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

Running title: *Dapagliflozin and Incident Type 2 Diabetes in DAPA-HF*

Authors:
Silvio E Inzucchi, MD[1]
Kieran F Docherty, MB, ChB[2]
Lars Køber, MD, DMSc[3]
Mikhail N Kosiborod, MD[4]
Felipe A Martinez, MD[5]
Piotr Ponikowski, MD, PhD[6]
Marc S Sabatine, MD, MPH[7]
Scott D Solomon, MD[8]
Subodh Verma, MD, PhD[9]
Jan Bělohlávek, MD, PhD[10]
Michael Böhm, MD, PhD[11]
Chern-En Chiang, MD, PhD[12]
Rudolf A. de Boer, MD, PhD[13]
Mirta Diez, MD[14]
Andre Dukát, MD, PhD[15]
Charlotta E.A. Ljungman, MD, PhD[16]
Olof Bengtsson, Ph Lic[17]
Anna Maria Langkilde, MD, PhD[17]
Mikaela Sjöstrand, MD, PhD[17]
Pardeep S Jhund, MBChB, MSc, PhD[2]
John JV McMurray, MD[2]
on behalf of the DAPA-HF Investigators and Committees

Affiliations:
[1]Section of Endocrinology, Yale University School of Medicine, New Haven, CT, USA
[2]BHF Cardiovascular Research Centre, University of Glasgow, Glasgow, UK
[3]Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark
[4]Saint Luke's Mid America Heart Institute and University of Missouri-Kansas City, Kansas City, Missouri, USA;
[5]National University of Cordoba, Cordoba, Argentina
[6]Wroclaw Medical University, Wroclaw, Poland;
[7]TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA
[8]Cardiovascular Division, Brigham and Women's Hospital, Boston, MA, USA
[9]Division of Cardiac Surgery, St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada
[10]2nd Department of Medicine - Cardiovascular Medicine, 1st Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Prague Czech Republic
[11]Internal Medicine Clinic III (Bohm), Saarland University Medical Center, Homburg/Saar, Germany
[12]Division of Cardiology, Taipei Veterans General Hospital and National Yang-Ming University, Taipei, Taiwan.
[13]Department of Cardiology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands.
[14] Division of Cardiology, Instituto Cardiovascular de Buenos Aires, Argentina
[15]Fifth Department of Internal Medicine, Comenius University in Bratislava, Bratislava, Slovakia
[16]Department of Molecular and Clinical Medicine and Cardiology, Sahlgrenska Academy, Gothenburg, Sweden;
[17]AstraZeneca, Gothenburg, Sweden;

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Corresponding author:
Silvio E. Inzucchi MD
Section of Endocrinology
Fitkin 106
Yale School of Medicine
333 Cedar Street
New Haven, CT 06520-8020

Objective

The SGLT2 inhibitor dapagliflozin reduced the risk of cardiovascular mortality and worsening heart failure in the Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure trial (DAPA-HF). This report explores the effect of dapagliflozin on incident type 2 diabetes in the non-diabetic cohort enrolled in the trial.

Research Design/Methods

The subgroup of 2605 patients with heart failure and reduced ejection fraction (HFrEF), no prior history of diabetes, and a HbA1c 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 HbA1c 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 HbA1c 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 93/1307 patients (7.1%) in the placebo group and 64/1298 (4.9%) in the dapagliflozin group. Dapagliflozin led to a 32% reduction in diabetes incidence (HR 0.68, 95% CI, 0.50-0.94; p=0.019.) More than 95% of the participants who developed type 2 diabetes had prediabetes at baseline (HbA1c 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.

INTRODUCTION

The prevalence of type 2 diabetes (T2D) continues to increase world-wide. 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 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 (HbA1c) 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 trial (DAPA-HF), 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 HbA1c was under the prevailing diagnostic threshold of 6.5%.[1]

METHODS

DAPA-HF was a multi-national randomized, placebo-controlled trial assessing the impact of dapagliflozin on cardiovascular mortality or worsening heart failure in 4744 patients with HFrEF. Inclusion criteria have been previously 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) ≤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 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, 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 total symptom score [TSS])[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 is the focus of this report.

