ORIGINAL RESEARCH

Safety and Efficacy of Rivaroxaban When Added to Aspirin Monotherapy Among Stabilized Post-Acute Coronary Syndrome Patients: A Pooled Analysis Study of ATLAS ACS-TIMI 46 and ATLAS ACS 2-TIMI 51

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Background—A residual risk of ischemic events following an acute coronary syndrome (ACS) remains despite antiplatelet therapy. The addition of an antithrombin as part of a "dual pathway" approach may further improve outcomes as thrombin generation persists for several months post-ACS. The present study evaluates the safety and efficacy of "dual pathway" therapy (rivaroxaban plus aspirin) as compared with aspirin monotherapy among post-ACS patients.

Methods and Results—A total of 1477 patients were analyzed in a pooled analysis of subsets of the ATLAS ACS-TIMI (Anti-Xa Therapy to Lower cardiovascular events in addition to Aspirin with or without thienopyridine therapy in Subjects with Acute Coronary Syndrome – Thrombolysis in Myocardial Infarction) 46 and ATLAS ACS 2-TIMI 51 trials including post-ACS patients receiving aspirin monotherapy and randomized to either rivaroxaban 2.5 mg BID or rivaroxaban 5 mg BID or placebo. The primary efficacy end point was a composite of cardiovascular death, myocardial infarction (MI), or stroke (ischemic, hemorrhagic, or of uncertain cause). The primary safety end point was TIMI-non-coronary artery bypass (CABG) major bleeding. The combined rivaroxaban group (2.5 or 5 mg BID) among stabilized post-ACS patients on a background of aspirin monotherapy was associated with a significant reduction in the primary end point as compared with placebo (hazard ratio=0.65, 95% CI=0.45–0.92, P=0.016). Although the combined rivaroxaban dose groups were associated with higher rates of non-CABG TIMI major bleeding, the 2.5 mg dose group was not, and the overall number of patients experiencing a non-CABG TIMI major bleeding event was low (1.5%).

Conclusions—Among patients in the immediate post-ACS period, a "dual pathway" approach using aspirin and low-dose rivaroxaban may reduce the risk of secondary atherothrombotic events, but increase bleeding risk.

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Key Words: acute coronary syndrome • anticoagulation • aspirin • rivaroxaban • thrombosis

Following an acute coronary syndrome (ACS), patients remain at risk for recurrent ischemic events.[1] Current guidelines recommend dual antiplatelet therapy (DAPT), utilizing aspirin and a thienopyridine, among post-ACS patients to minimize this risk of secondary atherothrombotic events.[2–5] However, at 1-year post-ACS, a 10% residual risk of cardiovascular events remains among patients treated with standard DAPT.[6,7] This increased risk may, at least in part, be attributed to persistent excess thrombin generation that continues for months following an ACS.[8] It is therefore plausible that the addition of an antithrombin as part of a "dual pathway strategy" (antiplatelet combined with an anti-thrombin strategy) may reduce subsequent

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Clinical Perspective

What Is New?

- This study pools data from ATLAS ACS-TIMI 46 (acute coronary syndrome-thrombolysis in myocardial infarction 46) trial and ATLAS ACS 2-TIMI 51 to evaluate the strategy of combining rivaroxaban with aspirin compared with treatment with aspirin alone in the period immediately following an acute coronary syndrome.
- The addition of rivaroxaban to aspirin reduced a composite of cardiovascular death, myocardial infarction, and stroke versus aspirin alone, primarily by a reduction in the risk of myocardial infarction.

What Are the Clinical Implications?

- The results are similar to those in the COMPASS trial (Cardiovascular Outcomes for People Using Anticoagulation Strategies), which showed that the addition of rivaroxaban at a dose of 2.5 mg BID to aspirin was superior to the administration of either agent alone, and was associated with reduction in cardiovascular and total mortality among stable coronary artery disease subjects.
- The addition of rivaroxaban to a single antiplatelet agent such as aspirin may be a viable alternative to triple therapy using rivaroxaban plus dual antiplatelet therapy.

events, as was seen in the ATLAS ACS-TIMI (Anti-Xa Therapy to Lower cardiovascular events in addition to Aspirin with or without thienopyridine therapy in Subjects with Acute Coronary Syndrome – Thrombolysis in Myocardial Infarction) studies of ACS patients.[9,10] This "dual pathway" strategy was most recently evaluated in the chronic setting in the COMPASS trial (Cardiovascular Outcomes for People Using Anticoagulation Strategies).[11] This trial compared rivaroxaban 2.5 mg BID plus aspirin 100 mg QD versus aspirin alone among patients with either stable coronary artery disease or peripheral artery disease who either did not require DAPT or in whom DAPT had been discontinued. The addition of rivaroxaban 2.5 mg BID to aspirin mono-antiplatelet therapy reduced the risk of cardiovascular death, MI, or stroke, as well as cardiovascular mortality.[11] Although there was an increase in major bleeding, there was no increase in either fatal or intracranial bleeding. The present analysis evaluates the strategy of combining rivaroxaban with aspirin versus treatment with aspirin alone in the period immediately following an ACS.

