The impact of geographic region on the COMMANDER-HF Trial

João Pedro Ferreira, MD, PhD[1]; John G. F. Cleland, MD[2]; Carolyn S.P. Lam, MD, PhD[3,4]; Dirk van Veldhuisen, MD, PhD[4]; William M. Byra, MD[5]; David A. La Police, BS[5]; Stefan D. Anker, MD, PhD[6,7]; Mandeep R. Mehra, MD[8]; Céline Leroy, MSc[1]; Valerie Eschwege, PhD[9]; Marie Toussaint-Hacquard, PharmD, PhD[9]; Patrick Rossignol, MD, PhD[1]; Barry Greenberg, MD[10]; Faiez Zannad, MD, PhD[1]

Author affiliations:

[1] Université de Lorraine, Centre d'Investigations Cliniques Plurithématique Inserm 1433, Nancy, France, CHRU de Nancy, Inserm U1116, Nancy, France, FCRIN INI-CRCT, Nancy, France.

[2] Robertson Centre for Biostatistics and Clinical Trials, University of Glasgow, Glasgow, Scotland.

[3] National Heart Centre Singapore, Duke-National University of Singapore, Singapore.

[4] Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands.

[5] Janssen Research and Development, Raritan, New Jersey.

[6] Berlin–Brandenburg Center for Regenerative Therapies, Berlin, Germany.

[7] Department of Cardiology, German Center for Cardiovascular Research partner site Berlin, Charite Universitatsmedizin Berlin, Berlin, Germany.

[8] Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.

[9] Laboratoire d'Hématologie Biologique, CHRU de Nancy, Nancy, France.

[10] Cardiology Division, Department of Medicine, University of California, San Diego, La Jolla.

Contact to:

Dr. João Pedro Ferreira

Centre d'Investigation Clinique 1433 module Plurithématique, CHRU Nancy - Hopitaux de Brabois, Institut Lorrain du Coeur et des Vaisseaux Louis Mathieu

4 rue du Morvan, 54500 Vandoeuvre les Nancy

Tel : +33 (0) 3 83 15 73 15

Fax : +33 (0) 3 83 15 73 24

Mail: j.ferreira@chru-nancy.fr

Abstract

Background: Globalization of cardiovascular trials increases generalizability. However, regional differences may also introduce heterogeneity in results.

Aims: To compare patient characteristics, outcomes and treatment effect amongst regions in the COMMANDER-HF trial.

Methods: Incidence-rates and interaction with treatment by prespecified regions: Eastern Europe (EE), Western Europe/South Africa (WE & SA), North America (NA), Asia-Pacific (AP), and Latin America (LA).

Results: Most patients (n=3224; 64.2%) were from EE, with 458 (9.1%) from WE & SA, 149 (3.0%) from NA, 733 (14.6%) from AP, and 458 (9.1%) from LA. Compared with EE, patients from WE & SA, NA, and AP were older and more likely to have coronary interventions and cardiac devices. Patients from EE had the lowest event rates. For the primary-outcome of myocardial infarction (MI), stroke or all-cause death, event rates (per 100py) in EE were 11.6 (10.8-12.5), WE & SA 19.5 (16.5-23.0), NA 14.2 (10.5-19.2), AP 17.7 (15.4-20.3), and LA 18.6 (15.6-22.1). There was a lower incidence of bleeding in EE. Blood concentrations of rivaroxaban at 4 weeks were undetectable in 21% patients from EE (n=128) compared to 5% in other regions (n=42). There was no evidence of treatment-by-region heterogeneity for the primary outcome ($interaction_p$=0.14), but a favourable effect on the secondary-outcome of MI, stroke or cardiovascular death was observed in WE & SA, NA, and LA, but not in EE and AP ($interaction_p$=0.017).

Conclusion: In COMMANDER-HF, patients from EE had a lower risk profile, fewer cardiovascular and bleeding events, possibly related to lower treatment adherence. These differences might have influenced the effect of rivaroxaban.

Key-words: regional differences; rivaroxaban; heart failure.

Condensed abstract

Globalization of cardiovascular trials increases generalizability. However, regional differences may also introduce heterogeneity in results. We compared patient characteristics, outcomes and treatment effect amongst the prespecified regions in the COMMANDER-HF trial: Eastern Europe (EE), Western Europe/South Africa (WE & SA), North America (NA), Asia-Pacific (AP), and Latin America (LA). Compared with EE, patients from WE & SA, NA, and AP were older and more likely to have coronary interventions and cardiac devices. Patients from EE had the lowest event rates including bleeding. Blood concentrations of rivaroxaban at 4 weeks were undetectable in 21% patients from EE compared to 5% in other regions. A favourable effect on the secondary-outcome of myocardial infarction, stroke or cardiovascular death was observed in WE & SA, NA, and LA, but not in EE and AP ($interaction_p$=0.017).

Abbreviation list

HF, heart failure

NPs, natriuretic peptides

LVEF, left ventricular ejection fraction

DAPT, dual anti-platelet therapy

MI, myocardial infarction

EE, Eastern Europe

WE & SA, Western Europe and South Africa

NA, North America

AP, Asia-Pacific

LA, Latin America

HR, hazard ratio

Introduction

Globalization of heart failure (HF) trials provides access to many research sites that enables a large number of patients to be enrolled in a timely fashion and potentially makes the results generalizable to a much broader population. However, there may be important regional differences in patient characteristics, outcomes, background treatment, treatment adherence practice patterns, health-care organization, social-support, level of income and inequality in income[1-3]. These differences may affect event-rates, the proportions of events contributing to a composite outcome (e.g., hospitalizations versus mortality), the adherence to treatment, and ultimately the observed treatment effect[3-5].

Regional heterogeneity may exist despite the application of uniform trial entry criteria[6-8]. Recent HF trials have required plasma natriuretic peptides (NP) as an entry criterion in order to exclude patients at low risk of events who may not even have HF[3, 6-8]. Although this may increase event rates, it may fail to address other regional factors. Accordingly, we compared patient characteristics, outcomes and treatment effect amongst prespecified regions in the COMMANDER-HF trial (Rivaroxaban in Patients with Heart Failure, Sinus Rhythm, and Coronary Disease), a contemporary, international, double-blind, randomized trial comparing the factor-Xa inhibitor rivaroxaban (2.5 mg twice daily) vs. placebo in addition to background antiplatelet therapy in patients with heart failure, coronary artery disease, reduced left ventricular ejection fraction and sinus rhythm following recent decompensation.

Methods

Study population

The study design of the COMMANDER-HF trial has been previously described[9, 10]. Key inclusion criteria included history of chronic HF for three or more months, treatment for decompensated HF in the previous 30 days, left ventricular ejection fraction (LVEF) of 40% or less, history of coronary artery disease, and absence of atrial fibrillation or other indication for chronic anticoagulation. Decompensated HF was defined by symptoms of worsening dyspnea or fatigue, objective signs of congestion, and/or adjustment of HF medications requiring hospital admission. Rivaroxaban or placebo was given in addition to background single or dual anti-platelet therapy (DAPT).

Study outcomes

The primary efficacy outcome was the composite of myocardial infarction, stroke or all-cause mortality. Secondary efficacy outcomes included death from cardiovascular causes, rehospitalization for worsening heart failure, rehospitalization for cardiovascular events, and the composite of rehospitalization for worsening heart failure or death from cardiovascular causes. Rivaroxaban did not reduce the incidence of the primary efficacy outcome nor the rate of HF re-hospitalization; however, the incidence of ischemic stroke was reduced[11], as well as the incidence of thrombo-embolic events[12]. The principal safety outcome was the composite of fatal bleeding or bleeding into a critical space with a potential for causing permanent disability. Secondary safety outcomes included bleeding events requiring hospitalization and clinically overt major bleeding events as defined by the International Society on Thrombosis and Haemostasis (ISTH) (i.e., associated with a decrease in hemoglobin level of ≥2 g/dL, transfusion of 2 or more units of packed red cells

or whole blood, a critical site [intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal], or a fatal outcome).

Investigators reported outcomes on detailed case report forms, which were verified by the sponsor's clinical operations team using source data. All participants provided written informed consent. The protocol was approved by the appropriate institutional review board or ethics committee at each site.

Based on a review of patient characteristics and event rates, blind to assigned treatment for the first 1,155 patients, the steering committee amended the enrolment criteria to require a plasma NT-pro BNP level $\geq$800 ng/L or BNP level $\geq$200 ng/L measured at any time between the index admission for decompensated HF and randomization in the local labs. Simultaneous with the amendment, enrolment in the Asia-Pacific region and several additional countries began[10]. Overall, 5,022 patients were enrolled, 3,582 in countries that enrolled both before and after the amendment and 1,440 in countries that enrolled only after the protocol amendment[13]. Most patients (included either before or after the amendment) were enrolled in Eastern Europe (64.2%; n = 3224) [13]. Median follow-up was 21.1 months (percentile$_{25\text{-}75}$, 12.9-32.8).

