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Research Letter | Nephrology

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

A Secondary Analysis of a Randomized Clinical Trial

Priya Vart, PhD; Niels Jongs, PhD; David C. Wheeler, MD; Hiddo J. L. Heerspink, PhD; Anna Maria Langkilde, PhD; Glenn M. Chertow, MD, MPH

Introduction

Relative to White patients, Black patients in North and South America often experience obstacles in accessing high-quality health care, including structural racism, and, in general, experience a distinct array of comorbid conditions and social determinants of health that can affect longevity, disease trajectory, health-related quality of life, and response to therapeutic interventions.^{1,2} Studies have reported that Black patients are more likely to develop salt-sensitive hypertension, less responsive to renin-angiotensin-aldosterone system inhibitors, and 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 among Black and White patients with CKD given concerns about comorbidities, barriers to care, and social determinants of health. This is a substudy of the DAPA-CKD trial (NCT03036150) that investigated the effectiveness and safety of dapagliflozin for patients with CKD (trial protocol and statistical analysis plan in [Supplement 1](#)). We hypothesized that because of previously reported differences in experiences regarding comorbidities, barriers to care, and social determinants of health, there could be differences in reported findings of effectiveness and safety of SGLT2 inhibitors among Black and White patients with CKD.

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 m² 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 due to widely reported disparities in experiences regarding comorbidities, barriers to care, and social determinants of health among Black and White patients in this region. 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).

+ Supplemental content

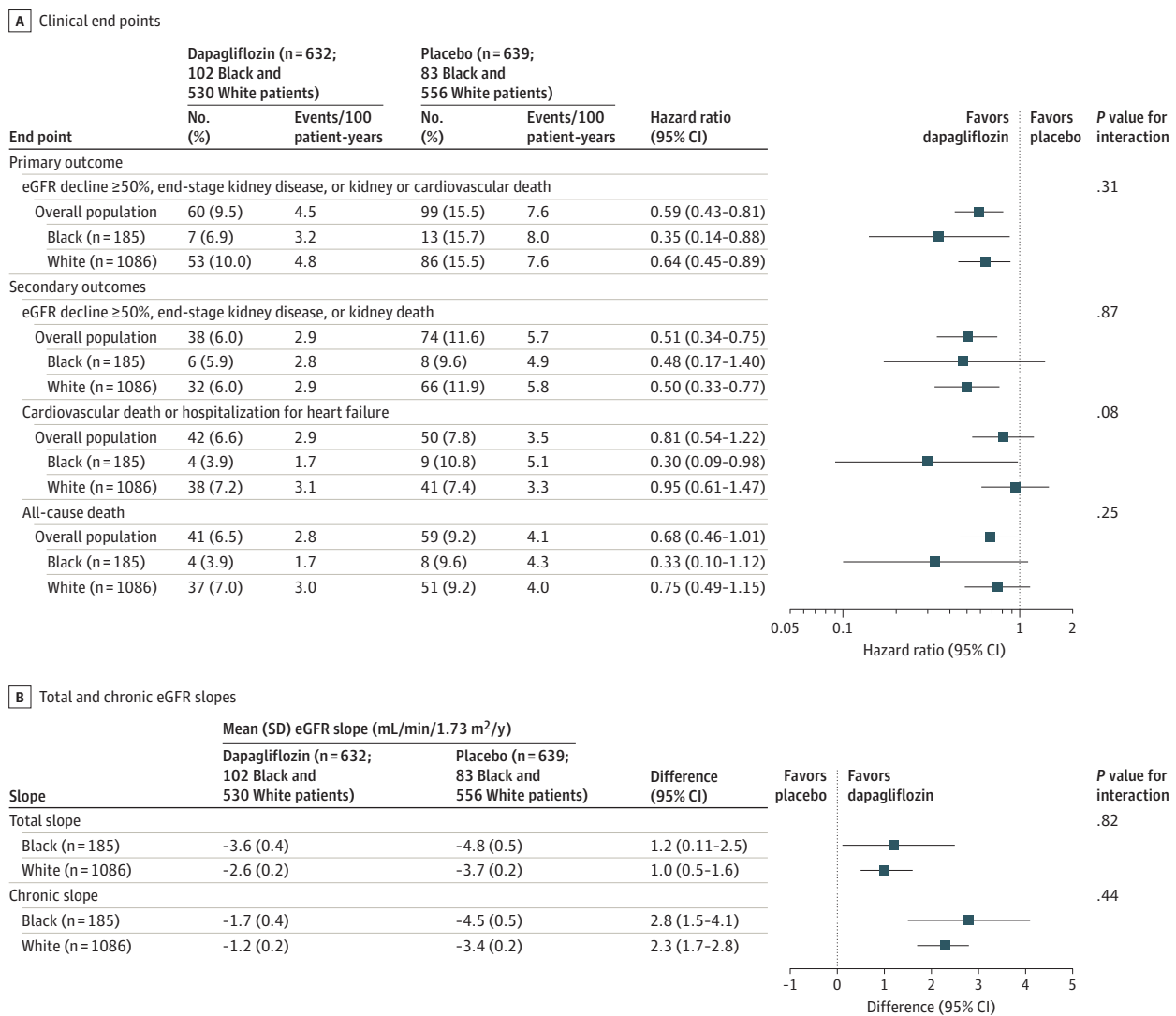
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Results

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 m²), 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 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 m²/y (95% CI, -0.11 to 2.5 mL/min/1.73 m²/y) for Black patients and 1.0 mL/min/1.73 m²/y (95% CI, 0.5-1.6 mL/min/1.73 m²/y) for White patients (*P* = .82 for interaction),

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



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.

and reduction in chronic (week 2 to the end of treatment) eGFR decline was 2.8 mL/min/1.73 m²/y (95% CI, 1.5-4.1 mL/min/1.73 m²/y) for Black patients and 2.3 mL/min/1.73 m²/y (95% CI, 1.7-2.8 mL/min/1.73 m²/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%).

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. In this secondary analysis, it was not possible to address differences in social determinants of health or structural barriers to access to care, and the study is limited by small numbers of Black and White patients included. With acknowledgment that race is a social construct, Black and White patients appeared to experience similar kidney and cardiovascular benefits of dapagliflozin in this study.

ARTICLE INFORMATION

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Correction: This article was corrected on May 12, 2023, to correct the omission of the study rationale and to include an acknowledgment that race is a social construct.

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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.

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Data Sharing Statement: See Supplement 3.

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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