Incidence of Hospitalization for Heart Failure Relative to Major Atherosclerotic Events in Type 2 Diabetes: A Meta-analysis of Cardiovascular Outcomes Trials

Julian W. Sacre,[1] Dianna J. Magliano,[2,3] and Jonathan E. Shaw[1]

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META-ANALYSIS

BACKGROUND

Emerging evidence points to heart failure as being a common first presentation of cardiovascular (CV) disease in type 2 diabetes.

PURPOSE

The purpose of this study was to determine whether hospitalization for heart failure (HHF) occurs more or less frequently than major adverse CV events (MACE) in people with type 2 diabetes.

DATA SOURCES

Placebo arms of CV outcomes trials in type 2 diabetes were included.

STUDY SELECTION

Sixteen CV outcomes trials were selected, including five dipeptidyl peptidase 4 inhibitor trials, seven glucagon-like peptide 1 receptor agonist trials, and four sodium–glucose cotransporter 2 inhibitor trials.

DATA EXTRACTION

We extracted incidence rates of HHF, myocardial infarction (MI), stroke, and the composite outcomes of CV death or HHF and MACE (CV death, nonfatal MI, or nonfatal stroke).

DATA SYNTHESIS

In two trials enriched with people with chronic kidney disease, HHF was more common than both MI and stroke. Among the remaining 14 trials, HHF was less frequent than MI in 13 (93%), with this difference being significant in 8 (57%); however, HHF surpassed stroke in all but 1 study (93%; significant in 7 studies [50%]). Heterogeneity among trials was moderate/high (I^2 >50%) and partly explained by HHF/MI correlating with age and previous MI history ($P < 0.05$). In seven trials that reported events stratified by presence/absence of preexisting CV disease, ratios of HHF/MI and HHF/stroke were similar between groups.

LIMITATIONS

Enrichment of trial populations with those at high risk of CV events limits generalizability.

CONCLUSIONS

Although less frequent than MI, HHF is a common event in type 2 diabetes, both in those with and those without prior CV disease.

[1]Clinical Diabetes and Epidemiology, Baker Heart and Diabetes Institute, Melbourne, Victoria, Australia
[2]Diabetes and Population Health, Baker Heart and Diabetes Institute, Melbourne, Victoria, Australia
[3]School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia

Corresponding author: Julian W. Sacre, julian.sacre@baker.edu.au

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Heart failure in people with type 2 diabetes has a poor prognosis marked by worse mortality outcomes than in many other diabetes-related cardiovascular (CV) diseases, including myocardial infarction (MI) (1). The extent to which heart failure in type 2 diabetes reflects antecedent ischemic or other concurrent heart disease, or is a direct consequence of diabetes per se ("diabetic cardiomyopathy"), remains contentious (2). Regardless of the etiology, there appears to be a sizeable proportion of individuals with type 2 diabetes for whom heart failure represents the first presentation of CV disease. Indeed, in a U.K. primary care–based study of 34,198 individuals with type 2 diabetes without prior CV disease, heart failure was a more frequent initial presentation of CV disease than was nonfatal MI (14.1% vs. 11.5% of presentations) (3). However, a limitation of these estimates, and indeed of most epidemiological studies examining heart failure in diabetes, is a reliance on clinical and administrative coding and the inherent subjectivity involved in heart failure diagnoses. Since adjudication by independent clinical events committees is the gold standard for assessing heart failure (4,5), a more robust determination of the incidence of heart failure relative to other CV events in type 2 diabetes may come from clinical trials. Although atherosclerotic CV disease continues to be the primary focus of trials of new glucose-lowering therapies, as reflected by three-point major adverse CV events (MACE) (i.e., nonfatal MI, nonfatal stroke, or CV death) persisting as the preferred primary end point, hospitalization for heart failure (HHF) has also been consistently reported in recent years (1). However, to our knowledge, the incidence of HHF in these trials relative to traditional MACE has not been examined. We therefore extracted data on HHF and other CV events from the placebo arms of CV outcomes trials in type 2 diabetes that have been conducted since the 2008 mandate by regulatory authorities for new glucose-lowering treatments to demonstrate CV safety (6) (the definition of HHF having remained relatively consistent since this guidance was introduced [7]). The incidence of HHF relative to MI, stroke, and other relevant end points was assessed both overall and after stratification according to CV disease history.

