Geographic variations in the PARADIGM-HF heart failure trial

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Aims	The globalization of clinical trials has highlighted geographic variations in patient characteristics, event rates, and treatment effects. We investigated these further in PARADIGM-HF, the largest and most globally representative trial in heart failure (HF) to date.
Methods and results	We looked at five regions: North America (NA) 622 (8%), Western Europe (WE) 1680 (20%), Central/Eastern Europe/Russia (CEER) 2762 (33%), Latin America (LA) 1413 (17%), and Asia-Pacific (AP) 1487 (18%). Notable differences included: WE patients (mean age 68 years) and NA (65 years) were older than AP (58 years) and LA (63 years) and had more coronary disease; NA and CEER patients had the worst signs, symptoms, and functional status. North American patients were the most likely to have a defibrillating-device (53 vs. 2% AP) and least likely prescribed a mineralocorticoid receptor antagonist (36 vs. 61% LA). Other evidence-based therapies were used most frequently in NA and WE. Rates of the primary composite outcome of cardiovascular (CV) death or HF hospitalization (per 100 patient-years) varied among regions: NA 13.5 (95% CI 11.7–15.6), WE 9.6 (8.6–10.6), CEER 12.3 (11.4–13.2), LA 11.2 (10.0–12.5), and AP 12.5 (11.3–13.8). After adjustment for prognostic variables, relative to NA, the risk of CV death was higher in LA and AP and the risk of HF hospitalization lower in WE. The benefit of sacubitril/valsartan was consistent across regions.
Conclusion	There were many regional differences in PARADIGM-HF, including in age, symptoms, comorbidity, background therapy, and event-rates, although these did not modify the benefit of sacubitril/valsartan.
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Introduction

The declining risk of adverse outcomes in patients with heart failure (HF) and reduced ejection fraction (HF-REF), resulting from the cumulative benefit of treatments over time, has meant that contemporary randomized controlled clinical trials require greater numbers of participants and longer follow-up to accrue the number of events needed to test the effect of new therapies.[1] In order to recruit a sufficient number of patients in a timely manner, and to improve generalizability of results, these trials now include participants from many different regions of the world.[2] On the other hand, geographical differences in demographics, race, ethnicity, other patient characteristics, aetiology of HF, co-morbidity, health care systems, physician-practice, and especially background therapy can raise questions about the applicability of the results of the trial in certain regions of the world.[2–14] In particular, there has been controversy about the effect of certain treatments in patients from the USA compared with those from the rest of the world.[3,15–17]

The prospective comparison of Angiotensin Receptor-neprilysin inhibitor with Angiotensin-converting−enzyme inhibitor to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF) is the largest trial in patients with HF and HF-REF to date and it is the most globally representative, with ∼8400 patients enrolled in 47 countries on six continents.[18] Our aim was to evaluate geographical differences in patient characteristics (age, sex, background pharmacotherapy, and comorbidity) and event rates. We also wanted to examine the effect of sacubitril/valsartan (formerly known as LCZ696) according to geographical region. Our hypothesis was that patient characteristics and outcomes would vary by geographic region in PARADIGM-HF but that the effect of sacubitril/valsartan, compared with enalapril, would not.

Methods

The design, baseline characteristics, and results of PARADIGM-HF have been published.[18–20] The Ethics Committee of each of the 1043 participating institutions (in 47 countries) approved the protocol, and all patients gave written, informed consent.

Study patients

Briefly, patients had New York Heart Association (NYHA) classes II−IV symptoms, a left ventricular ejection fraction (LVEF) ≤40% and modestly elevated plasma B-type natriuretic peptides. Patients were required to be taking an angiotensin converting enzyme inhibitor or angiotensin receptor blocker in a dose equivalent to enalapril 10 mg daily for at least 4 weeks before screening, along with a stable dose of a β-blocker (unless contraindicated or not tolerated) and a mineralocorticoid antagonist (MRA), if indicated. Key exclusion criteria included a systolic blood pressure (SBP) <95 mmHg, a serum potassium >5.4 mmol/L, or an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 at randomization.

Trial outcomes

The primary outcome was a composite of death from CV causes or a first hospitalization for HF. The secondary outcomes included death from any cause and change from baseline to 8 months in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS). In the present study, we examined the primary composite outcome and its components, as well as all-cause death. We further determined the proportion of patients experiencing a five or greater points reduction in their KCCQ-CSS as this is considered to be a clinically important deterioration in health-related quality of life (HRQL).[21] Safety outcomes included hypotension, elevation of serum creatinine, hyperkalaemia, cough, and angioedema, as previously reported.[18] We also reported total number of adverse, and serious adverse events according to geographic region. Furthermore, we assessed length of stay for all-cause hospitalizations during the study, and total days alive and out of hospital in the first year (*Figure 1*).

