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Transatlantic similarities and differences in major natural history endpoints of heart failure after acute myocardial infarction: a propensity-matched study of the EPHEsus trial

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Abstract

Background—Transatlantic differences in outcomes after acute myocardial infarction (AMI) have not been examined in propensity-matched studies.

Methods—In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHEsus), there were significant imbalances in baseline characteristics between patients from North America (n=858) and Europe (n=4646). Propensity scores for North America were calculated for each patient based on 64 baseline characteristics, and were then used to assemble 298 pairs of propensity-matched patients who were well-balanced on all measured baseline covariates. Matched Cox regression models were used to estimate transatlantic differences in outcomes during a mean follow-up of 16 months.

Results—There was no transatlantic difference in all-cause mortality (matched hazard ratio {HR}, 1.00; 95% confidence interval {CI}, 0.64–1.57; P=1.000). All-cause hospitalization occurred in 175 (rate, 8974/10,000 person-years) and 137 (rate, 5249/10,000 person-years) patients respectively from North America and Europe (matched HR when North America was compared with Europe, 1.89; 95% CI, 1.41–2.52; P<0.0001). Matched HRs (95% CIs) for cardiovascular and non-cardiovascular hospitalization for North America were respectively 1.35 (0.92–1.97; P=0.125) and 1.89 (1.31–2.72; P<0.0001). Among 5504 pre-match patients, unadjusted, multivariable-adjusted, and propensity-adjusted HRs for all-cause hospitalization for North America were 1.52 (95% CI, 1.38–1.68; P<0.0001), 1.16 (95% CI, 1.02–1.31; P=0.020), 1.41 (95% CI, 1.17–1.70; P<0.0001).

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Conclusion—Despite major transatlantic differences in baseline characteristics, there was no difference in post-AMI mortality. The increased non-cardiovascular hospitalization in North America may in part be due to transatlantic differences in patient preferences and access to care.

Keywords

Transatlantic variations; propensity score; post-AMI; mortality; hospitalization

1. Introduction

Increasingly larger international multicenter randomized clinical trials are needed to test efficacies of new therapies and interventions for patients with acute myocardial infarction (AMI) already receiving standard therapy [1-4]. However, regional variations in the natural history of patients may affect the validity, interpretation, and generalizability of the findings of international clinical trials. In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), 83% of participants were recruited from North America and Europe. The objective of this study was to examine transatlantic similarities and differences in patient characteristics and major natural history endpoints in EPHESUS using propensity matched design.

2. Materials and methods

2.1. Data source

The current analysis is based on original EPHESUS datasets obtained from Pfizer and was performed at the University of Alabama at Birmingham. EPHESUS was an international, randomized, double-blind, placebo-controlled clinical trial that randomized 6632 patients to receive eplerenone and placebo [2]. All patients were post-AMI with left ventricular ejection fraction $\leq 40\%$ with symptoms of heart failure and receiving standard medical therapy. They were followed up for a mean of 16 months. The design and results of the EPHESUS trial have been previously reported [2].

2.2. Geographic regions

Of the 6632 EPHESUS participants, 4646 were enrolled from Europe and 858 were enrolled from North America. Patients from North America were recruited from the United States and Canada, and those from Europe were recruited from Belgium, Bulgaria, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Ireland, Italy, the Netherlands, Norway, Poland, Portugal, Romania, Russia, Slovakia, Spain, Sweden, Switzerland, Ukraine, and the United Kingdom.

2.3. Study outcomes

Primary outcomes of interest for the current analysis were all-cause mortality and all-cause hospitalization during an average of 15.8 months of follow-up. We also studied the co-primary combined endpoint of cardiovascular hospitalization or cardiovascular mortality, and secondary endpoints of cardiovascular mortality, and hospitalization due to cardiovascular and non-cardiovascular causes. The cause of death or the primary diagnosis leading to hospitalization was adjudicated by a blinded EPHESUS critical-events committee [2].