METHODS

Study Selection

CV outcomes trials conducted in type 2 diabetes after the 2008 guidance (6) are well documented ($n = 16$) and cover three major classes of glucose-lowering drugs: dipeptidyl peptidase 4 inhibitors (DPP4is) (i.e., SAVOR [Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus] [8], EXAMINE [Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care] [9], TECOS [Trial Evaluating Cardiovascular Outcomes With Sitagliptin] [10], OMNEON [Study to Assess Cardiovascular Outcomes Following Treatment With Omarigliptin (MK-3102) in Participants with Type 2 Diabetes Mellitus] [11], and CARMELINA [Cardiovascular and Renal Microvascular Outcome Study With Linagliptin] [12]), glucagon-like peptide 1 receptor agonists (GLP-1RAs) (ELIXA [Evaluation of Lixisenatide in Acute Coronary Syndrome] [13], LEADER [Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results] [14], SUSTAIN-6 [Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes] [15], EXSCEL [Exenatide Study of Cardiovascular Event Lowering] [16], HARMONY [Albiglutide and Cardiovascular Outcomes in Patients With Type 2 Diabetes and Cardiovascular Disease] [17], REWIND [Researching Cardiovascular Events with a Weekly Incretin in Diabetes] [18], and PIONEER 6 [Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes] [19]), and sodium–glucose cotransporter 2 inhibitors (SGLT2is) (EMPA-REG OUTCOME [BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients] [20], CANVAS [Canagliflozin Cardiovascular Assessment Study Program] [21], DECLARE [Dapagliflozin Effect on Cardiovascular Events] [22], and CREDENCE [Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation] [23]). The strategy to identify and synthesize data for the current meta-analysis was therefore based on sourcing results from these known trials rather than a de novo literature search to identify potentially eligible studies (which would include older trials with nonconcordant heart failure end points) (7). All 16 trials met the following selection criteria: *1*) study population restricted to adults with type 2 diabetes; *2*) inclusion of a placebo arm; and *3*) CV outcomes including (at a minimum) HHF, MI, and stroke and all adjudicated according to definitions consistent with American College of Cardiology Foundation/American Heart Association recommendations (24).

Data Sources and Searches

Relevant data were extracted from multiple sources. First, we performed a PubMed search for all published articles arising from the 16 trials. The search strategy combined trial acronym and drug name terms (e.g., "REWIND" + "dulaglutide"), with results limited to reports of clinical trials and published no earlier than September 2013 (i.e., when the first of these trials [SAVOR and EXAMINE] were published). As of May 2020, 151 articles were returned by this search. In extracting data, we prioritized those articles that reported on the trial's primary end points. When specific variables or relevant subgroup results were missing, we scrutinized each of the following: *1*) secondary trial publications identified in our search, *2*) data publicly available on the trial's website (including links to published abstracts), *3*) reports on the websites of the sponsoring pharmaceutical company or relevant regulatory authorities (U.S. Food and Drug Administration and European Medicines Agency), and *4*) requests submitted directly to the study investigators or sponsor (for any outstanding missing data items). Full details of trial-specific data sources are described in the Supplementary Material.

Data Extraction

MI, stroke, HHF, and related composite end points, including "CV death or HHF" and three-point MACE (MI, stroke, or CV death), were extracted from the placebo arms of each trial. For individual events, incidence rates reflected the total number of participants who had the event during trial follow-up, not just the number of participants for whom the event was the first occurrence of a component of a composite end point (e.g., incidence rates of MI reflected the total number of participants who experienced one or more MIs during the trial rather than the smaller number of participants for whom MI was the first MACE). To maximize between-trial consistency, incidence rates

of MACE and its individual components exclusive of silent MIs and fatal events were prioritized (further details provided in the Supplementary Material, including Supplementary Figs. 1 and 2). For trials that reported results separately in individuals with established CV disease at baseline and in those with multiple risk factors (MRFs) for CV disease, subgroup-level incidence rates were also derived (specific eligibility criteria for these subgroups are listed in Supplementary Table 1). We then calculated the following incidence rate ratios (IRRs) and corresponding 95% CIs: HHF/MI, HHF/stroke, and "CV death or HHF"/MACE.

The following baseline clinical characteristics were extracted (for both the total population and each study subgroup, where available): mean age; BMI; glycated hemoglobin; diabetes duration; male/female distribution; proportions with established CV disease, history of MI, cerebrovascular disease, heart failure, and chronic kidney disease (CKD) (albuminuria and estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2); and proportion treated with insulin. Where these characteristics were unavailable for the placebo group only, summary data from the whole trial cohort were used.

Data Synthesis and Analysis

IRRs were pooled through random-effects meta-analysis using Stata 14 statistical software (StataCorp, College Station, TX). Heterogeneity was quantified by the I^2 and Cochran Q method, with I^2 thresholds of 25%, 50%, and 75% interpreted as indicating low, moderate, and high heterogeneity, respectively. Meta-regression was conducted to understand the relationship between IRRs and trial design/population factors. Comparisons of IRRs between CV disease and MRF subgroups were made through meta-regression modeling that tested for the effect of subgroup (CV disease vs. MRF) after accounting for the between-trial variation and subgroup-level covariates (e.g., percent male within the CV disease and MRF subgroups). $P < 0.05$ was considered statistically significant.

RESULTS

Characteristics of the 16 trial population placebo arms are displayed in Table 1. Two trials (CARMELINA and CREDENCE) were specifically enriched for participants with CKD (~60% with eGFR <60 mL/min/1.73 m^2 vs. 9–30% otherwise). Of the remaining 14 trials, 6 included only participants with established CV disease, and 8 featured both CV disease and MRF subgroups (where MRF as a proportion of the total ranged from 21% in SAVOR to 69% in REWIND). Mean age (range 60–66 years) and BMI (range 29–33 kg/m^2) were similar across all trials, as were proportions of men (range 60–72%, except for REWIND at 54%) and White race/ethnicity (66–85%). More variation was noted with respect to diabetes duration (range 7–16 years), glycated hemoglobin (7.2–8.7%), and proportions treated with insulin (23–65%). History of heart failure at baseline ranged from 9% to 28%. The pooled population (n = 69,031) had a median follow-up ranging from 1.3 to 5.4 years, during which 3,269 participants experienced a nonfatal MI, 1,720 experienced a nonfatal stroke, and 2,455 had an HHF event. Supplementary Fig. 3 displays the incidence rates of these events, by trial.

