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EDITORIAL COMMENT

The Challenge of Getting it Just Right

Optimizing Long-Term Antithrombotic Therapy After Acute Coronary Syndrome*

Christian T. Ruff, MD, MPH

Acute coronary syndrome (ACS) is associated with substantial morbidity and mortality (1,2). Initial treatment in the hospital consists of intensive antithrombotic therapy combining parenteral anticoagulation with antiplatelet therapy, whereas secondary prevention relies primarily on dual antiplatelet therapy (DAPT), most commonly aspirin and clopidogrel. However, patients with ACS remain at significant risk of recurrent adverse cardiovascular events (3). Mitigation of this risk requires a delicate balance between escalation of antithrombotic therapy to reduce ischemic events, while hoping the increase in bleeding is tolerable. This has been successful with regard to platelet inhibition, as substituting clopidogrel for the more potent $P2Y_{12}$ receptor antagonists, prasugrel and ticagrelor, reduces cardiovascular death, myocardial infarction (MI), and stroke in patients with ACS, at the expense of increasing major spontaneous bleeding (4,5). Regardless of the DAPT regimen, there remains a 9% to 11% risk of an adverse cardiovascular event within 1 year of ACS (3–5). This forces a broader consideration of where to intervene in the complex hemostatic interplay between the vascular endothelium, platelets, and the coagulation cascade to improve outcomes in patients with ACS (6).

Should long-term anticoagulation play a role in the care of ACS patients? Despite antiplatelet therapy, thrombin levels and coagulation activity remain elevated months after an event (6,7). Data from a meta-analysis, informed primarily by the WARIS II (Warfarin, Aspirin, Reinfraction Study II) and ASPECT-2 (Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis-2) trials, showed that addition of warfarin to aspirin post-ACS reduces recurrent MI (8–10), but at the cost of significant excess major bleeding. Given the safety concerns and difficulties and dangers associated with warfarin use in clinical practice, there has been little enthusiasm for incorporating long-term anticoagulation in the routine care of ACS patients.

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The emergence of the nonvitamin K oral anticoagulant agents (NOACs) has renewed interest in the potential of long-term anticoagulation. In patients with atrial fibrillation (AF), NOACS significantly reduce stroke and all-cause mortality, with similar protection from MI compared with warfarin (11). Importantly, NOACs are accompanied by markedly less serious bleeding, particularly intracranial hemorrhage. A critical question is whether this favorable risk/benefit profile translates to patients post-ACS. In this issue of the *Journal*, Hess et al. (12) present an important subgroup analysis from the APPRAISE-2 (Apixaban for Prevention of Acute Ischemic Events 2) trial with the factor Xa inhibitor apixaban to help inform this issue.

APPRAISE-2 was a double-blind, placebo-controlled trial that randomized patients with ACS to apixaban (5 mg, or 2.5 mg for patients who qualified for dose reduction) versus placebo (13). At the data safety monitoring committee's recommendation, APPRAISE-2 was stopped prematurely due to significant excess bleeding without any observed reduction in ischemic

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From the Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts. Dr. Ruff has received consulting fees from Bayer, Daiichi-Sankyo, Portola, and Boehringer Ingelheim; and grant support through his institution from Daiichi-Sankyo, AstraZeneca, Eisai, and Intarcia.

events. In this study, Hess et al. (12) evaluated whether the relative efficacy and safety of apixaban compared with placebo varied by concomitant antiplatelet therapy (aspirin alone vs. DAPT with aspirin plus clopidogrel). Regardless of background antiplatelet therapy, apixaban had no apparent benefit in reducing cardiovascular death, MI, and ischemic stroke compared with placebo, but there was a significant excess in Thrombolysis In Myocardial Infarction (TIMI) major bleeding. The authors should be credited for acknowledging the significant limitations of this study—most notably, a post-hoc subgroup analysis of a trial that was terminated early and almost certain residual confounding due to the markedly different baseline characteristics and post-randomization variables between patients prescribed single versus dual antiplatelet therapy. The authors did use extensive statistical measures to mitigate these concerns, including multivariable adjustment for covariates associated with the propensity to use aspirin or aspirin plus clopidogrel, and a time-dependent analysis to account for the actual antiplatelet regimen taken during follow-up, which is important because 19.2% of patients switched antiplatelet regimens after randomization.