2.4. Assembly of the study cohort

Because of the significant imbalances in baseline characteristics between patients from North America and Europe (Tables 1 and 2, and Figure 1), we assembled a propensity-

matched population in which patients recruited from North America and Europe would be well balanced (Table 1 and 2, and Figure 1) [5, 6]. We started by calculating propensity scores for North America for each patient using a non-parsimonious multivariable logistic regression model. In that model, North America was the dependent variable and the 64 baseline characteristics displayed in Figure 1 were used as covariates [7-9]. Using a greedy matching protocol, described elsewhere in detail, we matched 298 pairs of patients from North America and Europe who had similar propensity scores (Table 1 and 2, and Figure 1) [7].

Propensity score models are sample-specific adjusters and are not intended to be used for out-of-sample prediction or estimation of coefficients. As such, measures of fitness and discrimination are not important for the assessment of the model's effectiveness, which is best assessed by post-match balance. We assessed pre-match imbalances and post-match balances by estimating absolute standardized differences of covariates across the groups, which directly quantify the bias in the means (or proportions) [7-11]. Absolute standardized differences are expressed as a percentage of the pooled standard deviation and presented as Love plots [7,8]. An absolute standardized difference of 0% indicates no bias and values <10% indicate inconsequential bias.

2.5. Statistical analysis

For descriptive analyses, we used Pearson Chi square test and Wilcoxon rank-sum test for the pre-match, and McNemar's test and paired sample t-test for the post-match comparisons, as appropriate. We used stratified Cox regression models to estimate matched hazard ratios (HR) and 95% confidence intervals (CI) for North America for various outcomes, compared with those from Europe [7]. All statistical tests were evaluated using two-tailed 95% confidence levels, and data analyses were performed using SPSS for Windows version 15 [12].

2.6. Subgroup analyses

To determine if the transatlantic differences in all-cause mortality and all-cause hospitalization were homogenous across various subgroups, we conducted two separate subgroup analyses for all-cause mortality and all-cause hospitalization in all 5504 patients adjusting for propensity scores. For each of these analyses, we first calculated differences in absolute risk and then tested for interactions in multivariable Cox regression models.

3. Results

3.1. Baseline patient characteristics

Pre-match imbalances and post-match balances in baseline characteristics and therapy of patients from North America as compared with those from Europe are displayed in Table 1 and 2 respectively. Absolute standardized differences after matching were $\leq 10\%$ for all measured covariates, indicating substantial bias reduction (Figures 1).

3.2. Mortality: North America versus Europe

A total of 88 (15%) matched patients died from all causes, including 79 (13%) due to cardiovascular causes, during an average of 15.8 months of follow-up. All-cause mortality occurred in 15% (rate, 1168/10000 person-years) and 14% (rate, 1074/10000 person years) of patients respectively from North America and Europe (matched HR when North America was compared with Europe, 1.00; 95% CI, 0.64–1.57; $P=1.000$; Figure 2a and Table 3). In the pre-match cohort of 5504 patients, unadjusted, multivariable-adjusted and propensity-adjusted HRs for all-cause mortality associated with residence in North America were 1.09 (0.91–1.31; $P=0.354$), 0.97 (0.79–1.20; $P=0.797$) and 1.16 (0.84–1.62; $P=0.366$)

respectively (Table 4). The association between North America and all-cause mortality was homogeneous across various subgroups of patients (data not shown). Estimates of association of residence in North America (versus Europe) and cardiovascular mortality and the combined co-primary endpoint of cardiovascular hospitalization or cardiovascular mortality are displayed in Tables 3 and 4.

3.3. Hospitalization: North America versus Europe

A total of 312 (52%) patients were hospitalized from all causes, including 140 (23%) due to cardiovascular cause and 172 (29%) due to non-cardiovascular causes. All-cause hospitalization occurred in 59% (rate, 8974/10,000 person-years) and 46% (rate, 5249/10000 person-years) of patients respectively from North America and Europe (matched HR, 1.89; 95% CI, 1.41–2.52; $P<0.0001$; Figure 2b and Table 3). In the pre-match cohort of 5504 patients, unadjusted, multivariable-adjusted and propensity-adjusted HRs for all-cause hospitalization associated with residence in North America were 1.52 (1.38–1.68; $P<0.0001$), 1.16 (1.02–1.31; $P=0.020$) and 1.41 (1.17–1.70; $P<0.0001$) respectively (Table 4). Transatlantic difference in all-cause hospitalization was homogenous across a wide spectrum of subgroups of patients (Figure 3).

