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EDITORIAL COMMENT

Aspirin Resistance: A New Independent Predictor of Vascular Events?*

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Aspirin is an effective antiplatelet agent for preventing important clinical complications of atherothrombosis (1). Among 29,652 high-vascular-risk patients randomly allocated to long-term aspirin therapy, the rate of serious vascular events (nonfatal myocardial infarction, nonfatal stroke, or vascular death) after about two years was 12.9%, compared with 16.0% among 29,743 patients allocated to control (1). This is an odds reduction of 23% (standard deviation 2), a relative risk reduction of 19%, and an absolute risk reduction of 3.1% over two years, or 1.5% per year (1). Therefore, aspirin fails to prevent more than four-fifths (81%) of recurrent serious vascular events among high-risk patients, and one in eight high-risk patients (12.9%) experiences a recurrent vascular event in the next two years despite taking aspirin.

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There are several reasons why aspirin may not be totally effective in preventing recurrent serious vascular events, and these are listed in Table 1. One possible explanation that has recently attracted great interest is that some patients are resistant to the antiplatelet effects of aspirin. The term "aspirin resistance" has evolved to describe the failure of aspirin to produce an expected response on one or more laboratory measures of platelet activation and aggregation. As many as half of the population have thus been defined as aspirin resistant (2–8). However, laboratory definitions of "aspirin resistance" have varied according to the platelet function tests used, and no study has prospectively validated conventional platelet aggregometry as an independent predictor of subsequent serious vascular events.

In this issue of the *Journal*, Gum et al. (9) provide the first reliable evidence that aspirin resistance, as diagnosed by lack of suppression of optical platelet aggregation, correlates with confirmed (not just presumed) clinical unresponsiveness. In 2001 they had reported that 18 (5.5%, 95% confidence interval [CI]: 3.3% to 8.6%) of 325 patients with a prior history of coronary or cerebral vascular disease were aspirin resistant (8). Aspirin resistance was defined as the failure of aspirin 325 mg/day, given for a minimum of seven days before testing, to suppress agonist-induced platelet aggregation, as measured by optical platelet aggregometry. The cutoff for the diagnosis of aspirin resistance was derived from screening 40 in-house normal samples, but details as to how this cutoff was chosen were not provided. Gum et al. (9) now report the two-year follow-up of this cohort of patients. Follow-up was complete for 316 (97%) of the 326 patients included in this cohort, 16 of the 17 aspirin-resistant patients, and 300 of the 309 nonaspirin-resistant patients. A serious vascular event occurred in 34 patients (10%), including 4 of the 17 (23.5%, 95% CI: 6.8% to 49.9%) patients who were aspirin resistant and 30 of the 309 patients (9.7%, 95% CI: 6.6% to 13.6%) patients who were not aspirin resistant. Univariate analysis revealed that aspirin-resistant patients had a 3.1-fold excess hazard of serious vascular events (hazard ratio 3.1, 95% CI: 1.1 to 8.9) compared with nonaspirin-resistant patients. After adjusting for 12 potential prognostic factors, multivariate analysis indicated that aspirin resistance was associated with a 4.1-fold excess adjusted hazard of serious vascular events (hazard ratio 4.1, 95% CI: 1.4 to 12.1), independent of age, gender, and conventional vascular risk factors.

The work of Gum et al. (9) indicates that failure to achieve an anticipated effect of aspirin on a laboratory measure of platelet aggregation, which is present in about 1 in 20 high-risk patients, is an independent predictor of future risk of serious vascular events. However, their estimate of the magnitude of hazard is imprecise because the number of outcome events was small. The 95% CIs are consistent with an excess hazard as low as 1.4-fold and as much as 12-fold.

However, the work of Gum et al. (9) raises other questions. Is the definition of aspirin resistance now standardized, valid, and reliable? Are the results of this study reproducible, and can they be generalized to other laboratories and other patients? Is there now a role of screening for aspirin resistance in clinical practice? If so, what are the therapeutic implications of a diagnosis of aspirin resistance?

Is the definition of aspirin resistance now standardized, valid, and reliable, and are the results of this study generalizable? The definition of aspirin resistance used by Gum et al. (9) was based on the results of optical platelet aggregometry. This has potentially important implications for clinicians because, unlike many other laboratory measures of platelet function, optical platelet aggregometry is widely available and is routinely used to assess platelet function and to measure the antiplatelet effects of aspirin. However, there are various other techniques to measure platelet aggregometry, including whole-blood aggregometry (5,6), the platelet aggregate ratio (7), and the platelet reactivity index, a measure of in vivo platelet aggregation

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Table 1. Possible Mechanisms to Account for the Apparent Failure of Aspirin to Protect Some High-Risk Individuals From Recurrent Vascular Events

