Title: **Geographic Differences in Patients With Acute Myocardial Infarction in The PARADISE-MI Trial**

Running title: *Geographic differences in PARADISE-MI*

Authors:
Jawad H Butt MD[a,b]
Brian L Claggett PhD[c]
Zi M Miao MS[c]
Karola S Jering MD[c]
David Sim MBBS[d]
Peter van der Meer MD PhD[e]
Mpiko Ntsekhe MD PhD[f]
Offer Amir MD[g]
Myeong-Chan Cho MD PhD[h]
Jorge Carrillo-Calvillo MD[i]
Julio E Núñez MD[j]
Alberto Cadena MD[k]
Prafulla Kerkar MD[l]
Aldo P Maggioni MD[m]
Philippe G Steg MD[n]
Christopher B Granger MD[o]
Douglas L Mann MD[p]
Béla Merkely MD PhD[q]
Eldrin F Lewis MD MPH[r]
Scott D Solomon MD[c]
Yinong Zhou MD[s]
Lars Køber MD DMSc[b]
Eugene Braunwald MD[c]
John JV McMurray MD[a]
Marc A Pfeffer MD PhD[c]

Affiliations:
[a]British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, UK; [b]Department of Cardiology, Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark; [c]Cardiovascular Division, Brigham and Women's Hospital, Boston; [d]National Heart Center Singapore, Singapore; [e]Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; [f]Division of Cardiology, University of Cape Town & Groote Schuur Hospital, Cape Town, South Africa; [g]Cardiovascular Institute, Hadassah Medical Center, Jerusalem, Israel; [h]Department of Cardiology and Cardiocerebrovascular Center, Chungbuk National University Hospital, Cheongju, Korea; [i]Departamento de Cardiología, Hospital Central "Dr. Ignacio Morones Prieto" San Luis Potosí, San Luis Potosí. México; [j]Cardiology Department, Hospital Clínico Universitario de Valencia, INCLIVA Instituto de Investigación

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Sanitaria, Valencia, Spain; [k]Clínica de la Costa LTDA, Barranquilla, Colombia; [l]Department of Cardiology, KEM Hospital, Mumbai, Maharashtra, India; [m]ANMCO Research Center, Florence, Italy; [n]Université de Paris, AP-HP (Assistance Publique-Hôpitaux de Paris), FACT (French Alliance for Cardiovascular Trials) and INSERM U-1148, France; [o]Duke University Medical Center, Durham; [p]Department of Medicine, Washington University, St Louis, Missouri, USA; [q]Heart and Vascular Centre, Semmelweis University, Budapest, Hungary; [r]Division of Cardiovascular Medicine, Stanford University, Palo Alto, California; [s]Novartis Pharmaceutical Corporation, East Hanover, NJ, USA.

Address for Correspondence:
Professor John J.V. McMurray
British Heart Foundation Cardiovascular Research Centre
University of Glasgow
126 University Place, Glasgow, G12 8TA, United Kingdom
Tel: +44 141 330 3479
Fax: +44 141 330 6955
Email: john.mcmurray@glasgow.ac.uk

ABSTRACT

Introduction: The globalization of clinical trials has highlighted geographic differences in patient characteristics, treatments, and outcomes. We examined these differences in PARADISE-MI.

Methods and results: 23.0% were randomized in Eastern Europe/Russia, 17.5% in Western Europe, 12.2% in Southern Europe, 10.1% in Northern Europe, 12.0% in Latin America (LA), 9.3% in North America (NA), 10.0% in East/South-East Asia and 5.8% in South Asia (SA). Those from Asia, particularly SA, were different from patients enrolled in the other regions, being younger and thinner. They also differed in terms of comorbidities (high prevalence of diabetes and low prevalence of AF), type of MI (more often STEMI), and treatment (low rate of primary PCI). By contrast, patients from LA did not differ meaningfully from those randomized in Europe or NA. Use of ACE-inhibitor/ARB (34.8%) and beta-blockers (65.5%) was low in SA, whereas MRA use was lowest in NA (22%) and highest in Eastern Europe/Russia (53%). Rates of the primary composite outcome of cardiovascular death or incident HF varied two-fold among regions, with the lowest rate in SA (4.6/100person-years) and the highest in LA (9.2/100person-years). Rates of incident HF varied almost six-fold among regions, with the lowest rate in SA (1.0/100person-years) and the highest in Northern Europe (5.9/100person-years). The effect of sacubitril/valsartan was not modified by region.

Conclusion: In PARADISE-MI, there were substantial regional differences in patient characteristics, treatments and outcomes. Although the generalizability of these findings to a "real-world" unselected population may be limited, these findings underscore the importance of considering both regional and within-region differences when designing global clinical trials.

Key words: Myocardial infarction; heart failure; angiotensin blocker-neprilysin inhibitor; geographic region; clinical trial.

INTRODUCTION

In recent decades, cardiovascular outcome trials have become increasingly globalized.[1–5] The inclusion of participants from many different regions of the world not only ensures the timely recruitment of a sufficient number of patients but also improves the generalizability of results beyond Western Europe and Northern America where prior trials were usually conducted. However, globalization has meant that trials are now conducted across many different health care systems, with substantial geographical differences in demographics, comorbidities, other patient characteristics, and background pharmacological and interventional therapies among the patients enrolled.[6,7,16,17,8–15] Some differences may also arise because investigators employ trial inclusion and exclusion criteria differently in different geographic regions. As a result, event rates may also vary by region, and this variation may be greatest for non-fatal events leading to hospital admission.[6,7,16,17,8–15] Because of these differences, the effect of randomized therapy may also vary across geographic regions, and instead of increasing generalizability as hoped, heterogeneity in treatment effect may lead to questioning the applicability of the trial results to all regions of the world.[9,16,17]

The Prospective Angiotensin Receptor-Neprilysin Inhibitor (ARNI) versus Angiotensin-Converting Enzyme (ACE) Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events after Myocardial Infarction (PARADISE-MI) enrolled 5,661 patients with acute myocardial infarction (MI) complicated by a reduced left ventricular ejection fraction (LVEF), pulmonary congestion, or both in 41 countries on 6 continents.[3,18] In this large and globally representative trial, we performed a post hoc examination of geographical differences in patient characteristics, including demographics, comorbidities, management of MI, and clinical outcomes. We also investigated the effect of sacubitril/valsartan, compared with ramipril, according to geographical region.

METHODS

PARADISE-MI was a multinational, randomized, double-blind, active-controlled trial in patients with AMI, evaluating the efficacy and safety of sacubitril/valsartan compared with ramipril. The design, baseline characteristics, and primary results of PARADISE-MI are published.[3,18] The Ethics Committee of each of the 495 participating institutions in 41 countries approved the study protocol, and all patients gave written informed consent.

Study patients

Men and women ≥18 years of age, without known prior HF, with a spontaneous MI, were eligible for inclusion within 0.5 to 7 days of presentation if they had evidence of left ventricular systolic dysfunction (LVEF ≤40%) and/or transient pulmonary congestion requiring intravenous treatment during the index MI and had at least one of the following eight prespecified risk augmenting factors: 1) age ≥70 years; 2) diabetes mellitus; 3) prior MI; 4) estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 at screening; 5) atrial fibrillation associated with the index MI; 6) LVEF <30% associated with the index MI; 7) Killip class III or IV associated with the index MI; or 8) ST-segment elevation MI (STEMI) without reperfusion therapy within the first 24 h of presentation. Key exclusion criteria included clinical instability at the time of randomization (defined as treatment with intravenous diuretics, vasodilators, vasopressors, or inotropes in the 24 hours preceding randomization); eGFR <30 mL/min/1.73m^2; serum potassium >5.2 mmol/L; a history of angioedema; and known intolerance or contraindications to ACE inhibitor or ARB. A complete list of exclusion criteria is provided in the design paper.[18] After randomization, follow-up visits were scheduled for weeks 1, 2, and 4; months 2 and 4; and every 4 months thereafter.

Geographic regions

The following geographic regions according to the United Nations Classification were examined:[19] Northern Europe; Western Europe; Eastern Europe and Russia; Southern Europe; North America; Latin America; South Asia; East Asia; and South-East Asia **(Figure 1)**. A similar classification of regions has been used in other reports, including those from the EPICOR and EPICOR Asia registries.[20,21]We also examined geographic regions as defined in the primary paper: Asia/Pacific and others; Central Europe; Latin America; North America; and Western Europe.

Outcomes

The primary outcome in PARADISE-MI was the composite of cardiovascular death or incident HF (HF hospitalization or an outpatient episode of symptomatic HF treated with intravenous or sustained oral diuretic therapy). The secondary outcomes in the trial were a composite of HF hospitalization or cardiovascular death; a composite of HF hospitalization or an outpatient episode of symptomatic HF; a composite of non-fatal MI, non-fatal stroke, or cardiovascular death; the total number of (first and recurrent) non-fatal cardiovascular events (HF hospitalization, MI, or stroke) or cardiovascular death; cardiovascular death; and all-cause death. Clinical outcomes were adjudicated by an independent clinical endpoint committee blinded to treatment allocation. Prespecified safety analyses included serious adverse events, adverse events leading to discontinuation of trial treatment and adverse events of interest, including angioedema, hypotension, renal dysfunction, hyperkalaemia, and cough.

Statistical analyses

Patients were divided into eight subgroups, based on geographic region. Baseline characteristics were summarized as frequencies with percentages, means with standard deviation (SD), or medians with interquartile ranges. Differences in baseline characteristics were tested using the Chi-square test for categorical variables and the Kruskal-Wallis test and analysis of covariance test for non-normal and

normally distributed continuous variables, respectively. Time-to-event data were evaluated using Cox proportional-hazards models, stratified according to the type of MI, with randomized treatment, percutaneous coronary intervention at baseline, and geographic region included as factors. Total (first and recurrent) events were evaluated with negative binomial regression models with a Weibull baseline intensity function, with randomized treatment, type of MI, percutaneous coronary intervention at baseline, and geographic region included as factors.[22–24] In addition, hazard ratios and rate ratios for time-to-event data and total (first and recurrent) events, respectively, were stratified according to the type of MI and adjusted for randomized treatment, percutaneous coronary intervention at baseline, Killip class, age, sex, race, systolic blood pressure, body mass index, estimated glomerular filtration rate, LVEF, prior MI, diabetes, and atrial fibrillation/flutter. These variables were selected as they are associated with adverse outcomes in patients with MI. To address the competing risk of death, Fine–Gray competing risk analyses were performed to compare the risk of time-to-event outcomes (except for all-cause death) according to region. Subdistribution HRs, adjusted for the same variables as the Cox proportional-hazards models, with 95% CIs were reported. All analyses were conducted using STATA version 16.1 (College Station, TX). A P-value of 0.05 was considered statistically significant.

