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Efficacy of Dapagliflozin According to Geographic Location of Patients With Heart Failure

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ABSTRACT

BACKGROUND Because clinical characteristics and prognosis vary by geographic region in patients with heart failure (HF), the response to treatment may also vary. A previous report suggested that the efficacy of sodium-glucose cotransporter-2 inhibitor efficacy in heart failure with reduced ejection fraction (HFrEF) may be modified by region.

OBJECTIVES The goal of this study was to examine the efficacy and safety of dapagliflozin in patients with HF according to geographic region.

METHODS We conducted a patient-level pooled analysis of the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) and DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure) trials, which evaluated the effects of dapagliflozin in HFrEF and heart failure with mildly reduced ejection fraction (HFmrEF)/heart failure with preserved ejection fraction (HFpEF), respectively. The primary outcome was the composite of worsening HF or cardiovascular death.

RESULTS Among 11,007 patients, 5,159 (46.9%) were enrolled in Europe, 1,528 (13.9%) in North America, 1,998 (18.2%) in South America, and 2,322 (21.1%) in Asia. The rate of the primary outcome (per 100 person-years) was higher in North America (13.9 [95% CI: 12.5-15.4]) than in other regions: Europe 10.8 (95% CI: 10.1-11.5), South America 10.0 (95% CI: 9.0-11.1), and Asia 10.5 (95% CI: 9.5-11.5). The benefit of dapagliflozin on the primary outcome was not modified by region: dapagliflozin vs placebo HR: Europe, 0.85 (95% CI: 0.75-0.96); North America, 0.75 (95% CI: 0.61-0.93); South America, 0.72 (95% CI: 0.58-0.89); and Asia, 0.74 (95% CI: 0.61-0.91) (P interaction = 0.40). This was the same when evaluated separately for HFrEF (P interaction = 0.39) and HFmrEF/HFpEF (P interaction = 0.84). Patients in North America discontinued randomized treatment more frequently than did those elsewhere (placebo discontinuation: 21.8% in North America vs 6.4% in South America), but discontinuation rates did not differ between placebo and dapagliflozin by region.

CONCLUSIONS The efficacy and safety of dapagliflozin were consistent across global regions despite geographic differences in patient characteristics, background treatment, and event rates. (J Am Coll Cardiol 2023;82:1014–1026)

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Most contemporary randomized controlled clinical trials in heart failure (HF) are global, including participants from many different parts of the world.[1-8] As a result, the question always arises whether the efficacy and safety of treatment vary by geographic region. This is because of regional differences in biological and sociocultural variables, including age, sex, race, ethnicity, other patient characteristics such as blood pressure and adiposity, cause of HF, comorbidities, health care systems, physician practice, and background therapy.[1-8]

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Controversially, it has been suggested previously that the effects of certain treatments for HF differed between patients in the United States and those in the rest of the world and perhaps by race.[2-5,8] More recently, in the EMPEROR-Reduced (EMPagliflozin outcomE tRial in Patients With chrOnic Heart Failure With Reduced Ejection Fraction; NCT03057977) (n = 3,730), it was reported that the efficacy of the sodium-glucose cotransporter-2 (SGLT2) inhibitor empagliflozin in patients with HF and reduced ejection fraction differed significantly by region, with the greatest benefit in participants from Asia and the least among those in Europe.[5] However, most analyses based on geographic regions in individual trials are hampered by modest subgroup sizes and small numbers of events and can give unreliable results. To attempt to overcome this limitation, we examined whether the efficacy and safety of dapagliflozin in HF were consistent across regions using individual patient data from >11,000 participants enrolled in 2 placebo-controlled randomized trials, DAPA-HF (Dapagliflozin And Prevention of Adverse outcomes in Heart Failure; NCT03036124) and DELIVER (Dapagliflozin Evaluation to Improve the LIVEs of Patients With Preserved Ejection Fraction Heart Failure; NCT03619213).[9,10] The justification for this approach was the prior demonstration in pooled data from these 2 trials that the benefit of dapagliflozin was consistent across the spectrum of left ventricular ejection fraction (LVEF).[11] We are not aware of any prior analysis of a single treatment for HF that has included as many patients.

METHODS

TRIAL PATIENTS. The detailed trial designs and principal results of the DAPA-HF and DELIVER trials have been published.[9,10,12,13] Briefly, each trial enrolled patients with a diagnosis of HF, NYHA functional class II to IV, and elevated natriuretic peptides. The principal difference between the 2 trials was that patients with an LVEF ≤40% were randomized in DAPA-HF and those with an LVEF >40% were randomized in DELIVER (with evidence of structural heart disease, defined as either left atrial enlargement or left ventricular hypertrophy in DELIVER). In DAPA-HF, patients are required to have an N-terminal pro-B-type natriuretic peptide (NT-proBNP) level ≥600 pg/mL or, if hospitalized for HF within the previous 12 months, ≥400 pg/mL. Patients with atrial fibrillation or atrial flutter are required to have a level ≥900 pg/mL, irrespective of a history of HF hospitalization. In DELIVER, patients were required to have a level of NT-proBNP ≥300 pg/mL or, for those with atrial fibrillation or atrial flutter, ≥600 pg/mL. The key exclusion criteria were type 1 diabetes and an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 in DAPA-HF and <25 mL/min/1.73 m^2 in DELIVER.

In both trials, patients were randomly assigned to receive either dapagliflozin at a dosage of 10 mg once daily, or a matching placebo, in addition to standard therapy. Randomization was stratified based on a diagnosis of type 2 diabetes (either a history or HbA1c ≥6.5% confirmed at screening).

Both trials were approved by ethics committees at each investigative site, and written informed consent was obtained from each patient.

GEOGRAPHIC REGIONS. Patients were enrolled at 410 centers in 20 countries in DAPA-HF and at 353 centers in 20 countries in DELIVER. These countries were classified into 4 geographic regions: Europe, North America, South America, and Asia (Supplemental Table 1). For this analysis, as prespecified in the trial statistical analysis plan, Saudi Arabia was included in Europe.