Geographic regions

The following geographic regions were examined: North America (NA), Western Europe (WE), Central/Eastern Europe/Russia (CEER), Latin America (LA), and the Asia-Pacific (AP) region. The countries in each of these regions are listed in Appendix.

Statistical analysis

Data are reported as mean ± SD or median and interquartile ranges and as frequencies and percentages for categorical variables. Student's *t*-tests were used to compare baseline variables between regions. Cox proportional hazard models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for the time-to-event endpoints, and logistic regression analysis for the binomial endpoint of ≥5 point decline in KCCQ-CSS at 8 months follow-up. In analyses of treatment effect, the primary variable of interest was the interaction *P*-value for randomized treatment × geographic region. For analyses comparing risk according to region, we did unadjusted analyses and analyses including multivariable adjustment for treatment effect and other variables known to be predictors of risk in patients with HF-REF (see Supplementary material online, *List*). A two-tailed *P*-value of <0.05 was considered significant. Statistical analyses were performed using STATA, College Station, Texas, version 14.0.

Results

Of 8399 patients in PARADIGM-HF, 622 (7%) were randomized in NA, 1680 (20%) in WE, 2762 (33%) in CEER, 1413 (17%) in LA, and 1487 (18%) in the AP region.

Baseline characteristics

The majority of characteristics differed across regions (*Table 1* and see Supplementary material online, *Tables A* and *B*).

Age, sex, and race/ethnicity

Patients in WE, who were the most elderly (with a mean age 68.3 years), were an average of 10.5 years older than those enrolled in AP. The proportion of women was highest in LA (27%) and lowest in NA (17%). The proportion of patients who were black was highest in NA (19%).
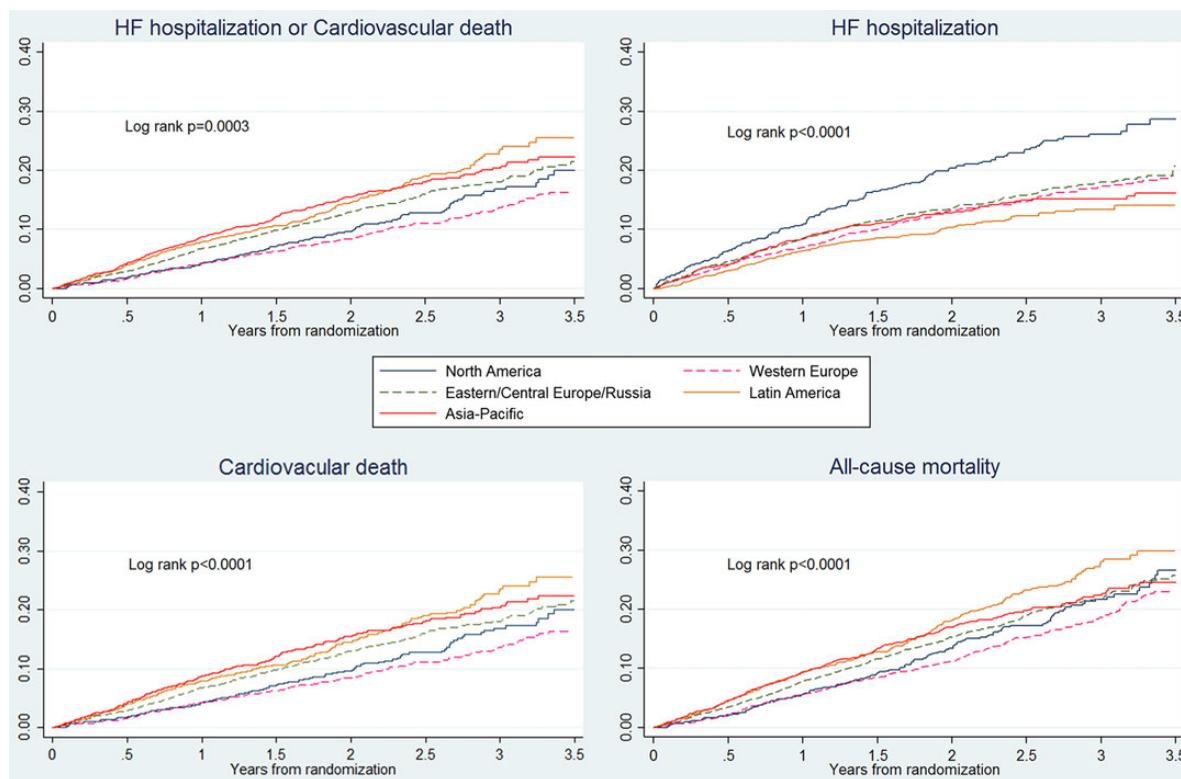
Figure 1 Kaplan−Meier plots of endpoints according to region.

