Rivaroxaban in Acute Coronary Syndromes: We Have a Compass and an Atlas, But Where Are We Headed?

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The rationale for combining anticoagulation and antiplatelet therapy for acute treatment of acute coronary syndrome (ACS) patients is well established. Atherosclerotic plaque disruption is responsible for the majority of acute coronary thrombosis events, and acute thrombus formation is dependent on both platelet aggregation and the coagulation cascade.[1] Accordingly, current guidelines for the management of ACS recommend acute antiplatelet and anticoagulant therapy for hospitalized ACS patients regardless of whether or not percutaneous coronary intervention (PCI) is performed.[2] However, there is also evidence that a hypercoagulable state persists long after the acute phase of ACS, which may partially explain the residual rates (5%–10%) of recurrent thrombotic events in the first year following ACS—rates that have only modestly improved over the past 2 decades despite advances in revascularization and potent antiplatelet therapy.[3–5] Thus, there is a rational expectation that combining oral anticoagulation with potent antiplatelet therapy may reduce the risk of recurrent thrombotic events, but the map of the treatment landscape for using this combination in post-ACS patients is evolving.

Decades of clinical trials support the hypothesis that addition of anticoagulation to antiplatelet therapy reduces the risk of recurrent thrombotic events in post-ACS patients. However, it comes with a cost of increased bleeding. A meta-analysis of clinical trials of warfarin,[6] most of which were conducted in the 1990s, showed that warfarin (when restricted to studies using a target international normalized ratio of 2–3) and aspirin were associated with a lower odds of death, myocardial infarction (MI), or stroke (odds ratio 0.73, 95% CI 0.63–0.84) compared with aspirin alone, but were

associated with a higher risk of major bleeding (odds ratio 2.37, 95% CI 1.63–3.29). Because of the complexities of warfarin management, the narrow therapeutic window, and the increased risk of bleeding, warfarin was never incorporated into the standard of care for post-ACS patients who have no other indication for chronic anticoagulation.

More recent studies investigated the safety and efficacy of direct oral anticoagulants for treatment of ACS. Compared with warfarin, direct oral anticoagulants have the advantage of more stable pharmacokinetics and ease of administration.[1] However, while warfarin was compared with aspirin monotherapy in an era in which percutaneous coronary revascularization was not widely used, the direct oral anticoagulants entered the current era of ACS treatment in which the majority of patients undergo percutaneous coronary revascularization and are treated with dual antiplatelet therapy with aspirin and a P2Y12 inhibitor for a year postevent, regardless of whether or not a PCI was performed.

APPRAISE-2 (Apixaban for Prevention of Acute Ischemic Events 2)[7] and ATLAS ACS 2-TIMI 51(Anti Xa Therapy to Lower Cardiovascular Events in Addition to ASA with or without Thienopyridine Therapy in Subjects with Acute Coronary Syndrome—Thrombolysis in Myocardial Infarction)[8] are the only phase III clinical trials to investigate the use of direct oral anticoagulants (apixaban and rivaroxaban, respectively) in postacute treatment of ACS. Both trials demonstrated a significant increase in major bleeding with their respective Factor Xa inhibitors compared with dual antiplatelet therapy. In APPRAISE-2, Thrombolysis in Myocardial Infarction (TIMI) major bleeding occurred more often with apixaban 5 mg bid (1.3%) compared with placebo (0.5%), which resulted in early termination of the trial. There was no corresponding improvement in the composite of cardiovascular death, MI, or ischemic stroke with apixaban (7.5%) compared with placebo (7.9%). In ATLAS ACS 2-TIMI 51, the risk of TIMI major bleeding was similarly increased in a dose-dependent manner for the 2 studied doses of rivaroxaban, 2.5 mg bid (1.8%) and 5 mg bid (2.4%), compared with placebo (0.6%). Intracranial hemorrhage was also increased with rivaroxaban 2.5 mg bid (0.4%) and 5 mg bid (0.7%) compared with placebo (0.2%). However, contrary to the

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findings of APPRAISE-2, in the primary analysis of the combined dosing arms, rivaroxaban (combined dose arms) reduced the composite of cardiovascular death, MI, or stroke compared with placebo (8.9% versus 10.7%, respectively). Further analysis demonstrated that both 2.5 and 5 mg bid dosing regimens improved the composite of cardiovascular death, MI, or stroke. Although rivaroxaban was effective at reducing these end points, excess bleeding has limited uptake of rivaroxaban into the standard treatment of post-ACS patients treated with dual antiplatelet therapy.