STUDY OUTCOMES. The primary outcome for both DAPA-HF and DELIVER was the composite of worsening HF or death of cardiovascular causes, analyzed as a time to first event. An episode of worsening HF was either an unplanned hospitalization or an urgent visit resulting in intravenous therapy for HF. In

ABBREVIATIONS AND ACRONYMS

eGFR = estimated glomerular filtration rate

HF = heart failure

HFmrEF = heart failure with mildly reduced ejection fraction

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

SGLT2 = sodium-glucose cotransporter-2

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Baseline Characteristics According to Geographic Regions

	Europe[a] (n = 5,159)	North America (n = 1,528)	South America (n = 1,998)	Asia (n = 2,322)	*P* Value
Age, y	70.0 ± 9.4	71.2 ± 10.8	68.3 ± 10.5	67.6 ± 12.1	<0.001
Female	1,877 (36.4)	492 (32.2)	804 (40.2)	683 (29.4)	<0.001
Race					<0.001
White	5,145 (99.7)	1,237 (81.0)	1,389 (69.5)	1 (0.0)	
Asian	8 (0.2)	58 (3.8)	4 (0.2)	2,320 (99.9)	
Black or African American	4 (0.1)	210 (13.7)	171 (8.6)	0 (0.0)	
Other	2 (0.0)	23 (1.5)	434 (21.7)	1 (0.0)	
Body mass index, kg/m^2	30.2 ± 5.6	31.6 ± 6.9	29.5 ± 5.9	24.7 ± 4.2	<0.001
Vital signs					
Heart rate, beats/min	71.7 ± 11.2	69.4 ± 11.5	70.3 ± 12.1	73.5 ± 12.3	<0.001
Systolic blood pressure, mm Hg	128.1 ± 14.8	122.8 ± 16.7	125.2 ± 16.6	121.6 ± 16.9	<0.001
Diastolic blood pressure, mm Hg	75.5 ± 9.5	71.0 ± 10.7	73.2 ± 10.5	72.1 ± 11.2	<0.001
Laboratory values and ECG findings					
HbA1c, %	6.5 ± 1.3	6.5 ± 1.3	6.8 ± 1.7	6.5 ± 1.3	<0.001
Creatinine, μmol/L	102.3 ± 29.4	110.2 ± 32.3	102.3 ± 32.9	102.0 ± 30.4	<0.001
eGFR, mL/min/1.73 m^2	62.7 ± 18.5	59.3 ± 19.1	64.3 ± 20.2	65.4 ± 20.5	<0.001
eGFR <60 mL/min/1.73 m^2	2,327 (45.1)	815 (53.4)	883 (44.2)	971 (41.8)	<0.001
NT-proBNP, ng/L	1,190.0 (721.0-2,137.0)	1,231.0 (701.0-2,136.1)	1,126.5 (642.4-2,228.8)	1,171.1 (719.0-2,031.0)	0.093
If baseline ECG in AF/AFL	1,551.5 (1,026.0-2,529.0)	1,597.5 (1,140.0-2,511.1)	1,520.5 (1,021.0-2,652.6)	1,487.0 (1,013.0-2,323.0)	0.12
If baseline ECG not in AF/AFL	928.9 (553.0-1,746.7)	1,035.0 (622.0-1,921.0)	947.5 (532.1-1,937.6)	989.0 (589.0-1,853.1)	0.021
AF/flutter on ECG	2,035 (39.5)	432 (28.3)	538 (26.9)	767 (33.0)	<0.001
Heart failure characteristics					
Prior HF hospitalization	2,419 (46.9)	582 (38.1)	639 (32.0)	1,150 (49.5)	<0.001
Time from diagnosis of HF to baseline					<0.001
≤6 mo	828 (16.0)	218 (14.3)	225 (11.3)	432 (18.6)	
>6-12 mo	656 (12.7)	136 (8.9)	275 (13.8)	330 (14.2)	
>1-2 y	784 (15.2)	229 (15.0)	332 (16.6)	336 (14.5)	
>2-5 y	1,281 (24.8)	384 (25.1)	497 (24.9)	512 (22.1)	
>5 y	1,610 (31.2)	561 (36.7)	669 (33.5)	707 (30.5)	
NYHA functional class					<0.001
II	3,331 (64.6)	1,121 (73.4)	1,608 (80.5)	1,856 (79.9)	
III/IV	1,828 (35.4)	406 (26.6)	390 (19.5)	466 (20.1)	
Baseline KCCQ-TSS	69.7 ± 20.9	68.2 ± 23.1	68.3 ± 24.0	81.5 ± 19.1	<0.001
Baseline LVEF, %	44.3 ± 12.4	44.0 ± 15.5	44.6 ± 14.8	43.8 ± 15.2	0.28
HF phenotype					<0.001
HFrEF	2,156 (41.8)	677 (44.3)	817 (40.9)	1,097 (47.2)	
HFmrEF/HFpEF	3,003 (58.2)	851 (55.7)	1,181 (59.1)	1,225 (52.8)	
Clinical history					
Type 2 diabetes	2,229 (43.2)	701 (45.9)	935 (46.8)	924 (39.8)	<0.001
Atrial fibrillation	2,865 (55.5)	785 (51.4)	631 (31.6)	1,002 (43.2)	<0.001
Hypertension	4,497 (87.2)	1,327 (86.8)	1,691 (84.6)	1,561 (67.2)	<0.001
Myocardial infarction	1,926 (37.3)	490 (32.1)	649 (32.5)	666 (28.7)	<0.001
CABG	795 (15.4)	369 (24.1)	208 (10.4)	204 (8.8)	<0.001
Stroke	513 (9.9)	142 (9.3)	181 (9.1)	227 (9.8)	0.67

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addition, we evaluated cardiovascular death, worsening HF event, all-cause death, total (first and repeat) HF hospitalizations, and the composite of total HF hospitalizations and cardiovascular deaths in this analysis, which were components of the primary outcome or secondary outcomes in either trial. All potential worsening HF events and all deaths were adjudicated by an independent clinical events committee. In DAPA-HF, the definition of cardiovascular death included deaths for which a non-cardiovascular cause was not determined. By contrast, in DELIVER, deaths for which the cause could not be determined were excluded from the definition of cardiovascular death. In this analysis, the definition of cardiovascular deaths included deaths of undetermined causes.

TABLE 1 Continued

	Europe[a] (n = 5,159)	North America (n = 1,528)	South America (n = 1,998)	Asia (n = 2,322)	*P* Value
Medical therapy					
ACE inhibitor	2,910 (56.4)	529 (34.6)	793 (39.7)	724 (31.2)	<0.001
In patients with HFrEF	1,431 (66.4)	284 (41.9)	432 (52.9)	515 (46.9)	<0.001
ARB	1,349 (26.1)	381 (24.9)	908 (45.4)	941 (40.5)	<0.001
In patients with HFrEF	467 (21.7)	139 (20.5)	290 (35.5)	412 (37.6)	<0.001
ARNI	262 (5.1)	281 (18.4)	86 (4.3)	180 (7.8)	<0.001
In patients with HFrEF	177 (8.2)	218 (32.2)	55 (6.7)	57 (5.2)	<0.001
ACE inhibitor or ARB	4,244 (82.3)	904 (59.2)	1,695 (84.8)	1,652 (71.1)	<0.001
In patients with HFrEF	1,892 (87.8)	418 (61.7)	721 (88.2)	923 (84.1)	<0.001
ACE inhibitor, ARB, or ARNI	4,499 (87.2)	1,170 (76.6)	1,777 (88.9)	1,828 (78.7)	<0.001
In patients with HFrEF	2,065 (95.8)	626 (92.5)	774 (94.7)	978 (89.2)	<0.001
Beta-blocker	4,716 (91.4)	1,345 (88.0)	1,738 (87.0)	1,936 (83.4)	<0.001
In patients with HFrEF	2,097 (97.3)	659 (97.3)	801 (98.0)	1,002 (91.3)	<0.001
MRA	2,944 (57.1)	542 (35.5)	1,152 (57.7)	1,399 (60.2)	<0.001
In patients with HFrEF	1,647 (76.4)	314 (46.4)	641 (78.5)	771 (70.3)	<0.001
Loop diuretic	4,264 (82.7)	1,261 (82.5)	1,429 (71.5)	1,682 (72.4)	<0.001
Digitalis	513 (9.9)	143 (9.4)	214 (10.7)	313 (13.5)	<0.001
In patients with AF	441 (15.4)	101 (12.9)	114 (18.1)	155 (15.5)	0.062
CRT-D or CRT-P	227 (4.4)	119 (7.8)	33 (1.7)	75 (3.2)	<0.001
CRT-D or ICD	744 (14.4)	439 (28.7)	105 (5.3)	122 (5.3)	<0.001

