Platelets play a critical role in ischemic heart disease, the cause of 10% of all deaths in Japan. Aspirin is the most commonly used antiplatelet agent for secondary prevention of ischemic heart disease, providing an estimated 20–25% reduction in the risk for serious vascular events in high-risk patients. Recurrent thrombotic events, however, have been reported in 10–20% of aspirin-treated patients and several studies have found an association between less-than-expected inhibition of in vitro aspirin-sensitive platelet function tests and the occurrence of adverse clinical outcomes. Adding complexity to the problem, conflicting results have been obtained with respect to whether aspirin’s antiplatelet effect is maintained or attenuated over time. Therefore, the extent to which platelets in Japanese patients are inhibited by aspirin, and the consistency of this inhibition over time, are of great interest.

Important strengths of this study include the relatively large group of subjects (239 at enrollment) over this time interval and that the study addressed the issue of platelet reactivity under real-life conditions in a Japanese population. As was the case with the aspirin-sensitive tests that were found to be associated with poor clinical outcomes, the aspirin-sensitive tests evaluated by Ikeda et al, that is, collagen-stimulated light transmission aggregometry and whole blood aggregation measured by screen filtration pressure, measure endpoints many steps removed from aspirin inhibition of platelet cyclooxygenase-1 (COX-1) and must be interpreted in that context. For example, the authors reported that at baseline 27% of aspirin-treated patients produced a threshold platelet aggregation response to 1 mg/L collagen, while only 10% of healthy aspirin-treated donors responded to this dose of collagen. Such patients with high on-treatment platelet reactivity may be at increased risk for poor clinical outcomes. But because many factors other than aspirin inhibition of platelet COX-1 contribute to collagen-stimulated platelet aggregation, not the least of which is the platelet collagen receptor Ia–IIa, it would be more correct to refer to this as platelet hyperreactivity rather than poor response to aspirin. In studies in which platelet COX-1 activity was evaluated by measuring serum thromboxane B2 (TxB2), the most direct measure of platelet COX-1 activity, poor aspirin inhibition of platelet COX-1 was infrequent (<2% of aspirin-treated patients undergoing cardiac catheterization). Nevertheless, high residual serum TxB2 has been associated with adverse clinical outcomes. In the same study, platelet hyperreactivity as measured using a COX-1-independent platelet function assay was also associated with subsequent adverse outcomes, indicating that multiple mechanisms contribute to poor clinical outcomes. Thus, changes in platelet reactivity to collagen over long-term aspirin treatment may reflect changes in risk for clinical events, but whether this would relate to residual COX-1 activity or other mechanisms is unclear.

Evaluating platelet function in a consistent manner over a 2-year span is itself a challenging task. Ikeda et al met this challenge by using collagen at several concentrations to define the concentration of agonist that gives half-maximal aggregation; an approach that potentially provides more reliable data than can be obtained with a single, arbitrarily chosen, agonist concentration. By this method, the authors demonstrated that platelet reactivity to collagen at enrollment (aspirin treatment for ≥6 months) is not increased after an additional 2 years aspirin treatment. Moreover, platelet reactivity to collagen after 2 years significantly correlated with platelet reactivity to collagen at enrollment, indicating that platelet hypo- or hyperreactivity to collagen is a consistent phenotype within individuals over time, raising the possibility of a genetic component, for example the 807 C/T polymorphism of the glycoprotein Ia gene. This consistent response raises the possibility that platelet hyperreactivity to collagen in these subjects may have pre-dated treatment with aspirin. Indeed, we demonstrated, using a variety of aspirin-sensitive platelet function tests, that a significant proportion of high post-aspirin platelet reactivity could be accounted for by pre-existing (prior to exposure to aspirin) platelet reactivity.

The present result, that platelet reactivity in an aspirin-sensitive platelet function test is maintained over 2 years of aspirin treatment, is consistent with that of the Berglund and Wallentin study, but differs from the results obtained by Pulcinelli et al, who, in a retrospective study of 150 aspirin-treated outpatients, reported a progressive increase in platelet reactivity to collagen between months 2 and 24 of aspirin treatment. Although it is unclear if it is significant, one diff-

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ference between these studies is that the subjects in the Pulcinelli et al study were aspirin naïve at enrollment, while those in the Ikeda et al report had been on aspirin for varying periods of time (≥6 months). Thus, subtle changes in reactivity to collagen occurring during early aspirin treatment would not have been seen by Ikeda et al. The increased heterogeneity, however, of the Ikeda et al study population reflects the reality that most at-risk cardiovascular patients are already being treated with aspirin, some for years, and addresses the important question of whether their platelet reactivity changes over time. Consistent aspirin inhibition and platelet reactivity to collagen in patients, rather than progressive loss of aspirin inhibition, is consistent with the finding that late stent thrombosis is infrequent in Japanese patients treated with the combination of ticlopidine and aspirin for long periods.15

In summary, the present study demonstrates a long-lasting effect of aspirin on platelet function in high-cardiovascular-risk Japanese patients. Further, consistency of the platelet hyperreactivity phenotype over time in individual patients may suggest a genetic component.

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