Circulation

ORIGINAL RESEARCH ARTICLE

Effect of Dapagliflozin on Heart Failure and Mortality in Type 2 Diabetes Mellitus

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et al

BACKGROUND: In DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58), the sodium-glucose cotransporter 2 inhibitor dapagliflozin reduced the composite end point of cardiovascular death/hospitalization for heart failure (HHF) in a broad population of patients with type 2 diabetes mellitus. However, the impact of baseline left ventricular ejection fraction (EF) on the clinical benefit of sodium-glucose cotransporter 2 inhibition is unknown.

METHODS: In the DECLARE-TIMI 58 trial, baseline heart failure (HF) status was collected from all patients, and EF was collected when available. HF with reduced EF (HFrEF) was defined as EF <45%. Outcomes of interest were the composite of cardiovascular death/HHF, its components, and all-cause mortality.

RESULTS: Of 17 160 patients, 671 (3.9%) had HFrEF, 1316 (7.7%) had HF without known reduced EF, and 15 173 (88.4%) had no history of HF at baseline. Dapagliflozin reduced cardiovascular death/HHF more in patients with HFrEF (hazard ratio [HR], 0.62 [95% CI, 0.45–0.86]) than in those without HFrEF (HR, 0.88 [95% CI, 0.76–1.02]; *P* for interaction=0.046), in whom the treatment effect of dapagliflozin was similar in those with HF without known reduced EF (HR, 0.88 [95% CI, 0.66–1.17]) and those without HF (HR, 0.88 [95% CI, 0.74–1.03]). Whereas dapagliflozin reduced HHF both in those with (HR, 0.64 [95% CI, 0.43–0.95]) and in those without HFrEF (HR, 0.76 [95% CI, 0.62–0.92]), it reduced cardiovascular death only in patients with HFrEF (HR, 0.55 [95% CI, 0.34–0.90]) but not in those without HFrEF (HR, 1.08 [95% CI, 0.89–1.31]; *P* for interaction=0.012). Likewise, dapagliflozin reduced all-cause mortality in patients with HFrEF (HR, 0.59 [95% CI, 0.40–0.88;) but not in those without HFrEF (HR, 0.97 [95% CI, 0.86–1.10]; *P* for interaction=0.016).

CONCLUSIONS: In the first sodium-glucose cotransporter 2 inhibitor cardiovascular outcome trial to evaluate patients with type 2 diabetes mellitus stratified by EF, we found that dapagliflozin reduced HHF in patients with and without HFrEF and reduced cardiovascular death and all-cause mortality in patients with HFrEF.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT01730534.

Clinical Perspective

What Is New?

- DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58) is the only sodium-glucose transporter 2 inhibitor cardiovascular outcome trial to date that had detailed baseline information on patients' left ventricular ejection fraction.
- In 17 160 patients with type 2 diabetes mellitus with either established atherosclerotic cardiovascular disease or multiple risk factors for atherosclerotic cardiovascular disease, sodium-glucose transporter 2 inhibition with dapagliflozin, in addition to standard contemporary cardiovascular medicines, reduced the risk of cardiovascular death or hospitalization for heart failure to a greater extent in patients with heart failure with reduced ejection fraction than in those without heart failure with reduced ejection fraction.
- This difference was driven by large reductions in cardiovascular death and all-cause mortality in patients with heart failure with reduced ejection fraction.

What Are the Clinical Implications?

- Our data warrant particular consideration for sodium-glucose transporter 2 inhibitors in patients with heart failure with reduced ejection fraction.

Type 2 diabetes mellitus (T2DM) is a well-established risk factor for heart failure (HF).[1] Both the incidence and prevalence of T2DM and HF are increasing globally, in part as a result of population aging.[2] Although much progress has been made in improving cardiovascular outcomes in patients with T2DM, reducing the risk of HF and related outcomes in such patients has lagged behind.[3] This dual epidemic of T2DM and HF creates an urgent need for effective therapies that can address the expected increased burden of HF[4,5] in general and specifically among patients with T2DM.