Values are mean ± SD, n (%), or median (IQR). [a]Including Saudi Arabia.

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; AFL = atrial flutter; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; CABG = coronary artery bypass graft; CRT = cardiac resynchronization therapy; ECG = electrocardiography; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; KCCQ-TSS = Kansas City Cardiomyopathy Questionnaire-Total Symptom Score; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

The following safety analyses included in both trials were reported: discontinuation of randomized treatment for any reason or because of an adverse event, volume depletion, renal adverse events, amputation, major hypoglycemia, and diabetic ketoacidosis.

STATISTICAL ANALYSES. Patients with LVEF ≤40% were classified as having heart failure with reduced ejection fraction (HFrEF), and those with LVEF >40% were classified as having heart failure with mildly reduced ejection fraction (HFmrEF)/heart failure with preserved ejection fraction (HFpEF). The baseline characteristics for the overall population, patients with HFrEF, and patients with HFmrEF/HFpEF were summarized according to geographic region, as mean ± SD or median (IQR) for continuous variables and n (%) for categorical variables. Differences in baseline characteristics were tested using the chi-square test for binary or categorical variables and the Kruskal-Wallis test and analysis of variance for non-normally and normally distributed continuous variables, respectively.

To evaluate the differences in primary outcome according to geographic region, Kaplan-Meier curves were plotted regardless of treatment assignment. Cox proportional hazards models, adjusted for treatment assignment and history of heart failure (HF) hospitalization (not for all-cause death) and stratified by diabetes status and trial, were used to compute HR (95% CI) for the time to first event according to geographic region (with Europe as the reference). To evaluate total events, we used the semiparametric proportional-rates model described by Lin et al,[14] which is an extension of the proportional hazards model and incorporates a robust SE estimator to consider the interdependence of events within each patient. The models, adjusted for treatment assignment and history of HF hospitalization and stratified by diabetes status and trial, were used to compute rate ratios (95% CI). In addition, HRs and rate ratios, adjusted for randomized treatment, history of HF hospitalization, age, sex, heart rate, systolic blood pressure, estimated glomerular filtration rate (eGFR), NT-proBNP (log-transformed), time from diagnosis from HF, NYHA functional class III or IV, LVEF, history of atrial fibrillation, history of hypertension, history of myocardial infarction, and history of stroke, were reported.

To compare the effects of dapagliflozin with placebo, time to first events were evaluated with Cox proportional hazards models, total events were

evaluated with semiparametric proportional rates models, and HR (95% CI) and rate ratio (95% CI) were reported according to geographic region. The presence of an interaction between geographic regions and the effect of treatment on the occurrence of each outcome was examined using a likelihood ratio test. These were also evaluated for patients with HFrEF or HFmrEF/HFpEF separately. The effect of randomized treatment across the range of LVEF in each region was modeled flexibly using restricted cubic splines with 3 knots. These models were adjusted for the history of HF hospitalization (except in the analysis of all-cause death) and stratified according to diabetes status and trial.

All analyses were conducted using STATA version 17.0 (StataCorp).

RESULTS

Among the 11,007 patients in the DAPA-HF and DELIVER pooled data set, patients were assigned equally to placebo (n = 5,503) and dapagliflozin (n = 5,504). Overall, 5,159 patients (46.9%) were enrolled in Europe, 1,528 patients (13.9%) in North America, 1,998 patients (18.2%) in South America, and 2,322 (21.1%) patients in Asia.

PATIENT CHARACTERISTICS. Baseline characteristics, including demographics, comorbidities, and functional status differed across geographic regions (**Table 1**). Patients were younger in Asia (mean age 67.6 years) and South America (68.3 years) than in Europe (70.0 years) and North America (71.2 years) and were more often female in South America (40.2%) and Europe (36.4%) than in North America (32.2%) and Asia (29.4%). Racial breakdown largely overlapped with geography (eg, almost all Asians lived in Asia), except for Black patients, who were enrolled principally in North America and South America (in the absence of the inclusion of African countries). Body mass index was lower in Asia than in other regions. Mean systolic blood pressure was substantially higher in Europe (128 mm Hg) and South America (125 mm Hg) than in North America (123 mm Hg) and Asia (122 mm Hg). Kidney function was worst in North America. Regarding other comorbidities, patients in Asia had a lower prevalence of type 2 diabetes, hypertension, and prior myocardial infarction compared with the other regions. Fewer patients had atrial fibrillation in South America (32%) and Asia (43%) than elsewhere (Europe 56%, North America 51%). Regarding HF characteristics, the mean baseline LVEF and median NT-proBNP level did not vary significantly across regions. Patients in South America and Asia had the largest proportion of patients in NYHA functional class II (81% in South America and 80% in Asia) compared with the other 2 regions (Europe 65%, North America 73%). However, patients in Asia had the highest (best) mean Kansas City Cardiomyopathy Questionnaire-Total Symptom Score (81.5), and the other 3 regions had similar Kansas City Cardiomyopathy Questionnaire-Total Symptom Scores. Patients in Asia had the highest frequency (49.5%) of prior HF hospitalization, and patients in South America had the lowest (32.0%). Similar trends in patient characteristics according to geographic regions were observed in patients with HFrEF and HFmrEF/HFpEF (Supplemental Tables 2 and 3).

BASELINE TREATMENT. Treatments varied strikingly by region. Angiotensin receptor blocker, rather than angiotensin-converting enzyme inhibitors, were used more often in Asia and Latin America than elsewhere. Sacubitril/valsartan was prescribed much more frequently in patients with HFrEF in North America (32.2%) than anywhere else: Europe 8.2%, South America 6.7%, and Asia 5.2%. The opposite was true for mineralocorticoid receptor antagonists: North America 46.4%, Europe 76.4%, South America 78.5%, and Asia 70.3%. Device use was more common in North America and Europe than elsewhere.

