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ORIGINAL ARTICLE

Global Differences in Heart Failure With Preserved Ejection Fraction

The PARAGON-HF Trial

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BACKGROUND: Heart failure with preserved ejection fraction (HFpEF) is a global public health problem with important regional differences. We investigated these differences in the PARAGON-HF trial (Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor With Angiotensin Receptor Blocker Global Outcomes in HFpEF), the largest and most inclusive global HFpEF trial.

METHODS: We studied differences in clinical characteristics, outcomes, and treatment effects of sacubitril/valsartan in 4796 patients with HFpEF from the PARAGON-HF trial, grouped according to geographic region.

RESULTS: Regional differences in patient characteristics and comorbidities were observed: patients from Western Europe were oldest (mean 75±7 years) with the highest prevalence of atrial fibrillation/flutter (36%); Central/Eastern European patients were youngest (mean 71±8 years) with the highest prevalence of coronary artery disease (50%); North American patients had the highest prevalence of obesity (65%) and diabetes (49%); Latin American patients were younger (73±9 years) and had a high prevalence of obesity (53%); and Asia-Pacific patients had a high prevalence of diabetes (44%), despite a low prevalence of obesity (26%). Rates of the primary composite end point of total hospitalizations for HF and death from cardiovascular causes were lower in patients from Central Europe (9 per 100 patient-years) and highest in patients from North America (28 per 100 patient-years), which was primarily driven by a greater number of total hospitalizations for HF. The effect of treatment with sacubitril-valsartan was not modified by region (interaction $P>0.05$).

CONCLUSIONS: Among patients with HFpEF recruited worldwide in PARAGON-HF, there were important regional differences in clinical characteristics and outcomes, which may have implications for the design of future clinical trials.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01920711.

Key Words: atrial fibrillation ■ coronary artery disease ■ heart failure ■ prevalence ■ risk factors

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WHAT IS NEW?

- In this post hoc analysis of the global PARAGON-HF trial (Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor With Angiotensin Receptor Blocker Global Outcomes in Heart Failure With Preserved Ejection Fraction), we described regional differences in patient characteristics and comorbidities of patients with heart failure with preserved ejection fraction.
- Patients from Western Europe were oldest with a high prevalence of atrial fibrillation, patients from Central Europe were youngest with the highest prevalence of coronary artery disease, North American patients were younger and had a high prevalence of obesity, and patients from Asia-Pacific had a high prevalence of diabetes.
- Rates of the primary composite end point (total hospitalizations for heart failure and death from cardiovascular causes) were lower in patients from Central Europe and highest in North America, primarily driven by differences in hospitalizations for heart failure, with no difference in mortality rates across regions.

WHAT ARE THE CLINICAL IMPLICATIONS?

- There are important regional differences in patient characteristics among patients with heart failure with preserved ejection fraction around the world.
- The similar mortality rates across regions despite differences in total hospitalization rates suggest that local hospitalization practice may importantly influence this outcome—a factor that should be carefully anticipated or accounted for in future clinical trials.
- The treatment and safety effects of sacubitril/valsartan are similar across regions.

Nonstandard Abbreviation and Acronyms

ACE	angiotensin-converting enzyme
AF	atrial fibrillation
aRR	adjusted rate ratio
BMI	body mass index
CAD	coronary artery disease
HF	heart failure
HFpEF	HF with preserved ejection fraction
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PARAGON-HF	Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor With Angiotensin Receptor Blocker Global Outcomes in HFpEF

Heart failure (HF) with preserved ejection fraction (HFpEF) is an increasing global public health issue and will become the dominant form of HF in aging populations.[1,2] Current HF outcome trials recruit patients from a large number of countries with considerable regional differences in background therapy, socioeconomic status, and healthcare practices.[3] This has increased representation of nonwhite patients and made results generalizable beyond Western Europe and North America. However, globalization of HFpEF trials has also raised concerns because of regional differences in diagnosis and outcomes.[3]

The PARAGON-HF trial (Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor With Angiotensin Receptor Blocker Global Outcomes in HFpEF) is the largest HFpEF trial to date,[4,5] including patients from 43 economically diverse countries, as well as substantially more patients from Asia than prior trials. The aims of this study were to (1) describe patient characteristics, including comorbidities, by geographic region, (2) investigate regional differences in quality of life and clinical outcomes, and (3) study the effects of sacubitril/valsartan, compared with valsartan in patients with HFpEF by region.