All patients underwent HbA1c testing (in the non-fasted state, precluding simultaneous fasting plasma glucose measurements) at baseline and at each study visit through a central laboratory, using the Bio-Rad Variant II HMT370 ion-exchange high-performance liquid chromatography (HPLC) assay (Bio-Rad, Hercules, CA, USA.) Those individuals with a prior diagnosis of T2D and those whose HbA1c was ≥6.5% at both the enrollment and randomization visits (i.e., repeated and confirmed, and therefore diagnosed with new 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 a HbA1c between 5.7-6.4%)[1] and individuals considered to have normoglycemia (similarly defined a HbA1c <5.7%). Incident diabetes was defined as either a HbA1c of ≥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 by using the two sample T-test and Wilcoxon rank-sum test for normal and non-normal continuous variables respectively, and the χ^2 test for categorical variables. In this exploratory analysis, the effect of dapagliflozin compared to placebo on incident diabetes was examined by means of hazard ratio (HR) and 95% confidence intervals (CI) 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, a further sensitivity analysis was performed using the method described by Fine and Gray, with incident diabetes as the outcome event and mortality due to any other cause as a competing risk.[7] We also performed a third analysis using a logistic regression model adjusting for HbA1c 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 HbA1c 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 using the date of the first HbA1c measurement ≥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 DM was examined in a Cox proportional hazards model where an indicator of a new DM diagnosis was entered into the model as a time-updated covariate (with follow-up time starting at randomization). The period at risk prior to a new diagnosis of DM was attributed to the group with no diagnosis of DM in order to calculate incidence rates which reflect patients' time-updated event status. The model was repeated with adjustment for randomised treatment allocation, age, sex, region, race, NYHA functional classification, left ventricular ejection fraction, body mass index, pulse, systolic blood pressure, serum creatinine, log NT-proBNP, 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 endpoint 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 HbA1c over time was analyzed using 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 using Stata version 16 (College Station, TX, USA). 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, 502/2371 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 386/2373 patients in the dapagliflozin group (16.3%; 11.6 events per 100 patient-years.) The relative risk was thereby reduced by 26% (hazard ratio [HR][0.74, 95% confidence interval [CI] 0.65, 0.85; p<0.001).[4] This benefit appeared to extend to patients across baseline glycemic categories as there, with 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-value for interaction=0.80.)[9]

Of the 4744 participants, 2139 (45%) were determined to have T2D at baseline, including 1983 (42%) with a previous established diagnosis and an additional 156 (3.3%) being newly identified based on a confirmed HbA1c ≥6.5% at baseline. Of the 2605 (55%) without diabetes, 1748 (67%) had prediabetes and 857 (33%) had normoglycemia based on their HbA1c levels. The baseline characteristics of these groups are compared in **Supplemental Table 1.** Major differences between patients with prediabetes and those with an HbA1c in the normoglycemic range included age (67.1 years ± 11.1 vs. 64.5 years ±12.5, p<0.001), BMI (27.4±5.8 vs. 26.8±5.6 kg/m^2, p=0.023) and (as expected, based on our definitions) mean HbA1c (6.0%±0.3 vs. 5.3%±0.2, p<0.001). Additionally, compared to normoglycemic patients, those with prediabetes more frequently had an ischemic etiology of heart failure, a lower mean eGFR and were more often treated with a diuretic.

At baseline, amongst patients without diabetes, the mean HbA1c was 5.8% ±0.4% in the placebo group and 5.7% ±0.4% in the dapagliflozin group. At 8 months the mean HbA1c in the placebo group was 5.8% ±0.6%, 5.8% ±0.4% in the dapagliflozin group, with a placebo-corrected difference of -0.04% (95%CI -0.07 to -0.01). **(Figure 1 A)** These data varied slightly, based on the presence of prediabetes at baseline (Figure 1 B). In those with prediabetes, mean baseline HbA1c levels were 5.9%±0.3% and 6.0%±0.3% in those treated with dapagliflozin and placebo, respectively. At 8-months following randomization, mean HbA1c had fallen slightly in both groups: -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 HbA1c in those treated with dapagliflozin and placebo was 5.3%±0.3% and 5.3%±0.2%, respectively. The corresponding changes in HbA1c at 8 months were +0.10% (95% CI +0.07 to +0.13) with dapagliflozin and +0.15% (95% CI +0.11 to +0.18) with placebo, yielding a placebo-corrected reduction of 0.05% (-0.10% to 0.00%, p=0.051) with dapagliflozin.