PATIENT OUTCOMES BY GEOGRAPHIC REGION. Patient outcomes varied by geographic region, and the variation was different for different outcomes (**Table 2**, **Figure 1**). Although North America had the highest rate of the primary composite endpoint, both cardiovascular and all-cause mortality were lower in that region than in others except Asia (which had the lowest rates of death). Conversely, North America had the highest (and Asia the second highest) rate of worsening HF events and rates of total HF hospitalizations. South America had the highest risk of unadjusted and adjusted cardiovascular and all-cause mortality, and Asia had the lowest (both regions were significantly different from the others).

The rates of the primary outcome increased with decreasing LVEF similarly across all regions studied (**Central Illustration**).

EFFICACY BY GEOGRAPHIC REGION. Although patient outcomes varied by geographic region, the efficacy of dapagliflozin did not; ie, region did not modify the effect of treatment on any outcome, as demonstrated by the tests for interaction shown in **Table 3**. Specifically, the dapagliflozin compared with placebo HR for the primary endpoint was 0.85 (95% CI: 0.75-0.96) in Europe, 0.75 (95% CI: 0.61-0.93) in North America, 0.72 (95% CI: 0.58-0.89) in

TABLE 2 Outcomes According to Geographic Regions

	Europe[a] (n = 5,159)	North America (n = 1,528)	South America (n = 1,998)	Asia (n = 2,322)
Primary outcome				
n (%)	1,039 (20.1)	337 (22.1)	347 (17.4)	398 (17.1)
Rate (95% CI)	10.8 (10.1-11.5)	13.9 (12.5-15.4)	10.0 (9.0-11.1)	10.5 (9.5-11.5)
Unadjusted HR (95% CI)[b]	ref	1.31 (1.16-1.48)	0.97 (0.86-1.10)	0.95 (0.84-1.06)
Adjusted HR (95% CI)[c]	ref	1.29 (1.14-1.47)	1.00 (0.88-1.14)	1.02 (0.90-1.15)
Cardiovascular death				
n (%)	582 (11.3)	136 (8.9)	234 (11.7)	180 (7.8)
Rate (95% CI)	5.6 (5.2-6.1)	5.1 (4.3-6.0)	6.5 (5.7-7.4)	4.4 (3.8-5.1)
Unadjusted HR (95% CI)[b]	ref	0.93 (0.77-1.12)	1.20 (1.03-1.40)	0.78 (0.66-0.92)
Adjusted HR (95% CI)[c]	ref	0.88 (0.73-1.07)	1.26 (1.08-1.48)	0.81 (0.68-0.97)
Worsening HF event				
n (%)	668 (13.0)	268 (17.5)	170 (8.5)	280 (12.1)
Rate (95% CI)	6.9 (6.4-7.5)	11.0 (9.8-12.4)	4.9 (4.2-5.7)	7.4 (6.5-8.3)
Unadjusted HR (95% CI)[b]	ref	1.62 (1.41-1.87)	0.75 (0.63-0.89)	1.02 (0.89-1.18)
Adjusted HR (95% CI)[c]	ref	1.59 (1.38-1.85)	0.77 (0.64-0.91)	1.09 (0.94-1.27)
All-cause death				
n (%)	832 (16.1)	214 (14.0)	345 (17.3)	237 (10.2)
Rate (95% CI)	8.1 (7.5-8.6)	7.9 (6.9-9.0)	9.6 (8.6-10.6)	5.8 (5.1-6.6)
Unadjusted HR (95% CI)[b]	ref	1.00 (0.86-1.16)	1.20 (1.06-1.36)	0.74 (0.64-0.85)
Adjusted HR (95% CI)[c]	ref	0.95 (0.81-1.10)	1.32 (1.16-1.51)	0.74 (0.64-0.86)
Total number of HF hospitalizations				
n	957	439	211	417
Rate (95% CI)	9.3 (8.5-10.2)	16.4 (14.1-19.3)	5.9 (4.9-7.0)	10.3 (9.0-11.9)
Unadjusted rate ratio (95% CI)[b]	ref	1.86 (1.55-2.23)	0.69 (0.56-0.84)	1.10 (0.93-1.29)
Adjusted rate ratio (95% CI)[c]	ref	1.81 (1.50-2.19)	0.71 (0.59-0.87)	1.14 (0.96-1.36)
Total number of HF hospitalizations and cardiovascular death				
n	1,539	575	445	597
Rate (95% CI)	14.9 (13.9-16.0)	21.5 (18.8-24.7)	12.4 (11.0-13.9)	14.8 (13.2-16.6)
Unadjusted rate ratio (95% CI)[b]	ref	1.51 (1.30-1.76)	0.89 (0.77-1.02)	0.98 (0.85-1.12)
Adjusted rate ratio (95% CI)[c]	ref	1.46 (1.24-1.71)	0.92 (0.80-1.07)	1.02 (0.88-1.18)

Rates are given per 100 patient-years. [a]Including Saudi Arabia. [b]Baseline model adjusted for randomized treatment and history of HF hospitalization (except in the analysis of all-cause death) and stratified by diabetes status and trial. [c]Adjusted for randomized treatment, history of HF hospitalization, age, sex, heart rate, systolic blood pressure, eGFR, NT-proBNP (log-transformed), time from diagnosis from HF, NYHA functional class III or IV, LVEF, history of atrial fibrillation, history of hypertension, history of myocardial infarction, history of stroke and stratified by diabetes status and trial.

ref = reference; other abbreviations as in Table 1.

South America, and 0.74 (95% CI: 0.61-0.91) in Asia (*P* interaction = 0.40) (Figure 2). This was also the case if patients were analyzed according to LVEF categories: ≤40% (*P* interaction = 0.39) and >40% (*P* interaction = 0.84) (Figure 3). In each region, the effect of dapagliflozin was consistent regardless of LVEF (Central Illustration).

