# International Geographic Variation in Event Rates in Trials of Heart Failure With Preserved and Reduced Ejection Fraction

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***Background***—International geographic differences in outcomes may exist for clinical trials of heart failure and reduced ejection fraction (HF-REF), but there are few data for those with preserved ejection fraction (HF-PEF).

***Methods and Results***—We analyzed outcomes by international geographic region in the Irbesartan in Heart Failure with Preserved systolic function trial (I-Preserve), the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM)-Preserved trial, the CHARM-Alternative and CHARM–Added HF-REF trials, and the Controlled Rosuvastatin Multinational Trial in HF-REF (CORONA). Crude rates of heart failure hospitalization varied by geographic region, and more so for HF-PEF than for HF-REF. Rates in patients with HF-PEF were highest in the United States/Canada (HF hospitalization rate 7.6 per 100 patient-years in I-Preserve; 8.8 in CHARM-Preserved), intermediate in Western Europe (4.8/100 and 4.7/100), and lowest in Eastern Europe/Russia (3.3/100 and 2.8/100). The difference between the United States/Canada versus Eastern Europe/Russia persisted after adjustment for key prognostic variables: adjusted hazard ratios 1.34 (95% confidence interval, 1.01–1.74; *P*=0.04) in I-Preserve and 1.85 (95% confidence interval, 1.17–2.91; *P*=0.01) in CHARM-Preserved. In HF-REF, rates of HF hospitalization were slightly lower in Western Europe compared with other regions. For both HF-REF and HF-PEF, there were few regional differences in rates of all-cause or cardiovascular mortality.

***Conclusions***—The differences in event rates observed suggest there is international geographic variation in 1 or more of the definition and diagnosis of HF-PEF, the risk profile of patients enrolled, and the threshold for hospitalization, which has implications for the conduct of future global trials. **(*Circulation*. 2015;131:43-53. DOI: 10.1161/CIRCULATIONAHA.114.012284.)**

**Key Words:** heart failure ■ hospitalization ■ mortality ■ ventricular ejection fraction



Recently, international regional differences in rates of mortality and morbidity in patients with chronic heart failure have been highlighted, as were the potential implications of these for the evaluation of the effects of treatments.[1–5] Specifically, in the Treatment of Preserved Cardiac Function with an Aldosterone Antagonist Trial (TOPCAT), the occurrence of the primary composite end point of cardiovascular death, hospitalization for heart failure, or resuscitation from cardiac arrest (which was a minor component) was much less common in patients from Russia or Georgia (unadjusted rate of 2.3 per 100 patient years in the placebo group) than in those enrolled in the United States, Canada, Argentina, or Brazil ("the Americas", 12.6 per 100 patient years).[5] This observation raises

**Editorial see p 7**
**Clinical Perspective on p 53**

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2 important questions. Firstly, was this a trial-specific concern in TOPCAT, or is it a more general issue in heart failure trials? Secondly, might this have been a problem specific to (or magnified in) heart failure with preserved ejection fraction (HF-PEF), given the greater difficulty in defining this type of heart failure than heart failure with reduced ejection fraction (HF-REF)?[6] To try and answer these questions, we have examined event rates in a number of other trials in both HF-PEF and HF-REF.[7–11]

## Methods

We analyzed event rates of patients in the Irbesartan in Heart Failure with Preserved systolic function (I-Preserve), and in the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM)-preserved trials, the only other large trials in HF-PEF (in addition to TOPCAT) that included patients from both Europe and North America. We also analyzed the CHARM–Alternative and CHARM–Added trials, as well as the Controlled Rosuvastatin Multinational Trial in HF (CORONA) trial, which enrolled patients with HF-REF. The design and principal findings of all of these trials have been reported.[7–11]

### Patients

The CHARM program consisted of 3 trials comparing candesartan with placebo in subjects with symptomatic HF (New York Heart Association [NYHA] class II–IV). In the present analysis, we pooled the 2 CHARM HF-REF trials, which enrolled patients with a left ventricular ejection fraction (LVEF) ≤40%. The CHARM-Alternative trial enrolled subjects with intolerance of an angiotensin-converting enzyme inhibitor, and the CHARM-Added trial enrolled subjects who were treated with an angiotensin-converting enzyme inhibitor at baseline. The CHARM-Preserved trial enrolled subjects with LVEF >40%, all of which had a history of cardiovascular (CV) hospitalization. However, for the present analysis, we only included patients from CHARM-Preserved with a LVEF ≥45% so as to create a population similar to I-Preserve (see below). The primary end point used in the overall CHARM program was all-cause mortality, whereas that for each of the component trials was the composite of CV death or HF hospitalization. The median follow-up for the overall program was 37.7 months. I-Preserve randomized subjects with HF-PEF to irbesartan or placebo. The inclusion criteria included LVEF ≥45%, age ≥60 years, and NYHA class II through IV symptoms and hospitalization for HF within the previous 6 months or NYHA class III through IV symptoms and ≥1 of an abnormal chest radiograph (pulmonary congestion), ECG (left ventricular hypertrophy or left bundle-branch block), or echocardiogram (left ventricular hypertrophy or enlarged left atrium). The primary outcome used in the I-Preserve trial was a composite of all-cause mortality or CV hospitalization, and the mean follow-up was 49.5 months.

CORONA compared rosuvastatin with placebo in patients ≥60 years of age with chronic HF-REF attributed to ischemic heart disease, who were in NYHA class II through IV, with a LVEF ≤40% (≤35% if NYHA II). The subjects enrolled were followed for a median of 32.8 months, and the primary end point in the CORONA trial was a composite of CV death, nonfatal myocardial infarction, or nonfatal stroke.

### Region

For each trial, we grouped patients according to region: (1) Eastern Europe and Russia, (2) Western Europe, (3) United States and Canada (no patients in CORONA), and (4) Latin America (only patients from I-Preserve). The countries within each region from which patients were recruited varied slightly according to trial, and are listed in Table I in the online-only Data Supplement. Patients from South Africa (all trials), Australia, Malaysia, and Singapore (CHARM trials) were excluded from the present analyses.

### Clinical Outcome

In this analysis, we evaluated all-cause mortality, the composite end point of CV death and hospitalization for heart failure, as well as CV death and hospitalization for heart failure separately in each of the included trials. Maximal length of follow-up was 70 months in I-Preserve, 48 months in all 3 studies of the CHARM program, and 44 months in CORONA. All analyses were performed as time to first event. These end points were defined using similar prespecified criteria in each trial as part of either the original primary or a secondary end point. In each trial the end points were adjudicated by an independent end point validation committee. Confirmation of heart failure hospitalization required patients to have typical symptoms and signs and intensification of heart failure therapy on admission. In CHARM and CORONA, intravenous therapy was required whereas intensification of oral therapy was also acceptable in I-Preserve, although we believe few cases were confirmed on this basis.

### Statistical Analysis

Baseline characteristics are presented as means with standard deviations for continuous variables and frequencies and percentages for categorical variables. For all outcomes, patients lost to follow-up were censored at last day known to be alive, and for analyses of HF hospitalization outcome, patients who died were censored. Unadjusted event rates were reported per 100 patient years of follow-up according to recruitment region. Cox proportional hazard models were used to calculate hazard ratios for other regions compared with Eastern Europe/Russia, adjusting for age, sex, race (white versus all other race), heart rate, systolic blood pressure, body mass index, NYHA class, LVEF, ischemic etiology and history of diabetes, atrial fibrillation, stroke, and coronary revascularization. Some other potentially important predictive variables were not available in all trials (eg, history of heart failure hospitalization, creatinine, natriuretic peptides). Only predictive variables available in every trial were included in the adjusted model. Although the proportion of nonwhite participants in CORONA was low (0.4%), excluding race from the model for CORONA did not change the results. Therefore, race was left in the model for consistency. The assumptions of the Cox model (proportional hazard, linearity of continuous variables, and no interactions) were tested and the models were found to be valid. We compared rates within each trial to avoid confounding regional differences with trial differences. Cumulative incidence curves were constructed for the composite of CV death and hospitalization for heart failure, as well as for all-cause mortality according to region for each trial.

