

Dapagliflozin and New-Onset Type 2 Diabetes in Patients with Chronic Kidney Disease or Heart Failure: Pooled Analysis of the DAPA-CKD and DAPA-HF Trials

Prof Peter Rossing, MD^{1,2}; Prof Silvio E. Inzucchi, MD³; Priya Vart, PhD⁴; Niels Jongs, PhD⁴; Kieran F. Docherty, MB ChB⁵; Pardeep S. Jhund, MB ChB⁵; Prof Lars Køber, MD⁶; Prof Mikhail N. Kosiborod, MD⁷; Prof Felipe A. Martinez, MD⁸; Prof Piotr Ponikowski, MD⁹; Prof Marc S. Sabatine, MD¹⁰; Prof Scott D. Solomon, MD¹⁰; Prof David L. DeMets, PhD¹¹; Olof Bengtsson, Ph Lic¹²; Magnus Lindberg, MSc¹²; Anna Maria Langkilde, MD¹²; Mikaela Sjöstrand, MD¹²; Bergur V. Stefansson, MD¹²; Cecilia Karlsson, MD¹²; Prof Glenn M. Chertow MD¹³; Prof Fan Fan Hou, MD¹⁴, Prof Ricardo Correa-Rotter, MD¹⁵; Prof Robert D. Toto, MD¹⁶; Prof David C. Wheeler, MD¹⁷; Prof John JV. McMurray, MD⁵; Prof Hiddo J.L. Heerspink, PhD^{4,18}

For the DAPA-CKD and DAPA-HF Trial Committees and Investigators

1. Steno Diabetes Center Copenhagen, Gentofte, Denmark
2. Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
3. Section of Endocrinology, Yale University School of Medicine, New Haven, Connecticut, USA
4. Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands
5. British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom
6. Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark

7. Saint Luke's Mid America Heart Institute and University of Missouri-Kansas
City, Kansas City, Missouri, USA
8. University of Cordoba, Cordoba, Argentina
9. Wroclaw Medical University, Wroclaw, Poland
10. Cardiovascular Division, Brigham and Women's Hospital, and Harvard
Medical School
11. Department of Biostatistics and Medical Informatics, University of Wisconsin,
Madison, Wisconsin, USA
12. BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden
13. Departments of Medicine and Epidemiology and Population Health, Stanford
University School of Medicine, Stanford, CA, USA
14. Division of Nephrology, Nanfang Hospital, Southern Medical University,
National Clinical Research Center for Kidney Disease, Guangzhou, China
15. National Medical Science and Nutrition Institute Salvador Zubirán, Mexico
City, Mexico
16. Department of Internal Medicine, UT Southwestern Medical Center, Dallas,
TX, USA
17. Department of Renal Medicine, University College London, London, UK
18. The George Institute for Global Health, Sydney, Australia

Corresponding author: Prof. Dr. Hiddo J.L. Heerspink

Department of Clinical Pharmacy and Pharmacology

De Brug 50D-1-015; EB70

University Medical Centre Groningen

PO BOX 30001

9700 AD Groningen

The Netherlands

Tel: +31 50 361 7859

Email: h.j.lambers.heerspink@umcg.nl

Target Journal: *Lancet Diabetes & Endocrinology*

Word count abstract: 246 (250)

Word count manuscript: 3,713 (3500)

Figures/tables: 4 figures/1 tables (5 total)

References: 29 (30)

Abstract

Background: Chronic kidney disease (CKD) and heart failure (HF) are insulin resistant states associated with a high incidence of diabetes. We assessed the effect of dapagliflozin on new-onset type 2 diabetes (T2D) in the DAPA-CKD (NCT03036150) and DAPA-HF (NCT03036124) trials using pooled individual participant data.

Methods: Participants with no prior history of diabetes and HbA1c <6.5% at baseline were included (4003 participants; DAPA-CKD n=1398 and DAPA-HF n=2605). New-onset T2D was a pre-specified exploratory endpoint and was identified by serial trial measurements of HbA1c (two consecutive values $\geq 6.5\%$), or following a clinical diagnosis of diabetes between trial visits. Time to new-onset T2D was analyzed in a Cox proportional Hazards model.

Findings: Over a median follow-up of 21.2 months, 126/2008 (6.3%) patients randomised to placebo and 85/1995 (4.3%) patients randomised to dapagliflozin developed T2D, corresponding to event rates of 3.9/100 patient-years and 2.6/100 patient-years, respectively (hazard ratio [95%CI] 0.67 [0.51, 0.88], $p=0.0040$). There was no heterogeneity between studies (p -interaction=0.77) and there was no clear evidence that the effect of dapagliflozin varied in pre-specified subgroups including sex, age, glycaemic status, body mass index, glomerular filtration rate, systolic blood pressure, and baseline cardiovascular medication use. More than 90% of the participants who developed T2D had prediabetes at baseline (HbA1c 5.7–6.4%). Mean HbA1c remained unchanged (placebo-adjusted change in the dapagliflozin group of -0.01% [95%CI -0.03, 0.01] at 12 months).

Interpretation: Treatment with dapagliflozin reduced the incidence of new-onset T2D in participants with CKD and HF without a reduction in HbA1c.

Funding: AstraZeneca.

