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Usefulness of Rivaroxaban for Secondary Prevention of Acute Coronary Syndrome in Patients With History of Congestive Heart Failure (from the ATLAS-ACS-2 TIMI-51 Trial)



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Patients with both acute coronary syndromes (ACS) and congestive heart failure are at an increased risk of recurrent cardiovascular (CV) events attributed in part to both excess thrombin generation and impaired fibrinolysis. We hypothesized that patients with the overlap of ACS and CHF would thus derive particular benefit from antithrombotic therapy with rivaroxaban. ATLAS-ACS-2 Thrombolysis in Myocardial Infarction-51 was a double-blind, multicenter, phase 3 clinical trial that randomized patients within 7 days of an ACS event to standard of care plus either rivaroxaban 2.5 mg BID, 5 mg BID, or placebo (n = 15,526). In this post hoc subgroup analysis, subjects with a history of CHF at randomization (n = 1,694) were evaluated. Among subjects with a history of CHF, both rivaroxaban doses reduced the primary composite end point of CV death, myocardial infarction, or stroke (2.5 mg BID vs placebo: hazard ratio [HR] 0.59, 95% confidence interval [CI] (0.42, 0.81), p = 0.001; 5 mg BID vs placebo: HR 0.61, 95% CI (0.44, 0.84), p = 0.002; p interaction = 0.006). Both doses of rivaroxaban reduced CV mortality (rivaroxaban 2.5 mg BID vs placebo: 4.1% vs 9.0%, HR 0.45, 95% CI [0.27, 0.74], p = 0.002; rivaroxaban 5 mg BID vs placebo: 5.8% vs 9.0%, HR 0.62, 95% CI [0.40, 0.96], p = 0.031) as well as all-cause mortality. There was no significant increase in noncoronary artery bypass graft-related Thrombolysis in Myocardial Infarction major bleeding with either dose of rivaroxaban as compared with placebo (rivaroxaban 2.5 mg BID = 0.4% vs rivaroxaban 5 mg BID = 1.1% vs placebo = 0.5%). Rivaroxaban also did not increase either intracranial hemorrhage or fatal bleeding. In conclusion, in ACS subjects with a history of CHF, secondary prevention with rivaroxaban reduced the composite of CV death, myocardial infarction, or stroke without an increase in noncoronary artery bypass graft-related major bleeding. These findings require further prospective evaluation in an adequately powered phase 3 study. © 2018 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license. (<http://creativecommons.org/licenses/by-nc-nd/4.0/>) (Am J Cardiol 2018;122:1896–1901)

There is an elevated risk of recurrent ischemic events after an acute coronary syndrome (ACS) despite currently available medical therapy. Dual antiplatelet therapy is often used to minimize this residual risk, but these antiplatelet

therapies may be ineffective due to excess thrombin generation that persists well after the ACS event.^{1,2} Congestive heart failure (CHF) patients are also at an increased risk for thrombotic events which is thought to be related to persistent activation of the renin-angiotensin-aldosterone neurohormonal system and the sympathetic nervous system leading to increases in both platelet aggregation and reduced fibrinolysis.^{3,4} Given this increase in thrombotic risk, several trials have evaluated the safety and efficacy of anticoagulation in patients with CHF. The Warfarin/Aspirin Study in Heart failure trial and the HELAS trial (Antithrombotic therapy in heart failure: a randomized comparison of warfarin vs aspirin) demonstrated that neither warfarin nor aspirin reduced the risk of myocardial infarction, nonfatal stroke, or death as compared with placebo.^{5,6} No completed randomized controlled trials, although, have prospectively evaluated the efficacy of the novel oral anticoagulants in the ACS—CHF overlap population. ATLAS ACS-2-Thrombolysis in Myocardial Infarction (TIMI)-51 was a randomized, double-blind, placebo-controlled trial that evaluated the efficacy

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and safety of rivaroxaban for the secondary prevention of atherothrombotic events after ACS.⁷ The purpose of this analysis was to evaluate the efficacy and safety of rivaroxaban among patients with a history of CHF to determine if this high-risk population derived particular benefit.