METHODS

Participants and Study Design

The design, baseline characteristics, and results of the PARAGON-HF trial have been published previously.[4–6] Briefly, the PARAGON-HF trial was a randomized, double-blind, parallel-group, active-controlled, 2-arm event-driven trial, comparing the efficacy and safety of sacubitril/valsartan versus valsartan in patients with HFpEF. Patients were eligible for enrollment if they had signs and symptoms of HF (New York Heart Association class II–IV), left ventricular ejection fraction of ≥45%, increased plasma concentrations of NT-proBNP (N-terminal pro-B-type natriuretic peptide; the degree of elevation depends on history of HF hospitalization within 9 months, and presence or absence of atrial fibrillation [AF]), and evidence of structural heart disease (increased left atrial size or left ventricular hypertrophy). The proportion of patients with AF at screening was limited to 33%. Coronary artery disease (CAD) was defined as a history of myocardial infarction, (unstable) angina pectoris, and a history of coronary artery bypass grafting. Obesity was defined as a body mass index (BMI) ≥30 kg/m^2. Patients entered sequential single-blind run-in periods before randomization, to ensure that both treatments were tolerated at half the target dosages. The study was approved by institutional review boards at individual study sites, and all patients signed written informed consent.

Participant characteristics were collected at screening, whereas some were assessed again at randomization. We report on the regional differences for all variables included at randomization unless otherwise stated. Countries were assigned to regions as previously defined[7]: Asia-Pacific/Other (Australia, China, India, Israel, Japan, South Korea, Philippines, Singapore, South Africa, and Taiwan), Central/Eastern Europe (Bulgaria, Croatia, Czech Republic, Greece, Hungary, Poland, Romania, Russia, Serbia, Slovakia, Slovenia, and Turkey), Latin America (Argentina, Brazil, Colombia, Guatemala, Mexico, and Peru), North America (Canada and the United States of

America), or Western Europe (Austria, Belgium, Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Spain, Sweden, Switzerland, and the United Kingdom).

Study Outcomes

The primary outcome of interest in this study was a total HF hospitalizations and cardiovascular death. All-cause mortality, cardiovascular mortality, total HF hospitalizations, and change from baseline to 8 months in Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score were evaluated as secondary outcomes.[6] The KCCQ overall summary score was used to study differences in patient-reported outcomes according to region and its relation to differences in risk factors. The KCCQ is a well-validated measure to assess quality of life in patients with HF and constitutes a combined score of 0 to 100, where a score closer to 100 means a better quality of life.[8]

Statistical Analyses

Baseline characteristics were compared according to region using the Student *t* test, ANOVA, or Kruskal-Wallis test for continuous variables where appropriate and χ^2 test for categorical variables. In secondary analyses, we explored regional patterns of comorbidity burden using hierarchical cluster analyses. We identify mutually exclusive subgroups of countries based on five subgroups, representing the regions, using comorbidities (BMI, diabetes, CAD, AF, stroke, hypertension, chronic obstructive pulmonary disease, estimated glomerular filtration rate, cancer, and anemia) as the variables of interest. We used Euclidean distances and used Ward's minimum variance method.[9] For survival analyses, all events from each patient were included using the semiparametric proportional rates method of Lin, Wei, Yang, Ying.[10] Cox proportional hazard models were used to compare the risk of first events according to region. We used the region with the lowest risk for the primary combined end point as the reference category. Multivariable adjustments were based on clinically relevant variables including age, sex, race, AF/flutter, diabetes, hospitalization for HF, body mass index, myocardial infarction, stroke, systolic blood pressure, estimated glomerular filtration rate, log-transformed NT-proBNP, left ventricular ejection fraction use of ACE (angiotensin-converting enzyme) inhibitor/angiotensin receptor blockers, β-blockers, mineralocorticoid receptor antagonists, and calcium channel blockers. Ghosh-Lin and cumulative incidence curves were used to show the cumulative recurrent and first events, respectively. Difference in KCCQ at baseline and 8 months between sacubitril/valsartan and valsartan was calculated and compared between regions. We tested for interaction between treatment (sacubitril/valsartan versus valsartan) and geographic region for primary and secondary outcomes. Analyses were performed with Stata version 15 and R version 3.5.2. All tests were performed 2-sided and a *P* value of <0.05 was considered statically significant.

RESULTS

Regional Differences in Patient Characteristics

Mean age of all randomized patients was 73±8 years: 52% were women. The largest proportion of patients in PARAGON-HF were from Central Europe (1715, 36%) followed by Western Europe (1390, 29%), Asia-Pacific (762, 16%), North America (559, 12%), and Latin America (370, 8%).

Patients from Central Europe were youngest (mean 71±8 years), and patients from Western Europe were oldest (mean 75±7 years, *P*<0.001, Table 1). The proportion of patients who were women was highest in Latin America (60%) and lowest in North America (47%). Obesity (BMI ≥30 kg/m^2) was most prevalent in North America (65%) and least prevalent in the Asia-Pacific region (26%). Median NT-proBNP was highest in patients from Western Europe (992, interquartile range, 485–1719 pg/mL), and lowest in patients from Central Europe (933, interquartile range, 430–1561 pg/mL). Patients from Central Europe most often reported a prior hospitalization for HF (50%) and patients from Latin America least often (40%). AF was most common in Western Europe (36%) and least common in patients from the North America (29%). CAD was most frequent in patients from Central Europe (50%) and least common in patients from Latin America (27%). The majority of patients across all regions had symptoms of exertional dyspnea, ranging from 84% of patients in North America to (98%) patients in Central Europe.