N-terminal pro B-type natriuretic peptide (NT pro-BNP) levels were available in a subset of patients in I-Preserve (3418 patients, 542 who were hospitalized at least once for heart failure). In an ancillary analysis, we adjusted the hazard ratio (HR) of heart failure hospitalization for baseline NT pro-BNP level, in addition to the variables mentioned above. All $P$ values are 2-sided, and a $P$ value of <0.05 was considered significant. All analyses were performed using Stata version 11 (Stata Corp. College Station, TX).

## Results

### Baseline Characteristics

The baseline characteristics of the patients enrolled in the trials in HF-PEF and HF-REF are shown by region in Tables 1 and 2 (HF-PEF) and Tables 3 and 4 (HF-REF).

### HF-PEF Trials

By design, patients in I-Preserve (Table 1) were older than those in CHARM-Preserved (Table 2) and more likely to be in NYHA class III or IV. They were also more likely to be female and have a history of hypertension but less likely to have an ischemic etiology. Patients in I-Preserve were more often treated with diuretics and mineralocorticoid receptor antagonists but less often treated with digoxin (despite a similar prevalence of atrial fibrillation). Within each trial, there were notable international geographic differences in baseline characteristics. For example, in CHARM-Preserved ischemic etiology was much more common in Eastern Europe/Russia (and this was also true, but to a lesser extent, in

**Table 1. Baseline Characteristics of Patients in I-Preserve Overall and According to Region of Randomization**

| | All Patients | Eastern Europe and Russia | Western Europe | United States and Canada | Latin America | *P* Value |
|---|---|---|---|---|---|---|
| I-Preserve | 4080 | 1480 | 1499 | 385 | 716 | |
| Age, mean y | 71.7±7.0 | 69.4±5.7 | 73.3±7.1 | 73.4±7.7 | 71.9±7.2 | <0.0001 |
| Female sex, n (%) | 2461 (60.3%) | 903 (61.0%) | 855 (57.0%) | 198 (51.4%) | 505 (70.5%) | <0.0001 |
| Race, n (%) | | | | | | <0.0001 |
| White | 3846 (94.3%) | 1480 (100%) | 1492 (99.5%) | 348 (90.4%) | 526 (73.5%) | |
| Black | 73 (1.8%) | 0 (0%) | 2 (0.1%) | 32 (8.3%) | 39 (5.4%) | |
| Other | 161 (3.9%) | 0 (0%) | 5 (0.3%) | 5 (1.3%) | 151 (21.1%) | |
| Ejection fraction | 0.59±0.09 | 0.58±0.08 | 0.60±0.10 | 0.59±0.08 | 0.60±0.09 | <0.0001 |
| NYHA class | | | | | | <0.0001 |
| I | 1 (0%) | 0 (0%) | 0 (0%) | 1 (0.3%) | 0 (0%) | |
| II | 868 (21.3%) | 342 (23.1%) | 370 (24.7%) | 91 (23.6%) | 65 (9.1%) | |
| III | 3098 (75.9%) | 1096 (74.1%) | 1105 (73.7%) | 285 (74.0%) | 612 (85.5%) | |
| IV | 112 (2.7%) | 41 (2.8%) | 24 (1.6%) | 8 (2.1%) | 39 (5.4%) | |
| Heart rate, bpm | 72±10 | 72±9 | 71±11 | 71±11 | 71±11 | 0.1402 |
| Systolic blood pressure, mm Hg | 136.4±15.0 | 137.1±12.2 | 137.6±16.3 | 131.6±17.9 | 134.9±15.0 | <0.0001 |
| Body mass index | 29.6±5.3 | 29.2±4.4 | 29.3±5.1 | 32.5±7.3 | 29.6±5.5 | <0.0001 |
| NT pro-BNP, median<br>Q1–Q3 | 341<br>133–967 | 277<br>117–757 | 427<br>155–1086 | 633<br>224–1431 | 268<br>111–820 | <0.0001 |
| eGFR, –l/min/1.73m$^2$ | 68.5±19.1 | 73.2±17.0 | 68.3±19.6 | 58.8±20.1 | 64.4±18.8 | <0.0001 |
| Ischemic etiology | 1012 (24.8%) | 479 (32.4%) | 363 (24.2%) | 92 (23.9%) | 78 (10.9%) | <0.0001 |
| Hypertensive etiology | 2608 (63.9%) | 927 (62.6%) | 875 (58.4%) | 198 (51.4%) | 608 (84.9%) | <0.0001 |
| Medical history, n (%) | | | | | | |
| Hypertension | 3610 (88.5%) | 1374 (92.8%) | 1226 (81.8%) | 331 (86.0%) | 679 (94.8%) | <0.0001 |
| Atrial fibrillation | 1206 (29.6%) | 357 (24.1%) | 553 (36.9%) | 161 (41.8%) | 135 (18.9%) | <0.0001 |
| Diabetes mellitus | 1115 (27.3%) | 338 (22.8%) | 434 (29.0%) | 160 (41.6%) | 183 (25.6%) | <0.0001 |
| Stroke | 396 (9.7%) | 110 (7.4%) | 169 (11.3%) | 59 (15.3%) | 58 (8.1%) | <0.0001 |
| PCI or CABG | 532 (13.0%) | 51 (3.4%) | 304 (20.3%) | 139 (36.1%) | 38 (5.3%) | <0.0001 |
| ICD | 12 (0.3%) | 0 (0.0%) | 7 (0.5%) | 4 (1.0%) | 1 (0.1%) | 0.0033 |
| CRT/PM | 252 (6.2%) | 36 (2.4%) | 137 (9.1%) | 51 (13.2%) | 28 (3.9%) | <0.0001 |
| Medication, n (%) | | | | | | |
| Loop-diuretic | 3382 (83.0%) | 1380 (93.2%) | 1151 (76.9%) | 328 (85.4%) | 523 (73.0%) | <0.0001 |
| ACEi/ARB | 1020 (25.0%) | 350 (23.6%) | 384 (25.7%) | 107 (27.9%) | 179 (25.0%) | 0.3262 |
| β-Blocker | 2394 (58.7%) | 1033 (69.8%) | 802 (53.6%) | 244 (63.5%) | 315 (44.0% | <0.0001 |
| Mineralocorticoid receptor antagonist | 630 (25.5%) | 261 (17.6%) | 239 (16.0%) | 51 (13.3%) | 79 (11.0%) | 0.0005 |
| Digoxin | 558 (13.7%) | 195 (13.2%) | 224 (15.0%) | 51 (13.3%) | 88 (12.3%) | 0.3046 |

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; I-Preserve, Irbesartan in Heart Failure with Preserved systolic function; NT pro-BNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; and PM, pacemaker.



I-Preserve). Patients randomized in Eastern Europe/Russia were youngest in both trials. In I-Preserve, the proportion of women varied by region (from 51.4% in USA/Canada to 70.2% in Latin America); however, in both CHARM-Preserved and I-Preserve the proportion of women was greater in Eastern Europe/Russia than in Western Europe. Patients in Eastern Europe/Russia had a lower prevalence of atrial fibrillation than in Western Europe or North America in both trials (lowest of all in Latin America in I-Preserve). The prevalence of diabetes mellitus was highest in North America in both trials, as was history of coronary revascularization. NT pro-BNP and estimated glomerular filtration rate also varied substantially with the former highest and latter lowest in the United States/Canada in I-Preserve (NT pro-BNP was not measured in CHARM-Preserved and estimated glomerular filtration rate was only measured in North American patients in CHARM-Preserved).