Despite the well-known association between T2DM and HF, there has not previously been any glucose-lowering agent that reduces the risk of HF in patients with T2DM. Recently, sodium-glucose cotransporter 2 (SGLT2) inhibition has emerged as an important therapeutic modality for reducing cardiovascular risk in T2DM. Across 3 large SGLT2 inhibitor (SGLT2i) cardiovascular outcome trials, EMPA-REG (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients),[6] the CANVAS program (Canagliflozin Cardiovascular Assessment Study),[7] and the DECLARE-TIMI 58 trial (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58),[8] SGLT2i reduced the risk of

the composite of cardiovascular death or hospitalization for HF (HHF), changing the landscape of T2DM management as a target for HF prevention.[6–8] There are various reports on whether the magnitude of benefit of SGLT2i depends on a history of HF.[9,10] However, the relationship between baseline left ventricular ejection fraction (EF) and the benefit of SGLT2 inhibition on reducing cardiovascular death and HHF has not been previously reported. In the present analyses, we examined the efficacy and safety of dapagliflozin according to baseline HF status and systolic left ventricular EF.

METHODS

We encourage parties interested in collaboration and data sharing to contact the corresponding author directly for further discussions.

Study Design

The study design, baseline characteristics, and main results of the DECLARE-TIMI 58 trial have been published previously.[8,11,12] In brief, DECLARE-TIMI 58 was a randomized, double-blind, multinational cardiovascular outcome trial comparing 10 mg dapagliflozin with placebo in 17 160 patients with T2DM with either established atherosclerotic cardiovascular disease (ASCVD) or multiple risk factors for ASCVD and with a creatinine clearance ≥60 mL/min. The emerging data on the benefit of SGLT2i on HHF prompted comprehensive data collection for each patient's HF history and capture of EF estimates when available in the clinical record in DECLARE-TIMI 58. Sites were to collect patients' history and pathogenesis of HF, baseline EF, and functional class at study entry and at all subsequent visits. Per protocol, patients with New York Heart Association class IV HF were excluded. Patients were followed up for a median of 4.2 years with regular visits and laboratory testing. The trial was approved by all institutional review committees, and written informed consent was obtained from all patients.

Outcomes

For these prespecified analyses, the key outcomes of interest are the dual primary composite end point of the trial of cardiovascular death or HHF, its individual components, and all-cause mortality (ACM). HHF was adjudicated according to US Food and Drug Administration consensus criteria as an event that fulfilled all of the following criteria: (1) required an admission to the hospital with a primary diagnosis of HF; (2) in-hospital stay ≥24 hours; (3) documentation of new or worsening symptoms caused by HF; (4) objective physical, laboratory, or diagnostic evidence of new or worsening HF; and (5) initiation or intensification of treatment for HF. The complete definition of HHF is described elsewhere.[8] Additional outcomes were major adverse cardiac events, which included the composite of cardiovascular death, myocardial infarction, and ischemic stroke, and the renal-specific outcome of a sustained decrease in estimated glomerular filtration rate ≥40% from baseline, end-stage renal disease, or renal death, as previously described.[8,11] The key outcomes were adjudicated in a blinded manner by an independent clinical events committee.

Statistical Analysis

Patients were stratified on the basis of the exact EF value if known or by qualitative function as follows. HF with reduced EF (HFrEF) was defined as having a prespecified EF cut point of <45% or severe/moderate left ventricular systolic dysfunction, with or without a reported history of HF. Patients who did not have HFrEF made up 2 groups: patients without history of HF and patients with HF without known reduced EF, the latter defined as those having a history of HF without known EF <45%. In sensitivity analyses, patients with HFrEF were subdivided into those with and those without a reported history of HF. In addition, patients with HF with confirmed EF ≥45% and those without a documented EF were analyzed separately. Furthermore, outcomes in patients across a range of EF cut points were also evaluated.

Baseline characteristics were reported as frequencies and percentages for categorical variables and as medians and interquartile ranges for continuous variables. The χ^2 test was used to compare for categorical variables, and the Wilcoxon test was used for continuous variables.

