Efficacy and Safety of Dapagliflozin in Patients With CKD Across Major Geographic Regions

Priya Vart1, Ricardo Correa-Rotter2, Fan Fan Hou3, Niels Jong1, Glenn M. Chertow4,5, Anna Maria Langkilde6, John J.V. McMurray7, Peter Rossing8,9, C. David Sjöström6, Bergur V. Stefansson6, Robert D. Toto10, Walter Douthat11, Elizabeth Escudero12, Rey Isidto13, Dinesh Khullar14, Harpreet S. Bajaj15, David C. Wheeler16 and Hiddo J.L. Heerspink1,17

1Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; 2The National Medical Science and Nutrition Institute Salvador Zubiran, Mexico City, Mexico; 3Division of Nephrology, Department of Medicine, Stanford University School of Medicine, Stanford, California, USA; 4Department of Epidemiology and Population Health, Stanford University School of Medicine, Stanford, California, USA; 5Late-Stage Development, Cardiovascular, Renal, and Metabolism, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden; 6Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK; 7Steno Diabetes Center Copenhagen, Gentofte, Denmark; 8Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; 9Department of Internal Medicine, UT Southwestern Medical Center, Dallas, Texas, USA; 10Department of Nephrology, Hospital Privado Universitario de Cordoba, Cordoba, Argentina; 11Division of Nephrology, Hospital Arzobispo Loayza, Cayetano Heredia University, Lima, Peru; 12Healthlink Medical, Dental, Surgical Clinics and Diagnostics Center, Iloilo City, Philippines; 13Department of Nephrology and Renal Transplant Medicine, Max Super Speciality Hospital, Saket, New Delhi, India; 14LMC Diabetes and Endocrinology, Brampton, Ontario, Canada; 15Department of Renal Medicine, University College London, London, UK; and 16The George Institute for Global Health, Sydney, Australia

Introduction: This study aimed to examine the efficacy and safety of dapagliflozin in the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial (NCT03036150) by geographic region.

Methods: Adults with chronic kidney disease (CKD) with or without type 2 diabetes, with estimated glomerular filtration rate (eGFR) 25 to 75 ml/min per 1.73 m² and urinary albumin-to-creatinine ratio (UACR) 200 to 5000 mg/g were randomized to dapagliflozin (10 mg once daily) or placebo. The primary end point was a composite of a sustained decline in eGFR of $50%, end-stage kidney disease or death from kidney or cardiovascular causes. We categorized recruiting countries into 4 broad global regions: Asia, Europe, Latin America, and North America. Of 4304 randomized patients, 1346 (31.3%) were from Asia, 1233 (28.6%) from Europe, 912 (21.2%) from Latin America, and 813 (18.9%) from North America.

Results: The relative risk of the primary composite end point was lower in patients randomized to dapagliflozin (relative to placebo) in all regions, with hazard ratios (95% CI) of 0.70 (0.48–1.00), 0.60 (0.43–0.85), 0.61 (0.43–0.86), and 0.51 (0.34–0.76) among patients from Asia, Europe, Latin America, and North America, respectively. There was no effect modification by region (interaction P = 0.77). Occurrence of serious adverse events (SAEs) was lower among patients randomized to dapagliflozin versus placebo (21.9% vs. 26.8%, 34.1% vs. 38.6%, 29.8% vs. 31.5%, and 34.9% vs. 41.0% in Asia, Europe, Latin America, and North America, respectively).

Conclusion: Dapagliflozin reduced kidney and cardiovascular events and prolonged survival in patients with CKD, with and without type 2 diabetes, with no apparent effect modification by geographic region.

Kidney Int Rep (2022) 7, 699–707; https://doi.org/10.1016/j.ekir.2022.01.1060
KEYWORDS: dapagliflozin; efficacy; regions; safety; SGLT-2 inhibitor
© 2022 International Society of Nephrology. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

In the past 2 decades, there has been a considerable increase in the number of global clinical trials with a sizeable increase in the recruitment of patients from developing countries. This trend has also been noted in trials of cardiovascular and CKD. Regional

Correspondence: Hiddo J.L. Heerspink, Department Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Hanzeplein 1, PO Box 30 000, 9700 AD Groningen, The Netherlands. E-mail: h.j.lambers.heerspink@umcg.nl
Received 11 November 2021; revised 18 January 2022; accepted 24 January 2022; published online 2 February 2022
difficulties in patient characteristics, comorbidities, and medical practice may result in differences in the efficacy and safety profiles of a drug across regions.