Amongst the 2605 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 baseline A1c (6.2 ±0.3 vs 5.7 ±0.4%; p<0.001), larger BMI (28.5 ±5.9 vs 27.1 ±5.7 kg/m^2; p=0.003), lower eGFR (61.5 ±17.4 vs 68.2 ±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 HbA1c remained in the non-diabetic range (see **Table 1**.)

Incident diabetes occurred in 93/1307 patients or 7.1% in the placebo group and 64/1298 or 4.9% in the dapagliflozin group. The rate per 100 patient-years was 5.0 (95% CI 4.1-6.1) versus 3.4 (2.7-4.3) in the placebo and dapagliflozin groups, respectively. Using 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 **Figure 2)** Separation of the event curves occurred early and was detectable by the 4-month visit. Results were very similar using the Fine & Gray model, which accounted for the competing risk of mortality; the effect size here was virtually identical at 31% (HR 0.69 [0.50-0.95]; p=0.021.) After adjustment for baseline HbA1c using a logistic regression model, the risk reduction was also similar (odds ratio, 0.72 [0.51-1.02]; p=0.068.) Furthermore, the results of a sensitivity analysis using the date of the first HbA1c measurement ≥6.5% as the date of onset of

new diabetes gave a consistent hazard ratio of 0.68 (95% CI 0.50-0.94; p=0.019) in favor of dapagliflozin.

Subgroup analysis

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

Effect of new-onset diabetes on risk of heart failure outcomes

The relationship between new onset diabetes and heart failure outcomes is shown in **Table 2**. Amongst 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 to 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 two-fold 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 [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 DM, respectively, with an unadjusted HR of

1.90 (1.18-3.05; p=0.008). After adjustments, however, this was no longer significant (HR 1.37 [0.83-2.24]).

DISCUSSION

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 (NNT) 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[11] to or somewhat higher[12-14] than 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 tended to be of longer duration, have generally enriched their cohorts for certain high-risk features (e.g., IGT, obesity) that ensured more frequent progression to diabetes, and 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 beta-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 Kansas City Cardiomyopathy Questionnaire (KCCQ)[6], may have contributed. Indeed, HF is known to be an insulin resistant state, likely the result of increased stress hormones and decreased physical activity.[22] Anything that improves HF may improve the metabolic milieu in which diabetes tends to develop. Due to a 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 HbA1c remained in non-diabetic 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 from certain glucose-lowering agents, such as metformin (RRR 31%)[16], rosiglitazone and pioglitazone (52% to 72%)[17,19,24], and acarbose (25%).[15] Treatment with anti-obesity drugs has also been assessed, with RRR in the same general range (orlistat, 37%[25]; topiramate/phentermine, 71 to 79%[26], and 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 a early pooled meta-analysis)[29], including valsartan (RRR 14%) in a dedicated diabetes prevention trial.[18] Of specific interest in a heart failure population, candesartan therapy was demonstrated to lower the risk of diabetes by 22%.[30] 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, 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 US Food and Drug Administration (FDA) 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.[31] However, those trial participants who did not develop diabetes experienced less microvascular events than those who did.[31] 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 non-diabetic individuals and, moreover, are not as 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.[32] 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) Trial, use of the alpha-glucosidase inhibitor acarbose reduced both the incidence of diabetes as well as that of myocardial infarction in IGT patients.[33] However, the latter effect could not be confirmed in the larger Acarbose Cardiovascular Evaluation (ACE) trial.[34] In 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 (TIA)[35] while also decreasing their development of new onset diabetes.[24] It remains unknown, however, if 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.[36]

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 SGLT2i trials in patients with T2D, the cardiovascular benefits of this glucose-lowering class appear to be largely disassociated from its glucose-lowering effect.[9,37] 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 the cardiovascular outcomes, although we did adjust for randomized treatment assignment. Nonetheless, it is possible that preventing diabetes might 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.[38] Third, DAPA-HF is the first trial showing a reduction in incident diabetes without a significant effect on mean HbA1c. Each of the prior positive diabetes prevention trials that reported baseline and on-trial HbA1c levels have 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.[39] Because there was no major change in mean HbA1c in the non-diabetic participants in DAPA-HF, such an argument may be less persuasive. Yet, since our outcome measure was essentially based on changes in HbA1c, 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 beta 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 some 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 HbA1c may partially allay such concerns. Moreover, this may be a semantic argument since even a quantifiable delay in the diabetes diagnosis could still potentially mitigate the deleterious health effects of chronic hyperglycemia over time. We did not, however, conduct a wash-out at the end of the trial with retesting for diabetes to assess whether patients who remained non-diabetic during active therapy might experience an increased incidence after stopping 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.[40] 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 SGLT2i. 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 HbA1c. We did not assess fasting plasma glucose or oral glucose tolerance, assessments which are more typical in standard diabetes prevention trials and, if performed, may potentially have affected 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 HbA1c were minimal, we don't feel 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 (HFpEF) or those without heart failure.