Methods

Study Population and Design

ATLAS ACS-TIMI 46 and ATLAS ACS 2-TIMI 51 investigated the efficacy and safety of rivaroxaban among men and women, more than 18 years of age, who were stabilized post-ACS, which was defined as one of the following: ST-segment–elevation myocardial infarction, non-ST-segment–elevation myocardial infarction, or unstable angina patients.[12,13] In both trials, patients were stratified according to the treating physician's intent to administer aspirin monotherapy or DAPT. ATLAS ACS-TIMI 46 (n=3491), a phase II dose-finding trial, randomized patients to one of the following: placebo, once-daily rivaroxaban (either 5 mg, 10 mg, or 20 mg), or twice-daily (BID) rivaroxaban (twice daily doses of 2.5 mg, 5 mg, 7.5 mg, or 10 mg) for a total duration of 6 months. ATLAS ACS 2-TIMI 51 (n=15 526), a phase III trial, randomized patients to placebo, rivaroxaban 2.5 mg BID, or rivaroxaban 5 mg BID for up to 31 months (mean=13.1 months). Major exclusion criteria included a platelet count $<90\ 000/mm^3$, hemoglobin concentration <10 g/dL, previous clinically significant gastrointestinal bleeding within the past 12 months, and previous intracranial hemorrhage.[12–14]

The present analysis pools patients who were stratified to receive aspirin monotherapy from both ATLAS ACS-TIMI 46 and ATLAS ACS 2-TIMI 51 who were subsequently randomized to rivaroxaban (2.5 mg BID or 5 mg BID) or placebo. In order to keep rivaroxaban doses consistent across both trials, only patients who were randomized to placebo, rivaroxaban 2.5 mg BID, or rivaroxaban 5 mg BID from ATLAS ACS-TIMI 46 were included. The primary efficacy end point was the composite of cardiovascular death, MI, or stroke (ischemic, hemorrhagic, or of uncertain cause). The primary safety end point was non–coronary artery bypass grafting (CABG) TIMI major bleeding. The studies were approved by national and institutional review committees and all subjects gave informed consent. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Statistical Analysis

All statistical analyses were performed using SAS version 9.4. Descriptive statistics were reported as mean and SD for normally distributed continuous variables, as median and interquartile range for non-normally distributed continuous variables, and as frequencies and percentages for categorical variables. Differences across treatment groups were tested using the independent samples *t* test or the Wilcoxon rank sum test for continuous variables and the χ^2 test of independence for categorical variables. Efficacy and safety end points were expressed as Kaplan–Meier estimates through 720 days, with patients from ATLAS ACS-TIMI 46 being censored after 6 months. Hazards ratios (HR) and 95% CI were generated using Cox proportional hazard models

Table 1. Baseline Characteristics of Patients on a Background of Aspirin Monotherapy: Pooled ATLAS ACS-TIMI 46 and ATLAS ACS 2-TIMI 51