HHF Relative to MI

IRRs for HHF/MI are displayed in Fig. 1*A*. Data for the two CKD-enriched trials were pooled separately given that they demonstrated substantively higher ratios than non–CKD-enriched trials ($P = 0.001$, with HHF > MI in both CKD-enriched trials). Although high heterogeneity ($I^2 = 86.7\%$; $P < 0.001$) among the remaining 14 trials precluded a reliable single pooled estimate of the IRR, MI was the more common event in all but 1 trial (93%), with the difference being statistically significant in 8 trials (57%). After adjusting for CKD enrichment as a categorical covariate (i.e., to adjust for the divergent results in CARMELINA and CREDENCE), meta-regression models demonstrated significant associations of HHF/MI with age (13% higher per 1-year increase [5–21%]) and MI history (8% higher per 10% lower proportion with prior MI [1–14%]). However, these covariates accounted for a relatively small proportion of the total heterogeneity (residual $I^2 \geq 70\%$). Borderline significant associations were also detected with male/female distribution (31% higher HHF/MI per 10% lower proportion of men [−6% to 82%]; $P = 0.099$), baseline CV disease history (7% higher HHF/MI per 10% lower proportion with prior CV disease [0% to 15%]; $P = 0.063$), baseline heart failure history (25% higher HHF/MI per 10% lower proportion with prior heart failure [−4% to 62%]; $P = 0.091$), and enrollment of a post–acute coronary syndrome population (i.e., the two trials ELIXA and EXAMINE, in which HHF/MI trended lower vs. all others; $P = 0.076$). Meta-regression results were similar in sensitivity analyses restricted to the 14 non–CKD-enriched trials.

HHF Relative to Stroke

IRRs for HHF/stroke are displayed in Fig. 1*B*. CKD-enriched trials again demonstrated elevated ratios ($P = 0.006$ vs. all other trials), with HHF being the more common event. In the other 14 trials, HHF also tended to be more frequent than stroke (93% of trials), with 7 (50%) demonstrating a statistically significant difference. However, moderate/high heterogeneity ($I^2 = 70.5\%$; $P < 0.001$) again precluded the calculation of a reliable pooled estimate for the magnitude of this difference, with meta-regression indicating a higher ratio of HHF/stroke in the ELIXA and EXAMINE trials of post–acute coronary syndrome patients ($P = 0.004$ vs. all others). No other associations were observed, although higher HHF/stroke correlated with a higher proportion of participants with eGFR <60 mL/min/1.73 m^2 among the 14 trials not enriched for people with CKD (20% higher HHF/stroke ratio per 10% higher proportion with reduced eGFR [2–42%]; $P = 0.033$).

"CV Death or HHF" Relative to MACE

Incidence of the composite of CV death or HHF was comparable to MACE in the two CKD trials but lower in all others ($P < 0.001$ for CKD-enriched vs. non–CKD-enriched trials) (Fig. 2). SUSTAIN-6 and PIONEER 6 did not report on the CV death or HHF composite end point and so were excluded from this analysis. Less heterogeneity was observed compared with IRRs for the individual events, albeit still moderate ($I^2 = 58\%$). However, no associations with trial population characteristics were detected on meta-regression.

Established CV Disease Versus MRF

Incidence rates of HHF, MI, and stroke in CV disease and MRF subgroups were extracted for 7 of 10 trials that included both participant subtypes (SAVOR, CARMELINA, and PIONEER 6 being the omitted trials that included MRF cohorts but for which subgroup-level data were

Table 1—Baseline characteristics of the placebo arm populations in each of the 16 CV outcomes trials

