Cardiovascular clinical research, including research of new therapies for heart failure (HF), is undergoing progressive globalization.1–4 This is caused in part by the improvement in chronic HF treatment with a decrease in event rates and the need to test smaller effects for new drugs (i.e., the requirement for large sample sizes), as well as by financial and recruitment challenges in regions such as North America (NA) and the desire to capitalize on emerging world markets. This shift in trial conduct is associated with a decreasing number of patients enrolled in NA and Western Europe (WE) and with increasing recruitment from Central Europe (CE), Latin America (LA), and, more recently, the Asia-Pacific (AP) region. Heterogeneity of geographical areas may, however, have a major impact on the results and interpretation of clinical trials.5–10 The Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial is the largest randomized controlled trial in patients with acutely decompensated HF, major differences in baseline characteristics, treatments, length of the hospital stay, and 30-day HF rehospitalization rates, and 180-day mortality were found in patients enrolled from different geographical areas. © 2016 Elsevier Inc. All rights reserved. (Am J Cardiol 2016;117:1771–1778)

A growing number of countries and geographical regions are involved in major clinical trials. Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure is the largest trial in acutely decompensated heart failure (HF) with patients from 5 geographical areas: North America (NA), Latin America (LA), Western Europe (WE), Central Europe (CE), and Asia-Pacific (AP). Data from the 5 geographical areas were compared including baseline characteristics, medications, 30-day outcomes (mortality or HF hospitalization), and 180-day mortality. Of the 7,141 study patients, 3,243 (45.4%) were from NA (average of 15.2 patients/site), 1,762 (24.7%) from AP (28.4 patients/site), 967 (13.5%) from CE (20.2 patients/site), 665 (9.3%) from LA (17.1 patients/site), and 504 (7.1%) from WE (14.4 patients/site). There were marked differences in co-morbidities, clinical profile, medication use, length of stay, 30-day event rates, and 180-day mortality by region. Compared with NA, the adjusted risk for death or HF hospitalization at 30 days was significantly lower in CE (odds ratio [OR] 0.46, 95% CI 0.33 to 0.64), WE (OR 0.52 95% CI 0.35 to 0.75), and AP (OR 0.62 95% CI 0.48 to 0.79) and numerically lower in LA (OR 0.77, 95% CI 0.57 to 1.04) with similar results for 180-day mortality. In conclusion, in patients with acutely decompensated HF, major differences in baseline characteristics, treatments, length of the hospital stay, and 30-day HF rehospitalization rates, and 180-day mortality were found in patients enrolled from different geographical areas.
### Table 1
Baseline characteristics of the patients subdivided by geographical areas