Plasma Concentrations of D-dimer and rivaroxaban

Treatment with rivaroxaban decreases plasma concentrations of D-dimer which can be used as a surrogate for treatment adherence[14]. Samples were taken at 4 weeks after randomization in a random subset of patients in the COMMANDER-HF whom had been randomized to rivaroxaban (n =394), stored as plasma at -20°C and plasma concentrations of D-dimer (Siemens Healthcare Diagnostics INNOVANCE®) measured in a core laboratory and expressed in ng/mL after the trial had ended.

Samples were also taken in a smaller random subset of patients, in whom D-dimers at 4-weeks had also been measured, for the measurement of plasma concentrations of rivaroxaban (n =170) after the trial had ended. Rivaroxaban has dose-proportional bioavailability and a predictable, dose-dependent pharmacokinetics. In a fasted state, rivaroxaban pharmacokinetics is linear up to about 15 mg/day and is not affected by food[15]. The administered oral dose of rivaroxaban is absorbed rapidly, with the maximum plasma concentration (Cmax) occurring 2–4 hours after tablet intake and its elimination may take up to 13 hours[15]. At total daily oral dose of 5 mg of rivaroxaban should provide a Cmax of 30 to 90 µg/l and a Cmin of 6 to 50 µg/l, depending on renal function, age and lean body mass[16]. In our study, rivaroxaban was measured using an anti-Factor Xa chromogenic assay (Method DiXaI [Hyphen BioMed®] on STARMax [Diagnostica Stago®] automat).

Statistical analysis

Baseline characteristics were described using means ± SD for normally distributed continuous variables, median (percentile$_{25\text{-}75}$) for skewed continuous variables, and number (proportion) for categorical variables, and compared across geographical regions. As prespecified, the studied regions were Eastern Europe (EE), Western Europe and South Africa (WE & SA), North America (NA), Asia-Pacific (AP), and Latin America (LA). Number and proportion of events, event-rates (per 100 person-years), and hazard ratios (HR) were compared across regions. The proportional hazards assumption was assessed by testing for significant trend in the change of HR over time and was not violated. Treatment effect was studied by the intention-to-treat principle and heterogeneity by region was assessed through an interaction term between region and treatment within the Cox model. Cumulative incidence rates were compared using the Nelson-Aalen method. A 2-sided p

value of <0.05 was considered significant. Stata® version 16 (StataCorp. 2019. College Station, TX: StataCorp LLC) was used for the statistical analysis.

Results

Baseline patients` characteristics by region

In COMMANDER-HF, 3224 (64.2%) patients were from EE, 458 (9.1%) from WE & SA, 149 (3.0%) from NA, 733 (14.6%) from AP, and 458 (9.1%) from LA. *Table 1*. Compared with EE, patients from WE & SA, NA, and AP were older and those from LA had a similar age. Most patients were treated with angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARBs), mineralocorticoid receptor antagonists (MRAs), and beta-blockers regardless of region. Digoxin was used more often in AP and LA, whereas angiotensin receptors neprilysin inhibitor (ARNi), percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), and cardiac devices were more frequent in WE & SA and NA. The baseline use of dual antiplatelet therapy was highest in AP (46%). Patients from EE were more likely to have had a prior myocardial infarction (MI), whereas diabetes was more common in other regions. The proportion of patients with anaemia was higher in WE & SA and NA. Patients from EE had better renal function (higher estimated glomerular filtration rate [eGFR]), lower plasma concentrations of BNP/NT-pro BNP and higher left ventricular ejection fraction (LVEF). Randomization was well balanced amongst regions (as per stratification procedure). *Table 1*. Numbers enrolled in each country is shown in *Supplemental Table 1*. Bulgaria, Poland, Russia, Ukraine and Romania contributed 83.2% of EE patients.

Event rates by region

Patients from EE had lower event rates compared with other regions. For the composite of MI, stroke or death the event rates per 100 person-years in EE were 11.6 (10.8-12.5), in WE & SA 19.5 (16.5-23.0), in NA 14.2 (10.5-19.2), in AP 17.7 (15.4-20.3), and in LA 18.6 (15.6-22.1). The same pattern was observed for the composite of MI, stroke and cardiovascular death, its individual components, HF hospitalizations and "pump failure" death. *Table 2*. The rate of bleeding events was lower in EE. Bleeding requiring hospitalization was much less common in EE: 0.8 (0.6-1.0) in EE, 2.0 (1.2-3.4) in WE & SA, 1.4 (0.5-3.6) in NA, 2.0 (1.3-3.0) in AP, and 1.8 (1.1-3.2) in LA. *Table 2*.

Treatment effect by region

For the primary outcome of MI, stroke or death, the overall effect of rivaroxaban was neutral with no significant interaction by region (p for interaction =0.14), but point estimates for the HR ranged widely from 0.65 in NA to 1.0 in EE and 1.11 in AP. Differences were accentuated for the outcome of MI, stroke or cardiovascular death, where there was evidence of treatment heterogeneity (p for interaction =0.017) with potential benefit in WE & SA and NA. Similar patterns were observed for cardiovascular death alone (p for interaction =0.062) but not the composite of HF hospitalization and cardiovascular death (p for interaction =0.20). In EE the efficacy and safety of rivaroxaban was overall neutral. *Figures 1, 2 & Table 3*.

Plasma concentrations of D-dimer and rivaroxaban

Plasma D-dimers were measured in 394 patients (EE n =223, WE & SA n =49, NA n =14, AP n =56, LA n=52). D-dimer levels decreased over 4 weeks in all regions, with the smallest change (95%CI) found in EE -89 (-241, 62) vs. -202 (-558, 154) in WE & SA, -594 (-1417, 229) in NA, -372 (-824, 80) in AP, and -801 (-1877, 275) in LA. Furthermore, in a subset of 170 patients randomized to rivaroxaban (EE n =128, WE & SA n =14, NA n =2, AP n =14, LA n

=12), there was no detectable blood concentration in 27 of 128 patients in EE (21.1%) at 4 weeks, compared to 2 of 42 patients from other regions (4.8%). The median concentrations were 37% lower in EE patients vs. rest of the world (28 vs. 45 µg/l, p =0.021). *Supplemental Table 2*.

The totality of the findings is summarized in the *Central Illustration*.

Discussion

This analysis suggests that regional differences might have contributed to the overall neutral treatment effect in the COMMANDER-HF trial. Geographic region was the only factor used to stratify randomisation, and while the p-value for interaction did not reach statistical significance for the primary outcome, it was significant for the secondary composite, which substituted all-cause mortality with cardiovascular deaths. The rate of both efficacy and bleeding events was lower in EE and the overall treatment effect neutral. Plasma concentrations of rivaroxaban were lower in EE and 21% of patients had no detectable levels. The fall in plasma D-dimer concentrations was also less pronounced with rivaroxaban in EE. These observations suggest lower rates of adherence in EE, possibly due to investigators being less selective about enrolling patients who were likely to comply with investigational treatments and thereby enhancing enrolment rates. Alternatively, investigators may have had less time to spend on educating their patients about the protocol because of high recruitment rates.

Important differences were also found in other regions. Patients in AP might have experienced an increased risk of HF-related “pump failure” death and an excessive risk of major bleeding, findings that may help explain the neutral treatment effect in this region for very different reasons than in EE. The more frequent use of DAPT in AP may explain the

higher observed bleeding rates in this region. LA patients had a highest rate of cardiovascular death but relatively few HF hospitalizations (the second lowest after EE), and the lowest MI rate, which might reflect important differences in health-care systems and HF treatment patterns. Regional differences in mortality rates and a "mismatch" between mortality and hospitalizations have also been documented in other trials. For example, in the PARADIGM-HF (angiotensin–neprilysin inhibition versus enalapril in heart failure) trial[17], patients from LA had higher mortality rates than WE and NA but HF hospitalization rates were lowest in LA[18]. These findings may reflect the differences in the health-care systems and access to care and thus endpoints such as HF hospitalizations and other major vascular endpoints including MI/revascularization, may not reflect the same disease severity across regions.

The primary region of patient enrolment for contemporary HF trials lies outside WE and NA. A meta-analysis of 300 trials showed that the proportion with their primary region of enrolment in NA or WE decreased from almost 70% to just over 50% within a decade [19]. An important driver of this trend is the greater speed of trial enrolment and lower costs in EE and LA [1]. This strategy may have drawbacks if the effect of treatment depends on background therapy and the organisation of health services and these are inhomogeneous. An intervention that is effective in one healthcare setting may not be effective in another.