Social habits

The proportion of current smokers was highest in NA (17%) and lowest in LA (10%). Daily alcohol consumption ($\geq$1 unit) was highest in WE (24%) and $\leq$10% in all other regions.

Heart failure status

The proportion of patients with mild vs. more severe symptoms also varied by region; whereas <15% of patients in most regions had moderate-to-severe symptoms, 20% of patients enrolled in NA were in NYHA class III/IV and this proportion was highest (44%) in CEER. The mean KCCQ-CSS (scales 0–100, with 0 equating to worst HRQL) was lowest (worst) in CEER (68) and NA (72), compared with the other regions; the mean KCCQ-CSS was highest in AP (79). The SD around the mean KCCQ-CSS varied also among regions and this was not explained only by the number of patients in each region.

Patients from CEER were most likely to report dyspnoea and fatigue and have signs of congestion. However, mean LVEF (32%) was highest in this region. NT-proBNP concentration was lower in patients from CEER, compared with most other regions, although the differences between regions were modest. The proportion of patients with a history of HF hospitalization varied substantially by region, being highest in CEER (71%) and lowest in LA (54%).

Anthropometric and physiological measures

Body mass index varied by region, being highest in NA (31 Kg/m^2) and lowest in AP (24 kg/m^2) (Table 1). Heart rate in patients without

atrial fibrillation (AF) was lowest in NA (70 b.p.m.) and WE (68 b.p.m.) and highest in AP (75 b.p.m.), consistent with the geographical variation in β-blocker use but inversely related to digoxin use (see below). Baseline SBP was highest in CEER (mean 126 mmHg) compared with 117 mmHg in AP and 118 mmHg in NA and LA, consistent with geographical variation in hypertension history (see below).

Coronary heart disease

An ischaemic aetiology was most common in CEER (70%) and NA (62%) and least common in LA (43%). Consistent with this, history of myocardial infarction was most frequent in CEER (50%) and NA (54%) and least frequent in LA (32%) and AP (34%). The proportions of patients with any manifestation of coronary disease and prior coronary revascularization varied in a similar way (Table 1).

Other co-morbidity

Co-morbidity was generally most common in NA (except a history of hypertension and AF which was highest in CEER). Co-morbidity was less common in LA and AP. The proportion of patients with chronic kidney disease (CKD) was lowest in AP (27%) and mean eGFR highest in that region (71 mL/min/1.73 m^2); mean eGFR was lowest in NA (61 mL/min/1.73 m^2), where there was also the greatest proportion with CKD (51%).

