Letters to the Editor

Aspirin Resistance, an Emerging, Often Overlooked, Factor in the Management of Patients with Coronary Artery Disease

A. N. Makaryus: *Clin Cardiol* 2006;29:144–148

To the Editor:

In his review of aspirin resistance, Makaryus¹ details the promising data concerning the long-term benefits of clopidogrel alone or in addition to standard aspirin therapy. Although clopidogrel may be an important addition to the long-term treatment of patients after acute coronary syndromes (ACS), its role in the immediate treatment of ACS events still needs elucidation.

The use of unfractionated heparin (UFH) has been the standard treatment for patients presenting with acute coronary syndromes, whether they had taken aspirin prior to their acute event or not. Early reports, in fact, suggested that patients who were taking aspirin prior to developing ACS (i.e., “aspirin failure”) had less severe presenting clinical events.^{2,3} But soon it became apparent that these “prior aspirin” patients had poorer outcomes when treated in the hospital with UFH and aspirin.^{4,5}

Analysis of three major ACS studies revealed that treatment of “prior aspirin” patients with either the low molecular weight heparin (LMWH) enoxaparin or the GPIIb/IIIa platelet receptor inhibitor tirofiban did significantly better than patients treated with UFH.^{4,5} What was particularly interesting in these studies is that patients who did not take aspirin before the time of admission for ACS had no apparent benefit from either enoxaparin or tirofiban over UFH.

These observations may give some insight into the mechanism of aspirin resistance, which may somehow affect platelet function as well as thrombin/fibrinogen reactivity. Alternatively, it may be that the composition of the emerging thrombus is changed.

Another important observation that was made in these studies is that the majority of patients who presented with ACS were taking aspirin prior to admission. In fact, the proportion of “prior aspirin” users in the TIMI 11B study was 84%.⁵ This suggests that many ACS studies that are now being conducted have a significant heterogeneity in potential responses to therapy that may not be apparent without looking at prior aspirin therapy as a separate group.

Whatever the mechanism, it is clear that aspirin users who suffer aspirin failure and develop an ACS must be considered a high-risk group. In this group, treatment with either a LMWH or the addition of a GPIIb/IIIa inhibitor to UFH should be considered.

In addition, studies of ACS should regard prior aspirin use as a separate risk group, with potentially different responses to study therapy.

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References

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Author's reply:

The letter by Lancaster underscores the point that aspirin resistance appears to be a heterogeneous process that requires further study. The exact mechanism in which the platelet appears to be the central actor requires investigation. Further study needs to focus on the different patient populations encountered (those with ACS, stable angina, prior aspirin use, who are aspirin naive, etc.) in order to assess the impact of aspirin resistance. Lancaster makes the important point that proper management strategy for patients in whom aspirin resistance is documented or suspected is uncertain at present. Prior studies have looked at the addition of other agents (i.e., heparin and/or GP IIb/IIIa inhibitor agents) in these patients. The question is not whether these agents are indicated in patients with ACS, but whether the clinician needs to adjust their use in the presence of aspirin resistance as a pre-identified additional risk factor. Indeed, most clinicians will agree that aspirin resistance likely puts the patient at greater risk and therefore should be considered a separate risk factor. At present, no guidelines have been established for this dilemma, as evidence indicating the best strategy is incomplete.

Once the mechanism of aspirin resistance is better defined, a greater understanding of the questions of screening patients for aspirin resistance, gender, or racial variation in the presence of aspirin resistance; adding clopidogrel to patients in whom we note aspirin resistance; or simply using higher doses of aspirin or adding other agents such as heparin and/or GP IIb/IIIa inhibitors can begin to be answered. These questions have great clinical implications for the management of patients with cardiovascular disease. Further studies to evaluate possible treatment options and to elucidate the exact mechanism of aspirin resistance need to be performed.

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