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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2022

Link to publication in University of Groningen/UMCG research database

Articles

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

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Abstract

Background Chronic kidney disease and heart failure are insulin resistant states associated with a high incidence of diabetes. We assessed the effect of dapagliflozin on new-onset type 2 diabetes in a pooled analysis of patient-level data from the DAPA-CKD and DAPA-HF trials.

Methods This study is a pooled analysis of individual participant data from two phase 3, randomised, double-blind, placebo-controlled, multicentre, clinical trials. Participants with no history of diabetes and HbA$_{1c}$ less than 6·5% (48 mmol/mol) at baseline were included in this pooled analysis. New-onset type 2 diabetes was a prespecified exploratory endpoint in both DAPA-CKD and DAPA-HF trials and is the focus of this analysis. New-onset type 2 diabetes was identified by serial trial measurements of HbA$_{1c}$ (two consecutive values ≥6·5% [≥48 mmol/mol]) or following a clinical diagnosis of diabetes between trial visits. Time to new-onset type 2 diabetes was analysed in a Cox proportional Hazards model from random assignment to end of treatment.

Findings 4003 participants (1398 [34·9%] from the DAPA-CKD trial and 2605 [65·1%] from the DAPA-HF trial) were included in our analysis: 1995 (49·8%) had received dapagliflozin and 2008 (50·2%) had received placebo. Over a median follow-up of 21·2 months (IQR 16·0 to 25·4), 126 (6·3%) of 2008 patients in the placebo group (event rate 3·9 per 100 patient-years) and 85 (4·3%) of 1995 patients in the dapagliflozin group (event rate 2·6 per 100 patient-years) developed type 2 diabetes (hazard ratio 0·67 [95% CI 0·51 to 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 prespecified subgroups including sex, age, glycaemic status, BMI, glomerular filtration rate, systolic blood pressure, and baseline cardiovascular medication use. More than 90% of the participants who developed type 2 diabetes had prediabetes at baseline (HbA$_{1c}$ 5·7% to 6·4% [39 to 46 mmol/mol]). Mean HbA$_{1c}$ remained unchanged (placebo-adjusted change in the dapagliflozin group of –0·01% [95% CI –0·03 to 0·01], –0·1 mmol/mol [95% CI –0·3 to 0·1] at 12 months).

Interpretation Treatment with dapagliflozin reduced the incidence of new-onset type 2 diabetes in participants with chronic kidney disease and HF without a reduction in HbA$_{1c}$.

Funding AstraZeneca.

Introduction

Globally, 463 million people are estimated to have diabetes; by 2040 the number is expected to increase to 700 million because of a growing population that is becoming older, less physically active, and with higher levels of 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 they are

difficult to implement widely and often fail in routine clinical practice. Bariatric surgery can also be used but is expensive, not widely available, and carries associated risks, such as the development of gallstones and nutritional deficiencies. 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 shown to improve clinical outcomes beyond diabetes prevention. According to the American Diabetes Association and other organisations, including Diabetes Canada, metformin is recommended for diabetes prevention in some individuals with prediabetes,[2] although implementation of this recommendation has

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. We searched PubMed for English language studies published from Jan 1, 2000, to Sept 1, 2021, using the search terms "SGLT2 inhibitors", "prediabetes", and "diabetes prevention". Sodium-glucose co-transporter-2 (SGLT2) inhibitors have not been used in studies dedicated to prevention of diabetes. The SGLT2 inhibitor, empagliflozin, was tested in patients with heart failure in two studies that included patients with and without diabetes, but it did not have a significant effect on new-onset diabetes in those without diabetes at baseline: in the EMPEROR-Preserved trial the hazard ratio (HR) for new-onset diabetes was 0·84 (95% CI 0·65–1·07) and in the EMPEROR-Reduced trial the HR for new-onset diabetes was 0·86 (0·62–1·19). To our knowledge, a pooled analysis remains to be seen.

Added value of this study
The SGLT2 inhibitor dapagliflozin was tested in two phase 3 studies: DAPA-CKD, which recruited patients with chronic kidney disease, and DAPA-HF, which recruited patients with

heart failure with reduced ejection fraction. Both studies included patients with or without diabetes. In this new analysis of pooled patient-level data evaluating new-onset diabetes in participants with no history of diabetes, dapagliflozin reduced new-onset diabetes (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 prespecified subgroups. Dapagliflozin was well tolerated. There was minimal difference in mean HbA_{1c} during the trial in those without diabetes.