Analyses were performed on an intention-to-treat basis, and safety events were analyzed during the on-treatment period unless otherwise noted. Hazard ratios (HRs) and 95% CIs were determined from Cox regression models that included trial stratification factors. To test for effect modification, the interaction terms were evaluated for baseline cardiac status (HFrEF or not HFrEF) and treatment strategy for each outcome with Cox regression models. The Kaplan–Meier method was used to estimate survival functions, and the Cox proportional hazards model was used for estimating the effects of covariates on the hazard of the occurrence of the event. Cumulative incidence rates were calculated from Kaplan–Meier failure rates. The number needed to treat is calculated for all key outcomes of interest as the inverse of the absolute risk difference between the event rate in the dapagliflozin group and in the placebo group. There was no statistical adjustment for multiple comparisons.

All analyses were performed with SAS software version 9.3 (SAS Institute Inc, Cary, NC) and Stata version 14.2 (StataCorp, College Station, TX). A 2-sided value of P<0.05 and CIs excluding 1.0 were considered to indicate statistical significance.

RESULTS

Of 17 160 patients, 671 (3.9% of total trial cohort) had an EF <45% and were classified as having HFrEF. A total of 1316 patients (7.7% of the total trial cohort) had a history of HF without a reduced EF (808 with a documented EF ≥45% and 508 without a documented EF) and were classified as having HF without known reduced EF. The remaining 15 173 patients (88.4%) had no history of HF and no documented reduced EF (3723 with a documented EF ≥45% and 11 450 with no documented EF).

The baseline demographics of patients with HFrEF, with HF without known reduced EF, and without a his-

tory of HF are summarized in the Table. Patients with HFrEF were more likely to be male and to have a history of ASCVD, particularly coronary artery disease. Patients with HF without known reduced EF were older, were more likely female, and had a higher prevalence of hypertension. Patients with a history of HF, especially those with HFrEF, were generally well treated with high proportions of evidence-based HF therapies, including 86.0% on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and 80.7% on β-blockers. Two-thirds were receiving diuretics, and 30.3% were taking mineralocorticoid receptor antagonists.

As previously reported, overall, dapagliflozin reduced the risk of cardiovascular death or HHF by 17% (HR, 0.83 [95% CI, 0.73–0.95]; P=0.005). However, dapagliflozin reduced the risk of cardiovascular death or HHF to a greater extent in patients with HFrEF (HR, 0.62 [95% CI, 0.45–0.86]) than in those without (HR, 0.88 [95% CI, 0.76–1.02]; P for interaction=0.046; Figure 1). Among those without HFrEF, the estimates of effect of dapagliflozin did not differ between patients with HF without known reduced EF and those without a history of HF (HR, 0.88 [95% CI, 0.66–1.17] and 0.88 [95% CI, 0.74–1.03], respectively; Figure 1). The heterogeneity was driven by dapagliflozin reducing cardiovascular death in patients with HFrEF (HR, 0.55 [95% CI 0.34–0.90]; P=0.02) but not in those without (HR, 1.08 [95% CI, 0.89–1.31]; P for interaction=0.012). Subtypes of cardiovascular death are listed in Table I in the online-only Data Supplement. Likewise, dapagliflozin significantly reduced ACM in patients with HFrEF (HR, 0.59 [95% CI, 0.40–0.88]; P=0.01) but not in those without (HR, 0.97 [95% CI, 0.86–1.10]; P for interaction=0.016). Conversely, dapagliflozin reduced HHF regardless of EF (HR, 0.64 [95% CI, 0.43–0.95] for HFrEF and 0.76 [95% CI, 0.62–0.92] for not HFrEF; P for interaction=0.45), with no heterogeneity of effect between patients with HF without known reduced EF (HR, 0.72 [95% CI, 0.50–1.04]) and those with no history of HF (HR, 0.77 [95% CI, 0.60–0.97]). The benefit of dapagliflozin in reducing cardiovascular death, HHF, and ACM in patients with HFrEF appeared early and extended throughout the trial for all of the key outcomes of interest (Figure 2). In contrast, the event curves for HHF started to diverge only after 1 year in patients with HF without known reduced EF and in patients without history of HF.

