Numerous trials have demonstrated a worse outcome for diabetic patients with acute coronary syndromes (ACS) compared with their nondiabetic counterparts. Because our knowledge of the influence of diabetes mellitus on ACS outcomes is based on subgroup analyses of randomized trials that are often post hoc and underpowered, most clinicians have not entertained the concept that we might consider approaching the diabetic patient differently. ACS trials, from the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial to the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial, have suggested that whereas diabetic patients may have a higher event rate, the relative risk with the use of the conventional antithrombotic therapies is comparable to that observed in the nondiabetic cohort. Numerous mechanisms may explain this increased risk. Diabetic patients are more likely to have other comorbidities, such as renal insufficiency and hypertension, that lead to worse outcomes. Diabetic patients often have early signs of heart failure, particularly diastolic heart failure, which can lead to increasing morbidity and mortality. Perhaps the most important difference is that type 2 diabetes mellitus is associated with a proinflammatory and a prothrombotic state. Of interest, in the insulin-resistant state, perhaps stress and impair endothelial function, presumably resulting in more platelet reactivity as well as procoagulant activity. Within the context that diabetic patients may require a more aggressive antithrombotic regimen, in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial of subjects with ACS, the point estimate of benefit for the diabetic subgroup with clopidogrel was only 15% compared with 20% overall. In the Optimizing Antiplatelet Therapy in Diabetes Mellitus (OPTIMUS) trial, diabetic patients with established coronary heart disease and on a stable dose of aspirin and clopidogrel 75 mg daily were evaluated for responsiveness to clopidogrel. Almost two thirds of the patients were considered hyporesponders. When these hyporesponders were randomly assigned to receive clopidogrel 75 mg QD or 150 mg QD, only the 150 mg QD group experienced a significant reduction in maximal platelet aggregation after ADP stimuli. Furthermore, in ACS clear evidence exists that a higher loading dose of clopidogrel such as 600 mg is associated with increased platelet inhibition and a greater fraction of responders compared with the conventional 300-mg dose. These clopidogrel dose-related findings are in the process of being replicated with outcomes in clinical trials. Thienopyridines inhibit the ADP P2Y₁₂ receptor/pathway. Ticlopidine is a first-generation thienopyridine that, in combination with aspirin, an inhibitor of the cyclooxygenase-1 pathway, enhances the platelet suppression effect. Because of a better safety profile and the ability to yield an antiplatelet effect more rapidly and effectively than ticlopidine, clopidogrel has evolved as a second-generation thienopyridine, selectively and irreversibly inhibiting the P2Y₁₂ receptor by an active metabolite generated through oxidation by the hepatic cytochrome P450 system. Prasugrel is a third-generation oral thienopyridine, also a specific and irreversible antagonist of the P2Y₁₂ receptor, but it is more rapidly absorbed and more completely metabolized than clopidogrel, with the potential to be a more potent platelet inhibitor to result in less interpatient variability. In a 2-phased study of patients undergoing percutaneous coronary intervention that compared a loading dose of prasugrel 60 mg to clopidogrel 600 mg and maintenance with prasugrel 10 mg per day to clopidogrel 150 mg per day, prasugrel was associated with a greater inhibition of platelet aggregation. The greater inhibition of platelet function with prasugrel when compared with the higher loading and maintenance doses of clopidogrel suggests that the superiority of one regimen over the other may be linked in large part to intrinsic properties of the compound. Because diabetic patients with ACS are at increased risk and historical data suggest that intense platelet blockade such as with glycoprotein IIb/IIIa receptor inhibitors may be of particular benefit, Wiviott et al, whose work is published in this issue of Circulation, explored the possible role of prasugrel in such a group of patients. The investigation reports the findings of the specified diabetic subgroup analysis from the Trial to Assess Improvement in Therapeutic Outcomes By Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38). This trial enrolled 13,608 intermediate- to high-risk ACS patients or patients with ST-segment elevation myocardial

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Acute Coronary Syndromes and Diabetes Mellitus
A Winning Ticket for Prasugrel

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Editorial

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infarction who were referred for percutaneous coronary intervention. Patients were randomly assigned to prasugrel 60 mg loading and 10 mg per day maintenance compared with clopidogrel 300 mg loading and 75 mg per day maintenance over 6 to 15 months. The primary end point, the composite of cardiovascular death, myocardial infarction, and stroke, was significantly reduced with prasugrel among subjects without diabetes mellitus (9.2% versus 10.6%, hazard ratio [HR] 0.86) and even more significantly in patients with diabetes mellitus (12.2% versus 17.0%, HR 0.70), particularly in those on insulin (14.3% versus 22.2%, HR 0.63). Although TIMI major hemorrhage was increased among subjects without diabetes mellitus on prasugrel (2.4% versus 1.6%, HR 1.43), the rates were similar among subjects with diabetes mellitus (2.6% versus 2.5%, HR 1.06). Overall, the net clinical benefit with prasugrel was greater for patients with diabetes than for patients without diabetes.

A number of important observations can be made from distilling these findings. First, the diabetic substudy of TRITON goes beyond the notion that diabetes is just a higher-risk group. The exaggerated response to prasugrel validates the concept that for diabetic patients the degree of platelet inhibition may be an important marker of outcome. Second, patients treated with insulin represent those who have had a longer duration of the disease or have had difficulty reaching a target level of hemoglobin A1C on oral therapy alone. The trial demonstrated an 8% absolute reduction in ischemic events for those treated with insulin, suggesting that prasugrel has durable effects across the spectrum of diabetes mellitus; this appears to be another unique finding of the study. Third, for those with diabetes mellitus, the difference in ischemic events was driven largely by a reduction in myocardial infarction; this finding is consistent with our understanding of the mechanism of cardiovascular events after ACS. Fourth, the overall TRITON-TIMI 38 findings raised concerns about excess of TIMI major bleeding in the prasugrel arm. The diabetic subgroup did experience a higher rate of TIMI major bleeding (2.6% versus 2.0%) compared with the nondiabetic cohort, but, regardless of the possible explanations, no difference was found in excess bleeding between clopidogrel (usual care) and prasugrel. However, before considering prasugrel as a well-justified alternative in terms of bleeding risk, larger cohort studies of diabetic individuals are needed. The analysis by Wiviott and colleagues has overcome the first challenge. This was to identify an important subgroup of patients who will enjoy a greater net clinical benefit from a more potent antiplatelet regimen. The next challenge for clinicians is to address the issue of a variable response to therapy between patients within the diabetic cohort; this will almost certainly be the subject of future investigation. The need for the use of glycoprotein IIb/IIIa inhibitors in the current era of potent dual antiplatelet therapy needs to be reassessed; with over one half of diabetic patients in TRITON receiving glycoprotein IIb/IIIa antagonists, it is possible that a better safety profile would have emerged without their routine use. Finally, the degree of chronic glycemic control and periprocedural hyperglycemia may play a role in the management of ACS patients undergoing percutaneous coronary interventions and could influence the effectiveness of antiplatelet therapy.

Although we should always be guarded in our interpretation of subgroups, one cannot help but feel that this prespecified analysis has uncovered a winning combination. The time has come to concede that diabetic patients with ACS are different from other ACS patients and not just a high-risk group. The prasugrel regimen studied in TRITON diabetic patients has moved the field markers and set a new standard.

Disclosures

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