To further evaluate the regional patterns above (which were based on the prespecified definitions of region), we performed hierarchical cluster analyses to determine how countries would naturally group based on clinical characteristics (comorbidities; Figure I in the Data Supplement). This agnostic approach revealed 5 clusters/subgroups (Table I in the Data Supplement): Low-comorbidity, consisting of primarily patients from Latin America (95%) with a higher proportion of women (61%), a lower prevalence of comorbidities including CAD (19%), AF (30%) and anemia (4%). A Young-lean group, consisting of younger patients (mean age: 72±8 years) from primarily the Asia-Pacific (66%) region, with a lower BMI (mean 27±5 kg/m^2). An Ischemic group, patients were the youngest (mean 72±8 years), primarily from Central Europe (63%), and had a high prevalence of CAD (47%). An Obese group, patients from primarily North America (84%), with a higher BMI (mean 32±5 kg/m^2) and higher prevalence of diabetes (52%) and CAD (49%). Lastly, an Elderly/AF was identified with the oldest patients (mean 75±7 years), exclusively from Western Europe (100%) and a higher prevalence of AF (42%).

Clinical Outcomes

The rate of the primary composite outcome of total HHF and cardiovascular death was lower in Central Europe (9.2 per 100 patient-years [95% CI, 8.4–10.1]) and higher in North America (27.9 per 100 patient-years [95% CI, 25.6–30.6]), *P* <0.001, Table 2, Figure 1). Differences persisted after multivariable adjustment, where

Table 1. Baseline Characteristics According To Region (Randomized Patients)

	Asia-Pacific	Central Europe	Latin America	North America	Western Europe	
	n=762	n=1715	n=370	n=559	n=1390	*P* global
Demographics						
Age, y	72±9	71±8	73±9	74±8	75±7	<0.001
%<55	25 (3%)	42 (2%)	15 (4%)	6 (1%)	11 (<1%)	<0.001
%>75	287 (38%)	502 (29%)	155 (42%)	261 (47%)	744 (54%)	<0.001
Women, n (%)	379 (50%)	885 (52%)	222 (60%)	264 (47%)	729 (52%)	0.003
Race, n (%)						<0.001
Asian	592 (78%)	0 (0%)	1 (<1%)	7 (1%)	7 (1%)	
Black	9 (1%)	0 (0%)	16 (4%)	74 (13%)	3 (<1%)	
Other	31 (4%)	1 (<1%)	139 (38%)	9 (2%)	0 (0%)	
White	130 (17%)	1714 (99%)	214 (58%)	469 (84%)	1380 (99%)	
SBP, mm Hg	128±16	132±14	129±15	127±16	132±17	<0.001
SBP ≥140 mm Hg, n (%)	161 (21%)	422 (25%)	73 (20%)	105 (19%)	371 (27%)	<0.001
Heart rate, bpm	73±13	71±12	70±11	69±12	69±12	<0.001
BMI, kg/m^2	28±5	31±5	30±5	32±5	30±5	<0.001
Obesity, n (%)						
BMI ≥30 kg/m^2	199 (26%)	943 (55%)	194 (53%)	362 (65%)	659 (47%)	<0.001
BMI ≥27.5 kg/m^2	330 (43%)	1301 (76%)	260 (71%)	443 (79%)	943 (68%)	<0.001
EF, %	58±8	56±8	59±9	59±7	58±8	<0.001
NYHA, n (%)						<0.001
I	48 (6%)	18 (1%)	18 (5%)	21 (4%)	32 (2%)	
II	585 (77%)	1299 (78%)	309 (84%)	410 (74%)	1103 (79%)	
III	123 (16%)	391 (23%)	42 (11%)	126 (23%)	250 (18%)	
IV	6 (1%)	7 (<1%)	0 (0%)	1 (<1%)	5 (<1%)	
KCCQ-CS at baseline	74±20	71±18	75±19	72±20	70±19	<0.001
NT-proBNP, pg/mL	915.5 [485.0, 1719.0]	833.0 [430.0, 1561.0]	855.0 [450.0, 1593.0]	911.0 [484.0, 1617.0]	992.0 [495.0, 1625.0]	0.002
Prior hospitalization for HF, n (%)	413 (54%)	862 (50%)	149 (40%)	275 (49%)	607 (44%)	<0.001
Medical history						
Diabetes, n (%)	336 (44%)	766 (45%)	142 (38%)	276 (49%)	542 (39%)	<0.001
Atrial fibrillation/flutter, n (%)	258 (34%)	527 (31%)	112 (30%)	164 (29%)	491 (36%)	0.016
Stroke, n (%)	95 (13%)	186 (11%)	20 (5%)	74 (13%)	133 (10%)	<0.001
Hospitalization for HF, n (%)	413 (54%)	862 (50%)	149 (40%)	275 (49%)	607 (44%)	<0.001
Myocardial infarction, n (%)	172 (23%)	411 (24%)	80 (22%)	134 (24%)	286 (21%)	0.21
CAD, n (%)	317 (42%)	863 (50%)	101 (27%)	276 (49%)	514 (37%)	<0.001
CABG, n (%)	84 (11%)	161 (9%)	22 (6%)	130 (23%)	173 (12%)	<0.001
PCI, n (%)	164 (22%)	339 (20%)	51 (14%)	157 (28%)	266 (19%)	<0.001
Hypertension, n (%)	697 (92%)	1682 (98%)	355 (96%)	541 (97%)	1309 (94%)	<0.001
Signs and symptoms						
Dyspnea on effort, n (%)	644 (85%)	1672 (98%)	329 (90%)	469 (84%)	1310 (94%)	<0.001
Dyspnea at rest, n (%)	12 (2%)	55 (3%)	8 (2%)	16 (3%)	48 (4%)	0.11
Paroxysmal nocturnal dyspnea, n (%)	26 (3%)	75 (4%)	15 (4%)	21 (4%)	54 (4%)	0.84
Edema, n (%)	224 (29%)	690 (40%)	131 (36%)	294 (53%)	487 (35%)	<0.001
JVP, N (%)	89 (12%)	141 (8%)	63 (17%)	160 (29%)	202 (15%)	<0.001
Rales, N (%)	38 (5%)	177 (10%)	38 (10%)	18 (3%)	74 (5%)	<0.001
Laboratory						
Creatinine, mg/dL	1.1±0.3	1.0±0.3	1.1±0.3	1.2±0.3	1.1±0.3	<0.001
eGFR, mL/(min·1.73 m^2)	64±20	66±19	63±19	57±18	60±18	<0.001

