CORRESPONDENCE

Rivaroxaban in Stable Cardiovascular Disease

TO THE EDITOR: In the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial by Eikelboom et al. (Oct. 5 issue),[1] patients with stable atherosclerotic vascular disease assigned to rivaroxaban (2.5 mg twice daily) plus aspirin had a lower incidence of ischemic stroke and better cardiovascular outcomes but more bleeding events than those assigned to aspirin alone. The results were consistent among subgroups that were analyzed. However, a trend toward a lower benefit and a higher risk of bleeding was seen in older patients. Those 75 years of age or older had a nonsignificant reduction for the primary outcome (a composite of cardiovascular death, stroke, or myocardial infarction) and a significantly higher risk of bleeding, findings that suggest that the net clinical benefit may not be the most favorable in high-risk patients. These findings seem markedly different from those reported previously in trials involving the use of non–vitamin K oral anticoagulants in atrial fibrillation.[2,3] A two-dimensional analysis conducted with subgroup assignment according to thromboembolic risk, as assessed with the use of the CHA_2DS_2-VASc score (which may predict the risk of both stroke and incident atrial fibrillation),[4] and bleeding risk, as assessed with the use of the HAS-BLED score, could help to establish the most appropriate population to target[5] with this new strategy among the huge population of patients with atherosclerotic disease.

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TO THE EDITOR: The justification for any new pharmacotherapy is contingent on a clear net clinical benefit. The COMPASS trial compared the effects of rivaroxaban, aspirin, or the combination for secondary prevention in patients with stable vascular disease. The benefits of low-dose rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily) versus aspirin therapy alone were highlighted on the basis of a 1.3% reduction in a composite primary end point of death, stroke, or myocardial infarction. However, the price to pay was a 1.2% increase in the rate of major bleeding. The authors' definition of major bleeding (although interesting) appears restrictive, since it does not include the need for blood transfusion. The authors conclude that there was a statistically significant net clinical benefit with

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combination therapy (see Table 3 of the article, available at NEJM.org). The risk of the composite net-clinical-benefit outcome of cardiovascular death, stroke, myocardial infarction, fatal bleeding, or symptomatic bleeding into a critical organ was lower with rivaroxaban plus aspirin than with aspirin alone (hazard ratio, 0.80; 95% confidence interval, 0.70 to 0.91; P<0.001), but this value was determined by excluding some components of the primary safety end point of major bleeding. We need clarification of the potential harm of rivaroxaban in this cohort before we set sail with COMPASS.

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TO THE EDITOR: Clinical adoption of an antithrombotic regimen is determined on the basis of its risk–benefit profile. The totality of evidence supports the concept of an "East Asian paradox" with respect to clinical outcomes in relation to the intensity of antithrombotic therapy.[1] During antiplatelet therapy, East Asians have a lower risk of ischemic events and a greater bleeding tendency (mainly in the gastrointestinal and central nervous systems) as compared with whites.[1,2]

The COMPASS trial suggests that adjunctive low-intensity anticoagulation therapy in addition to aspirin improves cardiovascular outcomes in patients with stable atherosclerotic cardiovascular disease. However, a regimen of 2.5 mg of rivaroxaban twice daily increased major bleeding by 1.18% in whites and 2.13% in Asians (of whom approximately 80% were East Asians) (Fig. 1). Moreover, the pharmacokinetic properties of rivaroxaban may differ between the races: 15 mg of rivaroxaban in Japanese patients yielded exposures similar to 20 mg of rivaroxaban in whites.[3] As compared with warfarin, 15 mg of rivaroxaban reduced the risks of both ischemic events and intracranial hemorrhage in a real-world East Asian cohort with atrial fibrillation.[4] Therefore, the COMPASS strategy may not be generalizable to East Asian populations. COMPASS may serve as further evidence to support the concept of tailoring antithrombotic therapy on the basis of race.

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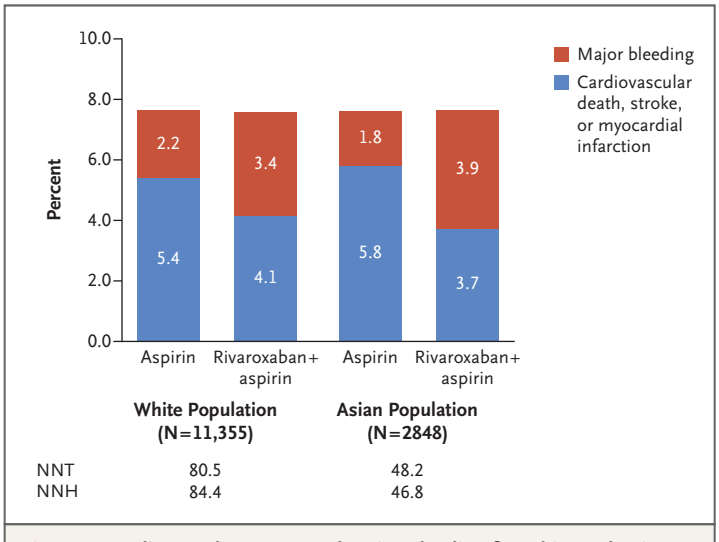

Figure 1. Cardiovascular Events and Major Bleeding for White and Asian Populations in the COMPASS Trial.

The data shown are based on findings from the subgroup analyses reported by Eikelboom et al.The use of combination therapy with rivaroxaban plus aspirin as compared with aspirin alone resulted in a greater reduction in cardiovascular events and a greater increase in major bleeding among Asian participants than white participants. NNH denotes number needed to harm, and NNT number needed to treat.