As expected, there was a gradient of baseline risk with 4-year rates of cardiovascular death or HHF in the placebo arm that was 27.1%, 14.8%, and 3.9% in patients with HFrEF, HF without known reduced EF, and no history of HF (P<0.01), respectively. Coupling the greater baseline risk with the greater relative risk reduction in patients with HFrEF, there were large absolute risk reductions in cardiovascular death or HHF, cardiovascular death, and ACM, with values of 9.2%, 5.2%,

Table. Baseline Characteristics by HF Category

	HFrEF (n=671)	HF Without Known Reduced EF (n=1316)	No History of HF (n=15 173)
Age, median (IQR), y	63 (58–68)	65 (60–69)	64 (60–68)
Male, %	84.2	57.2	62.1
Region, %			
North America	36.8	21.9	32.5
Europe	47.8	69.8	42.1
Latin America	3.7	3.3	11.9
Asia Pacific	11.6	5.0	13.5
BMI, median (IQR), kg/m^2	31.6 (28.2–36.0)	33.1 (29.5–37.6)	31.1 (27.7–35.2)
Hemoglobin A$_{1c}$, median (IQR), %	8.1 (7.4–9.2)	8.2 (7.5–9.3)	8.0 (7.3–9.0)
Duration of T2DM, median (IQR), y	10 (5–16)	10 (5–15)	11 (6–16)
History of dyslipidemia, %	93.3	80.9	79.8
Current tobacco use, %	14.8	13.8	14.6
History of hypertension, %	87.0	95.9	89.5
LVEF, median (IQR), %	38 (30–40)	55 (50–61)	60 (55–65)
eGFR by CKD-EPI equation, median (IQR), mL/min/1.73m^2	83 (66–95)	86 (70–96)	89 (76–97)
NYHA class, %			
I	32.4	37.5	NA
II	56.4	55.9	NA
III	10.8	6.2	NA
Unknown	0.5	0.5	NA
Main pathogenesis of HF, %			
Ischemic	63.5	49.6	NA
Nonischemic	15.2	14.5	NA
Unknown	21.3	35.9	NA
Established ASCVD, %	86.1	61.7	36.8
History of coronary artery disease	96.2	86.6	78.8
History of peripheral arterial disease	11.4	12.6	15.3
History of cerebrovascular disease	11.4	18.1	19.5
Baseline medications, %			
Antiplatelet	81.4	72.4	59.2
Statin or ezetimibe	91.4	77.6	74.0
ACE inhibitor or ARB	87.9	85.3	80.7
β-Blocker	87.8	77.2	48.9
Diuretic	66.9	63.1	37.5
Loop	46.3	34.9	6.8
Thiazide	13.3	17.6	22.8
Mineralocorticoid receptor antagonist	30.3	13.8	2.5

All $P<0.001$ except for current tobacco use ($P=0.735$) and history of peripheral artery disease ($P=0.007$). ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; IQR, interquartile; LVEF, left ventricular ejection fraction; NA, not available; NYHA, New York Heart Association; and T2DM, type 2 diabetes mellitus.

and 6.4%, leading to numbers needed to treat over 4 years of 11, 19, and 16.