(*Continued*)

Table 1. Continued

	Asia-Pacific	Central Europe	Latin America	North America	Western Europe	
	n=762	n=1715	n=370	n=559	n=1390	*P* global
eGFR <60 mL/min/1.73 m^2, n (%)	413 (54%)	1006 (59%)	195 (53%)	208 (37%)	632 (46%)	<0.001
Medication						
Diuretics, n (%)	685 (90%)	1663 (97%)	351 (95%)	541 (97%)	1345 (97%)	<0.001
ACE inhibitor/ARB, n (%)	610 (80%)	1599 (93%)	342 (92%)	399 (71%)	1189 (86%)	<0.001
MRA, n (%)	276 (36%)	501 (29%)	86 (23%)	97 (17%)	279 (20%)	<0.001
Beta-blockers, n (%)	542 (71%)	1502 (88%)	262 (71%)	446 (80%)	1069 (77%)	<0.001
CCBs, n (%)	229 (30%)	633 (37%)	107 (29%)	206 (37%)	465 (34%)	<0.001
Antiplatelets, n (%)	175 (23%)	219 (13%)	46 (12%)	82 (15%)	113 (8%)	<0.001
Anticoagulants, n (%)	155 (20%)	615 (36%)	74 (20%)	175 (31%)	532 (38%)	<0.001

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate; EF, ejection fraction; HF, heart failure; JVP, jugular venous pressure; KCCQ-CS, Kansas City Cardiomyopathy Questionnaire clinical summary; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCI, percutaneous coronary intervention; and SBP, systolic blood pressure

patients from North America (adjusted rate ratio [aRR], 2.84 [95% CI, 2.24–3.61]), Western Europe (aRR, 1.42 [95% CI, 1.18–1.71]), and Asia-Pacific (aRR, 1.94 [95% CI, 1.36–2.76]) were at a higher risk for the primary combined end point compared with patients from Central Europe. Patients from Latin America were at a similar lower risk for the primary end point compared with patients from Central Europe in both univariable and multivariable analyses (Table 2).

When investigating the individual components of the primary composite end point, patients from North America (aRR, 4.42 [95% CI, 3.48–5.18]), Western Europe (aRR, 1.95 [95% CI, 1.60–2.36]), and Asia-Pacific (aRR, 1.78 [95% CI, 1.41–2.26]) were at a greater risk for being hospitalized for HF (total HF hospitalizations) compared to patients from Central Europe (Figure 1). Patients from North America (adjusted hazard ratio, 1.05 [95% CI, 0.75–1.45]), Asia-Pacific (adjusted hazard ratio, 1.24 [95% CI, 0.78–1.99]), and Latin America (adjusted hazard ratio, 1.09 [95% CI, 0.71–1.66]) had a similar risk for cardiovascular death compared with patients from Central Europe. In the unadjusted model, patients from Western Europe had a similar unadjusted risk (adjusted hazard ratio, 0.91 [95% CI, 0.71–1.17]) but similar adjusted risk (RR, 0.77 [95% CI, 0.59–1.01]) of cardiovascular death when compared with patients from Central Europe (Figure 1). Differences in death from any cause followed similar patterns as cardiovascular death, with limited differences among regions (Table 2, Figure 1). Causes of death are shown in Table II in the Data Supplement; death due to pump failure was less common in Latin America (6% of deaths) and Central Europe (12% of deaths) and more common in patients from North America (32% of deaths, P<0.001). Patients from Western Europe (41%), Latin America (38%), and Central Europe (30%) were more likely to die from noncardiovascular causes compared with patients from Asia-Pacific (23%) and North America (26%).

