standards Consortium (CDISC) task force has provided guidance regarding the specific ascertainment of HF events, as employed in SAVOR-TIMI 53.(16,55,56) In addition, the Cardiovascular Safety Research Consortium has designed comprehensive examples of HF case report forms that may be adapted for use in trials of glucose lowering therapies.(57) In this systematic review, we found that no trial reported data for CV biomarkers, such as NPs, to contextualize the HF event definition. Assessment of NP level is inexpensive, widely utilized, and may improve the diagnostic accuracy of HF-related events. When available, trials should collect local NP level and other relevant data (e.g., cardiac imaging) from the time of a suspected HF event. Although differences in local laboratory assays could impede interpretation of NP data collected at the time of HF events, data reflecting levels in relation to local upper reference limits could be considered. We believe standardized definitions are critical for evaluating the impact of HF events on

other clinical outcomes. Indeed, although worsening HF events have been generally associated with poor subsequent prognosis, whether this relationship is consistent in the settings of specific glucose lowering therapies needs further study.(58)

4. **Centralized and Independent Endpoint Adjudication:** Despite potential incremental costs, we recommend incident and worsening HF events be adjudicated by an independent clinical events committee. The exact handling of these events within the trial design and statistical analysis plan can be debated and may vary by situation, but potential options include incorporation of a HF endpoint within a single extended MACE definition, co-primary endpoints with traditional and extended MACE endpoints, or a separate worsening HF composite or hierarchical endpoint.(40) Regardless, given variation in global trial conduct, biomarker ascertainment, and thresholds for patient and clinician hospitalization decisions, adjudication of HF events within DM trials should be strongly considered and is consistent with recommendations applied towards other types of outcome trials.(59) In future trials, we propose a worsening HF event be defined as worsening signs and symptoms of HF with confirmation of elevated NP level and requiring urgent or emergent treatment (e.g., intravenous diuretic administration). Consistent with evolving practice in HF clinical trials and accumulating data suggesting similarly poor prognosis for worsening HF patients in the inpatient and outpatient care settings, we suggest CV outcome trials consider capture of worsening HF events (according to pre-specified criteria) irrespective of the location of care (including ambulatory clinics, urgent care facilities, emergency departments, and hospitals).(58,60–62) Although such a procedure may carry a modest increase in trial cost and complexity, inclusion of the spectrum of worsening HF events may improve power for detecting therapeutic signals and would be congruent with trends among healthcare systems towards increasing emphasis on outpatient management of worsening HF to decrease costs associated with hospitalization.(62,63)

## Limitations

We recognize that a more comprehensive approach towards HF ascertainment in future trials has its limitations. Increasing the number of enrolled HF patients and HF-related data collection increases the cost and complexity of trial programs and may conflict with recent emphasis on pragmatic and streamlined trial design.(64) Additionally, biomarkers to aid in HF event ascertainment or adjudication are subject to significant variation with respect to rigor in collection and cut-offs employed. Furthermore, any transition from a traditional 3-component MACE to an extended MACE with a HF endpoint could dilute a signal for atherothrombotic CV events. Such concerns could be mitigated with incorporation of HF events as a co-primary or secondary endpoint. Regarding limitations specific to the present systematic review, although we carefully reviewed trial publications, FDA labeling documents, and FDA Advisory Committee records, it is possible that such retrospective data extraction was incomplete and we cannot rule out presence of additional collected, but unpublished, data by study sponsors or investigators. This limitation further underscores the

need for prospective and complete publication of HF-related data from trials of glucose lowering therapies going forward.

### Conclusions

Although others have called for greater focus on HF events in clinical trials of novel glucose lowering therapies, we present a comprehensive systematic review examining the ascertainment of HF data.(19,20) Even recently completed large CV outcome trials of novel glucose lowering agents lack sufficient details to fully appraise treatment effects on a HF endpoint or relative safety in patients with prevalent HF. Given increasing attention towards the variable risk of HF events with various glucose lowering therapies and drug classes, we believe limitations in these pre- and post-marketing trial experiences have hindered thorough understanding of the utility of novel glucose lowering therapies with respect to HF prevention, safety, and treatment. We strongly suggest that future CV outcome trials of glucose lowering therapies enroll a proportion of patients with baseline HF similar to the prevalence of HF in the general type 2 DM population. Improved data collection within such trials should include detailed profiling of patients with baseline HF and a rigorous assessment of downstream incident and worsening HF events using pre-specified and adjudicated endpoints. We believe these added efforts towards improved HF characterization within CV outcome studies of glucose lowering therapies have the important potential to a) inform HF prevention strategies b) better define the safety profile of glucose lowering therapies among the general type 2 DM population with respect to HF, and c) better inform the utility and design of dedicated trials evaluating the efficacy of glucose lowering therapies as potential treatments specifically for HF.