## HF-REF Trials

By design, patients in CORONA (Table 3) were older than in CHARM Alternative/Added (Table 4), and all patients in

**Table 2. Baseline Characteristics of Patients in CHARM-Preserved Overall and According to Region of Randomization to Region of Randomization**

| | All Patients | Eastern Europe and Russia | Western Europe | United States and Canada | *P* Value |
|---|---|---|---|---|---|
| CHARM-Preserved | 2401 | 274 | 1174 | 953 | |
| Age, mean y | 66.8±11.0 | 62.7±9.6 | 68.3±10.8 | 66.2±11.3 | <0.0001 |
| Female sex, n (%) | 1021 (42.5%) | 116 (42.3%) | 479 (40.8%) | 426 (44.7%) | 0.1941 |
| Race, n (%) | | | | | <0.0001 |
| White | 2254 (93.9%) | 274 (100%) | 1160 (100%) | 820 (86.0%) | |
| Black | 107 (4.5%) | 0 (0%) | 5 (0.4%) | 102 (10.7%) | |
| Other | 40 (1.7%) | 0 (0%) | 9 (0.8%) | 31 (3.3%) | |
| Ejection fraction | 0.56±0.09 | 0.54±0.08 | 0.56±0.09 | 0.57±0.08 | <0.0001 |
| NYHA class | | | | | <0.0001 |
| II | 1483 (61.8%) | 201 (73.4%) | 822 (70.0%) | 460 (48.3%) | |
| III | 878 (36.6%) | 71 (25.9%) | 336 (28.6%) | 471 (49.4%) | |
| IV | 40 (1.7%) | 2 (0.7%) | 16 (1.4%) | 22 (2.3%) | |
| Heart rate, bpm | 71±13 | 72±12 | 72±13 | 71±11 | 0.0437 |
| Systolic blood pressure, mm Hg | 136.6±18.7 | 136.0±17.4 | 139.1±19.3 | 133.7±17.7 | <0.0001 |
| Body mass index | 29.3±5.9 | 28.5±4.6 | 28.0±4.6 | 31.2±7.0 | <0.0001 |
| eGFR, –l/min/1.73m$^2$ | 72.4±25.5 | … | … | 72.4±25.5 | … |
| Ischemic etiology | 1293 (53.9%) | 200 (73.0%) | 638 (54.3%) | 469 (49.2%) | <0.0001 |
| Hypertensive etiology | 589 (24.5%) | 56 (20.4%) | 282 (24.0%) | 251 (26.3%) | 0.1150 |
| Medical history, n (%) | | | | | |
| Hypertension | 1573 (65.5%) | 199 (72.6%) | 638 (54.3%) | 736 (77.2%) | <0.0001 |
| Atrial fibrillation | 721 (30.0%) | 54 (19.7%) | 369 (31.4%) | 298 (31.3%) | 0.0004 |
| Diabetes mellitus | 668 (27.8%) | 59 (21.5%) | 233 (19.8%) | 376 (39.5%) | <0.0001 |
| Stroke | 206 (8.6%) | 23 (8.4%) | 89 (7.6%) | 94 (9.9%) | 0.1731 |
| PCI | 421 (17.5%) | 15 (5.5%) | 211 (18.0%) | 195 (20.5%) | <0.0001 |
| CABG | 497 (20.7%) | 19 (6.9%) | 218 (18.6%) | 260 (27.3%) | <0.0001 |
| ICD | 17 (0.7%) | 0 (0%) | 7 (0.6%) | 10 (1.0%) | 0.1540 |
| CRT/PM | 177 (7.4%) | 19 (6.9%) | 80 (6.8%) | 78 (8.2%) | 0.4646 |
| Medication, n (%) | | | | | |
| Loop-diuretic | 1789 (74.5%) | 193 (70.4%) | 810 (69.0%) | 786 (82.5%) | <0.0001 |
| ACEi/ARB | 437 (18.2%) | 18 (6.6%) | 184 (15.7%) | 235 (24.7%) | <0.0001 |
| β-Blocker | 1343 (55.9%) | 180 (65.7%) | 623 (53.1%) | 540 (56.7%) | 0.0006 |
| Mineralocorticoid receptor antagonist | 279 (11.6%) | 23 (8.4%) | 160 (13.6%) | 96 (10.1%) | 0.0082 |
| Digoxin | 641 (26.7%) | 58 (21.2%) | 275 (23.4%) | 308 (32.3%) | <0.0001 |

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CHARM-Preserved, Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity Preserved; CRT, cardiac resynchronization therapy; eGFR, estimated glomular filtration rate; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; and PM, pacemaker.

CORONA had an ischemic etiology. Patients in CORONA were more likely than those in CHARM-Alternative/Added to have a history of hypertension, atrial fibrillation, and stroke (but less likely to have had coronary revascularization). Patients in CORONA were more likely to be treated with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (ARB) (by design), a β-blocker, and a mineralocorticoid receptor antagonist (but less likely to be treated with digoxin) than those in CHARM-Alternative/Added. There were some international geographic differences within each trial. For example, patients in Eastern Europe/Russia were younger than in other regions and more often female in both trials. The proportion of patients in NYHA class II was smallest in Eastern Europe/Russia in CORONA, a trend that was also seen in CHARM. Mean LVEF and systolic blood pressure was higher in Eastern Europe/Russia than in other regions. History of coronary revascularization was less common in Eastern Europe/Russia than in other regions in both trials. There were also differences between regions in drug therapy. Mineralocorticoid receptor antagonist use was highest in Eastern Europe/Russia and digoxin use lowest in Western Europe, in both trials. The median NT pro-BNP level was similar in Eastern Europe/Russia and Western Europe in CORONA, the only HF-REF trial in which it was measured.

**Table 3. Baseline Characteristics of Patients in CORONA Overall and According to Region of Randomization**

| | All Patients | Eastern Europe and Russia | Western Europe | *P* Value |
|---|---|---|---|---|
| CORONA | 4897 | 2384 | 2513 | |
| Age, mean y | 72.8±7.1 | 71.1±6.6 | 74.3±7.1 | <0.0001 |
| Female sex, n (%) | 1142 (23.3%) | 605 (25.4%) | 537 (21.4%) | 0.0009 |
| Race, n (%) | | | | <0.0001 |
| White | 4870 (99.4%) | 2383 (100%) | 2487 (99.0%) | |
| Black | 10 (0.2%) | 1 (0.0%) | 9 (0.4%) | |
| Other | 17 (0.3%) | 0 (0.0%) | 17 (0.7%) | |
| Ejection fraction | 0.31±0.06 | 0.32±0.06 | 0.29±0.07 | <0.0001 |
| NYHA class | | | | <0.0001 |
| II | 1810 (37.0%) | 598 (25.1%) | 1212 (48.2%) | |
| III | 3015 (61.6%) | 1755 (73.6%) | 1260 (50.1%) | |
| IV | 72 (1.5%) | 31 (1.3%) | 41 (1.6%) | |
| Heart rate, bpm | 72±11 | 73±11 | 70±11 | <0.0001 |
| Systolic blood pressure, mm Hg | 129.4±16.3 | 130.4±14.4 | 128.4±17.9 | <0.0001 |
| Body mass index, units | 27.2±4.5 | 27.7±4.5 | 26.7±4.5 | <0.0001 |
| NT pro-BNP, median<br>Q1–Q3, units | 1431<br>609–3102 | 1421<br>568–2993 | 1437<br>631–3148 | 0.3375 |
| eGFR, –l/min/1.73m$^2$ | 54.5±14.6 | 57.2±13.8 | 52.0±14.9 | <0.0001 |
| Ischemic etiology | 4897 (100%) | 2384 (100%) | 2513 (100%) | … |
| Hypertensive etiology | 0 | 0 | 0 | … |
| Medical history, n (%) | | | | |
| Hypertension | 3092 (63.1%) | 1833 (76.9%) | 1259 (50.1%) | <0.0001 |
| Atrial fibrillation | 2023 (41.3%) | 997 (41.8%) | 1026 (40.8%) | 0.4807 |
| Diabetes mellitus | 1425 (29.1%) | 778 (32.6%) | 647 (25.7%) | <0.0001 |
| Stroke | 608 (12.4%) | 315 (13.2%) | 293 (11.7%) | 0.0994 |
| PCI | 565 (11.5%) | 155 (6.5%) | 410 (16.3%) | <0.0001 |
| CABG | 811 (18.2%) | 253 (11.2%) | 558 (25.4%) | <0.0001 |
| ICD | 135 (2.8%) | 15 (0.6%) | 120 (4.8%) | <0.0001 |
| CRT/PM | 553 (11.3%) | 245 (10.3%) | 308 (12.3%) | 0.0287 |
| Medication, n (%) | | | | |
| Loop-diuretic | 3694 (75.4%) | 1754 (74.5%) | 1940 (77.2%) | 0.0032 |
| ACEi/ARB | 4493 (91.8%) | 2176 (91.3%) | 2319 (92.2%) | 0.2394 |
| β-Blocker | 3644 (74.4%) | 1859 (78.0%) | 1785 (71.0%) | <0.0001 |
| Mineralocorticoid receptor antagonist | 1919 (39.2%) | 1095 (45.9%) | 824 (32.8%) | <0.0001 |
| Digoxin | 1619 (33.1%) | 873 (36.6%) | 746 (29.7%) | <0.0001 |

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CORONA, Controlled Rosuvastatin Multinational Trial in HF; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; NT pro-BNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; and PM, pacemaker.

