Dapagliflozin and the Incidence of Type 2 Diabetes in Patients With Heart Failure and Reduced Ejection Fraction: An Exploratory Analysis From DAPA-HF

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OBJECTIVE

The sodium–glucose cotransporter 2 inhibitor dapagliflozin reduced the risk of cardiovascular mortality and worsening heart failure in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial. This report explores the effect of dapagliflozin on incident type 2 diabetes (T2D) in the cohort without diabetes enrolled in the trial.

RESEARCH DESIGN AND METHODS

The subgroup of 2,605 patients with heart failure and reduced ejection fraction (HFrEF), no prior history of diabetes, and an HbA_{1c} of <6.5% at baseline was randomized to dapagliflozin 10 mg daily or placebo. In this exploratory analysis, surveillance for new-onset diabetes was accomplished through periodic HbA_{1c} testing as part of the study protocol and comparison between the treatment groups assessed through a Cox proportional hazards model.

RESULTS

At baseline, the mean HbA_{1c} was 5.8%. At 8 months, there were minimal changes, with a placebo-adjusted change in the dapagliflozin group of −0.04%. Over a median follow-up of 18 months, diabetes developed in 93 of 1,307 patients (7.1%) in the placebo group and 64 of 1,298 (4.9%) in the dapagliflozin group. Dapagliflozin led to a 32% reduction in diabetes incidence (hazard ratio 0.68, 95% CI 0.50–0.94; $P = 0.019$). More than 95% of the participants who developed T2D had prediabetes at baseline (HbA_{1c} 5.7–6.4%). Participants who developed diabetes in DAPA-HF had a higher subsequent mortality than those who did not.

CONCLUSIONS

In this exploratory analysis among patients with HFrEF, treatment with dapagliflozin reduced the incidence of new diabetes. This potential benefit needs confirmation in trials of longer duration and in people without heart failure.

The prevalence of type 2 diabetes (T2D) continues to increase worldwide. Once established, T2D can lead to several complications that can reduce both the quality and duration of life, such as retinopathy, nephropathy, neuropathy, and a variety of cardiovascular problems including heart failure. While there have been major achievements over the past three decades in reducing the risk of these complications through optimal control of glycemia, blood pressure, and lipids, the best way to avoid

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them may be to prevent diabetes itself. T2D is preceded by a prolonged asymptomatic phase marked by mild hyperglycemia (1), often referred to as "prediabetes." Safe and effective strategies to slow the otherwise progressive rise in blood glucose concentrations characterizing the transition from prediabetes to diabetes are needed. Several clinical trials have already demonstrated that T2D can in fact be prevented through lifestyle changes (healthy diet, weight loss, and increased physical activity), bariatric surgery, or the use of several glucose-lowering or weight loss medications (2). These studies have typically been conducted in higher-risk patients, such as those with prediabetes (usually, impaired glucose tolerance [IGT]), obesity, or both.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are newer glucose-lowering oral agents originally approved for use in patients with T2D requiring additional glycemic control beyond metformin. They lower blood glucose and glycosylated hemoglobin (HbA_{1c}) concentrations by inducing glucosuria. Notably, their use also leads to reductions in blood pressure and weight but does not increase the risk of hypoglycemia as monotherapy or when paired with metformin. Recent outcome trials involving T2D patients at high cardiovascular or renal risk (or both) have also demonstrated significant benefits from SGLT2 inhibitors in reducing major adverse cardiovascular events, heart failure hospitalization, and the progression of chronic kidney disease (3). Such data have earned certain members of this class specific label indications to prevent cardiovascular and kidney complications. In the recently concluded Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial, some of these advantages were extended to patients with heart failure and reduced ejection fraction (HFrEF)—the majority of whom did not have diabetes but were at high risk for its development (4). We took this opportunity to determine whether dapagliflozin could reduce the incidence of new T2D in patients enrolled in the trial without a prior diagnosis of diabetes and whose HbA_{1c} was under the prevailing diagnostic threshold of 6.5% (1).

RESEARCH DESIGN AND METHODS

DAPA-HF was a multinational randomized, double-blind, placebo-controlled trial assessing the impact of dapagliflozin on cardiovascular mortality or worsening heart failure in 4,744 patients with HFrEF. Inclusion criteria have previously been described (5). The major ones were a clinical diagnosis of heart failure with New York Heart Association (NYHA) functional class II–IV symptoms, left ventricular ejection fraction (LVEF) $\leq$40%, and elevated circulating concentrations of the N-terminal pro–B-type natriuretic peptide (NT-proBNP). Key exclusion criteria were a prior history of type 1 diabetes and an estimated glomerular filtration rate (eGFR) $<$30 mL/min/1.73 m^2.