Table I   Baseline characteristics according to region

	North America	Western Europe	Central/Eastern Europe/Russia	Latin America	Asia-Pacific	P-value
Number of patients	622 (7%)	1680 (20%)	2762 (33%)	1413 (17%)	1487 (18%)	
Age (years)	65.0 ± 11.4	68.3 ± 9.9	65.1 ± 10.0	63.0 ± 11.6	57.8 ± 11.9	<0.0001
Female sex, *n* (%)	108 (17%)	297 (18%)	641 (23%)	387 (27%)	292 (20%)	<0.0001
Caucasian, *n* (%)	466 (75%)	1645 (98%)	2712 (98%)	485 (34%)	11 (1%)	<0.0001
BMI (kg/m^2)	31 ± 7	29 ± 5	30 ± 5	27 ± 5	24 ± 4	<0.0001
Heart rate (b.p.m.)	70 ± 11	69 ± 11	74 ± 12	71 ± 11	75 ± 11	<0.0001
Syst. BP (mmHg)	118 ± 15	121 ± 16	126 ± 14	118 ± 14	117 ± 15	<0.0001
eGFR (mL/min/1.73 m^2)	59 (48, 71)	61 (50, 74)	67 (55, 80)	67 (55, 80)	72 (59, 85)	<0.0001
LVEF	0.27 ± 0.07	0.30 ± 0.06	0.32 ± 0.05	0.28 ± 0.06	0.28 ± 0.06	<0.0001
NYHA class, *n* (%)						<0.0001
I	23 (4%)	58 (4%)	33 (1%)	107 (8%)	119 (8%)	
II	476 (77%)	1292 (77%)	1512 (55%)	1148 (81%)	1180 (79%)	
III	117 (19%)	319 (19%)	1169 (42%)	156 (11%)	184 (13%)	
IV	4 (0%)	7 (0%)	45 (2%)	0 (0%)	3 (0%)	
KCCQ score	72 ± 21	73 ± 20	68 ± 19	79 ± 18	79 ± 16	<0.0001
NT-proBNP pg/mL[a] (IQR)	1580 (900, 3046)	1517 (857, 2888)	1599 (877, 3134)	1760 (917, 3645)	1714 (911, 3677)	0.0003
Medical history, *n* (%)						
Ischaemic aetiology	387 (62%)	980 (58%)	1942 (70%)	611 (43%)	863 (58%)	<0.0001
HF hospitalization	400 (64%)	948 (56%)	1961 (71%)	767 (54%)	894 (60%)	<0.0001
Hypertension	522 (84%)	1050 (63%)	2395 (87%)	956 (68%)	719 (48%)	<0.0001
Atrial fibrillation	245 (39%)	744 (44%)	1428 (52%)	334 (24%)	249 (17%)	<0.0001
Diabetes	299 (48%)	597 (36%)	936 (34%)	385 (27%)	515 (35%)	<0.0001
CKD (eGFR < 60[b])	319 (51%)	759 (45%)	950 (34%)	486 (34%)	397 (27%)	<0.0001

[a]NT-proBNP data are from the screening visit. Information on KCCQ score was only available for 7623 (92%) patients.
[b]mL/min/1.73 m^2.

Drug, device, and other treatments

Although β-blocker use was mandated by protocol (unless contra-indicated/not tolerated), there was still variability with the highest rate in NA (97%) and lowest in AP (89%) (*Table 2*). There was more striking variation in the use of mineralocorticoid receptor antagonists—prescribed least commonly in NA (36%) and most frequently in LA (65%). Digoxin use also varied greatly in patients with no history of AF—from 6% in WE to 42% in AP. There was less variation in digoxin use among patients with a history of AF (range 33% WE to 55% AP).

The use of non-HF medications also varied geographically. The highest rates of prescription of oral anticoagulants in patients with an AF history were in Europe (WE 82%, CEER 68%) and NA (63%) and lowest in AP (35%).

Device therapy varied substantially by region, being highest in NA and lowest in CEER, LA, and AP. For example, a defibrillating-device (ICD or CRT-D) had been implanted in 53% in NA but in only 7, 4, and 2% of patients in CEER, LA, and AP, respectively. Similarly, other guideline-recommended interventions varied by region. Influenza vaccination in the past year was most frequently reported in NA (51%) and WE (53%) but much less commonly elsewhere. A quarter to a third of patients in NA and WE were enrolled in a structured disease management programme but few patients were enrolled elsewhere. Prescription of an exercise regimen was provided in

between a fifth and a quarter of patients in NA, WE, and CEER but was uncommon elsewhere. These non-drug/device interventions were rarely used in AP.

Heart failure outcomes

Cardiovascular death or heart failure hospitalization
The unadjusted rate of the primary endpoint varied less between regions than the rate of HF hospitalization, with the following ranking from lowest to highest: WE (9.6 per 100 patient-years), LA, CEER, AP, and NA (13.5 per 100 patient-years). Using NA as the reference region, and after adjustment, WE exhibited a lower risk (adjusted HR 0.84, 95% CI 0.70, 1.01) but AP a higher risk (adjusted HR 1.36, 95% CI 1.05, 1.76). A supplementary analysis including South Africa, Israel, and Turkey in alternative geographical regions gave similar results (see Supplementary material online, *Table D*). We also compared Eastern/Central Europe and Russia (see Supplementary material online, *Table E*); the crude rates of the primary endpoint were similar but mortality rates were slightly higher and hospitalization rates lower, in Russia.

