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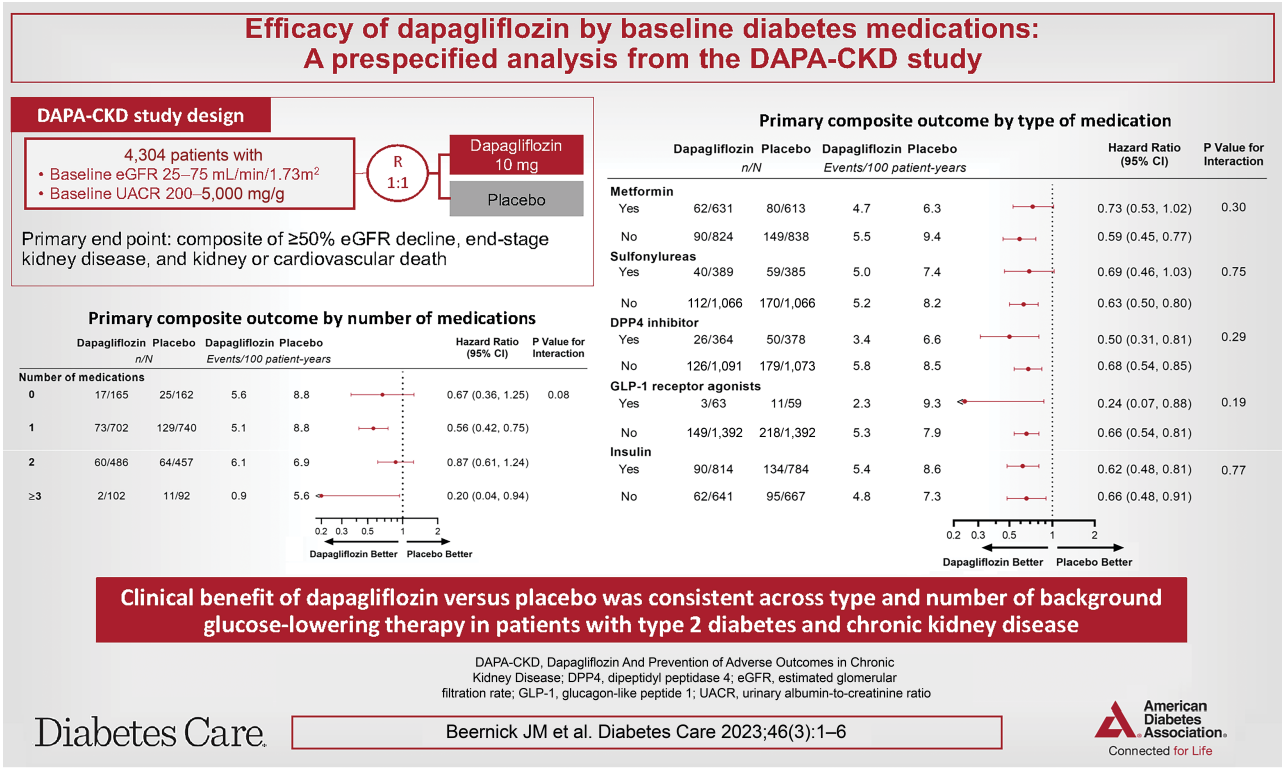

ARTICLE HIGHLIGHTS

- Dapagliflozin is nephroprotective in patients with chronic kidney disease, in whom many glucose-lowering therapies (GLTs) are not recommended.
- We aimed to determine whether the kidney benefits of dapagliflozin in patients with type 2 diabetes and chronic kidney disease varied by the baseline number and type of GLTs.
- The benefit of dapagliflozin in reducing the risk of kidney failure was consistent across GLT classes and number of GLTs.
- These data support the initiation of dapagliflozin regardless of background GLT use.

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Efficacy of Dapagliflozin by Baseline Diabetes Medications: A Prespecified Analysis From the DAPA-CKD Study

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OBJECTIVE

To determine whether the benefits of dapagliflozin in patients with type 2 diabetes and chronic kidney disease (CKD) in the Dapagliflozin And Prevention of Adverse Outcomes in CKD trial (DAPA-CKD) varied by background glucose-lowering therapy (GLT).

