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EDITOR'S PAGE

Thienopyridines: Time for Personalized Therapy?

Arterial thrombosis is largely mediated by platelet activity. Cardiovascular interventions, by virtue of the injury they produce and the hardware they leave, set the stage for increased platelet activity, promote the deposition of platelets, and produce a prothrombotic milieu. This fact has been well recognized in interventional cardiovascular medicine since its beginning. Early on, attempts to control thrombosis with anticoagulant drugs were largely abandoned in favor of antiplatelet therapy, and in fact one of the first randomized trials in interventional cardiology was a comparison of warfarin and aspirin therapy (1). As stenting became the default strategy for treating arterial thrombosis, the vascular rheology changed in a favorable way enabling less turbulence and more laminar flow within the vessel, thereby decreasing the incidence of acute thrombosis, which was seen much more commonly in the era before stents were available. The more recent introduction of drug-eluting stents has markedly reduced restenosis but, through the action of inhibited endothelial healing, has re-emphasized the importance of controlling arterial thrombosis. Dual antiplatelet therapy has become the standard after bare-metal and drug-eluting stenting, and guidelines reflect strategies that have been developed on the basis of evidence generated from the pivotal clinical trials (2). Those recommendations have recently been modified on the basis of conferences involving professional societies and governmental agencies. Many recommendations, however, are based on the opinion of experts rather than clear evidence.

Because the function of platelets in relation to interventional procedures is of such clinical interest, we have decided to focus this issue of *JACC: Cardiovascular Interventions* on a series of articles directed at platelets and platelet responsiveness. Thienopyridines, in addition to aspirin, have become the standard of care, but many issues remain to be resolved. Some of these are: How much thienopyridines should be administered acutely? How early should these agents be given before interventions? How long should the agents be continued after drug-eluting stenting? How can we safely interrupt these agents when procedures with a high risk of bleeding must be performed? How responsive is the patient to the antiplatelet therapy? And how can this responsiveness be reliably measured? New drugs are poised to enter the market, and important considerations regarding selection of more potent antiplatelet agents must balance effectiveness with safety, a relationship that might vary considerably, depending on patient characteristics. Patient-specific characteristics effecting clopidogrel response include drug–drug interactions, changes in bioavailability, and genetic variability in drug-metabolizing enzymes and transporters (3). Several of the articles in this mini-focus issue investigate methods to tailor clopidogrel therapy, some for individuals and some for larger populations.

Three articles assess altered clopidogrel dosing strategies as a means to improve outcomes and address some of the individual variability in clopidogrel pharmacokinetics (4–6). These studies highlight the complexities of this issue. Although the PRINC (Plavix Response in Coronary Intervention) study demonstrated that increasing both the loading and maintenance doses of clopidogrel was associated with improved platelet responsiveness overall, it seems that only those patients with decreased ability to create the active metabolite of clopidogrel (CYP2C19*2 or CYP2C19*4 variant allele carriers) truly benefited (4,5). The focus to date has been on "one size fits all" dosing for clopidogrel; the articles in this issue underscore the need to assess the individual patient.

Clopidogrel responsiveness is further clouded by the myriad of available ex vivo platelet aggregation tests. In this issue of *JACC: Cardiovascular Interventions* alone, 4 different methods of

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platelet aggregation testing were used. Although adenosine diphosphate–induced optical aggregation has been considered the gold standard for assessing clopidogrel effectiveness, it is time consuming and technically difficult. Point-of-care tests, such as the VerifyNow P2Y12 platelet function test (Accumetrics, Inc., San Diego, California), are being used more frequently both clinically and in research studies. Ex vivo measures of platelet aggregation are another means to tailor clopidogrel therapy for an individual patient. It is unclear which of these tests best predicts clopidogrel responsiveness.

It is likely that truly "personalized" clopidogrel therapy will require some combination of both genetic and ex vivo platelet aggregation testing. Although preliminary results for both of these modalities are promising, their role in practice still remains unclear.

Just as we are beginning to understand the role of individual patient variability in clopidogrel response, physicians will also soon be confronted with the question of which thienopyridine to use. Prasugrel data were presented to the Food and Drug Administration in September 2008, and although the need for further review of the data resulted in no action being taken, there might be a choice of agent in the near future. Prasugrel is metabolized in a more direct path, has a quicker onset of action, and is more potent than the current clopidogrel dosing. How will interventionalists use this agent, which might also have a greater bleeding risk? Some physicians in Europe are using the more potent agent acutely and shifting to clopidogrel for long-term administration. The data to drive the decisions are largely lacking except for concern for bleeding risk in patients who have had a prior cerebrovascular accident, are elderly, or are of small body size.

Cangrelor, an injectable thienopyridine with reversible platelet binding, is a very short half-life agent that might provide opportunities for very prompt antiplatelet activity and be useful as a bridge in patients who need to interrupt their therapy, because its effect will dissipate within a very short time.

Further investigation into many of the unresolved issues regarding protection of our patients from thrombosis after stent placement will undoubtedly be forthcoming. At the current time physicians caring for these patients have many questions, and guidelines are incomplete in their recommendations. Hopefully new evidence will be forthcoming in the near future to inform those guidelines so that patient care can be optimized. We look forward to publishing many of those pivotal investigations in this journal.

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