Letters to the Editor

Switching Thienopyridines: Hypothetical Versus Real Risks

I enjoyed reading the quality paper by Campo et al. (1) that tried to determine whether platelet response after thienopyridines is drug or class specific in a broad spectrum of post-stent patients. The team should be acknowledged for the effort and for realistic rates for low response after clopidogrel (21%), and ticlopidine (19%). The major take-home message conveyed to the readership is that clopidogrel-treated patients may be switched to ticlopidine if “resistance” is determined by the platelet tests. However, the practical implications of this idea are not obvious, may be dangerous, may not be supported by clinical or epidemiologic evidence, and deserve at least some clarification and/or adjustment.

In fact, low response to clopidogrel as a major risk factor for the worsened vascular outcomes has been suspected but never proven to be a real clinical phenomena, especially considering that no load 75 mg clopidogrel saved 119 lives, and provided an absolute mortality benefit after myocardial infarction in COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) (2). Also, none of the small observation studies monitor compliance by measuring clopidogrel metabolites in plasma. Therefore, “clopidogrel resistance” is a laboratory finding, rather than a clinically relevant hazard unless further randomized evidence became available (3).

On the other hand, substituting clopidogrel with ticlopidine definitely increases the bone marrow toxicity risks. Indeed, neutropenia and thrombocytopenia were 2-fold higher in the ticlopidine arm than in patients treated with clopidogrel in CLASSICS (Clopidogrel Aspirin Stent International Cooperative Study) (4). Doubled cytotoxicity rates after ticlopidine were confirmed in a post-stent study (5) and a recent meta-analysis of 11,668 patients (6). Therefore, the suggestion that in case of low platelet response after clopidogrel patients should be switched to ticlopidine is not valid. Unless there is proof that response after clopidogrel is indeed linked to the clinical outcomes, monitoring compliance and potential tailoring of dual antiplatelet regimens with aspirin and clopidogrel will be a safer alternative than switching thienopyridines.

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We welcome the thoughtful comments by Dr. Serebruany to our recent publication on clopidogrel poor responsiveness in a broad population undergoing coronary stenting (1). Our major focus was to assess whether clopidogrel poor responders display inadequate platelet inhibition also after ticlopidine administration. We found that the great majority (83%) of patients who were clopidogrel nonresponders became responsive to ticlopidine, reaching a higher level of platelet inhibition (platelet aggregation [PA] 69 ± 15 vs. 44 ± 18; p < 0.01).

On the other hand, 23 patients who were responsive to clopidogrel showed resistance to ticlopidine and correspondingly less platelet inhibition with this drug (PA 46 ± 15 vs. 70 ± 15; p < 0.01).

When taken together our findings strongly suggest that poor responsiveness to currently commercially available thienopyridines may frequently be a drug-specific more than a class-effect mechanism. This conclusion holds particularly true in consideration that in the currently recommended regimen ticlopidine at steady state

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Reply

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Relationship Between Atrial Fibrillation and Left Atrial Size

The paper by Bangalore et al. (1) in a recent issue of the Journal evaluated the role of diastolic dysfunction as measured by left atrial (LA) size and the associated risk for adverse cardiovascular events in patients undergoing stress echocardiography. The authors report indexed LA size as a predictor of cardiac events independent of traditional clinical risk factors. Patients with significant mitral valve disease and with significant left ventricular systolic dysfunction were appropriately excluded from this study. However, atrial fibrillation (AF) is another important potential confounder, because it is known to affect LA remodeling and geometry (2) and is a known risk factor for cardiovascular events, particularly stroke. This remodeling effect is independent of loading conditions within the LA and can occur in both chronic and paroxysmal AF (3). It would be important to know whether AF was included in the multivariate analysis as well as the percent of patients who carried the diagnosis of AF. Furthermore, if LA size could predict prognosis in the subgroup of patients without AF to a similar extent as that reported in this study, this would lend further validity to the authors’ argument to incorporate LA size into the prognostic interpretation of stress testing.

We agree with the comment of Dr. Goldberg about the relationships between atrial fibrillation (AF) and left atrial (LA) size. In the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) study of 4,060 patients with AF only 33% of patients had a normal LA size (1). Patients with dilated left atrium are more prone to AF, and patients with AF and a dilated left atrium are more likely to remain in AF than those with normal LA dimensions. Atrial fibrillation is also known to affect LA remodeling and geometry. In a prospective echocardiographic follow-up of patients with AF, atrial enlargement was shown to occur as a consequence of AF (2). Regardless of whether LA enlargement is a cause for or a consequence of AF, the prognosis is worse compared with patients with a normal LA size.

In our study cohort of 2,705 patients undergoing stress echocardiography (3), only 63 (2.3%) patients had either AF or atrial flutter. Analysis performed after excluding this cohort showed that LA size was able to further risk stratify patients undergoing stress echocardiography (Fig. 1). The results were similar for the multivariable analysis and incremental prognostic value analysis. Thus even after excluding patients with AF/atrial flutter, LA size provided independent and incremental value over standard risk factors, including left ventricular systolic dysfunction and ischemia, and was a powerful prognosticator. Therefore, it should be routinely used in the prognostic interpretation of stress echocardiography.

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