RESEARCH DESIGN AND METHODS

We randomized 4,304 adults (including 2,906 with type 2 diabetes) with a baseline estimated glomerular filtration rate (eGFR) 25–75 mL/min/1.73 m^2 and urinary albumin-to-creatinine ratio of 200–5,000 mg/g to dapagliflozin 10 mg or placebo once daily (NCT03036150). The primary end point was a composite of ≥50% eGFR decline, end-stage kidney disease, and kidney or cardiovascular cause of death. Secondary end points included a kidney composite end point (primary composite end point without cardiovascular death), a cardiovascular composite end point (hospitalized heart failure or cardiovascular death), and all-cause mortality. In this prespecified analysis, we investigated the effects of dapagliflozin on these and other outcomes according to baseline GLT class or number of GLTs.

RESULTS

The effects of dapagliflozin on the primary composite outcome were consistent across GLT classes and according to the number of GLTs (all interaction $P > 0.08$). Similarly, we found consistent benefit of dapagliflozin compared with placebo on the secondary end points regardless of background GLT class or number of GLTs. The same applied to the rate of decline in the eGFR rate and safety end points. Dapagliflozin reduced the initiation of insulin therapy during follow-up compared with placebo (hazard ratio 0.72; 95% CI 0.54–0.96; $P = 0.025$).

CONCLUSIONS

Dapagliflozin reduced kidney and cardiovascular events in patients with type 2 diabetes and CKD across baseline GLT class or classes in combination.

Optimization of glycemic control in patients with diabetes reduces the risk of microvascular complications, including kidney failure (1,2). However, achieving optimal glucose control can be challenging in patients with type 2 diabetes and chronic kidney disease (CKD) because impaired kidney function hampers the use of several oral or injectable glucose-lowering drugs (3) and increases the likelihood of hypoglycemia.

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ORIGINAL ARTICLE

Sodium–glucose cotransporter 2 (SGLT2) inhibitors were originally developed for the treatment of type 2 diabetes, and caution was advised when combining with glucose-lowering therapies (GLTs) that can cause hypoglycemia, such as insulin and sulfonylureas. SGLT2 inhibitors were later found to confer cardiovascular and kidney benefits, initially in patients with type 2 diabetes and normal or nearly normal kidney function (4–7). The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial demonstrated benefits in patients with type 2 diabetes and mild to moderate (stages 1–3) CKD (8). The Dapagliflozin and Prevention of Adverse Outcomes in CKD (DAPA-CKD) trial extended these benefits to patients with CKD without diabetes and to a sizeable fraction of patients with type 2 diabetes and moderate to advanced (stage 3b and 4) CKD, where several GLTs are not recommended or dose adjustment for kidney function is necessary (9). Specifically, the DAPA-CKD study, with many participants having reduced kidney function, provides an opportunity to explore whether the clinical benefits of SGLT2 inhibitors are present in patients with type 2 diabetes and CKD irrespective of whether they are treatment naive or already using metformin. To assess the clinical impact of combining dapagliflozin to different GLT groups, we undertook the current analysis to determine the relative safety and efficacy of dapagliflozin in patients with type 2 diabetes and stages 2–4 CKD treated with other GLTs alone or in combination.

RESEARCH DESIGN AND METHODS

Study Design and Participants

DAPA-CKD was a prospective, randomized, double-blind, placebo-controlled, multicenter trial conducted at 386 clinical practice sites in 21 countries (NCT03036150). The trial design and primary results have been published previously (9,10). DAPA-CKD recruited 4,304 participants with CKD with an estimated glomerular filtration rate (eGFR) of 25–75 mL/min/1.73 m^2 and a urinary albumin-to-creatinine ratio (UACR) of 200–5,000 mg/g, with or without type 2 diabetes. Patients with type 1 diabetes, polycystic kidney disease, lupus nephritis, or anti-neutrophil cytoplasmic antibody–associated vasculitis, as well as those receiving immunotherapy for primary or secondary kidney disease within 6 months prior to enrolment were excluded. All eligible participants were receiving treatment with a stable dose of an ACE inhibitor or angiotensin receptor blocker for ≥4 weeks prior to randomization, unless there was a documented intolerance to these drugs (10).