Effects of Sacubitril/Valsartan

Sacubitril/valsartan had a similar effect on the primary end point, cardiovascular death, and total HF hospitalizations when compared to valsartan across regions (Figure IIA through IIC in the Data Supplement, $P_{interaction}$ for all >0.05). Sacubitril/valsartan had a similar effect on improvement in the KCCQ-CS after 8 months, when compared with valsartan, across regions ($P_{interaction}$>0.05, Figure IID in the Data Supplement). Treatment-related adverse events (hypotension, elevated creatinine, hyperkalemia, angioedema, liver abnormalities) were generally infrequent and did not differ across regions (Table III in the Data Supplement, $P_{interaction}$>0.05 except for angioedema where numbers were too small for meaningful comparisons).

DISCUSSION

In PARAGON-HF, there were notable geographic differences in patient characteristics and outcomes. Patients from North America, Asia-Pacific, and Western Europe had strikingly higher HF hospitalization rates compared to patients from Central Europe. There was no significant heterogeneity in treatment response to sacubitril-valsartan among regions, and the drug was generally well-tolerated.

Few studies have enrolled such a large number of patients with HFpEF with global representation; for instance, more than a quarter of patients in PARAGON-HF were from the Asia-Pacific region[11]—the largest representation from the region in a single HFpEF trial. Regional differences in comorbidities in PARAGON-HF revealed geographically distinct patterns (Figure 2) that confirm observations from separate studies from each region. In Western Europe, patients with HFpEF from the Swede-HF registry showed a similar Elderly/AF phenotype and had a high mean age of 77, and 61% of

Table 2. Event Rates and Unadjusted and Adjusted Risk of the Primary Composite Outcome (Total Heart Failure Hospitalization or Cardiovascular Death) and Its Components According to Region

Outcomes	Asia-Pacific (n=762)	Central Europe (n=1715)	Latin America (n=370)	North America (n=559)	Western Europe (n=1390)
Total HHF+CV Death	332 events	466 events	83 events	478 events	544 events
	16.2 per 100py (14.5–18.0)	9.2 per 100py (8.4–10.1)	9.1 per 100py (7.3–11.3)	27.9 per 100py (25.6–30.6)	13.2 per 100py (12.1–14.4)
Unadj RR (95% CI)	1.77 (1.45–2.17)	ref	1.01 (0.73 –1.38)	3.01 (2.43–3.73)	1.42 (1.19–1.70)
P value	<0.001		0.95	<0.001	<0.001
Adj† RR (95% CI)	1.94 (1.36–2.76)	ref	1.13 (0.81 –1.58)	2.84 (2.24–3.61)	1.42 (1.18–1.71)
P value	<0.001		0.46	<0.001	0.001
Total HHF	253 events	324 events	55 events	417 events	438 events
	12.3 per 100py (10.9–13.9)	6.4 per 100py (5.8–7.2)	6.0 per 100py (4.6–7.9)	24.4 per 100py (22.2–26.9)	10.6 per 100py (9.6–11.6)
Unadj RR (95% CI)	1.93 (1.53–2.46)	ref	0.96 (0.65–1.44)	3.79 (2.98–4.81)	1.65 (1.34–2.03)
P value	<0.001		0.83	<0.001	<0.001
Adj† RR (95% CI)	1.78 (1.41–2.26)	ref	0.75 (0.48 –1.18)	4.24 (3.48–5.18)	1.95 (1.60–2.36)
P value	<0.001		0.21	<0.001	<0.001
Death CV causes*	79 (10.4%)	142 (8.3%)	28 (7.6%)	61 (10.9%)	106 (7.6%)
	3.8 per 100py (3.1–4.8)	2.8 per 100py (2.4–3.3)	3.1 per 100py (2.1–4.4)	3.6 per 100py (2.8–4.6)	2.6 per 100py (2.1–3.1)
Unadj HR (95% CI)	1.40 (1.06–1.85)	ref	1.14 (0.76–1.72)	1.25 (0.93–1.69)	0.91 (0.71–1.17)
P value	0.016		0.52	0.15	0.46
Adj† HR (95% CI)	1.24 (0.78–1.99)	ref	1.09 (0.71–1.66)	1.05 (0.75–1.45)	0.77 (0.59–1.01)
P value	0.36		0.72	0.79	0.056
Death from any cause	115 (15.1%)	236 (13.8%)	50 (13.5%)	90 (16.1%)	200 (14.4%)
	5.6 per 100py (4.7–6.7)	4.7 per 100py (4.1–5.3)	5.5 per 100py (4.2–7.2)	5.3 per 100py (4.3–6.5)	4.8 per 100py (4.2–5.6)
Unadj HR (95% CI)	1.25 (1.00–1.56)	ref	1.26 (0.93–1.72)	1.10 (0.87–1.41)	1.03 (0.85–1.25)
P value	0.053		0.14	0.42	0.75
Adj† HR (95% CI)	1.17 (0.81–1.67)	ref	1.21 (0.88–1.67)	0.87 (0.67–1.13)	0.83 (0.68–1.02)
P value	0.43		0.24	0.30	0.07