The increase in all-cause hospitalization associated with North America was primarily driven by an increase in non-cardiovascular hospitalizations (matched HR, 1.89; 95% CI, 1.31–2.72; $P<0.0001$; Figure 2c and Table 3). In the pre-match cohort of 5504 patients, unadjusted, multivariable-adjusted and propensity-adjusted HRs for non-cardiovascular hospitalization associated with residence in North America were 1.27 (1.11–1.45; $P<0.0001$), 1.13 (0.98–1.31; $P=0.091$) and 1.41 (1.11–1.80; $P=0.006$) respectively (Table 4). Estimates of associations of residence in North America (versus Europe) and cardiovascular hospitalization are displayed in Tables 3 and 4.

4. Discussion

There are three key findings of the current analysis. First, there were significant differences in prognostically important baseline characteristics between post-AMI patients recruited from Europe and North America. Second, there was no intrinsic transatlantic difference in mortality. Finally, compared with Europe, patients enrolled from North America had a higher hospitalization rate, which was primarily driven by a higher rate of non-cardiovascular hospitalization. These findings are important as they demonstrate intrinsic similarities in major natural history endpoints between post-AMI patients from North America and Europe as most large-scale multinational randomized clinical trials are often conducted in these two continents.

There are several potential explanations for the many imbalances in baseline characteristics between the two continents. While transatlantic imbalance in proportions of nonwhites is likely a reflection of racial distribution of populations in these two continents, other imbalances are likely due to variations in lifestyle, practice pattern, and health care system. For example, a higher prevalence of cardiovascular risk factors and morbidity in patients from North America may be explained by a higher mean body mass index and higher prevalence of smoking in those patients. The higher prevalence of the use of beta-blockers, statins, anti-platelet drugs, and coronary revascularization and shorter length of hospital stay during AMI in North America may be explained by higher cardiovascular risk and morbidity in patients from and practice pattern in North America. Interestingly, more secular baseline characteristics such as age, sex, use of aspirin and ACE inhibitors were well balanced between the continents. While some imbalances, such as the higher proportion of non-ST wave elevation AMI in patients from Europe, remain less well explained, it seems unlikely that there is a biological basis for this and other differences in baseline characteristics

between the continents. Similar regional differences in baseline characteristics have also been reported in patients with acute heart failure [13]. However, a greater degree of regional variations in baseline characteristics in heart failure may not be surprising, as unlike in AMI, there is no standard objective diagnostic criteria for heart failure.

Despite these many differences in baseline characteristics, there were no pre-match transatlantic differences in mortality. This may have been due to a balanced sharing of various risk factors at baseline. For example, patients from North America were less likely to be smokers, a marker of good prognosis, but were more likely to have diabetes, thus potentially canceling out each other. Similarly, they were more likely to have a low LVEF, but were more likely to receive beta-blockers. More importantly, in the matched population, in which patients were balanced on 64 key demographic, clinical and subclinical baseline covariates, there was no difference in mortality or cardiovascular hospitalization. This suggests an intrinsic prognostic similarity between post-AMI patients from these two continents and points to the homogeneity in major natural history endpoint in these two populations.

One of the unexpected findings of our study is the substantial transatlantic gap in all-cause hospitalization. This association is based on large number of events and persisted regardless of the methods used suggesting robustness of the association. It is unlikely that this difference in all-cause hospitalization may be explained by imbalances in baseline characteristics between post-AMI patients from North America and Europe as they were well balanced in our matched cohort. However, it is possible that patients from North America had a more severe disease progression during follow-up. It is also interesting to note that the transatlantic difference in all-cause hospitalization was primarily driven by an increase in non-cardiovascular hospitalization in North America. It may be explained by an imbalance in non-cardiovascular comorbidity at baseline. However, we had no data on baseline non-cardiovascular morbidity. This may also in part be explained by transatlantic difference in patient preference, practice pattern, and access to care.