Implications of all the available evidence
Our patient-level pooled analysis of DAPA-CKD and DAPA-HF suggests that dapagliflozin might 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 patients at a high risk of developing diabetes, including those with prediabetes.

been generally scarce. Moreover, such an intervention has also not been linked to improvement in other long-term outcomes, such as cardiovascular outcomes. Therefore, there is a need for an effective and safe treatment to prevent diabetes and its complications.

Sodium-glucose co-transporter-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 drugs 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 with or without type 2 diabetes, which showed cardiorenal benefits.[3,4] Dapagliflozin reduced a composite kidney endpoint of a 50% or more decline in estimated glomerular filtration rate (eGFR), end-stage kidney disease or eGFR less than 15 mL/min per 1·73 m², or cardiovascular or kidney mortality in patients with chronic kidney disease 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, in the Dapagliflozin and

Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial.[5]

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

Methods

Study design and participants
This analysis combines data from two phase 3, randomised, double-blind, placebo-controlled, multicentre, clinical trials: DAPA-CKD (NCT03036150)[6] and DAPA-HF (NCT03036124).[7] Details of the trials' design and study protocols have been published previously.[6,7]

The DAPA-CKD trial[6] was done at 386 sites in 21 countries (Argentina, Brazil, Canada, China, Denmark, Germany, Hungary, India, Japan, Mexico, Peru, Philippines, Poland, Russia, South Korea, Spain, Sweden, UK, Ukraine, USA, and Vietnam).[3,6] The primary objective was to determine whether dapagliflozin reduced the incidence of kidney and cardiovascular events in patients with chronic kidney disease with or without type 2 diabetes. Eligible participants were adults (≥18 years) with chronic kidney disease with an eGFR 25–75 mL/min per 1·73 m² and a urinary albumin-to-creatinine ratio (UACR) of 200–5000 mg/g (22·6–565·6 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 4 weeks before trial enrolment unless contraindicated. Patients were excluded

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See **Online** for appendix

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]

The DAPA-HF trial[7] was done at 410 sites in 20 countries (Argentina, Brazil, Bulgaria, Canada, China, Czech Republic, Denmark, Germany, Hungary, India, Japan, the Netherlands, Poland, Russia, Slovakia, Sweden, Taiwan, UK, USA, and Vietnam). The primary composite outcome was worsening heart failure or death from cardiovascular cause. Inclusion criteria included New York Heart Association functional class II–IV symptoms, left ventricular ejection fraction of 40% or less, and elevated circulating concentrations of the N-terminal pro–B-type natriuretic peptide (NT-proBNP). Key exclusion criteria were a history of type 1 diabetes and eGFR of less than 30 mL/min per 1·73 m².[7]

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

This pooled analysis included participants from the DAPA-HF and DAPA-CKD trials who did not have type 2 diabetes at baseline. A previous diagnosis of type 2 diabetes or an HbA1c 6·5% (48 mol/mol) or more at both the enrolment and randomisation visits (ie, repeated and confirmed and therefore considered a diagnosis of type 2 diabetes) were excluded from this analysis. Participants were classed as having prediabetes at baseline (as per the definition of the American Diabetes Association of an HbA1c between 5·7% and 6·4% [39 and 46 mmol/mol])[2] or normoglycaemia (defined as HbA1c <5·7% [39 mmol/mol]).

Randomisation and masking
In each of the trials, participants were randomly assigned (1:1) to receive either dapagliflozin or placebo. Randomisation was stratified by diagnosis of type 2 diabetes at enrolment in both trials, and by UACR (≤1000 mg/g or >1000 mg/g) in the DAPA-CKD trial. Participants and all trial personnel were masked to group assignment in both studies. More information on the randomisation and masking procedures of the DAPA-CKD[6] and DAPA-HF[7] trials have been published previously.

Procedures
Patients assigned to the dapagliflozin groups received 10 mg orally once daily; patients in the placebo groups received matched placebo in addition to standard care. After random assignment, in-person follow-up visits were done after 2 weeks, 2, 4 and 8 months, and continued at 4-month intervals. All patients underwent HbA_{1c} 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 ion-exchange high-performance liquid chromatography assay (Bio-Rad Laboratories, Hercules, CA, USA).

Outcomes
The incidence of a newly diagnosis of type 2 diabetes in participants without diabetes at baseline was a prespecified exploratory endpoint in both the DAPA-CKD and the DAPA-HF trials, and is the focus of this analysis. HbA_{1c} over time was also a prespecified exploratory endpoint in this analysis.