## Clinical Outcomes

The rates of the clinical outcomes of interest, defined as the first in-trial event, are shown in Tables 5 and 6 and in Figures 1 and 2.

## HF-PEF trials

### *Unadjusted Event Rates*

The unadjusted rate of death from any cause (Table 5 and Figure I in the online-only Data Supplement) was higher in the United States/Canada and Western Europe compared with Eastern Europe/Russia in both CHARM-Preserved and I-Preserve (and in I-Preserve the all-cause mortality rate in Latin America was similar to Eastern Europe/Russia). The unadjusted rate of cardiovascular mortality was also higher in the United States/Canada and Western Europe than in Eastern Europe/Russia in CHARM-Preserved, whereas rates were similar in I-Preserve.

The international geographic differences in rates of first heart failure hospitalization were much more striking. These were by far the highest in the United States/Canada and lowest in Eastern Europe/Russia in both trials. The rate of heart failure hospitalization in Western Europe was intermediate but closer to Eastern Europe/Russia (and Latin America) than the United States/Canada.

The rate of the cardiovascular composite outcome reflected the geographic differences in its components.

**Table 4. Baseline Characteristics of Patients in CHARM-REF Overall and According to Region of Randomization**

| | All Patients | Eastern Europe and Russia | Western Europe | United States and Canada | *P* Value |
|---|---|---|---|---|---|
| CHARM-Alternative+Added, n | 4233 | 485 | 2117 | 1631 | |
| Age, mean y | 64.8±11.0 | 62.7±10.9 | 65.5±10.4 | 64.7±11.6 | <0.0001 |
| Female sex, n (%) | 1092 (25.8%) | 135 (27.8%) | 521 (24.6%) | 436 (26.7%) | 0.1869 |
| Race, n (%) | | | | | <0.0001 |
| White | 3940 (93.1%) | 484 (99.8%) | 2076 (98.1%) | 1380 (84.6%) | |
| Black | 191 (4.5%) | 0 (0.0%) | 8 (0.4%) | 183 (11.2%) | |
| Other | 102 (2.4%) | 1 (0.2%) | 33 (1.6%) | 68 (4.2%) | |
| Ejection fraction | 0.29±0.08 | 0.32±0.06 | 0.29±0.07 | 0.27±0.08 | <0.0001 |
| NYHA class, n (%) | | | | | <0.0001 |
| II | 1387 (32.8%) | 138 (28.5%) | 778 (36.8%) | 471 (28.9%) | |
| III | 2706 (63.9%) | 324 (66.8%) | 1272 (60.1%) | 1110 (68.1%) | |
| IV | 140 (3.3%) | 23 (4.7%) | 67 (3.2%) | 50 (3.1%) | |
| Heart rate, bpm | 74±13 | 76±14 | 74±14 | 73±12 | <0.0001 |
| Systolic blood pressure, mm Hg | 127.6±18.8 | 132.0±16.1 | 128.7±19.3 | 124.7±18.7 | <0.0001 |
| Body mass index, units | 27.8±5.1 | 27.8±4.2 | 27.0±4.5 | 28.7±5.9 | <0.0001 |
| eGFR, –l/min/1.73m$^2$ | 70.7±25.2 | … | … | 70.7±25.2 | |
| Ischemic etiology | 2733 (64.6%) | 357 (73.6%) | 1337 (63.2%) | 1039 (63.7%) | <0.0001 |
| Hypertensive etiology | 282 (6.7%) | 42 (8.7%) | 144 (6.8%) | 96 (5.9%) | 0.0926 |
| Medical history, no. (%) | | | | | |
| Hypertension | 2078 (49.1%) | 291 (60.0%) | 806 (38.1%) | 981 (60.1%) | <0.0001 |
| Atrial fibrillation | 1132 (26.7%) | 125 (25.8%) | 566 (26.7%) | 442 (27.1%) | 0.7524 |
| Diabetes mellitus | 1179 (27.9%) | 136 (28.0%) | 468 (22.1%) | 575 (35.3%) | <0.0001 |
| Stroke | 365 (8.6%) | 33 (6.8%) | 160 (7.6%) | 172 (10.5%) | 0.0017 |
| PCI | 663 (15.7%) | 36 (7.4%) | 298 (14.1%) | 329 (20.2%) | <0.0001 |
| CABG | 1066 (25.2%) | 57 (11.8%) | 446 (21.1%) | 563 (34.5%) | <0.0001 |
| ICD | 163 (3.9%) | 1 (0.2%) | 61 (2.9%) | 101 (6.2%) | <0.0001 |
| CRT/PM | 400 (9.4%) | 38 (7.8%) | 167 (7.9%) | 195 (12.0%) | <0.0001 |
| Medication, n (%) | | | | | |
| Loop-diuretic | 3714 (87.7%) | 425 (87.6%) | 1831 (86.5%) | 1458 (89.4%) | 0.0270 |
| ACEi/ARB | 2382 (56.3%) | 234 (48.2%) | 1194 (56.4%) | 954 (58.5%) | 0.0003 |
| β-Blocker | 2364 (55.8%) | 287 (59.2%) | 1185 (56.0%) | 892 (54.7%) | 0.2146 |
| Mineralocorticoid receptor antagonist | 822 (19.4%) | 104 (21.4%) | 420 (19.8%) | 298 (18.3%) | 0.2366 |
| Digoxin | 2255 (53.3%) | 240 (49.5%) | 929 (43.9%) | 1086 (66.6%) | <0.0001 |

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CHARM-REF, -Alternative, +Added, Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity-Preserved, CHARM-Alternative, and CHARM–Added; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; and PM, pacemaker.

### *Adjusted Hazard Ratios*

After adjustment to take account of the differences in important prognostic variables between patients in the different regions, the geographic variation in heart failure hospitalization persisted, remaining significantly greater in North America, compared with Eastern Europe/Russia in both trials. In I-Preserve cardiovascular mortality (but not all-cause mortality) was lower in Western Europe than in Eastern Europe/Russia.

In a subset of patients in I-Preserve we also adjusted the rate of hospitalization for heart failure for baseline NT pro-BNP level. After this additional adjustment the HR decreased to 1.02 (95% confidence interval [CI], 0.74–1.14), *P*=0.89.