A recent and striking example was the TOPCAT (spironolactone for heart failure with preserved ejection fraction) trial, where patients from EE (Russia and Georgia) had low event rates (compared with patients from NA and LA), possibly due to different diagnostic standard being applied, and high rates of non-adherence leading to a neutral overall treatment effect[3, 20]. COMMANDER-HF and TOPCAT indicate that greater scrutiny of patient

enrolment and patient education about the protocol is required worldwide, but perhaps particularly in EE.

In lower income regions, patients may agree to participate in clinical trials in order to access better health-care. In some countries, payment for enrolling patients into trials are made directly to doctors rather than their hospital or university and employment and promotion of junior staff may depend on their ability to enrol patients into trials. These can act as perverse incentives to enrolling patients that are less likely to comply with the protocol. This accelerates recruitment to the detriment of good trial conduct. Once the patient is in the trial, they are there until the end (regardless of treatment adherence). The health-care professional is rewarded by inclusion and not by conduct. Cultural differences and beliefs may also have a major impact on therapeutic adherence and long-term compliance, with negative beliefs being more common among non-adherent patients[21, 22]. Although we cannot ascertain if patients enrolled in EE have more negative beliefs, many of EE countries lack public funding and rely on private financing and co-payments, which may limit the reimbursement and availability of essential medicines[23]. Hence, participating in the trial may serve as an incentive to access health-care regardless of therapeutic adherence. These issues need to be considered when designing future global trials[1].

Global clinical trials should require objective inclusion criteria that are less prone to investigator interpretation, ensure that financial incentives to recruitment are carefully controlled and confirm that participants are aware of the consequences for others if they are non-adherent without good reason. In COMMANDER-HF a mid-trial protocol amendment was performed to include NP thresholds for inclusion in order to overcome the low event-rates observed in EE. Patients enrolled post-amendment in EE were “sicker” and had higher event rates. However, this protocol amendment did not modify the neutral

effect of rivaroxaban and cannot overcome the low treatment adherence[13]. For improving the scrutiny about treatment adherence, blood and urine samples should be collected to monitor treatment adherence in "real-time" during the trial (and not *a posteriori*), and the corresponding attitudes in the case of important non-adherence (e.g., >10%) in certain centres or regions should be prespecified in the protocol (e.g., stopping recruitment in those centres or regions, improve monitoring and education, and readapt sample size). This is particularly important in trials with a median follow-up duration superior to one year, such as COMMANDER-HF, as after the first year of follow-up nearly 40% of trial participants might have stopped taking their trial medication[24].

Strengths and limitations

The inclusion of geographic region as a stratification variable in COMMANDER-HF, ensured a good balance between the rivaroxaban and placebo arms within regions. However, the trial was not powered to study the treatment effect within and between subgroups [25]. Notwithstanding, these findings along with those from TOPCAT, support that patients enrolled in EE countries may be less compliant with the trial good practices and future trials should take this information into account and implement some of the measures discussed in this manuscript (e.g., strict and objective entry criteria and real-time treatment adherence monitoring).

Conclusions

In the COMMANDER-HF trial important differences amongst geographic regions were observed in patient characteristics, the rate and pattern of events and treatment adherence that may have contributed to an overall neutral outcome. These differences were most marked in Eastern European countries that presented lower event rates and treatment

adherence. These observations highlight the need for greater scrutiny of trial conduct and treatment adherence.

Clinical perspectives

- The rate of both efficacy and bleeding events was lower in Eastern Europe and the overall treatment effect neutral.
- Plasma concentrations of rivaroxaban were lower and 21% of patients had no detectable levels in Eastern Europe.
- These regional differences might have contributed to the overall neutral treatment effect in the COMMANDER-HF trial.

Translational outlook

- Global clinical trials should require objective inclusion criteria that are less prone to investigator interpretation, ensure that financial incentives to recruitment are carefully controlled and confirm that participants are aware of the consequences for others if they are non-adherent without good reason.
- Blood levels of treatments should be routinely determined and action should be taken during the trial if adherence rates are low in certain regions (e.g., stop patient inclusion in areas with lower treatment adherence).

Disclosures

The authors report no conflicts of interest regarding the content of this manuscript.

Funding

The COMMANDER-HF trial was supported by Janssen Research and Development.

Acknowledgements JF, PR and FZ are supported by the RHU Fight-HF, a public grant overseen by the French National Research Agency (ANR) as part of the second "Investissements d'Avenir" program (reference: ANR-15-RHUS-0004), and by the French PIA project "Lorraine Université d'Excellence" (reference: ANR-15-IDEX-04-LUE). The biobanking for the rivaroxaban dosages is managed by Biological Resource Center Lorrain BB-0033-00035.

Bibliography

1. Tromp, J.; Ferreira, J. P.; Janwanishstaporn, S.; Shah, M.; Greenberg, B.; Zannad, F.; Lam, C. S. P., Heart failure around the world. *Eur J Heart Fail* **2019**.
2. Ferreira, J. P.; Girerd, N.; Rossignol, P.; Zannad, F., Geographic differences in heart failure trials. *Eur J Heart Fail* **2015**.
3. Pfeffer, M. A.; Claggett, B.; Assmann, S. F.; Boineau, R.; Anand, I. S.; Clausell, N.; Desai, A. S.; Diaz, R.; Fleg, J. L.; Gordeev, I.; Heitner, J. F.; Lewis, E. F.; O'Meara, E.; Rouleau, J. L.; Probstfield, J. L.; Shaburishvili, T.; Shah, S. J.; Solomon, S. D.; Sweitzer, N. K.; McKinlay, S. M.; Pitt, B., Regional Variation in Patients and Outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) Trial. *Circulation* **2015,** *131* (1), 34-42.
4. Dewan, P.; Rorth, R.; Jhund, P. S.; Ferreira, J. P.; Zannad, F.; Shen, L.; Kober, L.; Abraham, W. T.; Desai, A. S.; Dickstein, K.; Packer, M.; Rouleau, J. L.; Solomon, S. D.; Swedberg, K.; Zile, M. R.; McMurray, J. J. V., Income Inequality and Outcomes in Heart Failure: A Global Between-Country Analysis. *JACC Heart Fail* **2019**.
5. Ferreira, J. P.; Rossignol, P.; Dewan, P.; Lamiral, Z.; White, W. B.; Pitt, B.; McMurray, J. J. V.; Zannad, F., Income level and inequality as complement to geographical differences in cardiovascular trials. *Am Heart J* **2019,** *218*, 66-74.
6. McMurray, J. J. V.; Solomon, S. D.; Inzucchi, S. E.; Kober, L.; Kosiborod, M. N.; Martinez, F. A.; Ponikowski, P.; Sabatine, M. S.; Anand, I. S.; Belohlavek, J.; Bohm, M.; Chiang, C. E.; Chopra, V. K.; de Boer, R. A.; Desai, A. S.; Diez, M.; Drozdz, J.; Dukat, A.; Ge, J.; Howlett, J. G.; Katova, T.; Kitakaze, M.; Ljungman, C. E. A.; Merkely, B.; Nicolau, J. C.; O'Meara, E.; Petrie, M. C.; Vinh, P. N.; Schou, M.; Tereshchenko, S.; Verma, S.; Held, C.; DeMets, D. L.; Docherty, K. F.; Jhund, P. S.; Bengtsson, O.; Sjostrand, M.; Langkilde, A. M., Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med* **2019**.
7. Packer, M.; Butler, J.; Filippatos, G. S.; Jamal, W.; Salsali, A.; Schnee, J.; Kimura, K.; Zeller, C.; George, J.; Brueckmann, M.; Anker, S. D.; Zannad, F., Evaluation of the effect of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality of patients with chronic heart failure and a reduced ejection fraction: rationale for and design of the EMPEROR-Reduced trial. *Eur J Heart Fail* **2019,** *21* (10), 1270-1278.
8. Armstrong, P. W.; Pieske, B.; Anstrom, K. J.; Ezekowitz, J.; Hernandez, A. F.; Butler, J.; Lam, C. S. P.; Ponikowski, P.; Voors, A. A.; Jia, G.; McNulty, S. E.; Patel, M. J.; Roessig, L.; Koglin, J.; O'Connor, C. M., Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med* **2020**.