RESULTS

Of 5,661 patients in PARADISE-MI, 23.0% were randomized in Eastern Europe/Russia, 17.5% in Western Europe, 12.2% in Southern Europe, 10.1% in Northern Europe, 12.0% in Latin America, 9.3% in North America, 10.0% in East/South-East Asia and 5.8% in South Asia.

Baseline characteristics

Demographics

Patients in Northern Europe were the most elderly, with a mean age of 65.5 years and were an average of 8.2 years older than those enrolled in South Asia (who were the youngest). The proportion of women was highest in North America and Eastern Europe/Russia (27.5%) and lowest in Southern Europe (18.8%). The proportion of Black patients was low overall but highest in North America (8.0%) **[Table 1].**

Physiologic measures

BMI varied by region, being highest in Northern America (30.4 kg/m^2) and lowest in South Asia (24.6 kg/m^2). Systolic blood pressure was highest in Eastern Europe/Russia (123 mmHg), consistent with the geographic variation in a history of hypertension (see below) **[Table 1].**

Index MI

Pulmonary congestion varied greatly across regions, with the highest proportion in East/South-East Asia (72.8%) and the lowest in South Asia (31.2%). On the other hand, LVEF was highest among patients enrolled in East/South-East Asia (41.4%) and lowest among those from North America and Northern Europe (33.7% and 33.6%, respectively) **[Table 1, Supplementary Table 1]**. The proportion of patients with more than one risk-augmenting factor was highest in Southern Europe

(55.8%) and lowest in South Asia (46.7%). STEMI was more common in patients enrolled in South Asia (84.5%), but less common in North America (69.1%) and East/South-East Asia (69.7%) **[Table 1, Supplementary Table 1].**

The management of the index MI also varied substantially by region. The proportion of patients with coronary reperfusion was lowest in South Asia (83.3%) and highest in Southern Europe (93.8%). Drug-eluting stents were more commonly used in North America (89.2%) and Southern Europe (89.3%) and less in Latin America (59.4%) **[Table 1].**

Medical history

In general, comorbidity was less common in patients enrolled in South Asia. Prior MI and coronary revascularization were more common in North America and Southern Europe, whereas diabetes and prior stroke were most frequent in East/South-East Asia. Hypertension and current smoking were more common in Eastern Europe/Russia, and atrial fibrillation/flutter was most frequent in Northern and Western Europe. Chronic kidney disease (defined as eGFR <60 mL/min/1.73m^2) was more frequent in Western Europe and Eastern Europe/Russia (34.5% and 33.9%, respectively) than elsewhere **[Table 1].**

Medical treatment at randomization

A high proportion of patients (>88%) received dual antiplatelet therapy and statins across regions, although the proportion of each of these was lowest in South Asia **[Table 1, Figure 2]**. The use of beta-blockers varied greatly among regions, with the highest proportion in North America (92.0%) and the lowest in South Asia (65.5%). On the other hand, the use of mineralocorticoid-receptor antagonists was lowest in North America and South Asia (21.8% and 27.6%, respectively) and highest

in Eastern Europe/Russia (53.0%). Similarly, the use of diuretics was lowest in North America (30.5%) and highest in Eastern Europe/Russia (57.0%).

Biomarkers

Data on biomarkers at baseline according to region are shown in **Supplementary Table 2**.

Outcomes according to region

Primary composite outcome

The unadjusted rate of the primary composite outcome varied two-fold among regions, with the lowest rate in South Asia (4.6 per 100 person-years) and the highest in Latin America (9.2 per 100 person-years) **[Figure 3]**. After adjustment for prognostic variables, and using Western Europe as the reference, the risk of the primary endpoint was lower in other regions (except for Northern Europe and Latin America), but the lower risk was only statistically significant in Eastern Europe/Russia and North America **(Table 2)**.

Heart failure

The unadjusted rate of incident HF varied almost six-fold among regions, with the lowest rate in South Asia (1.0 per 100 person-years) and the highest in Northern Europe (5.9 per 100 person-years) **[Figure 3]**. After adjustment for prognostic variables, and using Western Europe as the reference, the risk of incident HF was lower in other regions (except for Northern Europe), but the lower risk was only statistically significant in Eastern Europe/Russia and South Asia **(Table 2).** The findings for HF hospitalization were similar.

Other cardiovascular outcomes

The unadjusted rate of non-fatal MI, non-fatal stroke, or cardiovascular death was lowest in South Asia and Eastern Europe/Russia (5.0 and 5.7 per 100 person-years, respectively) and highest in Northern Europe (8.5 per 100 person-years). After adjustment for prognostic variables, and using Western Europe as the reference, the risk of this outcome was numerically higher in other regions, but only statistically significant in Northern Europe **(Table 2)**.

Similarly, the unadjusted rate of total non-fatal cardiovascular events (i.e., HF hospitalization, MI, or stroke) and cardiovascular death was lowest in South Asia and Eastern Europe/Russia (7.1 and 9.5 per 100 person-years, respectively) and highest in Northern Europe (15.9 per 100 person-years). Compared with Western Europe, the risk of this outcome was significantly higher in Northern Europe only after adjustment for prognostic variables.

Death

The unadjusted rate of all-cause death varied approximately two-fold among regions, with the lowest rate in North America (2.4 per 100 person-years) and the highest in Latin America (5.3 per 100 person-years) although the rate in the other six regions differed little (range 3.9 to 4.7 per 100 person-years) **[Figure 3]**. After adjustment for prognostic variables, and using Western Europe as the reference, there was a trend toward a lower risk of all-cause death in North America, but a trend towards higher risk in the other regions, which was statistically significant in Eastern Europe/Russia **(Table 2).** The findings for cardiovascular death were overall similar.

The correlation between rates of all-cause mortality and rates of incident HF or HF hospitalization according to geographic region is shown in **Figure 4** and **Supplementary Table 3**. Patients in Eastern Europe/Russia and South Asia had the lowest incident HF/all-cause mortality ratio (0.66 and 0.22, respectively), whereas patients in North America had the highest ratio (1.99). A similar pattern was seen for HF hospitalization.

Adverse events according to region

The proportion of drug discontinuation for any reason was highest in North America (26.1%) and lowest in Latin America (9.3%), and drug discontinuation due to adverse events, and hypotension, occurred more frequently in North America and Northern Europe and less frequently in South Asia. However, hyperkalaemia occurred more frequently in South Asia and less so in Northern Europe (despite a slightly lower use of MRA in South Asia than in Northern Europe), and renal impairment and elevated serum creatinine level was more common in Western and Northern Europe and less in South Asia **(Table 3)**.

Effects of sacubitril/valsartan on outcomes according to region

The effect of sacubitril/valsartan, compared with ramipril, was consistent across regions for the CEC-adjudicated primary composite endpoint and secondary outcomes (P for interaction >0.05) **[Table 4]**. Treatment-related adverse events did not differ significantly across regions (P for interaction >0.05) **[Supplementary Table 4]**.

Regions as defined the primary manuscript

Data on patient characteristics, outcomes, and the effects of sacubitril/valsartan versus ramipril on clinical outcomes according to regions, as defined in the primary paper (i.e., Asia/Pacific and others; Central Europe; Latin America; North America; and Western Europe), are shown in Supplementary Table 5, 6, and 7, respectively.

DISCUSSION

In this post hoc analysis of PARADISE-MI, the characteristics of patients enrolled and the treatments they received varied substantially across the regions examined, as did the crude rates of the outcomes of interest.

Baseline characteristics

PARADISE-MI was more globally diverse than any prior high-risk acute MI trial, with the inclusion of participants from areas previously underrepresented (or not represented), with approximately 16% of patients enrolled in Asia and 9% in Latin America. By comparison, 80-90% of participants in EPHESUS and VALIANT were recruited in either Europe or North America.[13,21]

Examination of the characteristics of participants from these new regions is of interest. Those from Asia, particularly South Asia were notably different from patients enrolled in the other regions, being more often male, younger, and thinner. They also had a notably higher eGFR (possibly reflecting younger age) and heart rate (possibly reflecting the low rate of use of beta-blockers and lower prevalence of atrial fibrillation).[6,7,10,13,14] Patients enrolled in South Asia also differed markedly in terms of history (low rate of smoking and prior MI), comorbidities (high prevalence of diabetes, despite lower BMI, and very low prevalence of atrial fibrillation), type of MI (more often anterior and STEMI), and treatment (low rate of primary PCI and use of beta-blocker, statin, ACE inhibitor/ARB and MRA). By contrast, patients from Latin America did not differ meaningfully from those randomized in Europe or North America. The management of the index MI in the present study was broadly consistent with that observed in global "real-world" cohorts, including the EPICOR and EPICOR Asia registries, although the latter did not solely include high-risk MI patients.[20,21]

The small proportion of women overall enrolled in PARADISE-MI was also notable. Although the rate of myocardial infarction in the population is higher in men than in women, the percentage of

female participants in PARADISE-MI was disproportionately low, as has been highlighted in cardiovascular trials more generally.[22] The proportion of women also varied substantially by region and was highest in North America and Eastern Europe/Russia (27.5%) and lowest in Southern Europe (18.8%) along with Asia. This finding underscores the importance of recent initiatives to increase the representation of women in trials.

Finally, there were striking geographic differences in the use of secondary preventive treatments. In addition to the remarkably low rate of use of ACE inhibitor/ARB (34.8%) and beta-blockers (65.5%) in South Asia, MRA use was lowest in North America (22%), compared with the highest rate (53%) in Eastern Europe/Russia. Diuretic use also varied greatly, with the lowest and highest rates again in North America (30.5%) and Eastern Europe/Russia (57%), respectively. The low rate of use of ACE inhibitors/ARBs and beta-blockers after MI in South Asia (and Asia in general) has also been shown in "real-world" cohorts, including in the EPICOR and EPICOR Asia registries.[20,21]

Event rates

Using Western Europe as a reference, unadjusted event rates were generally highest in Latin America and Northern Europe. However, after adjustment for differences in prognostic variables between regions, few significant differences remained, and the pattern observed differed by the outcome.

The risk of the primary endpoint was significantly lower in Eastern Europe/Russia than in the reference region of Western Europe, yet patients in Eastern Europe/Russia had a significantly higher risk of all-cause mortality (and adjusted risk of cardiovascular death). This discrepancy was wholly explained by the much lower rate of incident HF events and HF hospitalization reported in Eastern Europe/Russia. Indeed, a 4 to 6-fold difference in these events was observed across the geographical regions studied (compared with a 2-fold difference in crude mortality rates). A similar paradoxical pattern of a low rate of the primary outcome, despite relatively high mortality, was observed in the

South Asian region (India) for the same reason. It is unclear whether this was due to a lower incidence of HF, lower ascertainment of incident HF, higher threshold for hospitalization or some combination of these.

A completely different picture was seen in North America. Patients in North America also had a significantly lower risk of the primary endpoint than in the reference region (Western Europe), but the risk of all cause-mortality was lower in North America than in other regions.