Mortality
The unadjusted rate of death from any cause varied modestly among regions with the following ranking from lowest to highest: WE (6.7 per 100 patient-years), NA, CEER, AP, and LA (10.1 per 100 patient-years)

Table 2 Pharmacological and device treatment

	North America	Western Europe	Central/Eastern Europe/Russia	Latin America	Asia-Pacific	P-value
Medication, n (%)						
Loop-diuretic	503 (81%)	1362 (81%)	2292 (83%)	1101 (78%)	1091 (73%)	<0.0001
β-Blocker	603 (97%)	1570 (94%)	2612 (95%)	1305 (92%)	1320 (89%)	<0.0001
MRA	225 (36%)	742 (44%)	1695 (61%)	916 (65%)	830 (56%)	<0.0001
Digoxin						
All	167 (27%)	307 (18%)	805 (29%)	495 (35%)	660 (44%)	<0.0001
History of AF	99 (40%)	248 (33%)	647 (45%)	171 (51%)	136 (55%)	<0.0001
No history of AF	68 (18%)	58 (6%)	155 (12%)	324 (30%)	523 (42%)	<0.0001
Oral anticoagulants						
All	205 (33%)	792 (47%)	1181 (43%)	274 (19%)	143 (10%)	<0.0001
History of AF	154 (63%)	606 (82%)	964 (68%)	180 (54%)	87 (35%)	<0.0001
No history of AF	51 (14%)	186 (20%)	217 (16%)	94 (9%)	56 (5%)	<0.0001
Devices						
Any CRT	130 (21%)	207 (12%)	113 (4%)	29 (2%)	42 (3%)	<0.0001
ICD or CRT-D	327 (53%)	559 (33%)	193 (7%)	61 (4%)	26 (2%)	0.0033

MRA, mineralocorticoid receptor antagonist; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; AF, atrial fibrillation.

(*Table 3*). Using NA as the reference and adjusting for differences between regions in prognostic variables, patients in LA (adjusted HR 1.62, 95% CI 1.24, 2.11) and AP (adjusted HR 1.35, 1.00, 1.82) exhibited a higher risk of death. The findings for CV death were similar.

Hospitalization

The unadjusted rate of HF hospitalization varied more among regions with the following ranking from lowest to highest: LA (5.3 per 100 patient-years), AP, WE, CEER, and NA (10.5 per 100 patient-years). Using NA as the reference, all other regions showed a significantly lower unadjusted risk of hospitalization. After adjustment, this difference persisted only in WE (adjusted HR 0.79, 95% CI 0.64, 0.98). Length of stay for hospitalization was shortest in NA and WE and longest in CEER (see Supplementary material online, *Table F*). Days alive and out of hospital in first year of study, varied between 345 and 351 days, with highest number in NA.

Health-related quality of life

The proportion of patients exhibiting a decrease of ≥5 points in KCCQ-CSS at 8 months was largest in NA, WE, and CEER (where around a third of patients deteriorated) and smaller in LA (24%) and AP (18%). The odds of deteriorating were significantly less in these latter regions in unadjusted analyses, but not after multivariable adjustment.

Consistency of effect of sacubitril/ valsartan on clinical outcomes by region

As shown in *Table 4*, the effect of sacubitril/valsartan was consistent across regions for the primary composite endpoint, its components and for all-cause mortality. The same was true for the effect of sacubitril/valsartan on deterioration in KCCQ.

Study drug tolerability

Adverse events varied considerably by region (see Supplementary material online, *Table C*). In the enalapril group, hypotension and renal impairment were most common in NA, hyperkalaemia was most common in CEER and cough most common in AP. The differences between sacubitril/valsartan and enalapril (more hypotension and less renal impairment and hyperkalaemia with the former) were consistent across regions. Study drug discontinuation for reasons other than death varied significantly by geographical region, from 32% in NA to 10% in AP.

Discussion

Although there are a few analyses of geographic variation among patients with acute HF, there is only one report from a trial, the Assessment of Treatment with Lisinopril and Survival study (ATLAS), in ambulatory patients with chronic HF-REF, published in 1998.[3,7,8,10,11] No acute or chronic HF trial has been as globally diverse as PARADIGM-HF which included patients from geographical areas under-represented in prior studies including LA and, especially, AP. More data were collected on baseline characteristics and treatment in PARADIGM-HF than in prior trials, including information on non-pharmacolgical/non-device recommendations, e.g. enrolment in disease management programmes.