After a screening visit during which inclusion and exclusion criteria were assessed and informed consent was obtained, eligible patients were randomized to receiving once-daily dapagliflozin 10 mg or matching placebo orally. Patients were evaluated at the clinical sites 2 weeks, 2 months, and 4 months after randomization and then every 4 months until the completion of the trial. The primary outcome of DAPA-HF was the composite of cardiovascular death or worsening heart failure, including heart failure hospitalization or urgent treatment with intravenous therapy in the outpatient setting. Secondary outcomes were the occurrence of heart failure hospitalization or cardiovascular death, heart failure hospitalization (first and recurrent) and cardiovascular death, change in heart failure symptoms (based on the validated Kansas City Cardiomyopathy Questionnaire [KCCQ] total symptom score) (6) from baseline to 8 months, a composite worsening renal function outcome, and death from any cause. The incidence of a new diagnosis of T2D in patients without diabetes at baseline was a prespecified exploratory endpoint and is the focus of this report.

All patients underwent HbA_{1c} testing (in the nonfasted state, precluding simultaneous fasting plasma glucose measurements) at baseline and at each study visit through a central laboratory, using the Bio-Rad VARIANT II ion-exchange high-performance liquid chromatography assay (Bio-Rad Laboratories, Hercules, CA). Those individuals with a prior diagnosis of T2D and those whose HbA_{1c} was $\geq$6.5% at both the enrollment and randomization visits (i.e., repeated and confirmed and therefore considered a diagnosis of T2D) were excluded from this analysis. The remaining participants constituted our study cohort, comprised of those with prediabetes at baseline (as per the definition of the American Diabetes Association [ADA] of an HbA_{1c} between 5.7 and 6.4%) (1) and individuals considered to have normoglycemia (similarly defined a HbA_{1c} $<$5.7%). Incident diabetes was defined as either an HbA_{1c} of $\geq$6.5%, measured in the central laboratory, on two consecutive follow-up visits or a clinical diagnosis of diabetes outside of the trial leading to the initiation of a glucose-lowering agent.

Statistics

Baseline characteristics were compared between groups with the two-sample *t* test and Wilcoxon rank-sum test for normal and nonnormal continuous variables, respectively, and the χ^2 test for categorical variables. In this exploratory

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analysis, the effect of dapagliflozin compared with placebo on incident diabetes was examined by means of hazard ratio (HR) and 95% CIs derived from Cox proportional hazards models with treatment allocation as the only factor in the model. To account for the competing risk of death from any cause, we performed a further sensitivity analysis using the method described by Fine and Gray (7), with incident diabetes as the outcome event and mortality due to any other cause as a competing risk. We also performed a third analysis using a logistic regression model adjusting for HbA_{1c} at baseline to assess consistency of the data, irrespective of the initial glycemic status. For all models, time to event was calculated as time from randomization to new-onset diabetes (with the time of the confirmatory HbA_{1c} measurement used or the investigator-reported date of diagnosis if recorded as an investigator-reported event) or time to death or censor—whichever occurred first. A sensitivity analysis was performed with the date of the first HbA_{1c} measurement $\geq$6.5% as the time to event of new-onset diabetes. The relative hazard of death from any cause and cardiovascular causes following a new diagnosis of diabetes was examined in a Cox proportional hazards model where an indicator of a new diabetes diagnosis was entered into the model as a time-updated covariate (with follow-up time starting at randomization). The period of risk prior to a new diagnosis of diabetes was attributed to the group with no diagnosis of diabetes for calculation of incidence rates that reflect patients' time-updated event status. The model was repeated with adjustment for randomized treatment allocation, age, sex, region, race, NYHA functional classification, LVEF, BMI, pulse, systolic blood pressure, serum creatinine, log NT-proBNP, and history of prior heart failure hospitalization, atrial fibrillation, stroke, myocardial infarction, hypertension, ischemic etiology, and use of implantable cardioverter defibrillator and/or cardiac resynchronization therapy. This analysis was repeated for the end point of recurrent heart failure hospitalizations and cardiovascular death by means of a semiparametric proportional rates model, in which the relative risk is reported as a rate ratio (8). Change in HbA_{1c} over time was analyzed with use of a mixed model for repeated measurements (adjusted for baseline values, visit, randomized treatment, and interaction of treatment and visit with a random intercept and slope per patient). All analyses were performed with Stata, version 16 (College Station, TX). A P value <0.05 was considered statistically significant.