Methods

ATLAS ACS-2-TIMI-51 was a randomized, double-blind, placebo-controlled phase 3 trial that enrolled 15,526 subjects at least 18 years of age who presented with symptoms of ACS and were diagnosed with STEMI, non-ST-elevation myocardial infarction (MI), or unstable angina. Subjects were recruited within 1 to 7 days after hospital admission for the index event. After stabilization and initial management strategies, subjects were administered aspirin, and were stratified by administration of thienopyridine (either clopidogrel or ticlopidine) at the discretion of the prescribing physician. Subjects were then randomly assigned to receive either rivaroxaban 2.5 mg BID, rivaroxaban 5 mg BID, or placebo and were followed up for 24 months (median of 13 months and up to 31 months).⁷ Major exclusion criteria included history of intracranial hemorrhage or history of either ischemic stroke or TIA in subjects receiving both aspirin and thienopyridine. Full inclusion and exclusion criteria have been previously published.⁸ This subgroup analysis focuses on subjects who reported a previous history of CHF at enrollment. This was determined by history and review of medical records, given that echocardiogram data before the index event was not collected. Furthermore, the investigators did not use postevent echocardiograms to classify patients, as a significant amount left ventricular dysfunction seen in the acute setting may subsequently resolve. The primary efficacy end point of this analysis was the composite of cardiovascular (CV) death, MI, or stroke. In addition, CHF-related deaths, defined as all deaths that have been adjudicated to be caused by CHF or cardiogenic shock, were also investigated. The primary safety end point was noncoronary artery bypass graft (CABG)-related TIMI major bleeding. Additional details of the end points, design, and results of ATLAS ACS-2-TIMI-51 have been previously described.^{7,8}

All analyses were performed using Stata version 13 (StataCorp, LP, Texas). Categorical variables were reported as frequencies and percentages. The mean \pm standard deviation was reported for parametric continuous variables, and the median (IQR) was reported for nonparametric continuous variables. Baseline characteristics were calculated for all eligible subjects who were randomized in the trial. Differences in means across treatment groups were compared using the analysis of variance test for continuous variables and chi-square test for categorical variables. Event rates were calculated as numerical percentages, not as Kaplan-Meier estimates. Hazard ratios (HR) with 2-sided 95% confidence intervals were calculated using Cox proportional hazard models and log-rank p values were reported. In all efficacy analyses, the stratification variable (i.e., intent to administer thienopyridine) was included as a covariate in the Cox regression models. In the safety analyses, however, the unstratified Cox proportional hazards models were used

due to the small number of events per each stratification group.

Efficacy analyses were performed in the modified intention-to-treat population, defined as all randomized subjects and the end point events that occurred after randomization and no later than either the completion of the treatment phase of the study (i.e., the global treatment end date), 30 days after early permanent discontinuation of the study drug, or 30 days after randomization for subjects who did not receive a study drug. Safety analyses were performed in the safety population, which included all subjects who received at least 1 dose of study drug and who were censored at 2 days after discontinuation of study drug.^{7,8} Testing between the combined-dose group for rivaroxaban and placebo was prespecified per the study protocol to preserve the alpha at a level of 0.05 based on the log-rank test. All tests were 2-sided, and p value of <0.05 was considered statistically significant. Before data unblinding, a total of 3 sites were excluded from the efficacy analyses due to violations of Good Clinical Practice guidelines. All safety and efficacy end points were adjudicated by an independent, blinded clinical events committee.

All analyses were performed by the PERFUSE Study Group using an independent copy of the complete clinical trial database. The investigators wrote all drafts of the manuscript and take responsibility for its content. The sponsors had the opportunity to review and comment on this manuscript but had no editorial authority. The corresponding investigator had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Out of the 15,526 subjects enrolled in the ATLAS-ACS2-TIMI 51 trial, a total of 1,694 subjects with history of CHF were included in this analysis. Subjects were evenly distributed in treatment arms. There were no significant differences in baseline characteristics between treatment arms (Table 1).