9. Zannad, F.; Greenberg, B.; Cleland, J. G.; Gheorghiade, M.; van Veldhuisen, D. J.; Mehra, M. R.; Anker, S. D.; Byra, W. M.; Fu, M.; Mills, R. M., Rationale and design of a randomized, double-blind, event-driven, multicentre study comparing the efficacy and safety of oral rivaroxaban with placebo for reducing the risk of death, myocardial infarction or stroke in subjects with heart failure and significant coronary artery disease following an exacerbation of heart failure: the COMMANDER HF trial. *Eur J Heart Fail* **2015,** *17* (7), 735-42.
10. Zannad, F.; Anker, S. D.; Byra, W. M.; Cleland, J. G. F.; Fu, M.; Gheorghiade, M.; Lam, C. S. P.; Mehra, M. R.; Neaton, J. D.; Nessel, C. C.; Spiro, T. E.; van Veldhuisen, D. J.; Greenberg, B., Rivaroxaban in Patients with Heart Failure, Sinus Rhythm, and Coronary Disease. *N Engl J Med* **2018**.
11. Mehra, M. R.; Vaduganathan, M.; Fu, M.; Ferreira, J. P.; Anker, S. D.; Cleland, J. G. F.; Lam, C. S. P.; van Veldhuisen, D. J.; Byra, W. M.; Spiro, T. E.; Deng, H.; Zannad, F.; Greenberg, B., A comprehensive analysis of the effects of rivaroxaban on stroke or transient ischaemic attack in patients with heart failure, coronary artery disease, and sinus rhythm: the COMMANDER HF trial. *Eur Heart J* **2019,** *40* (44), 3593-3602.
12. Greenberg, B.; Neaton, J. D.; Anker, S. D.; Byra, W. M.; Cleland, J. G. F.; Deng, H.; Fu, M.; La Police, D. A.; Lam, C. S. P.; Mehra, M. R.; Nessel, C. C.; Spiro, T. E.; van Veldhuisen, D. J.; Vanden Boom, C. M.; Zannad, F., Association of Rivaroxaban With Thromboembolic Events in Patients With Heart Failure, Coronary Disease, and Sinus Rhythm: A Post Hoc Analysis of the COMMANDER HF Trial. *JAMA Cardiol* **2019,** *4* (6), 515-523.
13. Cunningham, J. W.; Ferreira, J. P.; Deng, H.; Anker, S. D.; Byra, W. M.; Cleland, J. G. F.; Gheorghiade, M.; Lam, C. S. P.; La Police, D.; Mehra, M. R.; Neaton, J. D.; Spiro, T. E.; van Veldhuisen, D. J.; Greenberg, B.; Zannad, F., Natriuretic Peptide-Based Inclusion Criteria in a Heart Failure Clinical Trial: Insights From COMMANDER HF. *JACC Heart Fail* **2020**.
14. Baglin, T.; Keeling, D.; Kitchen, S., Effects on routine coagulation screens and assessment of anticoagulant intensity in patients taking oral dabigatran or rivaroxaban: guidance from the British Committee for Standards in Haematology. *Br J Haematol* **2012,** *159* (4), 427-9.
15. Kubitza, D.; Becka, M.; Voith, B.; Zuehlsdorf, M.; Wensing, G., Safety, pharmacodynamics, and pharmacokinetics of single doses of BAY 59-7939, an oral, direct factor Xa inhibitor. *Clin Pharmacol Ther* **2005,** *78* (4), 412-21.
16. Gosselin, R. C.; Adcock, D. M.; Bates, S. M.; Douxfils, J.; Favaloro, E. J.; Gouin-Thibault, I.; Guillermo, C.; Kawai, Y.; Lindhoff-Last, E.; Kitchen, S., International Council for Standardization in Haematology (ICSH) Recommendations for Laboratory Measurement of Direct Oral Anticoagulants. *Thromb Haemost* **2018,** *118* (3), 437-450.
17. McMurray, J. J.; Packer, M.; Desai, A. S.; Gong, J.; Lefkowitz, M. P.; Rizkala, A. R.; Rouleau, J. L.; Shi, V. C.; Solomon, S. D.; Swedberg, K.; Zile, M. R., Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* **2014,** *371* (11), 993-1004.
18. Kristensen, S. L.; Martinez, F.; Jhund, P. S.; Arango, J. L.; Belohlavek, J.; Boytsov, S.; Cabrera, W.; Gomez, E.; Hagege, A. A.; Huang, J.; Kiatchoosakun, S.; Kim, K. S.; Mendoza, I.; Senni, M.; Squire, I. B.; Vinereanu, D.; Wong, R. C.; Gong, J.; Lefkowitz, M. P.; Rizkala, A. R.; Rouleau, J. L.; Shi, V. C.; Solomon, S. D.; Swedberg, K.; Zile, M. R.; Packer, M.; McMurray, J. J., Geographic variations in the PARADIGM-HF heart failure trial. *Eur Heart J* **2016,** *37* (41), 3167-3174.
19. Vaduganathan, M.; Samman Tahhan, A.; Greene, S. J.; Okafor, M.; Kumar, S.; Butler, J., Globalization of heart failure clinical trials: a systematic review of 305 trials conducted over 16 years. *Eur J Heart Fail* **2018,** *20* (6), 1068-1071.
20. de Denus, S.; O'Meara, E.; Desai, A. S.; Claggett, B.; Lewis, E. F.; Leclair, G.; Jutras, M.; Lavoie, J.; Solomon, S. D.; Pitt, B.; Pfeffer, M. A.; Rouleau, J. L., Spironolactone Metabolites in TOPCAT - New Insights into Regional Variation. *N Engl J Med* **2017,** *376* (17), 1690-1692.
21. Gagnon, M. D.; Waltermaurer, E.; Martin, A.; Friedenson, C.; Gayle, E.; Hauser, D. L., Patient Beliefs Have a Greater Impact Than Barriers on Medication Adherence in a Community Health Center. *J Am Board Fam Med* **2017,** *30* (3), 331-336.

22. Sjölander, M.; Eriksson, M.; Glader, E. L., The association between patients' beliefs about medicines and adherence to drug treatment after stroke: a cross-sectional questionnaire survey. *BMJ Open* **2013,** *3* (9), e003551.
23. Vogler, S.; Österle, A.; Mayer, S., Inequalities in medicine use in Central Eastern Europe: an empirical investigation of socioeconomic determinants in eight countries. *Int J Equity Health* **2015,** *14*, 124.
24. Blaschke, T. F.; Osterberg, L.; Vrijens, B.; Urquhart, J., Adherence to medications: insights arising from studies on the unreliable link between prescribed and actual drug dosing histories. *Annu Rev Pharmacol Toxicol* **2012,** *52*, 275-301.
25. Pocock, S. J.; Assmann, S. E.; Enos, L. E.; Kasten, L. E., Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: current practice and problems. *Stat Med* **2002,** *21* (19), 2917-30.