RESULTS

The median duration of follow-up was 18.2 months (interquartile range 14.2–21.5). As previously reported, in the placebo group, 502 of 2,371 patients achieved the primary outcome of worsening heart failure or cardiovascular death (21.2% [15.6 events per 100 patient-years]), whereas this occurred in only 386 of 2,373 patients in the dapagliflozin group (16.3% [11.6 events per 100 patient-years]). The relative risk was thereby reduced by 26% (HR 0.74, 95% CI 0.65–0.85; $P < 0.001$) (4). This benefit appeared to extend to patients across baseline glycemic categories as there was no heterogeneity in the primary outcome based on the presence (HR 0.75, 95% CI 0.63–0.90; $P = 0.002$) or absence (HR 0.73, 95% CI 0.60–0.88; $P = 0.002$) of diabetes at baseline ($P_{interaction} = 0.80$) (9).

Of the 4,744 participants, 2,139 (45%) were determined to have T2D at baseline, including 1,983 (42%) with a previous established diagnosis and an additional 156 (3.3%) being newly identified based on a confirmed HbA_{1c} $\geq$6.5% at baseline. Of the 2,605 (55%) without diabetes, 1,748 (67%) had prediabetes and 857 (33%) had normoglycemia based on HbA_{1c} levels. The baseline characteristics of these groups are compared in Supplementary Table 1. Major differences between patients with prediabetes and those with an HbA_{1c} in the normoglycemic range included age (mean $\pm$ SD 67.1 $\pm$ 11.1 vs. 64.5 $\pm$ 12.5 years, $P < 0.001$), BMI (27.4 $\pm$ 5.8 vs. 26.8 $\pm$ 5.6 kg/m^2, $P = 0.023$) and (as expected, based on our definitions) HbA_{1c} (6.0% $\pm$ 0.3% vs. 5.3% $\pm$ 0.2%, $P < 0.001$), respectively. Additionally, compared with normoglycemic patients, those with prediabetes more frequently had an ischemic etiology of heart failure, more frequently had a lower mean eGFR, and were more often treated with a diuretic.

At baseline, among patients without diabetes, the mean $\pm$ SD HbA_{1c} was 5.8% $\pm$ 0.4% in the placebo group and 5.7% $\pm$ 0.4% in the dapagliflozin group. At 8 months the mean HbA_{1c} was 5.8% $\pm$ 0.5% in the placebo group and 5.8% $\pm$ 0.4% in the dapagliflozin group, with a placebo-corrected difference of -0.04% (95% CI -0.07 to -0.01) (Fig. 1). These data varied slightly, based on the presence of prediabetes at baseline (Fig. 1). In those with prediabetes, mean baseline HbA_{1c} levels were 5.9% $\pm$ 0.3% and 6.0% $\pm$ 0.3% in those treated with dapagliflozin and placebo, respectively. At 8 months following randomization, mean HbA_{1c} had fallen slightly in both groups: by -0.08% (95% CI -0.10 to -0.06) with dapagliflozin and by -0.04% (95% CI -0.07 to -0.02) with placebo, yielding a placebo-corrected reduction of -0.04% (95% CI -0.07 to 0.00; $P = 0.034$) with dapagliflozin. In normoglycemic patients, mean baseline HbA_{1c} in those treated with dapagliflozin and placebo was 5.3% $\pm$ 0.3% and 5.3% $\pm$ 0.2%, respectively. The corresponding changes in HbA_{1c} at 8 months were increases by 0.10% (95% CI 0.07–0.13) with dapagliflozin and 0.15% (95% CI 0.11–0.18) with placebo, yielding a placebo-corrected reduction of 0.05% (95% CI -0.10 to 0.00; $P = 0.051$) with dapagliflozin.

Among the 2,605 trial participants without diabetes at baseline, 157 (6.0%) developed T2D during follow-up, 150 (95.5%) of whom had prediabetes based on the ADA definition and 136 (86.6%) of whom had prediabetes using the more restrictive 6.0–6.4% criterion of the International Expert Committee (10). Those with incident T2D had a higher mean $\pm$ SD baseline HbA_{1c} (6.2% $\pm$ 0.3% vs. 5.7% $\pm$ 0.4%; $P < 0.001$), higher BMI (28.5 $\pm$ 5.9 vs. 27.1 $\pm$ 5.7 kg/m^2; $P = 0.003$), and lower eGFR (61.5 $\pm$ 17.4 vs. 68.2 $\pm$ 19.3 mL/min/1.73 m^2; $P < 0.001$) and were more commonly using a statin (72% vs. 61%; $P = 0.006$) than those whose HbA_{1c} remained in the nondiabetic range (see Table 1).