In ACS subjects with history of CHF, there was a significant reduction in the primary end point of CV death, MI, or stroke with the combined rivaroxaban doses, as well as each of rivaroxaban 2.5 mg BID and 5 mg BID when compared with placebo (rivaroxaban 2.5 mg BID vs placebo: 10.5% vs 17.2%, HR 0.59, 95% CI [0.42, 0.81], $p=0.001$; rivaroxaban 5 mg BID vs placebo: 11.2% vs 17.2%, HR 0.61, 95% CI [0.44, 0.84], $p=0.002$; Figure 1). The presence of CHF significantly modulated the treatment effect of rivaroxaban when efficacy was compared in patients with CHF were compared without patients without CHF (p interaction = 0.006; Figure 2). When the components of the primary composite end point were evaluated individually, both doses of rivaroxaban significantly reduced CV mortality (rivaroxaban 2.5 mg BID vs placebo: 4.1% vs 9.0%, HR 0.45, 95% CI [0.27, 0.74], $p=0.002$; rivaroxaban 5 mg BID vs placebo: 5.8% vs 9.0%, HR 0.62, 95% CI [0.40, 0.96], $p=0.031$). Both the 2.5 mg BID and 5 mg BID doses of rivaroxaban also significantly reduced all-cause mortality by 57% and 41%, respectively (Table 2). Myocardial

Table 1
Baseline characteristics of all randomized subjects with history of CHF

Characteristic	Rivaroxaban			Placebo (n = 558)
	2.5 mg BID (n = 562)	5 mg BID (n = 574)	Combined (2.5 mg BID or 5 mg BID) (n = 1,136)	
Age (years), mean ± SD	63.7 ± 10.1	63.2 ± 9.3	63.5 ± 9.7	63.9 ± 10.0
Male gender	374 (66.5%)	375 (65.3%)	749 (65.9%)	373 (66.9%)
Body mass index, mean ± SD	29.0 ± 5.0	28.7 ± 5.3	28.9 ± 5.1	28.3 ± 4.9
Creatinine clearance* (ml/min), mean ± SD	85.0 ± 30.9	85.2 ± 31.3	85.1 ± 31.1	82.0 ± 31.5
Dual antiplatelet therapy stratum	483 (85.9%)	492 (85.7%)	975 (85.8%)	488 (87.5%)
Past medical history				
Prior myocardial infarction	318 (56.6%)	314 (54.7%)	632 (55.6%)	320 (57.4%)
Prior ischemic stroke	27 (4.8%)	26 (4.5%)	53 (4.7%)	22 (3.9%)
Prior transient ischemic attack	6 (1.1%)	11 (1.9%)	17 (1.5%)	8 (1.4%)
Hypertension	499 (88.8%)	508 (88.5%)	1,007 (88.6%)	493 (88.3%)
Diabetes mellitus	198 (35.2%)	191 (33.3%)	389 (34.2%)	176 (31.5%)
Atrial Fibrillation	11 (2.0%)	14 (2.4%)	25 (2.2%)	16 (2.87%)
Index Hospitalization				
Time from index acute coronary syndrome to randomization (days), median (IQR)	5.5 (4.1, 6.6)	5.5 (4.1, 6.6)	5.5 (4.1, 6.6)	5.5 (4.2, 6.7)
Index Event				
STEMI	196 (34.9%)	199 (34.7%)	395 (34.8%)	176 (31.5%)
NSTEMI	124 (22.1%)	130 (22.7%)	389 (22.4%)	135 (24.2%)
Unstable angina	242 (43.1%)	245 (42.7%)	734 (43.3%)	247 (44.3%)
Percutaneous coronary intervention for index event	138 (24.6%)	155 (27.0%)	293 (25.8%)	138 (24.7%)
Coronary artery bypass graft for index event	0	0	0	2 (0.4%)
Medications				
Aspirin	558 (99.3%)	571 (99.5%)	1129 (99.4%)	554 (99.3%)
Thienopyridine	475 (84.5%)	483 (84.1%)	958 (84.3%)	481 (86.2%)
Beta-blocker	357 (63.5%)	352 (61.3%)	709 (62.4%)	364 (65.2%)
Calcium channel blocker	118 (21.0%)	112 (19.5%)	230 (20.2%)	99 (17.7%)
ACE inhibitor or Angiotensin receptor blocker	255 (45.4%)	253 (44.1%)	508 (44.7%)	269 (48.2%)
Statin	356 (63.3%)	379 (66.0%)	735 (64.7%)	352 (63.1%)