Recently, several large clinical trials investigating sodium-glucose cotransporter 2 inhibitors, initially developed for the treatment of hyperglycemia in type 2 diabetes, have shown favorable effects on kidney and cardiovascular outcomes in different patient populations. Some of these studies reported regional differences in efficacy. The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) trial reported the most pronounced effects on the composite outcome of heart failure hospitalization and cardiovascular death in patients from Asia and least pronounced effects in patients from Europe. These differences were also evident in a meta-analysis of 2 trials of sodium-glucose cotransporter 2 inhibitors in heart failure with reduced ejection fraction.

The DAPA-CKD trial enrolled patients from 4 geographic regions including Asia, Europe, Latin America, and North America. In the present study, we investigated whether there were meaningful regional differences in efficacy and safety of dapagliflozin among patients with CKD with and without type 2 diabetes.

### METHODS

#### Study Design and Participants

DAPA-CKD was a randomized, double-blind, placebo-controlled multicenter trial conducted at 386 study sites in 21 countries (broadly categorized into 4 regions—Asia, Europe, Latin America, and North America) from February 2017 until June 2020. Manuscripts describing details of the study design and the primary results have been published previously. Participating countries were, in a hierarchical order, the following: a composite kidney end point of ≥50% sustained decline in estimated GFR, kidney failure, or death from kidney disease; a composite cardiovascular end point of cardiovascular death or hospitalization for heart failure; and all-cause mortality. All efficacy end points were adjudicated by an independent event adjudication committee using rigorous prespecified end point definitions.

#### Safety

Given the extensive prior experience with dapagliflozin, ascertainment of AEs was limited to SAEs, AEs resulting in the discontinuation of study drug, and AEs of special interest (symptoms of volume depletion, kidney disease events, major hypoglycemia, bone fractures, amputations, potential diabetic ketoacidosis).

#### Regions

We broadly categorized participating sites into 4 geographic regions: Asia (participating countries: China, India, Japan, Philippines, South Korea, and Vietnam), Europe (participating countries: Denmark, Germany, Hungary, Poland, Russia, Spain, Sweden, United Kingdom, Ukraine), Latin America (participating countries: Argentina, Brazil, Mexico, Peru), and North America (participating countries: Canada, United States of America).

#### Efficacy End Points

The primary end point was a composite of sustained ≥50% decline in eGFR (confirmed by a second serum creatinine after at least 28 days), the onset of end-stage kidney disease (defined as maintenance dialysis for >28 days, kidney transplantation, or eGFR <15 ml/min per 1.73 m² confirmed by a second measurement after at least 28 days), or death from kidney or cardiovascular causes. Secondary end points were, in a hierarchical order, the following: a composite kidney end point of ≥50% sustained decline in estimated GFR, kidney failure, or death from kidney disease; a composite cardiovascular end point of cardiovascular death or hospitalization for heart failure; and all-cause mortality. All efficacy end points were adjudicated by an independent event adjudication committee using rigorous prespecified end point definitions.

#### Procedures

Eligible participants were randomly assigned to receive dapagliflozin 10 mg once daily or a matching placebo, in line with the sequestered, fixed-randomization schedule. Randomization was stratified by diabetes status and UACR (≥1000 or >1000 mg/g) at baseline. After randomization, in-person study visits were conducted after 2 weeks, 2, 4, and 8 months, and at 4-month intervals thereafter. At each follow-up visit, information on vital signs was recorded, blood and urine samples were obtained, and information on potential study end points, adverse events (AEs), concomitant therapies, and study drug adherence were collected.
Table 1. Characteristics of the patients at baseline according to major geographic region and randomized treatment assignment