## HF-REF Trials

### *Unadjusted Rates*

The unadjusted rate of death from any cause (and from cardiovascular causes) did not vary much by international geographic region in either CHARM Alternative/Added or CORONA (Table 6 and Figure II in the online-only Data Supplement), in contrast to the findings in HF-PEF. However, the rates of first heart failure hospitalization did vary by geographic region but not by as much as in HF-PEF or according to the same geographic pattern. In CHARM Alternative/Added, the rate of first hospitalization for heart failure was higher in the United States/Canada, compared with Eastern Europe/Russia and Western Europe. In CORONA (which was not conducted in the

**Table 5. Clinical Outcomes of Interest in HF-PEF Trials (CHARM-Preserved, I-Preserve) by Region**

| | Region | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Hazard Ratio (95% CI) | | | | | |
| | Eastern Europe and Russia | Western Europe | United States and Canada | Latin America | Western Europe vs Eastern Europe and Russia | | United States and Canada vs Eastern Europe and Russia | | Latin America vs Eastern Europe and Russia | |
| CHARM-Preserved (EF ≥45%) | | | | | | | | | | |
| No. of patients | 274 | 1174 | 953 | | Unadjusted | Adjusted* | Unadjusted | Adjusted* | Unadjusted | Adjusted* |
| Event rates per 100 py (95% CI) | | | | | | | | | | |
| All-cause mortality | 3.2 (2.2–4.6) | 5.4 (4.6–6.2) | 5.5 (4.7–6.5) | | 1.69 (1.13–2.53) *P*=0.01 | 1.20 (0.79–1.82) *P*=0.40 | 1.75 (1.16–2.63) *P*<0.01 | 1.28 (0.83–1.99) *P*=0.27 | | |
| Cardiovascular death | 2.1 (1.3–3.4) | 3.6 (3.0–4.3) | 3.7 (3.0–4.5) | | 1.69 (1.03–2.77) *P*=0.04 | 1.22 (0.73–2.04) *P*=0.45 | 1.74 (1.05–2.88) *P*=0.03 | 1.29 (0.75–2.21) *P*=0.35 | | |
| HF hospitalization | 2.8 (1.9–4.2) | 4.7 (4.0–5.5) | 8.8 (7.7–10.0) | | 1.66 (1.07–2.57) *P*=0.02 | 1.22 (0.78–1.92) *P*=0.39 | 2.99 (1.94–4.60) *P*<0.01 | 1.85 (1.17–2.91) *P*<0.01 | | |
| HF hospitalization or cardiovascular death | 4.4 (3.2–6.1) | 6.9 (6.0–7.8) | 10.9 (9.6–12.3) | | 1.53 (1.08–2.18) *P*=0.02 | 1.14 (0.79–1.64) *P*=0.49 | 2.38 (1.68–3.38) *P*<0.01 | 1.55 (1.07–2.25) *P*=0.02 | | |
| I-Preserve | | | | | | | | | | |
| No. of patients | 1480 | 1499 | 385 | 716 | Unadjusted | Adjusted* | Unadjusted | Adjusted* | Unadjusted | Adjusted* |
| Event rates per 100 py (95% CI) | | | | | | | | | | |
| All-cause mortality | 4.5 (4.0–5.1) | 5.9 (5.3–6.5) | 6.5 (5.4–7.9) | 4.8 (4.1–5.7) | 1.32 (1.13–1.55) *P*<0.01 | 1.04 (0.88–1.24) *P*=0.64 | 1.46 (1.16–1.83) *P*<0.01 | 0.94 (0.73–1.22) *P*=0.65 | 1.09 (0.89–1.33) *P*=0.42 | 1.02 (0.81–1.29) *P*=0.87 |
| Cardiovascular death | 3.7 (3.2–4.2) | 3.7 (3.2–4.2) | 4.4 (3.5–5.6) | 3.1 (2.5–3.8) | 1.02 (0.85–1.23) *P*=0.82 | 0.83 (0.68–1.02) *P*=0.08 | 1.20 (0.92–1.57) *P*=0.19 | 0.82 (0.60–1.12) *P*=0.21 | 0.86 (0.67–1.09) *P*=0.21 | 0.86 (0.65–1.13) *P*=0.28 |
| HF hospitalization | 3.3 (2.9–3.9) | 4.8 (4.2–5.4) | 7.6 (6.3–9.3) | 3.7 (3.1–4.5) | 1.39 (1.15–1.68) *P*<0.01 | 1.07 (0.87–1.31) *P*=0.55 | 2.23 (1.75–2.83) *P*<0.01 | 1.34 (1.01–1.77) *P*=0.04 | 1.09 (0.86–1.39) *P*=0.47 | 1.19 (0.91–1.56) *P*=0.20 |
| HF hospitalization or cardiovascular death | 6.1 (5.5–6.8) | 7.3 (6.7–8.1) | 10.3 (8.7–12.2) | 5.8 (5.0–6.8) | 1.18 (1.02–1.36) *P*=0.02 | 0.91 (0.78–1.06) *P*=0.23 | 1.65 (1.36–2.01) *P*<0.01 | 1.02 (0.82–1.28) *P*=0.84 | 0.94 (0.78–1.13) *P*=0.52 | 0.96 (0.77–1.18) *P*=0.69 |

Rates of all-cause mortality, cardiovascular mortality, heart failure (HF) hospitalization, and the composite of cardiovascular mortality or HF hospitalization are given per 100 person-years (py) of follow-up. Hazard ratios are adjusted for age, sex, ischemic etiology, and history of diabetes mellitus, atrial fibrillation, and coronary revascularization. CHARM-Preserved indicates Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity Preserved; CI, confidence interval; EF, ejection fraction; HF-PEF, heart failure with preserved EF; and I-Preserve, Irbesartan in Heart Failure with Preserved systolic function.

*Model adjusted for age, sex, race, heart rate, systolic blood pressure, body mass index, New York Heart Association class, ejection fraction, ischemic etiology, and history of diabetes mellitus, atrial fibrillation, stroke, and coronary revascularization.

United States/Canada) the rate of first hospitalization for heart failure was higher in Eastern Europe/Russia than in Western Europe. As a consequence, the rate of the composite outcome in CHARM Alternative/Added was higher in the United States/Canada than in Western Europe; in CORONA the rate was higher in Eastern Europe/Russia than in Western Europe.

### *Adjusted Hazard Ratios*

There was no major variation in all-cause or cardiovascular mortality rates by international geographic region, and this was not changed after adjusting for other prognostic variables. After adjustment, the rate of heart failure hospitalization remained lower in Western Europe than in Eastern Europe/Russia in both trials. The adjusted hazard for each outcome of interest did not differ between the United States/Canada compared with Eastern Europe/Russia in the CHARM HF-REF trials.

## Discussion

We found that rates of fatal and nonfatal events in patients with heart failure varied by international geographic region. However, this variation was notably greater for HF-PEF than for HF-REF and higher for heart failure hospitalization than for mortality. In 2 separate trials we found that unadjusted rates of both types of event in patients with HF-PEF were highest in the United States/Canada, intermediate in Western Europe, and lowest in Eastern Europe/Russia. In patients with HF-PEF, the difference in rates of heart failure hospitalization persisted after adjustment for regional differences in key prognostic variables. In HF-REF we found little international geographic variation in mortality and a different geographic pattern of heart failure hospitalization rates. These rates were still highest in the United States/Canada (although these data were available from only 1 trial) but intermediate in Eastern Europe/Russia and lowest in Western Europe (ie, the pattern was reversed in Europe compared with HF-PEF).

Our study was stimulated by the findings of TOPCAT, and our results are consistent with those of TOPCAT.[5] Indeed, the rate of the composite of cardiovascular death or heart failure hospitalization in the United States/Canada in CHARM-Preserved (10.9 per 100 patient years) and I-Preserve (10.3 per 100 patient years) was similar to that for the primary composite outcome of cardiovascular death, heart failure hospitalization, or resuscitated cardiac arrest (with the last component adding few events) reported in the Americas in TOPCAT (12.6 per 100 patient years). Our rates of cardiovascular death or heart failure hospitalization in Eastern Europe/Russia (4.4 and 6.1 per 100 patient years in CHARM-Preserved and I-Preserve, respectively) were not, however, quite as low as that of the primary outcome in TOPCAT in Georgia/Russia (2.3 per 100 patient years).