Research in Context

Evidence before this study

Prevalence of diabetes is increasing and there is a need to prevent diabetes in a safe and efficient way. Sodium-glucose cotransporter-2 (SGLT2) inhibitors have not been used in studies dedicated to prevention of diabetes. The SGLT2 inhibitor empagliflozin was tested in heart failure in two studies which included patients with and without diabetes but did not demonstrate a significant effect on new-onset diabetes in those without diabetes at baseline: In the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) the hazard ratio for new-onset diabetes was 0.84 (95%CI 0.65, 1.07) and in the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) the HR for new-onset diabetes was 0.86 (95%CI 0.62, 1.19). A pooled analysis remains to be seen.

Added value of this study

The SGLT2 inhibitor dapagliflozin was tested in DAPA-CKD in chronic kidney disease and in DAPA-HF in heart failure with reduced ejection fraction. Both studies included patients with or without diabetes. In an analysis of pooled individual participant data evaluating new-onset diabetes in subjects with no prior history of diabetes, dapagliflozin reduced new-onset diabetes with a HR 0.67 (95%CI 0.51, 0.88; $p=0.0040$). There was no heterogeneity between studies (p -interaction 0.77) and the benefit of dapagliflozin in prevention of type 2 diabetes was consistent across pre-specified subgroups. Dapagliflozin was well tolerated. There was minimal difference in mean HbA1c during the trial in those without diabetes.

Implications of all the available evidence

The patient level pooled analysis of DAPA-CKD and DAPA-HF suggest that dapagliflozin may significantly reduce new-onset diabetes in patients with chronic kidney disease and heart failure, in addition to the clinical benefits of reducing progression of kidney disease and heart failure. This is particularly relevant in high risk groups, including those with prediabetes.

Introduction

Globally, 463 million people are estimated to have diabetes, and in 2040 the number is expected to increase to 700 million because of a growing population that is becoming older, less physically active and with more obesity.¹ Diabetes is associated with excess morbidity and mortality due to premature cardiovascular disease and complications including retinopathy, nephropathy, and neuropathy. Preventing diabetes should reduce the incidence of these complications, particularly diabetic retinopathy, nephropathy, and neuropathy which are specific to the disease. Lifestyle interventions, including exercise and a healthy diet leading to weight loss, are recommended but difficult to implement widely, and such efforts in routine clinical practice often fail. Bariatric surgery can also be used but is expensive, not widely available, and carries associated risks. Some glucose-lowering and anti-obesity medications also reduce the risk of diabetes, mainly tested in patients with impaired glucose tolerance, but most have side effects and have not been demonstrated to improve clinical outcomes beyond diabetes prevention. According to the American Diabetes Association (ADA) and other organisations, metformin is recommended for diabetes prevention in certain individuals with prediabetes,² although implementation of this recommendation has generally been lacking. Moreover, such an intervention has also not been linked to improvement in other long-term outcomes. Thus there is a need for an effective and safe treatment to prevent diabetes and its complications.

Sodium–glucose cotransporter-2 (SGLT2) inhibitors induce glucosuria and were originally developed as glucose-lowering medications for type 2 diabetes. SGLT2 inhibitors, which are generally well tolerated, also reduce blood pressure, body weight, and albuminuria, and reduce the risks of adverse cardiovascular events and

kidney outcomes in patients with type 2 diabetes. Since these agents do not increase the risk of hypoglycaemia, and because their cardiorenal benefits were thought to be unrelated to improvements in glycaemic control, clinical trials with the SGLT2 inhibitors dapagliflozin and empagliflozin were initiated in patients with heart failure or chronic kidney disease (CKD) with or without type 2 diabetes and, in fact, demonstrated cardiorenal benefits.^{3,4} Dapagliflozin reduced a composite kidney endpoint of $\geq 50\%$ decline in estimated glomerular filtration rate (eGFR), end-stage kidney disease or eGFR < 15 mL/min/1.73 m² or cardiovascular or kidney mortality in patients with CKD also irrespective of diabetes status in the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial.³ Dapagliflozin also reduced cardiovascular mortality or worsening heart failure in participants with and without diabetes with heart failure with reduced ejection fraction (HFrEF), in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial.⁵

In this pre-specified analysis, using for the first time the pooled individual patient-level data from DAPA-CKD and DAPA-HF, we assessed the effects of dapagliflozin on new-onset type 2 diabetes and explored the association with baseline characteristics.

Methods

Trial Design and Participants

This analysis combines data from DAPA-HF and DAPA-CKD, two Phase 3, randomised, double-blind, placebo-controlled, multicentre clinical trials. Details of the trials' design and study protocols have been published previously.^{6,7}

In DAPA-CKD (NCT03036150), 4304 participants were recruited at 386 sites in 21 countries.^{3,6} The primary objective was to determine whether dapagliflozin reduced the incidence of kidney and cardiovascular events in patients with CKD with or without type 2 diabetes. Eligible participants were adult patients with CKD with an eGFR between 25 and 75 mL/min/1.73 m² and a urinary albumin-to-creatinine ratio (UACR) between 200 and 5000 mg/g (22.6 to 565.6 mg/mmol). Participants had to receive a stable dose of an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) for at least four weeks before trial enrolment unless contraindicated. Patients were excluded from the trial if they had type 1 diabetes, polycystic kidney disease, lupus nephritis, or anti-neutrophil cytoplasmic antibody-associated vasculitis. A detailed overview of inclusion and exclusion criteria has been published previously.⁶

DAPA-HF (NCT03036124) was designed to test the impact of dapagliflozin on cardiovascular mortality or worsening heart failure in 4744 patients with HFrEF. Inclusion criteria included New York Heart Association functional class II–IV symptoms, left ventricular ejection fraction \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 eGFR <30 mL/min/1.73 m².⁷

Randomisation and Procedures

In each of the trials, participants were randomly assigned in a 1:1 ratio to either dapagliflozin (10 mg orally once daily) or placebo. Randomisation was stratified by diagnosis of type 2 diabetes at enrolment (in both trials), and UACR ≤1000 mg/g or >1000 mg/g (in DAPA-CKD). After randomisation, in-person follow-up visits were conducted after 2 weeks, 2, 4 and 8 months, and continued at 4-month intervals. All patients underwent HbA1c 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).