The significant 56% increase in cardiovascular hospitalization in North America before matching is likely due to confounding. This association became non-significant after propensity score matching, and adjustment for propensity scores and other covariates in multivariable models in the pre-match cohort. To explore the impact of the length of stay for the index AMI on subsequent cardiovascular hospitalization, we conducted a post hoc analysis of the pre-match data adjusting for index AMI length stay variable only. Interestingly, when adjusted for the length of stay for the index AMI alone, the association between North America and cardiovascular hospitalization became weak and non-significant (length of stay adjusted HR, 1.06; 95% CI, 0.86– 1.30; P=0.580). Therefore, it is possible that increased post-AMI cardiovascular hospitalization in North America may, at least in part, be explained by a shorter length of hospital stay during index AMI.

The similarities in the major natural history endpoints for AMI patients recruited from North America and Europe suggest a biological homogeneity of these two populations which may add to the validity of interpretation of results of clinical trial conducted in these two continents. They also highlight the need to avoid subgroup analyses of clinical trials based in North American and Europe. Subgroup analyses without significant interaction and biological basis can be misleading. For example, in the MERIT-HF trial, a subgroup analysis demonstrated that metoprolol succinate extended release was only effective in reducing mortality in Europe but not in the US [14]. While fortunately this has not lead to underuse of metoprolol succinate extended release in the US, such subgroup analyses without underlying mechanistic rationale may be potentially misleading and may result in inappropriate use or underuse of therapy.

Our study has several limitations. Because of the major differences in baseline characteristics between patients across the continents and the use of a large number of variables in the propensity score model, we lost a large number of patients in the matching processes. While this limits the generalizability, it has increased the internal validity of our findings as excluded patients were too dissimilar to have any overlapping propensity scores. When baseline characteristics of patients are not well balanced, regression adjustments may be based on extrapolations beyond data and may not reflect true associations [15]. Further, we were able to replicate our key findings in the pre-match population using regression-based multivariable risk adjustments or adjustment for propensity scores. Even though we adjusted for many key variables, it is possible that these findings may be explained away by an unmeasured confounder. However, for an unmeasured covariate to become a confounder, it would need to be a near-perfect predictor of outcomes and be associated with exposure (residence in North America) and also not be strongly correlated with any of the 64 covariates used in our study.

In conclusion, AMI patients enrolled from North America and Europe had substantial differences in many key baseline characteristics. However, there were no intrinsic transatlantic differences in all-cause mortality or cardiovascular hospitalization. The transatlantic difference in all-cause hospitalization was primarily driven by non-cardiovascular hospitalization, suggesting potential transatlantic differences in patient preference, practice pattern and health care system. Findings from randomized clinical trials of patients with AMI based on homogenous populations in these two continents may be reliably interpreted, and will therefore be generalizable to most patients in North America and Europe, except for the inherent limitations associated with inclusion and exclusion criteria of a particular trial.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [16].

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Figure 1.

Love plots for absolute standardized differences before and after propensity score matching comparing covariate values for patients from North America and Europe in EPHEBUS (ACE=angiotensin-converting enzyme)

Figure 2a

Figure 2b

Figure 2c

Figure 2. Kaplan-Meier plots for (a) all cause mortality, (b) all cause hospitalization, and (c) non-cardiovascular (CV) hospitalization between North America and Europe in EPHEsus (CI=confidence interval; HR=hazard ratio)

Figure 3.

Association of residence in North America and all-cause hospitalization in subgroups of EPHESUS participants (ACEI=angiotensin-converting enzyme inhibitor; AMI=acute myocardial infarction; ARB=angiotensin-receptor blocker; CI=confidence interval; HR=hazard ratio)

Table 1
Baseline patient characteristics for EPHEsus participants from North America and Europe before and after propensity matching