Trial	Key inclusion criteria in addition to type 2 diabetes	*N*	Age (years)	Male (%)	Race/ ethnicity (% White)	BMI (kg/ m^2)	Diabetes duration (years)	HbA_{1c} (%)	Insulin therapy (%)	Prior CVD (%)	Prior HF (%)	eGFR <60 mL/min/1.73 m^2 (%)	Albuminuria (%)	Follow-up (years)
DPP4i														
SAVOR (2013)	- Atherosclerotic CVD, or - MRFs (male ≥55 years/female ≥60 years + ≥1 of HT, dyslipidemia, smoking)	8,212	65 ± 9	67	75	31.2	10.3	8.0 ± 1.4	41.2	78.7	12.8	29.2	38.5	2.1
EXAMINE (2013)	Acute coronary syndrome	2,679	61	68	73	28.7	7.3	8.0 ± 1.1	30.3	100	28.4	29.6	56.9	1.5
TECOS (2015)	Atherosclerotic CVD	7,339	66 ± 8	71	68	30.2	11.6	7.2 ± 0.5	22.9	100	18.3	22.9	28.1	3
OMNEON (2017)	Atherosclerotic CVD	2,102	64 ± 9	71	81	31.4	12.1	8.0 ± 0.9	33.3	100	14.3	11.3	NR	1.8
CARMELINA (2018)	- Albuminuria and CVD, or - CKD with or without CVD	3,485	66 ± 9	64	80	31.3	14.5	8.0 ± 1.0	57.2	NR	26.4	61.7	80	2.2
GLP-1RA														
ELIXA (2015)	Acute coronary syndrome	3,034	61 ± 10	69	76	30.2	9.4	7.6 ± 1.3	39	100	22.3	24.7	26.8	2.1
LEADER (2016)	- Atherosclerotic CVD, HF, CKD; or - Subclinical CVD (≥60 years + ≥1 of HT with LVH, kidney damage, LVD, or ABI <0.9)	4,672	64 ± 7	64	78	32.5	12.9	8.7 ± 1.5	45.6	72.2	17.8	22.3	37.2	3.8
SUSTAIN-6 (2016)	- Atherosclerotic CVD, HF, CKD; or - Subclinical CVD (≥60 years + ≥1 of HT with LVH, kidney damage, LVD, or ABI <0.9)	1,649	65 ± 8	60	82	32.8	13.6	8.7 ± 1.5	58.0	77.1	24.0	28.5	47.6	2.1
EXSCEL (2017)	- Any CV risk level - Recruitment designed to produce 70%/30% with/without a prior CV event	7,396	62	62	76	31.7	12	8.0	46.5	72.9	16.6	22.1	15.6	3.2
HARMONY (2018)	Atherosclerotic CVD	4,732	64 ± 9	69	85	32.3	14.2	8.7 ± 1.5	58	100	20	23.8	NR	1.6
REWIND (2019)	- Atherosclerotic CVD (≥50 years), - Subclinical CVD (≥55 years), or - MRFs (≥60 years)	4,682	66 ± 7	55	78	32.3	10.6	7.4 ± 1.0	24.2	33.2	8.9	22.7	35.5	5.4

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Table 1—Continued

Trial	Key inclusion criteria in addition to type 2 diabetes	*N*	Age (years)	Male (%)	Race/ ethnicity (% White)	BMI (kg/ m^2)	Diabetes duration (years)	HbA_{1c} (%)	Insulin therapy (%)	Prior CVD (%)	Prior HF (%)	eGFR <60 mL/min/1.73 m^2 (%)	Albuminuria (%)	Follow-up (years)
PIONEER 6 (2019)	- Atherosclerotic CVD, HF, CKD; or - Subclinical CVD (≥60 years + ≥1 of HT with LVH, kidney damage, LVD, or ABI <0.9)	1,592	66 ± 7	68	72	32.3	15.1	8.2 ± 1.6	60.4	74.2	12.6	26.5	NR	1.3
SGLT2i														
EMPA-REG (2015)	Atherosclerotic CVD	2,333	63 ± 9	72	72	30.7	NR	8.1 ± 0.8	48.6	99	10.5	26	40	3.1
CANVAS (2017)	- Atherosclerotic CVD, or - MRFs (≥50 years + ≥2 of diabetes duration ≥10 years, HT treatment, albuminuria, smoking, or low HDL-C)	4,347	63 ± 8	63	79	32.0	13.7	8.2 ± 0.9	50.7	73.5	15.1	21.4	30.2	3.6
DECLARE (2018)	- Atherosclerotic CVD, or - MRFs (male ≥55 years/ female ≥60 years + ≥1 of HT, dyslipidemia, smoking)	8,578	64 ± 7	62	79	32.0	10	8.3 ± 1.2	40.2	40.8	10.2	9.1	30.8	4.2
CREDENCE (2019)	Albuminuria and eGFR 30 to <90 mL/min/1.73 m^2	2,199	63 ± 9	67	66	31.3	16	8.3 ± 1.3	65.1	50.3	14.7	60.2	100	2.6

Data are mean ± SD or % unless otherwise indicated. ABI, ankle-brachial index; CVD, CV disease; HbA_{1c}, glycated hemoglobin; HDL-C, HDL cholesterol; HF, heart failure; HT, hypertension; LVD, left ventricular dysfunction; LVH, left ventricular hypertrophy; NR, not reported.