Incident diabetes occurred in 93 of 1,307 patients or 7.1% in the placebo group and 64 of 1,298 or 4.9% in the dapagliflozin group. The rate per 100 patient-years was 5.0 (95% CI 4.1–6.1) vs. 3.4 (2.7–4.3) in the placebo and dapagliflozin groups, respectively. With use of the Cox proportional hazards model, dapagliflozin led to a 32% reduction in diabetes incidence (HR 0.68, 95% CI 0.50–0.94; $P = 0.019$) (see Fig. 2). Separation of the event curves occurred early and was detectable by the 4-month visit. Results were very similar using the Fine and Gray

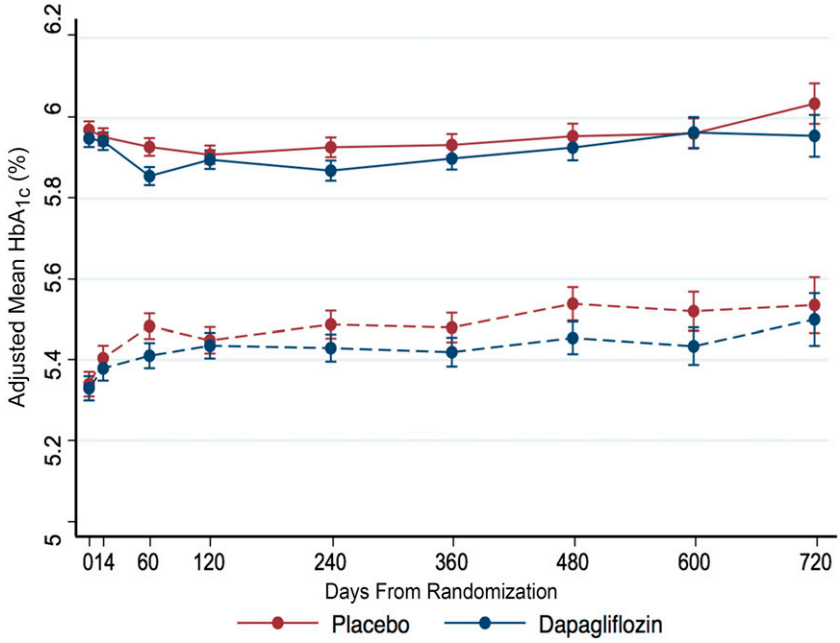

Figure 1—HbA_{1c} levels over time in the dapagliflozin vs. placebo groups. Solid lines represent trial participants with prediabetes at baseline (HbA_{1c} 5.7–6.4%) and dashed lines represent patients with normoglycemia at baseline (HbA_{1c} <5.7%). In both participants with prediabetes and participants with normoglycemia at baseline, HbA_{1c} changed minimally over time, with placebo-adjusted changes of −0.04% and −0.05% at 8 months, respectively, in the dapagliflozin groups.

model, which accounted for the competing risk of mortality; the effect size here was virtually identical at 31% (HR 0.69 [95% CI 0.50–0.95]; $P = 0.021$). After adjustment for baseline HbA_{1c} with a logistic regression model, the risk reduction was also similar (odds ratio 0.72 [95% CI 0.51–1.02]; $P = 0.068$). Furthermore, the results of a sensitivity analysis in which we used the date of the first HbA_{1c} measurement ≥6.5% as the date of onset of new diabetes gave a consistent HR of 0.68 (95% CI 0.50–0.94; $P = 0.018$) in favor of dapagliflozin.

Subgroup Analysis

There was no heterogeneity in the effect of dapagliflozin on diabetes prevention based on most key prespecified subgroups, including sex, race, prediabetes status, NYHA class, and median baseline ejection fraction (≤32% vs. >32%) (see Supplementary Fig. 1). The sole exceptions were age and baseline NT-proBNP levels. Younger individuals (≤65 years old) and those with NT-proBNP levels at or below the median appeared to garner a greater diabetes prevention benefit from active therapy than older individuals (≥65 years old) ($P_{interaction} = 0.04$) and those with higher NT-proBNP levels ($P_{interaction} = 0.01$), respectively. These interactions, however, were not adjusted for multiple comparisons and therefore could constitute chance findings.

Association Between New-Onset Diabetes and Risk of Heart Failure Outcomes

The relationship between new-onset diabetes and heart failure outcomes is shown in Table 2. Among the primary and key secondary cardiovascular outcomes, we found two significant relationships with diabetes onset as a time-updated; covariate. Following a new diagnosis of T2D, the rate of death from any cause was 16.6 per 100 patient-years compared with 7.2 for those who did not develop T2D during follow-up. The risk of death from any cause in patients with new-onset T2D was more than twofold that of patients who did not develop diabetes (unadjusted HR 2.20, 95% CI 1.36–3.55). After adjustment for baseline variables and treatment assignment, this heightened risk remained significant (adjusted HR 1.70 [95% CI 1.04–2.80]). Similar results were observed for death from cardiovascular causes. Considering the total number of heart failure hospitalizations (i.e., including recurrent events) and cardiovascular deaths, the event rates were 28.6 and 14.6 per 100 patient-years in those with and without new-onset diabetes, respectively, with an unadjusted HR of 1.90 (95% CI 1.18–3.05; $P = 0.008$). After adjustments, however, this was no longer significant (HR 1.37, 95% CI 0.83–2.24).