Randomization and Follow-up

Participants were randomly assigned to receive dapagliflozin (10 mg once daily) or matching placebo, in accordance with the sequestered, fixed-randomization schedule, with the use of balanced blocks to ensure an ∼1:1 ratio of the two regimens. Randomization was stratified according to the diagnosis of type 2 diabetes (yes or no) and the UACR (≤1,000 mg/g or >1,000 mg/g). Investigators used an interactive voice-response or Web-response system to determine trial group assignments. Randomization was monitored to ensure that a minimum of 30% of the participants were recruited to either the population with type 2 diabetes or the population without diabetes. Participants and all trial personnel (except the members of the independent data monitoring committee) were unaware of the trial group assignments (9). Following randomization, in-person study visits were performed after 2 weeks, 2, 4, and 8 months, and at 4-month intervals thereafter. At each follow-up visit, we recorded vital signs, sent blood and urine samples for laboratory assessment, and collected information on potential study end points, adverse events, concomitant therapies, and study drug adherence.

Outcomes

As described previously (10), the primary clinical trial end point was a composite of sustained ≥50% decline in the eGFR (confirmed by a second measurement after at least 28 days), onset of end-stage kidney disease (defined as maintenance dialysis for >28 days, kidney transplantation, or eGFR <15 mL/min/1.73 m^2 confirmed by a second measurement after at least 28 days), or death from a kidney or cardiovascular cause. Secondary end points were, in hierarchical order: a kidney-specific end point defined in the same way as the primary outcome but excluding death from a cardiovascular cause, a cardiovascular composite end point of cardiovascular death or hospitalization for heart failure, and all-cause mortality.

Number and Classes of GLTs

In this prespecified analysis, we included randomized patients with type 2 diabetes defined by a medical history of type 2 diabetes or a central laboratory HbA_{1c} value ≥6.5% (48 mmol/mol) at both screening and randomization visits. We examined the effect of dapagliflozin, compared with placebo, by individual GLT classes: biguanides (hereafter referred to as metformin), sulfonylureas, dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, and insulin, and by the number of GLTs at baseline. We examined the effects of dapagliflozin on the primary end point, a composite of sustained decline in eGFR of ≥50%, end-stage kidney disease, or death from kidney or cardiovascular causes, and on three secondary end points: a kidney-specific composite (the same as the primary composite end point without cardiovascular death), a composite of hospitalizations for heart failure and cardiovascular mortality, and all-cause mortality.

Statistical Analyses

The DAPA-CKD trial had 90% power to detect a relative risk reduction of 22% in the primary end point based on primary events being observed in 681 patients and a two-sided *P* value of 0.05. The present analyses were prespecified exploratory analyses. To quantify the relative effects on the primary and secondary end points, we fitted Cox proportional hazards regression models with treatment group assignment as the fixed-effect factor. We explored effect modification by each GLT class by using a GLT drug class times randomized treatment interaction. We determined the effects of dapagliflozin on the rate of decline in the eGFR from baseline to month 30 with the use of a two-slope model, described in detail elsewhere (9). We also determined the effects of dapagliflozin compared with placebo on the initiation of insulin therapy for at least 28 days during follow-up in patients not using insulin therapy at baseline by using Cox proportional hazards regression. We conducted statistical analyses using R 4.10 software (R Foundation for Statistical Computing, Vienna, Austria). We considered *P* values <0.05 statistically significant.