In sensitivity analyses, we subcategorized HFrEF patients by history of presence or absence of reported HF, and the results were directionally similar (Figure I in the online-only Data Supplement). Analyzing outcomes in patients with HF with EF known to be ≥45% and those without known EF, we found that the results were consistent. We also stratified patients across a range of EF cut points to characterize reduced EF, and a gradient of
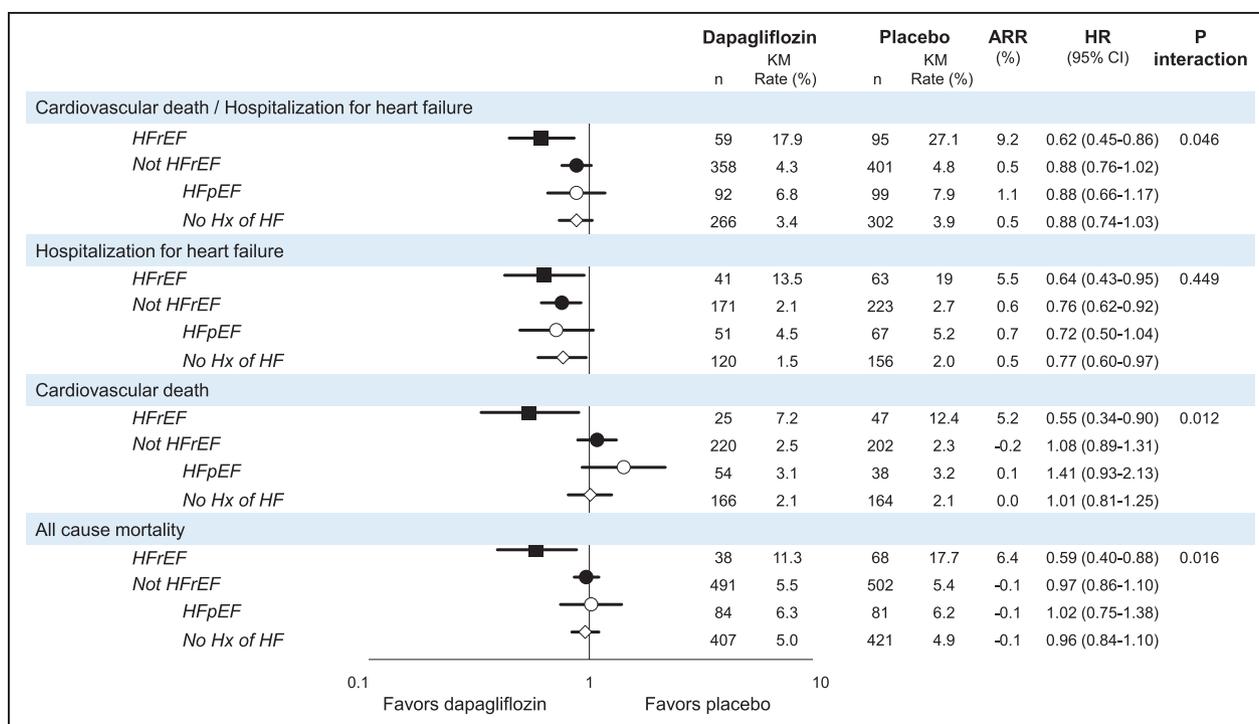
Figure 1. Cardiovascular outcomes by heart failure (HF) category.
There were 671 patients with HF with reduced ejection fraction (HFrEF) defined as left ventricular ejection fraction (EF) <45% (318 in the dapagliflozin group and 353 in the placebo group) and 16 489 patients without HFrEF (8264 in the dapagliflozin group and 8225 in the placebo group). There were 1316 patients with HF without known reduced EF defined as a history (hx) of HF without left ventricular EF <45% (662 in the dapagliflozin group and 654 in the placebo group). There were 15 173 patients without a history of HF and without left ventricular EF <45% (7602 in the dapagliflozin group and 7571 in the placebo group). P for interaction refers to an interaction between HFrEF and not HFrEF. Open circles and open diamonds are subsets of closed circles. ARR indicates absolute risk reduction; HR, hazard ratio; and KM, Kaplan–Meier.

efficacy was observed, with greater relative benefit with dapagliflozin in patients with worse EF, especially those with EF <30% (Figure II in the online-only Data Supplement). When confined to the subset of patients with a known EF, the results were consistent; we saw a similar reduction in HHF with dapagliflozin in HFrEF and HF without known reduced EF (HR, 0.64 [95% CI, 0.43–0.95] versus 0.74 [95% CI, 0.48–1.14]; P for interaction=0.615) but a greater reduction with dapagliflozin in cardiovascular death in patients with HFrEF (HR, 0.55 [95% CI, 0.34–0.90] versus 1.44 [95% CI, 0.83–2.49]; P for interaction=0.011). Exploring the association of baseline diuretic use in different HF subgroups, we found no effect modification of dapagliflozin efficacy for any outcome analyzed (Figure III in the online-only Data Supplement). Finally, the effects of dapagliflozin on major adverse cardiac events and the renal-specific outcome did not differ by HF subgroup (Figure IV in the online-only Data Supplement).

Safety outcomes are summarized in Table II in the online-only Data Supplement. Serious adverse events occurred more frequently in patients with HFrEF than in those without in both randomized groups. However, the safety profile of dapagliflozin versus placebo did not differ, with no effect modification by HF status (P for interaction for all >0.05).

DISCUSSION

In the present analyses, we have shown that SGLT2 inhibition with dapagliflozin reduced the risk of cardiovascular death or HHF to a greater extent in patients with HFrEF than in those without HFrEF. This difference was driven by large reductions in cardiovascular death and ACM in patients with HFrEF.