CONCLUSIONS

In this exploratory analysis from the DAPA-HF trial, treatment with the SGLT2 inhibitor dapagliflozin reduced the risk of incident diabetes by 32%, an effect predominantly driven by individuals with prediabetes at baseline. The absolute risk reduction was 2.2% (95% CI 0.4–4.0) with a number needed to treat of 46 (95% CI 25–283) over 18 months for people with a diabetes incidence of 5.0 per 100 patient-years. Of note, the incidence rate in the placebo group was similar to (11) or somewhat higher than (12–14) those measured in other HFrEF trials in which incident diabetes was tracked. However, it was lower than that observed in most traditional diabetes prevention trials, which have tended to be of longer duration, to have cohorts enriched for certain high risk features (e.g., IGT, obesity) that ensured more frequent progression to diabetes, and to have used diagnostic techniques of greater sensitivity (e.g., oral glucose tolerance test) (15–19).

Previous metabolic studies in people with diabetes have demonstrated that SGLT2 inhibitors, in addition to reducing blood glucose and body weight, also improve insulin sensitivity (20), decrease hyperinsulinemia (20), and enhance pancreatic β-cell function (21). Each of these mechanisms, if they also occur in individuals in prediabetes, could serve to reduce their risk of developing T2D. In DAPA-HF, a large cardiovascular outcomes trial, we were not able to explore whether any of these mechanisms were responsible for dapagliflozin's diabetes prevention effects. In this population, the potential additional benefit of increased physical activity in the dapagliflozin group, as suggested by improved scores on the KCCQ (6), may have contributed. Indeed, heart failure is known to be an insulin resistant state, likely the result of increased stress hormones and decreased physical activity (22). Anything that improves heart failure risk may improve the metabolic milieu in which diabetes

Table 1—Baseline characteristics by new-onset T2D status in patients without T2D at baseline

	No new-onset T2D	New-onset T2D	*P*
N	2,448	157	
Age, years	66.2 ± 11.7	66.7 ± 10.7	0.55
Sex, *n* (%)			0.86
Female	593 (24.2)	39 (24.8)	
Male	1,855 (75.8)	118 (75.2)	
Race, *n* (%)†			0.41
White	1,731 (70.7)	113 (72.0)	
Asian	593 (24.2)	32 (20.4)	
Black or African American	89 (3.6)	9 (5.7)	
Other	35 (1.4)	3 (1.9)	
Region, *n* (%)			0.31
Asia/Pacific	586 (23.9)	31 (19.7)	
Europe	1,129 (46.1)	74 (47.1)	
North America	324 (13.2)	18 (11.5)	
South America	409 (16.7)	34 (21.7)	
BMI, kg/m^2§	27.1 ± 5.7	28.5 ± 5.9	0.003
HbA_{1c}, %	5.7 ± 0.4	6.2 ± 0.3	<0.001
eGFR			
Mean, mL/min/1.73 m^2	68.2 ± 19.3	61.5 ± 17.4	<0.001
Rate <60 mL/min/1.73 m^2, *n* (%)	868 (35.5)	76 (48.4)	0.001
Systolic blood pressure, mmHg	120.6 ± 16.0	120.8 ± 17.3	0.84
NYHA functional classification, *n* (%)			0.40
II	1,737 (71.0)	104 (66.2)	
III	692 (28.3)	51 (32.5)	
IV	19 (0.8)	2 (1.3)	
LVEF, %	30.9 ± 6.9	30.5 ± 6.8	0.42
NT-proBNP, median (IQR), pg/mL	1,406 (828–2,463)	1,585 (832–2,984)	0.20
KCCQ-TSS, median (IQR)	79.2 (61.5–92.7)	75.0 (60.4–88.5)	0.049
Principal cause of heart failure, *n* (%)			0.12
Ischemic	1,249 (51.0)	92 (58.6)	
Nonischemic	983 (40.2)	50 (31.8)	
Unknown	216 (8.8)	15 (9.6)	
Medical history, *n* (%)			
Prior hospitalization for heart failure	1,128 (46.1)	74 (47.1)	0.80
Atrial fibrillation	950 (38.8)	72 (45.9)	0.079
Heart failure medication, *n* (%)			
Diuretic	1,982 (81.0)	142 (90.4)	0.003
ACE inhibitor	1,402 (57.3)	87 (55.4)	0.65
ARB	645 (26.3)	47 (29.9)	0.32
Sacubitril-valsartan	266 (10.9)	13 (8.3)	0.31
β-Blocker	2,338 (95.5)	153 (97.5)	0.25
Mineralocorticoid receptor antagonist	1,728 (70.6)	113 (72.0)	0.71
Digitalis	421 (17.2)	37 (23.6)	0.042
Statin	1,494 (61.0)	113 (72.0)	0.006