Does a "negative" substudy of a "negative" trial add to our ability to optimize long-term antithrombotic therapy in patients after ACS? The answer is a definitive "yes." This analysis helps us to contextualize and reconcile the results of APPRAISE-2 with other important findings in this field, particularly in relation to the WOEST (What Is the Optimal Antiplatelet & Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting) and ATLAS ACS 2-TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome 2-Thrombolysis In Myocardial Infarction 51) trials (14,15). The open-label WOEST trial randomized patients undergoing percutaneous coronary intervention (only 25% to 30% with ACS) with an indication for long-term anticoagulation (most for AF) to triple therapy with warfarin, aspirin, and clopidogrel or double therapy with warfarin and clopidogrel (14). Not surprisingly, dropping aspirin resulted in a >50% reduction in bleeding complications. More interestingly, double therapy was associated with a significant reduction in a broad composite of adverse cardiac and cerebrovascular events. How can a less potent antithrombotic regimen more effectively prevent ischemic events? By causing less bleeding: first, bleeding leads to discontinuation of both anticoagulant and antiplatelet therapy, so patients lose the ischemic protection afforded by those agents; second, bleeding results in a prothrombotic inflammatory state that further increases the risk of an ischemic event. A recent study of apixaban in AF demonstrated that bleeding (nonintracranial hemorrhage) was independently associated with a 12-fold excess of risk of death, ischemic stroke, or MI (16). Why was there an advantage to single-antiplatelet therapy in combination with warfarin in WOEST, but not to apixaban in APPRAISE-2? These trials are fundamentally different in that all patients in WOEST received warfarin because they had another indication for anticoagulation. WOEST tested whether we can optimize obligate full-dose anticoagulation in patients who also require antiplatelet therapy. In contrast, APPRAISE-2 tested whether it is possible to safely add *optional* full-dose anticoagulation for patients who require antiplatelet therapy. It is reasonable to conclude that if a patient with ACS requires full-dose anticoagulation for another indication, a less potent antiplatelet strategy may offer the best net clinical benefit, but there seems to be no role for full-dose long-term anticoagulation specifically for ACS.

The results of ATLAS ACS 2-TIMI 51 demonstrated that lower doses of rivaroxaban, 2.5 mg and 5 mg twice daily (full-dose: 20 mg once daily) in patients with ACS were associated with reductions in cardiovascular death, MI, and stroke compared with placebo (15). Both regimens were associated with excess bleeding. Why was rivaroxaban effective in reducing hard cardiovascular outcomes compared with placebo in patients with ACS, despite receiving triple therapy (almost all patients were on aspirin and clopidogrel), whereas there was no apparent benefit with apixaban, even in patients taking only aspirin? The dose, not the specific anticoagulant, is most likely the critical factor. The rivaroxaban doses tested in ACS were one-fourth to one-half of those tested for the AF and venous thromboembolism indication, suggesting a possible threshold effect when using anticoagulation in combination with antiplatelet therapy for ACS. Some suppression of the coagulation pathway is helpful, but too much exposes patients to unacceptable rates of bleeding and also diminished efficacy. Additional evidence from ATLAS ACS 2-TIMI 51 supports this premise: the 2.5-mg dose of rivaroxaban significantly reduced cardiovascular and all-cause mortality, but not the 5-mg dose. On this basis, rivaroxaban 2.5 mg was approved by the European Medicine Agency, but not by the U.S. Food and Drug Administration, for patients with recent ACS.

The results of this subanalysis of the APPRAISE-2 trial further clarify the existing data that full-dose anticoagulation, in combination with antiplatelet therapy of any kind in patients with ACS, results in substantial bleeding without any clear additional benefit and should only be considered when required for another condition. How to optimize such an antithrombotic regimen, especially in light of the myriad of new options, including 4 approved NOACs and the more potent antiplatelet therapies (prasugrel, ticagrelor, vorapaxar) not included in the previously mentioned studies, is critically important and the subject of ongoing investigation.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Christian T. Ruff, TIMI Study Group, Cardiovascular Division, Department of Medicine, Harvard Medical School, 350 Longwood Avenue, 1st Floor Offices, Boston, Massachusetts 02115. E-mail: cruff@partners.org.

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