Table 1. Characteristics of the population by the region of stratification

Factor	EE	WE & SA	NA	AP	LA	p-value
N.	**3224**	**458**	**149**	**733**	**458**	**-**
Age, years	65.8 ± 9.7	70.5 ± 10.6	67.0 ± 11.1	67.3 ± 11.1	64.9 ± 10.2	<0.001
Age ≥65	1773 (55.0%)	327 (71.4%)	82 (55.0%)	443 (60.4%)	238 (52.0%)	<0.001
Female	764 (23.7%)	97 (21.2%)	41 (27.5%)	146 (19.9%)	102 (22.3%)	0.11
Race						
White	3216 (99.8%)	439 (95.9%)	101 (67.8%)	13 (1.8%)	359 (78.4%)	<0.001
Black or African American	0 (0.0%)	3 (0.7%)	40 (26.8%)	1 (0.1%)	21 (4.6%)	
Asian	0 (0.0%)	4 (0.9%)	5 (3.4%)	716 (97.7%)	2 (0.4%)	
Other	8 (0.2%)	12 (2.6%)	3 (2.0%)	3 (0.4%)	76 (16.6%)	
ACEi/ARB	3094 (96.0%)	378 (82.5%)	130 (87.2%)	639 (87.2%)	419 (91.5%)	<0.001
MRA	2555 (79.2%)	297 (64.8%)	68 (45.6%)	545 (74.4%)	375 (81.9%)	<0.001
Beta-blocker	3049 (94.6%)	426 (93.0%)	143 (96.0%)	617 (84.2%)	407 (88.9%)	<0.001
Digoxin	154 (4.8%)	8 (1.7%)	21 (14.1%)	160 (21.8%)	90 (19.7%)	<0.001
Loop diuretic	3223 (100.0%)	452 (98.7%)	148 (99.3%)	723 (98.6%)	453 (98.9%)	<0.001
ARNi	7 (0.2%)	24 (5.2%)	7 (4.7%)	1 (0.1%)	2 (0.4%)	<0.001
Aspirin	3035 (94.1%)	414 (90.4%)	140 (94.0%)	639 (87.2%)	447 (97.6%)	<0.001
DAPT	1064 (33.0%)	138 (30.1%)	37 (24.8%)	334 (45.6%)	173 (37.8%)	<0.001
Diabetes	1187 (36.8%)	232 (50.7%)	86 (57.7%)	340 (46.4%)	207 (45.2%)	<0.001
Hypertension	2578 (80.0%)	317 (69.2%)	122 (81.9%)	442 (60.3%)	324 (70.7%)	<0.001
Myocardial infarction	2651 (82.2%)	317 (69.2%)	101 (67.8%)	416 (56.8%)	318 (69.4%)	<0.001
Stroke	289 (9.0%)	41 (9.0%)	21 (14.1%)	78 (10.6%)	24 (5.2%)	0.005
Cardiac device	52 (1.6%)	19 (4.1%)	7 (4.7%)	10 (1.4%)	6 (1.3%)	<0.001
PCI or CABG	1958 (60.7%)	331 (72.3%)	109 (73.2%)	493 (67.3%)	259 (56.6%)	<0.001
NYHA						
I	26 (0.8%)	20 (4.4%)	3 (2.0%)	74 (10.1%)	26 (5.7%)	<0.001
II	1242 (38.5%)	267 (58.3%)	69 (46.6%)	309 (42.2%)	331 (72.3%)	
III	1895 (58.8%)	167 (36.5%)	66 (44.6%)	244 (33.3%)	90 (19.7%)	
IV	61 (1.9%)	4 (0.9%)	10 (6.8%)	106 (14.5%)	11 (2.4%)	
BMI, kg/m2	28.5 ± 4.9	27.8 ± 5.5	29.4 ± 6.7	23.6 ± 3.8	28.3 ± 5.4	<0.001
BMI categories						
<25	777 (24.1%)	154 (33.8%)	43 (28.9%)	505 (68.9%)	123 (26.9%)	<0.001
25-29	1369 (42.5%)	172 (37.8%)	51 (34.2%)	192 (26.2%)	190 (41.5%)	
≥30	1077 (33.4%)	129 (28.4%)	55 (36.9%)	36 (4.9%)	145 (31.7%)	
SBP, mmHg	124.6 ± 14.0	120.3 ± 18.8	116.0 ± 17.4	119.1 ± 16.1	120.2 ± 16.7	<0.001
DBP, mmHg	75.0 ± 8.6	68.6 ± 10.7	69.3 ± 10.4	70.3 ± 11.0	72.7 ± 9.9	<0.001
D-dimer, ug/L	330.0 (200.0, 590.0)	475.0 (302.5, 817.5)	430.0 (285.0, 795.0)	385.0 (225.0, 760.0)	415.0 (245.0, 710.0)	<0.001
Hemoglobin, g/dL	13.7 ± 1.7	12.9 ± 1.9	12.5 ± 1.7	13.1 ± 2.0	13.4 ± 1.8	<0.001

Anemia	780 (24.2%)	208 (45.4%)	87 (58.4%)	313 (42.7%)	154 (33.6%)	<0.001
eGFR, mL/min/1.73m2	70.2 ± 22.8	60.2 ± 23.1	63.4 ± 24.0	65.6 ± 25.2	66.8 ± 23.6	<0.001
eGFR categories						
<30	50 (1.6%)	35 (7.6%)	12 (8.1%)	48 (6.5%)	18 (3.9%)	<0.001
30-59	1061 (32.9%)	212 (46.3%)	56 (37.6%)	282 (38.5%)	171 (37.3%)	
60-89	1556 (48.3%)	156 (34.1%)	58 (38.9%)	272 (37.1%)	196 (42.8%)	
≥90	557 (17.3%)	55 (12.0%)	23 (15.4%)	131 (17.9%)	73 (15.9%)	
BNP, pg/mL*	548.1 (296.9, 1171.3)	756.5 (413.0, 1202.4)	829.8 (527.0, 1480.0)	786.8 (442.1, 1360.0)	555.0 (298.0, 1030.0)	<0.001
NT-proBNP, pg/mL*	2831.0 (1448.0, 6479.0)	2752.0 (1547.0, 6423.5)	3617.0 (2374.0, 6380.0)	3302.5 (1940.5, 6495.5)	1938.0 (1116.0, 3836.0)	<0.001
LVEF, %	35.0 (30.0, 38.0)	30.0 (25.0, 35.0)	25.0 (20.0, 32.0)	32.0 (26.0, 36.0)	30.0 (25.0, 36.0)	<0.001
LVEF <35%	1710 (53.0%)	351 (76.6%)	131 (87.9%)	540 (73.7%)	333 (72.7%)	<0.001
Rivaroxaban	1610 (49.9%)	227 (49.6%)	74 (49.7%)	367 (50.1%)	229 (50.0%)	1.00

Legend: EE, Eastern Europe; WE & SA, Western Europe and South Africa; NA, North America; AP, Asia-Pacific; LA, Latin America; ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; ARNi, angiotensin-receptor neprilysin inhibitor; DAPT, dual anti-platelet therapy; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; NT-pro BNP, N-terminal pro brain natriuretic peptide; LVEF, left ventricular ejection fraction.

*BNP determined in 986 (19.6%) of the 5022 patients; NT-pro BNP determined in 2928 (58.3%) of the 5022 patients.

Table 2. Events, event rates and hazard ratios by the region of stratification

Region	EE	WE & SA	NA	AP	LA
Outcome					
MI, Stroke, Death					
Events, n. (%)	777 (24.1)	139 (30.4)	42 (28.2)	198 (27.0)	128 (28.0)
Event rates (per 100py)	11.6 (10.8 -12.5)	19.5 (16.5-23.0)	14.2 (10.5-19.2)	17.7 (15.4-20.3)	18.6 (15.6-22.1)
Hazard ratio (95%CI)	Ref.	1.63 (1.36-1.95)	1.21 (1.18-1.64)	1.46 (1.25-1.71)	1.53 (1.27-1.85)
MI, Stroke, CV death					
Events, n. (%)	694 (21.5)	114 (24.9)	34 (22.8)	168 (22.9)	111 (24.2)
Event rates (per 100py)	10.4 (9.6-11.2)	16.0 (13.3-19.2)	11.5 (8.2-16.1)	15.0 (12.9-17.4)	16.1 (13.4-19.4)
Hazard ratio (95%CI)	Ref.	1.48 (1.21-1.80)	1.09 (0.77-1.54)	1.37 (1.15-1.62)	1.47 (1.2-1.80)
MI					
Events, n. (%)	132 (4.1)	32 (7.0)	9 (6.0)	33 (4.5)	10 (2.2)
Event rates (per 100py)	2.0 (1.6-2.3)	4.4 (3.1-6.2)	3.0 (1.6-5.8)	2.9 (2.0-4.0)	1.4 (0.8-2.6)
Hazard ratio (95%CI)	Ref.	2.13 (1.45-3.14)	1.54 (0.78-3.02)	1.39 (0.94-2.04)	0.68 (0.36-1.3)
Stroke					
Events, n. (%)	69 (2.1)	14 (3.1)	4 (2.7)	25 (3.4)	15 (3.3)
Event rates (per 100py)	1.0 (0.8-1.3)	1.9 (1.1-3.2)	1.3 (0.5-3.6)	2.2 (1.5-3.2)	2.1 (1.3-3.6)
Hazard ratio (95%CI)	Ref.	1.77 (1.0-3.15)	1.29 (0.47-3.54)	2.01 (1.26-3.18)	1.99 (1.13-3.48)
All-cause death					
Events, n. (%)	673 (20.9)	114 (24.9)	38 (25.5)	161 (22.0)	116 (25.3)
Event rates (per 100py)	9.8 (9.1-10.6)	15.0 (12.5-18.0)	12.6 (9.2-17.3)	13.7 (11.8-16.0)	16.3 (13.5-19.5)
Hazard ratio (95%CI)	Ref.	1.50 (1.23-1.83)	1.27 (0.91-1.75)	1.36 (1.14-1.61)	1.61 (1.32-1.96)
CV death					
Events, n. (%)	587 (18.2)	87 (19.0)	29 (19.5)	128 (17.5)	98 (21.4)
Event rates (per 100py)	8.6 (7.9-9.3)	11.4 (9.3-14.1)	9.6 (6.7-13.8)	10.9 (9.2-13.0)	13.7 (11.3-16.7)
Hazard ratio (95%CI)	Ref.	1.30 (1.03-1.63)	1.10 (0.76-1.6)	1.22 (1.0-1.47)	1.53 (1.24-1.9)