Outcomes

The incidence of a new diagnosis of type 2 diabetes in participants without diabetes at baseline was a prespecified exploratory endpoint, and is the focus of this analysis. Those individuals with a prior diagnosis of type 2 diabetes, and those whose HbA1c was ≥6.5% (48 mmol/mol) at both the enrolment and randomisation visits (i.e., repeated and confirmed and therefore considered a diagnosis of type 2 diabetes) were excluded from this report. The remaining participants constituted our study cohort, comprised of those with prediabetes at baseline (as per the definition of the ADA of an HbA1c between 5.7 and 6.4%; 39 and 46 mmol/mol)² and individuals considered to have normoglycaemia (defined as HbA1c <5.7%; 39 mmol/mol). Incident diabetes was defined as either an HbA1c of ≥6.5% (48 mmol/mol),

measured in the central laboratory, on two consecutive follow-up visits or a clinical diagnosis of diabetes between visits leading to the initiation of a glucose-lowering agent. HbA1c over time was also a prespecified exploratory endpoint in this analysis.

Ethics

All patients provided written informed consent. The trials were approved by the ethics committee at each center, and were conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guideline and the Declaration of Helsinki.

Statistical Analysis

All analyses presented here followed the intention-to-treat principle. We report continuous variables as means and standard deviations for variables with approximate symmetric distributions. Baseline characteristics were compared between groups with the two-sample t-test, and the χ^2 test for categorical variables. Race was determined by the investigator / patient (self-reported). Given the very similar study designs, we conducted a pooled analysis based on the available individual patient-level data in a one-stage meta-analysis. In this pre-specified exploratory analysis, we examined the effect of dapagliflozin versus placebo on new-onset diabetes by means of Kaplan-Meier estimates and hazard ratios (HRs), with 95% confidence intervals (CIs) derived from proportional hazards (Cox) regression models stratified by study, and with treatment allocation as the only factor in the model. The heterogeneity of treatment effect between studies was assessed by an interaction between treatment and study in the Cox model. To explore the consistency of treatment effect across subgroups, the same model was applied to

each subgroup with an additional term for the interaction between treatment group and the subgroup variable. The proportional hazards assumption was assessed visually by log cumulative hazard plots. To account for the competing risk of death from any cause, we conducted a companion analysis using the method described by Fine and Gray,⁸ with incident diabetes as the outcome event and mortality due to any other cause as a competing risk. For all models, time to event was calculated as time from randomization to new-onset type 2 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 censored whichever occurred first. Change in HbA1c over time was analysed 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). The assumptions of the repeated measures analyses were visually evaluated by residual diagnostics plots. All analyses were performed with SAS software, version 9.4 (SAS Institute). Two-tailed p-values <0.05 were considered statistically significant.

Role of funding source

The sponsor of the study was involved in the study design, analysis, interpretation of data, writing of the report and the decision to submit the paper for publication. Both the DAPA-HF and DAPA-CKD trials were sponsored by AstraZeneca as a collaboration between the sponsor and academic-led steering committees. The steering committees of both trials, which included members of the sponsor, designed the study, supervised its conduct, and were responsible for reporting the results. All

authors had access to the analysis, and the decision to submit the manuscript was made jointly by all authors.

Results

In DAPA-CKD 1398 of 4304 participants (32.5%) did not have type 2 diabetes at baseline, and 697 were randomly assigned to dapagliflozin and 701 to placebo. The median duration of follow-up was 27.5 months (IQR, 23.3 to 31.3). In DAPA-HF, 2605 of 4744 participants (54.9%) did not have type 2 diabetes at baseline, and 1298 were randomly assigned to dapagliflozin and 1307 to placebo with a median duration of follow-up of 18.7 months (IQR, 14.7 to 22.0). Participants from DAPA-CKD compared with those from DAPA-HF were younger (mean age [SD] of 56.4 [14.6] vs 66.2 [11.6] years), had a greater proportion of women (32.9 vs 24.3%), a greater proportion who were reported as Asian (38.3 vs 24.0%), a modestly greater proportion on renin-angiotensin system blockade (97.1 vs 93.9%), a smaller proportion who were reported as White (53.6 vs 70.8%), and fewer had prediabetes at baseline (47.2 vs 67.1%). Body mass index (BMI) was similar in both studies (27.9 [5.6] vs 27.2 [5.7] kg/m², respectively). As expected, eGFR was lower in DAPA-CKD: 41.7 (11.7) vs 67.8 (19.2) mL/min/1.73m². Only 7.7% (107/1398) of participants in DAPA-CKD had heart failure. In contrast, in DAPA-HF 36.3% (946/2605) of the participants had CKD based on an eGFR <60 mL/min/1.73m².