SUMMARY

During active therapy, the SGLT2i dapagliflozin decreased the incidence of T2D by 32% in 2605 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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Guarantor Statement
SEI and KD are the guarantors of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Author Contribution Statement
SEI wrote the manuscript, developed the study, researched the data, and contributed to the discussion. KFD, PSJ, JJVM developed the study, collected and researched the data, contributed to the discussion and reviewed/edited the manuscript. LK, MNK, FAM. PP. MSS. SDS, OB, AML, MS developed the study, collected the data, contributed to the discussion, and reviewed/edited the manuscript. SV, JB, MB, CEC, RAdB, MD, AD, and CEAL collected the data, contributed to the discussion. and reviewed/edited the manuscript

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Figure Legends

Figure 1. HbA1c levels over time in the dapagliflozin vs. placebo groups

Panel A represents all patients without diabetes at baseline. In Panel B solid lines represent trial participants with prediabetes at baseline (HbA1c 5.7-6.4%) and dashed lines represent patients with normoglycemia at baseline (HbA1c <5.7%) In both groups, HbA1c changed minimally over time, with placebo-adjusted changes of -0.04% and -0.05% at eight months, respectively in the dapagliflozin groups.

Figure 2. Incidence of new onset T2D in dapagliflozin vs. placebo groups

The hazard ratio 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.

Supplemental Figure 1. Effect of dapagliflozin on incident diabetes by relevant subgroups

No heterogeneity of the treatment effect on incident T2D was found except for nominal interactions for age and baseline NT-proBNP.

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

	No New Onset T2D	New Onset T2D	p-value
	N=2448	**N=157**	
Age – yr	66.2±11.7	66.7±10.7	0.55
Sex - no (%)			0.86
Female	593 (24.2)	39 (24.8)	
Male	1,855 (75.8)	118 (75.2)	
Race – no. (%)†			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 – no. (%)			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)	
Body-mass index§	27.1±5.7	28.5±5.9	0.003
HbA1c – %	5.7±0.4	6.2±0.3	<0.001
Estimated GFR			
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 – no. (%)	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 – no. (%)			0.40
II	1,737 (71.0)	104 (66.2)	
III	692 (28.3)	51 (32.5)	
IV	19 (0.8)	2 (1.3)	
Left ventricular ejection fraction – %	30.9±6.9	30.5±6.8	0.42
Median NT-proBNP (IQR) – pg/ml	1406 (828-2463)	1585 (832-2984)	0.20
Median KCCQ-TSS (IQR)	79.2 (61.5-92.7)	75.0 (60.4-88.5)	0.049
Principal cause of heart failure – no. (%)			0.12
Ischemic	1,249 (51.0)	92 (58.6)	
Non-ischemic	983 (40.2)	50 (31.8)	
Unknown	216 (8.8)	15 (9.6)	
Medical history – no. (%)			
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 – no (%)			
Diuretic	1982 (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
Beta-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 mean (SD) unless otherwise indicated.
Percentages may not total 100 because of rounding.
ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, GFR glomerular filtration rate, IQR interquartile range, LVEF left ventricular ejection fraction, MRA mineralocorticoid receptor antagonist, N-terminal pro-B-type natriuretic peptide and NYHA New York Heart Association. KCCQ-TSS Kansas City Cardiomyopathy Questionnaire total symptom score - range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure. A score of 75 or above is considered to reflect satisfactory health status.
† Race was reported by the investigators
§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

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

	Event rate/100 PY	**Unadjusted HR (95% CI)**	**Adjusted HR (95% CI)***
All-cause mortality			
No new-onset T2D (n=2448)	7.2 (6.4-8.1)	1.00	1.00
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=2448)	5.8 (5.1-6.7)	1.00	1.00
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=2448)	14.6 (13.4-15.9)	1.00	1.00
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

*Adjusted for randomized treatment, age, sex, region, race, NYHA functional classification, left ventricular ejection fraction, body mass index, pulse, systolic blood pressure, serum creatinine, log NT-proBNP, history of previous 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 rat