Nevertheless, our findings in 2 separate trials, along with those of TOPCAT, suggest that the geographic differences in

**Table 6. Clinical Outcomes of Interest in HF-REF Trials (CHARM HF-REF Trials and CORONA) by Region**

| | Region | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | Hazard Ratio (95% CI) | | | |
| | Eastern Europe and Russia | Western Europe | United States and Canada | Western Europe vs Eastern Europe and Russia | | United States and Canada vs Eastern Europe and Russia | |
| CHARM-Alternative+Added | | | | | | | |
| No. of patients | 485 | 2117 | 1631 | Unadjusted | Adjusted* | Unadjusted | Adjusted* |
| Event rates per 100 py (95% CI) | | | | | | | |
| All-cause mortality | 10.5 (8.9–12.4) | 10.4 (9.6–11.3) | 10.2 (9.3–11.2) | 0.99 (0.82–1.18) *P*=0.89 | 0.88 (0.73–1.07) *P*=0.20 | 0.97 (0.80–1.17) *P*=0.75 | 0.81 (0.66–1.00) *P*=0.05 |
| Cardiovascular death | 8.5 (7.0–10.2) | 8.7 (7.9–9.5) | 8.4 (7.6–9.3) | 1.03 (0.84–1.26) *P*=0.78 | 0.93 (0.75–1.14) *P*=0.47 | 0.99 (0.80–1.22) *P*=0.93 | 0.83 (0.66–1.04) *P*=0.11 |
| HF hospitalization | 9.9 (8.3–11.9) | 8.7 (7.9–9.5) | 12.1 (11.1–13.3) | 0.89 (0.73–1.09) *P*=0.25 | 0.78 (0.63–0.96) *P*=0.02 | 1.21 (0.99–1.49) *P*=0.06 | 0.90 (0.72–1.11) *P*=0.33 |
| HF hospitalization or cardiovascular death | 15.2 (13.1–17.6) | 14.1 (13.1–15.1) | 17.2 (15.9–18.5) | 0.94 (0.80–1.10) *P*=0.44 | 0.84 (0.71–0.99) *P*=0.04 | 1.12 (0.95–1.32) *P*=0.17 | 0.89 (0.74–1.07) *P*=0.21 |
| CORONA | | | | | | | |
| No. of patients | 2384 | 2513 | | Unadjusted | Adjusted* | | |
| Event rates per 100 py (95% CI) | | | | | | | |
| All-cause mortality | 11.3 (10.4–12.2) | 12.4 (11.5–13.3) | | 1.10 (0.99–1.22) *P*=0.08 | 0.96 (0.86–1.08) *P*=0.54 | | |
| Cardiovascular death | 9.4 (8.7–10.2) | 9.3 (8.6–10.1) | | 0.98 (0.88–1.10) *P*=0.77 | 0.86 (0.76–0.98) *P*=0.03 | | |
| HF hospitalization | 12.9 (11.9–13.9) | 10.7 (9.8–11.6) | | 0.83 (0.75–0.93) *P*<0.01 | 0.80 (0.71–0.90) *P*≤0.01 | | |
| HF hospitalization or cardiovascular death | 19.1 (17.9–20.3) | 16.6 (15.5–17.7) | | 0.87 (0.80–0.95) *P*=0.01 | 0.81 (0.74–0.90) *P*<0.01 | | |

Rates of all-cause mortality, cardiovascular mortality, heart failure (HF) hospitalization, and the composite of cardiovascular mortality or HF hospitalization are given per 100 person-years (py) of follow-up. Hazard ratios are adjusted for age, sex, ischemic etiology, and history of diabetes mellitus, atrial fibrillation, and coronary revascularization. CHARM-Alternative+Added indicates Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity-Alternative and CHARM–Added; CI, confidence interval; CORONA, Controlled Rosuvastatin Multinational Trial in HF; and HF-REF, heart failure and reduced ejection fraction.

*Model adjusted for age, sex, race, heart rate, systolic blood pressure, body mass index, New York Heart Association class, ejection fraction, ischemic etiology, and history of diabetes mellitus, atrial fibrillation, stroke, and coronary revascularization.



event rates appear to be particularly pronounced for HF-PEF and especially for heart failure hospitalization (the composite primary end point was not decomposed into its components in the primary results publication from TOPCAT). Moreover, although patient characteristics varied considerably by geographic region in HF-PEF, the geographic variation in the rate of heart failure hospitalization persisted after adjustment for other predictors of adverse outcomes.

We believe that the finding that the disparities were not as large in HF-REF and did not show the same regional pattern raises more questions about international geographic variation in the diagnosis and management of patients with HF-PEF than about thresholds for hospital admission. The diagnosis of HF-PEF is more difficult than HF-REF. The symptoms and signs of heart failure are nonspecific and may have a noncardiovascular cause. For example, dyspnea and fatigue may be caused by advanced age, deconditioning, obesity, or hematologic and other comorbidities. Similarly, lower extremity edema may be caused by arthritis and venous insufficiency. A cardiac explanation for such symptoms and signs is made more likely by demonstration of left ventricular systolic dysfunction (ie, the patient probably has HF-REF). The diagnosis of HF-PEF, however, requires more advanced echocardiography techniques, invasive hemodynamic assessments, or biomarker measurements, the availability of which likely vary geographically and the interpretation of which can be complex.[6,12,13] Of interest in this respect, NT pro-BNP was measured at baseline in I-Preserve but the result was not made available to investigators (ie, it did not influence patient inclusion or exclusion in the trial). The median NT pro-BNP level varied by geographic region in a way that was consistent with the event rates (ie, was lowest in Eastern Europe/Russia and Latin America and highest in the United States/Canada). This calls into question the degree of cardiac dysfunction (or whether there was cardiac dysfunction at all) in patients in the low event-rate regions and raises the possibility of noncardiac causes of symptoms such as dyspnea and edema in these participants.[14] In addition, when we adjusted for baseline NT pro-BNP level in I-Preserve, the international geographical difference in heart failure hospitalization rates was eliminated.

There are previous reports of international geographic variation in trials in patients with chronic HF-REF. The

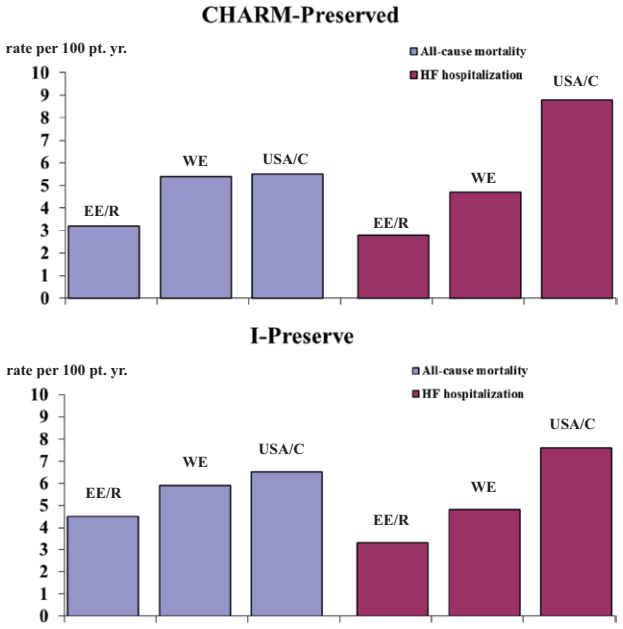


**Figure 1.** Rates of all-cause mortality and heart failure (HF) hospitalization per 100 person-years (py) of follow-up in Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM)-Preserved and Irbesartan in Heart Failure with Preserved systolic function (I-Preserve) trials by region: Eastern Europe/Russia (EE/R), Western Europe (WE), and United States/Canada (USA/C).

Assessment of Treatment with Lisinopril and Survival (ATLAS) trial investigators reported regional differences in baseline characteristics but did not report outcomes.[15] The Metoprolol Controlled-Release Randomised Intervention Trial in Heart Failure trial (MERIT-HF) investigators published a figure illustrating unadjusted all-cause mortality rates by country (rather than region).[16] This trial included 123 patients from the Czech Republic, 211 from Hungary, 102 from Poland, and 532 from the United States. The mortality rate was highest in the Czech Republic and lowest in the United States. Hospitalization rates were not reported. Rates of death (as opposed to proportion of deaths) have not been published for any other large trials in chronic HF-REF, as far as we are aware.