Statistical analysis
All analyses presented here followed the intention-to-treat principle. Safety analyses included all the participants who had undergone randomisation and received at least one dose of dapagliflozin or placebo. We report continuous variables as means (SD) 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 or self-reported by the patient. Given the very similar study designs, we did a pooled analysis based on the available individual patient-level data in a one-stage meta-analysis. In this prespecified 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% CIs derived from Cox proportional hazards 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 did 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 the time from randomisation to new-onset type 2 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), time to death, or censored, whichever occurred first. Change in HbA_{1c} over time was analysed with a mixed model for repeated measurements (adjusted for baseline values, visit, randomly assigned 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

	Dapagliflozin group (n=1995)	Placebo group (n=2008)
Study		
DAPA-HF trial	1298 (65·1%)	1307 (65·1%)
DAPA-CKD trial	697 (34·9%)	701 (34·9%)
Age, years	62·8 (13·5)	62·7 (13·6)
Age category, years		
≤65	1029 (51·6%)	1052 (52·4%)
>65	966 (48·4%)	956 (47·6%)
Sex		
Male	1456 (73·0%)	1455 (72·5%)
Female	539 (27·0%)	553 (27·5%)
Race*		
White	1291 (64·7%)	1302 (64·8%)
Black or African American	78 (3·9%)	74 (3·7%)
Asian	579 (29·0%)	581 (28·9%)
Other	47 (2·4%)	51 (2·5%)
Region		
Asia	560 (28·1%)	562 (28·0%)
Europe	844 (42·3%)	821 (40·9%)
North America	267 (13·4%)	265 (13·2%)
Latin America	324 (16·2%)	360 (17·9%)
Glycaemia subgroup		
Normoglycaemia	806 (40·4%)	789 (39·3%)
Prediabetes	1189 (59·6%)	1219 (60·7%)
HbA$_{1c}$, %	5·7 (0·4)	5·7 (0·4)
HbA$_{1c}$, mmol/mol	39 (4)	39 (4)
eGFR, mL/min per 1·73 m²	58·7 (21·1)	58·7 (21·0)
eGFR category, mL/min per 1·73 m²		
<30	107 (5·4%)	124 (6·2%)
30 to <45	499 (25·0%)	465 (23·2%)
45 to <60	516 (25·9)	525 (26·1%)
≥60	872 (43·7%)	893 (44·5%)
Systolic blood pressure, mmHg	125·0 (17·2)	124·6 (17·3)
Systolic blood pressure category, mmHg		
<130	1263 (63·3%)	1283 (63·9%)
≥130	732 (36·7%)	725 (36·1%)
Diastolic blood pressure, mmHg	75·6 (11·1)	75·4 (11·0)
Mean BMI, kg/m²	27·4 (5·7)	27·5 (5·7)
BMI category, kg/m²		
<25	632 (31·7%)	632 (31·5%)
25 to <30	765 (38·3%)	756 (37·6%)
≥30	595 (29·8%)	620 (30·9%)
		(Table continues on next column)

	Dapagliflozin group (n=1995)	Placebo group (n=2008)
(Continued from previous column)		
Heart failure at baseline	1356 (68·0%)	1356 (67·5%)
Coronary heart disease at baseline	804 (40·3%)	826 (41·1%)
Cardiovascular disease at baseline	1471 (73·7%)	1463 (72·9%)
Current smoker	277 (13·9%)	317 (15·8%)
Baseline medication		
Diuretics	1154 (57·8%)	1193 (59·4%)
Loop diuretics	1098 (55·0%)	1130 (56·3%)
Thiazides	213 (10·7%)	220 (11·0%)
ACE inhibitor/ARB	1897 (95·1%)	1907 (95·0%)
Statins	1143 (57·3%)	1176 (58·6%)
β-blocker	1459 (73·1%)	1445 (72·0%)
Mineralocorticoid receptor antagonists	940 (47·1%)	959 (47·8%)

Data are n (%) or mean (SD). Pooled data from the DAPA-CKD and DAPA-HF trials. ACE=angiotensin-converting enzyme. ARB=angiotensin receptor blocker. eGFR=estimated glomerular filtration rate. *Self reported.

***Table:* Baseline characteristics in participants without type 2 diabetes at baseline**

plots. All analyses were done with SAS (version 9.4). Two-tailed p values less than 0·05 were considered statistically significant.

Role of funding source

The sponsor (AstraZeneca) 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 who were employees of the sponsor, designed and supervised the study and were responsible for reporting the results.

Results

Between Feb 2, 2017, and April 3, 2020, 4304 participants were recruited to the DAPA-CKD trial,[3] of whom 1398 (32·5%) participants did not have type 2 diabetes at baseline and were included in this analysis: 697 (49·9%) were randomly assigned to receive dapagliflozin and 701 (50·1%) to receive placebo. The median duration of follow-up was 27·5 months (IQR 23·3–31·3).