Baseline characteristics

We found some inevitable differences between regions (e.g. in race and ethnicity), some possibly related to genetic background (e.g. low prevalence of AF in AP[22]). It is harder to explain other differences. Compared with NA and WE, where clinical trials were initially conducted, the average patient age was lower (especially in AP) and the proportion of women larger (especially in LA). Ischaemic aetiology

Table 3 **Event rate (per 100 patient-years) and risk of study endpoints according to region (North America reference region)**

	North America	Western Europe	Central/Eastern Europe and Russia	Latin America	Asia-Pacific
No. of patients	622	1680	2762	1413	1487
HF hospitalization or cardiovascular death	185	358	694	309	369
Event rates per 100 patient-years (95% CI)	13.5 (11.7–15.6)	9.6 (8.6–10.6)	12.3 (11.4–13.2)	11.2 (10.0–12.5)	12.5 (11.3–13.8)
Unadjusted HR	1.00 (ref.)	0.71 (0.59–0.85)	0.90 (0.76–1.06)	0.81 (0.67–0.97)	0.91 (0.76–1.08)
Adjusted[a] HR	1.00 (ref.)	0.84 (0.70–1.01)	1.07 (0.89–1.29)	1.16 (0.92–1.46)	1.36 (1.05–1.76)
HF hospitalization	144	244	402	146	192
Event rates per 100 patient-years (95% CI)	10.5 (8.9–12.4)	6.5 (5.7–7.4)	7.1 (6.5–7.8)	5.3 (4.5–6.2)	6.5 (5.6–7.5)
Unadjusted HR	1.00 (ref.)	0.62 (0.50–0.76)	0.66 (0.55–0.80)	0.48 (0.38–0.61)	0.60 (0.48–0.75)
Adjusted[a] HR	1.00 (ref.)	0.79 (0.64–0.98)	0.94 (0.75–1.17)	0.81 (0.60–1.09)	1.01 (0.72–1.40)
Cardiovascular death	90	192	419	236	252
Event rates per 100 patient-years (95% CI)	5.8 (4.7–7.2)	4.8 (4.1–5.5)	6.8 (6.2–7.5)	8.2 (7.2–9.3)	8.0 (7.1–9.1)
Unadjusted HR	1.00 (ref.)	0.91 (0.71–1.6)	1.17 (0.93–1.47)	1.41 (1.10–1.79)	1.38 (1.08–1.75)
Adjusted[a] HR	1.00 (ref.)	0.92 (0.71–1.19)	1.25 (0.97–1.62)	1.74 (1.29–2.36)	1.71 (1.22–2.39)
All-cause mortality (no. of events)	123	271	510	291	279
Event rates per 100 patient-years (95% CI)	8.0 (6.7–9.5)	6.7 (6.0–7.6)	8.3 (7.6–9.1)	10.1 (9.0–11.3)	8.9 (7.9–10.0)
Unadjusted HR	1.00 (ref.)	0.85 (0.69–1.05)	1.05 (0.86–1.28)	1.28 (1.04–1.59)	1.12 (0.91–1.39)
Adjusted[a] HR	1.00 (ref.)	0.92 (0.74–1.15)	1.11 (0.88–1.38)	1.62 (1.24–2.11)	1.35 (1.00–1.82)
Significant worsening in KCCQ clinical score (≥5) at 8 months[b]	208 (34%)	564 (34%)	870 (32%)	338 (24%)	264 (18%)
Unadjusted OR	1.00 (ref.)	1.01 (0.83–1.22)	0.91 (0.76–1.10)	0.63 (0.51–0.77)	0.43 (0.35–0.53)
Adjusted[a] OR	1.00 (ref.)	1.09 (0.89–1.34)	0.97 (0.79–1.20)	0.88 (0.68–1.12)	0.98 (0.74–1.30)

Information on KCCQ score was only available for 7623 (92%) patients.
ICD, ischaemic aetiology and history of myocardial infarction, diabetes, AF, and stroke.
[a]Model adjusted for age, sex, treatment arm, race, HF duration, heart rate, SBP, body mass index, NYHA class, ejection fraction, KCCQ score, and glomerular filtration rate.
[b]Scores on the Kansas City Cardiomyopathy Questionnaire (KCCQ) range from 0 to 100 (higher scores indicating fewer symptoms).

was least frequent in LA, which was also reported in two acute HF trials, presumably reflecting different causes of HF on that continent, including Chagas cardiomyopathy.[7,8]

Regarding HF status, we found that the greatest differences were between CEER and the rest of the World. Specifically, CEER patients had worse symptoms and more severe functional limitation as evaluated by the investigators (NYHA class) and reported by patients (KCCQ-CSS). Consistent with this, signs (dyspnoea, oedema, and rales) and prior HF hospitalization were more common. However, patients from CEER had the highest average LVEF and lowest NT-proBNP and, overall, examination of regional patterns showed no clear relationship between objective measurements of cardiac dysfunction and symptom frequency and physical limitation.