Note: p value for all comparisons was nonsignificant

* Creatinine clearance was calculated using the Cockcroft-Gault equation.

infarction was significantly reduced among subjects who received rivaroxaban 5 mg BID, and a favorable trend was also observed in those who received 2.5 mg BID ($p=0.076$; Table 2). There was no significant reduction in stroke in either rivaroxaban arm when compared with placebo.

CHF-related deaths occurred in 0.7% ($n=4$) patients receiving rivaroxaban 2.5 mg BID, 2.1% ($n=12$) patients receiving rivaroxaban 5 mg BID, and 2.3% ($n=13$) patients receiving placebo. Compared with placebo, rivaroxaban 2.5 mg BID was associated with significant reduction in the incidence of CHF-

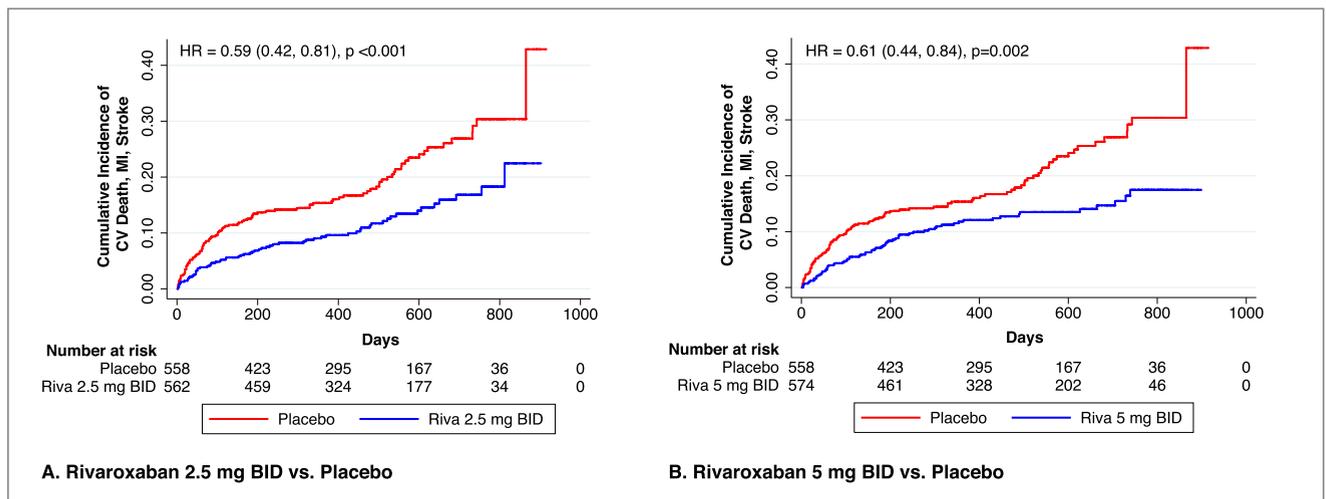


Figure 1. Cumulative incidence of CV death, myocardial infarction, or stroke with rivaroxaban versus placebo in patients with CHF.