Data and Resource Availability

Data underlying the findings described in this manuscript may be obtained in

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accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at http://www.vivli.org. Data for studies not listed on Vivli can be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

RESULTS

Of the 4,304 randomized patients in DAPA-CKD, 2,906 (68%) had a documented medical history of type 2 diabetes or had undiagnosed type 2 diabetes and were therefore included in the analysis. Of these, 1,244 (43%) were on metformin, 1,598 (55%) were on insulin, 774 (27%) on sulfonylureas, 742 (26%) on DPP-4 inhibitors, and 122 (4%) on GLP-1 receptor agonists. Other GLTs, such as thiazolidinediones ("glitazones") and acarbose, were rarely used. At baseline, 327 patients (11%) were without diabetes treatment, 1,442 (50%) were treated with one GLT, 943 (32%) with two, and 194 (7%) with three or more. Baseline characteristics of patients by number of GLTs at baseline are summarized in Table 1.

During a median follow-up of 2.4 years, the effect of dapagliflozin on the primary composite end point (hazard ratio [HR] 0.64; 95% CI 0.52–0.79) was consistent irrespective of the number of prescribed GLTs at baseline (interaction $P = 0.08$) (Fig. 1*A*). When considering individual GLT classes (Fig. 1*B*), there was no effect modification by GLT class (all interaction $P \geq 0.19$). We found similar benefits of dapagliflozin irrespective of background GLT class for the kidney composite (HR 0.57; 95% CI 0.45–0.73; interaction $P = 0.05$), cardiovascular composite (HR 0.70; 95% CI 0.53–0.92; interaction $P = 0.93$), and all-cause mortality (HR 0.74; 95% CI 0.55–0.98; interaction $P = 0.47$) end points (Supplementary Fig. 1).

The effect of dapagliflozin compared with placebo on the rate of eGFR decline is shown in Supplementary Fig. 2. Overall, compared with placebo, dapagliflozin reduced the annual rate of change in eGFR from baseline to end of treatment (difference of 0.95 mL/min/1.73 m^2 per year; 95% CI 0.63–1.27) with consistent effects regardless of the number of GLTs

Table 1—Baseline characteristics by number of GLTs

	Dapagliflozin 10 mg*†				Placebo*			
Number of GLTs	0	1	2	≥3	0	1	2	≥3
Age, years	63.4 (11.6)	64.3 (10.1)	64.0 (9.1)	65.1 (8.3)	64.5 (10.7)	65.2 (9.4)	64.2 (9.2)	64.1 (9.8)
Female sex, *n* (%)	43 (26.1)	249 (35.5)	169 (34.8)	33 (32.4)	45 (27.8)	269 (36.4)	130 (28.4)	27 (29.3)
Weight, kg	81.1 (20.9)	82.2 (20.6)	84.5 (21.1)	87.2 (21.5)	78.0 (17.8)	84.0 (21.5)	85.6 (21.6)	83.7 (20.9)
BMI, kg/m^2	29.1 (5.8)	29.9 (6.2)	30.8 (6.3)	31.3 (5.9)	28.4 (5.2)	30.6 (6.5)	30.7 (6.4)	30.3 (5.7)
Blood pressure, mmHg								
Systolic	135.7 (17.5)	139.2 (17.5)	139.0 (17.8)	140.4 (17.2)	138.2 (17.5)	140.0 (17.7)	140.1 (16.3)	136.9 (14.9)
Diastolic	76.8 (11.5)	76.2 (10.7)	77.0 (9.7)	75.9 (9.6)	76.8 (10.7)	76.4 (10.1)	76.7 (9.5)	75.8 (8.3)
eGFR, mL/min/1.73 m^2	39.4 (11.7)	42.0 (12.0)	47.3 (12.9)	49.5 (10.8)	39.2 (11.1)	41.7 (12.2)	47.2 (12.6)	48.2 (12.5)
UACR, mg/g	972.0 (498.5–1,769.0)	1,025.8 (449.9–2,245.0)	1,069.2 (491.6–2,304.4)	777.8 (431.0–1,643.1)	1,054.0 (566.8–1,918.1)	1,000.8 (497.2–2,018.5)	1,026.5 (460.5–2,010.5)	869.0 (484.1–2,021.1)
HbA_{1c}, %	6.8 (1.4)	7.7 (1.6)	8.1 (1.7)	8.3 (1.4)	6.8 (1.3)	7.7 (1.6)	8.1 (1.6)	8.5 (1.8)
HbA_{1c}, mmol/mol	51 (15)	61 (18)	65 (19)	67 (15)	51 (14)	61 (18)	65 (18)	69 (20)
CV history, *n* (%)	65 (39.4)	319 (45.4)	213 (43.8)	43 (42.2)	59 (36.4)	344 (46.5)	211 (46.2)	27 (29.3)