Data presented as means ± SD unless otherwise indicated. Percentages may not total 100 because of rounding. KCCQ total symptom score (KCCQ-TSS): range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure. A score of ≥75 is considered to reflect satisfactory health status. IQR, interquartile range. †Race was reported by the investigators. §BMI is calculated as weight in kilograms divided by the square of the height in meters.

tends to develop. Due to relatively small numbers of cases of new-onset diabetes, we could not conduct an analysis to determine whether improved functional scores occurred more often in those whose HbA_{1c} remained in the nondiabetic range.

With the increasing prevalence of diabetes throughout the world, simple, safe, and effective preventive strategies are needed. Lifestyle changes are widely and appropriately endorsed as the optimal initial strategy, with relative risk reduction (RRR) for new-onset diabetes reported to be as high as 58% (16,23). Several medications have also been tested, with benefits seen for certain glucose-lowering agents, such as metformin (RRR 31%) (16), rosiglitazone and pioglitazone (52–72%) (17,19,24), and acarbose (25%) (15). Treatment with antiobesity drugs has also been assessed, with RRR in the same general range (orlistat, 37% [25]; topiramate/phentermine, 71–79% [26], liraglutide, 79% [27]; and lorcaserin, 23% [28]). Finally, several ACE inhibitors and angiotensin II receptor blockers (ARBs) have been shown to reduce the incidence of new diabetes (by 25% in an early pooled meta-analysis) (29), including valsartan (RRR 14%) in a dedicated diabetes prevention trial (18). Of specific interest in a population with heart failure, candesartan therapy was demonstrated to lower the risk of diabetes by 22% (12). It is therefore significant that dapagliflozin reduced the risk of new-onset diabetes even in heart failure patients, the vast majority of whom were treated with an ACE inhibitor or ARBs. Of all of these potential therapies, only metformin has been recommended by the ADA for diabetes prevention (23) and only in the highest-risk patients with prediabetes. This is based on its long safety record, its low cost, and the fact that it is already considered "foundation therapy" for early T2D. Of note, no drug has yet been formally approved by the U.S. Food and Drug Administration for the specific indication of diabetes prevention.

Diabetes prevention studies have predominately focused on the progression of hyperglycemia and have not been powered to assess the impact of diabetes prevention on chronic vascular complications. Logically, if diabetes is prevented, patients would be at lower risk for developing microvascular complications, such as diabetic retinopathy or diabetic nephropathy. In the Diabetes Prevention Program (DPP), the investigators did not find any overall differences in aggregate microvascular complications between the lifestyle, metformin, and placebo groups (30). However, those trial participants who did not develop diabetes experienced fewer microvascular events than those who did (30). These data suggest that diabetes prevention could, over time, reduce at least some of the highly morbid complications of this disease.

It is even more difficult to demonstrate any effect of diabetes prevention on macrovascular events, since atherosclerotic cardiovascular disease and its sequelae also develop in individuals without diabetes and, moreover, are not as

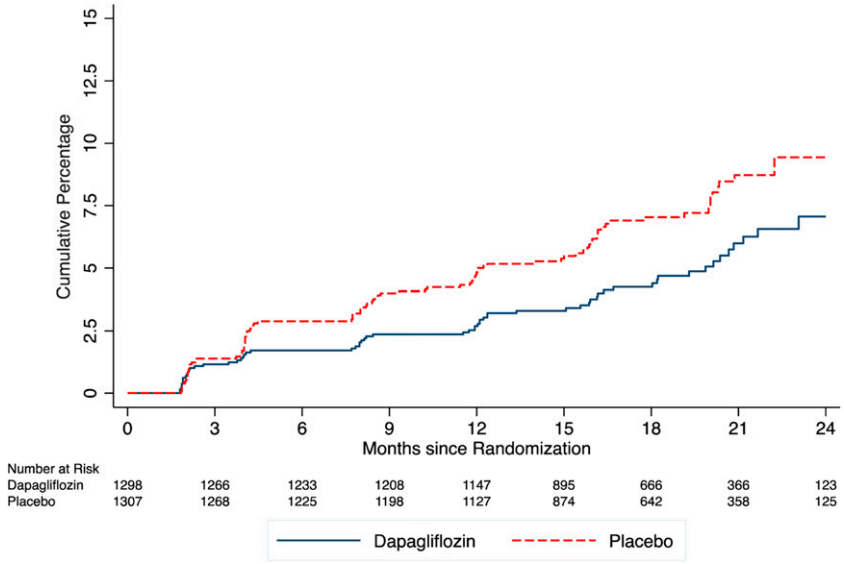

Figure 2—Incidence of new-onset T2D in dapagliflozin vs. placebo groups. The HR for incident T2D in the dapagliflozin group compared with placebo was 0.68 (95% CI 0.50–0.94; $P = 0.019$), with an early divergence of the event curves.