As observed previously, the rate of prior coronary intervention was highest in NA,[7,8,11] followed closely by WE; patients in CEER had less prior coronary intervention but the rates in this region were still considerably higher than in LA and AP. Despite similar recommendations regarding ICD and CRT use in all major guidelines, an even more extreme pattern of disparity of use was seen, with a 30-fold difference in use of a defibrillating-device between NA and

AP.[7,8,11] Of all regional variation, use of procedures, devices, and surgery showed the greatest differences, probably, in part, reflecting economic differences.

Variation in HF medication use was less pronounced but was still substantial, at least for MRAs. Prescription of MRAs showed exactly the opposite pattern to use of devices i.e. was least common in NA and WE and most frequent in the other regions with lower device use. Patients in NA and WE had the lowest eGFR (and highest proportion of patients with CKD) which may have led to reluctance to prescribe, although the entry eGFR in PARADIGM-HF would not have precluded safe use of a MRA, and other explanations may exist.[23] Among patients without a history of AF, there was also an almost seven-fold difference in digoxin prescription, with the highest use in AP (42%) and lowest use in WE (6%), illustrating the dramatic decline in digitalis glycoside use in certain regions of the world (in ATLAS 80% of sinus rhythm patients in NA and 57% in continental Europe were treated with digoxin).[3]

Of non-HF drugs, the greatest variation was in use of oral anticoagulants which were much less frequently prescribed in AP, where under-treatment of AF patients with these agents has been highlighted recently.[24]

Table 4 Treatment effect according to region (sacubitril/valsartan vs enalapril hazard ratio and 95% confidence interval)

	Overall HR (95% CI)	North America HR (95% CI)	Western Europe HR (95% CI)	Central/Eastern Europe and Russia HR (95% CI)	Latin America HR (95% CI)	Asia-Pacific HR (95% CI)	P for interaction
HF hospitalization or cardiovascular death	0.80 (0.73–0.87)	0.66 (0.49–0.88)	0.88 (0.71–1.08)	0.78 (0.67–0.91)	0.72 (0.57–0.90)	0.85 (0.69–1.04)	0.4363
HF hospitalization	0.79 (0.71–0.89)	0.70 (0.50–0.97)	0.89 (0.69–1.15)	0.80 (0.66–0.98)	0.69 (0.50–0.96)	0.85 (0.64–1.12)	0.6851
Cardiovascular death	0.80 (0.71–0.89)	0.70 (0.46–1.06)	0.84 (0.63–1.11)	0.80 (0.66–0.97)	0.73 (0.57–0.95)	0.79 (0.62–1.01)	0.9317
All-cause mortality	0.84 (0.76–0.93)	0.77 (0.54–1.11)	0.99 (0.78–1.26)	0.80 (0.67–0.95)	0.81 (0.65–1.03)	0.81 (0.64–1.03)	0.6207
Significant worsening in KCCQ clinical score (≥5) at 8 months[a]	0.83 (0.75–0.92)[b]	0.85 (0.61–1.19)[b]	0.85 (0.69–1.04)[b]	0.83 (0.70–0.97)[b]	0.83 (0.65–1.06)[b]	0.79 (0.61–1.03)[b]	0.7380

Information on KCCQ score was only available for 7623 (92%) patients.
[a]Scores on the Kansas City Cardiomyopathy Questionnaire (KCCQ) range from 0 to 100 (higher scores indicating fewer symptoms).
[b]Effect of sacubitril/valsartan on worsening KCCQ clinical score (≥5) at 8 months was estimated by logistic regression, and is shown as odds ratios (ORs). Information on KCCQ score was only available for 7623 (92%) patients.

The use of other guideline recommendations, including influenza vaccination, exercise prescription, and enrolment in disease management programmes, varied greatly between regions. For example, influenza vaccination was used in around half of patients in NA and WE but rarely outside these regions. Similar patterns were observed for the other non-drug/non-device recommendations.

Collectively, our data show the use of guideline-recommended therapies is highest in NA and WE, with less application in CEER and LA and least use in AP. The one striking exception was use of MRAs, as described above.

Clinical outcomes

Despite the considerable heterogeneity in baseline characteristics and treatment, the crude rate of all-cause mortality varied modestly and was only clearly higher in one region—LA—compared with the others. However, after adjustment the risk of all-cause and cardiovascular death was found to be higher in LA and in AP, compared with NA. Both of the former regions also had the highest average NT-proBNP levels and lower LVEF (mean 28%) compared with the others (except NA which had the lowest LVEF−mean 27%). However, the higher risk of death persisted (or even increased) after adjusting for these and additional differences in known prognostic variables suggesting other biological factors, social, and environmental influences or aspects of health care provision in these regions contribute to the observed differences in survival. There may also be geographical differences in the treatment of comorbidities such as coronary artery disease, CKD, and AF which might also affect outcome.