Data are presented as mean (SD) or median (interquartile range), unless indicated otherwise. CV, cardiovascular; GLT, glucose-lowering therapies. *Tests for trend show that in the dapagliflozin and placebo groups, participants using more GLTs had, at baseline, a higher body weight ($P < 0.01$ for both groups), BMI ($P < 0.02$ for both groups), eGFR ($P < 0.001$ for both groups), and HbA_{1c} ($P < 0.001$ for both groups), and were more likely to have a cardiovascular disease history ($P < 0.001$ for both groups). †Baseline characteristics were balanced between the dapagliflozin and placebo groups in each number of GLT stratum ($P > 0.05$ for all).

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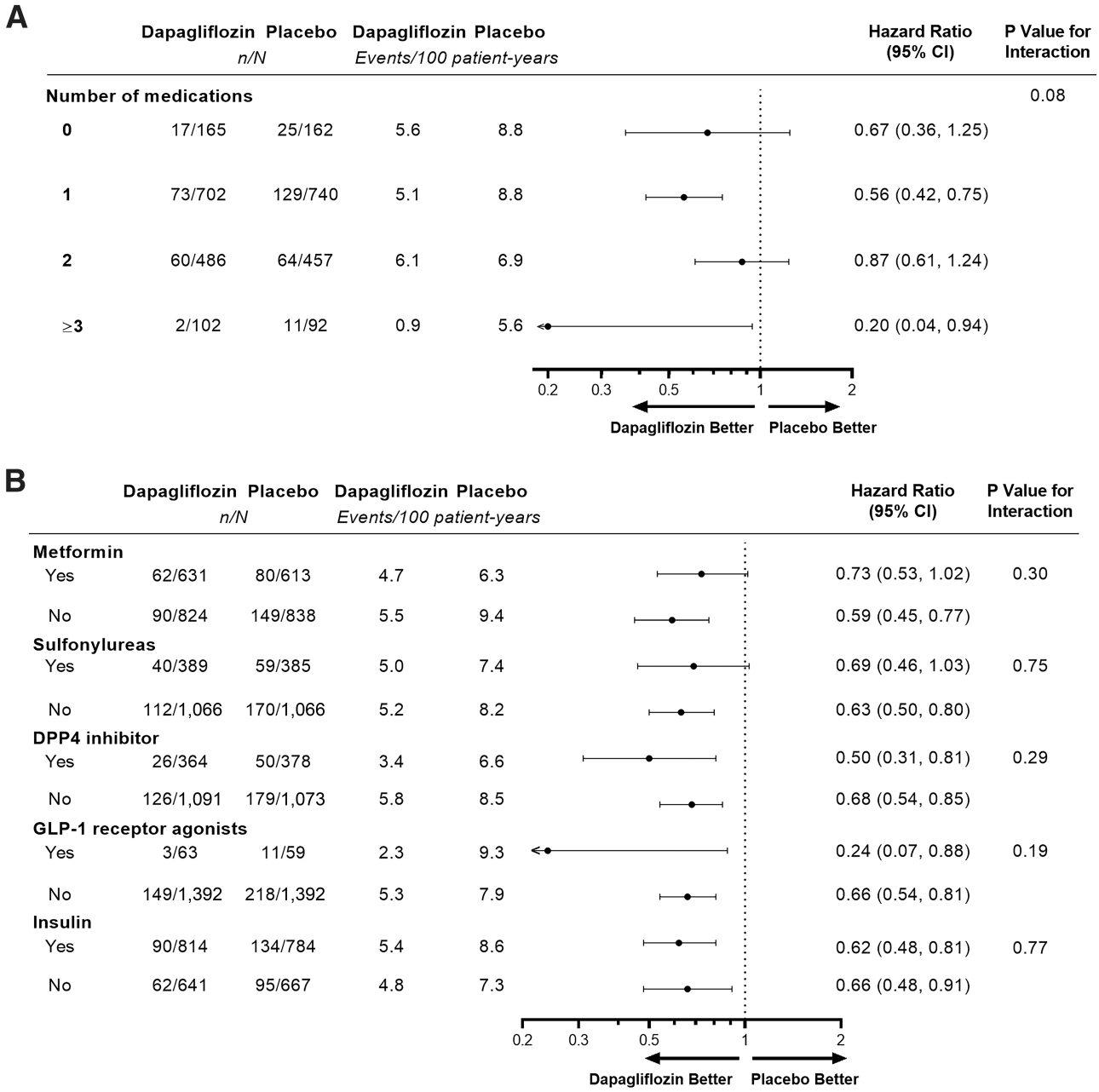