The high unadjusted event rates in Latin America and Northern Europe were also reflected in a higher adjusted risk of cardiovascular death in these 2 regions, compared with Western Europe, of the composite of cardiovascular death, myocardial infarction, and stroke in Northern Europe. The high crude rates and adjusted risk in the Northern European region is one of the surprising findings in this study, although do reflect the geographic variations in population mortality related to coronary heart disease reported within Europe which have raised interesting questions about other potential influences such as diet, lifestyle, climate, and environment on outcomes.

To our knowledge, EPHESUS is the only large trial in which geographical variation in clinical outcomes was examined in patients with an acute MI complicated by left ventricular dysfunction and/or pulmonary congestion. In EPHESUS, there was no difference in cardiovascular and all-cause mortality between patients recruited in North America and Europe (as a whole). However, the conduct of EPHESUS and PARADISE-MI was different, and the former trial, which was conducted 20 years ago, was not as geographically diverse as the latter. [25] However, the significant regional variation in HF hospitalization rates in PARADISE-MI was broadly consistent with that observed in more recent HF trials, most of which also found that hospitalization rates were lowest in Eastern Europe/Russia and, in PARADIGM-HF, South Asia (but higher in North America).[6–8,26] The greater variation across regions in HF hospitalization rates, compared with mortality rates, is not unexpected given the differences in health care systems and access, thresholds for admission, and programs to prevent

hospitalizations. What is clear is that there is not a direct correlation between hospitalization rates for HF and mortality rates with, for example, similar mortality rates in both Asian regions and Northern and Southern Europe and Eastern Europe/Russia but markedly different rates of hospitalization across these regions.

Regional differences in outcomes after MI have also been examined in large, international registries. For example, in the EPICOR and EPICOR Asia registries, patients enrolled in Latin America had a higher 2-year mortality rate in than any of the other regions examined.[20,21] Although this is consistent with our findings, there were also some notable differences. Whereas the mortality rate in Northern Europe was among the highest in PARADISE-MI, the opposite was true in EPICOR. This discrepancy may reflect differences in MI phenotype (i.e., patients enrolled in PARADISE-MI were high-risk patients) and characteristics (e.g., individuals from Northern Europe were much older in PARADISE-MI than in EPICOR).[20,21]

Importantly, the present study also revealed significant differences within, as well as between, regions, e.g., South Asian compared with East and South-East Asia and, as alluded to above, within Europe, beyond the usual comparison between Eastern Europe/Russia and the rest of that continent. This finding underscores the importance of considering both regional and within-region differences when designing global clinical trials (see below).[26,27]

It is also worth noting the major decline in mortality associated with high-risk acute MI. In the VALIANT trial, the annualized mortality rate was 9.8 per 100 person-years compared with 4.2 per 100 person-years in PARADISE-MI, with such striking changes in event rates a major factor driving the globalization of clinical trials, as discussed below.

Implications

Advances in the pharmacological and procedural management of patients with acute MI have led to significant improvements in prognosis,[28–31] and contemporary clinical trials require large numbers of events to detect even a moderately large effect of therapy. To recruit the number of patients needed promptly, and to improve the generalizability of results, new therapies are increasingly tested in global trials.[1–5] However, the substantial geographic differences in demographics, comorbidities, other patient characteristics, health care systems, and background evidence-based therapies, can also be of concern.[9,16,17] Despite common inclusion and exclusion criteria, there was considerable geographic variation in patient characteristics, treatments, and outcomes in PARADISE-MI. With an increasing understanding of these differences, more informed choices can be made about the most appropriate countries to include in specific trials. For example, countries with a low rate of HF hospitalization will slow the rate of accrual of this endpoint and likely increase treatment heterogeneity by region when examining the effect of a new therapy, such as sacubitril/valsartan, the major effect of which is on HF hospitalization. Similar considerations are relevant to the inclusion of women and certain racial minorities in trials. Monitoring of patient characteristics and event rates by region (and even within regions) during the conduct of the trial is advisable, and capping enrolment by country may be appropriate.[1,32]

Limitations

This study has some limitations. First, this was not a prospectively planned analysis. Like any other clinical trial, PARADISE-MI had prespecified eligibility criteria for enrolment in the trial; patients enrolled in clinical trials are not fully representative of the general population (e.g., the use of evidence-based therapy is greater in clinical trials and very high-risk patients are excluded, and the degree of exclusion may vary by region), which may affect the generalizability of our results to a "real-world" unselected population. Second, although region was a prespecified subgroup, the trial

was not specifically powered to evaluate regional differences. As a result, the tests for interaction between region and the effect of treatment were likely to be substantially underpowered. Third, we compared recognized geographical regions, but there may also be significant differences between countries within these regions, which were not captured by regional classification. Fourth, the number of patients recruited in certain regions was limited (e.g., South Asia), and the number of Black patients enrolled was low. Fifth, although we performed multivariable adjustment when comparing outcomes between regions, the possibility of residual confounding cannot be excluded.

Conclusion

In PARADISE-MI, there were substantial regional differences in patient characteristics, treatments, and outcomes after acute MI complicated by left ventricular dysfunction and/or pulmonary congestion. Although the generalizability of these findings to a "real-world" unselected population may be limited, these findings underscore the importance of considering both regional and within-region differences when designing global clinical trials.

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Conflict of interest

Dr. Butt reports advisory board honoraria from Bayer, outside the submitted work. Dr Claggett has received consulting fees from Boehringer Ingelheim. Dr Solomon has received research grants from Actelion, Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, Bristol Myers Squibb, Celladon, Cytokinetics, Eidos, Gilead, GlaxoSmithKline, Ionis, Lilly, Mesoblast, MyoKardia, National Institutes of Health/NHLBI, Neurotronik, Novartis, NovoNordisk, Respicardia, Sanofi Pasteur, Theracos, US2.AI; and has consulted for Abbott, Action, Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GlaxoSmithKline, Lilly, Merck, Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Cardurion, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellPro-Thera, Moderna, American Regent, and Sarepta. Dr. McMurray reports grants from AstraZeneca. The other authors declare no conflict of interest.

Data availability statement

Trial data will be made available by the sponsor, Novartis, in accordance with their data sharing policy.

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FIGURE LEGENDS

Figure 1. Geographic regions

Countries were assigned to the following regions defined by the United Nations Classification: Northern Europe: Denmark, Finland, Norway, Sweden, United Kingdom (including South Africa and Australia); Western Europe: Austria, Belgium, France, Germany, Netherlands, Switzerland; Eastern Europe and Russia: Bulgaria, Czech Republic, Hungary, Poland, Romania, Russian Federation, Slovakia; Southern Europe: Croatia, Greece, Italy, Portugal, Spain, Turkey, Israel; North America: United States, Canada; Latin America: Argentina, Brazil, Colombia, Mexico, Peru; South Asia: India; East Asia and South-East Asia: China, Korea, Taiwan, Philippines, Singapore, Thailand. South Africa and Australia were assigned to the Northern Europe region, as these are part of the British Commonwealth. Israel was assigned to the Southern Europe region.

Figure 2. Medical treatment according to region

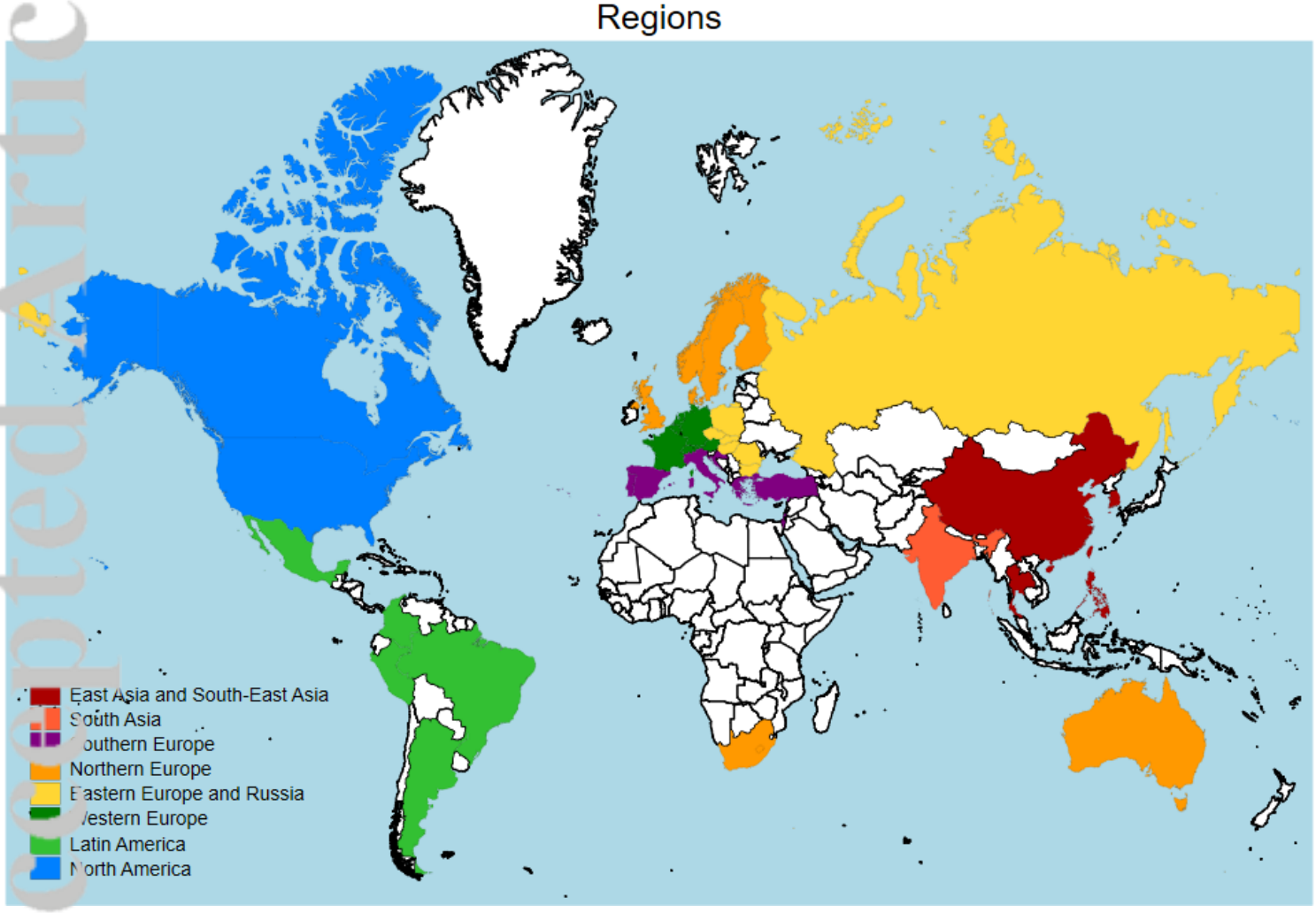
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid-receptor antagonist.

