A New Era in Secondary Prevention after Acute Coronary Syndrome

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During the past two decades, the use of antiplatelet therapies has been the focus of new studies of secondary prevention after acute coronary syndromes, with more than 75% of patients in contemporary practice treated with dual antiplatelet therapy (aspirin plus a thienopyridine) on hospital discharge.[1] Despite increases in the use of antiplatelet therapies and the development of more potent antiplatelet therapies (prasugrel and ticagrelor), the residual risk of death, myocardial infarction, or stroke up to 1 year after acute coronary syndromes remains high[2,3] (Table 1). This represents a therapeutic challenge, since the balance between risk (major bleeding) and benefit (reduction in ischemic events) becomes more delicate with time as the ischemic risk tends to diminish.[6]

The use of an anticoagulant, in addition to antiplatelet therapy, for secondary prevention has been explored in the past two decades with limited success. The first trials explored the use of warfarin with aspirin but did not show superiority, probably because of the challenges of maintaining a safe and adequate level of anticoagulation with warfarin. Subsequently, a low-molecular-weight heparin (dalteparin) versus placebo plus aspirin was tested in 1506 patients after hospitalization for an acute coronary syndrome.[7] During the 6-week treatment phase, there was a significant reduction in the rate of a composite of death or myocardial infarction (P=0.04), and major bleeding events were rare. However, the treatment effect disappeared with longer-term follow-up, and subcutaneous administration limited the duration of treatment that could be tested.

Later, an oral direct thrombin inhibitor (ximelagatran) was developed, and results were reported from a dose-ranging trial of four doses of ximelagatran versus placebo, starting within 14 days after an acute coronary syndrome.[8] In the combined-dose group, there was a significant reduction in the rate of a composite of death, nonfatal myocardial infarction, or nonfatal stroke at 6 months in the ximelagatran group as compared with the placebo group (7% vs. 11%; odds ratio, 0.66; 95% confidence interval, 0.48 to 0.90), with a small but increased rate of bleeding (2% vs. 1%). However, because liver toxicity occurred, the development of ximelagatran ceased. Thus, these early trials documented that combining antiplatelet and anticoagulant therapies could potentially offer long-term benefit, if the right therapeutic profile could be developed for the outpatient setting, such as good oral bioavailability, reliable anticoagulant effect, and an acceptable safety profile.

A new oral direct thrombin inhibitor (dabigatran) and oral factor Xa inhibitors (apixaban and rivaroxaban) appear to fit these criteria, with good bioavailability and reliable anticoagulant effects shown for the prevention of deep venous thrombosis and thromboembolism.[9] However, recently published data have indicated that these agents, when tested in patients after an acute coronary syndrome, have raised safety concerns. Increasing doses of dabigatran were tested in a randomized trial involving 1861 patients enrolled within 7 days after an acute coronary syndrome, and bleeding events were more common with higher doses, whereas rates of ischemic events were similar in all dose groups.[10] Conversely, a single dose of apixaban was tested in a trial involving 7392 patients who were enrolled approximately 6 days after an acute coronary syndrome, but the trial was prematurely terminated because of an increased risk of significant bleeding events (including intracranial hemorrhage) with no observed reduction in ischemic events (Table 1).[4]

In this issue of the *Journal*, Mega et al.[5] report the results of the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51 (ATLAS ACS 2–TIMI 51) trial (ClinicalTrials.gov number, NCT00809965), a landmark study that is the culmination of two decades of searching for another approach for combining antiplatelet and anticoagulant therapies. A total of 15,526 patients who were hospitalized for an acute coronary syndrome were randomly assigned to receive one of two doses of rivaroxaban (2.5 mg or 5 mg twice daily) or placebo. The rate of the primary end point (a composite of death from cardiovascular causes, myocardial infarction, or stroke) was reduced in both groups receiving rivaroxaban, as compared with placebo, with a rate of 9.1% in the 2.5-mg group

Table 1. Rates of Ischemic and Bleeding Events in Drug Trials for Acute Coronary Syndrome.*