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## ABBREVIATIONS

| | |
|---|---|
| **CV** | cardiovascular |
| **DM** | diabetes mellitus |
| **DPP-4** | dipeptidyl peptidase-4 |
| **EF** | ejection fraction |
| **FDA** | U.S. Food and Drug Administration |
| **GLP-1** | glucagon-like peptide 1 |
| **HF** | heart failure |
| **MACE** | major adverse cardiovascular events |
| **NP** | natriuretic peptide |

**SGLT-2** sodium-glucose co-transporter 2

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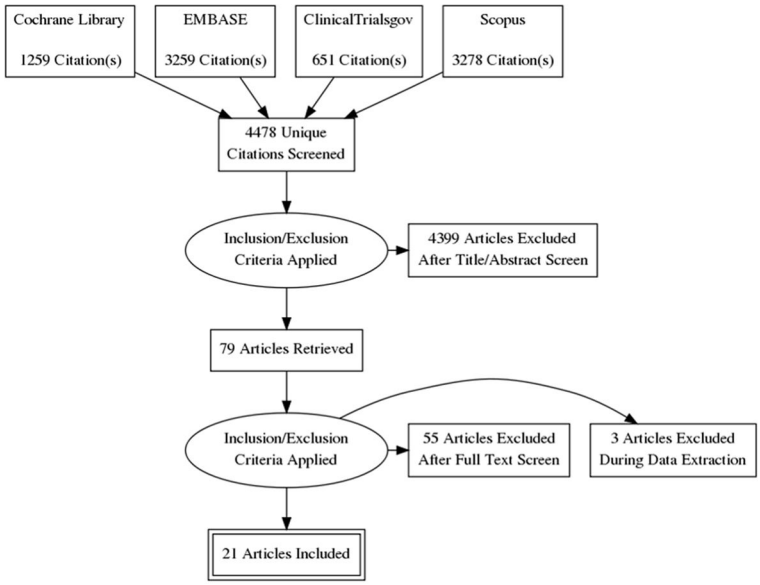
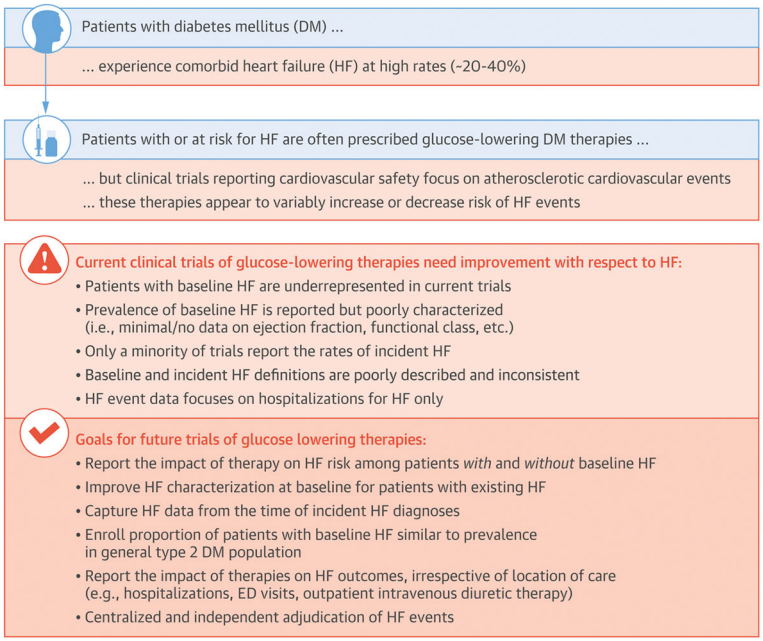



**Figure 1. PRISMA Flow Diagram of Search Strategy and Study Selection**

Abbreviations: PRISMA= Preferred Reporting Items for Systematic Reviews and Meta-Analyses.




**Central Illustration. Framework for Improving Characterization of Heart Failure in Cardiovascular Outcome Trials of Patients with Diabetes**

DM, diabetes mellitus; ED, emergency department; EF, ejection fraction; HF, heart failure; IV, intravenous; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