Between Feb 15, 2017, and Aug 17, 2018, 4744 patients were recruited to the DAPA-HF trial.[5] 2605 (54·9%) of 4744 participants did not have type 2 diabetes at baseline and were included in this analysis: 1298 (49·8%) were randomly assigned to receive dapagliflozin and 1307 (50·1%) to receive placebo. The median duration of follow-up was 18·7 months (IQR 14·7–22·0).

Participants in the DAPA-CKD trial (mean age 56·4 years [SD 14·6]) were younger than those from the DAPA-HF trial (66·2 years [11·6]). More women were included in the DAPA-CKD trial (460 [32·9%]) compared with the DAPA-HF trial (632 [24·3%]); additionally, more people of Asian heritage (535 [38·3%] in the DAPA-CKD trial vs 625 [24·0%] in the DAPA-HF trial)[9,10] and more people receiving renin-angiotensin system blockade (1357 [97·1%] in the DAPA-CKD trial vs 2447 [93·9%] in the DAPA-HF trial) were included in the in

the DAPA-CKD trial. A smaller proportion were reported as White (749 [53·6%] in the in the DAPA-CKD trial *vs* 1844 [70·8%] in the in the DAPA-HF trial)[9,10] and fewer people with prediabetes at baseline (660 [47·2%] in the DAPA-CKD trial *vs* 1748 [67·1%] in the in the DAPA-HF trial) were included in the DAPA-CKD trial. Mean BMI was similar in both studies (27·9 kg/m² [SD 5·6] in the DAPA-CKD trial *vs* 27·2 [5·7] kg/m² in the DAPA-HF trial).[9,10] As expected, mean eGFR was lower in DAPA-CKD (41·7 mL/min per 1·73m² [SD 11·7] in the DAPA-CKD trial *vs* 67·8 mL/min per 1·73m² [19·2] in the DAPA-HF trial).[9,10] 107 (7·7%) of 1398 participants in the DAPA-CKD trial had heart failure, whereas 946 (36·3%) of 2605 participants in the DAPA-HF trial had chronic kidney disease, based on an eGFR of less than 60 mL/min per 1·73m².[9,10]

In the pooled dataset of 4003 participants (1398 [34·9%] from the DAPA-CKD trial and 2605 [65·1%] from the DAPA-HF trial) without type 2 diabetes at baseline: 1995 (49·8%) were randomly assigned to receive dapagliflozin and 2008 (50·1%) to receive placebo. Median duration of follow-up of was 21·2 months (IQR 16·0 to 25·4). Overall, 453 (11·3%) of 4003 participants discontinued randomised therapy; 3991 (99·7%) completed the trial. Baseline clinical characteristics are reported in the table. The pooled population stratified by baseline prediabetes versus normoglycaemic status is reported in the appendix (pp 15–16). During follow-up there was minimal difference in mean HbA$_{1c}$ between participants who received dapagliflozin and those who received placebo (figure 1). At 12 months, HbA$_{1c}$ was unchanged from baseline in both groups, with a between-group difference of –0·01% (95% CI –0·03 to 0·01; –0·1 mmol/mol [95% CI –0·3 to 0·1]). Results were nearly identical when comparing dapagliflozin and placebo by baseline prediabetes and normoglycaemic status (figure 2).

During follow-up, 211 (5·3%) of 4003 participants developed incident type 2 diabetes. New-onset type 2 diabetes was diagnosed by elevated HbA$_{1c}$ at two consecutive visits in 177 (84%) of 211 patients and following a clinical diagnosis of diabetes between trial visits in the remaining 34 (16%) patients. Baseline clinical characteristics of patients who did or did not develop new-onset diabetes are provided in the appendix (pp 17–19).

In patients randomly assigned to receive dapagliflozin, 85 (4·3%) of 1995 participants developed incident type 2 diabetes (2·6 events per 100 patient-years of follow-up) compared with 126 (6·3%) of 2008 participants in the placebo group (3·9 events per 100 patient-years of follow-up; HR 0·67 [95% CI 0·51–0·88]; p=0·0040). The between-group difference emerged 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 with Fine and Gray's proportional sub-distribution hazards method (HR 0·67 [95% CI 0·51–0·89]; p=0·0047). 81 (6·8%) of 1189 patients in the dapagliflozin group with prediabetes at baseline developed diabetes (4·2 events per 100 patient-years of follow-up) compared with 118 (9·7%) of 1219 in the placebo group (6·2 events per 100 patient-years of follow-up; HR 0·69 [95% CI 0·52–0·91]; p=0·0097; figure 4). In patients with normal HbA$_{1c}$ at baseline in the dapagliflozin group, new-onset diabetes was seen in four (<1%) of 806 participants (event rate 0·3 per 100 patient-years; figure 4) compared with eight (1%) of 789 participants in the placebo group (event rate 0·6 per 100 patient-years; p=0·24).