<i>n</i> (%) or mean ($\pm$ SD)	Before propensity matching			After propensity matching		
	Europe (n = 4646)	North America (n = 858)	<i>P</i> value	Europe (n = 298)	North America (n = 298)	<i>P</i> value
Age, years	64.3 ($\pm$ 11.4)	64.6 ($\pm$ 11.8)	0.372	65.4 ($\pm$ 11.6)	64.7 ($\pm$ 12.1)	0.455
Women	1380 (30)	238 (28)	0.246	86 (29)	78 (26)	0.530
Nonwhite race	30 (0.6)	113 (13)	<0.0001	18 (6)	18 (6)	1.000
Smoking status						
Current	1468 (32)	220 (26)		83 (28)	93 (31)	
Never	1954 (42)	248 (29)	<0.0001	95 (32)	94 (32)	0.779
Former	1224 (26)	390 (46)		120 (40)	111 (37)	
Days of index AMI hospitalization	17.2 ($\pm$ 10.3)	10.0 ($\pm$ 7.9)	<0.0001	12 ($\pm$ 5)	12 ($\pm$ 11)	0.848
ST-segment elevation during index AMI	3451 (74)	396 (46)	<0.0001	170 (57)	178 (60)	0.554
Days to randomization	7.3 ($\pm$ 2.9)	6.9 ($\pm$ 3.1)	<0.0001	7.0 ($\pm$ 3.0)	6.8 ($\pm$ 3.1)	0.395
Past medical history						
AMI	1226 (26)	314 (37)	<0.0001	88 (30)	96 (32)	0.523
Angina pectoris	1916 (41)	436 (51)	<0.0001	134 (45)	135 (45)	1.000
Hypertension	2820 (61)	554 (65)	0.032	170 (57)	162 (54)	0.575
Diabetes mellitus	1355 (29)	408 (48)	<0.0001	125 (42)	115 (39)	0.471
HF	661 (14)	199 (23)	<0.0001	54 (18)	48 (16)	0.567
HF hospitalization	326 (7)	133 (16)	<0.0001	35 (12)	27 (9)	0.332
Killip status						
I	553 (12)	293 (34)	<0.0001	67 (23)	70 (24)	0.989
II	3171 (68)	401 (47)		172 (58)	171 (57)	
III	807 (17)	124 (15)		48 (16)	44 (15)	
IV	115 (2.5)	40 (5)		11 (3.7)	13 (4.4)	
BMI, kilogram/m ²	27.3 ($\pm$ 4.3)	28.5 ($\pm$ 5.4)	<0.0001	27.8 ($\pm$ 4.5)	27.7 ($\pm$ 4.8)	0.843
Systolic BP, mm Hg	120 ($\pm$ 16)	117 ($\pm$ 17)	<0.0001	117 ($\pm$ 16)	115 ($\pm$ 17)	0.216
Diastolic BP, mm Hg	74 ($\pm$ 10)	67 ($\pm$ 11)	<0.0001	69 ($\pm$ 11)	68 ($\pm$ 10)	0.364
Pulse, beats per minute	74 ($\pm$ 11)	76 ($\pm$ 13)	<0.0001	75 ($\pm$ 12)	76 ($\pm$ 12)	0.479