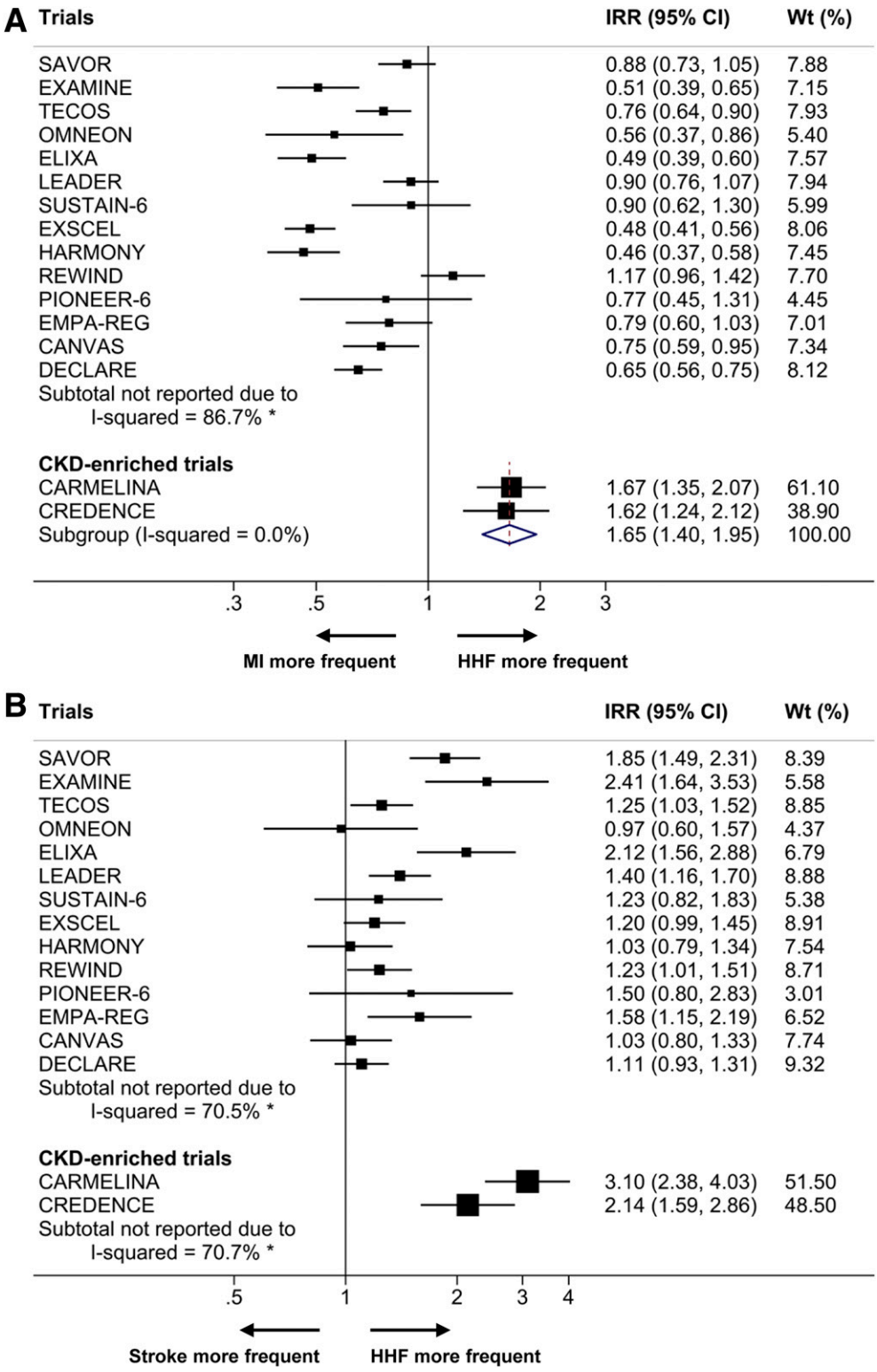

Figure 1—Meta-analysis of the IRR of HHF relative to MI (*A*) and HHF relative to stroke (*B*). Forest plots are stratified by whether trials were enriched for participants with CKD. *Moderate-high heterogeneity precluded a reliable single pooled estimate of the IRRs for the 14 non–CKD-enriched trials and of the HHF/stroke ratio for the 2 CKD-enriched trials. Error bars indicate 95% CIs. Wt, weight.

unavailable) (Fig. 3*A*). Baseline characteristics of the CV disease and MRF subgroups within each trial are displayed in Supplementary Table 2, with the most notable between-group differences being in proportions of participants who were male and who had prior heart failure (both being higher in the subgroups with CV disease). The HHF/MI ratio tended to be higher in the MRF group than in the CV disease group in most studies ($P = 0.051$ for MRF vs. CVD overall) (Fig. 3*B*);