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
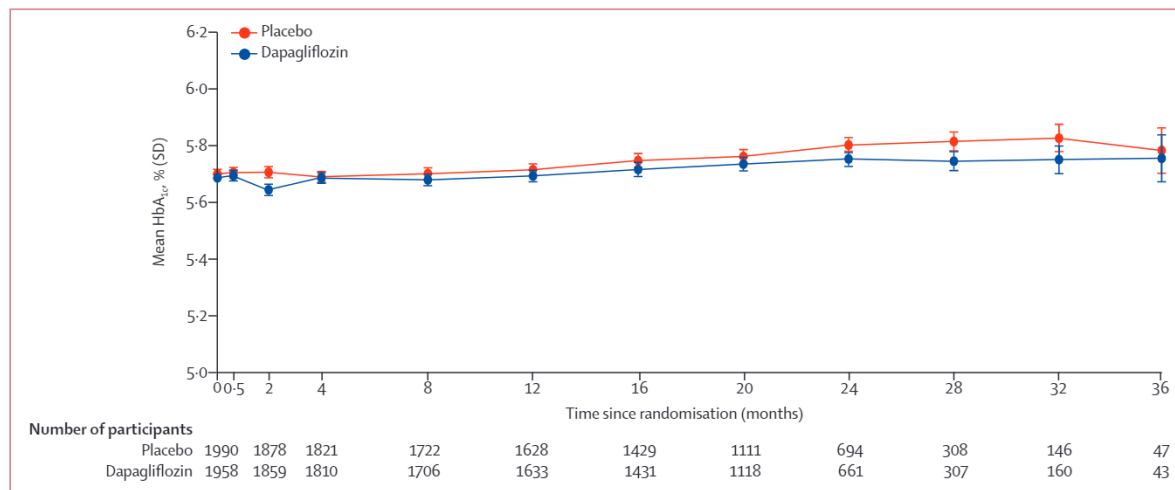

Figure 1: Change in HbA$_{1c}$ over time in patients without type 2 diabetes at baseline in the DAPA-CKD and DAPA-HF trials
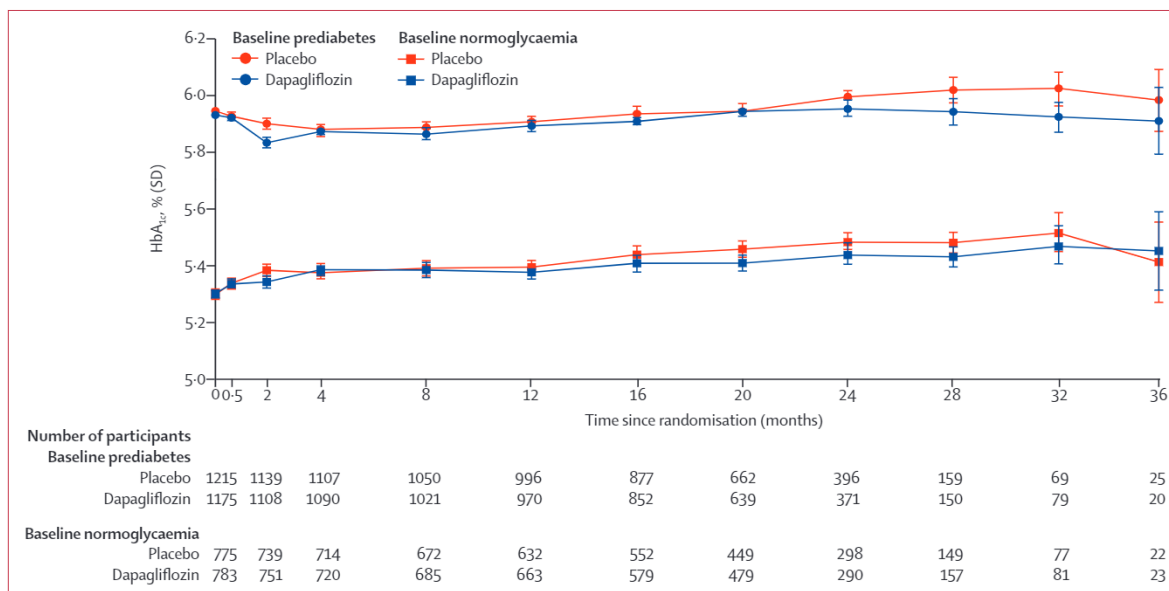Pooled data from the DAPA-CKD and DAPA-HF trials.