| Characteristic          | Asia (N = 1346) | Europe (N = 1233) | Latin America (N = 912) | North America (N = 813) |
|-------------------------|-----------------|-------------------|-------------------------|-------------------------|
|                         | Dapagliptin     | Placebo           | Dapagliptin             | Placebo                 |
|                         | n = 692         | n = 654           | n = 610                 | n = 623                 |
| Age, years, mean (SD)   | 59.0 (12.5)     | 59.1 (12.8)       | 61.8 (12.3)             | 62.1 (11.7)             |
|                         | 165 (23.8)      | 157 (24.0)        | 62.6 (10.8)             | 63.1 (11.5)             |
| Cardiovascular disease, n (%) | 240 (34.7)     | 222 (33.9)        | 198 (31.8)              | 158 (35.2)              |
| Race, n (%)             | 692 (100)       | 654 (100)         | 7 (1.1)                 | 4 (0.9)                 |
| Asian                   | 62 (20.2)       | 6 (1.9)           | 7 (1.1)                 | 4 (0.9)                 |
| Black or African American | 0 (0.0)        | 0 (0.0)           | 0 (0.0)                 | 0 (0.0)                 |
| Other                   | 0 (0.0)         | 0 (0.0)           | 0 (0.0)                 | 0 (0.0)                 |
| White                   | 0 (0.0)         | 0 (0.0)           | 594 (97.4)              | 610 (97.9)              |
| Body mass index (kg/m²), mean (SD) | 25.7 (4.1)     | 25.5 (4.2)        | 30.8 (5.6)              | 31.5 (5.8)              |
| Mean UACR, mg/g (IQR)   | 984 (493–1790)  | 1000 (493–1790)   | 1043 (487–1821)         | 914 (488–1808)          |
| HbA1c, %, mean (SD)     | 6.9 (1.7)       | 6.8 (1.6)         | 43.1 (12.6)             | 44.1 (12.5)             |
| UACR >1000 mg/g, n (%)  | 30 (40.9)       | 29 (39.1)         | 291 (46.7)              | 240 (35.4)              |
| ACE inhibitor/ARB       | 678 (98.0)      | 673 (97.4)        | 606 (99.3)              | 614 (98.6)              |
| Diuretic                | 152 (22.0)      | 149 (22.8)        | 329 (53.9)              | 341 (54.7)              |
| Insulin                 | 205 (48.8)      | 185 (45.4)        | 194 (52.9)              | 213 (52.7)              |
| DPP-4 inhibitors        | 160 (36.5)      | 167 (41.4)        | 81 (22.1)               | 82 (20.3)               |
| Biguanides              | 144 (29.9)      | 120 (29.8)        | 178 (48.5)              | 202 (50.0)              |

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; IQR, interquartile range; UACR, urinary albumin-to-creatinine ratio; USA, United States of America.

Potential diabetic ketoacidosis events were adjudicated by an independent adjudication committee.

Statistical Analysis

The overall analytical approach and prespecified statistical analysis plan have been previously published.10-12 Briefly, all analyses presented here followed the intention-to-treat principle. For analysis of primary and secondary end points, we performed time-to-event analyses using a proportional hazards (Cox) regression stratified by randomization factors (diabetes status and UACR) and adjusting for baseline eGFR. We present corresponding hazard ratios and 95% CIs from model parameter coefficients and standard errors, respectively. To evaluate for effect modification by region, we included a multiplicative interaction term between randomized treatment and region. Where possible, treatment efficacy was investigated among patients with and without diabetes separately within each region. We assessed for nonuniformity of hazard ratios with Akaike’s information criterion.

We considered 2-tailed P < 0.05 to indicate statistical significance. We performed all analyses with Stata version 14.2 (Stata Corp).

RESULTS

Of 4304 randomized patients, 1346 (31.3%) were from Asia, 1233 (28.6%) from Europe, 912 (21.2%) from Latin America, and 813 (18.9%) from North America. Baseline characteristics of randomized patients stratified by regions are presented in Table 1. The mean age was slightly lower among patients in Asia and higher among patients in North America compared with patients in Europe and Latin America. The mean Quetelet index (body mass index) was lowest in Asia and highest in North America. The level of systolic blood pressure and duration of diabetes was lower among participants from Asia compared with participants from Europe and Latin America. The level of systolic blood pressure and duration of diabetes was lower among participants from Asia compared with participants from Europe and Latin America.
patients in Asia compared with patients in other major geographic regions. The proportion of patients with diabetes was highest in North America. eGFR was similar across regions, but UACR was lower in North America and higher in Latin America. Prevalence of cardiovascular disease was lowest among patients in Asia. A similar proportion of patients were on angiotensin-converting enzyme inhibitor/angiotensin receptor blocker across regions.