Characteristics	ATLAS ACS-TIMI 46 (n=427)			ATLAS ACS 2-TIMI 51 (n=1050)			Combined (N=1477)		
	Combined Rivaroxaban (n=174)	Placebo (n=253)	*P* Value	Combined Rivaroxaban (n=697)	Placebo (n=353)	*P* Value	Combined Rivaroxaban (n=871)	Placebo (n=606)	*P* Value
Age (y), mean±SD	60.3±9.8	60.3±9.3	0.952	63.9±9.7	64.7±10.8	0.220	63.2±9.8	62.9±10.4	0.569
≥65, n (%)	67 (38.5%)	94 (37.2%)	0.777	321 (46.1%)	178 (50.4%)	0.180	388 (44.6%)	272 (44.9%)	0.898
≥75, n (%)	6 (3.4%)	5 (2.0%)	0.367	92 (13.2%)	75 (21.2%)	<0.001	98 (11.3%)	80 (13.2%)	0.258
Sex, male, n (%)	122 (70.1%)	172 (68.0%)	0.640	372 (53.4%)	201 (56.9%)	0.273	494 (56.7%)	373 (61.6%)	0.063
Weight (kg) (mean±SD)	82.6±17.3	81.0±14.5	0.312	78.8±16.3	76.7±15.4	0.050	79.5±16.6	78.5±15.1	0.212
Cr Cl (mL/min) (mean±SD)	90.9±34.4	87.3±27.7	0.253	83.6±31.0	80.5±32.8	0.141	85.0±31.8	83.3±31.0	0.292
Medical history									
Prior MI, n (%)	45 (25.9%)	70 (27.7%)	0.679	276 (39.6%)	118 (33.4%)	0.051	321 (36.9%)	188 (31.0%)	0.020
Hypertension, n (%)	128 (73.6%)	188 (74.3%)	0.863	588 (84.4%)	308 (87.3%)	0.211	716 (82.2%)	496 (81.9%)	0.861
Diabetes mellitus, n (%)	32 (18.4%)	55 (21.7%)	0.399	276 (39.6%)	142 (40.2%)	0.844	308 (35.4%)	197 (32.5%)	0.256
Hypercholesterolemia, n (%)	92 (52.9%)	112 (44.3%)	0.080	427 (61.3%)	216 (61.2%)	0.982	519 (59.6%)	328 (54.1%)	0.037
Renal insufficiency, n (%)	5 (2.9%)	2 (0.8%)	0.127	25 (3.6%)	16 (4.5%)	0.455	30 (3.4%)	18 (3.0%)	0.613
Active smoking, n (%)	87 (50.0%)	129 (51.0%)	0.841	216 (31.0%)	94 (26.6%)	0.143	303 (34.8%)	223 (36.8%)	0.427
Atrial fibrillation	15 (8.6%)	16 (6.3%)	0.369	5 (0.7%)	6 (1.7%)	0.197	20 (2.3%)	22 (3.6%)	0.129
Index hospitalization									
STEMI, n (%)	74 (42.5%)	114 (45.1%)	0.844	124 (17.8%)	58 (16.4%)	0.242	198 (22.7%)	172 (28.4%)	0.004
NSTEMI, n (%)	40 (23.0%)	58 (22.9%)		155 (22.2%)	95 (26.9%)		195 (22.4%)	153 (25.2%)	
Unstable angina, n (%)	60 (34.5%)	81 (32.0%)		418 (60.0%)	200 (56.7%)		478 (54.9%)	281 (46.4%)	
PCI for index event, n (%)	15 (8.6%)	21 (8.3%)	0.907	28 (4.0%)	23 (6.5%)	0.075	43 (4.9%)	44 (7.3%)	0.062
CABG for index event, n (%)	1 (0.6%)	0 (0.0%)	0.408	9 (1.3%)	10 (2.8%)	0.077	10 (1.2%)	10 (1.7%)	0.412
Time from index ACS to randomization (d), median (IQR)	5.0 (4.0–7.0)	5.0 (4.0–6.0)	0.892	5.0 (3.4–6.0)	4.9 (3.7–6.0)	0.826	5.0 (3.6–6.1)	5 (4.0–6.0)	0.132
Time from randomization to study drug (d) median (IQR)	1.22 (0.7–2.4)	1.3 (0.6–3.2)	0.764	6.4 (1.1–9.3)	6.7 (1.6–9.2)	0.440	5.1 (1.0–8.5)	3.7 (0.8–7.8)	0.026
Medications									
Aspirin, n (%)	172 (98.9%)	252 (99.6%)	0.570	693 (99.4%)	350 (99.2%)	0.693	865 (99.3%)	602 (99.3%)	>0.999
β-Blocker, n (%)	155 (89.1%)	215 (85.0%)	0.221	429 (61.6%)	205 (58.1%)	0.277	584 (67.1%)	420 (69.3%)	0.360
ACE-I or ARB, n (%)	130 (74.7%)	199 (78.7%)	0.341	286 (41.0%)	154 (43.6%)	0.421	416 (47.8%)	353 (58.3%)	<0.001
Statin, n (%)	131 (75.3%)	175 (69.2%)	0.168	487 (69.9%)	241 (68.3%)	0.596	618 (71.0%)	416 (68.7%)	0.341
Calcium channel blocker, n (%)	31 (17.8%)	45 (17.8%)	0.994	144 (20.7%)	79 (22.4%)	0.520	175 (20.1%)	124 (20.5%)	0.862