Figure 2: Change in HbA$_{1c}$ over time in participants with normoglycaemia or prediabetes at baseline
Pooled data from the DAPA-CKD and DAPA-HF trials. Normoglycaemia is defined as HbA$_{1c}$ more than 5·7% (39 mmol/mol). Prediabetes is defined as HbA$_{1c}$ 5·7–6·4% (39–48 mmol/mol).
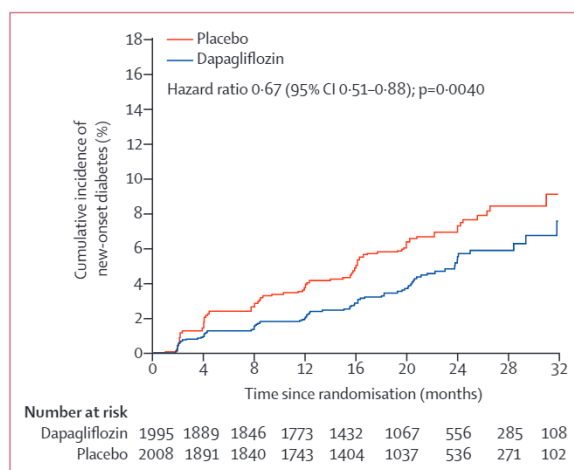

Figure 3: Incidence of type 2 diabetes in patients without type 2 diabetes at baseline
Pooled data from the DAPA-CKD and DAPA-HF trials.

cardiovascular medications used at baseline (figure 4). Key exceptions were a more pronounced risk reduction in younger participants (<65 years of age *vs* ≥65 years; p interaction 0·048; figure 4) and in patients with higher systolic blood pressure (≥130 mmHg *vs* <130 mmHg; p interaction 0·036; figure 4). However, these findings should be interpreted with caution because interactions were not adjusted for multiple comparisons. In addition, when we added age (p=0·13), systolic blood pressure (p=0·14), or body weight (p=0·66) as a continuous variable in the model, the interactions between dapagliflozin treatment and these patient characteristics were not significant.

In patients with no type 2 diabetes at baseline, dapagliflozin was generally well tolerated; fewer participants reported serious adverse events in the dapagliflozin group (598 [30·0%] of 1991 patients) compared with the placebo group (648 [32·3%] of 2004 patients). However, discontinuation of investigational product was more frequent in the dapagliflozin group (104 [5·2%] patients) than in the placebo group (88 [4·4%]; appendix p 20). Discontinuation was most often due to cardiac or renal disorders or infections (appendix p 21).

Discussion

SGLT2 inhibitors are glucosuric drugs that were originally developed to treat hyperglycaemia in patients with type 2 diabetes. Subsequent trials showed that SGLT2 inhibitors also reduce cardiovascular and renal complications of type 2 diabetes. More recently, their benefits have been extended to individuals with heart failure and chronic kidney disease, irrespective of diabetes status. In this prespecified exploratory analysis of pooled data from two complementary phase 3 studies, the DAPA-CKD and DAPA-HF trials, our findings suggest that dapagliflozin appears to have an additional benefit in reducing new-onset type 2 diabetes compared with placebo (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 HbA$_{1c}$, older age, and higher 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