**Primary End Point**

Median follow-up duration was 1.9 years in Asia, 2.3 years in Europe and Latin America, and 2.1 years in North America. Event rates (per 100 patient-years) for the primary composite end point were 4.2, 4.4, 5.8, and 4.2 in patients randomized to dapagliflozin and 6.3, 6.7, 9.0, and 8.5 in patients randomized to placebo in Asia, Europe, Latin America, and North America, respectively. Figure 1a to d shows the cumulative incidence of the primary composite end point in both randomized groups, stratified by region. Relative risk reductions in the corresponding regions were the following: hazard ratio (95% CI) 0.70 (0.48–1.00), 0.60 (0.43–0.85), 0.61 (0.43–0.86), and 0.51 (0.34–0.76), respectively. Absolute risk reductions were 3.3% (0.3–6.4), 4.9% (1.4–8.5), 6.1% (1.5–10.8), and 8.0% (3.5–12.6) in Asia, Europe, Latin America, and North America, respectively. There was no evidence of heterogeneity of benefit on relative or absolute risk reductions by region (interaction P = 0.8 and 0.4, respectively) (Figure 2). Results were also consistent among patients with and without diabetes within each region (Supplementary Table S1). There was no apparent violation of the proportional hazards assumption.

**Secondary End Points**

Similar to the primary end point, treatment with dapagliflozin led to a reduction in the incidence of the composite kidney end point, the composite cardiovascular end point, and all-cause death in patients across all regions. For all 3 secondary end points, there was no heterogeneity of benefit on relative or absolute risk reduction by region (Figure 2). Supplementary Figures S1A to D, S2A to D, and S3A to D show the cumulative incidence of the 3 secondary end points in both randomized groups, across the 4 designated.
there were regional differences in the effects of trial results vis-à-vis efficacy and safety within regions. If regional differences are sizable, they have the potential to meaningfully influence the interpretation of clinical trial results vis-à-vis efficacy and safety within regions. In the current analysis, we aimed to determine whether there were regional differences in the effects of dapagliflozin on kidney and cardiovascular end points.

We showed consistently favorable effects, despite differences in baseline characteristics and concomitant medication use, with substantial relative and absolute risk reductions of the primary composite end point and 3 secondary end points, including all-cause mortality. The safety profile of dapagliflozin was also similar across regions.

In line with our findings, other clinical trials using sodium-glucose cotransporter 2 inhibitors showed health benefits across regions. For instance, in the CREDENCE trial comparing canagliflozin and placebo in patients with type 2 diabetes and CKD (eGFR 30–90 ml/min per 1.73 m²), there was no regional heterogeneity in efficacy for the composite end point of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes. Similarly, canagliflozin and ertugliflozin in patients with type 2 diabetes and increased risk of cardiovascular disease showed no regional heterogeneity in efficacy for a composite end point of cardiovascular death, myocardial infarction, or ischemic stroke.

Regional differences in the efficacy of sodium-glucose cotransporter 2 inhibitors have been reported for patients with heart failure. In the
### Table 2. Safety by major geographic region

