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RESEARCH LETTER

Rivaroxaban 2.5 mg Twice Daily Plus Aspirin Reduces Venous Thromboembolism in Patients With Chronic Atherosclerosis

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The COMPASS trial (Cardiovascular Outcomes for People using Anticoagulation Strategies) demonstrated that, in patients with chronic coronary artery disease and peripheral artery disease (PAD), the combination of rivaroxaban 2.5 mg twice daily and aspirin 100 mg once daily compared with aspirin 100 mg once daily reduced cardiovascular death, stroke, or myocardial infarction by 24% and mortality by 18%, and increased bleeding by 70%.[1,2] Rivaroxaban 5 mg twice daily was not superior to aspirin.[1] Here we report the effects on venous thromboembolism (VTE).

The study protocol was approved by all relevant institutional review boards, and all patients provided written informed consent. The data that support the findings of this study are available from the corresponding author on reasonable request.

We compared baseline characteristics among those who experienced VTE and those who did not by using a χ^2 test for categorical variables and a 2-sample Wilcoxon test for continuous variables. For comparison of the outcomes in rivaroxaban plus aspirin and rivaroxaban alone compared with aspirin alone groups, we used stratified Cox proportional hazards regression to estimate hazard ratios and 95% CIs and a stratified log-rank test to test for statistical significance of any differences.

Of the 27 395 randomly assigned patients, 102 experienced VTE. Compared with patients who did not experience VTE, those who experienced VTE during the trial were significantly older (71.2 versus 68.2 years, P=0.004), had a higher body mass index (29.9 versus 28.3 kg/m^2, P=0.01), had lower blood pressure (133/75 versus 136/78, $P_{\text{for diastolic blood pressure}}$=0.01), were more likely to be a current or former smoker (78.4% versus 68.0%, P=0.02), and were more likely to be taking a diuretic (39.2% versus 29.7%, P=0.04). The combination of rivaroxaban 2.5 mg twice daily and aspirin 100 mg once daily compared with aspirin 100 mg once daily reduced the risk of VTE by 39% (25 [0.3%] versus 41 [0.4%]; hazard ratio, 0.61 [95% CI, 0.37–1.00]; P=0.05), with similar estimates of treatment effect for deep vein thrombosis and pulmonary embolism, and on deaths within 30 days of VTE, as well (Table). Effects were consistent across subgroups (ie, no significant interactions) defined by age (≤65 versus >65 years), history of cancer (yes versus no), vascular beds involved (1 versus ≥2), estimated glomerular filtration rate (<60 versus ≥60 mL·min^{-1}·1.73 m^{-2}), heart failure (yes versus no), or diabetes (yes versus no). Rivaroxaban 5 mg twice daily did not reduce VTE (Table).

No trials have been designed specifically to evaluate rivaroxaban 2.5 mg twice daily for the prevention of VTE. However, the VOYAGER PAD trial (Vascular Outcomes Study of ASA [acetylsalicylic acid] Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD) involving 6564 patients who had recently undergone revascularization for PAD demonstrated that rivaroxaban 2.5 mg twice daily compared with placebo on a background of antiplatelet therapy reduced VTE by 39% (25 [0.8%] versus 41 [1.3%]; hazard ratio, 0.61 [95% CI, 0.37–1.00]).[3] Taken together, the results of COMPASS

Key Words: aspirin ■ coronary artery disease ■ peripheral artery disease ■ rivaroxaban ■ venous thromboembolism

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Table. Rates of Venous Thromboembolism, Deep Vein Thrombosis, Pulmonary Embolism, and Death Within 30 Days of Venous Thromboembolism in Patients Randomly Assigned to the Combination of Rivaroxaban 2.5 mg Twice Daily Plus Aspirin 100 mg Once Daily, Rivaroxaban 5 mg Twice Daily, or Aspirin 100 mg Once Daily

Event	Rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily (n=9152)		Rivaroxaban 5 mg twice daily (n=9117)		Aspirin 100 mg once daily (n=9126)		Rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily vs aspirin 100 mg once daily		Rivaroxaban 5 mg twice daily vs aspirin 100 mg once daily	
	No. of first events (%)	Annual rate (%/y)	No. of first events (%)	Annual rate (%/y)	No. of first events (%)	Annual rate (%/y)	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Venous thromboembolism	25 (0.3)	0.1	36 (0.4)	0.2	41 (0.4)	0.2	0.61 (0.37–1.00)	0.05	0.88 (0.56–1.38)	0.58
Deep vein thrombosis	13 (0.1)	0.07	23 (0.3)	0.1	19 (0.2)	0.1	0.68 (0.34–1.38)	0.28	1.21 (0.66–2.23)	0.53
Pulmonary embolism	13 (0.1)	0.07	13 (0.1)	0.07	22 (0.2)	0.1	0.59 (0.30–1.17)	0.12	0.59 (0.30–1.18)	0.13
Death within 30 days of venous thromboembolism	2 (0.02)	0.01	3 (0.03)	0.02	5 (0.05)	0.03	0.40 (0.08–2.05)	0.25	0.60 (0.14–2.51)	0.48

Deep vein thrombosis and pulmonary embolism are not mutually exclusive events. Percent (%) is the proportion of patients with an outcome. Percent per year (%/y) is the rate per 100 patient-years of follow-up.

Nonstandard Abbreviations and Acronyms

PAD	peripheral artery disease
VTE	venous thromboembolism

and VOYAGER PAD indicate that the combination of rivaroxaban 2.5 mg twice daily and aspirin reduces VTE in patients with coronary artery disease and PAD.

The event rates for VTE among patients with chronic coronary artery disease and PAD enrolled in the COMPASS trial were ≈5-fold lower than the rates of arterial vascular events. In COMPASS, we enrolled 32.5% of patients (8912/27 395) from 10 middle-income countries; this may in part explain the low event rates, because VTE appears to be less common in low- and middle-income countries than in high-income countries.[4] It is also likely that the widespread use of antithrombotic therapy (all patients received aspirin, rivaroxaban, or their combination) in the COMPASS trial contributed to the low event rate. In the VOYAGER PAD trial, the 3-year Kaplan-Meier event rates for VTE were 0.8% among patients randomly assigned to the combination of rivaroxaban and aspirin compared with 1.7% among those randomly assigned to antiplatelet therapy alone,[3] which is substantially higher than the 3-year Kaplan-Meier event rates seen in COMPASS (combination 0.56%, aspirin 0.69%). However, VOYAGER PAD included patients within 10 days after peripheral revascularization who are at higher risk of VTE than patients enrolled in COMPASS, most of whom were ambulatory at the time of enrollment.

Previous studies have demonstrated that aspirin alone reduces the risk of VTE by 20% to 30% in medical and surgical patients,[5] and the data presented here indicate that rivaroxaban 2.5 mg twice daily provides a 39% relative risk reduction when added to aspirin. If the benefits of these 2 therapies are additive, the combination of rivaroxaban 2.5 mg twice daily and aspirin 100 mg once daily can be expected to reduce the risk of VTE by 60% to 70%.

ARTICLE INFORMATION

Registration: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01776424.

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