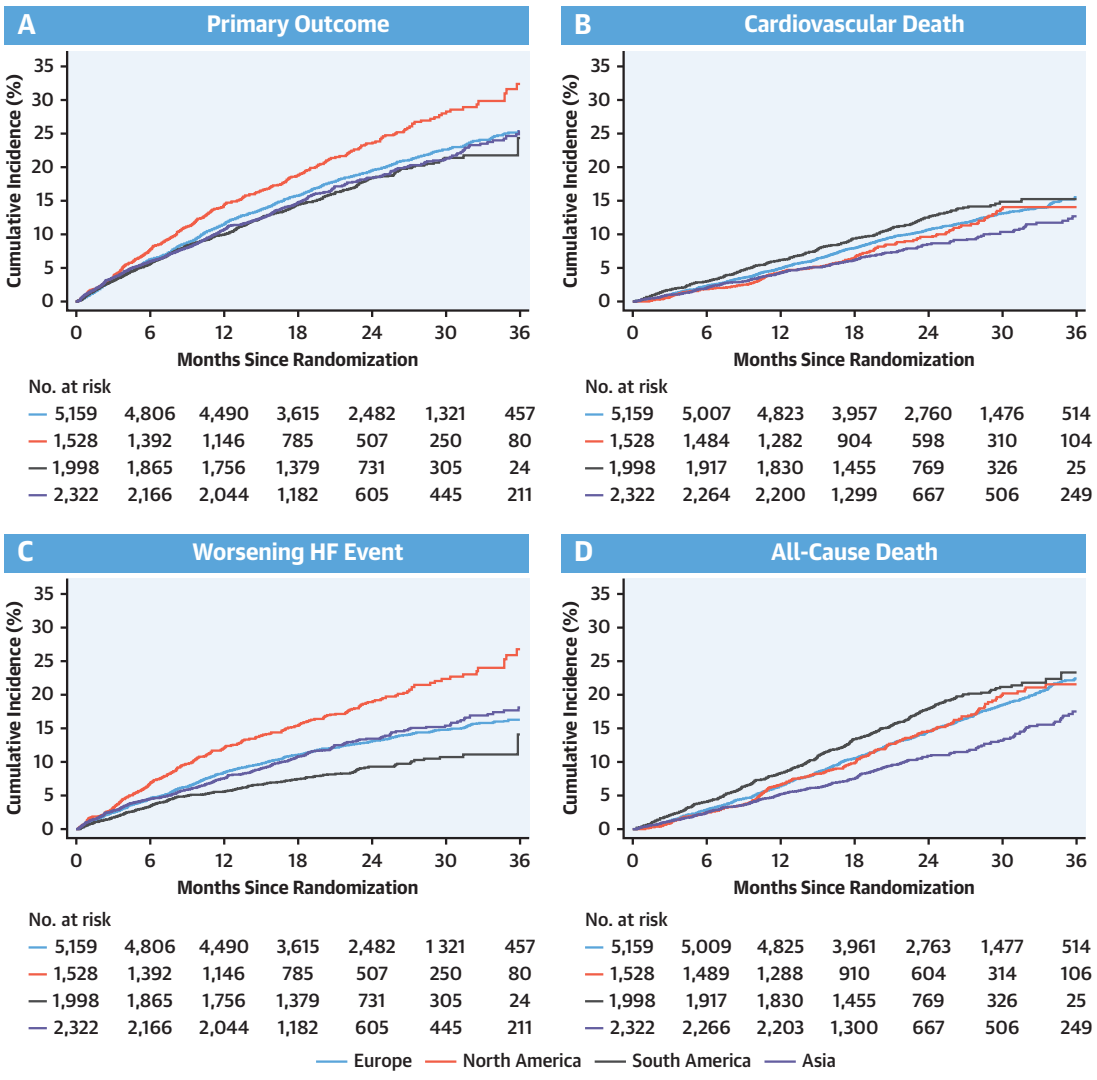
SAFETY, TOLERABILITY, AND TREATMENT DISCONTINUATION BY GEOGRAPHIC REGION. Adverse events and rates of treatment discontinuation by geographic region are shown in Table 4. Patients in North America were the most likely, and those in South America least likely, to discontinue randomized treatment for any reason (in the placebo group, 21.8% in North America vs 6.4% in South America). The safety profiles in patients receiving placebo and dapagliflozin were similar in each region.

DISCUSSION

The key findings of this study were that although patient characteristics, background treatment, and outcomes varied considerably by geographic region, the efficacy and safety of dapagliflozin did not, reinforcing the consistency of benefit of this class of treatment across all subgroups examined to date and highlighting the potential value to the estimated 64 million patients living with HF worldwide.[15,16]

Surprisingly, relatively few studies have given a truly global perspective on variations in clinical

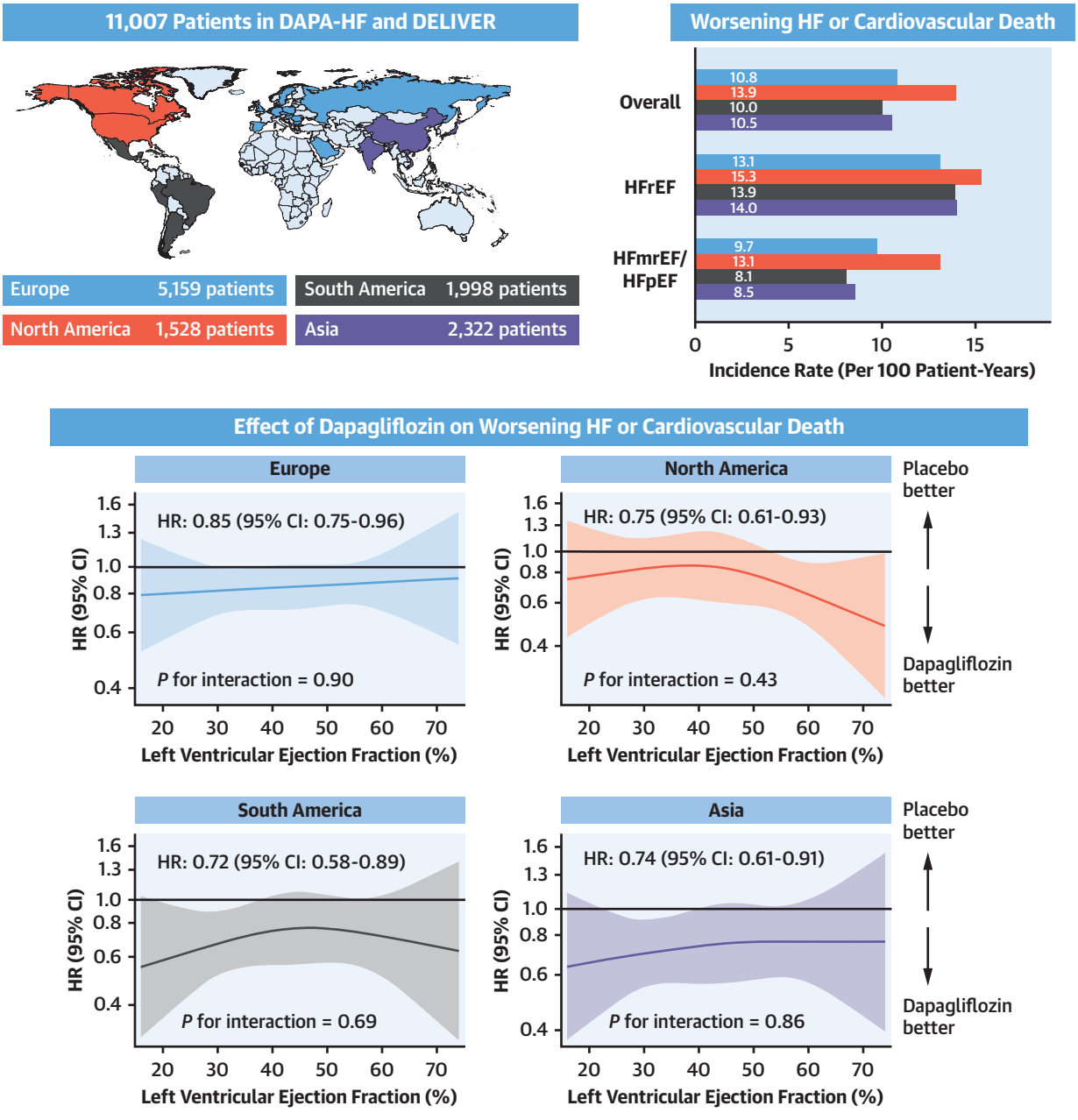
FIGURE 1 Kaplan-Meier Curves for Each Outcome According to Geographic Region