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**Table 1**

Reporting of baseline heart failure among cardiovascular outcomes trials of glucose lowering medications

| Trial | Drug class / Intervention | N | HF reported? | Definition of baseline HF | Proportion of HF | Ejection fraction reported? | NYHA class reported?* | Natriuretic peptide level reported? | HF treatment reported? |
|---|---|---|---|---|---|---|---|---|---|
| **EXSCEL (2017)**(26) | GLP-1 receptor agonists | 14,752 | Yes | not described | 16.2% | Yes | Yes | No | No |
| **CANVAS (2017)**(53) | SGLT-2 inhibitors | 4,330 | Yes | not described | 11.9% | No | Yes | No | No |
| **CANVAS-R (2017)**(53) | SGLT-2 inhibitors | 5,812 | Yes | not described | 16.3% | No | Yes | No | No |
| **LEADER (2016)**(21) | GLP-1 receptor agonists | 9,340 | Yes | not described | 17.8% | No | Yes | No | No |
| **SUSTAIN 6 (2016)**(22) | GLP-1 receptor agonists | 3,297 | Yes | not described | 23.6% | No | Yes | No | No |
| **EMPA-REG OUTCOME (2015)**(17,24) | SGLT-2 inhibitors | 7,020 | Yes | described | 10.1% | No | Yes | No | Yes† |
| **ELIXA (2015)**(31) | GLP-1 receptor agonists | 6,068 | Yes | not described | 22.4% | No | Yes | No | No |
| **TECOS (2015)**(65) | DPP-4 inhibitors | 14,671 | Yes | not described | 18.3% | No | Yes | No | No |
| **AleCardio (2014)**(30) | PPAR modulator | 7,226 | Yes | not described | 10.5% | No | Yes | Yes | No |
| **EXAMINE (2013)**(23,29) | DPP-4 inhibitors | 5,380 | Yes | not described | 27.9% | No | Yes | Yes | No |
| **SAVOR-TIMI 53 (2013)**(16,28) | DPP-4 inhibitors | 16,492 | Yes | not described | 12.8% | No | No | Yes[c] | No |
| **ORIGIN (2012)**(32) | Glargine insulin | 12,537 | HF listed as exclusion criterion | - | - | No | - | No | - |
| **BARI 2D (2009)**(27) | Oral glucose lowering therapy vs. insulin provision | 2,368 | Yes | not described | 6.7% | Yes | Yes | No | No |
| **RECORD (2009)**(15) | PPAR modulator | 4,447 | Treatment for HF listed as exclusion criterion but baseline HF was reported | not described | 0.5% | No | No | No | No |
| **HEART2D (2009)**(25) | Prandial vs. basal insulin | 1,115 | No | - | - | Yes | - | No | - |
| **VADT (2009)**(36,66,67) | Intensive glucose therapy | 1,791 | No | - | - | No | Yes | No | - |
| **ACCORD (2008)**(14) | Intensive glucose therapy | 10,251 | Yes | not described | 4.9% | No | Yes | No | No |
| **ADVANCE (2008)**(13) | Intensive glucose therapy | 11,140 | No | - | - | No | - | No | - |
| **ADOPT (2006)**(39) | Thiazolidinedione vs. Metformin vs. Sulfonylurea | 4,360 | HF listed as exclusion criterion | - | - | No | Yes | No | - |
| **PROactive (2005)**(37) | PPAR modulator | 5,238 | No | - | - | No | Yes | No | - |
| **UKPDS (1998)**(38) | Intensive glucose therapy | 5,102 | No | - | - | No | - | No | - |

Abbreviations: DPP = dipeptidyl peptidase; GLP = glucagon-like peptide; HF = heart failure; PPAR = peroxisome proliferator-activated receptor; SGLT = sodium-glucose co-transporter

*Data provided or referenced in trial selection criteria

†Although most HF patients were treated with renin-angiotensin-aldosterone-system inhibitors and beta-blockers, no data were available regarding doses of drugs, other therapies in the chronic HF armamentarium, or degree of optimization.

‡Baseline NT-proBNP data available for 12,301 patients

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**Table 2**

Trials assessing incident heart failure during study follow-up

| Trial | Definition of new onset HF | Adjudicated results? | % new onset heart failure during trial follow-up | Specify inpatient vs. outpatient diagnosis of new HF? | Ejection fraction at HF diagnosis reported? | Natriuretic peptide at HF diagnosis reported? | Characterize HF treatment at time of new HF diagnosis? | Characterize clinical events subsequent to new HF diagnosis? |
|---|---|---|---|---|---|---|---|---|
| **EMPA-REG OUTCOME (2015)**(17,24) | Data provided on introduction of loop diuretics | Unclear if introduction of loop diuretics adjudicated | 10.2% | No | No | No | No* | No |
| **ELIXA (2015)**(31) | Data provided on hospitalization for HF among patients without prior HF | HF hospitalization adjudicated | 2.4% | Inpatient | No | No | No | No |
| **EXAMINE (2013)**(23,29) | Data provided on hospitalization for HF among patients without prior HF | HF hospitalization adjudicated | 1.7% | Inpatient | No | No† | No‡ | No |
| **SAVOR-TIMI 53 (2013)**(16,28) | Data provided on hospitalization for HF among patients without prior HF | HF hospitalization adjudicated | 2.3% in saxagliptin arm; 1.7% in placebo arm§ | Inpatient | No | No | No// | No |
| **ORIGIN (2012)**(32) | Data provided on hospitalization for HF in setting of baseline HF listed as trial exclusion criterion | HF hospitalization adjudicated | 5.2% | Inpatient | No | No | No | No |
| **BARI 2D (2009)**(27) | Not provided | Yes | 17.9% | No | No | No | No | No |