In contrast to the post-ACS population, in which the efficacy of rivaroxaban is countered by an excess of bleeding, the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies)[9] trial established a role for rivaroxaban in treatment of patients with stable coronary artery disease or peripheral arterial disease. COMPASS investigated the use of rivaroxaban plus aspirin versus aspirin monotherapy among patients with stable atherosclerotic vascular disease, 91% of whom had stable coronary artery disease. Patients requiring dual antiplatelet, nonaspirin antiplatelet therapy, or oral anticoagulation were excluded from the trial. Patients were randomized to rivaroxaban 5 mg bid alone, rivaroxaban 2.5 mg bid with aspirin, or aspirin alone. Rivaroxaban 2.5 mg bid plus aspirin reduced the risk of cardiovascular death, stroke, or MI by 24% compared with aspirin alone. Major bleeding was more common in the rivaroxaban plus aspirin group compared with aspirin alone, but there was no difference in fatal or intracranial bleeding or bleeding into a critical organ; thus, the net clinical benefit favored rivaroxaban 2.5 mg bid plus aspirin. Based on the findings of COMPASS, rivaroxaban now carries a US Food and Drug Administration indication for reducing cardiovascular events in patients with chronic coronary or peripheral arterial disease.

In this issue of the *Journal of the American Heart Association* (*JAHA*), Gibson and colleagues[10] report a secondary analysis of the efficacy and safety of rivaroxaban (2.5 or 5 mg bid) compared with placebo in a pooled subset of ACS patients from the ATLAS ACS-TIMI 46 (phase II) and ATLAS ACS 2-TIMI 51 (phase III) trials who were treated with aspirin monotherapy. Importantly, randomization in the trials was stratified by the intention to use aspirin monotherapy. After pooling the 2 trials and the 2 rivaroxaban dosing arms into a combined rivaroxaban cohort, the primary finding in the aspirin monotherapy subgroup (N=1477) was a reduction in the composite end point of cardiovascular death, MI, or stroke compared with placebo (11.4% versus 16.3%, hazard ratio 0.65, 95% CI 0.45–0.92, *P*=0.016), with a reduction in MI accounting for most of the benefit. Rivaroxaban 5 mg bid, when analyzed separately, resulted in a significant reduction in the composite end point, whereas rivaroxaban 2.5 mg bid did not. Rivaroxaban (combined doses) resulted in more TIMI

non–coronary artery bypass graft major bleeding (1.5% versus 0%) and clinically significant bleeding (8.4% versus 5.0%) compared with placebo. This finding was also confined primarily to the 5 mg bid dose.

Gibson and colleagues conclude that a "dual pathway approach targeting platelet aggregation and thrombin generation may be an effective and safe strategy to reduce the residual risk of an ischemic event in the post-ACS setting." However, there are several important factors that limit the applicability of their analysis and conclusion to the post-ACS population at large. The current analysis was, by design, restricted to the small proportion (7.7%) of randomized patients treated with aspirin monotherapy. Since dual antiplatelet therapy is the standard-of-care treatment for patients with acute MI as well as unstable angina patients undergoing PCI,[2] these patients were likely different in clinically important ways from those who received dual antiplatelet therapy. For example, it is not surprising that unstable angina, rather than acute MI, was the qualifying event in 50% of the aspirin monotherapy patients, and that PCI was performed in only 6% of patients. These percentages differ greatly from the ATLAS ACS-2 TIMI 51 trial at large[8] (24% unstable angina, 60% PCI or coronary artery bypass grafting) and the contemporary PLATO (Study of Platelet Inhibition and Patient Outcomes)[5] trial that compared ticagrelor with clopidogrel in ACS patients (17% unstable angina and 61% PCI).

The authors provided supplemental tables stratifying the efficacy and safety outcomes according to whether the qualifying event was unstable angina or MI. Rivaroxaban (combined doses) reduced the composite of cardiovascular death, MI, or stroke in the MI cohort (13.9% versus 22.4%), but not in the unstable angina cohort (9.6% versus 11.8%). Conversely, an increase in bleeding with rivaroxaban (combined doses) compared with placebo was evident only in the unstable angina cohort (1.7% versus 0.0%). The relatively large absolute risk reduction in cardiovascular death, MI, or stroke without a corresponding increase in bleeding in the MI subset of this analysis of patients who did not receive dual antiplatelet therapy is intriguing and may represent a population worthy of further prospective investigation.

Thus, the current study raises a potential new direction in mapping the terrain of oral anticoagulation in post-ACS patients. COMPASS established a role for rivaroxaban plus aspirin in stable coronary disease for which aspirin monotherapy has been the standard of care. ATLAS ACS-2 TIMI 51 demonstrated a role for rivaroxaban in reducing residual thrombotic risk in the post-ACS setting, but excess bleeding has limited application of this strategy in practice. The current analysis may direct us to a subset of ACS patients—acute MI patients treated with a noninvasive strategy—in whom the efficacy and safety profile is tipped in favor of treatment with rivaroxaban plus aspirin. However, unlike COMPASS, the path for studying this strategy should be against dual antiplatelet

therapy, the current guidelines-recommended post-ACS antithrombotic treatment.

Disclosures

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