In the pooled dataset of 4003 participants without type 2 diabetes at baseline, 1995 were randomised to dapagliflozin and 2008 to placebo with a median duration of follow up of 21.2 months (IQR, 16.0 to 25.4). Overall, 11.3% (453/4,003) discontinued randomised therapy and 99.7% (3991/4003) completed the trial. The two treatment groups were well matched for baseline clinical characteristics (**Table 1**). **Supplementary Table S1** shows the pooled population stratified by baseline prediabetes versus normoglycaemic status. During follow up there was minimal

difference in mean HbA1c amongst participants treated with dapagliflozin and those treated with placebo (**Figure 1**). At 12 months, HbA1c was unchanged from baseline in both groups, with a between-group difference of -0.01% (95%CI -0.03, 0.01). Results were nearly identical when comparing dapagliflozin and placebo by baseline prediabetes and normoglycaemic status (**Figure 2**).

During follow-up, 211 of 4003 participants (5.3%) developed incident type 2 diabetes and 3792 of 4003 (94.7%) remained free of diabetes. New-onset type 2 diabetes was diagnosed by elevated HbA1c at two consecutive visits in 177 of 211 (84%) patients, and following a clinical diagnosis of diabetes between trial visits in 34 of 211 (16%) patients. Baseline clinical characteristics of patients who did or did not develop new-onset diabetes are provided in **Supplementary Table S2**.

In patients randomised to dapagliflozin, 85 of 1995 (4.3%) participants developed incident type 2 diabetes corresponding to an event rate of 2.6 per 100 patient-years of follow-up compared to 126 (6.3%) of 2008 in the placebo group (3.9 events per 100 patient-years of follow-up). This resulted in a HR of 0.67 (95%CI 0.51, 0.88; $p=0.0040$). The between-group difference emerged early during the trial, after 4 months, and persisted throughout follow-up (**Figure 3**). There was no significant heterogeneity by trial (p -interaction 0.77). Results were nearly identical when accounting for competing risk of mortality using Fine and Gray's proportional sub-distribution hazards method (HR 0.67 [0.51, 0.89]; $p=0.0047$). In patients with prediabetes at baseline 81 of 1189 (6.8%) developed diabetes corresponding to an event rate of 4.2 per 100 patient-years of follow-up, compared with 118 of 1219 (9.7%) in the placebo group (6.2 events per 100 patient-years of follow up), HR 0.69

(95%CI 0·52, 0·91); $p=0\cdot0097$). In patients with normal HbA1c at baseline randomized to dapagliflozin, new-onset diabetes was seen in 4 of 806 (0·5%) participants (event rate 0·3 per 100 patient-years) compared with 8 of 789 (1·0%) participants in the placebo group (event rate 0·6 per 100 patient-years).

There was also no heterogeneity of the effect of dapagliflozin on the risk of new-onset type 2 diabetes across most key prespecified subgroups, including sex, baseline glycaemic status, BMI, eGFR, race, region and cardiovascular medications used at baseline (**Figure 4**). Notable exceptions were a more pronounced risk reduction in younger participants (<65 years of age vs. ≥ 65 years; p -interaction 0·048) and amongst patients with higher systolic blood pressure (≥ 130 mmHg vs. <130 mmHg; p -interaction 0·036). These findings should be interpreted with caution, however, as interactions were not adjusted for multiple comparisons. In addition, when we added age, or systolic blood pressure, or body weight as a continuous variable in the model, the interaction between dapagliflozin treatment and these patient characteristics was not significant (p -interaction all $>0\cdot13$).

Dapagliflozin was generally well tolerated; there were fewer serious adverse events with dapagliflozin 598/1991 (30·0%) than placebo 648/2004 (32·3%), but discontinuation of investigational product was more frequent with dapagliflozin 104/1991 (5·2%) than placebo 88/2004 (4·4%) in patients with no type 2 diabetes at baseline (**Supplementary Tables S3**). Discontinuation was most often due to cardiac or renal disorders or infections (**Supplementary Table S4**).

Discussion

SGLT2 inhibitors are glucosuric agents that were originally developed to treat hyperglycaemia in type 2 diabetes. Subsequent trials found surprising benefits to reduce cardiovascular and renal complications of this disease. More recently, their benefits have been extended to individuals with heart failure and CKD, irrespective of diabetes status. In this pre-specified exploratory analysis of pooled data from the complementary phase 3 studies DAPA-CKD and DAPA-HF, we demonstrated that dapagliflozin appears to have an additional benefit in reducing new-onset type 2 diabetes (HR 0·67 [95%CI 0·51, 0·88]). As expected, new-onset type 2 diabetes was most frequent in participants with prediabetes and participants characterised by higher HbA1c, age, and BMI. In addition, participants with new-onset type 2 diabetes had more cardiovascular disease and thus more frequent use of cardiovascular medications at baseline.

The reduction in risk for new-onset type 2 diabetes with dapagliflozin was consistent across most key subgroups, although perhaps more prominent in younger participants and those with elevated blood pressure. In DAPA-HF, the incidence of new-onset diabetes was 5·0 per 100 patient-years in the placebo group, comparable with or higher than some previous studies in HF,⁹⁻¹¹ but lower than in the empagliflozin preserved and reduced ejection fraction HF trials (7·4 and 10·6 per 100 patient-years respectively), perhaps because the patients in those trials were older and had more obesity compared with DAPA-HF.^{4,12} In DAPA-CKD, the incidence of new-onset diabetes was 2·4 per 100 patient-years, slightly more than in the Chronic Renal Insufficiency Cohort (CRIC) study (1·8 per 100 patient-years), where the mean age was also lower,¹³ but lower than in the African American Study of Kidney

Disease and Hypertension (AASK) where it was 3·8 per 100 patient-years, perhaps because participants in that trial were Black with a high prevalence of hypertension.¹⁴ Our pooled analysis is unique by including many more people with low eGFR. The findings are consistent both in people with eGFR above 45 mL/min/1·73m² or below 45 mL/min/1·73m² (where there is less glucosuria and little glucose-lowering effect), which support potential direct benefits on the underlying pathogenesis of type 2 diabetes, such as on β -cell function and/or insulin sensitivity.