clearly related to the degree of hyperglycemia as are microvascular complications. In the DPP, those patients who were assigned to lifestyle intervention and who experienced reduced incidence of diabetes also enjoyed improvement in several cardiovascular risk factors—but not in actual cardiovascular events (31). Indeed, any effect of diabetes prevention on actual cardiovascular complications may be difficult to confirm in a trial, given their multifactorial nature and the many years required for their evolution. In the Study to Prevent NIDDM (STOP-NIDDM), use of the α-glucosidase inhibitor acarbose reduced both incidence of diabetes and that of myocardial infarction in IGT patients (32). However, the latter effect could not be confirmed in the larger Acarbose Cardiovascular Evaluation trial (33). In the Insulin Resistance Intervention after Stroke (IRIS) trial, treatment with the thiazolidinedione pioglitazone reduced the incidence of both stroke and myocardial infarction in an insulin resistant group of patients with recent stroke or transient ischemic attack (34) while also decreasing the patients' development of new-onset diabetes (24). It remains unknown, however, whether these two effects were necessarily linked. Finally, indirect evidence from follow-up of the original Da Qing study cohort suggested that T2D prevention, at least through lifestyle changes, may eventually attenuate future all-cause mortality (35).

DAPA-HF is noteworthy for diabetes specialists for three reasons. First, it is the first study to suggest a diabetes prevention effect from an SGLT2 inhibitor. Some might argue that diabetes prevention is not important in an older, sicker population of patients with limited life expectancy. However, this first foray into the field of diabetes prevention with SGLT2 inhibition could spark other trials in younger, healthier groups of patients—who might benefit to a greater degree by avoiding or at least delaying incident diabetes. Second, it is the first study to demonstrate that a single drug may prevent both diabetes and death, albeit in a specific group of patients with heart failure. Further investigation will, of course, be necessary to determine whether and to what extent these outcomes may be associated. Our finding that those patients who developed new-onset diabetes had a higher mortality rate does not at all prove that diabetes prevention mediated this benefit. Indeed, in previous post hoc analyses from other SGLT2 inhibitor trials in patients with T2D, the cardiovascular benefits of this glucose-lowering class appear to be largely disassociated from its glucose-lowering effect (9,36). The patients who developed new-onset diabetes had more advanced heart failure at baseline and, therefore, were at higher risk initially. Also, since those participants who did not develop diabetes were more likely to be on dapagliflozin, our observations may be confounded by the effect of dapagliflozin on cardiovascular outcomes, although we did adjust for randomized treatment assignment. Nonetheless, it is possible that preventing diabetes might

Table 2—Primary and key secondary outcomes with the event of new-onset T2D as a time-updated covariate

	Event rate/100 PY (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)*
All-cause mortality			
No new-onset T2D ($n = 2,448$)	7.2 (6.4–8.1)	1.00 (reference)	1.00 (reference)
New-onset T2D ($n = 157$)	16.6 (10.5–26.3)	2.20 (1.36–3.55); $P = 0.001$	1.70 (1.04–2.80); $P = 0.035$
Cardiovascular death			
No new-onset T2D ($n = 2,448$)	5.8 (5.1–6.7)	1.00 (reference)	1.00 (reference)
New-onset T2D ($n = 157$)	14.7 (9.0–24.1)	2.43 (1.46–4.06); $P = 0.001$	1.77 (1.04–3.02); $P = 0.035$
Total HF hospitalizations (including recurrent) and cardiovascular death**			
No new-onset T2D ($n = 2,448$)	14.6 (13.4–15.9)	1.00 (reference)	1.00 (reference)
New-onset T2D ($n = 157$)	28.6 (20.1–40.6)	1.90 (1.18–3.05); $P = 0.008$	1.37 (0.83–2.24); $P = 0.22$

PY, person-years. *Adjustment for randomized treatment, age, sex, region, race, NYHA functional classification, LVEF, BMI, pulse, systolic blood pressure, serum creatinine, log NT-proBNP, and history of previous heart failure (HF) hospitalization, atrial fibrillation, stroke, myocardial infarction, hypertension, ischemic etiology, and use of implantable cardioverter defibrillator and/or cardiac resynchronization therapy. **Estimates presented are rate ratios.

