

Prasugrel and Clopidogrel: What Will Their Roles Be?

An editorial on what recent clinical trials have shown
us about new antiplatelet agents.

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Data from recent clinical trials have indicated that antiplatelet therapy is an important component of coronary angioplasty and stenting procedures, as well as in lowering cardiovascular morbidity and mortality rates in peripheral arterial disease (PAD) patients. Little information is available on the efficacy of antiplatelet therapy after peripheral intervention. Patients with PAD are considered to be high risk for coronary artery disease even if they are asymptomatic, and data would suggest that aggressive antiplatelet therapy is warranted.

Extended-release dipyridamole, when combined with aspirin, has shown clinical benefit for secondary ischemic stroke reduction. Ticlopidine showed benefit in ischemic stroke reduction but caused aplastic anemia or thrombotic thrombocytopenia purpura as a rare complication. The switch to clopidogrel was then easily accepted because it was believed to have equal clinical efficacy without the risk of these hematologic side effects. Since this switch, clopidogrel has been well accepted and argued to be “the best” antiplatelet agent; however, recent concerns regarding its relatively slow onset of action and variable clinical antiplatelet effects have arisen. Now, a new drug—prasugrel—has shown promise to address the shortcomings of clopidogrel.

The bioavailability of prasugrel is more consistent than that of clopidogrel, and the action of the cytochrome P450 system turns out the active metabolite more efficiently. Also, there is more sustained

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platelet inhibition when comparing the standard daily dose of 10 mg of prasugrel to 75 mg of clopidogrel. Furthermore, the PRINCIPLE-TIMI 44 trial showed that the 60-mg load of prasugrel was better than the 600-mg load of clopidogrel, and the maintenance dose of 10 mg was better than even a 150-mg daily dose of clopidogrel.¹

TRITON-TIMI 38 showed the same trend; from a platelet inhibition standpoint, prasugrel prevented clinical events better than did clopidogrel.² A further subanalysis of this same trial showed the risk of coronary stent thrombosis to be significantly reduced in the prasugrel-treated patients compared to the clopidogrel group. This difference was shown for both bare-metal and drug-eluting stent patients.³

In patients with PAD, the CAPRIE study demonstrated that more aggressive platelet inhibition (with clopidogrel and aspirin) lowered morbidity and mortality rates when compared to aspirin alone.⁴ Based on the previous trials, it stands to reason that the better the platelet inhibition, the better the clinical avoidance of

thrombotic/ischemic events. This suggests that prasugrel could, would, and *should* be easily accepted as the primary antiplatelet agent in the PAD patient.

The peripheral market often follows the trends of the coronary market despite considerable differences between the two anatomies and the training of the physicians treating both sets of patients. In many instances, tips, tricks, and lessons learned from the cardiologists are readily adapted by peripheral interventionists. This is particularly true when it comes to pharmaceuticals because cardiologists study a more homogeneous population and can standardize care much easier than can peripheral interventionists.

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Peripheral stent thrombosis does not carry the same clinical negativity as coronary stent thrombosis; however, limb salvage is obviously of critical importance to patients. These PAD patients have systemic atherosclerosis and usually die from cardiovascular or cerebrovascular events. Symptomatic PAD should be regarded as a cardiovascular risk equivalent, and aggressive medical therapy must be provided. Platelet inhibition trials in the PAD population will need to be done to show benefit, but there is little doubt in my mind as to the outcome of such studies.

THE IMPACT OF PRASUGREL

Does the bleeding risk shown in the TRITON-TIMI 38 temper interest for prasugrel? I would answer this with a qualified *yes* and *no*. Prasugrel showed a 2.4% major bleeding risk compared to clopidogrel, which was 1.8%. These drugs—like any drug—should be used with caution. Importantly, the study suggests that the optimal dose for platelet inhibition may not be the same as used in the trial. Perhaps similar efficacy (lower thrombotic/ischemic events) can be seen with lower doses of prasugrel while lowering the potential bleeding threshold.

Some patients are at higher risk of bleeding, such as patients with previous cerebrovascular accidents and/or transient ischemic attacks, patients >75 years of age, and patients weighing <132 lbs. Platelet assays would need to be performed in these higher-risk groups in order to determine the ideal dose. There will be less tol-

erance for significant bleeding in patients undergoing peripheral procedures—particularly carotid angioplasty with stenting (eg, risk of intracranial hemorrhage after opening up a tight carotid stenosis) and low-risk procedures (eg, iliac percutaneous transluminal angioplasty with stenting). Dentists, surgeons, anesthesiologists, and other health care providers would cringe at the thought of having to do a low-risk procedure on a patient that is on a drug (prasugrel) that might cause excessive bleeding. This concern has altered the use of clopidogrel as well as the choice of procedure (ie, the ubiquitous use of drug-eluting stents for coronary intervention).

The balance will also hinge on drug cost, patient tolerance, and compliance. These elements are not inconsequential and can significantly affect the balance between safety and efficacy. Many of our patients take multiple medications, and when faced with yet another expensive pill, they raise concern as to its necessity. When this necessary pill causes an ill feeling, rash, easy bruising, or other non-life-threatening symptoms, they will frequently stop the drug on their own.

Will prasugrel be easily accepted when unleashed on the waiting public? Will these patients or even our government be able to pay for the drug? Time will tell, but prasugrel promises to provide another step forward, and I would predict it to be the preferred antiplatelet agent in our symptomatic PAD population. ■

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