ACE-I indicates angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin-II receptor blocker; CABG, coronary artery bypass graft; Cr Cl, creatinine clearance; IQR, interquartile range; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.

stratified by trial. All *P* values are reported as nominal *P* values. Efficacy analyses were performed in an intent-to-treat approach among all randomized patients. Events from the ATLAS ACS-TIMI 46 trial were included if they had occurred after randomization, through the end of the study at 6 months, regardless of drug discontinuation. Events from the ATLAS ACS 2-TIMI 51 trial were included if they had occurred after randomization and either no later than the completion of the treatment phase of the study (ie, global treatment end date), 30 days after early permanent study drug discontinuation, or 30 days after randomization if no study drug was received. Safety analyses were performed in the safety population, which included all patients who received at least 1 dose of study drug. Safety events from ATLAS ACS-TIMI 46 were included through the end of study, and events from ATLAS ACS 2-TIMI 51 were included if they

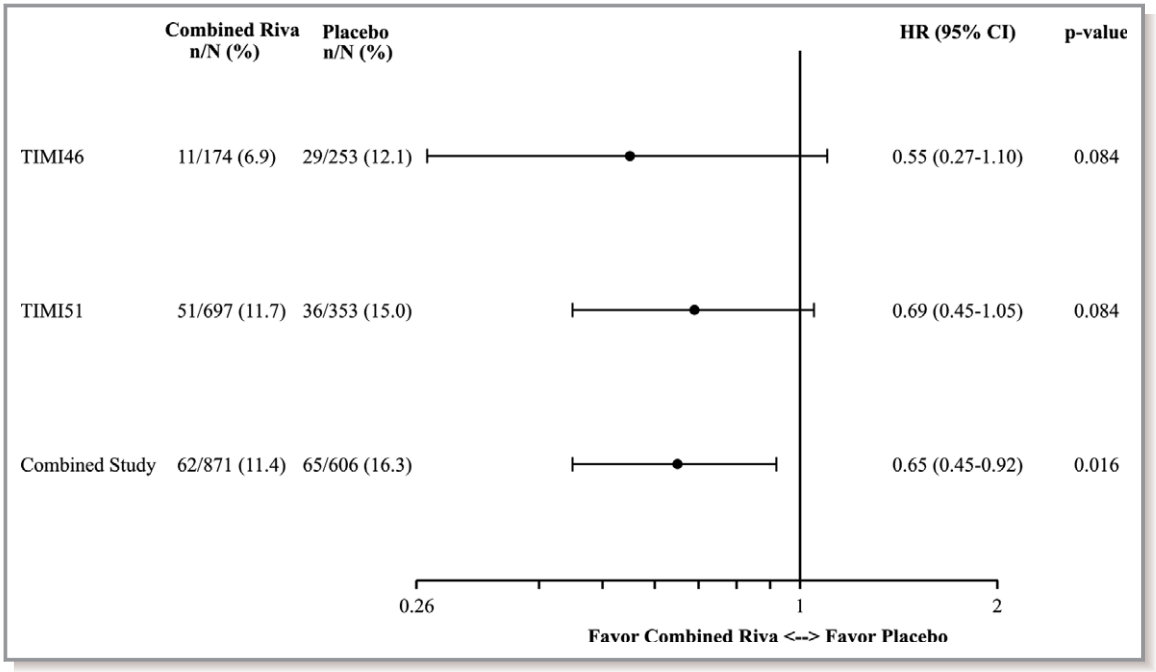

Figure 1. Forest plot for the primary efficacy end point for ATLAS ACS-TIMI 46, ATLAS ACS 2-TIMI 51, and both trials combined. *P* values are based on the unstratified log rank test and HR (95% CI) are based on unstratified Cox Proportional Hazard Models for each individual trial analysis. *P* values for the combined analysis are based on the log rank test and HR (95% CI) are based on Cox Proportional Hazard Models stratified by trial. Scale of the *x*-axis was based on log transformation of the ratio. Percentages are Kaplan–Meier estimates. HR indicates hazard ratio; TIMI, thrombolysis in myocardial infarction.

occurred within 2 days following study drug discontinuation. Sensitivity analyses through 6 months were performed since subjects in ATLAS ACS-TIMI 46 were only followed for 6 months.