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Asia / Pacific (n=1762)</th>
<th>Central Europe (n=967)</th>
<th>Latin America (n=665)</th>
<th>North America (n=3243)</th>
<th>Western Europe (n=504)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NT-proBNP (pg/mL)</strong></td>
<td>4658 (2206, 9679)</td>
<td>3861(1879, 7783)</td>
<td>5031 (2200, 11000)</td>
<td>4799 (2413, 9247)</td>
<td>4000 (1487, 9140)</td>
<td>0.001 NP</td>
</tr>
<tr>
<td><strong>BUN (mg/dL)</strong></td>
<td>24.8 (18.0, 37.2)</td>
<td>24.1 (18.0, 36.1)</td>
<td>39.1 (23.1, 55.1)</td>
<td>24.1 (17.0, 34.1)</td>
<td>24.1 (12.8, 52.8)</td>
<td>0.001 NP</td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mmHg)</strong></td>
<td>120 (100, 134)</td>
<td>120 (100, 134)</td>
<td>120 (110, 140)</td>
<td>124 (110, 140)</td>
<td>124 (110, 140)</td>
<td>0.001 NP</td>
</tr>
<tr>
<td><strong>Creatinine (mg/dL)</strong></td>
<td>1.0 (0.8, 1.5)</td>
<td>1.0 (0.8, 1.5)</td>
<td>1.0 (0.8, 1.5)</td>
<td>1.0 (0.8, 1.5)</td>
<td>1.0 (0.8, 1.5)</td>
<td>0.001 NP</td>
</tr>
<tr>
<td><strong>Dyspnea</strong></td>
<td>1103 (62.6%)</td>
<td>711 (73.5%)</td>
<td>429 (64.5%)</td>
<td>1824 (56.3%)</td>
<td>348 (69.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Nocturnal dyspnea</strong></td>
<td>659 (37.4%)</td>
<td>256 (26.5%)</td>
<td>236 (35.5%)</td>
<td>1418 (43.7%)</td>
<td>156 (31.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Orthopnea</strong></td>
<td>1117 (63.6%)</td>
<td>625 (64.6%)</td>
<td>473 (71.2%)</td>
<td>1962 (60.6%)</td>
<td>272 (52.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Peripheral Edema</strong></td>
<td>971 (55.1%)</td>
<td>783 (81.0%)</td>
<td>540 (81.2%)</td>
<td>2674 (82.5%)</td>
<td>362 (71.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Weight Gain</strong></td>
<td>804 (45.8%)</td>
<td>642 (66.7%)</td>
<td>455 (68.4%)</td>
<td>2444 (75.5%)</td>
<td>328 (65.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Weight Loss</strong></td>
<td>1527 (86.7%)</td>
<td>901 (93.2%)</td>
<td>638 (95.9%)</td>
<td>2669/3240 (82.4%)</td>
<td>466 (92.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Pulmonary edema</strong></td>
<td>1527</td>
<td>901</td>
<td>638</td>
<td>2669</td>
<td>466</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Pulmonary edema</strong></td>
<td>516 (33.8%)</td>
<td>404 (44.4%)</td>
<td>233 (36.5%)</td>
<td>1130 (42.3%)</td>
<td>184 (39.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>&lt; 1/3 lung fields</strong></td>
<td>1011 (66.2%)</td>
<td>497 (55.2%)</td>
<td>405 (63.5%)</td>
<td>1539 (57.7%)</td>
<td>282 (60.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mmHg)</strong></td>
<td>120 (110, 134)</td>
<td>130 (116, 140)</td>
<td>120 (110, 140)</td>
<td>124 (110, 140)</td>
<td>124 (110, 140)</td>
<td>0.001 NP</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure (mmHg)</strong></td>
<td>76 (70, 80)</td>
<td>80 (70, 80)</td>
<td>70 (70, 80)</td>
<td>72 (64, 83)</td>
<td>70 (60, 80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Respiration rate (breaths/min)</strong></td>
<td>24 (22, 26)</td>
<td>24 (22, 26)</td>
<td>24 (22, 26)</td>
<td>22 (20, 24)</td>
<td>23 (20, 26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Heart rate (beats/min)</strong></td>
<td>88 (78, 99)</td>
<td>84 (72, 98)</td>
<td>80 (70, 94)</td>
<td>80 (70, 91)</td>
<td>80 (69, 92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>62.5 (54.0, 72.0)</td>
<td>83.9 (73.0, 97.3)</td>
<td>73.0 (62.0, 84.0)</td>
<td>87.4 (73.0, 106)</td>
<td>80.0 (68.8, 92.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>23.7 (21.0, 26.7)</td>
<td>28.9 (25.6, 33.3)</td>
<td>27.0 (23.9, 31.1)</td>
<td>29.9 (25.5, 35.5)</td>
<td>27.7 (24.2, 31.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

All data are shown as n (%) or median (Q1, Q3) unless otherwise specified.

**BMI** = body mass index; **BNP** = brain natriuretic peptide; **BUN** = blood urea nitrogen; **CABG** = coronary artery bypass grafting; **NP** = nonparametric test; **NT-proBNP** = N-terminal pro brain natriuretic peptide; **NYHA** = New York Heart Association; **PCI** = percutaneous coronary intervention.
with acute decompensated HF (ADHF). It was a global, clinical trial, which included patients from each of the 5 major geographical regions of the world. Importantly, it was the first large-scale acute HF trial to enroll patients from the AP region. Compared with previous analyses of geographical differences in HF trials, the fairly large sample sizes from each of the world regions allowed a robust analysis of the impact of geographical area on the clinical characteristics and outcomes of patients with acute HF.