ACE indicates angiotensin-converting enzyme; Adj, adjusted; ARB, angiotensin receptor blocker; BMI, body mass index; CV, cardiovascular; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HF, heart failure; HHF, hospitalization for heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; py, patient-years; RR, rate ratio; and SBP, systolic blood pressure; Unadj, unadjusted.

*N, % of patient, incident rate.

†Adjusted for age, sex, race, atrial fibrillation/flutter, DM, hospitalization for HF, BMI, MI, stroke, SBP, eGFR, NT-proBNP, LVEF, use of ACE inhibitors/ARBs, β-blockers, MRAs, and calcium channel blockers.

patients reported a history of AF.[12] Both AF and HFpEF are considered diseases of the elderly. However, the incidence of AF in HFpEF is higher than expected from older age alone.[13] A proinflammatory state, associated with aging, might link both HFpEF and AF and could explain the occurrence of this phenotype. The Obese pattern of comorbidities in North America highlights the importance of obesity for HFpEF in this region[14,15] and corroborates earlier reports suggesting that >80% of patients with HFpEF in the United States are overweight or obese, which is associated with increased filling pressures and reduced exercise tolerance.[14,16] Importantly, excess adipose tissue has been postulated to cause myocardial stiffening and fibrosis via its proinflammatory properties.[17] In Asia, there was a high prevalence of diabetes with a lower BMI,[11,18,19] which was also previously found in Asian Sudden Cardiac Death in Heart Failure registry (ASIAN-HF).[11,18,19] An article using cluster analyses to identify patterns of multimorbidity in ASIAN-HF supports the existence of a *Lean* phenotype with a high prevalence of diabetes.[20]The propensity of Asians to deposit fat more in the visceral space might explain the existence of this phenotype. Indeed, the prevalence of diabetes is far greater in Asians compared to whites at a lower BMI.[19] The existence of this phenotype also provides clinical evidence suggesting that cardiometabolic disturbances may be key drivers of cardiac malfunction beyond the influence of excess weight per se. Yet, patients included in PARAGON-HF are selected as part of a clinical trial. It is therefore unclear how generalizable our results are to real-world HF populations. Results from the present study show