<i>n</i> (%) or mean ($\pm$ SD)	Before propensity matching		<i>P</i> value	After propensity matching		<i>P</i> value
	Europe (n = 4646)	North America (n = 858)		Europe (n = 298)	North America (n = 298)	
Sodium, mEq/L	140 ($\pm$ 4)	139 ($\pm$ 4)	<0.0001	139 ($\pm$ 4)	139 ($\pm$ 3)	0.285
Potassium, mEq/L	4.27 ($\pm$ 0.44)	4.36 ($\pm$ 0.47)	<0.0001	4.31 ($\pm$ 0.42)	4.30 ($\pm$ 0.44)	0.717
Creatinine, mg/dl	1.12 ($\pm$ 0.32)	1.12 ($\pm$ 0.37)	0.753	1.14 ($\pm$ 0.35)	1.12 ($\pm$ 0.37)	0.386
Glucose, mg/dl	129 ($\pm$ 64)	153 ($\pm$ 75)	<0.0001	144 ($\pm$ 75)	143 ($\pm$ 64)	0.877
Calcium, mg/dl	8.7 ($\pm$ 2.0)	9.1 ($\pm$ 0.82)	<0.0001	9.1 ($\pm$ 0.61)	9.1 ($\pm$ 0.77)	0.583
Magnesium, mg/dl	2.2 ($\pm$ 0.43)	2.1 ($\pm$ 0.28)	0.001	2.1 ($\pm$ 0.43)	2.1 ($\pm$ 0.24)	0.538
Phosphorus, mg/dl	3.5 ($\pm$ 0.76)	3.8 ($\pm$ 2.2)	<0.0001	3.7 ($\pm$ 0.74)	3.6 ($\pm$ 0.66)	0.489
CPK, mg/dl	286 ($\pm$ 370)	197 ($\pm$ 254)	<0.0001	238 ($\pm$ 320)	246 ($\pm$ 310)	0.734
Uric acid, mg/dl	6.2 ($\pm$ 3.26)	7.5 ($\pm$ 21)	<0.0001	7.0 ($\pm$ 10)	7.0 ($\pm$ 2.0)	0.675
AlkPhos, unit/L	142 ($\pm$ 100)	88 ($\pm$ 37)	<0.0001	98 ($\pm$ 53)	98 ($\pm$ 46)	0.999
Albumin, g/dl	3.8 ($\pm$ 0.61)	3.5 ($\pm$ 0.5)	<0.0001	3.5 ($\pm$ 0.5)	3.5 ($\pm$ 0.5)	0.874
Total cholesterol, mg/dl	199 ($\pm$ 49)	171 ($\pm$ 39)	<0.0001	178 ($\pm$ 45)	179 ($\pm$ 39)	0.702
LDL, mg/dl	126 ($\pm$ 52)	93 ($\pm$ 32)	<0.0001	111 ($\pm$ 52)	101 ($\pm$ 32)	0.006
HDL, mg/dl	43 ($\pm$ 101)	38 ($\pm$ 13)	0.178	39 ($\pm$ 22)	40 ($\pm$ 12)	0.629
Triglyceride, mg/dl	168 ($\pm$ 112)	182 ($\pm$ 95)	<0.0001	192 ($\pm$ 266)	177 ($\pm$ 86)	0.373
Hemoglobin, g/dl	13.4 ($\pm$ 1.7)	12.8 ($\pm$ 1.8)	<0.0001	13 ($\pm$ 2)	13 ($\pm$ 2)	0.685
White blood cell, $10^3/\mu$ L	8.6 ($\pm$ 2.9)	9.4 ($\pm$ 3.0)	<0.0001	9.1 ($\pm$ 3)	9.3 ($\pm$ 3)	0.617
Platelet, $10^3/\mu$ L	249 ($\pm$ 80)	282 ($\pm$ 101)	<0.0001	275 ($\pm$ 104)	266 ($\pm$ 98)	0.279
LVEF, %	33.7 ($\pm$ 5.6)	30.4 ($\pm$ 7.2)	<0.0001	32 ($\pm$ 7)	32 ($\pm$ 7)	0.886

AlkPhos=alkaline phosphatase; AML=acute myocardial infarction; BMI=body mass index; CPK=creatinine phosphokinase; HDL=high density lipoprotein; HF=heart failure; LDL=low density lipoprotein
LVEF=left ventricular ejection fraction

Table 2
Baseline therapy in EPHEBUS participants from North America and Europe, before and after propensity matching

<i>n</i> (%) or mean (<i>±SD</i>)	Before propensity matching			After propensity matching		
	Europe (n = 4646)	North America (n = 858)	<i>P</i> value	Europe (n = 298)	North America (n = 298)	<i>P</i> value
Revascularization or reperfusion in 14 days [*]	1933 (42)	463 (54)	<0.0001	153 (51)	150 (50)	0.865
CABG	19 (0.4)	38 (4.4)	<0.0001	5 (1.7)	4 (1.3)	1.000
PTCA	893 (19)	353 (41)	<0.0001	107 (36)	104 (35)	0.857
Thrombolysis	1215 (26)	202 (24)	0.108	70 (24)	76 (26)	0.631
Medications						
Eplerenone	2323 (50)	431 (50)	0.900	149 (50)	154 (52)	0.748
ACE inhibitors	3889 (84)	730 (85)	0.314	260 (87)	260 (87)	1.000
ARB	125 (3)	53 (6)	<0.0001	17 (6)	14 (5)	0.720
Beta-blockers	3489 (75)	706 (82)	<0.0001	233 (78)	236 (79)	0.845
Nitrates	3042 (66)	503 (59)	<0.0001	168 (56)	162 (54)	0.679
Aspirin	4086 (88)	759 (89)	0.669	259 (87)	267 (90)	0.382
Anti-platelet drugs	1076 (23)	443 (52)	<0.0001	122 (41)	128 (43)	0.677
Anticoagulants	817 (18)	111 (13)	0.001	44 (15)	42 (14)	0.908
Statins	1918 (41)	579 (68)	<0.0001	188 (63)	186 (62)	0.933
Other lipid lowering agents	52 (1)	35 (4)	<0.0001	8 (3)	10 (3)	0.815
Digoxin	541 (12)	253 (30)	<0.0001	54 (18)	54 (18)	1.000
Loop diuretics	2486 (54)	532 (62)	<0.0001	178 (60)	169 (57)	0.523
Other diuretics	442 (10)	52 (6)	0.001	18 (6)	14 (5)	0.585
Potassium supplements	705 (15)	238 (28)	<0.0001	67 (23)	63 (21)	0.769
CCB	855 (18)	116 (14)	0.001	43 (14)	39 (13)	0.731
Anti-arrhythmic drugs	534 (12)	96 (11)	0.797	27 (9)	35 (12)	0.350