Abbreviations: HF = heart failure

*Analyses compared adjudicated and investigator-reported HF events with new initiation of loop diuretics.

†Longitudinal NT-proBNP data provided for trial patients with and without baseline HF, but not provided at time of new onset HF event.

‡Data regarding new initiation of loop diuretics by treatment arm in those with or without baseline HF were available.

§Data represent 2-year study follow-up.

//US Food and Drug Administration Advisory Committee records included information on symptoms and HF therapies at time of hospitalization for HF, but did not distinguish between event representing incident HF versus worsening of established HF.

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**Table 3**

Heart failure outcome reporting among cardiovascular outcome trials of glucose lowering medications

| Trial | Reporting of fatal HF events? | Reporting of HF hospitalizations? | Reporting of HF emergency visit? | Reporting of outpatient worsening HF? | HF-event part of the primary composite endpoint? | Adjudication of reported HF events? |
|---|---|---|---|---|---|---|
| **CANVAS (2017)**(53) | No | Yes | No | No | No | Yes |
| **CANVAS-R (2017)**(53) | No | Yes | No | No | No | Yes |
| **LEADER (2016)**(21) | No | Yes | No | No | No | Yes |
| **SUSTAIN 6 (2016)**(22) | No | Yes | No | No | No | Yes |
| **EMPA-REG OUTCOME (2015)**(17,24) | Yes | Yes | No* | No | No | Yes |
| **ELIXA (2015)**(31) | No | Yes | No | No | No | Yes |
| **TECOS (2015)**(65) | No | Yes | No | No | No | Yes |
| **AleCardio (2014)**(30) | No | Yes | No | No | No | Yes |
| **EXAMINE (2013)**(23,29) | No | Yes | No | No | No | Yes |
| **SAVOR-TIMI53 (2013)**(16,28)† | Yes | Yes | No | No | No | Yes |
| **ORIGIN (2012)**(32) | No | Yes | No | No | Yes | Yes |
| **BARI 2D (2009)**(27) | No | No | No | No | No | - |
| **RECORD (2009)**(15,33,34) | Yes | Yes | No | No | No | Yes‡ |
| **HEART2D (2009)**(25)§ | No | No | No | No | No | - |
| **VADT (2009)**(36,66) | Yes | Yes‖ | No | No | Yes | Yes |
| **ACCORD (2008)**(14) | Yes | Yes# | No | No | No | Yes |
| **ADVANCE (2008)**(13)** | No | No | No | No | No | - |
| **ADOPT (2006)** (39)†† | No | No | No | No | No | - |
| **PROactive (2005)**(37) | Yes | Yes | No | Yes | No | Yes‡‡ |
| **UKPDS (1998)**(38)§§ | No | No | No | No | No | - |

Abbreviations: HF = heart failure

*The hospitalization for HF event definition was expanded during the trial to include overnight admissions, emergency room visits, and inpatient stays requiring changes in oral diuretics (not just intravenous diuretics), but data isolated to emergency room visits are not reported

†Defined based on the standardized Clinical Data Interchange Standards Consortium event definitions

‡HF death was prospectively adjudicated. Subsequently, HF death and HF hospitalization events underwent a separate post-hoc adjudication process.

§Reported rates of “congestive heart failure” as an adjudicated individual outcome during follow-up. Precise definition not reported.

//Congestive heart failure defined by International Classification of Diseases, Ninth Revision code as “≥1 inpatient occurrence primary discharge.”

#HF events were discussed during the Food and Drug Administration Advisory Committee meeting

**Primary manuscript reports the rate of heart failure, defined as the composite of death due to heart failure, hospitalization for heart failure, or worsening New York Heart Association class. Data for individual endpoint components not provided.

††“Congestive heart failure” data represented investigator-reported adverse event. Precise definition not reported.

##Post-hoc retrospective adjudication of HF death and HF hospitalization.

§§Heart failure endpoint defined by clinical symptoms (not associated with myocardial infarction) confirmed by Kerley B lines, râles, raised jugular venous pressure, or third heart sound. No precise data reported for fatal HF events or HF hospitalization