JAMA Network Open

Research Letter | Nephrology

# Effectiveness and Safety of Dapagliflozin for Black vs White Patients With Chronic Kidney Disease in North and South America

## A Secondary Analysis of a Randomized Clinical Trial

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## Introduction

Black and White patients experience a distinct array of comorbid conditions and can respond differently to interventions.[1,2] Black patients are more likely to develop salt-sensitive hypertension, less responsive to renin-angiotensin-aldosterone system inhibitors, and nearly 4-fold more likely to develop progressive chronic kidney disease (CKD), leading to kidney failure.[3-5] Sodium-glucose cotransporter-2 (SGLT2) inhibitors have been demonstrated to lower risks of progressive kidney disease, cardiovascular events, and premature death for patients with CKD. However, it is unclear whether the effectiveness and safety of SGLT2 inhibitors differ between Black and White patients with CKD. This substudy of the DAPA-CKD trial (NCT03036150) investigated the effectiveness and safety of dapagliflozin for Black vs White patients with CKD (trial protocol and statistical analysis plan in Supplement 1).

## Methods

This is a post hoc secondary analysis of the DAPA-CKD trial, a randomized, double-blind, placebo-controlled, multicenter trial conducted at 386 study sites in 21 countries from February 2, 2017, to June 12, 2020.[6] All participants provided written informed consent, and the trial was approved by an ethics committee at each trial site. This study followed the CONSORT reporting guideline. A 2-tailed $P < .05$ indicated statistical significance. The methods and patient flow diagram are presented in the eMethods and eFigure in Supplement 2, respectively. A total of 4304 adults with CKD, with or without type 2 diabetes, with estimated glomerular filtration rate (eGFR) of 25 to 75 mL/min/1.73 $m^2$ and urinary albumin to creatinine ratio of 200 to 5000 mg/g were randomized to dapagliflozin (10 mg/d) or placebo. This analysis included only Black and White patients enrolled in North and South America. Race was self-reported. Primary end point was a composite of 50% or more sustained eGFR decline, end-stage kidney disease (ESKD), or death from kidney or cardiovascular disease. Secondary end points were a kidney composite end point of 50% or more sustained eGFR decline, ESKD, or death from kidney disease; a cardiovascular composite end point of hospitalization for heart failure or death from cardiovascular disease; and all-cause mortality. All analyses were performed using Stata, version 14.2 (StataCorp).

## Results

Of 4304 patients (mean [SD] age, 61.8 [12.8] years; 33.1% women), 1725 (40.1%) were enrolled in North and South America. Of these, 185 (10.7%) were Black, and 1086 (63.0%) were White. Mean age was lower (62 vs 65 years) and proportion of women higher (44.3% vs 29.4%) for Black vs White patients. Mean eGFR (44 vs 43 mL/min/1.73 $m^2$), median urinary albumin to creatinine ratio (897 vs 809 mg/g), prevalence of diabetes (72.4% vs 72.5%), and other baseline characteristics were similar between Black and White patients, except for history of heart failure (15.1% vs 8.0%). During median follow-up of 2.2 years, 20 Black patients (10.8%) and 139 White patients (12.8%) developed the

+ Supplemental content

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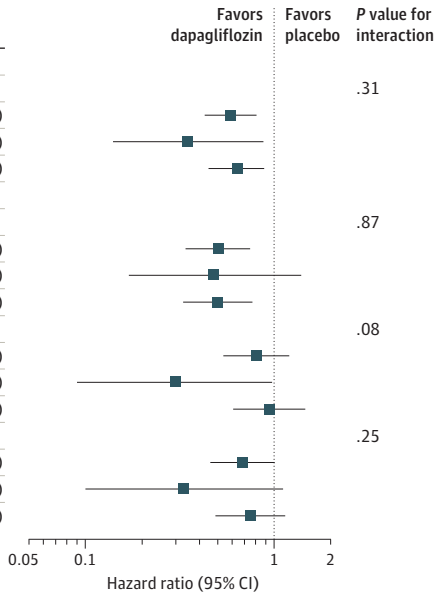
primary composite end point, corresponding to event rates of 5.3 and 6.2 per 100 patient-years, respectively. Dapagliflozin was associated with reduced risk of the primary composite end point vs placebo for Black (hazard ratio [HR], 0.35; 95% CI, 0.14-0.88) and White patients (HR, 0.64; 95% CI, 0.45-0.89; *P* = .31 for interaction) (**Figure**). Consistent benefits were associated with all secondary end points (Figure). Reduction in total (randomization to end of follow-up) eGFR decline with dapagliflozin was 1.2 mL/min/1.73 $m^2$/y (95% CI, −0.11 to 2.5 mL/min/1.73 $m^2$/y) for Black patients and 1.0 mL/min/1.73 $m^2$/y (95% CI, 0.5-1.6 mL/min/1.73 $m^2$/y) for White patients (*P* = .82 for interaction), and reduction in chronic (week 2 to the end of treatment) eGFR decline was 2.8 mL/min/1.73 $m^2$/y (95% CI, 1.5-4.1 mL/min/1.73 $m^2$/y) for Black patients and 2.3 mL/min/1.73 $m^2$/y (95% CI, 1.7-2.8 mL/min/1.73 $m^2$/y) for White patients (*P* = .44 for interaction). Serious adverse events were less frequent with dapagliflozin than with placebo among Black patients (30.4% vs 39.8%) and White patients (34.9% vs 39.0%).