Cause	Mechanism
Wrong diagnosis	Nonatherothrombotic causes of vascular disease
Not taking the drug	Nonadherence to aspirin (poor compliance)
Insufficient drug	Higher dose of aspirin required
Different pathway	Alternative "upstream" pathways of platelet activation that are not blocked by aspirin
	Aspirin-insensitive thromboxane biosynthesis
Drug interactions	Drugs that interfere with the antithrombotic effects of aspirin
Other predisposing factors	Platelet glycoprotein polymorphisms
	Increased platelet turnover states

induced during the process of blood collection (2,10,11). These techniques collectively identify an inadequate response to aspirin in 5% to 60% of patients with atherothrombosis of the cerebral, coronary, or peripheral circulations (2–11). It is difficult to assess which technique is the most accurate and valid measure of aspirin resistance without direct comparisons of their clinical relevance (such as capacity to discriminate patients at risk of recurrent vascular events). Timing may also be an important determinant of the validity of tests of aspirin resistance because several serial studies of platelet aggregometry suggest that the antiplatelet effects of aspirin vary over time (4,6,12). By contrast, other studies have found suppression of platelet aggregation in all patients tested (13,14) without attenuation of the antiplatelet effect during 24 months of follow-up (14). These divergent results most likely reflect differences in the definition of aspirin resistance as well as methodologic differences in the performance and interpretation of platelet aggregometry studies among laboratories (15).

The PFA-100 (Dade Behring, Deerfield, Illinois) is a semiautomated platelet function analyzer that has recently been proposed as an alternative to conventional platelet aggregometry to identify aspirin-resistant individuals (16). It allows rapid assessment of platelet adhesion/aggregation and is increasingly being used in clinical practice to screen for inherited or acquired haemostatic disorders. However, the PFA-100 does not provide a specific measure of the antiplatelet effects of aspirin (17) and may lack sensitivity for measuring the antiplatelet effects of low-dose aspirin (18).

Skin bleeding time has also been used to measure the antiplatelet effects of aspirin (19,20), but it is a nonspecific measure of platelet function, is operator dependent, and has limited reproducibility.

Most recently, a continuous and graded association was demonstrated between increasing levels of urinary 11-dehydro thromboxane B_2 and risk of future clinical events (21). However, because the concentration of 11-dehydro thromboxane B_2 in the urine reflects both platelet and nonplatelet sources of thromboxane generation, this may not be a specific measure of the antiplatelet effects of aspirin. Furthermore, the predictive value of 11-dehydro thromboxane B_2 concentrations in an individual patient has not been demonstrated and requires further evaluation.

These data highlight the limitations of existing laboratory measures of the antiplatelet effects of aspirin as well as the need to develop a standardized definition of aspirin resistance. A suitable definition of aspirin resistance should not only incorporate an absent or attenuated laboratory response to a therapeutic antiplatelet dose of aspirin (for example, at least 75 mg/day for 5 days) in a compliant patient that correlates significantly and independently with its effects in preventing atherothrombotic vascular events; it also requires a specific, accurate, and reproducible laboratory measure of the antiplatelet effects of aspirin, the results of which can be generalized to other laboratories and patients. None of the currently available laboratory tests of the antiplatelet effects of aspirin has yet been demonstrated to meet adequately these criteria.

Is there now a role of screening for aspirin resistance in clinical practice? Even if aspirin resistance could be defined and reliably diagnosed by laboratory testing, screening for aspirin resistance (in asymptomatic individuals, and symptomatic patients who experience a thrombotic complication despite aspirin therapy) could still only be recommended if the results of screening (positive and negative) influenced clinical management (such as optimizing prediction of risk of serious vascular event) or led to treatments that improved patient outcome in a cost-effective manner.

What are the therapeutic implications of a diagnosis of aspirin resistance? There are presently no specific treatments for aspirin resistance. However, several strategies may further reduce the risk of thrombotic complications in patients who are prescribed aspirin for vascular prevention (Table 1). First, the underlying cause of any vascular event should be accurately diagnosed because between 5% and 40% of these events are not caused by atherothrombosis and may require alternative or additional treatments (22). Second, poor compliance or inadequate aspirin dosing (at least 75 mg/day appears to be optimal for long-term use [4]) should be considered as possible causes of thrombotic complications. The 5% of patients that cannot tolerate aspirin or are allergic to aspirin should be treated with the adenosine diphosphate receptor antagonist clopidogrel (23). Third, alternative antithrombotic strategies should be considered in patients who experience a thrombotic complication during aspirin therapy. Clopidogrel blocks pathways of platelet activation and aggregation that cannot be blocked by aspirin and should be considered as a substitute for, or additional treatment to, aspirin. Clopidogrel is superior to aspirin for the prevention of vascular events in a broad category of high-risk vascular patients (23,24), whereas the combination of clopidogrel plus aspirin is superior to aspirin alone in patients with non–ST-segment elevation acute coronary syndrome (25) or undergoing percutaneous coronary intervention (26,27). The combination of dipyridamole

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plus aspirin (28) or warfarin plus aspirin (29) may also provide incremental benefit compared with aspirin alone.

There is now good evidence that a substantial proportion of individuals treated with aspirin fail to achieve an anticipated response on commonly used laboratory measures of the antiplatelet effects of aspirin. Further work is required to standardize and validate laboratory tests of the antiplatelet effects of aspirin and to identify therapeutic strategies that can modify the results of these investigations and thereby reduce the risk of future thrombotic complications. In the meantime, however, clinicians should ensure the continued use of aspirin in all eligible patients and a high level of compliance with aspirin therapy in treated patients. Despite the known limitations of aspirin, the appropriate use of this simple, proven treatment will continue to prevent many thousands of premature atherothrombotic vascular events each year.

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