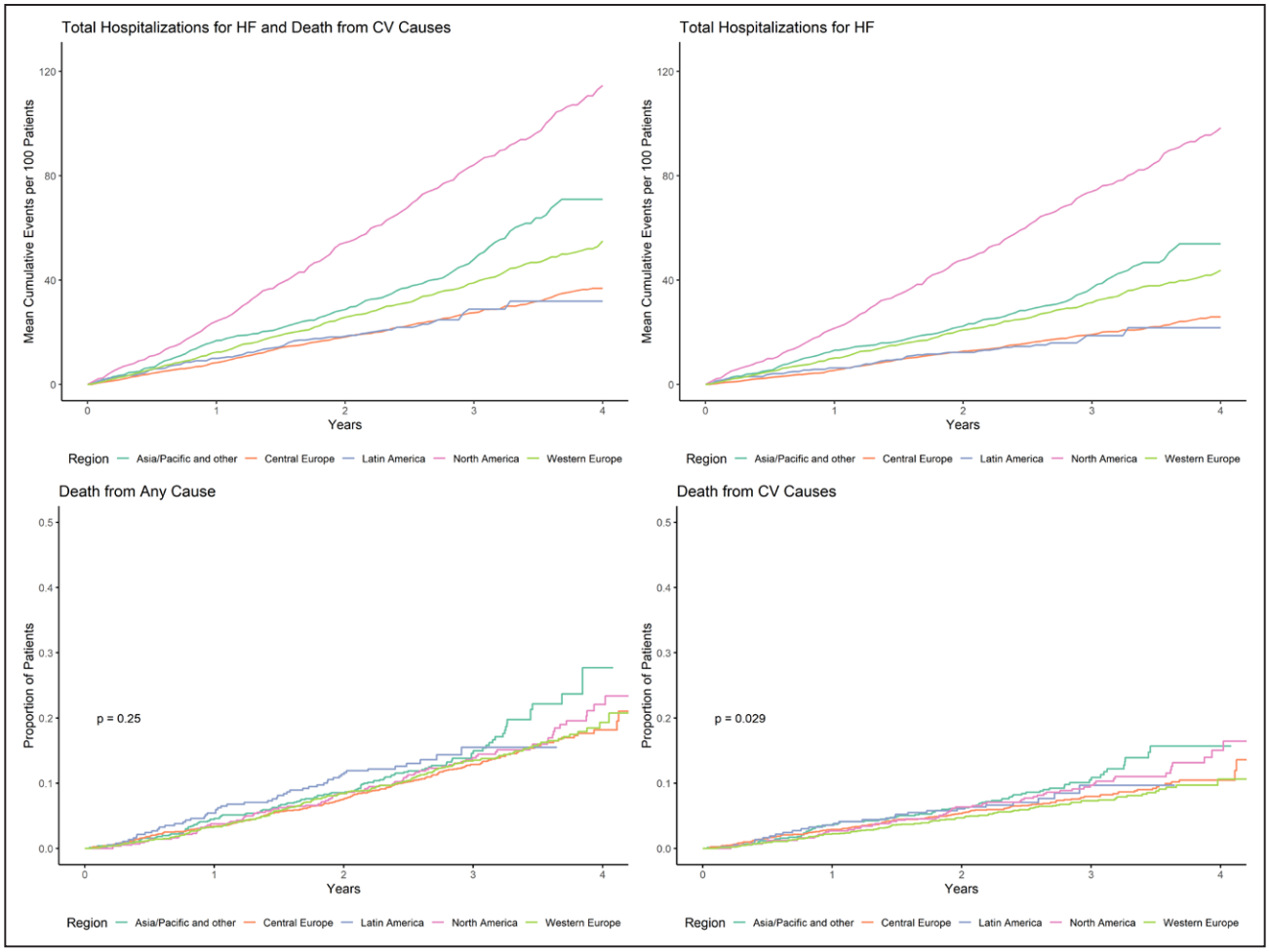

Figure 1. Ghosh-Lin and cumulative incidence curves stratified according to region for the primary combined outcome, total hospitalizations for heart failure (HF), death from any cause, and death from cardiovascular (CV) causes.

that using an agnostic approach, the majority of countries are clustered in similar geographic groups. Some countries, however, are clustered outside of their geographic region—a case in point are Singapore and Israel, which were classified together with Canada and North America in the same cluster, although being in different geographic regions. This suggests that a geographic classification of countries might not fully capture the ethnic and socioeconomic diversity within regions and that other factors, such as country income levels, quality of clinical care, and cultural/lifestyle factors,[21,22] might determine regional differences in patient characteristics, which deserves further study.

Despite regional differences in patient characteristics and HF hospitalization rates, all-cause death rates were similar among regions in PARAGON-HF. Similarly, post hoc analyses of the I-Preserve (Irbesartan in Heart Failure With Preserved Systolic Function) and CHARM-Preserved (Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity-Preserved) trials showed little regional variation in death rates.[23] These data provide some reassurance on the generalizability of HFpEF diagnosis and trial results to different regions of the world. In contrast, in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial), all-cause death rates in Russia/Georgia were notably lower compared to that in the Americas[24]—an observation postulated to be related to the hospitalization criterion in TOPCAT which, by meaning different things in different regions, may have led to enrollment of a lower risk population without true HFpEF.[25] This subjective variation may be overcome by objective inclusion criteria based on increased natriuretic peptides or presence of cardiac structural or functional abnormalities—as applied uniformly to all patients in PARAGON-HF.

The implication of regional differences for the assessment of HF hospitalization as an end point also warrants consideration. Although the primary end point of PARAGON-HF was narrowly missed, the observed 13% reduction in the primary end point (albeit nonsignificant) with sacubitril-valsartan, compared with valsartan, was driven almost entirely by a reduction of 15% in HF hospitalizations, and sensitivity analyses stratified by country