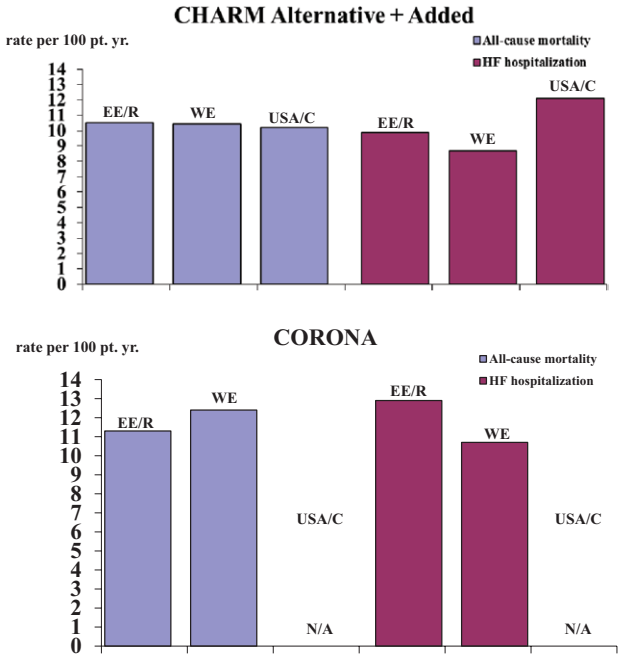


**Figure 2.** Rates of all-cause mortality and heart failure (HF) hospitalization per 100 person-years (py) of follow-up in the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity-Alternative and CHARM–Added (CHARM-Alternative+Added) and Controlled Rosuvastatin Multinational Trial in HF (CORONA) trial by region: Eastern Europe/Russia (EE/R), Western Europe (WE), and United States/Canada (USA/C).

International geographic variation in short-term outcomes was reported in the Placebo-Controlled Randomized Study of the Selective A(1) 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). In PROTECT, 60- and 180-day event rates were generally lowest in Russia and highest in North America, but this trial included relatively few patients and events within each region.[17] The much larger Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan Program (EVEREST) also reported outcomes in patients hospitalized with acute heart failure (and with a LVEF ≤40%) over a median follow-up of 9.9 months according to region of enrollment.[18] Although crude death rates were highest in North America and lowest in Eastern Europe, the adjusted risk of death was significantly higher in South America (HR, 1.42; 95% CI, 1.15–1.76), relative to North America, and somewhat higher, but not significantly so, in Western Europe (HR, 1.16; 95% CI, 0.95–1.42) and Eastern Europe (HR, 1.17; 95% CI, 0.98–1.41). We did not find any regional difference in unadjusted or adjusted mortality rates in the 2 chronic HF-REF trials we were able to analyze, although we did not have patients from Latin America.

For the composite outcome of cardiovascular death or heart failure hospitalization, the HRs for South America, Western Europe, and Eastern Europe, relative to North America, were 1.11 (95% CI, 0.94–1.32), 1.10 (95% CI, 0.93–1.28), and 0.84 (95% CI, 0.73–0.97), respectively. Rates of heart failure hospitalization were not reported separately, but the proportion of patients readmitted for heart failure was similar in all 3 regions. We too found a slightly but not significantly lower rate of this composite outcome in Eastern Europe compared with North America (in the CHARM HF-REF trials), but neither EVEREST nor the CHARM HF-REF trials showed the international geographic variation in heart failure hospitalization apparent in the HF-PEF trials.

Our findings are not about clinical practice but are, we believe, very relevant (along with the results of TOPCAT) to future trials in HF-PEF. Use of strict inclusion and exclusion criteria that incorporate measures of disease severity should reduce patient heterogeneity and lead to a more consistent risk of adverse outcomes across regions. Natriuretic peptides are the most obvious example of such a criterion/measure, and our findings in the subset of patients in I-Preserve with a baseline NT pro-BNP level strongly

support their value in this respect. Clearly, some variation in mortality will remain, in part because of differences in noncardiovascular death rates (eg, from smoking-related lung disease and cancer) and cardiovascular death (related to differences in lifestyle and use of background disease-modifying cardiovascular medications and devices), as well as possible differences in selection of patients, including physician or patient willingness to enroll.[19] Heart failure hospitalization rates may still vary more than mortality rates because these are more likely to be influenced by local health-care system organization and practice than is mortality. However, this may be an unduly pessimistic perspective because, after adjustment, the regional differences in heart failure hospitalization rates in I-Preserve, which had more stringent inclusion criteria, were less marked than in CHARM-Preserved, which had less stringent enrollment criteria.

There were limitations to our study as with any report of this type. There are few trials in HF-PEF available for analysis. There are also few contemporary trials in chronic HF-REF with enrollment in all regions of interest (for example, the 2 most recent pharmacological trials and 2 most recent device trials did not recruit in both Europe and North America).[20–23] We may not have measured or fully adjusted for all important variables influencing fatal and nonfatal outcomes in heart failure. We analyzed data from clinical trials that enroll selected patients because of inclusion and exclusion criteria, other patient factors (eg, ability and willingness to participate), and investigator factors (including financial incentives); therefore, extrapolation of our findings to clinical practice should be done with caution.

Regional rates of hospitalizations may also vary according to cultural practices of physicians, thresholds for hospitalizations, and access to health care, and we did not have information on management practices and health system approaches in every country and at every stage of heart failure.[24]

In summary, we found that rates of fatal and nonfatal events in patients with heart failure vary by international geographic region and that this variation is greater in those with HF-PEF, compared with HF-REF. Although this variation was attenuated by adjustment for regional differences in patient characteristics, it persisted, especially for heart failure hospitalization. Better definition of patients enrolled in trials in HF-PEF might reduce this variation and identify a population more likely to respond to effective heart failure treatments.

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## Disclosures

None.

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## CLINICAL PERSPECTIVE

In this study we examined international geographical variations in event rates in 5 large clinical trials in heart failure. We compared the rates of hospitalization for heart failure, all-cause, and cardiovascular death in Eastern Europe/Russia, with Western Europe and the United States/Canada. In patients with heart failure and preserved ejection fraction (HF-PEF) we found higher rates of heart failure hospitalization in the United States/Canada compared with Eastern Europe/Russia, but less difference for patients with heart failure and reduced ejection fraction (HF-REF). The observed differences in event rates suggests international geographic variation in 1 or more of the following: the definition and diagnosis of HF-PEF, the risk profile of patients enrolled, the threshold for heart failure hospitalization, or some other factor. This finding has implications for the conduct of future global trials in HF-PEF. Greater standardization of entry criteria and the baseline risk profile of patients may reduce such variation.

# International Geographic Variation in Event Rates in Trials of Heart Failure With Preserved and Reduced Ejection Fraction