SGLT2i have emerged as a class of glucose-lowering agents that significantly improve cardiovascular outcomes in patients with T2DM. In particular, cardiovascular outcomes trials have shown that at least 3 members of this class robustly reduce the risk of the composite of cardiovascular death or HHF.[13] An analysis from EMPA-REG Outcomes suggested no significant heterogeneity of benefit on cardiovascular death or HHF with empagliflozin in patient with and without a history of HF. In contrast, in the CANVAS program, there was a greater reduction in the risk of cardiovascular death or HHF in patients with a history of HF. However, these analyses did not have the benefit of detailed baseline information on patients' left ventricular EF as was collected during the conduct of DECLARE-TIMI 58. DECLARE-TIMI 58 was also unique in that it was the largest SGLT2i cardiovascular outcome trial conducted to date, included a broad population, and had cardiovascular death or
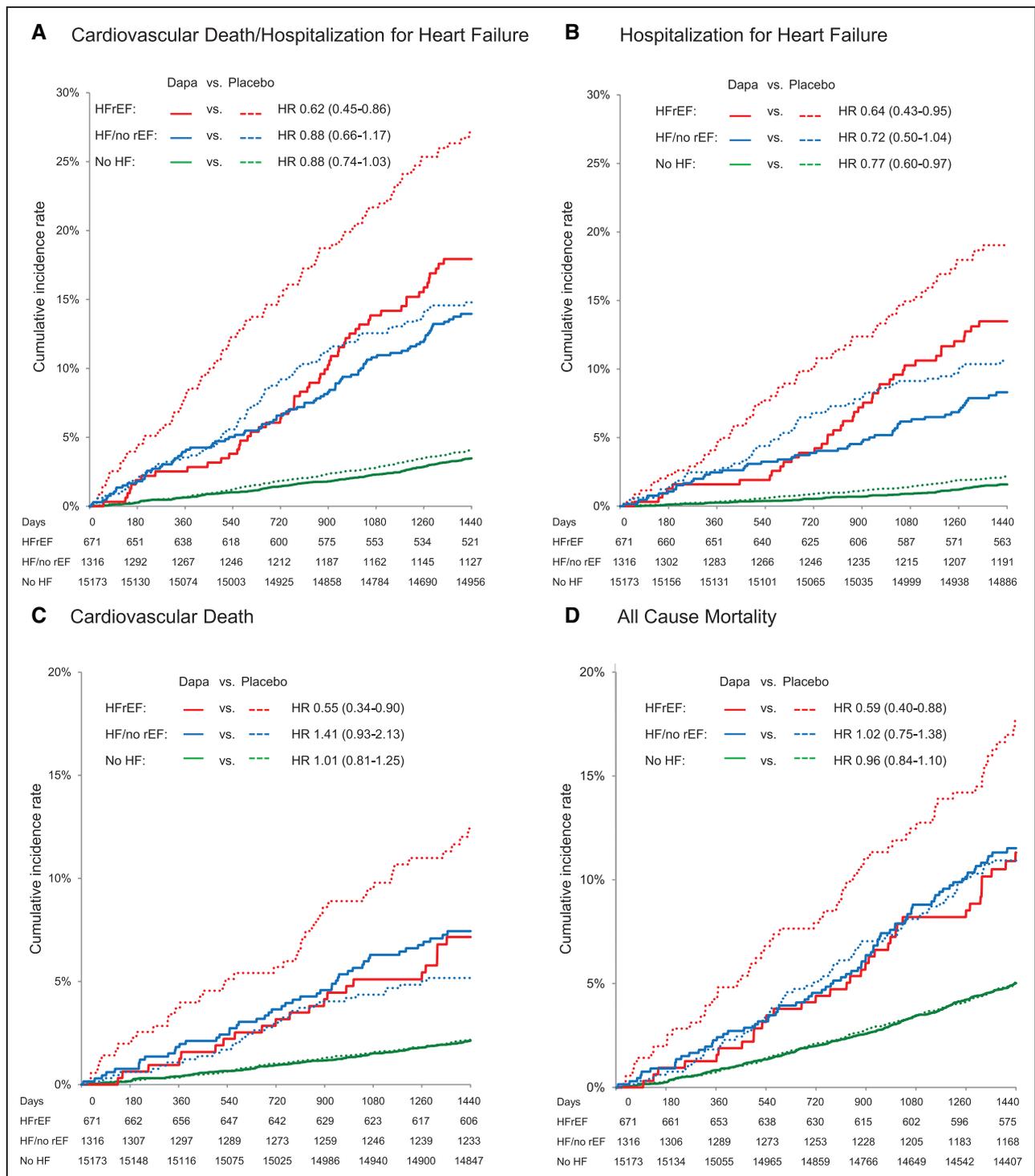
Figure 2. Kaplan–Meier curves stratified by different heart failure (HF) categories.
The Kaplan–Meier rate compares treatment with dapagliflozin vs placebo for the outcomes indicated. **A**, Cardiovascular death or hospitalization for HF (HHF). **B**, HHF. **C**, Cardiovascular death. **D**, All-cause mortality. Solid line represents dapagliflozin (Dapa); dotted line represents placebo. Numbers at risk are shown at the bottom. HFrEF indicates HF with reduced ejection fraction; HR, hazard ratio; and rEF, reduced ejection fraction.