Figure 3. Incidence rates of outcomes per 100 person-years according to region

Figure 4. Correlation between rate of all-cause mortality and rate of adjudicated heart failure endpoints according to region

HF, heart failure.

The events rates are calculated as the number of events per 100 person-years of follow-up. Incident HF is defined as the composite of HF hospitalization or outpatient HF.



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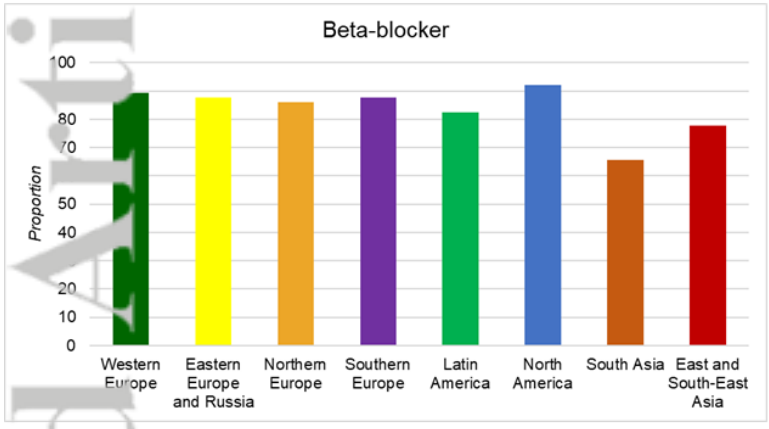

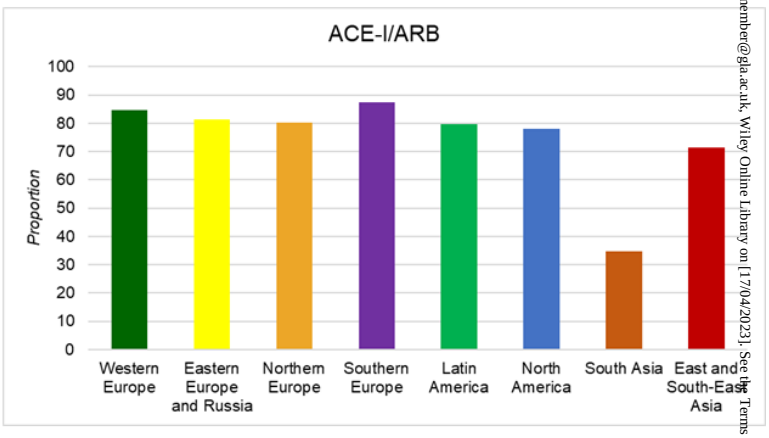

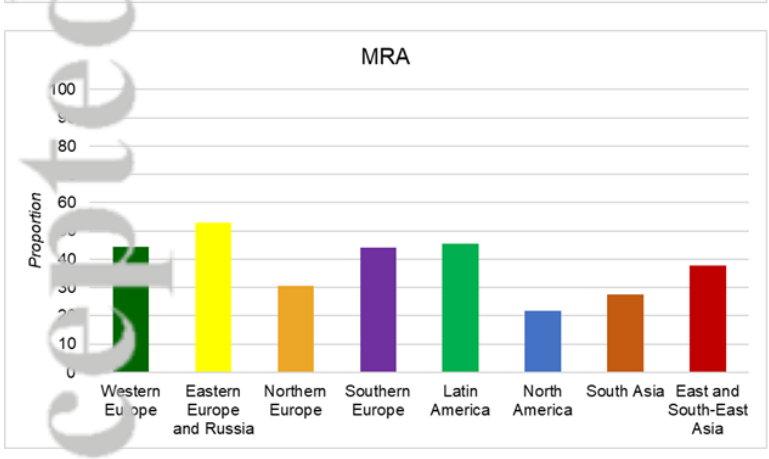

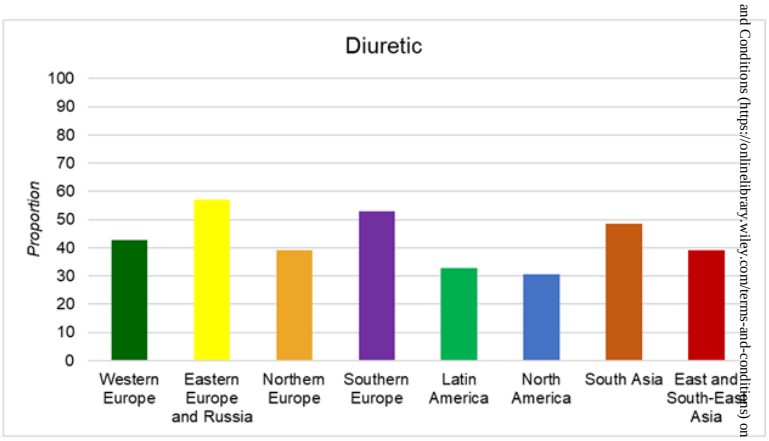

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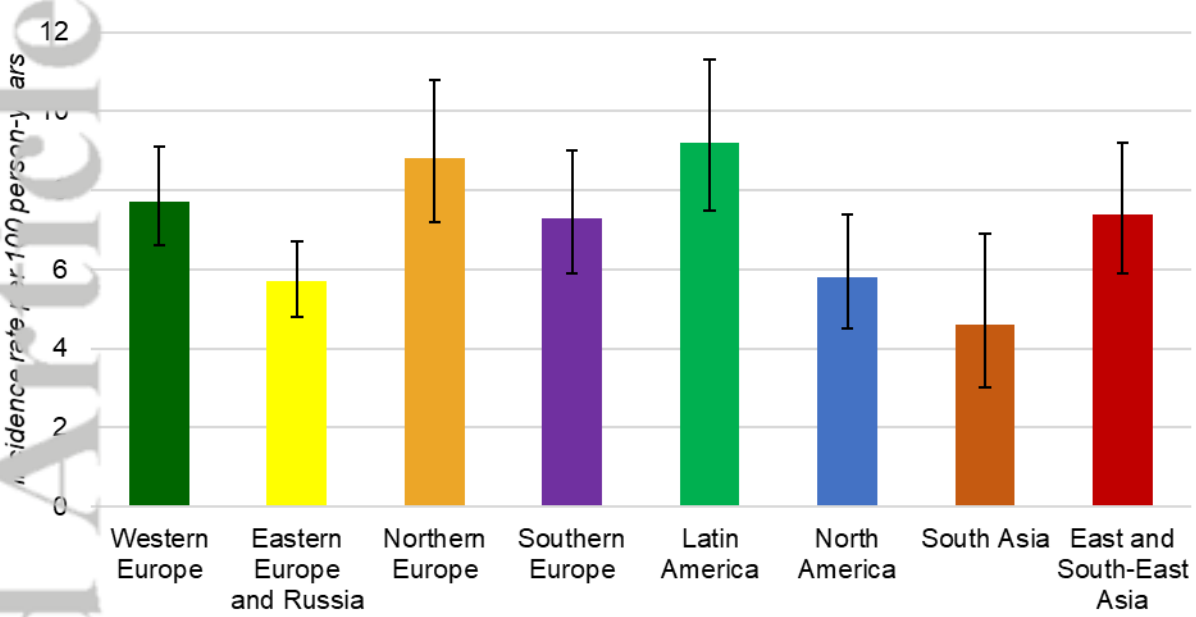
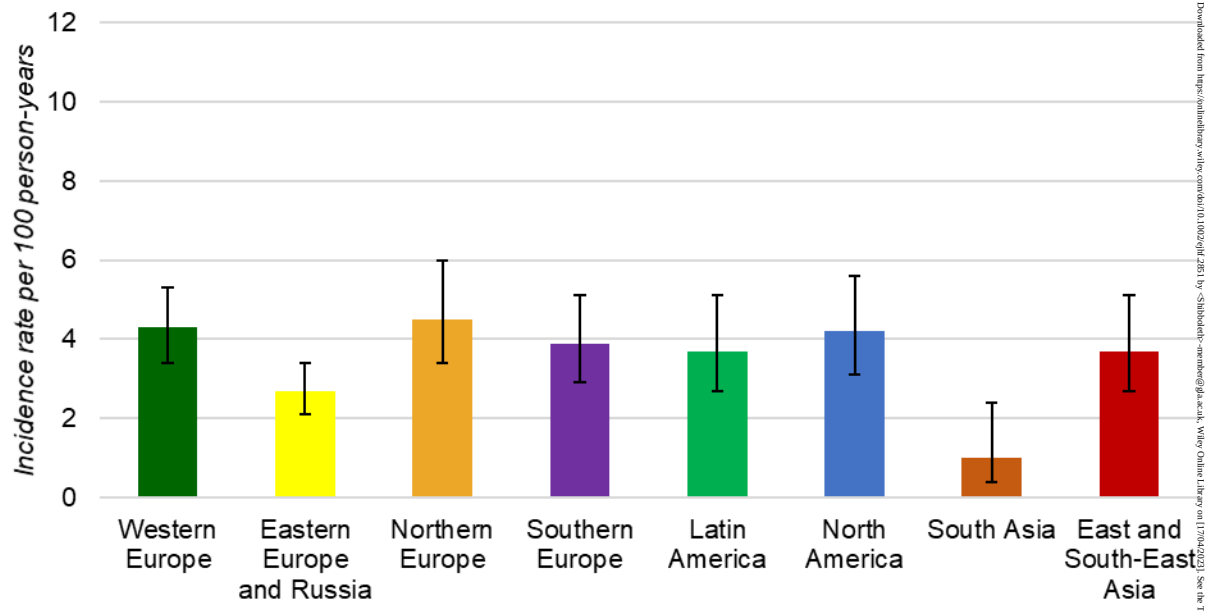
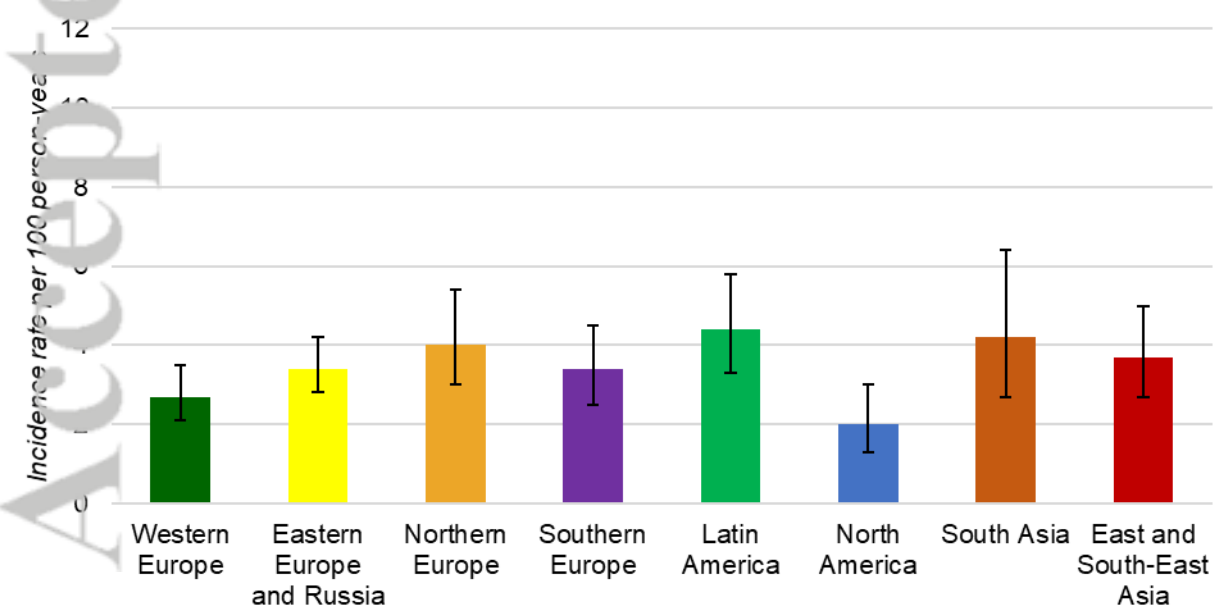
Primary composite outcome