Figure 1—The primary end point by the number of baseline GLTs (*A*) and by the type of GLT at baseline (*B*).

(interaction $P = 0.88$) or background GLT class (all interaction $P \geq 0.087$).

During follow-up, 78 and 109 patients in the dapagliflozin and placebo group, respectively, started insulin treatment for at least 28 days (HR 0.72; 95% CI 0.54–0.96; $P = 0.025$) (Fig. 2). The results were similar when the effect of dapagliflozin was analyzed in patients starting insulin for any day (HR 0.68; 95% CI 0.51–0.90; $P < 0.01$) (Supplementary Fig. 3).

Supplementary Table 1 summarizes the adverse events leading to study drug discontinuation, serious adverse events, and major hypoglycemia events stratified by baseline use/nonuse of GLTs. There was no increase in risk of these events irrespective of the number of GLTs or background GLT class.

CONCLUSIONS

In this prespecified analysis of the DAPA-CKD trial, we found that the benefit of dapagliflozin compared with placebo in reducing the risk of the primary and secondary kidney and cardiovascular end points among patients with type 2 diabetes and CKD was consistent across all classes of commonly used GLTs and according to the number of GLTs. We also found that dapagliflozin reduced the initiation of insulin therapy during follow-up compared with placebo.

The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline recommends metformin and SGLT2 inhibitors as first-line GLT in patients with type 2 diabetes and CKD (11). Metformin was the most commonly used GLT next to insulin in the DAPA-CKD trial. However, the proportion of patients using metformin (43%) was lower than that observed in other SGLT2 inhibitor trials in patients with type 2 diabetes at high

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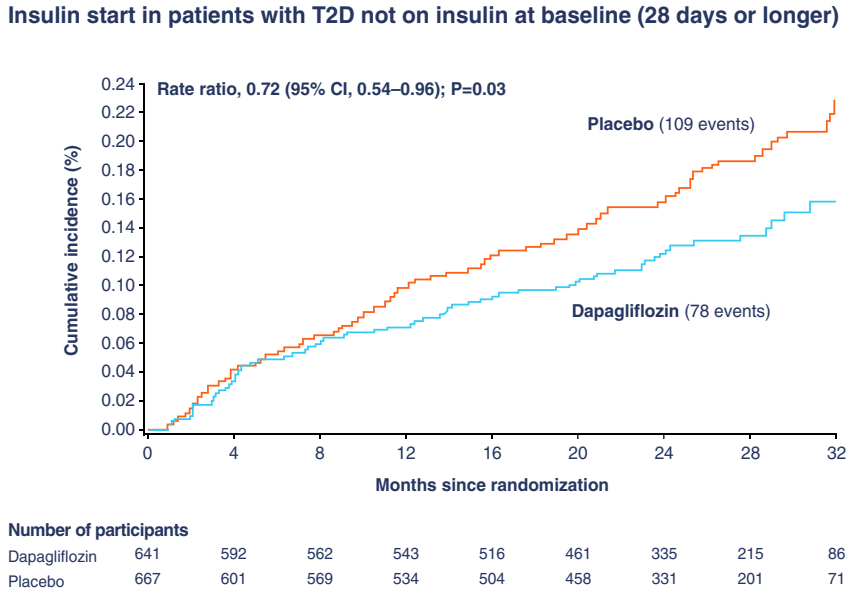