Sudden death					
Events, n. (%)	287 (8.9)	29 (6.3)	7 (4.7)	59 (8.1)	23 (5.0)
Event rates (per 100py)	4.2 (3.7-4.7)	3.8 (2.7-5.5)	2.3 (1.1-4.9)	5.0 (3.9-6.5)	3.2 (2.1-4.8)
Hazard ratio (95%CI)	Ref.	0.89 (0.61-1.31)	0.55 (0.26-1.16)	1.17 (0.88-1.55)	0.74 (0.49-1.14)
"Pump failure" death					
Events, n. (%)	201 (6.2)	40 (8.7)	14 (9.4)	49 (6.7)	46 (10.0)
Event rates (per 100py)	2.9 (2.6-3.4)	5.3 (3.9-7.2)	4.6 (2.7-7.8)	4.2 (3.2-5.5)	6.4 (4.8-8.6)
Hazard ratio (95%CI)	Ref.	1.73 (1.23-2.43)	1.53 (0.89-2.63)	1.33 (0.97-1.82)	2.07 (1.50-2.85)
CV death or HF hosp.					
Events, n. (%)	1092 (33.9)	211 (46.1)	70 (47.0)	326 (44.5)	162 (35.4)
Event rates (per 100py)	18.6 (17.5-19.7)	37.7 (33.0-43.2)	30.8 (24.3-38.9)	36.8 (33.0-41.0)	26.9 (23.0-31.4)
Hazard ratio (95%CI)	Ref.	1.80 (1.55-2.09)	1.58 (1.24-2.02)	1.74 (1.53-1.97)	1.29 (1.09-1.52)
HF hosp.					
Events, n. (%)	760 (23.6)	175 (38.2)	61 (40.9)	267 (36.4)	117 (25.6)
Event rates (per 100py)	12.9 (12.1-13.9)	31.3 (27.0-36.3)	26.8 (20.9-34.5)	30.1 (26.7-34.0)	19.4 (16.2-23.3)
Hazard ratio (95%CI)	Ref.	2.11 (1.79-2.48)	1.97 (1.52-2.56)	2.0 (1.74-2.31)	1.32 (1.08-1.6)
Bleeding main safety					
Events, n. (%)	19 (0.6)	4 (0.9)	0	10 (1.4)	8 (1.8)
Event rates (per 100py)	0.3 (0.2-0.4)	0.5 (0.2-1.4)	0	0.9 (0.5-1.6)	1.1 (0.6-2.3)
Hazard ratio (95%CI)	Ref.	1.74 (0.59-5.13)	0	2.71 (1.25-5.85)	3.58 (1.56-8.21)
ISTH-major bleeding					
Events, n. (%)	14 (3.1)	4 (2.7)	33 (4.5)	17 (3.7)	46 (1.4)
Event rates (per 100py)	0.9 (0.7-1.2)	1.9 (1.1-3.2)	1.4 (0.5-3.6)	2.9 (2.1-4.1)	2.4 (1.5-3.9)
Hazard ratio (95%CI)	Ref.	1.76 (0.99-3.15)	1.34 (0.49-3.68)	2.58 (1.69-3.93)	2.16 (1.27-3.7)
Bleeding req. hosp.					
Events, n. (%)	54 (1.7)	15 (3.3)	4 (2.7)	23 (3.1)	13 (2.8)
Event rates (per 100py)	0.8 (0.6-1.0)	2.0 (1.2-3.4)	1.4 (0.5-3.6)	2.0 (1.3-3.0)	1.8 (1.1-3.2)
Hazard ratio (95%CI)	Ref.	2.25 (1.27-3.99)	1.60 (0.58-4.41)	2.13 (1.3-3.47)	1.95 (1.06-3.57)

Legend: EE, Eastern Europe; WE & SA, Western Europe and South Africa; NA, North America; AP, Asia-Pacific; LA, Latin America; MI, myocardial infarction; CV, cardiovascular; HF, heart failure; ISTH, International Society on Thrombosis and Haemostasis.

Major bleeding is defined by the ISTH as overt bleeding associated with a decrease in hemoglobin level of at least 2 g/dL, transfusion of two or more units of packed red cells or whole blood, a critical site (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal), or a fatal outcome.

Table 3. Treatment effect (rivaroxaban vs. placebo) by the region of stratification

Region	EE	WE & SA	NA	AP	LA	Interaction P
Outcome, HR (95%CI)						
MI, Stroke, Death	1.0 (0.87-1.15)	0.76 (0.54-1.06)	0.65 (0.35-1.21)	1.11 (0.84-1.46)	0.73 (0.52-1.04)	0.14
MI, Stroke, CV death	1.0 (0.86-1.16)	0.61 (0.42-0.89)	0.46 (0.22-0.94)	1.07 (0.79-1.45)	0.72 (0.49-1.04)	0.017
MI	0.94 (0.67-1.33)	0.99 (0.5-1.98)	0.28 (0.06-1.33)	0.74 (0.37-1.47)	0.25 (0.05-1.16)	0.27
Stroke	0.81 (0.50-1.3)	0.16 (0.04-0.72)	0.32 (0.03-3.09)	1.09 (0.50-2.4)	0.36 (0.12-1.14)	0.14
All-cause death	1.02 (0.88-1.19)	0.87 (0.6-1.25)	0.62 (0.32-1.19)	1.16 (0.85-1.58)	0.81 (0.56-1.17)	0.31
CV death	1.02 (0.87-1.2)	0.67 (0.44-1.03)	0.43 (0.2-0.94)	1.15 (0.81-1.62)	0.81 (0.55-1.21)	0.062
Sudden death	0.93 (0.73-1.17)	0.61 (0.29-1.29)	0.72 (0.16-3.21)	0.80 (0.48-1.33)	1.09 (0.48-2.47)	0.82
"Pump failure" death	1.11 (0.84-1.47)	0.60 (0.31-1.13)	0.38 (0.12-1.21)	1.74 (0.97-3.11)	0.92 (0.51-1.64)	0.056
CV death or HF hosp.	1.04 (0.93-1.17)	0.86 (0.65-1.12)	0.62 (0.38-0.99)	1.04 (0.84-1.3)	0.94 (0.69-1.27)	0.20
HF hosp.	1.06 (0.92-1.22)	0.80 (0.59-1.08)	0.65 (0.39-1.09)	0.94 (0.74-1.2)	1.11 (0.77-1.6)	0.21
Bleeding main safety	0.9 (0.37-2.21)	0.33 (0.03-3.16)	1.0 (0.12-8.11)	2.37 (0.61-9.16)	0.14 (0.02-1.16)	0.13
ISTH-major bleeding	1.47 (0.89-2.42)	1.81 (0.61-5.39)	0*	2.73 (1.27-5.87)	0.70 (0.27-1.85)	0.19
Bleeding req. hosp.	1.71 (0.94-3.12)	2.33 (0.60-9.01)	0*	2.22 (0.77-6.38)	1.0 (0.29-3.45)	0.55

Legend: EE, Eastern Europe; WE & SA, Western Europe and South Africa; NA, North America; AP, Asia-Pacific; LA, Latin America; MI, myocardial infarction; CV, cardiovascular; HF, heart failure; ISTH, International Society on Thrombosis and Haemostasis; HR, hazard ratio; CI, confidence interval.

*Unprecise estimates.

Major bleeding is defined by the ISTH as overt bleeding associated with a decrease in hemoglobin level of at least 2 g/dL, transfusion of two or more units of packed red cells or whole blood, a critical site (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal), or a fatal outcome.

Figure 1. Forest plot representing the treatment effect on the time-to-first myocardial infarction, stroke or all-cause death and the same composite with cardiovascular death instead of all-cause death by the region of stratification

Legend: EE, Eastern Europe; WE & SA, Western Europe and South Africa; NA, North America; AP, Asia-Pacific; LA, Latin America; MI, myocardial infarction.

Figure 2. Nelson-Aalen cumulative incidence curves for the time-to-first myocardial infarction, stroke or cardiovascular death, heart failure hospitalization or cardiovascular death, and any hospitalization due to bleeding by the region of stratification.

Legend: EE, Eastern Europe; WE & SA, Western Europe and South Africa; NA, North America; AP, Asia-Pacific; LA, Latin America; MI, myocardial infarction; CV, cardiovascular; HF, heart failure.

Central Illustration. Main findings of the COMMANDER-HF trial according to the prespecified world region.