| Outcome, n (%) | Dapagliflozin (N = 2149) | Placebo (N = 2149) | Odds ratio (95% CI) | P value interaction |
|----------------|--------------------------|-------------------|--------------------|-------------------|
| Asia (n = 1344) | 690                      | 654               |                    |                   |
| Europe (n = 1229) | 609                      | 620               |                    |                   |
| Latin America (n = 912) | 449                      | 463               |                    |                   |
| North America (n = 813) | 401                      | 412               |                    |                   |
| Discontinuation due to adverse event | 0.8 | | | |
| Overall | 118 (5.5) | 123 (5.7) | 0.97 (0.74–1.26) | |
| Asia (n = 1344) | 33 (4.8) | 35 (5.3) | 0.91 (0.56–1.49) | |
| Europe (n = 1229) | 35 (5.7) | 36 (5.8) | 0.98 (0.60–1.58) | |
| Latin America (n = 912) | 23 (5.1) | 29 (6.3) | 0.82 (0.46–1.44) | |
| North America (n = 813) | 27 (6.7) | 23 (5.6) | 1.24 (0.69–2.22) | |
| Any serious adverse event | 0.8 | | | |
| Overall | 633 (29.5) | 729 (33.9) | 0.81 (0.72–0.93) | |
| Asia (n = 1344) | 151 (21.9) | 175 (26.8) | 0.77 (0.60–0.99) | |
| Europe (n = 1229) | 208 (34.1) | 239 (38.6) | 0.82 (0.65–1.04) | |
| Latin America (n = 912) | 134 (29.8) | 146 (31.5) | 0.92 (0.70–1.23) | |
| North America (n = 813) | 140 (34.9) | 169 (41.0) | 0.78 (0.58–1.03) | |
| Adverse events of interest | | | | |
| Amputation | | | | 0.7 |
| Overall | 35 (1.6) | 39 (1.8) | 0.89 (0.56–1.41) | |
| Asia (n = 1344) | 3 (0.4) | 5 (0.8) | 0.56 (0.13–2.35) | |
| Europe (n = 1229) | 9 (1.5) | 11 (1.6) | 0.83 (0.34–2.02) | |
| Latin America (n = 912) | 12 (2.7) | 15 (3.2) | 0.81 (0.37–1.76) | |
| North America (n = 813) | 11 (2.7) | 8 (1.9) | 1.41 (0.56–3.56) | |
| Any definite or probable diabetic ketoacidosis | | | | |
| Overall | 0 | 2 (0.1) | | |
| Asia (n = 1344) | 0 | 1 (0.1) | | |
| Europe (n = 1229) | 0 | 0 | | |
| Latin America (n = 912) | 0 | 0 | | |
| North America (n = 813) | 0 | 1 (0.2) | | |
| Fracture | | | | 0.7 |
| Overall | 85 (4.0) | 69 (3.2) | 1.25 (0.90–1.72) | |
| Asia (n = 1344) | 22 (3.2) | 21 (3.2) | 1.00 (0.54–1.86) | |
| Europe (n = 1229) | 21 (3.4) | 19 (3.1) | 1.12 (0.60–2.12) | |
| Latin America (n = 912) | 20 (4.4) | 13 (2.8) | 1.62 (0.80–3.30) | |
| North America (n = 813) | 22 (5.5) | 16 (3.9) | 1.45 (0.75–2.82) | |
| Renal related adverse event | | | | 0.6 |
| Overall | 155 (7.2) | 188 (8.7) | 0.82 (0.65–1.02) | |
| Asia (n = 1344) | 28 (4.1) | 29 (4.4) | 0.92 (0.54–1.57) | |
| Europe (n = 1229) | 37 (6.1) | 47 (7.6) | 0.78 (0.50–1.22) | |
| Latin America (n = 912) | 33 (7.3) | 51 (11.0) | 0.65 (0.41–1.03) | |
| North America (n = 813) | 57 (14.2) | 61 (14.8) | 0.97 (0.65–1.44) | |
| Major hypoglycemia | | | | 0.7 |
| Overall | 14 (0.6) | 28 (1.3) | 0.50 (0.26–0.96) | |
| Asia (n = 1344) | 3 (0.4) | 8 (1.2) | 0.35 (0.09–1.33) | |
| Europe (n = 1229) | 1 (0.2) | 5 (0.8) | 0.20 (0.02–1.75) | |
| Latin America (n = 912) | 7 (1.6) | 11 (2.4) | 0.65 (0.25–1.71) | |
| North America (n = 813) | 3 (0.7) | 4 (1.0) | 0.80 (0.18–3.64) | |
| Volume depletion | | | | 0.4 |
| Overall | 127 (5.9) | 90 (4.2) | 1.44 (1.09–1.90) | |
| Asia (n = 1344) | 27 (3.9) | 18 (2.7) | 1.44 (0.78–2.68) | |
| Europe (n = 1229) | 35 (5.7) | 34 (5.5) | 1.05 (0.64–1.71) | |
| Latin America (n = 912) | 21 (4.7) | 13 (2.8) | 1.70 (0.84–3.44) | |
| North America (n = 813) | 44 (11.0) | 25 (8.1) | 1.92 (1.15–3.20) | |

*Includes death.