	n/N		Event rate (per 100 patients per year)		Hazard ratio (95% CI)	p interaction
	Dapagliflozin	Placebo	Dapagliflozin	Placebo		
Age (years)						
≤65	30/1029	62/1052	1·7	3·5	0·48 (0·31–0·73)	0·048
>65	55/966	64/956	3·5	4·3	0·83 (0·58–1·19)	
Sex						
Male	67/1456	86/1455	2·8	3·7	0·79 (0·57–1·09)	0·06
Female	18/539	40/533	1·9	4·4	0·43 (0·25–0·75)	
Race						
White	60/1291	84/1302	2·7	3·8	0·71 (0·51–0·99)	0·91
Black	5/78	9/74	3·9	7·9	NC	
Asian	19/579	31/581	2·2	3·6	0·61 (0·34–1·08)	
Other	1/47	2/51	1·1	2·0	NC	
Glycaemic status						
Prediabetes	81/1189	118/1219	4·2	6·2	0·69 (0·52–0·91)	0·58
Normoglycaemia	4/806	8/789	0·3	0·6	NC	
Baseline eGFR (mL/min per 1·73 m²)						
<30	2/107	5/124	0·9	2·1	NC	0·48
30 to <45	24/499	25/465	2·7	3·1	0·88 (0·50–1·54)	
45–60	29/516	39/525	3·4	4·4	0·75 (0·46–1·21)	
≥60	30/872	57/893	2·2	4·3	0·52 (0·34–0·81)	
Systolic blood pressure (mm Hg)						
<130	60/1263	73/1283	3·0	3·7	0·84 (0·59–1·18)	0·036
≥130	25/732	53/725	1·9	4·1	0·45 (0·28–0·73)	
BMI (kg/m²)						
<30	58/1397	70/1388	2·6	3·2	0·82 (0·58–1·16)	0·08
≥30	27/595	56/620	2·6	5·2	0·49 (0·31–0·78)	
Coronary heart disease						
Yes	48/804	66/826	3·9	5·3	0·73 (0·50–1·06)	0·44
No	37/1191	60/1182	1·8	3·0	0·59 (0·39–0·89)	
Statins at baseline						
Yes	60/1143	85/1176	3·1	4·5	0·71 (0·51–0·99)	0·57
No	25/852	41/832	1·8	3·0	0·60 (0·37–0·99)	
β blockers at baseline						
Yes	72/1459	104/1145	3·2	4·8	0·68 (0·50–0·91)	0·77
No	13/536	22/563	1·2	2·0	0·60 (0·30–1·20)	
Loop diuretics at baseline						
Yes	56/1098	95/1130	3·4	5·7	0·60 (0·43–0·83)	0·17
No	29/897	31/878	1·8	1·9	0·90 (0·54–1·50)	
Thiazide at baseline						
Yes	12/213	12/220	3·2	3·2	1·06 (0·47–2·36)	0·24
No	73/1782	114/1788	2·5	4·0	0·63 (0·47–0·84)	

0·2 0·5 1·0 2·0 3·0

← Favours dapagliflozin   Favours placebo →

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. eGFR=estimated glomerular filtration rate. NC=not calculated.

subgroups, although perhaps more prominent in younger participants and those with elevated blood pressure. In the DAPA-HF trial, the incidence of new-onset diabetes was 5·0 per 100 patient-years in the placebo group, which is similar to findings from the Carvedilol Or Metoprolol European Trial (COMET)[11] and higher than the findings from the Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity Program (CHARM)[12] and Aliskiren alone or in combination with enalapril versus enalapril among patients with chronic heart failure with and without diabetes: a subgroup analysis from the ATMOSPHERE trial;[13] however, the incidence of new-onset diabetes in the DAPA-HF trial is lower than in the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced; 10·6 per 100 patient-years)[4] and Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Preserved Ejection Fraction (EMPEROR-Preserved; 7·4 per 100 patient-years) trials,[14] perhaps because the

patients in those trials were older and had higher levels of obesity compared with the DAPA-HF trial. In the DAPA-CKD trial, the incidence of new-onset diabetes was 2·4 per 100 patient-years, slightly more than in the Chronic Renal Insufficiency Cohort study (1·8 per 100 patient-years), in which the mean age was also lower than our findings.[15] However, the incidence reported in the DAPA-CKD trial was lower than in the African American Study of Kidney Disease and Hypertension (AASK), in which incidence of new-onset type 2 diabetes was 3·8 per 100 patient-years; the higher incidence in AASK might be because more participants were Black with a high prevalence of hypertension.[14] Our pooled analysis is unique because it includes many more people with low eGFR. The findings are consistent both in people with a eGFR of more than 45 mL/min per 1·73m² and those with a eGFR less than 45 mL/min per 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 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.[16–20]