ACE=angiotensin-converting enzyme; ARB=angiotensin-receptor blocker; BMI=body mass index; CABG=coronary artery bypass graft; CCB=calcium channel blockers; PTCA=percutaneous transluminal coronary angioplasty

^{*} This number may not be the exact sum of the three reperfusion or revascularization procedures as some patients received more than one procedure

Table 3
Outcomes in EPHEUS participants from North America and Europe after propensity matching

	Rate, per 10,000 person-years follow-up (events / follow-up in years)		Rate difference* (per 10,000 person-years)	Hazard ratio (95% confidence interval)	P value
	Europe	North America			
After matching	n = 298	n = 298		Matched	
All-cause mortality	1074 (42 / 391)	1168 (46 / 394)	+ 93	1.00 (0.64–1.57)	1.000
All-cause hospitalization	5249 (137 / 261)	8974 (175 / 195)	+ 3725	1.89 (1.41–2.52)	<0.0001
Cardiovascular hospitalization or cardiovascular death	2681 (89 / 332)	3123 (99 / 317)	+ 442	1.17 (0.85–1.61)	0.334
Cardiovascular mortality	997 (39 / 391)	1015 (40 / 394)	+ 18	1.00 (0.63–1.60)	1.000
Cardiovascular hospitalization	1928 (64 / 332)	2397 (76 / 317)	+ 470	1.35 (0.92–1.97)	0.125
Non-cardiovascular hospitalization	2246 (73 / 325)	3536 (99 / 280)	+ 1290	1.89 (1.31–2.72)	0.001

* Rate differences are calculated by subtracting rates for Europe from those for North America

Table 4
Outcomes in EPHESUS participants from North America and Europe before propensity matching

Outcomes (n, %)	Hazard ratio (95% confidence interval)	P value
All-cause mortality (828, 15%)		
Unadjusted	1.09 (0.91–1.31)	0.354
Multivariable-adjusted	0.97 (0.79–1.20)	0.797
Propensity-adjusted	1.16 (0.84–1.62)	0.366
All-cause hospitalization (2482, 45%)		
Unadjusted	1.52 (1.38–1.68)	<0.0001
Multivariable-adjusted	1.16 (1.02–1.31)	0.020
Propensity-adjusted	1.41 (1.17–1.70)	<0.0001
Cardiovascular hospitalization or cardiovascular death (1522, 28%)		
Unadjusted	1.29 (1.14–1.47)	<0.0001
Multivariable-adjusted	0.97 (0.82–1.14)	0.684
Propensity-adjusted	1.09 (0.86–1.39)	0.478
Cardiovascular mortality (713, 13%)		
Unadjusted	1.01 (0.83–1.23)	0.927
Multivariable-adjusted	0.94 (0.74–1.18)	0.586
Propensity-adjusted	1.07 (0.75–1.53)	0.721
Cardiovascular hospitalization (1029, 19%)		
Unadjusted	1.56 (1.34–1.81)	<0.0001
Multivariable-adjusted	1.20 (0.99–1.44)	0.058
Propensity-adjusted	1.13 (0.85–1.50)	0.392
Non-cardiovascular hospitalization (1453, 26%)		
Unadjusted	1.27 (1.11–1.45)	<0.0001
Multivariable-adjusted	1.13 (0.98–1.31)	0.091
Propensity-adjusted	1.41 (1.11–1.80)	0.006