Refining Antithrombotic Therapy for Atrial Fibrillation and Acute Coronary Syndromes or PCI

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Approximately 1 in 5 persons with atrial fibrillation will undergo percutaneous coronary intervention (PCI) or have an acute coronary syndrome. Anticoagulation in such patients is challenging. Dual antiplatelet therapy for acute coronary syndrome[1] and PCI[2] prevents platelet-mediated coronary events, such as myocardial infarction and stent thrombosis. By contrast, in patients with atrial fibrillation, oral anticoagulation prevents cardioembolic events (mainly stroke) to a greater extent than dual antiplatelet therapy.[3] When patients with atrial fibrillation undergo PCI or have an acute coronary syndrome, oral anticoagulation and dual antiplatelet therapy (usually with aspirin and clopidogrel) have been combined — a so-called triple antithrombotic strategy. However, this approach has been scrutinized because it increases the risk of serious bleeding.[4] Modified anticoagulation regimens that reduce bleeding risk without increasing the incidence of coronary or cardioembolic events are therefore needed. In two recent trials, there was a lower incidence of bleeding events when a direct oral anticoagulant was used in combination with clopidogrel (with the omission of aspirin altogether; i.e., a dual pathway regimen) than when a warfarin-based triple-therapy regimen was used.[5,6] However, these trials were not powered to detect moderate increases in the incidence of coronary ischemic events, and it was not possible to determine whether the lower risk of bleeding was due to the use of a direct oral anticoagulant or to the early discontinuation of aspirin.

Lopes and colleagues now shed light on these issues by presenting in the *Journal*[7] the results of the AUGUSTUS trial, a two-by-two factorial, randomized comparison of apixaban with a vitamin K antagonist and of aspirin with placebo that involved 4614 patients. The trial evaluated the effects of these interventions on bleeding events in patients with atrial fibrillation who had an acute coronary syndrome or underwent PCI (or both). A two-by-two factorial design is efficient in that it permits the separate evaluation of two or more interventions within a single trial. Apixaban, at a dose known to prevent cardioembolic stroke related to atrial fibrillation,[8] led to a convincingly lower risk of all types of bleeding, as well as to a lower incidence of hospitalization. Although the comparison of apixaban with a vitamin K antagonist was open label and the time in the therapeutic range for the vitamin K antagonist comparator was just 59%, these data are robust and consistent with those from other trials evaluating direct oral anticoagulants.[5-8] Given the totality of data, a direct oral anticoagulant should now routinely be recommended for patients with atrial fibrillation who have an acute coronary syndrome or undergo PCI.

In the double-blind comparison of aspirin with placebo, aspirin led to a higher risk of bleeding. This finding is not surprising because it has been well established for many years that aspirin increases the risk of bleeding (mainly gastrointestinal bleeding).[9] Whether the incidence of coronary ischemic events is increased when aspirin is omitted (on a background of direct oral anticoagulant and clopidogrel) is really the key unknown. The findings from this trial do not necessarily provide reassuring evidence that early discontinuation of aspirin therapy after an acute coronary syndrome or PCI is warranted in all patients.

First, the risk of coronary thrombotic events — including myocardial infarction, urgent revascularization, and stent thrombosis — was higher (although not significantly higher) in the placebo group than in the aspirin group, and the incidence of stent thrombosis was nearly twice as high in the placebo group. It would be incorrect to interpret the lack of a significant P value as no difference, because although the AUGUSTUS trial was a large trial evaluating this question, it was still substantially underpowered for coronary ischemic events. The consistency of the trends toward more thrombotic events in the placebo group than in the aspirin group strongly suggests that there may very well have been a significant difference if more patients had been enrolled.

Second, the highest risk period for coronary ischemic events is in the days and weeks after

the index event. Patients were not enrolled in this trial until a mean of 1 week (and up to 2 weeks) after the index event or PCI, a period during which patients were receiving aspirin. Thus, the effect of very early withdrawal of aspirin therapy still remains uncertain, and caution is advised during this time period. Finally, because of its lower bleeding profile, clopidogrel was the $P2Y_{12}$ inhibitor that was used most commonly in the dual pathway regimen, and there is uncertainty regarding its response variability and efficacy, particularly without aspirin.

Given these data, clinical decision making should continue to be based on a balanced assessment of three competing risks: cardioembolic stroke, coronary ischemic events, and bleeding. This assessment should include not only demographic and clinical variables regarding these risks but also the clinical setting as well as the angiographic complexity of PCI and risks associated with the procedure.[10] In patients with a low risk of thrombotic events (e.g., those undergoing elective PCI who do not have high-risk clinical or angiographic features) or a high risk of bleeding, early omission of aspirin therapy and treatment with a direct oral anticoagulant plus clopidogrel is entirely warranted. However, in patients undergoing complex, multivessel, or high-risk PCI or in those presenting with high-risk acute coronary syndrome, aspirin should probably not be routinely omitted for at least several weeks or longer, depending on bleeding risk. Although guideline committees will now have to grapple with incorporating the results of the AUGUSTUS trial into specific recommendations, it is clear that a one-size-fits-all policy is unlikely to apply in these patients.

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