Type 2 diabetes is an ever-increasing problem worldwide, challenging for patients and societies, resulting in comorbidities, and reduced quality-of-life and functional capacity. It is a burden to families, and leads to excess costs to health care systems, and lost productivity due to inability to work. Although the management of diabetes has improved significantly in recent years with effective new therapies, prevention of diabetes is obviously preferable.¹⁵⁻¹⁸

SGLT2 inhibitors exert their glucose-lowering effects through the blockade of glucose reabsorption in the proximal nephron, leading to loss of glucose (and thus calories) in the urine, with reduction in hyperglycaemia and body weight. This effect is independent of insulin. However, the very fact that the diabetes prevention effect of dapagliflozin (similar in size to that of metformin) occurs without significant reduction in HbA1c suggests that this benefit is not merely the result of a biochemical reduction in glycaemia. Reduction in HbA1c has been routinely observed in other diabetes prevention trials with other glucose-lowering medications, leading some to propose that the agents do nothing more than 'mask' underlying diabetes. The fact that HbA1c was essentially stable during this study, suggests that

the diabetes prevention effects of dapagliflozin reflects an indirect benefits on underlying pathophysiological process integral to the progression from prediabetes to diabetes. These may include reductions in insulin resistance and/or improvements beta-cell function through the off-loading glucose toxicity. Admittedly, at a patient level, it is difficult to disentangle the glucose-lowering effects from the diabetes prevention effects of any diabetes medication.¹⁹ Improvements in peripheral insulin sensitivity through weight loss may be important, but the reduction in body weight with SGLT2 inhibitors is most likely not sufficient enough to explain the observed reduction in new-onset diabetes. It is also possible that improvement in symptoms and health-related quality-of-life, associated with more activity, could be beneficial. Improvements in hepatic insulin sensitivity may also contribute, as treatment with canagliflozin for 24 weeks has been shown to reduce liver fat content and improve hepatic insulin sensitivity and insulin secretion.²⁰⁻²² Recently, the PRE-D trial compared the effect of 13 weeks intervention with dapagliflozin, metformin, exercise or placebo on glucose variability (measured as mean amplitude of glycaemic excursions) in patients with prediabetes.²³ Dapagliflozin was the only intervention to provide a significant reduction in glucose variability of 17.2% (95%CI 0.8, 30.9; $p=0.041$), which changed slightly less with exercise (15.4% [95%CI -1.1, 29.1]; $p=0.065$), and not at all with metformin or placebo. In line with our findings, dapagliflozin did not reduce HbA1c ($<0.1\%$) in that trial.

SGLT2 inhibitors have not been tested in previous diabetes prevention studies. New-onset diabetes was not reduced with empagliflozin in the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) where the HR for new-onset diabetes was 0.84 (95%CI

0·65, 1·07), nor was it reduced in the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) where the HR for new-onset diabetes was 0·86 (95%CI 0·62, 1·19).⁴ The reduced ejection fraction subgroup from DAPA-HF was recently published;²⁴ herein we extend and strengthen the findings, pooling the data from DAPA-HF and DAPA-CKD, a study which instituted the same intervention (dapagliflozin 10 mg daily versus placebo) under a similar protocol (with longer follow-up, despite early trial termination), in distinct populations at risk. Subgroup analysis by age and systolic blood pressure categories suggested that the effect of dapagliflozin may vary according to these baseline characteristics. However, when age and systolic blood pressure were fitted as continuous variables they did not modify the benefit of dapagliflozin in diabetes prevention. Moreover, since we did not adjust for multiplicity and the p-values indicated borderline significant effects, we interpret these results that the prevention of diabetes with dapagliflozin is not modified by any tested baseline characteristic.

Previous diabetes prevention studies have generally focused on high-risk groups with impaired glucose tolerance or obesity, to ensure high-risk of progression to diabetes. Interventions have been lifestyle intervention with weight loss and exercise, which reduced new-onset diabetes by up to 58%,²⁵ pharmacological interventions targeting glucose (acarbose, metformin, or thiazolidinediones) with risk reduction up to 72%,²⁵⁻²⁷ or weight loss medications with risk reduction up to 79%.²⁸ These studies were designed to demonstrate prevention of diabetes, but were unable to determine whether prevention of diabetes translates into a reduced risk of micro- or macrovascular damage. Only the long term follow-up of the lifestyle intervention Da

Qing Study suggested reduced cardiovascular events and improved survival after three decades.²⁹ In our pooled analysis of DAPA-HF and DAPA-CKD, follow-up was relatively short; further long-term studies will be needed to determine if diabetes prevention, specifically with an SGLT2 inhibitor, might lead to any additional benefits beyond those already recognised from a cardiovascular and kidney perspective. Since it is already recognised that the cardiorenal benefits of this class do not pertain to their glucose-lowering effects, this may be difficult to prove. Nonetheless, since diabetes itself is associated with worse outcomes in both heart failure and CKD populations, avoiding the progression from prediabetes to more advanced glycaemic abnormalities may indeed have intrinsic health advantages. In DAPA-CKD and DAPA-HF as the majority of participants who developed new-onset diabetes had prediabetes, future prevention studies should focus on this subgroup, or other high risk individuals such as those with a family history of diabetes.

