Therapeutic Failure or Resistance to Aspirin

Gum et al. (1) recently published a highly cited study about the potential clinical consequences of aspirin resistance as assessed by aggregometry in patients undergoing elective cardiac catheterization. In a recent reply to comments raised by Steinhubl et al. (2), Topol and colleagues (3) acknowledge the real possibility of a type II error to detect an association between long-term outcomes and aspirin-resistance status as determined by the Platelet Function Analyzer (PFA-100). In fact, this is a little surprising, because previous studies indicated that PFA-100 results are highly predictive of clinical outcome in stroke patients receiving aspirin (4) and in patients with percutaneous interventions of peripheral arteries who received clopidogrel (5). It is interesting to note that, based on the percentages of aspirin-sensitive and aspirin-resistant patients presented in Gum et al. (1), Gum et al. (6), and Topol et al. (3), the total number of patients experiencing adverse events is 35 and 43 for aggregometry and PFA-100, respectively. This inconsistency needs further clarification.

What should make the reader more concerned is the high likelihood for an alpha error regarding the main outcome of Gum et al. (1) concerning aggregometry: the total number of aspirin-resistant subjects is limited (n = 17 of 326), of whom only four (24%) experienced an adverse outcome, as compared to 10% of aspirin-responsive patients. Therefore, statistical significance (p = 0.03) relies on only four events in aspirin-resistant patients, and even one event less in this group would be likely to yield an insignificant p value. Considering that the investigators used two methods to assess aspirin resistance (6), the PFA-100 and the aggregometry, a p value correction, if done for the two end points, would also result in an insignificant p value. Thus, statistical significance is not very robust.

The late occurrence of events is conspicuous because it contrasts with what has been observed for the clinical efficacy of aspirin versus placebo, where mortality curves cross after 18 to 24 months (7). This further increases the chances for an alpha error.

Finally, Topol et al. (3) discuss the poor correlation between aggregometry and PFA-100. This is not surprising when differences between methods are considered. The PFA-100 fulfills several of the characteristics of an ideal and rather physiological platelet-function test (8,9). First, whole blood is used rather than platelet-rich plasma. Second, it is a high shear system. This is important, because the cyclo-oxygenase inhibitor aspirin and the purinergic receptor inhibitor clopidogrel are primarily used for arterial indications, which are characterized by high shear rates.

In summary, several trials (1,4,5,10) have generated interest in investigating the clinical consequences of aspirin and clopidogrel non-responsiveness, which, it is hoped, will result in adequately powered confirmatory studies with pivotal results.

REFERENCES


REPLY

In response to the letter by Dr. Jilma, I believe we have fully addressed his concerns in our primary report (1) and the subsequent correspondence (2). The conclusion of our study was that “further investigation to confirm our findings... should be performed.” We fully acknowledged the relatively small sample size, number of events, and potential for alpha error (1). We also duly noted the poor correlation of the Platelet Function Analyzer (PFA) results despite Dr. Jilma’s expectations.

Rather than investigator “resistance,” we invite Dr. Jilma to perform meaningful prospective research to define further the natural history of anti-platelet drug lack of responsiveness.

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