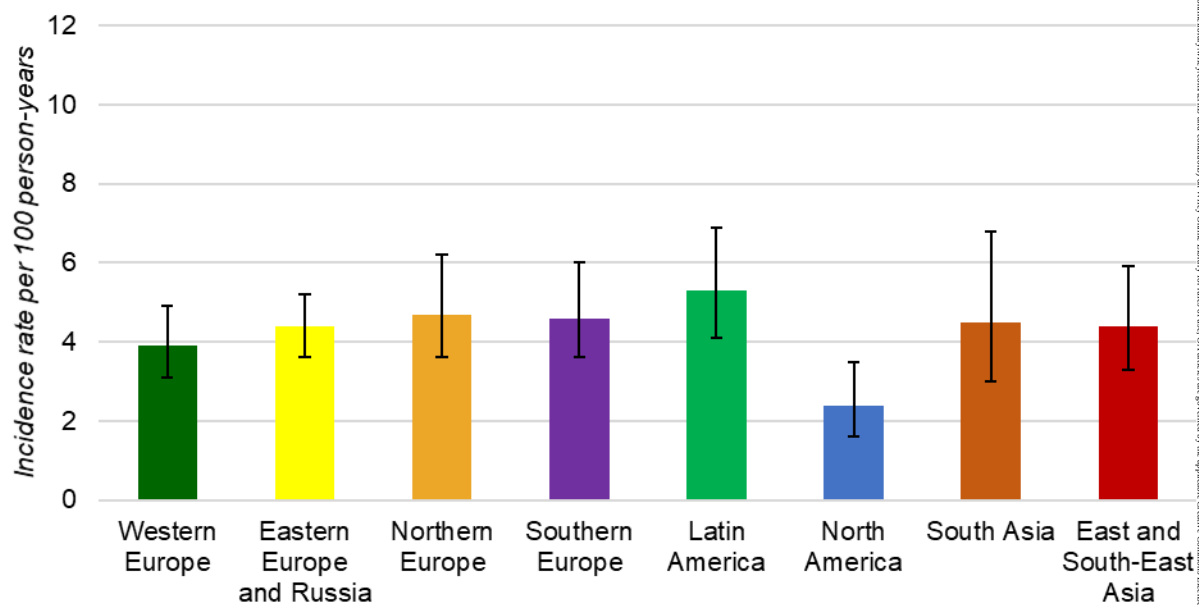
HF hospitalisation



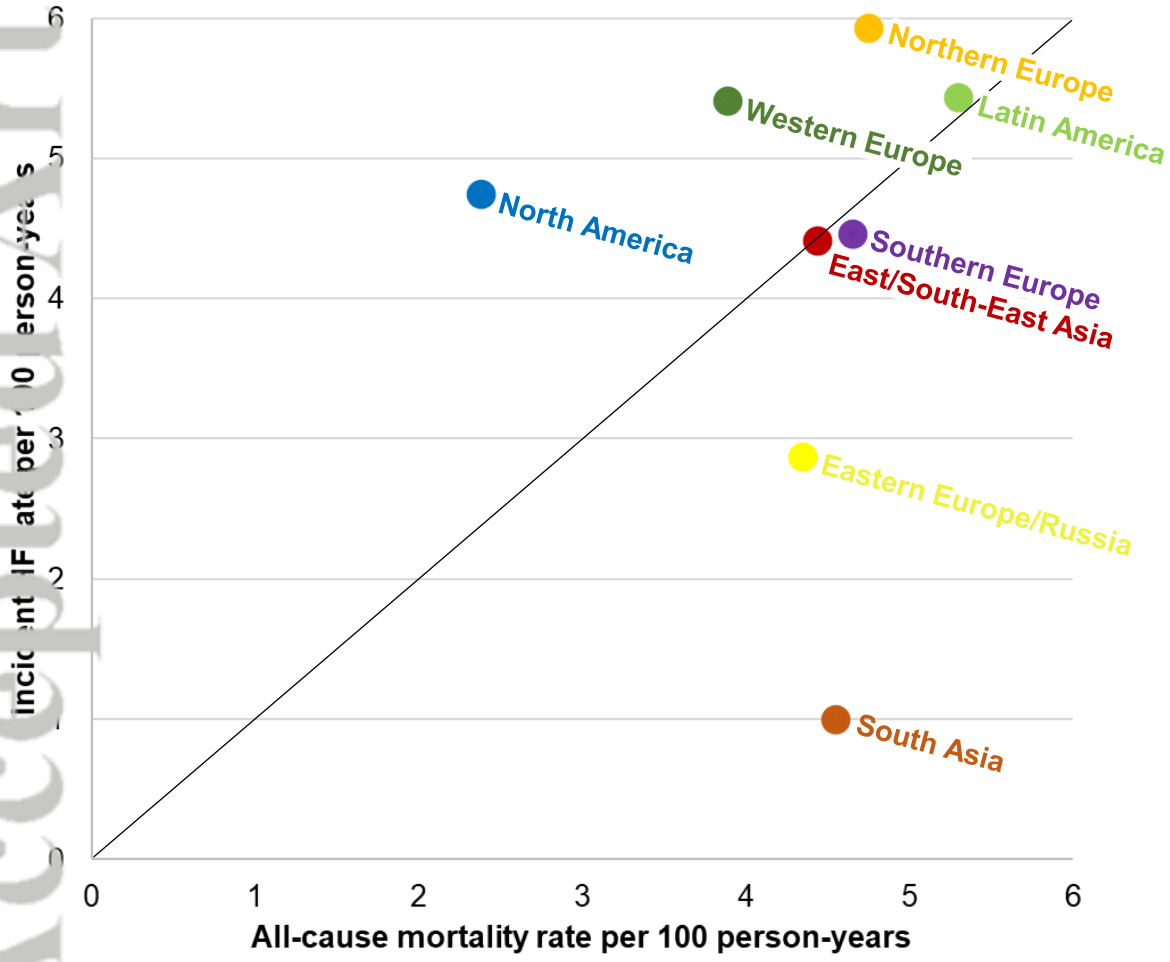
Cardiovascular death



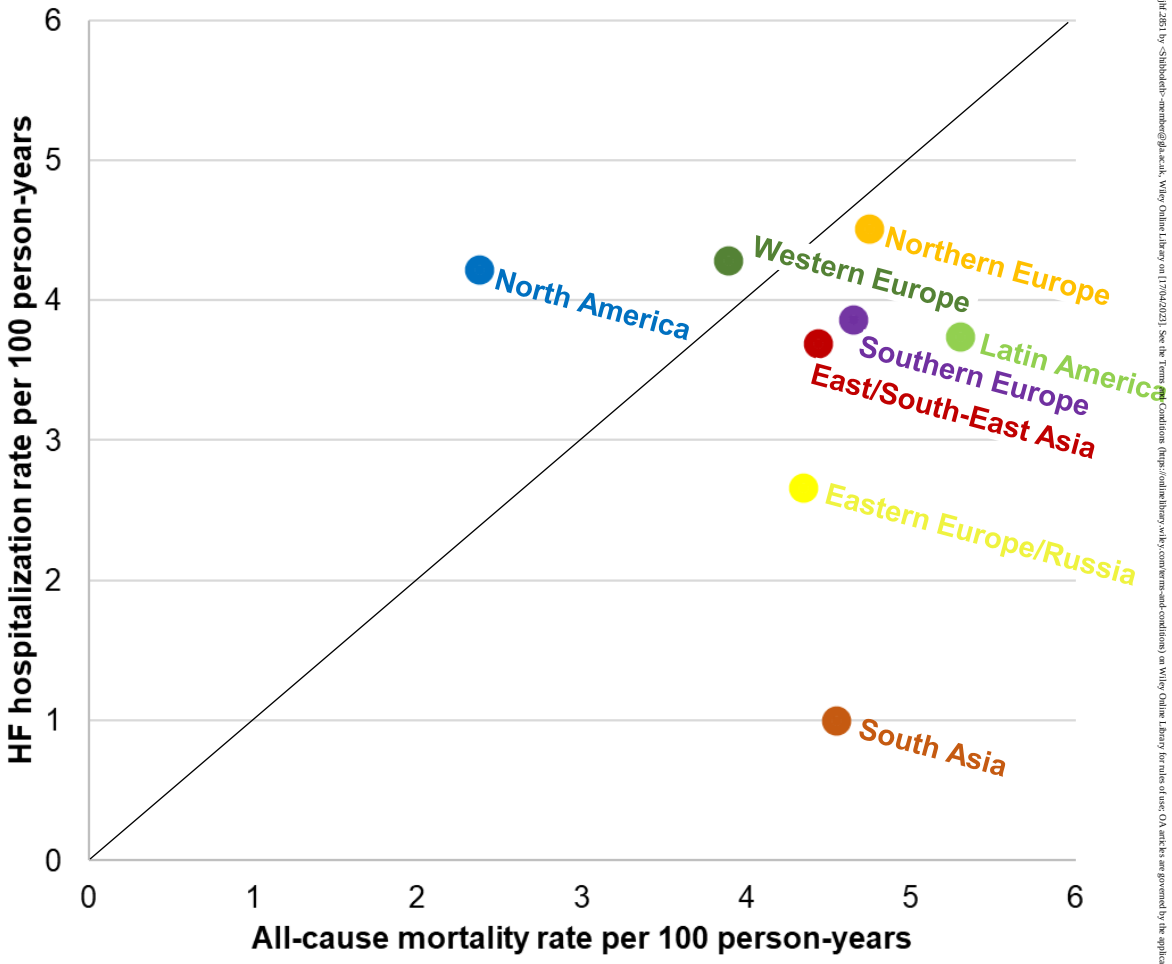
All-cause death



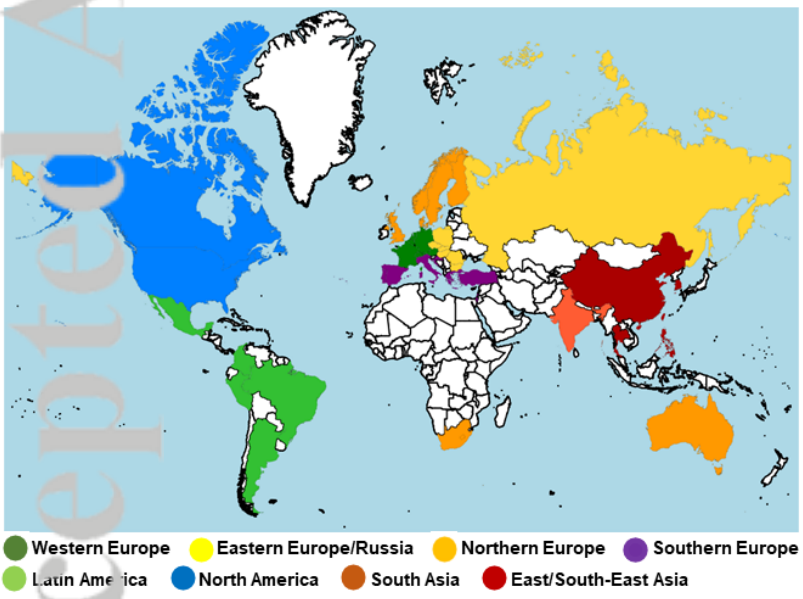
a) Incident HF and all-cause mortality rates