Surgical or spontaneous/nonsurgical amputation, excluding amputation due to trauma.

*Based on predefined list of preferred terms.

Adverse event with the following criteria confirmed by the investigator: (i) symptoms of severe impairment in consciousness or behavior, (ii) need of external assistance, (iii) intervention to treat hypoglycemia, (iv) prompt recovery of acute symptoms after the intervention.
EMPEROR-Reduced trial, the relative risk reduction for a composite end point of heart failure hospitalization and cardiovascular death was only 6% in Europe and was 45% in Asia. In EMPEROR-Reduced, the majority of events captured within the composite cardiovascular end point were hospitalized heart failure events. Effect estimates were no doubt influenced by the fact that acute events of heart failure exacerbation were more often treated in outpatient settings in Europe compared with other regions. In a time-to-event analysis of any composite end point, nonfatal events are counted before deaths. Therefore, the inclusion of a region where nonfatal events are less likely to be “counted” could result in an attenuated estimate of the treatment effect. Indeed, when nonfatal heart failure events that were treated in an outpatient setting were included in the analysis, the point estimate of benefit on the composite cardiovascular end point in Europe changed from 6% to 26% but was unchanged in other regions. In contrast, there was no regional variation in the effect of empagliflozin on cardiovascular mortality, the other component of the composite end point. Moreover, a previous study in patients with type 2 diabetes and in DAPA-CKD (wherein the contribution of heart failure hospitalization to the composite cardiovascular end point was similar in Europe and Asia), there was little to no regional variation in the effect of dapagliflozin on the composite cardiovascular end point.

Despite standardized inclusion and exclusion criteria, there were notable regional differences in the baseline clinical characteristics that could reflect biological differences, differences in access to healthcare, or other social determinants of health. Patients from Latin America had higher levels of albuminuria and systolic blood pressure, and patients from Asia had more favorable cardiovascular risk factor profiles (e.g., lower body mass index and systolic blood pressure and lower prevalence of diabetes and cardiovascular disease at baseline) compared with patients from other regions. These regional differences in baseline clinical characteristics may explain the increased incidence of the primary composite end point, secondary kidney composite end point, and all-cause mortality in Latin America and the reduced incidence of the composite cardiovascular end point and all-cause mortality in patients from Asia compared with other regions. Of note, compared with Europeans (a mostly White population), body mass index was lower in patients from Asia, but the prevalence of diabetes was similar. This phenomenon has been well described; the Asian population have a roughly similar risk of type 2 diabetes compared with White people, despite a lower body mass index.

There were substantial regional differences in anti-diabetic medication use. Insulin was used more frequently in Latin America and North America. Fewer patients with diabetes in Asia were treated with insulin and/or biguanides, and roughly twice as many patients in Asia were treated with dipeptidyl peptidase-4 inhibitors compared with patients in Europe or Latin America. This may indicate limited access to insulin and biguanides in Asia and/or may indicate a difference in prescription patterns between regions. Indeed, previous reports have suggested dipeptidyl peptidase-4 inhibitors to be more effective in improving glycemic levels in the Asian population than other populations, which may have prompted its use more often in Asia compared with other regions.

The strengths of the present analyses include the relatively large sample size from 4 major geographic regions, with the collection of detailed information on baseline clinical characteristics. Analysis was prespecified, and data were collected under a single protocol from all target regions. The protocol did not restrict or mandate the use of any cardiovascular or glucose-lowering medications with the exception that angiotensin-converting enzyme-inhibitors and angiotensin receptor blockers be used except when contraindicated. As such, the results are more generalizable across and within the geographic regions studied. There are also several limitations. The definition of regions was based on broad continental geography; only 21 countries were included, with only a few countries in each geographic region, and were largely high and upper-middle-income countries, limiting generalizability. In addition, interpreting differences across regions is difficult because they may reflect several influences other than geography, including race/ethnicity, genetics, cultural differences, diet and lifestyle, type of health care system, economics, and even climate and other environmental factors.