Limitations of our study include lack of fasting or stimulated glucose concentrations, or assessments of insulin sensitivity or resistance. We also did not assess glycaemia after stopping study medication to determine if there remains any effect after “wash-out”. Given the lack of significant effects on HbA1c, however, we would not expect any significant increases in the marker after stopping study drug. Differences in design between the trials did not afford us the opportunity to perform subgroup analyses by baseline ejection fraction, NTproBNP or UACR as these parameters of underlying disease severity were not available in both trials.

In conclusion, this pre-specified exploratory analysis of pooled data from the complementary Phase 3 DAPA-CKD and DAPA-HF trials including participants with

CKD or HFrEF without type 2 diabetes, demonstrated that treatment with dapagliflozin reduced the incidence of new-onset type 2 diabetes, an effect that was consistent across most subgroups and on par with that observed with the most commonly used medication for diabetes prevention, metformin. The effect was seen without a change in HbA1c, which could suggest that this benefit is not merely a 'masking' of diabetes but some fundamental effect on the pathogenesis of diabetes, perhaps improved beta-cell function and/or enhanced insulin sensitivity. The diabetes prevention effects of SGLT2 inhibition demonstrated herein should now be assessed in a broader prediabetes population, not necessarily with the comorbidities afflicting participants in DAPA-HF and DAPA-CKD. Any long-term benefits of diabetes prevention remain to be demonstrated in these as well as other populations.

Acknowledgements

The DAPA-CKD and DAPA-HF studies were funded by AstraZeneca.

The authors thank all investigators, trial teams, and patients for their participation in the trial.

The authors would also like to acknowledge Marco Favretto and Nicola Truss, inScience Communications, London, UK, for assistance in preparation of figures and editing the manuscript. This support was funded by AstraZeneca.

Author Contributions

All authors had access to the analysis and had the final responsibility to submit for publication. OB and ML analysed the data and PR and HJLH wrote the first draft of the manuscript. All authors reviewed the manuscript drafts, provided approval of the final version for submission, and take responsibility for the accuracy and integrity of the data.

Data sharing statement

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at <https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure>.

Declaration of interests

PR received funding to his institution from AstraZeneca for participating in the steering committee for DAPA-CKD. He has received funding to his institution for advisory boards from Sanofi Avensis, and Boehringer Ingelheim; from Bayer, Gilead and Novo Nordisk for steering committees; from Novo Nordisk, Bayer and Eli Lilly for lectures. Has received grants from Novo Nordisk, and has held stock in Novo Nordisk in the past 3 years.

SEI received funding from AstraZeneca for participating in the steering committee for DAPA-HF. He received consultancy fees from Abbott, VTV Therapeutics, Esperion, Pfizer, Merck; fees for clinical trial committee participation, advisory roles and travel costs from Boehringer Ingelheim, AstraZeneca, and Novo Nordisk; and honoraria for lectures from Merck, and AstraZeneca.

PV and NJ have nothing to declare.

KFD received funding to his employer, University of Glasgow, from AstraZeneca for DAPA-HF. He has received honoraria for lectures from AstraZeneca and Eli Lilly.

PSJ's employer, the University of Glasgow has been paid by AstraZeneca for his time working on the DAPA-HF and DELIVER trials, by Novartis for work on the PARADIGM-HF and PARAGON-HF trials and Novo Nordisk. Speakers and advisory board fees from AstraZeneca, Boehringer Ingelheim, Novartis. Research funding Boehringer Ingelheim and Analog Devices Inc.

LK reports other support from AstraZeneca and personal fees from Novartis and Bristol Myers Squibb as a speaker.

MNK received payment to his institution for participation in DAPA-HF. He received grant payment to his institution from Boehringer Ingelheim and received personal fees and/or fees to his institution for consultancy from Amgen, Applied Therapeutics,

AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Esperion Therapeutics, Janssen, Merck, Novo Nordisk, Sanofi, and Vifor Pharma. He received honoraria for lectures to himself and his institution from AstraZeneca, Boehringer Ingelheim, and Novo Nordisk; from Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi and Vifor Pharma or participation on DSMB for advisory boards. Received study drug for a clinical trial from AstraZeneca and Boehringer Ingelheim.

FAM reports personal fees from AstraZeneca. M.S.S. reports grants from Bayer, Daiichi Sankyo, Eisai, GlaxoSmithKline, Pfizer, Poxel, Quark Pharmaceuticals, and Takeda; grants and personal fees from Amgen, AstraZeneca, Intarcia, Janssen Research and Development, The Medicines Company, MedImmune, Merck, and Novartis; and personal fees from Anthos Therapeutics, Bristol Myers Squibb, CVS Caremark, DalCor, Dyrnamix, Esperion, IFM Therapeutics, and Ionis.

PP reports personal fees and other from AstraZeneca, Boehringer Ingelheim, Bayer, BMS, Cibiem, Novartis, and RenalGuard; personal fees from Pfizer, Servier, Respicardia, and Berlin-Chemie; other from Amgen; and grants, personal fees, and other from Vifor Pharma.