b) HF hospitalization and all-cause mortality rates



PARADISE-MI enrolled 5,661 patients with high-risk AMI complicated by reduced LVEF, pulmonary congestion, or both in 41 countries on 6 continents



There were substantial regional differences in outcomes, underscoring the importance of considering regional differences when designing global clinical trials

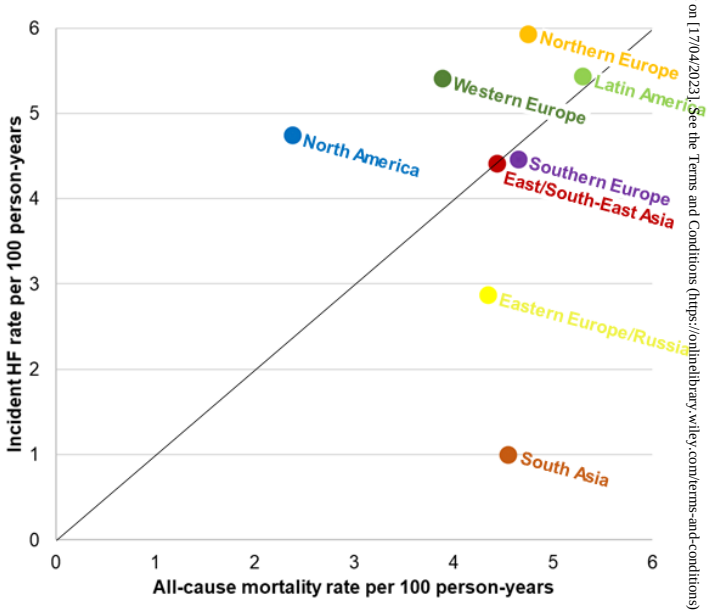


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Table 1. Baseline characteristics according to region

	Overall N=5,661	Western Europe N=989	Eastern Europe and Russia N=1,304	Northern Europe N=574	Southern Europe N=690	Latin America N=679	North America N=528	South Asia N=330	East and South-East Asia N=567	P-value
Age (years), mean (SD)	63.7 ± 11.5	65.3 ± 11.9	63.7 ± 10.7	65.5 ± 11.0	64.3 ± 11.9	63.9 ± 11.1	63.0 ± 11.5	57.3 ± 11.5	62.8 ± 11.5	<0.001
Age, N (%)										
<70 years	3,711 (65.6)	578 (58.4)	878 (67.3)	327 (57.0)	431 (62.5)	467 (68.8)	362 (68.6)	283 (85.8)	385 (67.9)	
≥70 years	1,950 (34.4)	411 (41.6)	426 (32.7)	247 (43.0)	259 (37.5)	212 (31.2)	166 (31.4)	47 (14.2)	182 (32.1)	
Female sex, N (%)	1,363 (24.1)	232 (23.5)	358 (27.5)	131 (22.8)	130 (18.8)	178 (26.2)	145 (27.5)	66 (20.0)	123 (21.7)	<0.001
Race, N (%)										<0.001
Asian	953 (16.8)	17 (1.7)	0 (0.0)	3 (0.5)	8 (1.2)	2 (0.3)	27 (5.1)	330 (100.0)	566 (99.8)	
Black	75 (1.3)	5 (0.5)	0 (0.0)	4 (0.7)	1 (0.1)	23 (3.4)	42 (8.0)	0 (0.0)	0 (0.0)	
White	4,263 (75.3)	931 (94.1)	1300 (99.7)	516 (89.9)	670 (97.1)	400 (58.9)	446 (84.5)	0 (0.0)	0 (0.0)	
Other	370 (6.5)	36 (3.6)	4 (0.3)	51 (8.9)	11 (1.6)	254 (37.4)	13 (2.5)	0 (0.0)	1 (0.2)	
Physiologic measures, mean (SD)										
Heart rate (bpm)	75.7 ± 11.8	76.1 ± 12.7	74.3 ± 10.4	75.6 ± 13.5	74.1 ± 11.2	75.1 ± 10.7	77.0 ± 13.1	80.0 ± 10.6	77.0 ± 11.5	<0.001
Pulse pressure (mmHg)	47.2 ± 11.8	47.4 ± 12.7	47.8 ± 10.4	47.2 ± 13.3	47.7 ± 12.9	46.4 ± 10.8	47.0 ± 12.3	43.8 ± 10.3	47.3 ± 11.3	<0.001
Systolic blood pressure (mmHg)	120.9 ± 13.3	120.6 ± 14.3	123.2 ± 11.7	120.7 ± 15.8	119.2 ± 13.6	119.5 ± 12.4	120.3 ± 13.6	121.7 ± 11.7	119.9 ± 13.1	<0.001
Diastolic blood pressure (mmHg)	73.8 ± 9.8	73.3 ± 10.3	75.3 ± 8.4	73.5 ± 11.1	71.5 ± 10.2	73.1 ± 9.4	73.4 ± 9.8	77.8 ± 7.5	72.7 ± 10.1	<0.001
BMI (kg/m^2)	28.1 ± 5.0	28.1 ± 4.8	29.0 ± 4.8	28.8 ± 5.0	28.2 ± 4.5	28.3 ± 4.7	30.4 ± 6.3	24.6 ± 3.9	25.0 ± 3.9	<0.001
eGFR (mL/min/1.73m^2)	71.8 ± 22.4	69.1 ± 20.9	69.4 ± 21.5	69.9 ± 19.8	71.9 ± 23.7	77.8 ± 24.8	72.4 ± 21.9	81.1 ± 24.7	70.9 ± 21.1	<0.001
eGFR (mL/min/1.73m^2), N (%)										
<60	1,716 (31.0)	335 (34.5)	434 (33.9)	180 (32.3)	223 (32.9)	147 (22.1)	151 (29.7)	61 (18.8)	185 (33.8)	
≥60	3,813 (69.0)	635 (65.5)	846 (66.1)	377 (67.9)	454 (67.1)	518 (77.9)	357 (70.3)	264 (81.2)	362 (66.2)	
Left ventricular ejection fraction, mean (SD)	36.5 ± 9.4	34.2 ± 8.0	37.5 ± 8.9	33.6 ± 8.5	36.7 ± 8.9	39.5 ± 10.2	33.7 ± 8.6	34.4 ± 6.3	41.4 ± 11.9	<0.001
Left ventricular ejection fraction, N (%)										
<30	1,189 (21.3)	263 (27.3)	252 (19.3)	162 (29.0)	133 (19.4)	97 (14.7)	140 (26.6)	73 (22.1)	69 (12.5)	
≥30	4,390 (78.7)	700 (72.7)	1052 (80.7)	396 (71.0)	552 (80.6)	565 (85.3)	387 (73.4)	257 (77.9)	481 (87.5)	
Pulmonary congestion, N (%)	3,056 (54.0)	437 (44.2)	758 (58.1)	264 (46.0)	389 (56.4)	460 (67.7)	232 (43.9)	103 (31.2)	413 (72.8)	<0.001
>1 risk-augmenting factors, N (%)	2,954 (52.2)	536 (54.2)	678 (52.0)	304 (53.0)	385 (55.8)	338 (49.8)	257 (48.7)	154 (46.7)	302 (53.3)	0.05
Index MI, N (%)										
Location of MI										<0.001
Anterior	3,853 (68.1)	683 (69.1)	883 (67.7)	398 (69.3)	457 (66.2)	441 (64.9)	360 (68.2)	254 (77.0)	377 (66.5)	
Inferior	1,053 (18.6)	185 (18.7)	257 (19.7)	117 (20.4)	117 (17.0)	134 (19.7)	86 (16.3)	62 (18.8)	95 (16.8)	
Other	755 (13.3)	121 (12.2)	164 (12.6)	59 (10.3)	116 (16.8)	104 (15.3)	82 (15.5)	14 (4.2)	95 (16.8)	
STEMI	4,291 (75.8)	763 (77.1)	1010 (77.5)	456 (79.4)	506 (73.3)	517 (76.1)	365 (69.1)	279 (84.5)	395 (69.7)	<0.001
Coronary reperfusion	5,037 (89.0)	903 (91.3)	1119 (85.8)	523 (91.1)	647 (93.8)	582 (85.7)	492 (93.2)	275 (83.3)	496 (87.5)	<0.001
STEMI without reperfusion within 24 h	496 (8.8)	85 (8.6)	95 (7.3)	42 (7.3)	28 (4.1)	108 (15.9)	11 (2.1)	65 (19.7)	62 (10.9)	<0.001
Thrombolytic therapy	253 (4.5)	2 (0.2)	48 (3.7)	16 (2.8)	19 (2.8)	65 (9.6)	12 (2.3)	51 (15.5)	40 (7.1)	<0.001
Percutaneous coronary intervention	4,980 (88.0)	897 (90.7)	1109 (85.0)	513 (89.4)	647 (93.8)	575 (84.7)	488 (92.4)	259 (78.5)	492 (86.8)	<0.001
Drug-eluting stent	4,458 (78.7)	870 (88.0)	940 (72.1)	471 (82.1)	616 (89.3)	403 (59.4)	471 (89.2)	251 (76.1)	436 (76.9)	<0.001
Killip class										<0.001
I-II	4,045 (73.8)	719 (74.0)	984 (75.6)	417 (75.8)	531 (77.5)	501 (75.8)	385 (75.5)	139 (56.7)	369 (66.2)	