Figure 2—Initiation of insulin therapy in patients with type 2 diabetes (T2D) for ≥28 days during follow-up between the dapagliflozin and placebo groups.

cardiovascular risk, most likely because clinical practice guidelines do not recommend metformin in patients with an eGFR <30 mL/min/1.73 m^2 due to a perceived risk of lactic acidosis. Studies have suggested that the benefit of SGLT2 inhibitors may be attenuated in patients using metformin (12,13), but the present results of the DAPA-CKD trial and other trials and meta-analysis did not confirm this finding. These data support guideline recommendations that suggest that SGLT2 inhibitors be initiated in patients with type 2 diabetes at high or very high cardiovascular risk, irrespective of whether they are treatment naive or already using metformin (14).

Many clinical practice guidelines now recommend SGLT2 inhibitors in patients with cardiovascular disease, CKD, and heart failure (11,15,16). Clinical practice guidelines also recommend GLP-1 receptor agonists in patients with atherosclerotic cardiovascular disease (1,11). An analysis from the Canagliflozin Cardiovascular Assessment Study (CANVAS) program reported that the HbA_{1c}-, body weight-, and blood pressure-lowering effects of canagliflozin were accentuated in patients using, compared with not-using, GLP-1 receptor agonists at baseline (17). In addition, the Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial suggested that the effect of dapagliflozin in reducing the risk of heart failure hospitalizations or cardiovascular death was more pronounced in participants using GLP-1 receptor agonists compared with those not using these agents (18). We could not confirm this finding; however, the number of patients using GLP-1 receptor agonists in DAPA-CKD was low.

The data presented here suggest that dapagliflozin can be safely administered and poses little to no risk for hypoglycemia irrespective of background GLTs or number of GLTs. As reported previously, dapagliflozin only reduced HbA_{1c} in DAPA-CKD participants with type 2 diabetes by 0.1% (19). This phenomenon is most likely caused by less filtration of glucose in patients with CKD, attenuating glycemic efficacy, and causing a low risk of hypoglycemia. In addition, patients were treated according to international or local guidelines. Because HbA_{1c} was treated according to local practice guidelines, adjustments to background GLTs could be made during the trial, which could have masked an effect of dapagliflozin on HbA_{1c}. There was thus no restriction for introducing additional GLTs, which may have contributed to the small HbA_{1c}-lowering effect. The current data provide further evidence that the risk of hypoglycemia remains low irrespective of background GLTs. These data confirm the positive risk benefit profile of dapagliflozin and supports evolving clinical practice guidelines to routinely initiate SGLT2 inhibitors in patients with type 2 diabetes and CKD.

A limitation of this prespecified analysis is that background GLT was not stratified and that some of the subgroups were small, limiting statistical power. In addition, background GLT was based on patient-specific characteristics, prescriber patterns, and regional guidelines and recommendations. These factors may determine clinical outcomes, and the results should be interpreted with this in mind.

In summary, this prespecified analysis of the DAPA-CKD trial supports the safety and efficacy of dapagliflozin used in conjunction with other GLTs in patients with type 2 diabetes and CKD to lower the risks of cardiovascular events and progressive kidney disease.