Kaplan-Meier curves according to geographic region for the **(A)** primary outcome, **(B)** cardiovascular death, **(C)** worsening HF event, and **(D)** all-cause death. Europe includes Saudi Arabia. HF = heart failure.

outcomes among outpatients with chronic HF, although there are more reports describing patients hospitalized with HF, notably the recent REPORT-HF (International REgistry to assess medical Practice with lOngitudinal obseRvation for Treatment of Heart Failure).[17] Our findings are consistent with those of the other most contemporary studies in ambulant patients with chronic HF. In particular, we found similar regional variations in age (younger patients in Asia and South America), NYHA functional class (better among patients in Asia and South America), systolic blood pressure (higher in Europe and lower in North America and Asia), atrial fibrillation (less prevalent in South America and Asia) and treatment (higher use of sacubitril/valsartan and implanted cardiac devices in North America and Europe but a persistently low rate of use of mineralocorticoid receptor antagonists in North America compared with the rest of the world).[3-8] The pattern of outcomes observed was also largely similar to that seen in prior reports, with the highest rates of hospitalization evident in North America and Asia (and lowest in South America) and, conversely, the lowest rates of death in Asia and North America (and highest in South America).[3-8] Therefore, although the rates of the

CENTRAL ILLUSTRATION **Outcome and the Effect of Dapagliflozin According to Geographic Region**



Kondo T, et al. J Am Coll Cardiol. 2023;82(10):1014–1026.

(Top Left) Geographic regions included in the DAPA-HF and DELIVER trials. **(Top Right)** Incidence rates of worsening HF or cardiovascular death overall, and according to geographic regions, for patients with HFrEF, and HFmrEF/HFpEF. **(Bottom)** Effect of dapagliflozin on worsening HF or cardiovascular death across the range of LVEF in each geographic region. Models were adjusted for history of HF hospitalization and stratified by diabetes status and trial. **Horizontal black line** shows an HR of 1.00 (unity). **Solid colored lines** represent continuous HRs, and the **shaded areas** represent 95% CI. An HR of <1.00 indicates a benefit of dapagliflozin over placebo. The range of LVEF represents 1st to 99th percentiles. HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction.

TABLE 3 Effect of Randomized Treatment on Outcomes According to Regions

	Europe[a]		North America		South America		Asia		
	Placebo (n = 2,571)	Dapagliflozin (n = 2,588)	Placebo (n = 765)	Dapagliflozin (n = 763)	Placebo (n = 995)	Dapagliflozin (n = 1,003)	Placebo (n = 1,172)	Dapagliflozin (n = 1,150)	*P* Interaction
Primary outcome									
n (%)	553 (21.5)	486 (18.8)	188 (24.6)	149 (19.5)	200 (20.1)	147 (14.7)	226 (19.3)	172 (15.0)	
Rate (95% CI)	11.6 (10.7-12.6)	9.9 (9.1-10.9)	15.9 (13.8-18.3)	12.0 (10.2-14.0)	11.7 (10.2-13.5)	8.3 (7.1-9.8)	12.0 (10.5-13.6)	9.0 (7.7-10.4)	
HR (95% CI)	0.85 (0.75-0.96)		0.75 (0.61-0.93)		0.72 (0.58-0.89)		0.74 (0.61-0.91)		0.40
Cardiovascular death									
n (%)	293 (11.4)	289 (11.2)	81 (10.6)	55 (7.2)	136 (13.7)	98 (9.8)	97 (8.3)	83 (7.2)	
Rate (95% CI)	5.7 (5.1-6.4)	5.6 (5.0-6.3)	6.1 (4.9-7.6)	4.0 (3.1-5.3)	7.6 (6.4-9.0)	5.4 (4.4-6.6)	4.7 (3.9-5.8)	4.1 (3.3-5.1)	
HR (95% CI)	0.98 (0.84-1.16)		0.65 (0.46-0.92)		0.71 (0.55-0.93)		0.87 (0.65-1.16)		0.074
Worsening HF event									
n (%)	367 (14.3)	301 (11.6)	154 (20.1)	114 (14.9)	99 (10.0)	71 (7.1)	161 (13.7)	119 (10.4)	
Rate (95% CI)	7.7 (7.0-8.5)	6.2 (5.5-6.9)	13.0 (11.1-15.2)	9.1 (7.6-11.0)	5.8 (4.8-7.1)	4.0 (3.2-5.1)	8.5 (7.3-10.0)	6.2 (5.2-7.4)	
HR (95% CI)	0.80 (0.68-0.93)		0.70 (0.55-0.90)		0.70 (0.51-0.94)		0.72 (0.57-0.91)		0.75
All-cause death									
n (%)	418 (16.3)	414 (16.0)	122 (16.0)	92 (12.1)	186 (18.7)	159 (15.9)	129 (11.0)	108 (9.4)	
Rate (95% CI)	8.1 (7.4-8.9)	8.0 (7.3-8.8)	9.1 (7.7-10.9)	6.7 (5.5-8.2)	10.4 (9.0-12.0)	8.8 (7.5-10.2)	6.3 (5.3-7.5)	5.3 (4.4-6.4)	
HR (95% CI)	0.98 (0.86-1.13)		0.73 (0.56-0.96)		0.84 (0.68-1.04)		0.85 (0.66-1.09)		0.22
Total number of HF hospitalizations									
n (%)	535	422	270	169	129	82	242	175	
Rate (95% CI)	10.4 (9.2-11.8)	8.2 (7.2-9.4)	20.5 (16.6-25.4)	12.5 (10.0-15.9)	7.2 (5.8-9.2)	4.5 (3.5-6.0)	11.9 (10.0-14.4)	8.7 (7.1-10.8)	
Rate ratio (95% CI)	0.79 (066-0.94)		0.61 (0.45-0.83)		0.62 (0.44-0.88)		0.72 (0.54-0.95)		0.44
Total number of HF hospitalizations and cardiovascular death									
n (%)	828	711	351	224	265	180	339	258	
Rate (95% CI)	16.1 (14.6-17.8)	13.8 (12.4-15.3)	26.6 (22.2-32.1)	16.6 (13.7-20.3)	14.8 (12.7-17.4)	9.9 (8.3-11.9)	16.7 (14.4-19.6)	12.8 (10.8-15.3)	
Rate ratio (95% CI)	0.86 (0.74-0.99)		0.62 (0.47-0.81)		0.67 (0.53-0.85)		0.76 (0.60-0.96)		0.11

Rates are given per 100 patient-years. Models were adjusted for history of HF hospitalization (except in the analysis of all-cause death) and stratified by diabetes status and trial. [a]Including Saudi Arabia.
HF = heart failure.