III-IV	1,437 (26.2)	253 (26.0)	318 (24.4)	133 (24.2)	154 (22.5)	160 (24.2)	125 (24.5)	106 (43.3)	188 (33.8)	
Length of hospital stay (days), mean (SD)		7.7 ± 5.2	8.2 ± 5.5	5.7 ± 6.8	8.0 ± 14.9	6.0 ± 3.7	4.0 ± 4.6	4.0 ± 2.2	8.0 ± 17.1	<0.001
Time to randomization (days), mean (SD)	4.3 ± 1.8	4.0 ± 1.8	4.3 ± 1.7	4.0 ± 1.8	4.6 ± 1.7	5.0 ± 1.5	4.1 ± 1.8	3.5 ± 1.6	4.9 ± 1.7	<0.001
Medical history, N (%)										
Prior MI	920 (16.3)	163 (16.5)	196 (15.0)	93 (16.2)	142 (20.6)	118 (17.4)	103 (19.5)	29 (8.8)	76 (13.4)	<0.001
Prior CABG or PCI	934 (16.5)	191 (19.3)	150 (11.5)	93 (16.2)	154 (22.3)	121 (17.8)	127 (24.1)	20 (6.1)	78 (13.8)	<0.001
Prior stroke	263 (4.6)	48 (4.9)	69 (5.3)	21 (3.7)	33 (4.8)	25 (3.7)	24 (4.5)	1 (0.3)	42 (7.4)	<0.001
Hypertension	3,676 (64.9)	572 (57.8)	1028 (78.8)	303 (52.8)	473 (68.6)	447 (65.8)	384 (72.7)	103 (31.2)	366 (64.6)	<0.001
Diabetes	2,401 (42.4)	317 (32.1)	507 (38.9)	187 (32.6)	363 (52.6)	318 (46.8)	244 (46.2)	155 (47.0)	310 (54.7)	<0.001
Atrial fibrillation/flutter	784 (13.8)	180 (18.2)	216 (16.6)	106 (18.5)	102 (14.8)	54 (8.0)	69 (13.1)	5 (1.5)	52 (9.2)	<0.001
Current smoking	1,196 (21.1)	196 (19.8)	368 (28.2)	103 (17.9)	190 (27.5)	100 (14.7)	80 (15.2)	19 (5.8)	140 (24.7)	<0.001
Implantable cardioverter-defibrillator, N (%)	19 (0.3)	4 (0.4)	3 (0.2)	3 (0.5)	4 (0.6)	1 (0.1)	2 (0.4)	1 (0.3)	1 (0.2)	0.83
Medical treatment at randomization, N (%)										
Dual antiplatelet therapy	5,222 (92.2)	885 (89.5)	1223 (93.8)	519 (90.4)	644 (93.3)	640 (94.3)	486 (92.0)	292 (88.5)	533 (94.0)	<0.001
Beta-blocker	4,827 (85.3)	883 (89.3)	1143 (87.7)	494 (86.1)	605 (87.7)	560 (82.5)	486 (92.0)	216 (65.5)	440 (77.6)	<0.001
Mineralocorticoid-receptor antagonist	2,338 (41.3)	438 (44.3)	691 (53.0)	176 (30.7)	304 (44.1)	309 (45.5)	115 (21.8)	91 (27.6)	214 (37.7)	<0.001
Diuretic	2,521 (44.5)	423 (42.8)	743 (57.0)	225 (39.2)	364 (52.8)	223 (32.8)	161 (30.5)	160 (48.5)	222 (39.2)	<0.001
Statin	5,370 (94.9)	933 (94.3)	1255 (96.2)	548 (95.5)	640 (92.8)	657 (96.8)	504 (95.5)	296 (89.7)	537 (94.7)	<0.001
ACEI/ARB*	4,436 (78.4)	836 (84.5)	1062 (81.4)	461 (80.3)	603 (87.4)	542 (79.8)	412 (78.0)	115 (34.8)	405 (71.4)	<0.001

**Within 7 days before randomization.*

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; bpm, beats per minute; CABG, coronary artery bypass graft surgery; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction.

Table 2. Adjudicated clinical events according to region

Clinical endpoint committee-adjudicated	Western Europe N=989	Eastern Europe and Russia N=1,304	Northern Europe N=574	Southern Europe N=690	Latin America N=679	North America N=528	South Asia N=330	East and South-East Asia N=567
Primary composite outcome								
N	139	139	92	90	92	61	23	75
Event rate per 100 person-years (95% CI)	7.7 (6.6-9.1)	5.7 (4.8-6.7)	8.8 (7.2-10.8)	7.3 (5.9-9.0)	9.2 (7.5-11.3)	5.8 (4.5-7.4)	4.6 (3.0-6.9)	7.4 (5.9-9.2)
HR (95% CI)*	Reference	0.71 (0.56-0.90)	1.15 (0.88-1.50)	0.94 (0.72-1.23)	1.00 (0.77-1.30)	0.77 (0.57-1.04)	0.50 (0.32-0.78)	0.90 (0.68-1.19)
HR (95% CI)**	Reference	0.77 (0.60-0.99)	1.14 (0.86-1.51)	0.88 (0.66-1.16)	1.07 (0.78-1.47)	0.70 (0.50-0.97)	0.65 (0.26-1.60)	0.84 (0.36-1.95)
sHR (95% CI)**	Reference	0.77 (0.60-1.00)	1.15 (0.87-1.53)	0.87 (0.65-1.16)	1.07 (0.77-1.50)	0.70 (0.50-0.98)	0.63 (0.25-1.59)	0.83 (0.35-1.95)
HF hospitalization or cardiovascular death								
N	120	134	79	84	77	57	23	69
Event rate per 100 person-years (95% CI)	6.6 (5.5-7.9)	5.5 (4.6-6.5)	7.4 (6.0-9.2)	6.8 (5.5-8.4)	7.6 (6.1-9.5)	5.3 (4.1-6.9)	4.6 (3.0-6.9)	6.7 (5.3-8.5)
HR (95% CI)*	Reference	0.80 (0.63-1.03)	1.14 (0.86-1.51)	1.03 (0.78-1.36)	0.96 (0.72-1.29)	0.83 (0.61-1.14)	0.58 (0.37-0.91)	0.95 (0.71-1.28)
HR (95% CI)**	Reference	0.89 (0.68-1.16)	1.14 (0.85-1.55)	0.97 (0.71-1.31)	1.05 (0.74-1.49)	0.80 (0.57-1.13)	0.67 (0.27-1.66)	0.78 (0.33-1.83)
sHR (95% CI)**	Reference	0.89 (0.68-1.16)	1.15 (0.85-1.56)	0.96 (0.71-1.30)	1.05 (0.73-1.51)	0.80 (0.57-1.13)	0.65 (0.26-1.65)	0.77 (0.33-1.84)
HF hospitalization or outpatient HF								
N	97	70	62	55	54	50	5	45
Event rate per 100 person-years (95% CI)	5.4 (4.4-6.6)	2.9 (2.3-3.6)	5.9 (4.6-7.6)	4.5 (3.4-5.8)	5.4 (4.2-7.1)	4.7 (3.6-6.3)	1.0 (0.4-2.4)	4.4 (3.3-5.9)
HR (95% CI)*	Reference	0.52 (0.38-0.71)	1.12 (0.81-1.53)	0.82 (0.59-1.14)	0.85 (0.61-1.19)	0.91 (0.65-1.28)	0.16 (0.06-0.39)	0.78 (0.55-1.11)
HR (95% CI)**	Reference	0.52 (0.38-0.72)	1.05 (0.75-1.47)	0.73 (0.52-1.04)	0.86 (0.58-1.27)	0.73 (0.50-1.06)	0.19 (0.05-0.65)	0.67 (0.26-1.71)
sHR (95% CI)**	Reference	0.52 (0.38-0.72)	1.05 (0.74-1.48)	0.74 (0.52-1.04)	0.85 (0.56-1.31)	0.75 (0.51-1.12)	0.18 (0.05-0.64)	0.65 (0.25-1.70)
HF hospitalization								
N	78	65	48	48	38	45	5	38
Event rate per 100 person-years (95% CI)	4.3 (3.4-5.3)	2.7 (2.1-3.4)	4.5 (3.4-6.0)	3.9 (2.9-5.1)	3.7 (2.7-5.1)	4.2 (3.1-5.6)	1.0 (0.4-2.4)	3.7 (2.7-5.1)
HR (95% CI)*	Reference	0.61 (0.44-0.85)	1.07 (0.75-1.54)	0.89 (0.62-1.27)	0.74 (0.50-1.09)	1.01 (0.70-1.46)	0.20 (0.08-0.49)	0.82 (0.55-1.20)
HR (95% CI)**	Reference	0.61 (0.43-0.86)	1.03 (0.70-1.50)	0.79 (0.54-1.17)	0.73 (0.46-1.16)	0.85 (0.57-1.28)	0.19 (0.05-0.68)	0.56 (0.21-1.46)
sHR (95% CI)**	Reference	0.61 (0.43-0.87)	1.03 (0.70-1.50)	0.80 (0.55-1.16)	0.73 (0.44-1.20)	0.88 (0.59-1.33)	0.19 (0.05-0.67)	0.54 (0.20-1.45)
Cardiovascular death								
N	53	86	46	44	46	23	21	40
Event rate per 100 person-years (95% CI)	2.7 (2.1-3.5)	3.4 (2.8-4.2)	4.0 (3.0-5.4)	3.4 (2.5-4.5)	4.4 (3.3-5.8)	2.0 (1.3-3.0)	4.2 (2.7-6.4)	3.7 (2.7-5.0)
HR (95% CI)*	Reference	1.18 (0.84-1.67)	1.49 (1.00-2.21)	1.27 (0.85-1.90)	1.36 (0.91-2.02)	0.74 (0.46-1.22)	1.27 (0.76-2.12)	1.27 (0.84-1.91)
HR (95% CI)**	Reference	1.56 (1.07-2.27)	1.57 (1.03-2.40)	1.30 (0.84-2.02)	1.63 (1.00-2.66)	0.81 (0.47-1.38)	3.87 (0.63-23.80)	2.69 (0.45-16.14)
sHR (95% CI)**	Reference	1.55 (1.05-2.28)	1.57 (1.02-2.40)	1.29 (0.82-2.02)	1.62 (0.97-2.72)	0.81 (0.47-1.39)	3.71 (0.68-20.20)	2.64 (0.50-13.81)
Non-fatal MI, non-fatal stroke, or cardiovascular death								
N	106	139	91	89	79	67	25	68
Event rate per 100 person-years (95% CI)	5.7 (4.7-6.9)	5.7 (4.8-6.7)	8.5 (6.9-10.5)	7.1 (5.7-8.7)	7.8 (6.2-9.7)	6.4 (5.0-8.1)	5.0 (3.4-7.4)	6.6 (5.2-8.3)
HR (95% CI)*	Reference	0.96 (0.75-1.24)	1.51 (1.14-1.99)	1.25 (0.94-1.66)	1.19 (0.89-1.59)	1.12 (0.82-1.52)	0.76 (0.49-1.18)	1.09 (0.80-1.48)