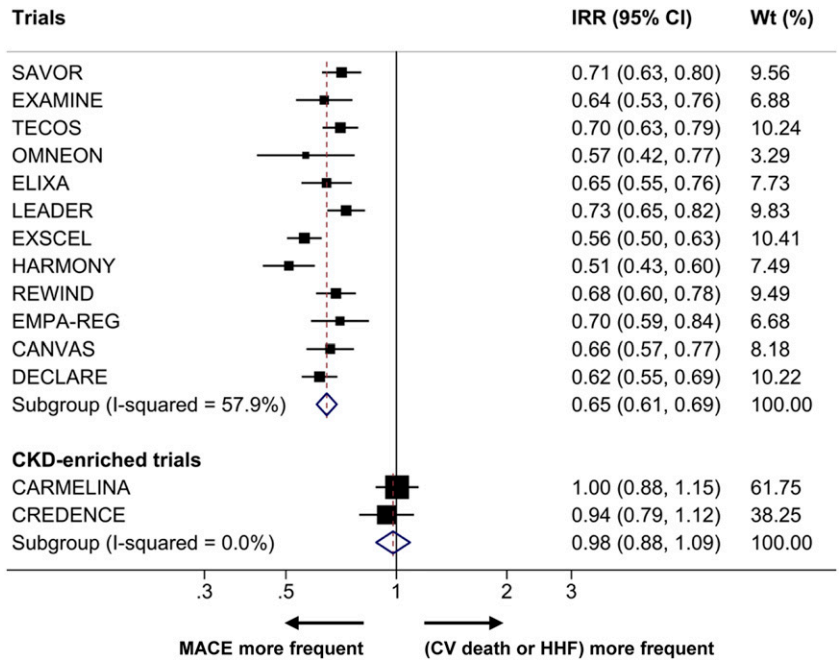

Figure 2—Meta-analysis of the IRR of "CV death or HHF" relative to MACE. The forest plot is stratified by whether trials were enriched for participants with CKD. The MACE composite end point included any of CV death, MI, or stroke. Error bars indicate 95% CIs. Note that SUSTAIN-6 and PIONEER 6 did not report the CV death or HHF composite end point and were not included in this analysis. Wt, weight.

however, this difference was attenuated after adjustment for sex and prior heart failure. HHF/stroke trended lower in the MRF group ($P = 0.068$ for MRF vs. CVD overall) (Fig. 3*C*), but the difference was again not apparent following adjustment for the same covariates.

DISCUSSION

In this meta-analysis of 16 CV outcomes trials conducted in participants with type 2 diabetes at high risk of CV events, we observed HHF to be less frequent than MI in all but three, two of which were enriched for CKD. Heterogeneity of the pooled estimates precluded more precise quantitation but appeared to be driven in part by variation in predictive clinical factors. CKD was a strong effect modifier, with HHF incidence substantially elevated relative to both MI and stroke in the two trials enriched with people with CKD. Consequently, the composite end point of CV death or HHF reached parity with the incidence of MACE in these trials. Notably, the incidence of HHF relative to both MI and stroke was similar in participants with and without established CV disease after accounting for between-group differences in clinical characteristics.

Frequency of Heart Failure in Clinical Trials in Type 2 Diabetes

Heart failure is often referred to as a "common" manifestation of CV disease in individuals with type 2 diabetes (25); however, the difficulty of its diagnosis has made quantitation difficult. Since observational studies have typically relied on hospital episode coding or investigator self-report, both of which are subject to bias, independently adjudicated heart failure end points in clinical trials may provide the most robust estimates of frequency (5,26). However, while such end points have been featured in trials of glucose-lowering therapy for almost two decades (7), substantive variability in definitions has presented a major challenge to data pooling and historical comparisons of event rates (4,5). In the setting of a recent systematic review indicating that HHF adjudication has been relatively consistent throughout the past decade (7), we performed a meta-analysis of contemporary CV outcomes trials that deliberately excluded older/less comparable data. Although specific trial selection is unconventional for a meta-analysis, those included were readily identifiable in that they represented all DPP4i, GLP-1RA, and SGLT2i outcomes trials conducted after the 2008 regulatory guidance concerning the requirement for new glucose-lowering therapies to demonstrate CV safety (27). All 16 trials used a definition of HHF that mandated a minimum length of stay, signs/symptoms of heart failure (incorporating physical examination findings and objective imaging/laboratory data), and initiation or intensification of anti–heart failure therapy (as per American College of Cardiology Foundation/American Heart Association guidance on CV event definitions [24]). However, it is important to recognize some limitations carried by these HHF outcome data: *1*) The incidence of HHF likely underestimates the overall burden of heart failure because of the exclusion of cases managed in the outpatient setting; *2*) a lack of detailed phenotyping precluded any opportunity to examine hospitalization for specific heart failure subtypes (e.g., heart failure with reduced vs. preserved ejection fraction, ischemic vs. nonischemic); and *3*) the extent to which incident HHF reflected new-onset heart failure versus exacerbation of existing heart failure is unclear given that prior heart failure at baseline relied on investigator self-report rather than on the same level of rigorous adjudication criteria applied to in-trial episodes of HHF.

Our results are nonetheless supportive of a 2014 review that was partly reliant on older trials that either did not define or did not prospectively adjudicate heart failure (1). Although pooled estimates were not reported in that review, heart failure was interpreted to occur at a "similar" frequency to MI and stroke, albeit with some variation dependent on trial entry criteria. In the present analysis, HHF was the second most frequent nonfatal CV event in type 2 diabetes (i.e., behind MI but ahead of stroke). However, similar to the above-mentioned review, we also observed significant heterogeneity that was partly explained by differences in trial population characteristics. More prevalent CKD clearly predisposed to a higher incidence of HHF relative to atherosclerotic events, a finding that substantiates previous observations of heart failure occurring more frequently than both MI and stroke in diabetic nephropathy trials (i.e., RENAAL [Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan] [28] and IDNT [Irbesartan Diabetic Nephropathy