SGLT2 inhibitors exert their glucose-lowering effects through the blockade of glucose reabsorption in the proximal nephron, leading to loss of glucose in the urine, with reduction in hyperglycaemia and body weight. This effect is independent of insulin. However, the effect of dapagliflozin (similar in size to that of metformin) occurs without significant reduction in HbA_{1c} which suggests that this benefit is not only the result of a biochemical reduction in glycaemia. Reduction in HbA_{1c} has been routinely observed in other diabetes prevention trials with other glucose-lowering medications, leading some to propose that the drugs only mask underlying diabetes. HbA_{1c} was essentially stable during this study, which suggests that the diabetes preventative effects of dapagliflozin reflects an indirect benefit on underlying pathophysiological process integral to the progression from prediabetes to diabetes. These might include reductions in insulin resistance and improvements to β-cell function through the off-loading glucose toxicity. However, at a patient level, it is difficult to disentangle the glucose-lowering effects from the diabetes preventative effects of any diabetes medication.[21] Improvements in peripheral insulin sensitivity through weight loss might 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 might also contribute because treatment with canagliflozin for 24 weeks has been shown to reduce liver fat content and improve hepatic insulin sensitivity and insulin secretion.[22–24] In 2019, the PRE-D trial[25] compared the effects of 13 weeks intervention with four different strategies—dapagliflozin, metformin, exercise, or placebo—on glucose variability (measured as mean amplitude of glycaemic excursions) in patients with prediabetes. Dapagliflozin was the only intervention to provide a significant reduction in glucose variability of 17·2% (95% CI 0·8 to 30·9; p=0·041), which reduced slightly with exercise (15·4% [–1·1 to 29·1]; p=0·065), and not at all with metformin or placebo. In line with our findings, dapagliflozin did not reduce HbA_{1c} (<0·1%) in the PRE-D trial.[25]

SGLT2 inhibitors have not been tested in previous diabetes prevention studies. New-onset diabetes was not reduced with empagliflozin in the EMPEROR-Preserved trial,[14] in which the HR for new-onset diabetes was 0·84 (95% CI 0·65–1·07), nor was it reduced in the EMPEROR-Reduced trial,[4] in which the HR for new-onset diabetes was 0·86 (0·62–1·19).[4] The reduced ejection fraction subgroup from the DAPA-HF trial was published in 2021.[26] In this analysis we extend and strengthen the findings of the DAPA-HF and DAPA-CKD trials by pooling the data from two trials—the two studies used the same intervention (dapagliflozin 10 mg daily versus placebo) under a similar protocol (with longer follow-up, despite early termination of the DAPA-CKD trial[6]). Subgroup analysis by age and systolic blood pressure categories suggested that the effect of dapagliflozin might 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, because we did not adjust for multiplicity and the p values indicated borderline significant effects, we interpret that these results showed 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 the participants included have a high-risk of progression to diabetes. Interventions have focused on lifestyle, 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%,[27–29] or weight loss medications with risk reduction up to 79%.[30] These studies were designed to show prevention of diabetes, but were unable to determine whether prevention of diabetes translates into a reduced risk of microvascular or macrovascular damage. Only the long-term follow-up of the lifestyle

intervention used in the Da Qing study[31] suggests reduced cardiovascular events and improved survival after three decades. In our pooled analysis of the DAPA-HF and DAPA-CKD trials, follow-up was relatively short; future long-term studies will be needed to determine if diabetes prevention with an SGLT2 inhibitor might lead to any additional benefits beyond those already recognised from a cardiovascular and kidney perspective. Because it is already recognised that the cardiorenal benefits of SGLT2 inhibitors does not pertain to their glucose-lowering effects, any additional benefits caused by diabetes prevention might be difficult to prove. Nonetheless, because diabetes itself is associated with worse outcomes in patients with heart failure and chronic kidney disease, avoiding the progression from prediabetes to more advanced glycaemic abnormalities has intrinsic health advantages. Because most patients in the DAPA-CKD and DAPA-HF trials who developed new-onset diabetes had prediabetes at baseline, future prevention studies should focus on this subgroup, or other individuals at a high risk of developing diabetes, such as those with a family history of diabetes.

Limitations of our study include the absence 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. However, because of the absence of significant effects on HbA$_{1c}$ 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 do subgroup analyses by baseline ejection fraction, NTproBNP, or UACR because these parameters of underlying disease severity were not available in both trials.

In conclusion, this prespecified exploratory analysis of pooled data from the complementary phase 3 DAPA-CKD and DAPA-HF trials, including participants with chronic kidney disease or heart failure with reduced ejection fraction without type 2 diabetes, showed that treatment with dapagliflozin reduced the incidence of new-onset type 2 diabetes, an effect that was consistent across most subgroups and similar to that observed with the most commonly used medication for diabetes prevention, metformin. The effect was seen without a change in HbA$_{1c}$, which could suggest that this benefit is not merely a masking of diabetes but some fundamental effect on the pathogenesis of diabetes, perhaps improved β-cell function or enhanced insulin sensitivity. The diabetes prevention effects of SGLT2 inhibition we report should now be assessed in a broader prediabetes population, not necessarily with the comorbidities afflicting participants in the DAPA-HF and DAPA-CKD trials. Any long-term benefits of diabetes prevention remain to be shown in these and other populations.

For **AstraZeneca's data sharing policy** see https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure

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