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Duality of Interest. The trial was funded by AstraZeneca. F.P. has served as a consultant, on advisory boards, or as educator for AstraZeneca, Novo Nordisk, Boehringer Ingelheim, Sanofi, Mundipharma, Merck Sharpe & Dohme, Novartis, and Amgen, and has received research grants to the institution from Novo Nordisk, Boehringer Ingelheim, Amgen, and AstraZeneca. G.D.L. has received lecture fees from Sanofi, AstraZeneca, and Janssen, and has served as a consultant for AbbVie, Sanofi, Novo Nordisk, AstraZeneca, Boehringer Ingelheim, and Merck Sharp & Dohme. G.M.C. has received fees from AstraZeneca for service on the DAPA-CKD trial steering committee, serves on the board of directors for Satellite Healthcare, has served on other trial steering committees for Akebia, AstraZeneca, Gilead, Sanifit, and Vertex, and on data safety monitoring boards for Angion, Bayer, Mineralys, and ReCor, and has served as an advisor and received fees and/or stock options from Ardelyx, CloudCath, Cricket, DiaMedica, Durect, DxNow, Miromatrix, Outset, Physiowave, and Unicycive. J.J.V.M. has received payments to his employer, Glasgow University, for his work on clinical trials, consulting, and other activities from AstraZeneca, Cytokinetics, KBP Biosciences, Amgen, Bayer, Theracos, Ionis Pharmaceuticals, Dalcor Pharmaceuticals, Novartis, GlaxoSmithKline, Bristol-

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Myers Squibb, Boehringer Ingelheim, Cardurion, and Alnylam, and has received personal lecture fees from Abbott, Alkem Metabolics, Eris Life Sciences, Hickma, Lupin, Sun Pharmaceuticals, Medscape/Heart.org, ProAdWise Communications, Radcliffe Cardiology, Servier, and the Corpus. A.M.L. and C.D.S. are employees and stockholders of AstraZeneca. R.C.-R. has received honoraria from AbbVie, AstraZeneca, GlaxoSmithKline, Medtronic, and Boehringer Ingelheim, has lectured for Amgen, Janssen, Takeda, AstraZeneca, and Boehringer Ingelheim, and has received research support from GlaxoSmithKline, Novo Nordisk, and AstraZeneca. P.R. has received honoraria to Steno Diabetes Center Copenhagen for steering group membership and/or lectures and advice from AstraZeneca, Novo Nordisk, Bayer, and Eli Lilly, advisory board participation from Sanofi Aventis and Boehringer Ingelheim, and steering group participation from Gilead. R.D.T. reports consultancy fees from Akebia, AstraZeneca, Boehringer Ingelheim, Bayer, Chinook Pharma, Medscape, Novo Nordisk, Otsuka, Reata, and Vifor. D.C.W. has received consultancy fees from AstraZeneca and personal fees from Amgen, Astellas, Bayer, Boehringer Ingelheim, Gilead, GlaxoSmithKline, Janssen, Napp, Mundipharma, Reata, Tricida, Vifor Fresenius, and Zydus. H.J.L.H. has received honoraria paid to his institution (University Medical Center Groningen) for participation in steering committees from AstraZeneca, Janssen, Gilead, Bayer, Chinook, and CSL Pharma, honoraria for participation in advisory boards from Merck, Mitsubishi Tanabe, Janssen, and Mundipharma, fees for consultancy from AstraZeneca, AbbVie, Retrophin, Boehringer Ingelheim, and Novo Nordisk, and research grant support from AstraZeneca, AbbVie, Janssen, and Boehringer Ingelheim. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. J.M.B. and F.P. wrote the first draft. J.M.B., F.P., and H.J.L.H. had full access to the data and had the final responsibility for the decision to submit for publication. J.M.B., N.J., G.D.L., and H.J.L.H. analyzed the data. J.M.B., F.P., N.J., G.D.L., G.M.C., J.J.V.M., A.M.L., R.C.-R., P.R., C.D.S., R.D.T., D.C.W., and H.J.L.H. reviewed the manuscript drafts and provided approval for the final version for submission. H.J.L.H. is the guarantor 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.

Prior Presentation. Parts of this study were presented in abstract form at the 82nd Scientific Sessions of the American Diabetes Association, virtual and at New Orleans, LA, 3–7 June 2022.

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