Previous Aspirin Use in Acute Coronary Syndromes
More Than a Marker?

We read with interest the analysis of the merged Thrombolysis In Myocardial Infarction (TIMI) database showing an increased risk of myocardial infarction (MI) but not death in patients with acute coronary syndromes (ACS) who were previously on aspirin therapy (1). The authors conclude that previous aspirin use was “a marker as opposed to a pathophysiologic factor related to an increased risk” for ACS. They explain that “although prior aspirin use was associated with an increase in the risk of recurrent MI and the composite end point. this may be attributable to confounders that cannot be corrected for, aspirin resistance, or both.”

In their discussion, the authors point to meta-analysis reports of 4 ACS trials, PURSUIT (Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy) (2), TIMI 11B (3), ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q wave Coronary Events), and PRISM-PLUS (Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms) (4), which all showed a similar increase in recurrent MI and composite endpoints but lack of increased mortality in the groups previously taking aspirin.

Unfortunately, the authors did not emphasize the unique presentations of previous aspirin users and their differential responses to antithrombotic and antiplatelet therapy that were common in all 4 reports. We believe that such analysis make a pathophysiologic link much more plausible.

First, in all 4 trials (as well as in the current report), participants who were previously taking aspirin were significantly less likely to present with MI than those not taking aspirin. Conversely, during their hospital course and after discharge, previous aspirin users collectively had a significantly higher number of recurrent MIs than those not previously on aspirin therapy. This “paradoxical” effect of previous aspirin use may also explain why some reports have shown worse outcomes in previous aspirin users, whereas others have shown better outcomes or no difference (5–7).

The most impressive evidence that there is a pathophysiologic effect of previous aspirin use, however, is the finding in all 4 studies that the benefit of low molecular weight heparin or the addition of platelet glycoprotein IIb/IIIa inhibitors to unfractionated heparin (UFH) is noted only in patients previously using aspirin. This effect is so strong that it has been argued (8) that the beneficial effect of enoxaparin in the TIMI 11B trial relied on the fact that 84% of the patients enrolled were previous aspirin users, and so were responsive to enoxaparin over UFH. If the majority of patients were not previously taking aspirin, the study findings may have been negative.

Although previous aspirin users in these 4 trials had more comorbidities than the group not previously using aspirin, these demographic differences were not present within the previous aspirin user group, and so risk factors alone cannot explain the heterogeneous response to antithrombin and antiplatelet therapies compared with UFH; nor can they explain why the differential response does not exist in the group not previously using aspirin (8).

We believe that these data highly suggest that patients with “aspirin failure” have a pathophysiologically distinct thrombus with unique properties. Furthermore, we believe that the phenomenon of aspirin failure should be called “clinical aspirin resistance” (to distinguish it from “laboratory aspirin resistance”) because it exists clinically, but, at present, there is no reliable method for measuring it in the laboratory (9).

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Reply

Although Dr. Lancaster and colleagues claim that we “did not emphasize the unique presentations of previous aspirin users,” we actually did—in the abstract of our paper: “Prior aspirin use was associated with less severe types of ACS at presentation (e.g., unstable angina >non–ST-segment elevation MI >ST-segment elevation MI) than their nonaspirin user counterparts (p < 0.0001)” (1). We then devote an entire paragraph in the Discussion section to this, complete with a list of 7 references: “Our study also found that prior aspirin use was associated with less severe forms of ACS at the time of presentation, a finding consistent with those of nearly all of the previously mentioned studies (9–11,33) and others as well (36–38).” We are not sure how we could have emphasized it more clearly.
We disagree with their claim that “the benefit of low molecular weight heparin or the addition of platelet glycoprotein IIb/IIIa inhibitors to unfractionated heparin (UFH) is noted only in patients previously using aspirin.” The data do not support this. Specifically, the interaction p value for low molecular weight heparin versus UFH in the TIMI (Thrombolysis In Myocardial Infarction) 11B trial was $p = 0.376$ (2), and for platelet glycoprotein IIb/IIIa inhibition versus placebo in the PURSUIT trial, it was $p = 0.534$ (3) Indeed, the PURSUIT investigators state clearly in the abstract of their paper: “In a multivariable model, eptifibatide did not have a different treatment effect in prior aspirin users compared with nonusers ($p = 0.534$).” As such, the rest of their argument of the “differential response” does not hold because there is not a differential response.

But even if a marker did identify a population with a differential response, that would not necessarily implicate it in the pathophysiology of the benefit. A case in point is troponin. In TACTICS–TIMI 18, we prospectively demonstrated that an early invasive strategy provides particular benefit in troponin-positive patients (4). This does not mean that the invasive strategy had a myocardial necrosis-sparing effect in this population.

Thus, we do not follow any of the authors’ arguments regarding aspirin resistance. We believe that our analysis of 16 trials strongly supports the fact that previous aspirin use is a marker of high risk, but further research is needed with other more specific markers to identify actual aspirin resistance.

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