Evidenced-Based Antithrombotic Therapy for Acute Coronary Syndromes

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Patients with diabetes mellitus (DM) and acute coronary syndromes (ACSs) are at particularly high risk for recurrent cardiovascular events, including death. The reason for this increased risk is multifactorial, including underutilization of evidence-based medications in these patients (1). More research is needed to identify both the optimal antithrombotic strategy and duration of therapy, and greater attention is needed to implement therapies that have been shown to lower clinical events and mortality in this high-risk population. Together with lifestyle modification, improved attention to therapy can go a long way toward reducing ACS-related morbidity and mortality among people with diabetes.

Aspirin has been considered the mainstay of treatment for all patients with ACS, and its use is supported by strong and consistent evidence in current international guidelines (2,3). While a recent small study suggested that more frequent aspirin dosing would be beneficial in patients with DM (4), the CURRENT/OASIS7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent EveNTs/Optimal Antiplatelet Strategy for InterventionS) trial, a large study that included almost 6,000 patients with DM, was not able to show that a high dose of aspirin was superior to a low dose (5). Other recent trials have also shown that use of platelet function testing for aspirin responsiveness does not improve clinical outcomes (6) such as death, myocardial infarction (MI), and stroke.

Although clopidogrel, combined with aspirin, has been used successfully to prevent thrombotic events in patients with ACS (7), patients with DM have consistently been shown to have higher on-treatment platelet reactivity and worse clinical outcomes (8,9). Further, a high dose of clopidogrel was not superior to a standard dose in the CURRENT/OASIS7 trial, a finding that did not differ by DM status (5). Therefore treatment with novel and more potent platelet inhibitors have been recommend, particularly for patients with DM (2).

Ticagrelor is an oral, nonthienopyridine P2Y12 inhibiting agent with a reversible and direct action on the receptor that provides faster, greater, and more consistent platelet inhibition than clopidogrel (10). The Platelet Inhibition and Patient Outcomes (PLATO) trial showed that ticagrelor was superior to clopidogrel for the prevention of cardiovascular death, MI, or stroke in a diverse population of ACS patients (11). A prespecified substudy from the PLATO trial showed that patients with DM and higher levels of glucose and HbA_{1c} had higher levels of all evaluated ischemic and bleeding end points. Compared with clopidogrel, ticagrelor reduced cardiovascular death, MI, or stroke as well as total mortality and stent thrombosis. This finding was consistently observed and did not differ by diabetes status, insulin treatment, and glycemic control (12).

In this issue of *Diabetes*, DiNicolantonio and Serebruany (13) address the issue of aspirin dosing after acute coronary syndromes in patients with DM. The authors are challenging recommendations of the European Society of Cardiology (3), the American College of Chest Physicians (14), and the FDA by arguing that a low dose of aspirin to these patients when treated with ticagrelor is inappropriate.

The protocol of the PLATO trial specified a single loading dose (160–500 mg allowed, ≤325 mg preferred) for patients not previously on aspirin, just before randomization, and a maintenance treatment with open-label aspirin, 75–100 mg daily, except when contraindicated or not tolerated. After coronary stenting, the protocol allowed 325 mg daily aspirin for ≤6 months.

A large number of preplanned exploratory analyses were performed in the PLATO trial, and a nominally significant treatment interaction for geographic region (P = 0.045) was observed. Clopidogrel was associated with a nonsignificant trend of better outcome for North America alone, while ticagrelor was associated with better outcome in the other regions combined (11). Within the ticagrelor group, the lowest event rates were observed in patients receiving low-dose aspirin and highest in those receiving high-dose aspirin. In contrast, event rates in clopidogrel-assigned patients were similar with high- or low-dose aspirin. The interaction was independently evaluated in exploratory analyses performed by the sponsor and the Duke Clinical Research Institute. Both analyses showed that the aspirin maintenance dose accounted for 80–100% of the observed regional interaction (15). Nonetheless, despite the large number of analyses supporting the potential role of aspirin dosing as a cause of the treatment-by-region interaction, these analyses also suggested that the observation may also have been explained by chance alone. Although possible biological hypotheses have been proposed, none has been proven to support aspirin as a potential explanation for the observed interaction.

When used in combination with other platelet inhibitors in the setting of acute and long-term treatment in patients with ACS, stable coronary artery disease, or postpercutaneous coronary intervention with or without DM, the optimal dose of aspirin is still not clearly defined from data generated by large randomized controlled trials. The PLATO trial was not designed to evaluate aspirin therapy,

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and it is not possible to draw any conclusions about the optimal dose or duration of aspirin in any subgroup or nonrandomized treatment options. There is a need to reevaluate the use of aspirin and its optimal dose and duration in relation to whether it is used alone or in combination with other platelet or coagulation inhibitors. However, the totality of all studies support current guidelines stating that in patients with ACS independent of DM status, low-dose maintenance aspirin in combination with a P2Y12 receptor inhibitor is likely associated with the most favorable outcomes in the U.S. and elsewhere.

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