HR (95% CI)**	Reference	1.08 (0.82-1.41)	1.50 (1.12-2.03)	1.18 (0.87-1.60)	1.38 (0.98-1.95)	1.15 (0.83-1.60)	1.66 (0.53-5.25)	2.03 (0.67-6.13)
HR (95% CI)**	Reference	1.08 (0.82-1.42)	1.51 (1.12-2.03)	1.18 (0.87-1.60)	1.37 (0.96-1.96)	1.15 (0.83-1.60)	1.62 (0.53-4.97)	1.99 (0.68-5.84)
Total non-fatal cardiovascular events (HF hospitalization, MI, or stroke) or cardiovascular death								
N	228	239	181	173	127	150	36	139
Event rate per 100 person-years (95% CI)	11.7 (9.8-14.1)	9.5 (8.0-11.2)	15.9 (12.8-20.1)	13.2 (10.7-16.3)	12.0 (9.9-14.7)	13.3 (10.4-17.2)	7.1 (4.5-11.9)	12.9 (10.1-16.7)
RR (95% CI)*	Reference	0.79 (0.60-1.04)	1.44 (1.03-2.00)	1.11 (0.81-1.53)	0.91 (0.65-1.27)	1.09 (0.77-1.53)	0.54 (0.33-0.87)	1.06 (0.75-1.48)
RR (95% CI)**	Reference	0.87 (0.66-1.16)	1.44 (1.04-2.00)	1.11 (0.81-1.53)	1.02 (0.71-1.47)	1.01 (0.72-1.44)	0.85 (0.31-2.35)	1.11 (0.43-2.91)
All-cause death								
N	76	110	54	61	56	27	23	48
Event rate per 100 person-years (95% CI)	3.9 (3.1-4.9)	4.4 (3.6-5.2)	4.7 (3.6-6.2)	4.6 (3.6-6.0)	5.3 (4.1-6.9)	2.4 (1.6-3.5)	4.5 (3.0-6.8)	4.4 (3.3-5.9)
HR (95% CI)*	Reference	1.08 (0.81-1.45)	1.23 (0.87-1.74)	1.23 (0.88-1.72)	1.22 (0.86-1.73)	0.60 (0.39-0.94)	1.04 (0.65-1.66)	1.08 (0.75-1.55)
HR (95% CI)**	Reference	1.39 (1.01-1.91)	1.26 (0.86-1.83)	1.27 (0.88-1.83)	1.42 (0.92-2.18)	0.64 (0.40-1.05)	4.02 (0.72-22.46)	2.92 (0.54-15.78)

**Stratified according to type of myocardial infarction (adjusted for in the analysis of total non-fatal cardiovascular events) and adjusted for randomized treatment and percutaneous coronary intervention at baseline.*

***Stratified according to type of myocardial infarction (adjusted for in the analysis of total non-fatal cardiovascular events) and adjusted for randomized treatment, percutaneous coronary intervention at baseline, Killip class, age, sex, race, systolic blood pressure, body mass index, estimated glomerular filtration rate, left ventricular ejection fraction, diabetes, and atrial fibrillation/flutter.*

CI, confidence interval; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; RR, rate ratio; sHR, sub-distribution hazard ratio.

Table 3. Adverse events according to region

	Overall N=5,661	Western Europe N=982	Eastern Europe and Russia N=1,303	Northern Europe N=574	Southern Europe N=686	Latin America N=677	North America N=524	South Asia N=330	East and South-East Asia N=560	P-value
Drug discontinuation (while alive), N (%)	1,018 (18.1)	244 (24.8)	205 (15.7)	114 (19.9)	120 (17.5)	63 (9.3)	137 (26.1)	47 (14.2)	88 (15.7)	<0.001
Drug discontinuation due to adverse event, N (%)	736 (13.0)	151 (15.4)	147 (11.3)	90 (15.7)	99 (14.4)	62 (9.2)	82 (15.6)	26 (7.9)	79 (14.1)	<0.001
Study drug dose at 2 months, N (%)										
No treatment	485 (9.0)	106 (11.3)	113 (9.0)	52 (9.4)	39 (5.9)	42 (6.4)	52 (10.3)	24 (7.9)	57 (10.6)	0.002
Target dose	3,197 (59.0)	583 (61.9)	694 (55.1)	386 (70.1)	384 (58.5)	418 (63.6)	282 (55.6)	150 (49.2)	300 (55.8)	<0.001
Any serious adverse event, N (%)	2,272 (40.1)	491 (50.0)	443 (34.0)	284 (49.5)	284 (41.4)	249 (36.8)	252 (48.1)	60 (18.2)	209 (37.3)	<0.001
Adverse events of interest, N (%)										
Cough	626 (11.1)	124 (12.6)	56 (4.3)	98 (17.1)	40 (5.8)	51 (7.5)	91 (17.4)	56 (17.0)	110 (19.6)	<0.001
Angioedema	31 (0.6)	6 (0.6)	7 (0.5)	5 (0.9)	0 (0.0)	3 (0.4)	4 (0.8)	0 (0.0)	6 (1.1)	0.18
Hypotension	1,422 (25.2)	309 (31.5)	196 (15.0)	231 (40.2)	156 (22.7)	102 (15.1)	227 (43.3)	45 (13.6)	156 (27.9)	<0.001
Renal impairment*	655 (11.6)	169 (17.2)	99 (7.6)	93 (16.2)	69 (10.1)	50 (7.4)	75 (14.3)	24 (7.3)	76 (13.6)	<0.001
Hyperkalaemia	586 (10.4)	90 (9.2)	166 (12.7)	42 (7.3)	61 (8.9)	68 (10.0)	66 (12.6)	50 (15.2)	43 (7.7)	<0.001
Cancer	156 (2.8)	56 (5.7)	17 (1.3)	30 (5.2)	15 (2.2)	8 (1.2)	20 (3.8)	1 (0.3)	9 (1.6)	<0.001
Laboratory abnormalities, N (%)										
Elevated serum creatinine level										
Creatinine ≥2.0 mg/dL	333 (6.1)	60 (6.4)	83 (6.6)	39 (7.1)	41 (6.1)	32 (4.8)	27 (5.3)	13 (4.1)	36 (6.6)	0.49
Creatinine ≥2.5 mg/dL	132 (2.4)	26 (2.8)	34 (2.7)	18 (3.3)	13 (1.9)	11 (1.7)	12 (2.4)	4 (1.3)	14 (2.6)	0.47
Creatinine ≥3.0 mg/dL	57 (1.0)	10 (1.1)	17 (1.3)	8 (1.4)	5 (0.7)	2 (0.3)	7 (1.4)	3 (1.0)	5 (0.9)	0.45
Elevated potassium level										
>5.5 mmol/L	764 (14.0)	126 (13.5)	238 (18.9)	40 (7.2)	109 (16.3)	84 (12.6)	57 (11.2)	63 (20.1)	47 (8.6)	<0.001
>6.0 mmol/L	187 (3.4)	27 (2.9)	56 (4.4)	11 (2.0)	25 (3.7)	26 (3.9)	11 (2.2)	18 (5.8)	13 (2.4)	0.011

**The broad standardized Medical Dictionary for Regulatory Activities queries (SMQs) are shown.*

Table 4. Effects of sacubitril/valsartan compared with ramipril on adjudicated clinical events according to region

Clinical endpoint committee-adjudicated	Overall N=5,661 (HR 95% CI)	Western Europe N=989 HR (95% CI)	Eastern Europe and Russia N=1,304 HR (95% CI)	Northern Europe N=574 HR (95% CI)	Southern Europe N=690 HR (95% CI)	Latin America N=679 HR (95% CI)	North America N=528 HR (95% CI)	South Asia N=330 HR (95% CI)	East and South-East Asia N=567 HR (95% CI)	P-value for interaction
Primary composite outcome	0.90 (0.78-1.04)	0.88 (0.63-1.23)	1.10 (0.79-1.54)	0.54 (0.35-0.83)	0.75 (0.49-1.14)	1.11 (0.73-1.66)	1.10 (0.67-1.82)	0.70 (0.31-1.61)	1.12 (0.71-1.77)	0.17
HF hospitalization or cardiovascular death	0.91 (0.78-1.07)	0.90 (0.63-1.28)	1.16 (0.82-1.62)	0.56 (0.35-0.89)	0.67 (0.43-1.03)	1.21 (0.77-1.90)	1.21 (0.72-2.04)	0.70 (0.31-1.61)	0.99 (0.62-1.60)	0.13
HF hospitalization or outpatient HF	0.84 (0.70-1.02)	0.90 (0.60-1.34)	0.94 (0.59-1.50)	0.42 (0.25-0.73)	0.73 (0.43-1.25)	0.95 (0.56-1.62)	1.00 (0.57-1.74)	3.87 (0.43-34.63)	1.21 (0.67-2.19)	0.16
HF hospitalization	0.87 (0.71-1.06)	0.94 (0.60-1.46)	1.02 (0.63-1.66)	0.43 (0.23-0.80)	0.62 (0.35-1.11)	1.02 (0.54-1.93)	1.16 (0.65-2.08)	3.87 (0.43-34.63)	1.05 (0.55-2.00)	0.19
Cardiovascular death	0.87 (0.71-1.08)	0.81 (0.47-1.40)	1.11 (0.73-1.70)	0.80 (0.45-1.44)	0.78 (0.43-1.42)	1.20 (0.67-2.14)	0.91 (0.40-2.07)	0.55 (0.23-1.33)	0.65 (0.34-1.22)	0.73
Non-fatal MI, non-fatal stroke, or cardiovascular death	0.90 (0.77-1.05)	0.81 (0.55-1.19)	1.14 (0.82-1.59)	0.83 (0.55-1.26)	0.77 (0.51-1.18)	1.22 (0.78-1.90)	0.75 (0.46-1.21)	0.60 (0.27-1.35)	0.93 (0.58-1.50)	0.50
Total non-fatal cardiovascular events (HF hospitalization, MI, or stroke) or cardiovascular death*	0.83 (0.69-0.98)	0.80 (0.54-1.18)	1.04 (0.70-1.55)	0.66 (0.40-1.12)	0.64 (0.40-1.01)	1.11 (0.72-1.70)	0.67 (0.38-1.19)	0.56 (0.18-1.80)	0.81 (0.43-1.52)	0.55
All-cause death	0.88 (0.73-1.05)	0.71 (0.45-1.12)	1.19 (0.82-1.73)	0.78 (0.45-1.34)	0.97 (0.58-1.60)	1.16 (0.69-1.97)	0.92 (0.43-1.96)	0.59 (0.25-1.36)	0.53 (0.29-0.96)	0.31

**Rate ratios were reported.*

CI, confidence interval; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.