play a role in improving heart failure outcomes, since the coexistence of diabetes is known to worsen overall prognosis in heart failure patients. A recent large cohort study from Denmark, for example, revealed that the onset of diabetes after a first hospitalization for heart failure is associated with a nearly 50% higher mortality (37). Third, DAPA-HF is the first trial showing a reduction in incident diabetes without a significant effect on mean HbA_{1c}. Each of the prior positive diabetes prevention trials that reported HbA_{1c} levels at baseline and during the trial has demonstrated small but significant differences in this biomarker of average glycemia between the active therapy and placebo groups (16,19,27,28). This has raised concerns that the diabetes "prevention" effects of the study drug may have merely reflected numerical reductions in glucose concentrations and therefore represented nothing more than a masking of the underlying disease process (38). Because there was no major change in mean HbA_{1c} in the participants without diabetes in DAPA-HF, such an argument may be less persuasive. Yet, since our outcome measure was essentially based on changes in HbA_{1c}, differential effects of the two treatment arms on this measure at an individual patient level over time likely drove the risk reduction. Admittedly, it is very difficult to disentangle the glucose lowering from the diabetes prevention effects of any diabetes medication. Nonetheless, our findings may provide further insights into the underlying effect of SGLT2 inhibition on β-cell dysfunction in the progression from prediabetes to diabetes—a notion that will require further study of a more mechanistic nature.

Limitations

Our study has several limitations. As noted, in diabetes prevention studies involving glucose-lowering agents, questions arise as to whether the apparent reduction in the incidence of diabetes is measurable only because of transient reductions in glycemia, merely delaying diagnosis but not actually preventing disease progression per se. The lack of a significant effect of dapagliflozin on mean HbA_{1c} may partially allay such concerns. Moreover, this may be a semantic argument, since even a quantifiable delay in diabetes diagnosis could still potentially mitigate the deleterious health effects of chronic hyperglycemia over time. We did not, however, conduct a washout at the end of the trial with retesting for diabetes to assess whether patients who remained without diabetes during active therapy might experience an increased incidence after stopping the study drug. Accordingly, we could not determine whether the effect of dapagliflozin on new-onset diabetes would extend beyond the fixed duration of drug exposure. Traditional diabetes prevention trials have demonstrated a relatively rapid increase in diabetes incidence in a significant proportion of participants at the end of such a washout period (39). So, prevention effects are likely to be strongest during active therapy with glucose-lowering agents and there is no a priori reason to think this would not be the case with an SGLT2 inhibitor. In this event-driven heart failure study with a higher-than-expected event rate for the primary outcome, the study duration was shorter than in most diabetes prevention trials. Whether the effect of dapagliflozin on new-onset diabetes would persist beyond 18 months is speculative. In the longer T2D prevention trials, the effects of the investigational agent appear to persist for up to 3–4 years with no narrowing of the event curves over time (16,17,25,27). Because DAPA-HF was designed as a heart failure trial, we captured diabetes "events" mainly on the basis of periodic measurement of HbA_{1c}. We did not assess fasting plasma glucose or oral glucose tolerance; these assessments are more typical in standard diabetes prevention trials and, if performed, can potentially affect the results. We also did not measure erythropoietin levels (which have been reported to increase after SGLT2 inhibition). Conceivably, increased red blood cell turnover, after erythropoietin stimulation, might affect rates of hemoglobin glycation. However, since the actual differences in HbA_{1c} were minimal, we do not feel that this explains the differential effect on the incidence of new-onset diabetes. Finally, because of the population studied in DAPA-HF, these data cannot necessarily be extrapolated to a non-HFrEF population, including those with heart failure with preserved ejection fraction or those without heart failure.

Summary

During active therapy, the SGLT2 inhibitor dapagliflozin decreased the incidence of T2D by 32% in 2,605 participants in the DAPA-HF trial who did not have diabetes at baseline. This effect was principally driven by participants with prediabetes at baseline. Interestingly, this effect size is nearly identical to that demonstrated in the DPP with metformin (16), the drug most commonly considered for use in diabetes prevention. While the major role of dapagliflozin in HFrEF is to reduce cardiovascular mortality and worsening of heart failure, decreasing the incidence of new diabetes may be considered an additional benefit. These data need to be confirmed with dapagliflozin and/or other SGLT2 inhibitors in trials of longer duration and in a broader population of patients with prediabetes who do not necessarily have heart failure. Finally, further investigation will also be required to explore any potential links between diabetes prevention and the cardiovascular benefits in this patient population.

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