Event	TRITON–TIMI 38		PLATO		APPRAISE-2†		ATLAS ACS 2–TIMI 51‡	
	Prasugrel	Clopidogrel	Ticagrelor	Clopidogrel	Apixaban	Placebo	Rivaroxaban (2.5 mg)	Placebo
	percent							
Death, myocardial infarction, or stroke	10.7	12.7	10.2	12.3	8.8	8.9	9.1	10.7
Death from cardiovascular causes	2.1	2.4	4.0	5.1	2.8	3.0	2.7	4.1
Bleeding								
Major TIMI (non-CABG)	2.4	1.8	2.8	2.2	1.3	0.5	1.8	0.6
Fatal	0.4	0.1	0.3	0.3	0.1	0	0.1	0.2
Intracranial	0.3	0.3	0.3	0.2	0.3	0.1	0.4	0.2

* APPRAISE-2 denotes Apixaban for Prevention of Acute Ischemic Events 2 (ClinicalTrials.gov number, NCT00831441), ATLAS ACS 2–TIMI 51 Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51 (NCT00809965), PLATO Study of Platelet Inhibition and Patient Outcomes (NCT00391872), and TRITON–TIMI 38 Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38 (NCT00097591). The median follow-up for end-point ascertainment was 8 months in APPRAISE-2, 13 months in ATLAS ACS 2–TIMI 51, 9 months in PLATO, and 14.5 months in TRITON–TIMI 38.[2-5] Patients were enrolled within 6 days after the onset of acute coronary syndrome in APPRAISE-2 and ATLAS ACS 2–TIMI 51, within 24 hours after hospital arrival in PLATO, and at the time of percutaneous coronary intervention in TRITON–TIMI 38. CABG denotes coronary-artery bypass grafting.

† Approximately 81% of patients were treated with a thienopyridine at the time of randomization.

‡ Approximately 93% of patients were treated with a thienopyridine at the time of randomization.

and 8.8% in the 5-mg group versus 10.7% (P=0.008) in the placebo group. There were also reductions in rates of death from both cardiovascular causes and any cause for the 2.5-mg dose but not for the 5-mg dose. There was a consistent treatment benefit across a number of important subgroups, but the proportions of patients who were at least 75 years of age (9.0%) or female (25%) were small, and more than 75% of patients had normal renal function. Thus, the results may not be applicable to higher-risk patients with an acute coronary syndrome who are commonly treated in routine practice.

The rate of major bleeding (according to TIMI criteria) that was not related to coronary-artery bypass grafting was increased by nearly a factor of 4 in patients receiving rivaroxaban versus those receiving placebo (2.1% vs. 0.6%, P<0.001), and the rate of intracranial hemorrhage was increased by a factor of 3 (0.6% vs. 0.2%, P=0.009), whereas rates of fatal bleeding were similar. In each case, however, bleeding rates were lower in the 2.5-mg group than in the 5.0-mg group. Many of the major bleeding events occurred after 180 days, with no plateau effect observed, and the risk of bleeding was consistent among all major subgroups, with numerically higher rates of bleeding in lighter-weight and elderly patients, as well as in those with reduced renal function and those enrolled in North America.

We believe that the results of this study are an important development for relatively young and healthy patients with an acute coronary syndrome. However, there is much work still to be done, since a large proportion of patients with an acute coronary syndrome who are treated in routine practice are elderly with multiple coexisting illnesses.[1] Given the exquisite balance between bleeding risks and ischemic benefits of treatment, we need a better understanding of the role of rivaroxaban in higher-risk patients. In particular, the finding that patients with an acute coronary syndrome who are receiving either rivaroxaban or apixaban are at higher risk for intracranial hemorrhage indicates that better predictors of this event are needed. However, it should be recognized that this finding has also been observed in trials with more potent antiplatelet therapies (Table 1) and may be concentrated in patients with a history of cerebrovascular disease.

Thus, a new era of secondary prevention after an acute coronary syndrome has begun and will be characterized by the need to balance ischemic versus bleeding risks when selecting the type, number, and duration of antithrombotic therapies for individual patients. Although further studies are needed to delineate the time dependency of risks during long-term treatment and how prediction of these risks will inform treatment selection, the results of this study indicate that riv-

aroxaban will play an important role in the future of optimized secondary prevention.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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