**Figure. Effectiveness of Dapagliflozin for Black vs White Patients in North and South America**

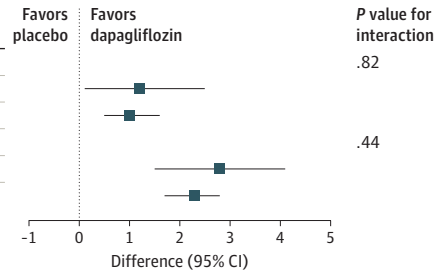
A Clinical end points

| End point | Dapagliflozin (n = 632; 102 Black and 530 White patients) No. (%) | Events/100 patient-years | Placebo (n = 639; 83 Black and 556 White patients) No. (%) | Events/100 patient-years | Hazard ratio (95% CI) | *P* value for interaction |
|---|---|---|---|---|---|---|
| Primary outcome | | | | | | |
| eGFR decline ≥50%, end-stage kidney disease, or kidney or cardiovascular death | | | | | | .31 |
| Overall population | 60 (9.5) | 4.5 | 99 (15.5) | 7.6 | 0.59 (0.43-0.81) | |
| Black (n = 185) | 7 (6.9) | 3.2 | 13 (15.7) | 8.0 | 0.35 (0.14-0.88) | |
| White (n = 1086) | 53 (10.0) | 4.8 | 86 (15.5) | 7.6 | 0.64 (0.45-0.89) | |
| Secondary outcomes | | | | | | |
| eGFR decline ≥50%, end-stage kidney disease, or kidney death | | | | | | .87 |
| Overall population | 38 (6.0) | 2.9 | 74 (11.6) | 5.7 | 0.51 (0.34-0.75) | |
| Black (n = 185) | 6 (5.9) | 2.8 | 8 (9.6) | 4.9 | 0.48 (0.17-1.40) | |
| White (n = 1086) | 32 (6.0) | 2.9 | 66 (11.9) | 5.8 | 0.50 (0.33-0.77) | |
| Cardiovascular death or hospitalization for heart failure | | | | | | .08 |
| Overall population | 42 (6.6) | 2.9 | 50 (7.8) | 3.5 | 0.81 (0.54-1.22) | |
| Black (n = 185) | 4 (3.9) | 1.7 | 9 (10.8) | 5.1 | 0.30 (0.09-0.98) | |
| White (n = 1086) | 38 (7.2) | 3.1 | 41 (7.4) | 3.3 | 0.95 (0.61-1.47) | |
| All-cause death | | | | | | .25 |
| Overall population | 41 (6.5) | 2.8 | 59 (9.2) | 4.1 | 0.68 (0.46-1.01) | |
| Black (n = 185) | 4 (3.9) | 1.7 | 8 (9.6) | 4.3 | 0.33 (0.10-1.12) | |
| White (n = 1086) | 37 (7.0) | 3.0 | 51 (9.2) | 4.0 | 0.75 (0.49-1.15) | |