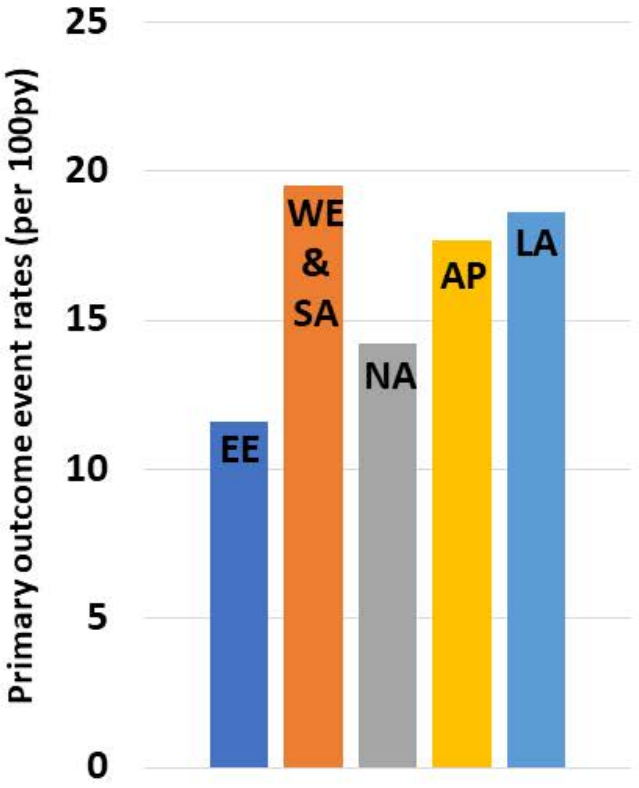
Caption: Patients from Eastern Europe presented lower event rates, lower treatment adherence and a neutral effect of rivaroxaban.

Legend: TTx, treatment.

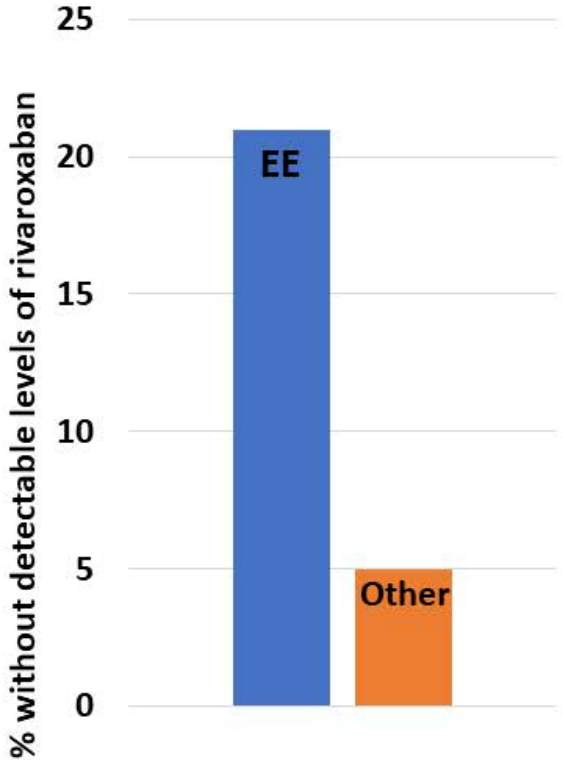
COMMANDER-HF 5 prespecified regions:

Eastern Europe (EE), Western Europe and South Africa (WE & SA), North America (NA), Asia-Pacific (AP), and Latin America (LA)