HHF as one of the dual primary end points. These more granular data allowed us to identify EF as a strong tool to determine which patients derived particular mortality benefit from SGLT2i. The high baseline risk and the large relative risk reductions in the subset with HFrEF led to large absolute risk reductions. Thus, only 16 patients with T2DM and HFrEF would need to be treated for 4 years to prevent a death. Moreover, this benefit was seen in patients who were already treated with standard contemporary cardiovascular medicines such

as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, and diuretics.

In contrast, our analyses did not show a mortality benefit with dapagliflozin in patients with HF without known reduced EF. However, this finding should be interpreted in the context of the overall trial population. This was not a dedicated HF trial. The trial included a very small proportion of patients with estimated glomerular filtration rate <60 mL·min^{-1}·1.73 m^{-2}, and the cardiovascular benefits of SGLT2 inhibition tend to be greater in those with worse renal function.[13]

SGLT2i block glucose reclamation in the proximal renal tubules, thereby increasing the urinary excretion of both glucose and sodium. However, the interplay between T2DM and HF is complex and multifactorial, and mechanisms of potential benefit in HF may extend beyond simple intravascular volume loss.[14,15] Most recently, the EMPA-HEART trial (Effects of Empagliflozin on Cardiac Structure in Patients With Type 2 Diabetes; NCT02998970), a mechanistic study of empagliflozin, showed that the addition of the SGLT2i reduced left ventricular mass, which has a strong association with cardiac events, particularly HF. However, the study had a small sample size and short follow-up, and although the diuretic effects of SGLT2i may be one of the short-term effects, additional long-term information about left ventricular chamber size, left ventricular volume, and diastolic function may enrich our understanding of the mechanisms by which SGLT2i act to reduce HHF and mortality risk.

Two-thirds of patients with HFrEF used diuretics at baseline; however, there was no apparent increase in volume depletion events or acute renal failure events. We also noted no increase in diabetic ketoacidosis or amputation with the addition of dapagliflozin in this group, which have been among the concerns with SGLT2i agents.

There are some limitations with our study. This was not a trial designed specifically to assess patients with HF. To that end, left ventricular EF values were available in one-third of the randomized patients; however, this is likely consistent with clinical practice given that just under 40% of DECLARE-TIMI 58 participants had established ASCVD, and only 12% had a known history of HF. Second, we did not specify a time window before enrollment during which EF had to be determined and requested the most recent EF known before enrollment. Thus, some patients with preserved EF could have had a reduced EF previously that recovered. We also accepted data on EF from a variety of modalities (echocardiography, MRI, etc), although such an approach is also typical in dedicated HF trials. Finally, there are no universally acknowledged definitions for HF with preserved EF, and we based our predefined EF cut point on various guidelines and the literature.[16–19] To address these issues, we have confirmed these results with sensitivity analyses using various EF cut points and

clinical subgroups. Reassuringly, the results consistently showed a greater treatment effect with dapagliflozin in the reduced EF group. Despite these limitations, we had the opportunity to study the impact of EF in >5000 patients, the largest group reported for SGLT2i, and our data, together with additional data from ongoing trials in patients with HFrEF and HF with preserved EF with and without T2DM (eg, Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure [NCT03036124], Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure [NCT03619213], Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction [NCT03057977], Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction [NCT03057951], Dapagliflozin in Preserved Ejection Fraction Heart Failure [NCT03030235]), should provide valuable insights into the benefits of SGLT2i on HHF and mortality.