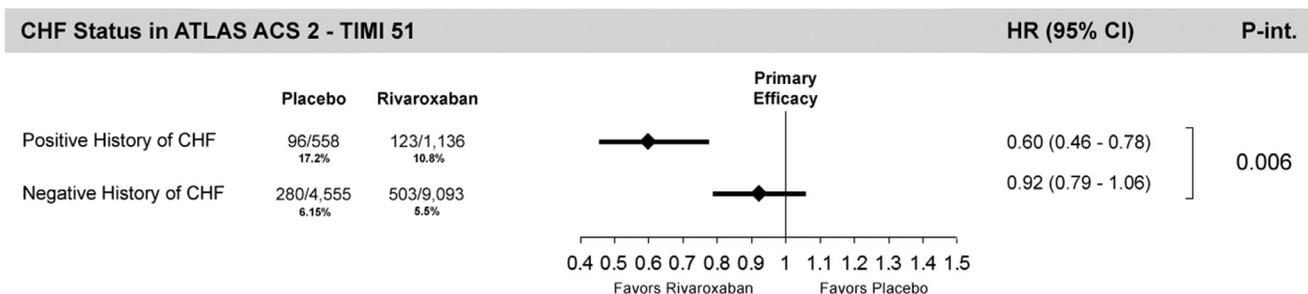


Figure 2. Primary efficacy end point in subjects with history of CHF versus subjects without previous history of CHF in ALTAS ACS 2-TIMI-51.

related deaths (Relative Risk [RR]=0.30, 95% CI [0.08 to 0.78], $p=0.03$), whereas rivaroxaban 5 mg BID was not (RR 0.90, 95% CI [0.46, 1.58], $p=0.78$).

Overall, the incidence of bleeding events was low in this subgroup of CHF subjects. The primary safety end point of non-CABG TIMI major bleeding occurred in 0.4% ($n=2$) subjects receiving rivaroxaban 2.5 mg BID, 1.1% ($n=6$) subjects receiving rivaroxaban 5 mg BID, and 0.5% ($n=3$) subjects receiving placebo (2.5 mg BID vs placebo: HR 0.65, 95% CI [0.11, 3.88], $p=0.63$; 5 mg BID vs placebo: HR 1.92, 95% CI [0.48, 7.67], $p=0.36$; Table 3). Similarly, there were no significant differences in the risk of either intracranial hemorrhage or fatal bleeding when either dose of rivaroxaban was compared with placebo. Notably, fatal bleeding occurred most frequently in the placebo group ($n=3$), and no fatal bleeding events were present with rivaroxaban 5 mg BID (Table 3).

Discussion

In patients with history of CHF and an ACS event rivaroxaban significantly reduced the risk of recurrent MI, stroke, and CV death without an increase in either fatal bleeding, intracranial hemorrhage, or non-CABG-related major bleeding. The presence of CHF was identified as a significant treatment modifier, and the benefits of rivaroxaban in the CHF population were nearly twice as great as in the overall population (40% vs 16% relative risk reduction). No other subgroup in the ATLAS 2-TIMI 51 trial demonstrated a positive interaction term. Much of this benefit was driven by a near 50% reduction in either CV or all-cause mortality. The number of patients needed to treat to prevent a death from any cause was only 19 patients for the 2.5 mg BID dose of rivaroxaban and 29 patients for the 5 mg BID rivaroxaban dose.

The precise mechanism of death in trials is not always entirely clear. Some deaths are attributable to CHF-related deaths, which were demonstrated to be significantly reduced with rivaroxaban 2.5 mg BID as compared with placebo. Deaths, however, may have also been attributable to MI, and possibly also attributable to pulmonary embolism, an end point which was not recorded as an endpoint in the trial. It is notable that in medically ill patients, factor Xa inhibition may reduce both fatal and irreversible arterial events (MI and ischemic stroke) as well as venous events (pulmonary embolism and VTE mortality).⁹ CHF patients do have a high risk of pulmonary embolism,¹⁰⁻¹⁴ and this

may have been a more common mode of death in the subgroup of CHF patients than in the trial as a whole. In contradistinction to the main ATLAS-ACS2-TIMI 51 analysis, the mortality benefit observed in CHF subjects in this study was not offset by an increase in TIMI major bleeding, and the rate of fatal bleeding over the 2-year follow-up remained numerically lower in the rivaroxaban groups as compared with placebo. Consistent with the main ATLAS-ACS2-TIMI 51 results, there was a more substantial reduction in the risk of MI in the rivaroxaban 5 mg BID group.⁷ In contrast, there was a higher rate of fatal bleeding in the 5 mg BID than the 2.5 mg BID group, and this may have offset some of the mortality benefits in the 5 mg BID group.⁷