In conclusion, despite notable differences in baseline characteristics across regions, dapagliflozin reduced the risk of kidney and cardiovascular disease events and all-cause mortality in all regions, with no evidence of heterogeneity in efficacy or safety. These findings support the use of dapagliflozin in patients with CKD with and without type 2 diabetes across major regions around the world.

**DISCLOSURE**

RCR is a member of the Executive Committee of the DAPA-CKD study and has received grants/contracts from GlaxoSmithKline and Novo Nordisk, consulting fees from Boehringer Ingelheim and Chinook, and payment/
honorary as a speaker or advisor from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Janssen, and Novo Nordisk. FFH is a member of the DAPA-CKD study executive committee and is a study investigator. She has received personal fees from AbbVie. GMC has received fees from AstraZeneca for the DAPA-CKD trial steering committee, research grants from NIDDK, and support for research staff attending meetings from Amgen; participated in data safety monitoring boards for Bayer and Recor; is on the board of directors for Satellite Healthcare and on trial steering committees for Akebia, Gilead, Sanofi, and Verte; and holds stock options or stock options with Ardelyx, CloudCath, Durect, DxNow, Miromatrix, Outset, and Unicycive. AML, CDS, and BVS are employees and stockholders of AstraZeneca. JJVM has received payments to his employer, Glasgow University, for his work on clinical trials, consulting, and other activities from AstraZeneca, Cytokinekinetics, KBP Biosciences, Amgen, Bayer, Theracos, Ionis Pharmaceuticals, Dalcro Pharmaceuticals, Novartis, GlaxoSmithKline, Bristol 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. PR 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. 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. He has participated in DSMB or advisory boards for Bayer, Viofor, Akebia, and Otsuka. HSB has received honoraria for lectures from Eli Lilly, Novo Nordisk, and Medscape and received support for congress attendance from Novo Nordisk and AstraZeneca. DCW provides ongoing consultancy services to AstraZeneca and received personal fees from Bayer, Boehringer Ingelheim, Astellas, GlaxoSmithKline, Janssen, Napp, Mundipharma, Reata, Vifor Fresenius, and Tricida. HJLH has received funding/honoraria and consulting fees to his institution for Steering Committee membership and/or advisory board participation from AstraZeneca (DAPA-CKD study), AbbVie, Travere Pharmaceuticals, Janssen, Gilead, Bayer, Chinook, Merck, and CSL Pharma; consulting fees from Boehringer Ingelheim and Novo Nordisk; and honoraria for lectures from AstraZeneca; and has participated in advisory boards for Mitsubishi Tanabe and Mundipharma. All the other authors declared no competing interests.

ACKNOWLEDGMENTS

The authors thank all investigators, trial teams, and patients for their participation in the trial. The authors would also like to acknowledge Nicola Truss and Holly McAlister, inScience Communications, London, UK, for assistance in editing and preparation of figures. This support was funded by AstraZeneca. This study was supported by AstraZeneca. 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.

DATA SHARING

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.

AUTHOR CONTRIBUTIONS

PV, RCR, and HJLH had access to the data and had the final responsibility to submit for publication. HJLH and NJ analyzed and can verify the data, and PV and RCR wrote the first draft of the manuscript. All authors had access to the data, reviewed the manuscript drafts, provided approval of the final version for submission, and take responsibility for the accuracy and integrity of the data.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Efficacy of dapaglifoxin for the primary composite endpoint by major geographic region and type 2 diabetes status.

Figure S1. Cumulative incidence of a composite end point of ≥50% sustained decline in estimated GFR, kidney failure, or death from kidney disease by major geographic region.

Figure S2. Cumulative incidence of a composite end point of cardiovascular death or hospitalization for heart failure by major geographic region.

Figure S3. Cumulative incidence of all-Cause Mortality by major geographic region.

CONSORT 2010 checklist of information to include when reporting a randomized trial.