**Methods**

The design and results of the ASCEND-HF trial have been reported previously. Briefly, the trial was an international, double-blind, placebo-controlled study evaluating the effectiveness and safety of nesiritide in addition to standard care versus standard care alone in 7,141 patients with ADHF. The trial was conducted from May 2007 to August 2010 at 398 centers in 30 countries throughout the world. Detailed inclusion and exclusion criteria have been described elsewhere. The 2 primary end points were a composite end point of all-cause mortality or HF readmission up to 30 days after randomization and the change in early dyspnea relief after study drug initiation.

Data on patient characteristics were collected during the baseline hospitalization. Rehospitalization and fatal events within 30 days after randomization were reviewed and categorized by an independent, blinded Clinical Events Committee. HF hospitalization was classified as previously described. In brief, HF hospitalization required typical treatment for worsening HF. All-cause mortality was assessed through 180 days.

Enrollment took place in 30 countries in NA, LA, Europe, Asia, and Australia. For this analysis, countries were assigned to 1 of 5 geographical regions based on previous work: North America (NA) included the USA and Canada; LA included Argentina, Chile, Colombia, Brazil, and Mexico; WE included France, Germany, Greece, the Netherlands, Italy, Israel, Norway, Sweden, and the United Kingdom; CE included Bulgaria, Czech Republic, Lithuania, Poland, Romania, and Ukraine; and AP included Australia, India, China, Malaysia, New Zealand, Korea, Singapore, Taiwan, and Thailand.

Patients from different geographical areas were compared with respect to demographic, clinical, and laboratory data and clinical outcomes. All data are shown as median (interquartile range) or n (%) unless otherwise specified. Outcomes of interest included length of the initial hospital stay (LOS), and the 30-day postrandomization outcome of all-cause mortality or HF hospitalization, and all-cause mortality. In addition, we assessed 180-day mortality by world region. For mortality and rehospitalization
Table 3 Medication and device use at discharge in the subgroup of patients with LVEF \( \leq 40\% \)^a

<table>
<thead>
<tr>
<th></th>
<th>Asia / Pacific (n=1416)</th>
<th>Central Europe (n=581)</th>
<th>Latin America (n=324)</th>
<th>North America (n=1838)</th>
<th>Western Europe (n=181)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loop Diuretics</td>
<td>1200/1401 (85.7%)</td>
<td>503/562 (89.5%)</td>
<td>283/323 (87.6%)</td>
<td>1665/1821 (91.4%)</td>
<td>169/180 (93.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total daily loop diuretic dose, mg</td>
<td>40 (40, 80)</td>
<td>40 (40, 120)</td>
<td>40 (40, 80)</td>
<td>80 (40, 160)</td>
<td>60 (8, 125)</td>
<td>&lt;0.001 NP</td>
</tr>
<tr>
<td>ACE Inhibitor/ARB</td>
<td>68.5%</td>
<td>74.9%</td>
<td>71.3%</td>
<td>1150/1837 (62.6%)</td>
<td>75.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aldosterone antagonist†</td>
<td>624/1320 (47.3%)</td>
<td>335/466 (71.9%)</td>
<td>168/265 (63.4%)</td>
<td>601/1799 (33.4%)</td>
<td>97/172 (56.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>52.3%</td>
<td>73.1%</td>
<td>52.2%</td>
<td>1333/1837 (72.6%)</td>
<td>72.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Digoxin</td>
<td>47.7%</td>
<td>34.6%</td>
<td>39.8%</td>
<td>508/1837 (27.7%)</td>
<td>24.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>1.8%</td>
<td>0.3%</td>
<td>6.2%</td>
<td>16.5%</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>8.2%</td>
<td>34.9%</td>
<td>18.8%</td>
<td>40.3%</td>
<td>14.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oral/Topical Nitrates</td>
<td>32.6%</td>
<td>12.9%</td>
<td>12.3%</td>
<td>23.2%</td>
<td>14.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Implantable cardioverter Defibrillator</td>
<td>6/1321 (0.5%)</td>
<td>24/466 (5.2%)</td>
<td>4/265 (1.5%)</td>
<td>413/1799 (23.0%)</td>
<td>18/172 (10.5%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Denominator as per the column heading unless otherwise noted.
† LVEF cutoff ≤35% for aldosterone antagonists and ICD.