Results

Baseline Characteristics

A total of 19 017 patients were randomized in ATLAS ACS-TIMI 46 (n=3491) and ATLAS ACS 2-TIMI 52 (n=15 526), of whom 1814 were on aspirin monotherapy (n=761 and n=1053, respectively). Of those, 427 patients from ATLAS ACS-TIMI 46 were included in the analysis after excluding patients with other rivaroxaban doses, and 1050 patients from ATLAS ACS 2-TIMI 51 were included in the analysis (after excluding patients before unblinding from 3 sites that violated Good Clinical Practice guidelines) for a total of n=1477 patients. Baseline characteristics were well balanced between treatment groups for both ATLAS ACS-TIMI 46 and ATLAS ACS 2-TIMI 51.[12,13] In the pooled analysis, baseline characteristics were overall balanced between treatment groups, but compared with placebo, patients receiving rivaroxaban were more likely to have experienced unstable angina as their index event, had a history of prior MI, or history of hypercholesterolemia, and were less likely to be receiving an angiotensin-converting enzyme-inhibitor or an angiotensin-II receptor blocker (Table 1). There was a longer duration between randomization and administration of the first dose of study drug among patients treated with rivaroxaban (Table 1). Of note, only a minority of patients underwent percutaneous coronary intervention during the index event in both rivaroxaban and placebo arms (4.9% versus 7.3%, *P*=NS) or had a history of atrial fibrillation (2.3% versus 3.6%, *P*=NS).

Efficacy End Points

When the aspirin monotherapy was evaluated separately, both ATLAS ACS-TIMI 46 and ATLAS ACS 2-TIMI 51 demonstrated that the combined rivaroxaban doses were not associated with a reduction in the primary end point composite of cardiovascular death, MI, or stroke compared with placebo (in ATLAS ACS-TIMI 46: combined rivaroxaban doses=11/174 (6.9%) versus placebo=29/253 (12.1%); HR=0.55, 95% CI=0.27–1.10, *P*=0.084) and in ATLAS ACS 2-TIMI 51: combined rivaroxaban doses=51/697 (11.7%) versus placebo=36/353 (15.0%); HR=0.69, 95% CI=0.45–1.05, *P*=0.084) (Figure 1). When data from the 2 trials were pooled, rivaroxaban (combined dose) was associated with a significant reduction in the primary end point as compared with placebo (combined rivaroxaban doses=62/871 (11.4%) versus placebo=65/606 (16.3%); HR=0.65, 95% CI=0.45–0.92, *P*=0.016) (Figure 2, Table 2).

Similarly, rivaroxaban 5 mg BID significantly reduced the primary end point as compared with placebo (rivaroxaban 5 mg BID=30/445 (12.6%); HR=0.78, 95% CI=0.63–0.98, *P*=0.030). Rivaroxaban 2.5 mg BID was not associated with a reduction compared with placebo (rivaroxaban 2.5 mg BID=32/426 (10.2%); HR=0.69, 95% CI=0.45–1.07, *P*=0.093). Results were consistent through 6 months (Table S1).

When the individual components of the composite end point were evaluated, combined rivaroxaban doses were associated with significant reduction in the risk of MI (HR=0.54, 95% CI=0.34–0.85, *P*=0.008). When the doses were compared with placebo separately, a significant association was observed among patients receiving the rivaroxaban 5 mg BID dose (HR=0.70, 95% CI=0.52–0.95, *P*=0.018). However, rivaroxaban 2.5 mg BID dose was not associated with a reduction compared with placebo (HR=0.59, 95% CI=0.34–1.04, *P*=0.064). No significant differences between rivaroxaban and placebo were observed with respect to cardiovascular death, stroke, or all-cause death (Table 2).

Safety End Points

The combined rivaroxaban doses significantly increased the risk of TIMI non-CABG major bleeding as compared with placebo (Figure 2, Table 3), but the total number of bleeding events was small (combined rivaroxaban=8/857 [1.5%]). This increase in major bleeding was not significant in the low-dose 2.5 mg BID group compared with placebo (2/420 [1.3%] versus 0/599, respectively, *P*=0.15). Clinically significant bleeding was also increased in the combined rivaroxaban dose arms (combined rivaroxaban=47/857 [8.4%] versus placebo=15/599 [5.0%]; HR=1.91, 95% CI=1.06–3.45, *P*=0.03). Of note, however, the increased rate of TIMI non-CABG major bleeding and clinically significant bleeding was primarily driven by the increased risk of bleeding with rivaroxaban 5 mg BID only, and not the lower dose of rivaroxaban 2.5 mg BID (Table 3). In contrast, rivaroxaban 2.5 mg BID was not associated with an increase in any bleeding type when compared with placebo. Analyses through 6 months demonstrated consistent results (Table S2).