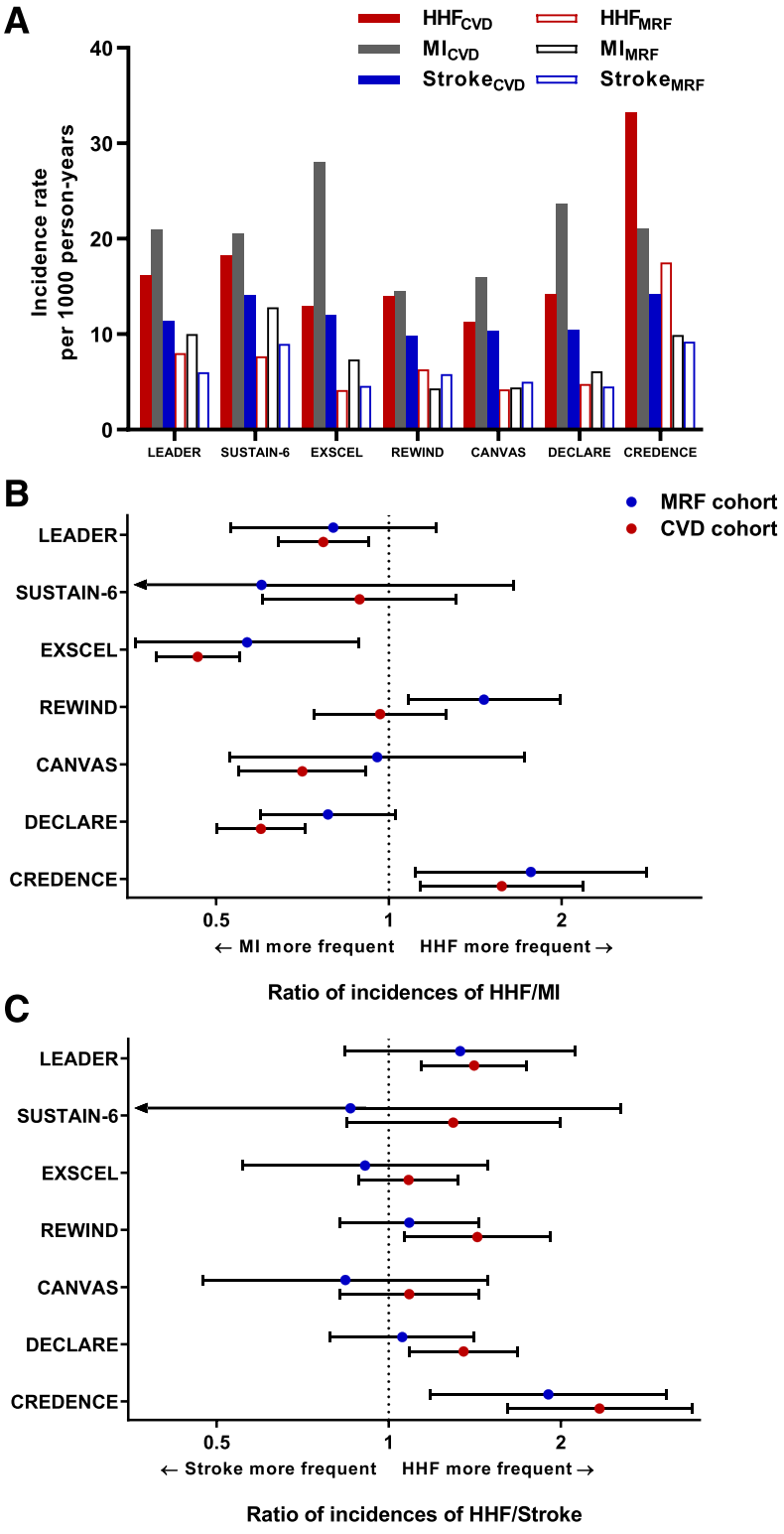

Figure 3—Comparison of CV event rates between CV disease (CVD) and MRF subgroups. *A*: Rates of HHF, MI, and stroke in the placebo arms of the CVD and MRF subgroups of seven trials that included participants both with and without established CVD at baseline. *B* and *C*: Subgroup-level IRRs of HHF relative to MI and HHF relative to stroke, respectively, for each trial. Error bars indicate 95% CIs. Note that in contrast to data in Figs. 1 and 2, some CVD- and MRF-specific incidence rates included silent MIs (LEADER and SUSTAIN-6) and fatal MI and stroke events (EXSCEL) because of differences in trial reporting. These trials were retained in CVD vs. MRF analyses since such differences are unlikely to bias within-trial subgroup comparisons (Figs. 1 and 2 having focused on between-trial comparisons).

Trial] [29]), although once again, heart failure was less rigorously defined in those trials than in those of the current review (1). Aside from CKD constituting an independent risk factor for heart failure in type 2 diabetes, it should also be acknowledged that there may be a potential difficulty in determining whether hospitalizations with fluid overload are related to heart failure or to CKD itself. Fluid overload that is due primarily to worsening of renal function may be very difficult to differentiate from heart failure. Thus, in populations enriched with CKD, there could be overestimates of HHF events. However, such uncertainty likely occurs most commonly in the setting of chronic cardiac dysfunction, which may well still be contributing to the clinical presentation.