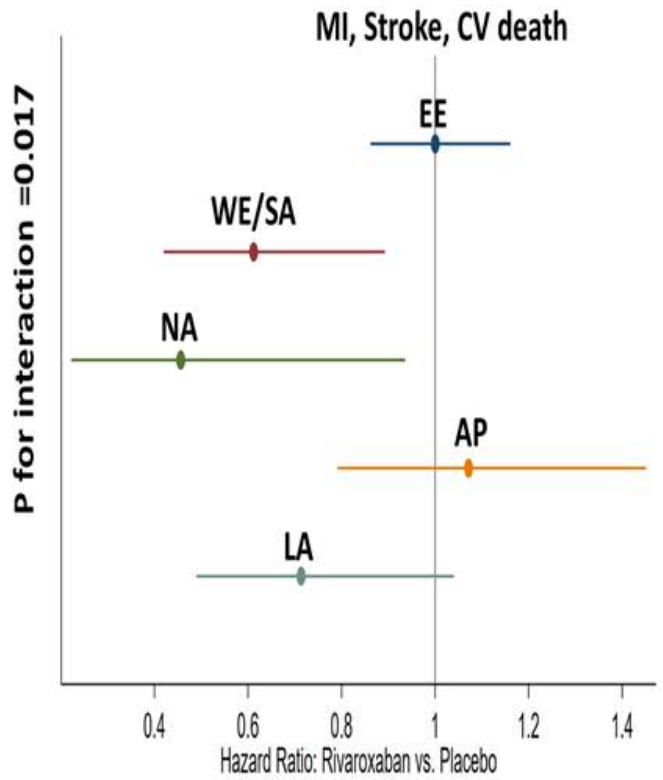
EE: lower event rates

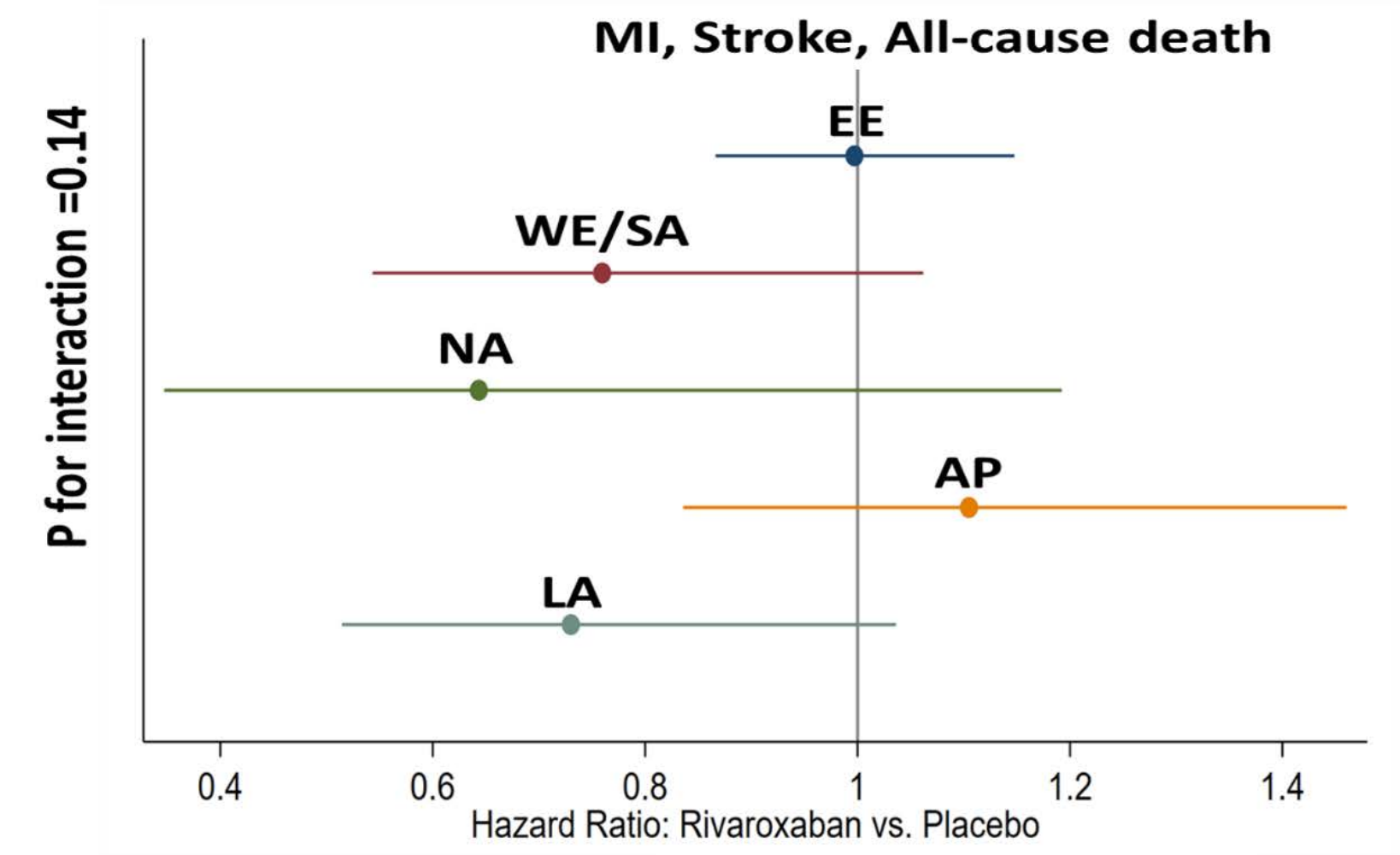


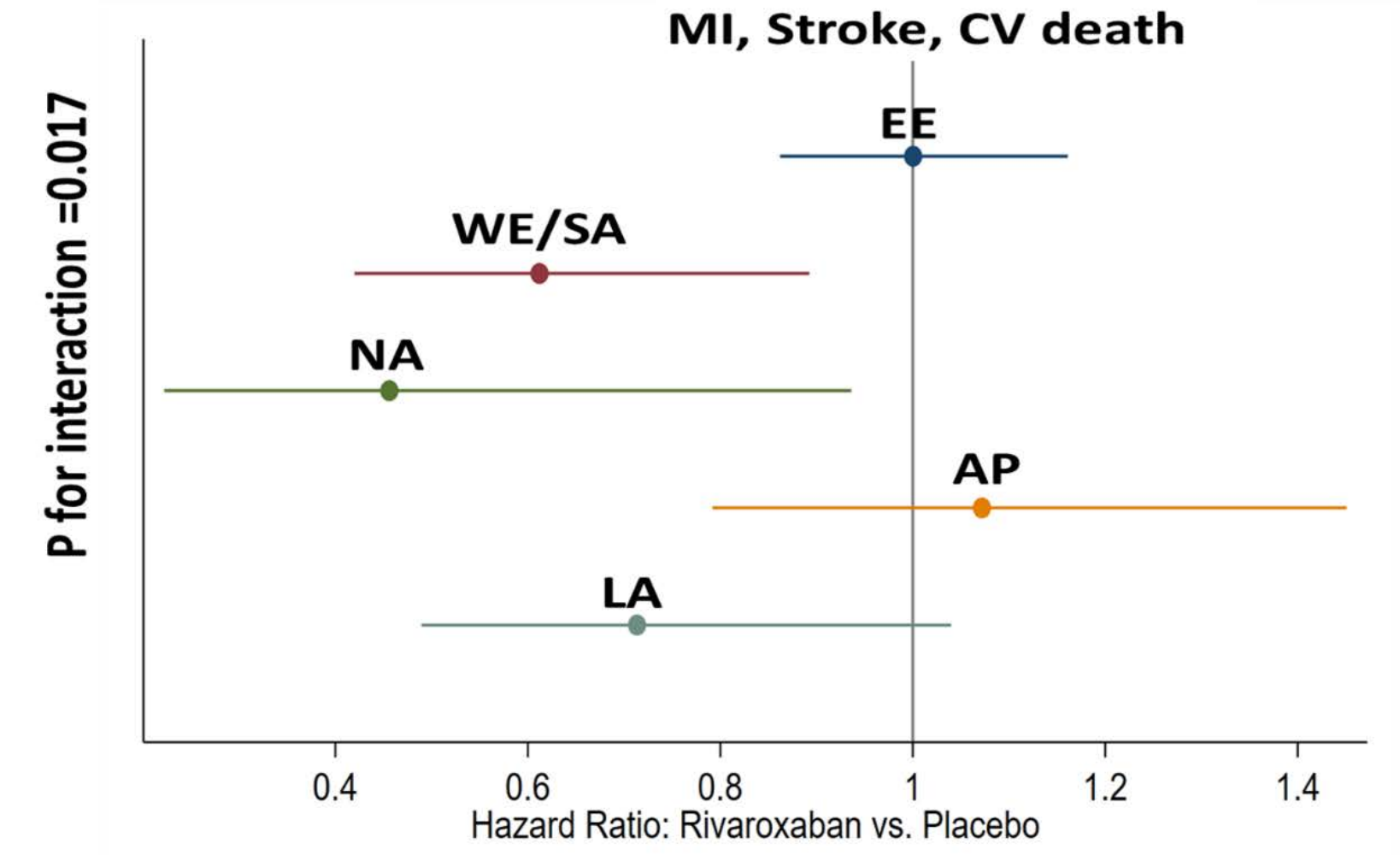
EE: lower ttx adherence

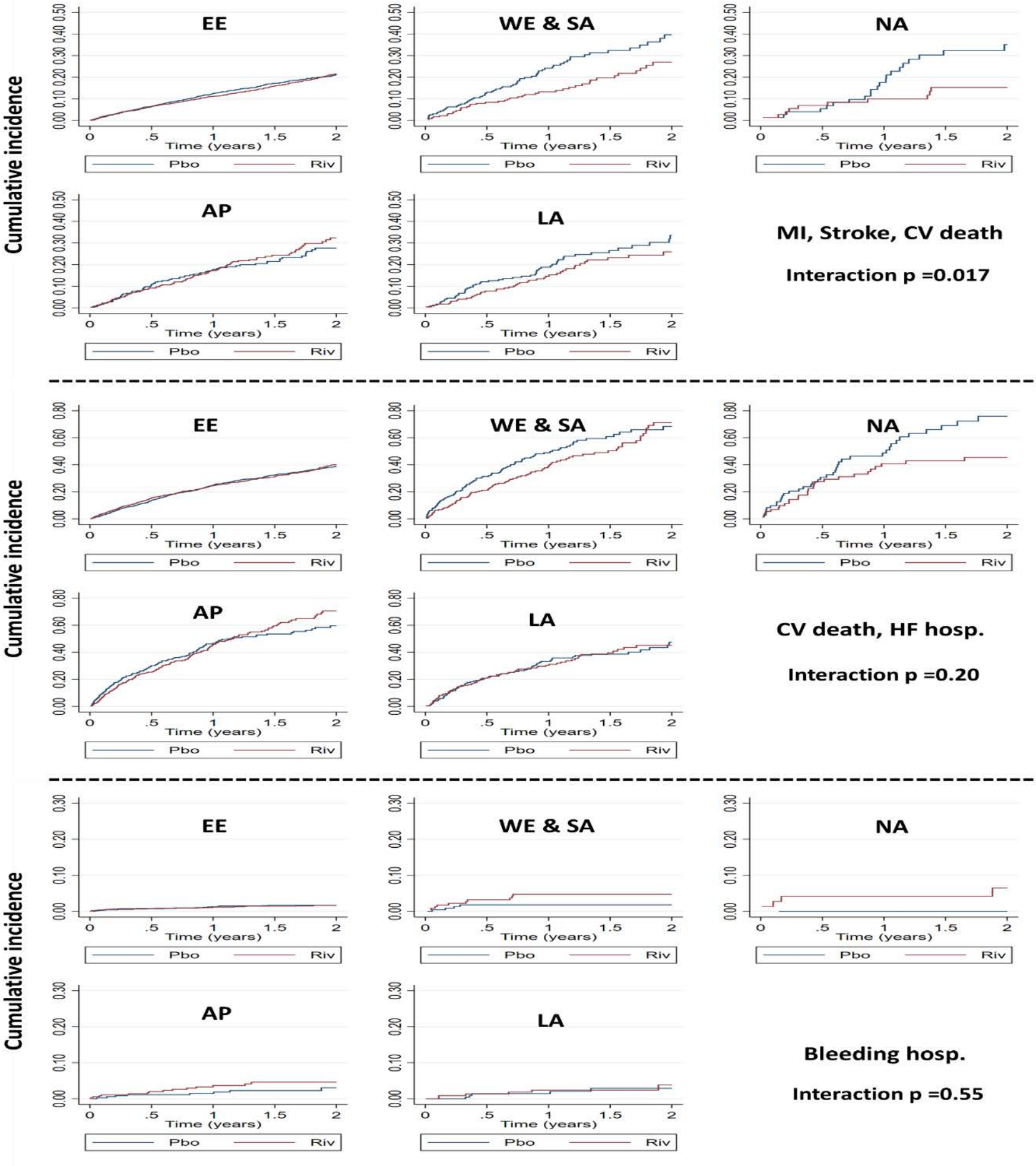


EE: no ttx effect




MI, Stroke, All-cause death
P for interaction =0.14
EE
WE/SA
NA
AP
LA
0.4
0.6
0.8
1
1.2
1.4
Hazard Ratio: Rivaroxaban vs. Placebo


MI, Stroke, CV death
P for interaction =0.017
EE
WE/SA
NA
AP
LA
0.4
0.6
0.8
1
1.2
1.4
Hazard Ratio: Rivaroxaban vs. Placebo


Cumulative incidence
EE
WE & SA
NA
AP
LA
0.00 0.10 0.20 0.30 0.40 0.50
0 .5 1 1.5 2
Time (years)
Pbo
Riv
MI, Stroke, CV death
Interaction p =0.017
Cumulative incidence
EE
WE & SA
NA
AP
LA
0.00 0.20 0.40 0.60 0.80
0 .5 1 1.5 2
Time (years)
Pbo
Riv
CV death, HF hosp.
Interaction p =0.20
Cumulative incidence
EE
WE & SA
NA
AP
LA
0.00 0.10 0.20 0.30
0 .5 1 1.5 2
Time (years)
Pbo
Riv
Bleeding hosp.
Interaction p =0.55