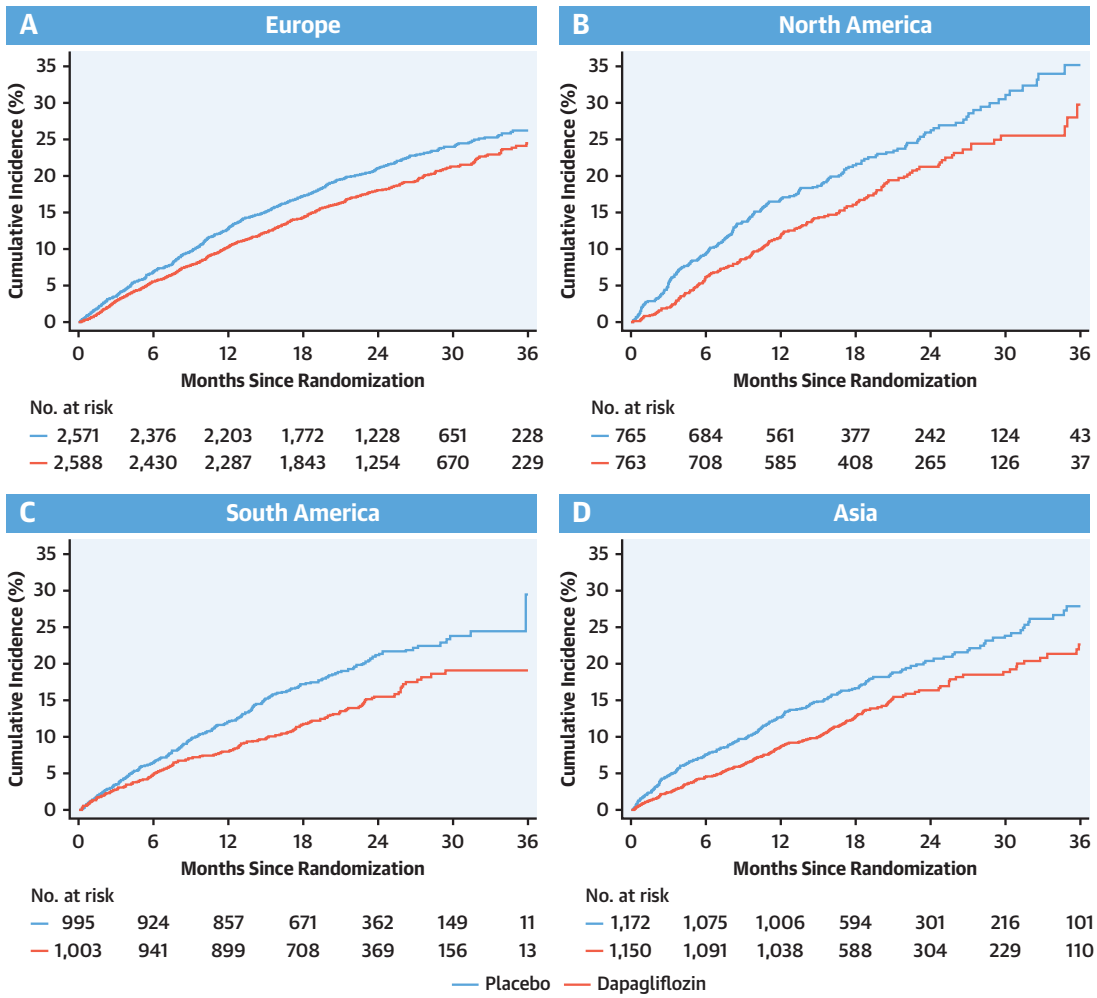
primary composite outcome varied relatively little by region, the rates of the components constituting the composite did, emphasizing the importance of decomposing any composite into its parts when analyzing the results of trials. The differential geographic contribution of each component may also have implications for assessing the efficacy of therapy on a regional basis. For example, taking an implantable cardioverter-defibrillator as an extreme example of treatment with a greater effect on death than HF hospitalization, it may be difficult to demonstrate a consistent benefit of such treatment

TABLE 4 Adverse Events of Dapagliflozin Compared With Placebo According to Regions

	Europe[a]		North America		South America		Asia		
	Placebo (n = 2,567)	Dapagliflozin (n = 2,585)	Placebo (n = 763)	Dapagliflozin (n = 760)	Placebo (n = 994)	Dapagliflozin (n = 1,003)	Placebo (n = 1,171)	Dapagliflozin (n = 1,146)	*P* Interaction
Discontinuation of study drug for any reason	308 (12.0)	336 (13.0)	166 (21.8)	155 (20.4)	64 (6.4)	62 (6.2)	162 (13.8)	140 (12.2)	0.40
Discontinuation of study drug due to an adverse event	118 (4.6)	167 (6.5)	81 (10.6)	58 (7.6)	25 (2.5)	15 (1.5)	73 (6.2)	54 (4.7)	<0.001
Volume depletion[b]	66 (2.6)	79 (3.1)	57 (7.5)	58 (7.6)	38 (3.8)	49 (4.9)	38 (3.3)	41 (3.6)	0.87
Renal adverse event[c]	94 (3.7)	89 (3.4)	60 (7.9)	61 (8.0)	54 (5.4)	53 (5.3)	53 (4.5)	34 (3.0)	0.40
Amputation	24 (0.9)	20 (0.8)	9 (1.2)	6 (0.8)	3 (0.3)	6 (0.6)	2 (0.2)	0 (0.0)	N/A
Major hypoglycemia	2 (0.1)	3 (0.1)	2 (0.3)	5 (0.7)	4 (0.4)	2 (0.2)	3 (0.3)	2 (0.2)	0.50
Diabetic ketoacidosis	0 (0.0)	3 (0.1)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	N/A

Values are n (%). A total of 18 randomized patients were excluded from the safety analysis because these were performed in patients who had undergone randomization and received at least 1 dose of dapagliflozin or placebo. [a]Including Saudi Arabia. [b]Any serious adverse event or adverse event that led to discontinuation of dapagliflozin or placebo that was suggestive of volume depletion in DELIVER. [c]Any renal serious adverse event or adverse event that led to discontinuation of dapagliflozin or placebo in DELIVER.
N/A = not applicable.