Table 4 Patient outcomes by region

<table>
<thead>
<tr>
<th></th>
<th>Asia / Pacific (n=1762)</th>
<th>Central Europe (n=967)</th>
<th>Latin America (n=665)</th>
<th>North America (n=3243)</th>
<th>Western Europe (n=504)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of hospitalization, days</td>
<td>5.0 (4.0, 9.0)</td>
<td>10.0 (8.0, 15.0)</td>
<td>6.0 (4.0, 8.0)</td>
<td>5.0 (4.0, 8.0)</td>
<td>8.0 (5.0, 11.0)</td>
<td>&lt; 0.001 NP</td>
</tr>
<tr>
<td>Mortality or HF rehospitalization at 30-days</td>
<td>125 (7.5%)</td>
<td>49 (5.1%)</td>
<td>71 (11.0%)</td>
<td>404 (12.7%)</td>
<td>37 (7.7%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mortality at 30-days</td>
<td>66 (3.8%)</td>
<td>30 (3.1%)</td>
<td>43 (6.5%)</td>
<td>111 (3.4%)</td>
<td>23 (4.6%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Mortality at 180-days</td>
<td>200 (11.6%)</td>
<td>88 (9.3%)</td>
<td>112 (17.3%)</td>
<td>426 (13.3%)</td>
<td>74 (15.1%)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Data are shown as median (interquartile range) or n (%).

patients from AP and CE compared with other regions. Nearly, all subjects from Europe versus 64% of those from NA were white. Black and Hispanic patients were 32.1% and 6.5%, respectively, of the subjects from NA, Asian patients constituted 97.2% of the subjects from AP, and Hispanic patients constituted 97.3% of those from LA.

The proportion of subjects with a history of coronary artery disease (CAD) was higher in the patients from CE, NA, and WE versus subjects from AP and LA. Previous percutaneous coronary intervention was most common in NA and WE, whereas other regions such as CE had less previous percutaneous coronary intervention despite the high prevalence of CAD and previous myocardial infarction. A history of hypertension was also more common in the subjects from NA, LA, CE, and WE compared with those from AP. The proportions of patients with atrial fibrillation were highest in CE (57%) and lowest in AP (17%). Other co-morbidities, such as chronic respiratory disease and cerebrovascular disease were also more frequent in patients from NA, WE, and CE than in LA and AP. An exception was the prevalence of diabetes, which was similarly high in AP (42%) as compared with other regions (29% to 49%).

Systolic blood pressure at baseline was higher in the patients from CE (median 130 mm Hg) versus patients in NA and WE (124 mm Hg in both regions) and patients from LA and AP (median 120 mm Hg). Heart rate was higher in patients from AP and CE compared with other regions.

Patients from AP were younger than in other world regions. Nearly, all subjects from Europe versus 64% of those from NA were white. Black and Hispanic patients were 32.1% and 6.5%, respectively, of the subjects from NA, Asian patients constituted 97.2% of the subjects from AP, and Hispanic patients constituted 97.3% of those from LA.

The proportion of subjects with a history of coronary artery disease (CAD) was higher in the patients from CE, NA, and WE versus subjects from AP and LA. Previous percutaneous coronary intervention was most common in NA and WE, whereas other regions such as CE had less previous percutaneous coronary intervention despite the high prevalence of CAD and previous myocardial infarction. A history of hypertension was also more common in the subjects from NA, LA, CE, and WE compared with those from AP. The proportions of patients with atrial fibrillation were highest in CE (57%) and lowest in AP (17%). Other co-morbidities, such as chronic respiratory disease and cerebrovascular disease were also more frequent in patients from NA, WE, and CE than in LA and AP. An exception was the prevalence of diabetes, which was similarly high in AP (42%) as compared with other regions (29% to 49%).

Systolic blood pressure at baseline was higher in the patients from CE (median 130 mm Hg) versus patients in NA and WE (124 mm Hg in both regions) and patients from LA and AP (median 120 mm Hg). Heart rate was higher in patients from AP and CE compared with other regions.
Heart Failure/Geographic Differences in ASCEND-HF