B Total and chronic eGFR slopes

| Slope | Mean (SD) eGFR slope (mL/min/1.73 $m^2$/y) Dapagliflozin (n = 632; 102 Black and 530 White patients) | Placebo (n = 639; 83 Black and 556 White patients) | Difference (95% CI) | *P* value for interaction |
|---|---|---|---|---|
| Total slope | | | | .82 |
| Black (n = 185) | -3.6 (0.4) | -4.8 (0.5) | 1.2 (0.11-2.5) | |
| White (n = 1086) | -2.6 (0.2) | -3.7 (0.2) | 1.0 (0.5-1.6) | |
| Chronic slope | | | | .44 |
| Black (n = 185) | -1.7 (0.4) | -4.5 (0.5) | 2.8 (1.5-4.1) | |
| White (n = 1086) | -1.2 (0.2) | -3.4 (0.2) | 2.3 (1.7-2.8) | |




A, Clinical end points. B, Total (randomization to end of follow-up) and chronic (3 months to end of follow-up) estimated glomerular filtration rate (eGFR) slopes.

## Discussion

Among Black and White patients with CKD, dapagliflozin was associated with reduced risks of progressive kidney disease (including kidney failure), cardiovascular events, and all-cause mortality, with safety similar to that of placebo. This secondary analysis is limited by small numbers of Black and White patients; therefore, the power to detect effect modification by designated race was low. However, based on available information, Black and White patients appear to experience similar kidney and cardiovascular benefits of dapagliflozin.

### ARTICLE INFORMATION

**Accepted for Publication:** March 17, 2023.

**Published:** April 27, 2023. doi:10.1001/jamanetworkopen.2023.10877



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**Author Contributions:** Drs Vart and Chertow had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

*Concept and design:* All authors.

*Acquisition, analysis, or interpretation of data:* Vart, Jongs, Wheeler, Langkilde, Chertow.

*Drafting of the manuscript:* Vart, Wheeler, Chertow.

*Critical revision of the manuscript for important intellectual content:* All authors.

*Statistical analysis:* Vart, Jongs, Chertow.

*Obtained funding:* Wheeler.

*Administrative, technical, or material support:* Wheeler, Heerspink.

*Supervision:* Wheeler, Langkilde, Chertow.

**Conflict of Interest Disclosures:** Dr Vart reported receiving grants from AstraZeneca during the conduct of the study. Dr Wheeler reported receiving personal fees from AstraZeneca during the conduct of the study; personal fees from Astellas, Boehringer Ingelheim, Bayer, GlaxoSmithKline, Janssen, Gilead, Merck Sharp and Dohme, George Clinical, Intas, ProKidney, Tricida, Vifor, and Zydus outside the submitted work; and performing guideline development for KDIGO. Dr Heerspink reported receiving research support from and serving as a consultant for AstraZeneca during the conduct of the study; serving as a consultant for Bayer, Chinook Tx, CSL Behring, Dimerix, Eli Lilly, Fresenius, Gilead, Novartis, and Travere Therapeutics outside the submitted work; receiving grants and research support from Boehringer Ingelheim and Janssen outside the submitted work; and receiving grants from and serving as a consultant for NovoNordisk outside the submitted work. Dr Langkilde reported being a full-time employee and shareholder of AstraZeneca during the conduct of the study. Dr Chertow reported receiving personal fees from AstraZeneca during the conduct of the study; receiving personal fees from Akebia, Ardelyx, Gilead, Reata, Sanifit, Vertex, and Satellite Healthcare outside the submitted work; serving on the advisory board for and holding stock options in CloudCath, Durect, Miromatrix, Outset, and Univycive outside the submitted work; and receiving grants to institution from CSL Behring Steering Committee outside the submitted work. No other disclosures were reported.

**Funding/Support:** This trial was funded by AstraZeneca.

**Role of the Funder/Sponsor:** AstraZeneca had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and review, or approval of the manuscript prior to submission for technical and scientific accuracy.

**Meeting Presentation:** This study was presented at the American Society of Nephrology Kidney Week 2022; November 5, 2022; Orlando, Florida.

**Data Sharing Statement:** See Supplement 3.

**Additional Contributions:** We also acknowledge Lise Magnollay, PhD, and Parita Sheth, PhD, inScience Communications, for assistance with the editing of the draft report and preparation of the figures (support funded by AstraZeneca). The authors also thank all investigators, trial teams, and patients for their participation in the DAPA-CKD Trial.

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## SUPPLEMENT 1.

**Trial Protocol and Statistical Analysis Plan**

## SUPPLEMENT 2.

**eMethods.**

**eFigure.** Flow Chart of Study Sample Selection

## SUPPLEMENT 3.

**Data Sharing Statement**