Efficacy of Vasopressin Antagonism in hEart failuRE: Outcome Study With Tolvaptan (EVEREST), the only other large trial reporting long-term outcomes according to region (in patients with acute HF), observed similar crude mortality rates in NA, LA, and WE (no patients from AP were included).[7] The adjusted risk of death was highest in LA. The Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT), another acute HF trial, is the only study to have reported outcomes in AP as well as the Americas and Europe.[11] In that study, all-cause mortality at 12 months was highest in AP (and high in LA). Interestingly, however, these other two studies reported quite different findings about EE with the lowest risk of death in that region in EVEREST but the second highest (after AP) in ASTRONAUT. There has been recent controversy about a low event rate in CEER[17] and it is interesting that both PARADIGM-HF and ASTRONAUT did not observe low event rates in this region. Notably, unlike EVEREST, both PARADIGM-HF and ASTRONAUT required elevated natriuretic peptides for inclusion, perhaps helping ensure correct diagnosis and selection of patients at risk of events.

Greater variation in HF hospitalization rates, compared with mortality, might have been predicted, given the likely differences in decision making about admission, community programmes to prevent hospitalization, thresholds for admission and even provision and availability of hospital beds between regions. However, again, only one region was clearly different from the others and that was NA, which had almost twice the crude rate of HF hospitalization compared with LA, although the differences between regions were greatly attenuated by adjustment, with only WE having a significantly lower risk. There was also no convincing evidence of 'competing risk' influencing our findings, i.e. regions with higher

mortality did not consistently have lower admission rates. In ASTRONAUT, NA patients also had a much higher unadjusted HF hospitalization rate than elsewhere, although in EVEREST the crude re-admission rates did not vary greatly between regions.[7,11]

Health-related quality of life

We are not aware of prior reports of geographic variation in patient-reported outcomes. A clinically important deterioration in KCCQ-CSS after 8 months was significantly less likely in LA and AP (in unadjusted analyses) than elsewhere and it is notable that these two regions had the highest baseline KCCQ-CSS (i.e. the best HRQL). This finding illustrates the clear discrepancy between patient-reported outcomes and clinical events, given that these two regions had the highest all-cause and cardiovascular mortality rates.

Treatment effect

Despite the differences highlighted, we did not identify any modification of the effect of sacubitril/valsartan by geographical region—the benefit over enalapril was consistent for all outcomes across all regions, contrasting with controversy about consistency of benefit of β-blockers in HF-REF and spironolactone in HF with preserved ejection fraction (HF-PEF).[15–17]

Implications

Globalization of clinical trials is a reality that has highlighted regional disparities of many types.[2,9,13] Some are demographic and biologically determined and unavoidable whereas others reflect variation in clinical practice and economic influences. Despite this, we found that the key outcomes constituting trial endpoints varied less than has been suggested previously. This may reflect more standardized inclusion and exclusion criteria in HF-REF trials compared with trials in HF-PEF and acute HF, and, in PARADIGM-HF in particular, the use of a natriuretic peptide inclusion criterion. The latter may be an even more important consideration in trials in patients with (HF-PEF).[12] Although we found no variation in treatment effect by region, inevitably questions will also remain about the applicability of the findings of trials enrolling a large proportion of patients from regions where certain evidence-based therapies are substantially underused (e.g. MRAs in NA and ICDs in the rest of the world).

Limitations

Our study has a number of limitations. Although PARADIGM-HF is the largest HF trial to date, it is a single study. The analyses conducted were retrospective and PARADIGM-HF was not designed to evaluate geographical differences in HF. Because our analyses involved comparisons of many different variables across several regions, statistically significant differences may have arisen through the play of chance. Although we performed multivariable adjustments, we may not have captured the effect of all predictors influencing the outcomes studied. While we examined recognized geographical regions, differences may also exist between countries within these regions and these may be more marked in some regions than others, e.g. AP compared with NA. The number of patients recruited in NA was limited ($n = 622$), although analyses showed similar benefit for these patients compared with other regions. The low number of black patients ($n = 6$) in WE probably reflects selection bias in trial

enrolment. As with any trial, the generalizability of the findings to 'real-world' patients may be limited.

Conclusion

There were many regional differences in PARADIGM-HF, including in age, symptoms, comorbidity, background therapy, and event-rates, although these did not modify the benefit of sacubitril/valsartan.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Authors' contributions

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