HHF was also more common relative to MI with older age and where the proportion of participants with a history of MI was lower. These relationships were not borne out in analyses of HHF relative to stroke, although the HHF/stroke ratio was, notably, higher in the two trials that enrolled only patients with acute coronary syndrome. This may reflect a bias in selecting a cohort predisposed to cardiac rather than to other manifestations of CV disease. Such variations in the relative appearance of CV events according to CKD status, age, and cardiac history are relevant to considerations over the optimal drug class for CV prevention in type 2 diabetes since SGLT2is are recommended to reduce risks of HHF and MACE, while GLP-1RAs are recommended to reduce risks only of MACE.

Heart Failure in People With and Without Prior CV Disease

Although data from primary care has shown heart failure to be one of the most common initial manifestations of CV disease in type 2 diabetes (3), the concept of its presentation in the absence of prior ischemic heart disease—reflecting in part a distinct diabetic cardiomyopathy—remains somewhat controversial (30). In our analysis of seven trials that included participants with and without established CV disease, we observed a higher absolute incidence of HHF in those with established CV disease, in keeping with higher rates of all CV events. However, the excess of MI over HHF was actually smaller in the group without prior CV disease, contrary to what would

be expected if macrovascular disease was responsible for the majority of heart failure cases in type 2 diabetes. HHF incidence rates in the MRF groups cannot be used to infer an exact proportion of participants for whom HHF represents a first CV event, since we did not have unit record data and could not be certain that HHF events were not preceded by another CV event occurring earlier during study follow-up. However, if such a sequence of events was always the case, we estimate (by applying rates of HHF in the prior CV disease group to the MRF subgroups who experienced MI or stroke) that the incidence rates of HHF in the MRF groups would be <10% of those actually observed. Thus, when HHF occurred in the MRF groups, it must have been the first CV event in the majority of cases. Nevertheless, in the MRF groups, there were still only two trials (CREDENCE and REWIND) in which HHF was significantly more frequent than MI.

Study Limitations

Although clinical trials are attractive from the perspective of offering high-quality, adjudicated HHF data, the findings may have limited generalizability to other populations. Furthermore, the trials contributing to this meta-analysis were enriched with participants with established CV disease. Even those studies that featured a subgroup without prior CV disease enrolled participants at high risk of an event. However, since this serves to increase the absolute rates of all CV events, the IRRs of HHF/MI and HHF/stroke and their relationships with clinical characteristics are nevertheless likely to remain relevant to the type 2 diabetes population more broadly. Another limitation of these clinical trial data comes from the relatively short duration of follow-up (1.3–5.4 years), which may underestimate the relative appearance of CV outcomes with longer lead times or older age of onset. Exclusion of silent MIs—necessitated by their adjudication in only a small number of studies—represents another limitation to our analysis. From trials that did adjudicate silent MIs, the extent of consequent underestimation of the incidence of any MI (silent or symptomatic) can be expected to be between ~2% (based on OMNEON; personal communication, I. Gantz) and 22% (based on LEADER). In any case, broadening the scope of MI would only serve to further entrench it as the most frequent nonfatal CV event, with HHF in second. Although meta-regression analyses revealed some of the factors influencing the IRRs, these did not fully explain the observed heterogeneity. A larger number of trials may have revealed other contributory trial design or population factors. In turn, the smaller number of trials that included an MRF cohort, as well as the relatively small sizes of these cohorts as a proportion of their trial's total, led to some relatively imprecise IRRs in the MRF versus CV disease comparison. Also contributing to imprecision of these subgroup-specific estimates was variability across trials in the definition of CV disease itself, as well as in the candidate criteria for the MRF cohort, which included a mix of conventional risk factors (e.g., dyslipidemia) and/or indications of subclinical CV disease (e.g., abnormal left ventricular structure/function). Nevertheless, between-group differences in the CV disease and MRF cohorts were similar in magnitude and direction across trials, suggesting no substantive bias arising from such differences. Finally, the increasing use of troponins and natriuretic peptides over time in the diagnosis of MI and HHF, respectively, may have influenced the observed incidence of each and, therefore, the ratio between them.

In conclusion, HHF is one of the most frequent nonfatal CV events in clinical trials in type 2 diabetes, second only to MI (and even surpassing MI in the context of CKD). This was true for those with and without prior CV disease. Our results do not confirm earlier studies that reported heart failure to be more common than MI (3) but do support the notion that it is a major contributor to first and recurrent CV events. The extent to which this discrepancy may reflect different outcomes (adjudicated HHF vs. local clinician diagnoses) or populations studied (clinical trial participants at high CV risk vs. the broader type 2 diabetes population seen in primary care) remains uncertain. Regardless, our findings strengthen the argument for inclusion of HHF in primary or coprimary composite end points of CV outcomes trials in type 2 diabetes. Beyond trial design, heart failure would appear to be worthy of a similar level of prioritization as traditional atherosclerotic events in primary prevention interventions in type 2 diabetes. With aging populations worldwide, the importance of developing new therapies with efficacy to reduce the burden of heart failure in type 2 diabetes (as has been achieved with SGLT2is) (31,32) will only increase.

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