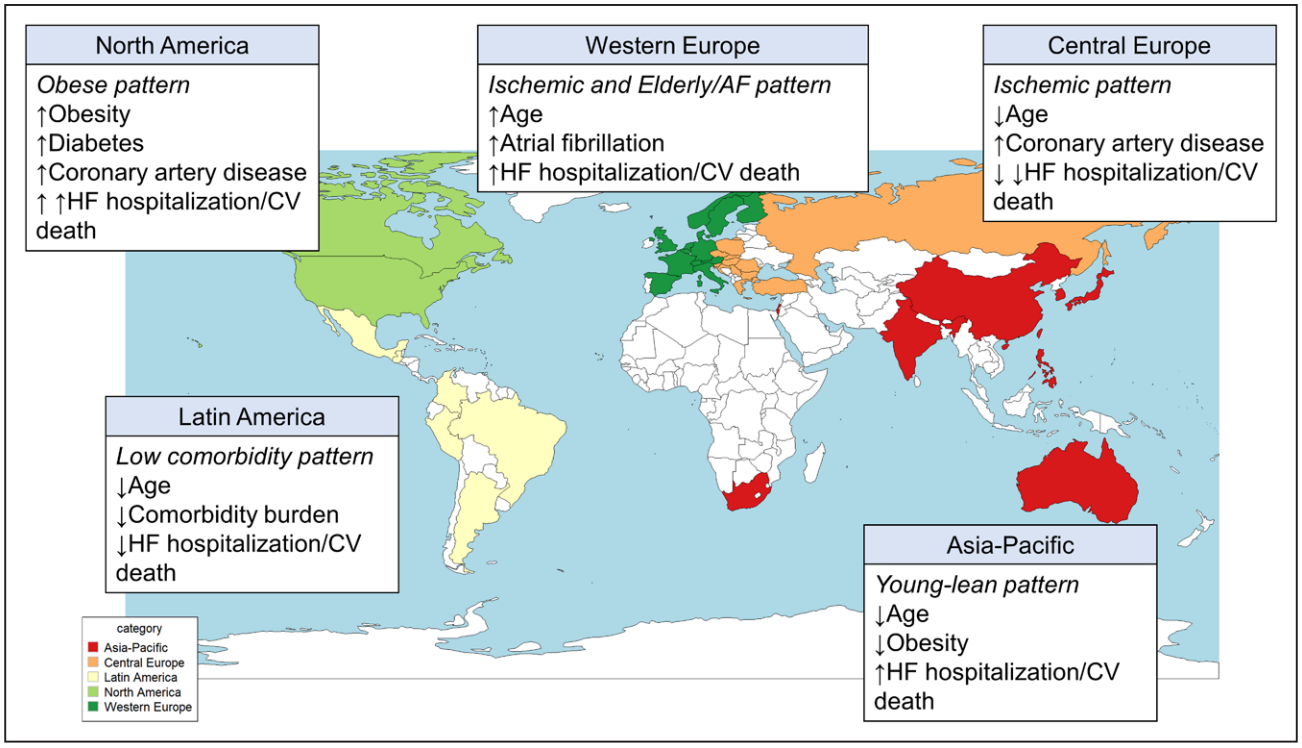

Figure 2. Map showing countries according to region with summary of the main findings per region.
AF indicates atrial fibrillation; CV, cardiovascular; and HF, heart failure.

revealed a stronger effect of sacubitril-valsartan compared to stratifying by region.[6] Significant heterogeneity within region may have contributed to these findings; for instance, the Asia-Pacific region included patients enrolled in diverse countries including Australia, China, India, Israel, Japan, South Korea, Philippines, Singapore, South Africa, and Taiwan. More homogeneity of hospitalization practice may be expected across a single country (compared to a region), and patients from countries with high baseline risk of HF hospitalization may be more likely to demonstrate benefit with respect to HF hospitalization. Country-level factors that may impact recurrent HF hospitalization risk apart from disease severity or treatment effect include, for example, differing lengths of stay, differences in healthcare systems, or income inequality.[21,22] In contrast, despite differences in patient characteristics, mortality rates were similar across regions in PARAGON-HF. Thus, future HFpEF clinical trials using HF hospitalization (and particularly total hospitalizations including first and recurrent events) as an end point should carefully anticipate and account for differences in local HF hospitalization practice, beyond disease severity alone, in determining rehospitalization risk. Although there were differences between quality of life at baseline as reported earlier,[26] sacubitril/valsartan did not show regional heterogeneity in the effect on change of quality of life during follow-up.

Several limitations of this analysis should be noted. As in any clinical trial, there is likely bias and arbitrariness in site selection and willingness of patients to participate in a randomized placebo-controlled clinical trials. Patients enrolled in clinical trials might differ significantly from the HF population at large; therefore, it is unclear how results of the present study are reflective of real-world populations. PARAGON-HF included patients with mildly reduced left ventricular ejection fraction between 45% and 50%. Although region was a prespecified subgroup, the PARAGON-HF study was not specifically powered to evaluate regional differences; significant differences in results should thus be interpreted with caution. Differences exist between countries within regions not captured by regional classification. Geographic regions are highly heterogenous with participants having different ethnicities and socioeconomic backgrounds. It is unclear how ethnic and by extension genetic variations might have influenced results of this study.

CONCLUSIONS

In PARAGON-HF, there were notable geographic differences in patient characteristics and outcomes. Phenotypic patterns included Low-comorbidity patients primarily from Latin America, Young-lean patients primarily from Asia-Pacific and Western Europe, Ischemic patients primarily from Central Europe and Western Europe, Obese patients primarily from North America, and Elderly/AF patients from Western Europe. Despite regional differences in patient characteristics, all-cause

mortality showed low variability. The marked regional differences in HF hospitalizations suggest different hospitalization practices independent of regional differences in comorbidity burden or disease severity. The treatment effects of sacubitril/valsartan on both the primary combined outcome of total hospitalizations for HF or cardiovascular death or its individual components and quality of life were similar across regions.

ARTICLE INFORMATION

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Supplemental Materials

Tables I–III
Figures I–II

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