Table 5

<table>
<thead>
<tr>
<th>Region</th>
<th>Death / HF rehospitalization at day 30 OR (95% CI)</th>
<th>Death at day 30 OR (95% CI)</th>
<th>Death at 180-days HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia-Pacific</td>
<td>0.62 (0.48, 0.79)</td>
<td>0.93 (0.67, 1.31)</td>
<td>0.77 (0.63, 0.94)</td>
</tr>
<tr>
<td>Central Europe</td>
<td>0.46 (0.33, 0.64)</td>
<td>0.87 (0.57, 1.32)</td>
<td>0.67 (0.52, 0.86)</td>
</tr>
<tr>
<td>Latin America</td>
<td>0.77 (0.57, 1.04)</td>
<td>1.10 (0.75, 1.62)</td>
<td>0.85 (0.66, 1.08)</td>
</tr>
<tr>
<td>Western Europe</td>
<td>0.52 (0.35, 0.75)</td>
<td>0.82 (0.51, 1.32)</td>
<td>0.77 (0.58, 1.01)</td>
</tr>
<tr>
<td>Overall P-value</td>
<td>&lt;0.00001</td>
<td>0.66</td>
<td>0.0011</td>
</tr>
</tbody>
</table>

* Adjustment variables as follows: mortality 30 days and 1 to 180 days: age, baseline BUN (log), sodium, systolic blood pressure dichotomized at 140 mm Hg, and dyspnea (at rest vs moderate exercise); death/HF hospitalization 30 days: age (dichotomized at 55y), baseline BUN (log), cerebrovascular disease, creatinine (log), depression, dyspnea (at rest vs moderate exercise), HF hospitalization in last year, qualifying episode jugular venous distension (yes/no), sodium (continuous and truncated at 140), systolic blood pressure dichotomized 140, and baseline chronic respiratory disease.

Despite fairly similar median creatinine values across world regions, patients from LA and WE had higher values of serum blood urea nitrogen. Serum N-terminal pro brain natriuretic peptide (NT-proBNP) plasma levels were slightly higher in the patients from LA, NA, and AP compared with the patients from Europe. QRS duration was longer in patients from WE and NA compared with other regions. Median left ventricular ejection fraction (LVEF) was slightly lower in NA and AP.

Medication and device use data are presented in Table 2 (all patients) and Table 3 (patients with known reduced LVEF). Table 4 and Figure 1 present outcomes data by region. After risk adjustment (Table 5), death through 30 days did not significantly differ across world regions, whereas 30-day mortality or HF hospitalization and 180-day deaths were comparatively greater in NA. Lost-to-follow-up (LTFU) numbers at 30 days also varied by world region with the lowest LTFU in NA at 39 (1.2%) and higher LTFU numbers in other world regions: 36 (1.7%) in CE, 36 (2.0%) in AP, 14 (2.1%) in LA, and 12 (2.4%) in WE.

Discussion

Our study shows major differences in the clinical characteristics, medications, 30-day rehospitalization rates, and 180-day mortality between patients with ADHF enrolled from different geographical areas. Compared with previous studies of regional differences, this was the first global ADHF trial including patients from the AP region and, differently from recent trials, patients from NA are largely represented.

Globalization of randomized clinical trials for the assessment of new therapies is a hallmark of current research. It is therefore critical to assess potential differences in the characteristics, treatment, and outcomes between the patients from different geographical areas. This issue has been assessed both in retrospective analyses of HF randomized controlled trials and in registries of patients with HF or may or may not have an influence on the effects of drug treatment. For instance, in the primary publication of the ASCEND trial, enrolling location was the only subgroup analysis that demonstrated a differential association with the primary end point of all-cause death or HF rehospitalization through 30 days as LA location favored nesiritide over placebo. Importantly, despite being prespecified, these data should be viewed as hypothesis-generating given the large number of subgroups tested and the potential for statistical chance.

Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) was the first trial in ADHF with a large number of patients enrolled from Eastern Europe. It showed meaningful differences with the patients from Eastern Europe having the highest values of systolic blood pressure and LVEF and the lowest values of serum blood urea nitrogen and NT-proBNP plasma levels and, accordingly, the best outcomes. Similar data were found in the present analysis of the ASCEND-HF trial although with less marked differences. In the recent Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT) analysis, lower short-term rehospitalization and similar mortality was also seen in Eastern Europe as compared with WE. Thus, data support a consistent finding of marked regional differences in short-term clinical outcomes that are driven by rehospitalization.