Discussion

In a pooled analysis of the patients receiving aspirin monotherapy in the ATLAS ACS trials, the addition of rivaroxaban to aspirin reduced cardiovascular death, MI, and stroke versus aspirin alone, primarily by a reduction in the risk of MI. Rivaroxaban administration also increased the rate of the

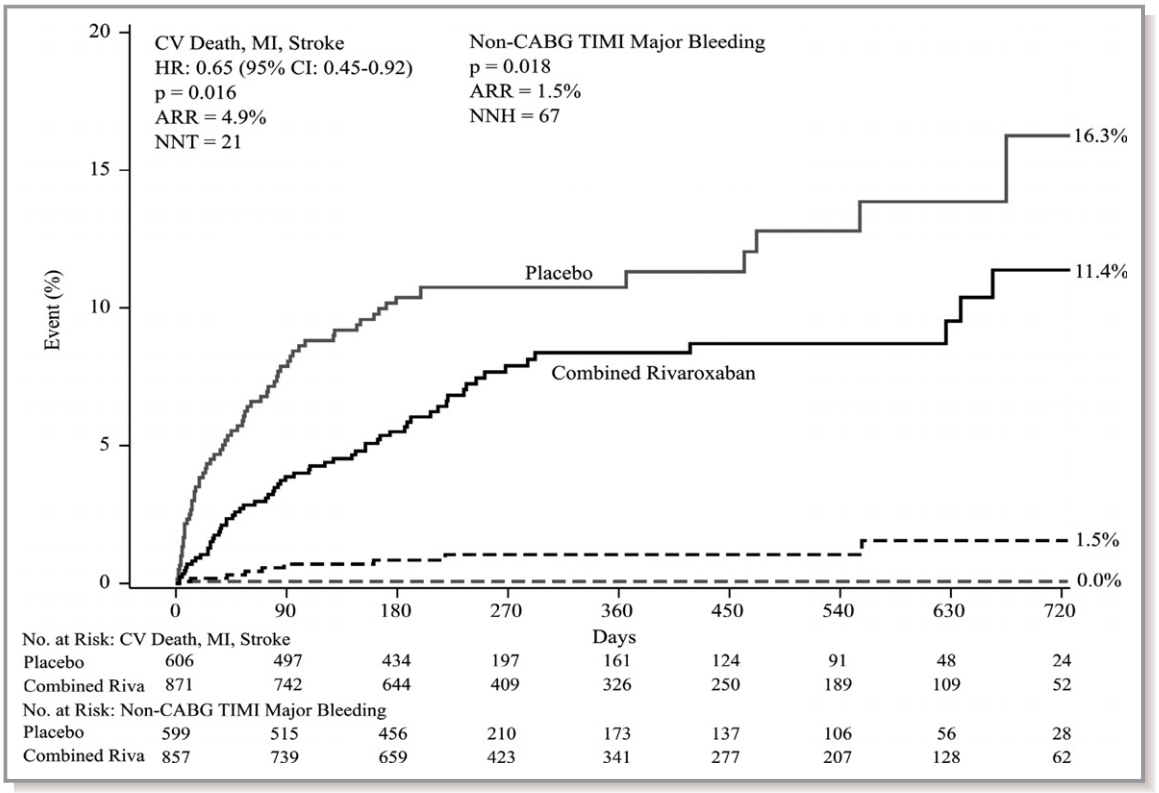

Figure 2. Kaplan–Meier curve for primary efficacy and primary safety outcome in the pooled analysis. Efficacy outcomes are displayed in solid lines. Safety outcomes are displayed in dashed line. ARR indicates absolute risk reduction; CABG, coronary artery bypass grafting; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; NNT, number needed to treat; TIMI, thrombolysis in myocardial infarction.