MSS received an institutional research grant from AstraZeneca for DAPA-HF. He received institutional research grants from Abbott, Amgen, Anthos Therapeutics, Bayer, Daiichi-Sankyo, Eisai, Intarcia, IONIS, Medicines Company, MedImmune, Merck, Novartis, Pfizer, and Quark Pharmaceuticals. He has received consulting fees from Althera, Amgen, Anthos Therapeutics, AstraZeneca, Bristol-Myers Squibb, CVS Caremark, DalCor, Dr. Reddy's Laboratories, Fibrogen, IFM Therapeutics, Intarcia, MedImmune, Merck, Moderna, and Novo Nordisk. Additionally, Dr. Sabatine is a member of the TIMI Study Group, which has also received institutional research

grant support through Brigham and Women's Hospital from: Regeneron, Roche, and Zora Biosciences.

SDS received payment to his institution for participation in DAPA-HF. He received grants to his institution from Actelion, Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, BMS, Celladon, Cytokinetics, Eidos, Gilead, GSK, Ionis, Lilly, Mesoblast, MyoKardia, NIH/NHLBI, Neurotronik, Novartis, NovoNordisk, Respicardia, Sanofi Pasteur, Theracos, and US2.AI. He received fees for consultancy from Abbott, Action, Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boeringer-Ingelheim, BMS, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GSK, Lilly, Merck, Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Cardurion, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellProThera, Moderna, American Regent, and Sarepta. He received honoraria for lectures from Novartis and AstraZeneca.

DLD received funding from AstraZeneca for participating in the steering committee for DAPA-HF. Consulting fees from AstraZeneca, Frontier Science – Madison Office, and 3D Communication. He receives royalties or licenses for Fundamentals of Clinical Trials, Data Monitoring Committees: Practical Perspective, Data Monitoring Committees: A Case Studies Approach, and Statistical Methods for Clinical Trials. He has received honoraria for lectures from Vanderbilt University and Harvard University: CME Course on Clinical Trials; and honoraria for participation on DSMB or advisory boards for Patient Centered Outcome Research Institute, Bristol Meiers Squibb, Sanifit, Tricidia, Boston Scientific, Actelion, Medtronic, Duke University, Lisa Nova, Mesoblast, GlaxoSmithKline, DalCor, and Cardiovascular Research Foundation.

OB, ML, AML, MS, BVS, and CK are employees and stockholders of AstraZeneca.

GMC received funding from AstraZeneca for participating in the steering committee for DAPA-CKD. He has received research support from Amgen, DSMB participation from Bayer and ReCor. He is on the board of directors for Satellite Healthcare, has participated on trial steering committees for Akebia, Gilead, Sanifit, Vertex. He holds stock in Ardelyx, loudCath, Durect, DxNow, Micromatrix, Outset, and Unicycive.

FFH is a member of the DAPA-CKD study executive committee and is a study investigator. She has received personal fees from Abbvie.

RC-R received funding from AstraZeneca for participating in the steering committee for DAPA-CKD. He has received research grants from GSK, and Novo Nordisk. He has received consulting fees from Boehringer Ingelheim, and Chinook; and honoraria for advisory boards or lectures from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Janssen, and Novo Nordisk.

RDT received funding from AstraZeneca for participating in the steering committee for DAPA-CKD. He has received fees for consultancy from Boehringer Ingelheim, Reata Pharma and Chinook Pharma. He has received honoraria for lectures from Medscape, and Medical Education Resources; and participated in DSMB or advisory boards for Bayer, Viofor, Akebia and Otsuka.

DCW provides ongoing consultancy services to AstraZeneca. He has received fees for DSMB or advisory boards from Zydus and Gilead and received personal fees from Bayer, Boehringer Ingelheim, Astellas, GSK, Janssen, Napp, Mundipharma, Vifor, TRicida, Zydus, and Amgen.

JJVMs employer, Glasgow University, has been paid by AstraZeneca (who market dapagliflozin) for time spent as Principal Investigator of DAPA-HF and Co-principal Investigator of DELIVER and DETERMINE (trials using dapagliflozin) in heart failure and meetings and other activities related to these trials. AstraZeneca has also paid

travel and accommodation for these meetings. These payments were made through a Consultancy with Glasgow University and he did not receive personal payments in relation to this trial/this drug. He has received personal lecture fees from Abbott, Alkem Metabolics, Eris Lifesciences, Hikma, Lupin, Sun Pharmaceuticals, Medscape/Heart.Org, ProAdWise Communications, Radcliffe Cardiology, Servier, and the Corpus. His employer has received other fees from Cytokinetics (steering committee, travel), KBP Biosciences (advisor, travel), Amgen (steering committee, travel), Bayer (steering committee), Theracos (investigator, travel), Ionis Pharmaceuticals (consultant, travel), DalCor (steering committee), Novartis (investigator and steering committee, travel), GSK (investigator and steering committee, travel), BMS (steering committee), Boehringer Ingelheim (consultant), Cardurion (advisory board), and Alnylam (advisory board).

HJLH institution's received grant funding and honoraria for consultancy as a member of the steering committee of the DAPA-CKD trial. Research grants paid to his employer from AstraZeneca, Boehringer Ingelheim, Janssen and Novo Nordisk for clinical trials. Consulting fees, paid to his employer, from Abbvie, Boehringer Ingelheim, Traveer Pharmaceuticals, Novo Nordisk. Fees for steering committee membership paid to his employer from Bayer, Chinook, CSL Pharma, Janssen, and Gilead. Honoraria for lectures from AstraZeneca and Mitsubishi Tanabe. He received honoraria for advisory board participation for Merck (paid to his employer), Mitsubishi Tanabe, and Mundipharma.