FIGURE 2 **Effects of Dapagliflozin on the Primary Outcome in Each Geographic Region**



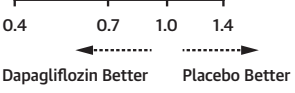
Kaplan-Meier curves for primary outcome according to randomized treatment in **(A)** Europe, **(B)** North America, **(C)** South America, and **(D)** Asia. Europe includes Saudi Arabia.

among a modest number of participants enrolled in countries with low mortality rates. Interestingly, the trends in regional variation in characteristics and outcomes were similar in patients with HFrEF and HFmrEF/HFpEF.

However, we did not find any heterogeneity in the effect of dapagliflozin on the primary endpoint or its components in the present analyses. Perhaps the most robust finding was for the composite of total (first and repeat) hospitalizations and cardiovascular deaths, given that, for this outcome, the regional subgroups individually had a large number of events. As well as showing no modification of the effect of treatment by region, as indicated by the *P* interaction of 0.11, the benefit of dapagliflozin was nominally significant within each geographic subgroup. Clearly, the question arises why the EMPEROR-Reduced investigators found a significant difference in treatment effect by region. We believe the difference between our present observations and the EMPEROR-Reduced results likely reflects the number of events in the 2 studies and the resultant statistical power. For example, in the regions with the most divergent treatment effect, the EMPEROR-Reduced trial had a total of 296 hospitalizations for HF in Europe and 206 in Asia; by contrast, the corresponding numbers were 957 and 417, respectively, in the present analysis. Consequently, we believe the findings of the present

FIGURE 3 Effect of Dapagliflozin by Region and Heart Failure Phenotype

	n (%)		Events Per 100 Person-Years		HR (95% CI)	Interaction *P* value
	Placebo	Dapagliflozin	Placebo	Dapagliflozin		
Overall						0.40
Europe	553 (21.5)	486 (18.8)	11.6 (10.7-12.6)	9.9 (9.1.-10.9)	0.85 (0.75-0.96)	
North America	188 (24.6)	149 (19.5)	15.9 (13.8-18.3)	12.0 (10.2-14.0)	0.75 (0.61-0.93)	
South America	200 (20.1)	147 (14.7)	11.7 (10.2-13.5)	8.3 (7.1-9.8)	0.72 (0.58-0.89)	
Asia	226 (19.3)	172 (15.0)	12.0 (10.5-13.6)	9.0 (7.7-10.4)	0.74 (0.61-0.91)	
HFrEF						0.39
Europe	218 (20.6)	193 (17.6)	14.3 (12.5-16.3)	12.0 (10.4-13.8)	0.83 (0.69-1.01)	
North America	73 (21.3)	54 (16.2)	17.6 (14.0-22.2)	12.9 (9.9-16.9)	0.74 (0.52-1.05)	
South America	97 (23.3)	62 (15.5)	16.9 (13.8-20.6)	10.8 (8.4-13.9)	0.64 (0.47-0.88)	
Asia	114 (20.6)	77 (14.2)	17.1 (14.2-20.5)	11.1 (8.9-13.9)	0.65 (0.49-0.87)	
HFmrEF/HFpEF						0.84
Europe	335 (22.2)	293 (19.6)	10.4 (9.3-11.5)	8.9 (8.0-10.0)	0.86 (0.74-1.01)	
North America	115 (27.3)	95 (22.1)	14.9 (12.4-17.9)	11.5 (9.4-14.0)	0.76 (0.58-1.00)	
South America	103 (17.8)	85 (14.1)	9.1 (7.5-11.0)	7.1 (5.8-8.8)	0.78 (0.58-1.04)	
Asia	112 (18.1)	95 (15.7)	9.2 (7.6-11.1)	7.7 (6.3-9.5)	0.83 (0.63-1.10)	



Effects of dapagliflozin on the primary outcome (composite of time to first occurrence of worsening heart failure or death of cardiovascular causes) according to geographic region and by heart failure phenotype (all patients, HFrEF, and HFmrEF/HFpEF). Europe includes Saudi Arabia. Models were adjusted for history of HF hospitalization and stratified by diabetes status and trial (in overall). Rates are given per 100 patient-years. *P* interaction between HF phenotype (HFrEF and HFmrEF/HFpEF) and the effect of randomized treatment on primary outcome were 0.83 in Europe, 0.90 in North America, 0.34 in South America, and 0.22 in Asia. HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

analysis are more robust and support the conclusion that the effects of SGLT2 inhibitors do not vary by geographic region. We also know of no plausible explanation for why they should, given that race, body habitus, and background therapy, among others, do not modify the action of these drugs.[18-27] No previous reports have examined the treatment benefits of SGLT2 inhibitors by region in patients with HFpEF, but we found no significant interaction between treatment and regions in either HFrEF or HFpEF.

Finally, it is interesting to note that the rate of discontinuation of randomized treatment varied markedly across geographic regions (even in the placebo group), with a surprisingly high rate in patients from North America, where more than 1 in 5 patients stopped treatment (compared with about 1 in 15 patients in South America). Although this did not appear to diminish the overall efficacy of dapagliflozin in North America, understanding why discontinuation of treatment is so much higher in this region compared with other regions will be important. Notably, the discontinuation rates and adverse events did not differ between placebo and dapagliflozin by region.

STUDY LIMITATIONS. As with any analysis of this type, there are limitations. The patients included were selected according to specific trial inclusion and exclusion criteria, and our results may not be generalizable to all patients with HF in the general population. Trial participants are usually better treated than patients in the "real world." In common with most other reports of this type, we did not have patients from Africa, which is a failure common to most global trials. Analyses like the present one cannot account for many other potential influences on outcomes, including climate and other environmental factors, diet and lifestyle, cultural influences, urban-rural mix, and economic considerations.[18,19,28,29] Although we examined standard geographic regions, heterogeneity in patient characteristics and outcomes exists within regions as well as between regions.[8]

CONCLUSIONS

Although patient characteristics, treatment and outcomes varied considerably by geographic region, the efficacy and safety of dapagliflozin were consistent across regions.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Despite geographic variations in patient characteristics, background treatments, and outcomes, the relative safety and efficacy of dapagliflozin compared with placebo is not modified by the geographic location of patients with heart failure.

TRANSLATIONAL OUTLOOK: Further efforts are needed to assure equitable access to SGLT2 inhibitor therapy for patients with heart failure around the world.

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APPENDIX For supplemental tables, please see the online version of this paper.