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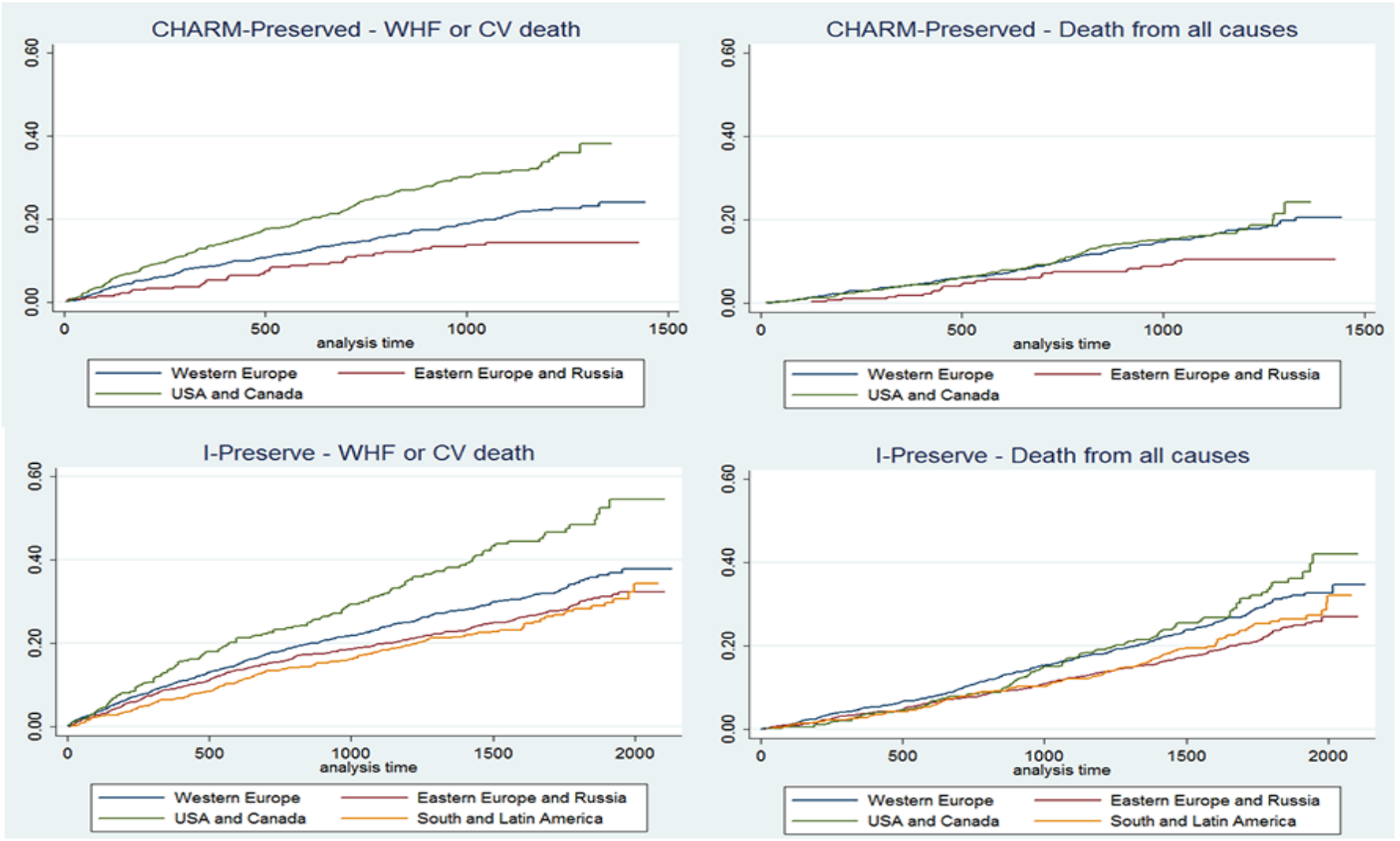
# Supplemental Material

**Supplementary Table 1 Countries within each region according to trial**

| | Eastern Europe and Russia | Western Europe | USA and Canada | Latin America |
|---|---|---|---|---|
| The CHARM Programme | Czech Republic, Hungary, Poland, Russia. | Belgium, Denmark, Finland, France, Germany, Iceland, Italy, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, UK/Ireland. | Patients from both countries included. | No patients |
| CORONA | Bulgaria, Czech Republic, Hungary, Poland, Romania, Russia, Slovakia | Belgium, Denmark, Finland, France, Germany, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, UK/Ireland. | No patients | No patients |
| I-Preserve | Czech Republic, Hungary, Poland, Russia | Belgium, Denmark, France, Germany, Greece, Italy, Norway, Portugal, Spain, Sweden, Switzerland, Netherlands, UK/Ireland. | Patients from both countries included. | Argentina, Brazil, Mexico. |

Patients from Australia, Malaysia, Singapore (CHARM) and South Africa (all trials), were excluded.

**Supplementary Figure 1**



**Supplementary Figure 2**

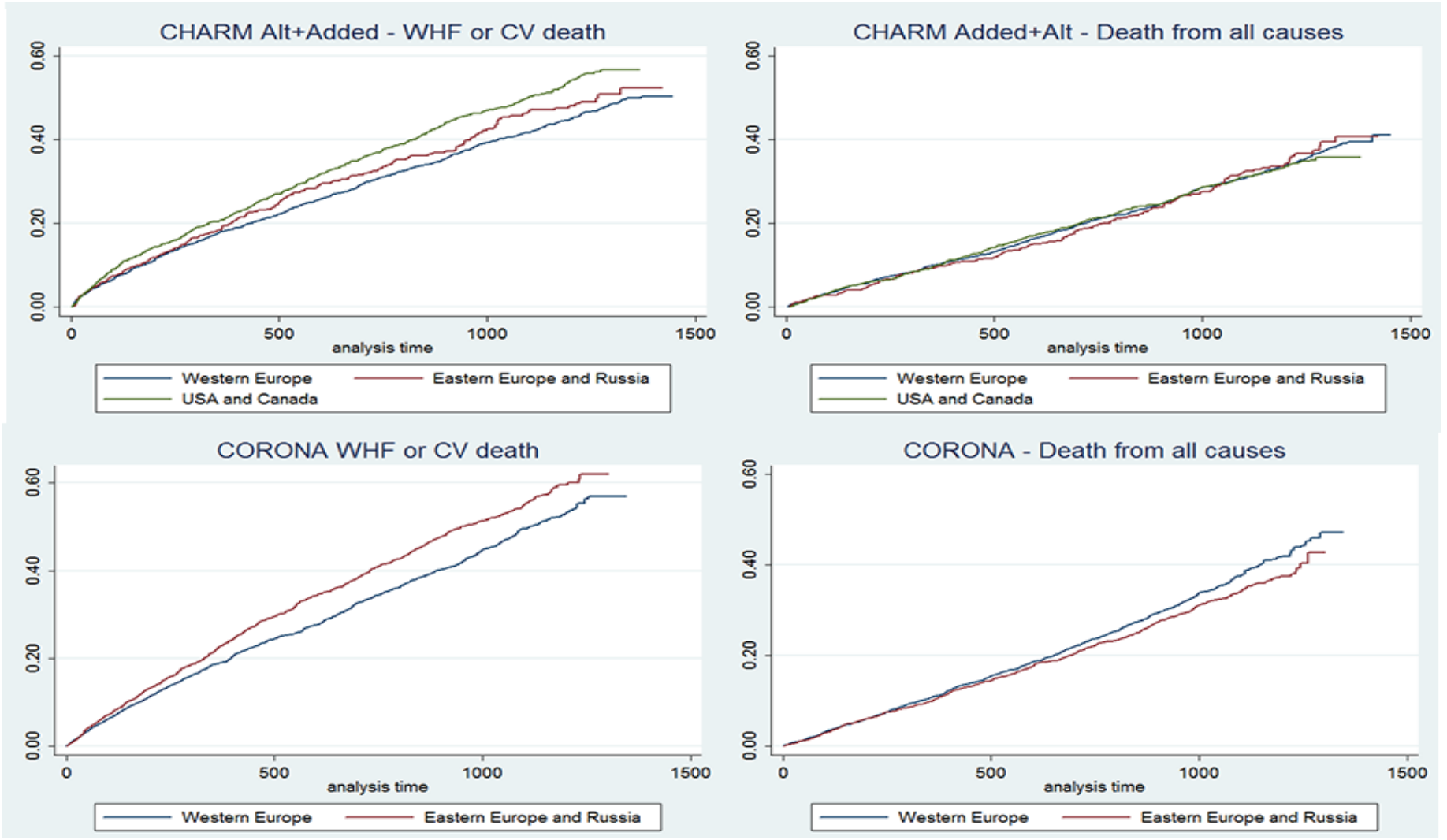


**Figure legends:**

| | |
|---|---|
| Supplementary Figure 1 | Cumulative incidence of a composite of heart failure (HF) hospitalization or cardiovascular death, and all-cause mortality per 100 person-years (py) of follow-up in CHARM-Preserved and I-Preserve by region: Eastern Europe/Russia (EE/R), Western Europe (WE) and United States of America/Canada (USA/C). |
| Supplementary Figure 2 | Cumulative incidence of a composite of heart failure (HF) hospitalization or cardiovascular death, and all-cause mortality per 100 person-years (py) of follow-up in the CHARM HF-REF trials and CORONA by region: Eastern Europe/Russia (EE/R), Western Europe (WE) and United States of America/Canada (USA/C). |