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TO THE EDITOR: The COMPASS investigators have reported better outcomes with rivaroxaban (2.5 mg twice daily) plus aspirin than with aspirin alone in patients with stable atherosclerotic vascular disease. The net-clinical-benefit outcome, defined as a composite of cardiovascular death, stroke, myocardial infarction, fatal bleeding, or symptomatic bleeding into a critical organ, was also lower with rivaroxaban plus aspirin than with aspirin alone (4.7% vs. 5.9%, P<0.001). However, had the net-clinical-benefit outcome been defined as cardiovascular death, stroke, myocardial infarction, or major bleeding, no advantage of the combination of rivaroxaban plus aspirin would have been found (7.2% vs. 7.3%). The result is therefore dependent on the definition used for net clinical benefit. Difficulties in the interpretation of net clinical benefit can also arise when "hard" clinical outcomes such as cardiovascular death are combined with "soft" clinical outcomes such as myocardial infarction that include cardiac ischemic symptoms with a limited rise in cardiac biomarker levels.[1]

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: In the COMPASS trial, the addition of rivaroxaban (2.5 mg twice daily) to aspirin (100 mg once daily) led to a significant reduction in a composite end point of cardiovascular death, stroke, and myocardial infarction in patients with atherosclerosis. This finding was largely driven by a lower incidence of ischemic stroke in the rivaroxaban-plus-aspirin group and the group receiving rivaroxaban alone (5 mg twice daily) than in the aspirin-alone group, whereas rates of myocardial infarction were similar between groups. The daily administration of 20 mg of rivaroxaban prevents stroke in patients with atrial fibrillation,[1] and anti-Xa activity persists at lower doses.[2] COMPASS excluded patients receiving anticoagulation but not patients with atrial fibrillation[3]; 8% of all strokes occurred in 392 such patients (see Table 2 of the article). Furthermore, many thousands of patients would be expected to have subclinical atrial fibrillation in this high-risk elderly group.[4]

Have the COMPASS investigators systematically recorded the prevalence of subclinical and incident atrial fibrillation during the trial? Underrecognition or undertreatment of atrial fibrillation could account for the observed reduction in ischemic stroke with rivaroxaban. Understanding the mechanism of benefit might enable more targeted use of rivaroxaban and aid the design of strategies to reduce both plaque thrombosis and cardioembolic stroke.

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THE AUTHORS REPLY: Fauchier et al. question whether elderly participants benefited from the combination of rivaroxaban and aspirin as compared with aspirin alone, and Jeong et al. question whether the results are generalizable to East Asians. In prespecified subgroup analyses, we found no evidence of an interaction between treatment and either age group or race for the primary outcome, major bleeding, or mortality, and the net benefit of combination therapy was consistent irrespective of age and race. In the absence of significant tests for interaction, the overall estimate from the trial is likely to provide the most reliable estimate of the treatment effect in subgroups.

Ajani and Helft et al. raise questions about the net-benefit analysis, which was a composite

of the components of the primary outcome (cardiovascular death, stroke, or myocardial infarction) and serious bleeding events of similar importance (fatal, intracranial, and critical organ bleeding). At the request of regulators, we used a "liberal" definition of major bleeding that included any bleed associated with presentation to an acute care facility. This definition led to the inclusion of several less important bleeds as major bleeds. Among the 713 participants with major bleeding, 197 (27.6%) received a blood transfusion within 48 hours, and 88 (12.3%) were discharged without hospitalization. The results of the analysis for net benefit based on major vascular events and severe bleeds (a 20% lower risk) are clearly favorable and are consistent with risk of death that was 18% lower in the group receiving combination therapy. We consider mortality to be the best measure of net clinical benefit. In addition to the lower rates of major vascular events associated with the combination of rivaroxaban and aspirin, the rate of vascular amputations in the subgroup with peripheral artery disease was 60% lower (11 vs. 28 events, P=0.007).[1]

Cahill et al. question whether the reduced risk of stroke is due to the prevention of cardioembolic strokes in patients with subclinical atrial fibrillation. Patients with atrial fibrillation who required anticoagulation were not eligible for inclusion in COMPASS, and the number of strokes that occurred in participants reported to have atrial fibrillation after trial entry (7 events in the combination group vs. 11 events in the aspirin group) is too small to account for the large difference in the rate of stroke. In addition to being associated with a lower rate of stroke, the combination of rivaroxaban and aspirin was associated with lower risks of cardiovascular death, of a composite of myocardial infarction or sudden cardiac death,[2] and of major adverse events in the limbs,[1] indicating the benefit of preventing events in multiple territories.

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Since publication of their article, the authors report no further potential conflict of interest.

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Surgery for Drug-Resistant Epilepsy in Children

TO THE EDITOR: The study by Dwivedi and colleagues (Oct. 26 issue)[1] on the efficacy of surgery in children with drug-resistant epilepsy includes more patients than either of the two previous randomized, controlled trials of epilepsy surgery. Also, it covers the whole pediatric age span and includes diverse surgical procedures.[2,3] However, we have a concern related to the report of serious adverse events in 33% of the patients in the surgery group. Usually, major unexpected complications are reported in less than 5% of the patients in studies of epilepsy surgery.[4,5] The explanation is probably that expected adverse events (e.g., the worsening of preexisting hemiparesis) are included here, since all the children who underwent hemispherotomies were reported to have had serious adverse events. This factor is clarified in the Supplementary Appendix of the article (available at NEJM.org), but a reader might miss this information and consider that pediatric epilepsy surgery may carry too high a risk as compared with the potential benefit.

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No potential conflict of interest relevant to this letter was reported.

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