References

1. Federation ID. IDF Diabetes Atlas 9th edition. 2019.
2. Standards of Medical Care in Diabetes-2021. *Diabetes Care* 2021; **44**(Suppl 1): S1-S225.
3. Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med* 2020.
4. Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med* 2020; **383**(15): 1413-24.
5. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med* 2019; **381**(21): 1995-2008.
6. Heerspink HJL, Stefansson BV, Chertow GM, et al. Rationale and protocol of the Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) randomized controlled trial. *Nephrol Dial Transplant* 2020; **35**(2): 274-82.
7. McMurray JJV, DeMets DL, Inzucchi SE, et al. A trial to evaluate the effect of the sodium-glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF). *Eur J Heart Fail* 2019; **21**(5): 665-75.
8. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *Journal of the American Statistical Association* 1999; **94**(446): 496-509.
9. Torp-Pedersen C, Metra M, Charlesworth A, et al. Effects of metoprolol and carvedilol on pre-existing and new onset diabetes in patients with chronic heart failure: data from the Carvedilol Or Metoprolol European Trial (COMET). *Heart* 2007; **93**(8): 968-73.
10. Yusuf S, Ostergren JB, Gerstein HC, et al. Effects of candesartan on the development of a new diagnosis of diabetes mellitus in patients with heart failure. *Circulation* 2005; **112**(1): 48-53.
11. Kristensen SL, Mogensen UM, Tarnesby G, et al. Aliskiren alone or in combination with enalapril vs. enalapril among patients with chronic heart failure with and without diabetes: a subgroup analysis from the ATMOSPHERE trial. *Eur J Heart Fail* 2018; **20**(1): 136-47.
12. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N Engl J Med* 2021.
13. Jepson C, Hsu JY, Fischer MJ, et al. Incident Type 2 Diabetes Among Individuals With CKD: Findings From the Chronic Renal Insufficiency Cohort (CRIC) Study. *Am J Kidney Dis* 2019; **73**(1): 72-81.
14. Thornley-Brown D, Wang X, Wright JT, Jr., et al. Differing effects of antihypertensive drugs on the incidence of diabetes mellitus among patients with hypertensive kidney disease. *Arch Intern Med* 2006; **166**(7): 797-805.
15. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med* 2015.
16. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med* 2019; **380**(24): 2295-306.

17. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet* 2019; **394**(10193): 121-30.
18. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2016; **375**(4): 311-22.
19. Scheen AJ. Preventing, delaying, or masking type 2 diabetes with metformin in the diabetes prevention program? *Diabetes Care* 2003; **26**(9): 2701; author reply -3.
20. Cusi K, Bril F, Barb D, et al. Effect of canagliflozin treatment on hepatic triglyceride content and glucose metabolism in patients with type 2 diabetes. *Diabetes Obes Metab* 2019; **21**(4): 812-21.
21. Merovci A, Mari A, Solis-Herrera C, et al. Dapagliflozin lowers plasma glucose concentration and improves β -cell function. *J Clin Endocrinol Metab* 2015; **100**(5): 1927-32.
22. Merovci A, Solis-Herrera C, Daniele G, et al. Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. *J Clin Invest* 2014; **124**(2): 509-14.
23. Færch K, Blond MB, Bruhn L, et al. The effects of dapagliflozin, metformin or exercise on glycaemic variability in overweight or obese individuals with prediabetes (the PRE-D Trial): a multi-arm, randomised, controlled trial. *Diabetologia* 2021; **64**(1): 42-55.
24. Inzucchi SE, Docherty KF, Køber L, et al. Dapagliflozin and the Incidence of Type 2 Diabetes in Patients With Heart Failure and Reduced Ejection Fraction: An Exploratory Analysis From DAPA-HF. *Diabetes Care* 2021; **44**(2): 586-94.
25. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *NEnglJMed* 2002; **346**(6): 393-403.
26. Gerstein HC, Yusuf S, Bosch J, et al. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 2006; **368**(9541): 1096-105.
27. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 2002; **359**(9323): 2072-7.
28. le Roux CW, Astrup A, Fujioka K, et al. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. *Lancet* 2017; **389**(10077): 1399-409.
29. Gong Q, Zhang P, Wang J, et al. Morbidity and mortality after lifestyle intervention for people with impaired glucose tolerance: 30-year results of the Da Qing Diabetes Prevention Outcome Study. *Lancet Diabetes Endocrinol* 2019; **7**(6): 452-61.

Figure Legends

Figure 1: Change in HbA1c over time in patients without type 2 diabetes at baseline in the DAPA-CKD and DAPA-HF trials

Pooled data from the DAPA-CKD and DAPA-HF trials

Figure 2: Change in HbA1c over time in participants with normoglycaemia (HbA1c <5.7%; 39 mmol/mol) or pre-diabetes (HbA1c 5.7 to 6.4%; 39 to 48 mmol/mol) at baseline

Pooled data from the DAPA-CKD and DAPA-HF trials

Figure 3: Incidence of type 2 diabetes in patients without type 2 diabetes at baseline

Pooled data from the DAPA-CKD and DAPA-HF trials

Figure 4: Effect of dapagliflozin on the reduction in risk of incident type 2 diabetes based on pre-specified baseline subgroups

Pooled data from the in the DAPA-CKD and DAPA-HF trials