primary safety end point, TIMI Non-CABG Major Bleeding. There is persistent excess thrombin generation following an acute coronary syndrome,[8,15] which makes the addition of factor Xa inhibition by rivaroxaban to standard antiplatelet therapy a plausible strategy for secondary prevention of atherothrombotic events. The rivaroxaban 5 mg BID dose tended to be more effective than the 2.5 mg BID dose, but the 5 mg BID dose was associated with a 1.7% increase in TIMI non-CABG major bleeding, while the 2.5 mg BID dose was not. It should be noted, however, that the overall number of bleeds in all 3 study arms was low. While rivaroxaban resulted in a significant reduction in the primary efficacy end point, the absolute benefit may have been underestimated by the high proportion (≈50%) of enrolled patients with unstable angina as index event (Tables S3 and S4). This cohort is lower risk at baseline, and may include patients misdiagnosed as having had coronary thrombosis. Recently, the COMPASS trial showed that the addition of rivaroxaban at a dose of 2.5 mg BID to aspirin was superior to the administration of either agent alone, and was associated with reduction in cardiovascular and total mortality among stable coronary artery disease patients.[11] Our results are similar to that of COMPASS, but demonstrate that rivaroxaban in combination with aspirin reduces major adverse cardiovascular events in the acute phase of treatment for coronary artery disease, manifested as ACS. It is notable that the addition of rivaroxaban was more effective in reducing recurrent MI (relative risk reduction=46%) during the early post MI period in the pooled ATLAS trials (in which the drug was started a median of 4.7 days after the index event), while it was more effective in reducing the risk of stroke (relative risk reduction=42%) during the chronic phase of disease management in the COMPASS trial.[11] The results of the ATLAS trials contrast with those of the APPRAISE 2 trial.[12,13,16] There are several possible reasons for this difference, including: the exclusion of patients with prior stroke in ATLAS-2, dosing (25% of atrial fibrillation dose in ATLAS-2, versus 100% in APPRAISE), and early termination of APPRAISE because of excess bleeding.[17,18]

While low-dose rivaroxaban reduced overall mortality in the ATLAS ACS 2-TIMI 51 trial, the increased risk of bleeding associated with triple therapy using rivaroxaban plus DAPT may limit the uptake of this strategy. Thus, the addition of rivaroxaban to a single antiplatelet agent such as aspirin as shown in this analysis and in the COMPASS trial may be a viable alternate strategy. In the WOEST (What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting) trial, among patients who underwent intracoronary stent placement and who required anticoagulation, aspirin was removed from the triple therapy strategy of vitamin K antagonist plus thienopyridine plus aspirin, which yielded a 64% reduction in bleeding with preserved efficacy.[19] Similarly, in the PIONEER AF-PCI (Open-Label, Randomized, Controlled, Multicenter Study Exploring

Table 2. Kaplan–Meier Estimates and Hazard Ratios for Primary and Secondary Efficacy End Points According to the Different Dosages of Rivaroxaban Among Patients on a Background of Aspirin Monotherapy

	Rivaroxaban				Rivaroxaban 2.5 mg BID vs Placebo		Rivaroxaban 5 mg BID vs Placebo		Rivaroxaban Combined vs Placebo	
	2.5 mg BID (n=426)	5 mg BID (n=445)	Combined (n=871)	Placebo (n=606)	Hazard Ratio, 95% CI	*P* Value	Hazard Ratio, 95% CI	*P* Value	Hazard Ratio, 95% CI	*P* Value
Primary end point	32 (10.2%)	30 (12.6%)	62 (11.4%)	65 (16.3%)	0.69 (0.45–1.07)	0.093	0.78 (0.63–0.98)	0.030	0.65 (0.45–0.92)	0.016
Cardiovascular death	14 (5.8%)	10 (5.1%)	24 (5.4%)	16 (3.2%)	1.17 (0.56–2.46)	0.673	0.89 (0.59–1.33)	0.559	0.96 (0.50–1.84)	0.904
Myocardial infarction	18 (6.5%)	15 (8.0%)	33 (7.3%)	44 (11.7%)	0.59 (0.34–1.04)	0.064	0.70 (0.52–0.95)	0.018	0.54 (0.34–0.85)	0.008
Stroke	3 (0.8%)	9 (3.0%)	12 (1.9%)	9 (2.6%)	0.42 (0.11–1.58)	0.186	1.08 (0.67–1.72)	0.756	0.82 (0.34–1.98)	0.653
All-cause death	15 (6.3%)	10 (5.1%)	25 (5.6%)	16 (3.2%)	1.25 (0.61–2.59)	0.546	0.89 (0.59–1.33)	0.559	1.00 (0.52–1.90)	0.994
Net clinical outcome	33 (11.2%)	32 (12.9%)	65 (12.1%)	65 (16.3%)	0.71 (0.46–1.09)	0.118	0.81 (0.66–1.01)	0.059	0.68 (0.48–0.97)	0.032

Percentages are Kaplan–Meier estimates. *P* values are based on the log rank test stratified by trial. Hazard ratios are based on Cox Proportional Hazard Models stratified by trial. Analyses were completed through 720 days.