The benefit observed in this subgroup of subjects may be due at least in part to the persistent generation of excess thrombin after ACS and the propensity of CHF subjects to have reduced fibrinolysis.^{2,15,16} Furthermore CHF, independent of the presence of atherosclerosis and ACS, has been associated with activated platelets, elevated thrombin levels, and more rapid formation of compact plasma fibrin clots predisposing patients to thromboembolic disease.^{17,18} It should also be noted that myocytes have thrombin receptors on their surface, and binding of thrombin to these receptors may mediate reperfusion injury and apoptosis.¹⁹⁻²²

There are important differences between previous studies which failed to demonstrate a benefit of anticoagulation therapy in the setting of CHF^{5,6,23} and the present study. These studies enrolled a broader cohort of CHF subjects and were not limited to CHF subjects who also had an ACS event. These studies assessed warfarin and did not assess the efficacy of factor Xa inhibition. This ATLAS-ACS2-TIMI 51 substudy provides hypothesis generating data that indicates CHF patients who recently sustained ACS may be a potential target population for prolonged anticoagulation therapy to reduce recurrent ACS events. Given these findings, the phase 3 COMMANDER-HF trial was designed to test the hypothesis that rivaroxaban 2.5 mg BID reduces the composite of all-cause mortality, MI, or stroke in 5,000 patients with concomitant CHF and CAD.²⁴ Data from COMMANDER-HF will be the first randomized-controlled trial to prospectively validate or reject the hypothesis that rivaroxaban reduces recurrent ACS events in patient with CHF as part of a secondary prevention strategy.

Table 2
Efficacy outcomes in subjects with history of CHF

Efficacy end point	Combined Riva vs Placebo			Riva 2.5 mg BID vs Placebo			Riva 5 mg BID vs Placebo					
	Event rate		HR (95% CI)	p value	Event rate		HR (95% CI)	p value	Event Rate		HR (95% CI)	p value
	Placebo n = 558	Riva n = 1,136			Placebo n = 558	Riva n = 562			Placebo n = 558	Riva n = 574		
Primary efficacy end point (n = 219)	96 (17.2%)	123 (10.8%)	0.60 (0.46, 0.78)	p < 0.001	96 (17.2%)	59 (10.5%)	0.59 (0.42, 0.81)	p = 0.001	96 (17.2%)	64 (11.2%)	0.61 (0.44, 0.84)	p = 0.002
Cardiovascular death (n = 106)	50 (9.0%)	56 (4.9%)	0.53 (0.36, 0.78)	p = 0.001	50 (9.0%)	23 (4.1%)	0.45 (0.27, 0.74)	p = 0.002	50 (9.0%)	33 (5.8%)	0.62 (0.40, 0.96)	p = 0.031
Myocardial infarction (n = 118)	50 (9.0%)	68 (6.0%)	0.63 (0.44, 0.90)	p = 0.012	50 (9.0%)	36 (6.4%)	0.68 (0.44, 1.04)	p = 0.076	50 (9.0%)	32 (5.6%)	0.58 (0.37, 0.91)	p = 0.017
Stroke (n = 29)	10 (1.8%)	19 (1.7%)	0.92 (0.43, 1.97)	p = 0.82	10 (1.8%)	7 (1.7%)	0.68 (0.26, 1.80)	p = 0.44	10 (1.8%)	12 (2.1%)	1.13 (0.49, 2.62)	p = 0.78
All-cause death (n = 108)	52 (9.3%)	56 (1.7%)	0.51 (0.35, 0.75)	p = 0.001	52 (9.3%)	23 (4.1%)	0.43 (0.26, 0.71)	p = 0.001	52 (9.3%)	33 (5.8%)	0.59 (0.38, 0.92)	p = 0.019

Note: All hazard ratios and 95% confidence intervals are based on the Cox proportional hazards models stratified by the use of thienopyridine from the modified-intention-to-treat (mITT) populations from the time of randomization until the end of the trial. mITT population included the randomized subjects and the end point events that occurred after randomization and no later than the completion of the treatment phase of the study (i.e., the global treatment end date), 30 days after early permanent discontinuation of the study drug, or 30 days after randomization for subjects who did not receive a study drug.