Unlike previous studies, ASCEND-HF was the first ADHF trial in which patients from the AP area were included, with 97.2% of these patients of Asian ethnicity. Distinct characteristics were found in this geographical area. Patients from AP were younger, were less likely to have hypertension, CAD, and other co-morbidities, except for diabetes, and were less likely to receive angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and β blockers. These findings confirm previous surveys from this area. Despite these differences, and differently from what was suggested by other studies, outcomes of the patients from AP were similar to other areas. It is possible that the favorable effects of lower age and less co-morbidities were counterbalanced by the untoward effects of the lower use of HF therapies. These findings are distinct from the Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT) study which showed the highest risk for mortality in the AP region. Importantly, the AP population in ASTRONAUT was different from ASCEND with significantly more ischemic origin (78% vs 48% in ASCEND) and restriction to HF with reduced LVEF in ASTRONAUT.

The present analysis extends the findings of an earlier assessment of global variation in quality of care in ASCEND-HF. The previous analysis focused on regional differences in discharge quality indicators such as medication and device use as well as blood pressure control. In terms of meeting performance opportunities, there were regional differences observed with CE highest at 64% conformity with quality of care targets, followed by NA (63%), WE (61%), LA (56%), and AP (51%; p <0.0001). This previous analysis did not explore potential implications on clinical outcomes as in the present analysis.
The present study shows an important geographic difference between LOS, rehospitalizations, and mortality as outcome measurements in ADHF trials. Although LOS and rehospitalization rates were highly dependent on geographical differences, short-term mortality rates after risk adjustment were not. Early postdischarge rehospitalization rates are influenced by many variables, such as co-morbidities and social factors, not necessarily related with the severity of HF. The poor correlation between 30-day rehospitalization rates and 30-day mortality rates has been shown in previous analyses. These observations may be due in part to the increased co-morbidity burden in NA as well as additional markers of increased disease severity such as lower blood pressure and EF as well as higher NT-proBNP level and wider QRS. Moreover, the usage of angiotensin-converting enzyme inhibitors and aldosterone antagonists was lower in NA compared with other regions despite lower EF likely related to lower blood pressure and worse renal function as well as differential prescribing patterns in the context of shorter LOS as seen previously. These risk factors may have led to increased mortality in NA despite protective effects related to higher usage of implantable cardioverter defibrillators (ICDs). We adjusted the clinical outcomes based on previously established covariate lists that have been consistently used in the ASCEND data set. However, both recognized and unrecognized factors, which were not adjusted for may have influenced these results, and we cannot rule out residual confounding. For instance, there may have also been underreporting of mortality in some regions given differential LTFU across enrolling regions.

Future trials could consider specifying requirements for background guideline-directed medical therapy before trial start.
enrollment. Although these recommendations would provide
support for the argument that a novel therapy provides
incremental benefit beyond current standard of care, this
approach also has limitations. For instance, prescriptive trial
entry criteria for specific medications are a challenge when
costs for these background therapies are not covered as part
of trial involvement. These considerations are particularly
relevant in geographical regions without universal health
care systems and with variable medication coverage.
Moreover, questions of generalizability of study results can
arise when background therapies in the setting of a trial are
distinct from usual care.

The present findings also highlight the importance of
recognizing these regional differences when selecting sites
for a future trial. For earlier phase investigation, it may be
necessary to select sites from specific world regions to enroll
patients with the underlying substrate considered as the most
sensitive to the effects of the novel therapy. For instance,
certain myocardial-targeting drugs could work more favorably
in those patients with larger areas of viable myocardium.
Moreover, the regional differences should also be
recognized when selecting trial end points and determining
appropriate enrolling regions. Differential use of ICDs in-
fluences mode of death and the prevalence of co-morbidities
influences the proportion of noncardiovascular clinical
events which both may affect a study’s statistical power.
Future studies could consider either stratification by region
or inclusion of region as an adjustment factor for outcomes
involving rehospitalization or hospital LOS. Although short-
term mortality rates across regions were similar after
adjustment, regional differences in long-term event rates
suggest that it might be wise when designing clinical trials
to consider these differences when calculating sample size
or determining the distribution of subjects between regions.
This was a retrospective analysis from a clinical trial with
specific entry criteria such that generalizability is uncertain.
However, ASCEND represents that largest ADHF data set
to date and has larger representation of each of the world
regions compared with many earlier analyses. We defined
the different geographical regions based on previous studies,
but regional differences exist even within these groupings.

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Supplementary Data

Supplementary data associated with this article can be
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