Table 3. Kaplan–Meier Estimates and Hazard Ratios for Safety End Points According to the Different Dosages of Rivaroxaban Among Patients on a Background of Aspirin Monotherapy

	Rivaroxaban				Rivaroxaban 2.5 mg BID vs Placebo		Rivaroxaban 5 mg BID vs Placebo		Rivaroxaban Combined vs Placebo	
	2.5 mg BID (n=420)	5 mg BID (n=437)	Combined (n=857)	Placebo (n=599)	Hazard Ratio 95% CI	*P* Value	Hazard Ratio 95% CI	*P* Value	Hazard Ratio 95% CI	*P* Value
TIMI non-CABG major bleeding	2 (1.3%)	6 (1.7%)	8 (1.5%)	0 (0.0%)	…	0.154	…	0.003	…	0.018
TIMI major bleeding	2 (1.3%)	6 (1.7%)	8 (1.5%)	2 (0.3%)	1.01 (0.14–7.18)	0.991	2.01 (0.89–4.54)	0.074	2.64 (0.54–12.82)	0.214
TIMI minor bleeding	1 (0.2%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	…	0.310	…	…	…	0.473
TIMI bleeding requiring medical attention	16 (5.3%)	22 (8.5%)	38 (6.9%)	13 (4.7%)	1.47 (0.70–3.10)	0.311	1.45 (1.02–2.06)	0.034	1.76 (0.93–3.34)	0.080
Clinically significant bleeding	19 (6.8%)	28 (10.0%)	47 (8.4%)	15 (5.0%)	1.47 (0.74–2.93)	0.268	1.53 (1.11–2.11)	0.007	1.91 (1.06–3.45)	0.030

Percentages are Kaplan–Meier estimates. *P* values are based on the log rank test stratified by trial. Hazard Ratios are based on Cox Proportional Hazard Models stratified by trial. Analyses were completed through 720 days. CABG indicates coronary artery bypass graft; TIMI, thrombolysis in myocardial infarction.

Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention) trial, again among patients undergoing stenting with atrial fibrillation, aspirin was removed and the strategy of rivaroxaban plus a thienopyridine alone without aspirin reduced bleeding by 41% relative to conventional triple therapy using a vitamin K antagonist with similar results being observed with respect to efficacy.[20]

While the present analysis evaluated the safety and efficacy of adding rivaroxaban to low-dose aspirin versus low-dose aspirin alone, the GEMINI-ACS-1 (A Study to Compare the Safety of Rivaroxaban Versus Acetylsalicyclic Acid n Addition to Either Clopidogrel or Ticagrelor Therapy in Participants with Acute Coronary Syndrome) trial assessed the safety of adding rivaroxaban 2.5 mg BID to a thienopyridine versus the safety of adding aspirin to a thienopyridine in the setting of acute coronary syndromes.[21] The addition of rivaroxaban at a dose of 2.5 mg BID to a thienopyridine resulted in no difference in either TIMI non-CABG clinically significant bleeding, nor ischemic events as compared with the standard of care of adding aspirin to a thienopyridine. Taken together, these data should inform the design of future trials to determine the optimal combination of aspirin, P2Y12 inhibitors and non-vitamin K oral anticoagulants for ACS.

Conclusions

The “dual pathway” approach targeting both platelet aggregation and thrombin generation may be an effective and safe strategy to reduce the residual risk of an ischemic event in the immediate post-ACS setting. Among post-ACS patients receiving aspirin monotherapy, low-dose rivaroxaban was associated with significant reduction in secondary atherothrombotic events.

Disclosures

W.J. Gibson reports receiving consulting fees from nference and ImmPACT-Bio. C.M. Gibson reports being an employee of the Baim Institute; receiving consulting fees from Bayer, Janssen, Johnson & Johnson, the Medicines Company, Boston Clinical Research Institute, Eli Lilly, Gilead Sciences, Novo Nordisk, Pfizer, and WebMD and grant support from Angel Medical, Bayer, CSL Behring, Janssen, Johnson & Johnson, and Portola Pharmaceuticals. P. Burton reports being an employee of Janssen and holding stock in Johnson & Johnson. A. N. Plotnikov reports being an employee of Janssen Pharmaceuticals Research & Development. E. Braunwald reports receiving grant support through his institution from Daiichi-Sankyo, AstraZeneca, Novartis, Duke University, Merck, and GlaxoSmithKline; being an uncompensated consultant and

lecturer for Merck and Novartis; being a consultant for The Medicines Company and Theravance; and being a compensated lecturer for Medscape. The remaining authors have no disclosures to report.

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