Note: Subjects from 3 sites were excluded from the efficacy analyses prior to unblinding due to violation of good clinical practice guidelines.

Note: All endpoints were adjudicated by an independent, blinded clinical events committee (CEC).

Table 3
Safety outcomes in subjects with history of CHF

Safety end point	Combined Riva vs Placebo			Riva 2.5 mg BID vs Placebo			Riva 5 mg BID vs Placebo					
	Event Rate % (n)		HR (95% CI)	p value	Event Rate % (n)		HR (95% CI)	p value	Event Rate % (n)		HR (95% CI)	p value
	Placebo n = 555	Riva n = 1,124			Placebo n = 555	Riva n = 556			Placebo n = 555	Riva n = 568		
Non-CABG TIMI major bleeding (n = 11)	3 (0.5%)	8 (0.7%)	1.29 (0.34, 4.86)	p = 0.71	3 (0.5%)	2 (0.4%)	0.65 (0.11, 3.88)	p = 0.63	3 (0.5%)	6 (1.1%)	1.92 (0.48, 7.67)	p = 0.36
Intracranial hemorrhage (n = 5)	3 (0.5%)	2 (0.2%)	0.32 (0.05, 0.1.93)	p = 0.22	3 (0.5%)	1 (0.2%)	0.32 (0.03, 3.11)	p = 0.33	3 (0.5%)	1 (0.2%)	0.32 (0.03, 3.07)	p = 0.32
Fatal bleeding (n = 5)	3 (0.5%)	2 (0.2%)	0.32 (0.05, 1.92)	p = 0.21	3 (0.5%)	2 (0.4%)	0.65 (0.11, 3.87)	p = 0.63	3 (0.5%)	0	-	-

Note: All hazard ratios and 95% confidence intervals are based on the unstratified Cox proportional hazards models from the safety population from the time of randomization until the end of the trial (stratification by intended thienopyridine use was not conducted due to the small number of events per group). Safety population includes subjects at the time of administration of the first dose of a study drug until 2 days after the discontinuation of a study drug.

Note: All end points were adjudicated by an independent, blinded clinical events committee (CEC).

Conclusion

In patients with history of CHF who experience an ACS event, secondary prevention with rivaroxaban was associated with a significant reduction of the composite of CV death, MI, or stroke without an increase in either fatal or non-CABG-related major bleeding. These favorable hypothesis generating findings are being prospectively assessed in the ongoing Phase 3 COMMANDER study.

Conflicts of Interest

SK, YD, MM, MC, and FV have no conflict of interest to disclose. EB has received research grant support from Abbott, AstraZeneca, Amgen, Bayer Healthcare, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Merck (SPRI), Pfizer, Roche (Diagnostics), Sanofi-Aventis, Johnson & Johnson, and has been a consultant for Merck (no compensation), Amorceyte, Daiichi Sankyo, The Medicines Co., Ikaria, CardioRentis, Sanofi-Aventis, and CVRx (no compensation). DLB has received research grant support from AstraZeneca, Amgen, Eli Lilly, Pfizer, and Sanofi-Aventis. PB and ANP are employed by and own stock in Johnson & Johnson. CB has received research grant support from Johnson & Johnson and Bayer Healthcare. CMG has received research grant support from Johnson & Johnson, Bayer Healthcare, Bristol-Myers Squibb, Portola Pharmaceuticals, Sanofi-Aventis, The Medicines Co., Eli Lilly and Company, Johnson & Johnson, Bayer Healthcare, GlaxoSmithKline, Merck Schering Plough, and Boehringer Ingelheim.

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