Conclusions

The present study shows that dapagliflozin reduces HHF in a broad spectrum of patients with T2DM and high cardiovascular risk regardless of EF, with greatest absolute risk reduction in patients at highest risk, and reduces cardiovascular death and ACM in patients with HFrEF

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Disclosures

REFERENCES

1. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. *Am J Cardiol.* 1974;34:29–34.
2. Thrainsdottir IS, Aspelund T, Thorgeirsson G, Gudnason V, Hardarson T, Malmberg K, Sigurdsson G, Rydén L. The association between glucose abnormalities and heart failure in the population-based Reykjavik study. *Diabetes Care.* 2005;28:612–616. doi: 10.2337/diacare.28.3.612
3. Rawshani A, Rawshani A, Gudbjörnsdottir S. Mortality and cardiovascular disease in type 1 and type 2 diabetes. *N Engl J Med.* 2017;377:300–301. doi: 10.1056/NEJMc1706292
4. Cavender MA, Steg PG, Smith SC Jr, Eagle K, Ohman EM, Goto S, Kuder J, Im K, Wilson PW, Bhatt DL; REACH Registry Investigators. Impact of diabetes mellitus on hospitalization for heart failure, cardiovascular events, and

death: outcomes at 4 years from the Reduction of Atherothrombosis for Continued Health (REACH) Registry. *Circulation.* 2015;132:923–931. doi: 10.1161/CIRCULATIONAHA.114.014796

5. Bertoni AG, Wagenknecht LE, Kitzman DW, Marcovina SM, Rushing JT, Espeland MA; Brain Natriuretic Peptide Subgroup of the Look AHEAD Research Group. Impact of the look AHEAD intervention on NT-pro brain natriuretic peptide in overweight and obese adults with diabetes. *Obesity (Silver Spring).* 2012;20:1511–1518. doi: 10.1038/oby.2011.296

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; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med.* 2015;373:2117–2128. doi: 10.1056/NEJMoa1504720

7. Neal B, Perkovic V, Matthews DR. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med.* 2017;377:2099. doi: 10.1056/NEJMc1712572

8. 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; DECLARE–TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2019;380:347–357. doi: 10.1056/NEJMoa1812389

9. Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME® Trial Investigators. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial. *Eur Heart J.* 2016;37:1526–1534. doi: 10.1093/eurheartj/ehv728

10. Rådholm 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. doi: 10.1161/CIRCULATIONAHA.118.034222

11. 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. doi: 10.1016/j.ahj.2018.01.012

12. Raz I, Mosenzon O, Bonaca MP, Cahn A, Kato ET, Silverman MG, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Gause-Nilsson IAM, Langkilde AM, Johansson PA, Sabatine MS, Wiviott SD. DECLARE-TIMI 58: participants' baseline characteristics. *Diabetes Obes Metab.* 2018;20:1102–1110. doi: 10.1111/dom.13217

13. 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. doi: 10.1016/S0140-6736(18)32590-X

14. Zelniker TA, Braunwald E. Cardiac and renal effects of sodium-glucose co-transporter 2 inhibitors in diabetes: JACC state-of-the-art review. *J Am Coll Cardiol.* 2018;72:1845–1855. doi: 10.1016/j.jacc.2018.06.040

15. Heerspink HJ, Perkins BA, Fitchett DH, Husain M, Cherney DZ. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. *Circulation.* 2016;134:752–772. doi: 10.1161/CIRCULATIONAHA.116.021887

16. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013;128:1810–1852. doi: 10.1161/CIR.0b013e31829e8807

17. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; ESC Scientific Document Group. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* 2016;37:2129–2200. doi: 10.1093/eurheartj/ehw128

18. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. *Eur Heart J.* 2011;32:670–679. doi: 10.1093/eurheartj/ehq426

19. Redfield MM. Heart failure with preserved ejection fraction. *N Engl J Med.* 2017;376:897. doi: 10.1056/NEJMc1615918