REFERENCES

1. Thiers FA, Sinskey AJ, Berndt ER. Trends in the globalization of clinical trials. Nat Rev Drug Discov. 2008;7:13–14.
2. Vaduganathan M, Samman Tahhan A, Greene SJ, et al. Globalization of heart failure clinical trials: a systematic review of 305 trials conducted over 16 years. Eur J Heart Fail. 2018;20:1068–1071. https://doi.org/10.1002/ejhf.1130
3. Dewan P, Rorth R, Jhund PS, et al. Income inequality and outcomes in heart failure: a global between-country analysis.
4. Ferreira JP, Rossignol P, Dewan P, et al. Income level and inequality as complement to geographical differences in cardiovascular trials. *Am Heart J.* 2019;218:66–74. https://doi.org/10.1016/j.ahj.2019.08.019

5. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med.* 2016;375:323–334. https://doi.org/10.1056/NEJMoa1515920

6. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med.* 2017;377:644–657. https://doi.org/10.1056/NEJMoa1611925

7. Lam CSP, Ferreira JP, Pfarr E, et al. Regional and ethnic influences on the response to empagliflozin in patients with heart failure and a reduced ejection fraction: the EMPEROR-Reduced trial. *Eur Heart J.* 2021;42:4442–4451. https://doi.org/10.1093/eurheartj/ehab360

8. Zannad F, Ferreira JP, Pocock SJ, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet.* 2020;396:819–829. https://doi.org/10.1016/S0140-6736(20)31824-9

9. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med.* 2020;383:1436–1446. https://doi.org/10.1056/NEJMoa2024816

10. 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;35:274–282. https://doi.org/10.1093/ndt/gfaa234

11. Wheeler DC, Stefansson BV, Batiushin M, et al. The dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD) trial: baseline characteristics. *Nephrol Dial Transplant.* 2020;35:1700–1711. https://doi.org/10.1093/ndt/gfaa234

12. Wheeler DC, Stefansson BV, Jongs N, et al. Effects of dapagliflozin on major adverse kidney and cardiovascular events in patients with diabetic and non-diabetic chronic kidney disease: a prespecified analysis from the DAPA-CKD trial. *Lancet Diabetes Endocrinol.* 2021;9:22–31. https://doi.org/10.1016/S2213-8587(20)30369-7

13. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in Type 2 diabetes and nephropathy. *N Engl J Med.* 2019;380:2295–2306. https://doi.org/10.1056/NEJMoa1811744

14. Wysham CH, Bhattacharyya A, Tsoukas M, et al. Consistent outcomes with canagliflozin (CAN) in patients with Type 2 diabetes across geographic regions—results from the canagliflozin CardioVascular assessment study (CANVAS) program. *Diabetes.* 2018;67(suppl 1):1193.

15. Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med.* 2020;383:1425–1435. https://doi.org/10.1056/NEJMoa2004967

16. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in Type 2 diabetes. *N Engl J Med.* 2019;380:347–357. https://doi.org/10.1056/NEJMoa1812389

17. Chen JC, Malik V, Jia W, et al. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA.* 2009;301:2129–2140. https://doi.org/10.1001/jama.2009.726

18. Basu S, Yudkin JS, Kehlenbrink S, et al. Estimation of global insulin use for type 2 diabetes, 2018–30: a microsimulation analysis [published correction appears in *Lancet Diabetes Endocrinol.* 2019;7:e1]. *Lancet Diabetes Endocrinol.* 2019;7:25–33. https://doi.org/10.1016/S2213-8587(18)30303-6

19. Kim YG, Hahn S, Oh TJ, et al. Differences in the glucose-lowering efficacy of dipeptidyl peptidase-4 inhibitors between Asians and non-Asians: a systematic review and meta-analysis. *Diabetologia.* 2013;56:696–708. https://doi.org/10.1007/s00125-012-2827-3

20. Cai Y, Zeng T, Wen Z, Chen L. Ethnic differences in efficacy and safety of alogliptin: a systematic review and meta-analysis. *Diabetes Ther.* 2018;9:177–191. https://doi.org/10.1007/s13300-017-0352-6