Narrative Review: Aspirin Resistance and Its Clinical Implications

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Aspirin is currently the most cost-effective drug for the secondary prevention of cardiovascular disease, but treatment failures are relatively common. Several factors have been linked to these recurrent vascular events in patients prescribed aspirin, including smoking, drug interactions, nonadherence, comorbid conditions, and aspirin resistance. The term *aspirin resistance* has been used to describe not only an absence of the expected pharmacologic effects of aspirin on platelets but also poor clinical outcomes, such as recurrent vascular events, in patients treated with aspirin. Aspirin resistance is perhaps more precisely understood as the phenomenon of measurable, persisting platelet activation that occurs in patients prescribed a therapeutic dose of aspirin and may underlie an unknown proportion of aspirin treatment failures. Key challenges for future research are to standardize a definition of aspirin resistance and to compare whether different measures of platelet activation, either alone or in combination, independently predict cardiovascular events. These challenges must be met before researchers conduct studies to assess the clinical utility of testing on patient outcomes and cost-effective prescribing.

Ann Intern Med. 2005;142:370-380. www.annals.org

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Coronary heart disease and stroke are common causes of death and morbidity in western countries. Aspirin is the single most important drug in the secondary prevention of atherothrombotic disease. Its effectiveness has been well established in clinical trials and meta-analyses, with roughly a 25% reduction in rates of recurrence (1, 2). However, some patients experience recurrent vascular events despite treatment with aspirin, a phenomenon that has been called *aspirin resistance*. This paper reviews the concept of aspirin resistance, its measurement, and its clinical consequences for patients prescribed aspirin.

Methods

During the second week of January 2004, we searched MEDLINE and EMBASE using predefined search terms (Appendix, available at www.annals.org). Abstracts were reviewed, and relevant full-text articles were obtained. Reference lists of identified publications were scrutinized for additional studies. Landmark articles (such as the Antiplatelet Trialists' Collaboration reviews) were identified, along with editorials and other review articles. We also searched the databases of the Cochrane Collaboration and the Centre for Reviews and Dissemination and consulted experts in the field to obtain additional data.

Articles were included in the review if they addressed the phenomenon of aspirin resistance (or synonymous conditions such as nonresponsiveness) and its cause, measurement, or clinical consequences (coronary heart disease, cerebrovascular disease, or peripheral vascular disease). Given a wide range of publication types, we gave priority to reviews or meta-analyses, cohort studies, and case–control studies. Case reports were excluded, as were studies that used bleeding time as the primary measurement of platelet function. Bleeding time varies widely, lacks reproducibility, has poor sensitivity and specificity, and lacks correlation with other indicators of platelet activation; in addition, it cannot be used to quantify platelet dysfunction in patients with thrombocytopenia (3, 4).

How Does Aspirin Work?

Aspirin works by inhibiting the prostaglandin-producing enzyme cyclooxygenase, which converts arachidonic acid into prostaglandins (**Figure**) (5). Prostaglandins have several important physiologic actions, including inflammation, fever, protection of the gastric mucosa, regulation of renal function, and platelet aggregation (6). The platelet prostaglandin thromboxane A_2 increases expression of fibrinogen receptors on platelet membranes, facilitating fibrin cross-links between platelets to form a platelet plug. Thromboxane A_2 also acts synergistically with other products released by activated platelets (such as adenosine diphosphate, fibrinogen, and factor V) to further augment platelet aggregation.

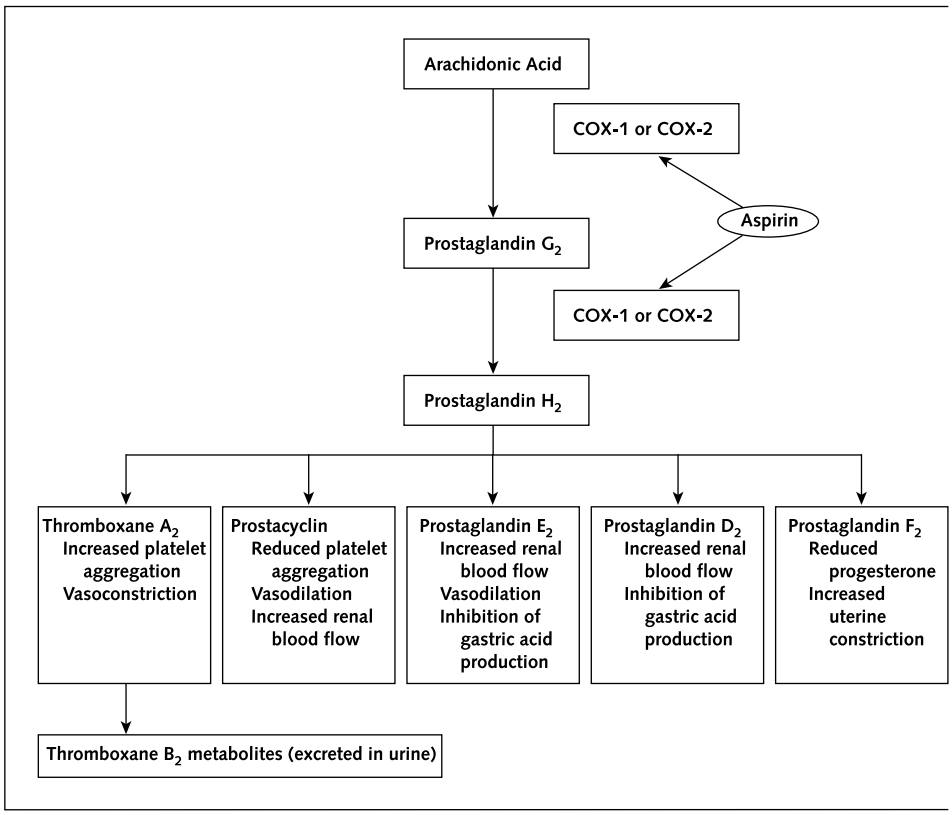
Cyclooxygenase exists in 2 isoforms, COX-1 and COX-2. The former is present in nearly all cells, while COX-2 is normally absent from cells but may be produced in response to inflammatory stimuli (6). Aspirin works by irreversibly acetylating COX-1 in platelets, preventing arachidonic acid from reaching the enzyme's binding and catalytic sites (7). This results in reduced prostaglandin biosynthesis for the platelet's lifetime of 8 to 10 days and especially reduces the production of thromboxane A_2. Because COX-1 inhibition in platelets is irreversible, regular low doses of aspirin lead to more than 95% suppression of thromboxane A_2 generation after several days' dosing.

After a single dose of aspirin, platelet COX-1 activity recovers by about 10% per day, in line with platelet turnover (platelets are anucleate and cannot resynthesize COX-1) (5). Additional mechanisms have also been proposed for some of aspirin's clinical effects in cardiovascular disease, including inhibition of platelet aggregation by neutrophils, effects on the endothelium, and antioxidant effects (8–10).

See also:

Web-Only
Conversion of figures and tables into slides

Figure. **Production of prostaglandins from arachidonic acid and their main physiologic actions.**



COX = cyclooxygenase.

WHY DOES ASPIRIN NOT ALWAYS WORK?

Recurrent vascular events are not infrequent in patients prescribed aspirin for secondary prevention. During 6-month follow-up of 8000 patients with unstable angina or non–ST-segment elevation myocardial infarction, Mehta and Yusuf (11) reported that 6% of patients experienced further vascular events. By 2 years, the recurrent vascular event rate was still 6% to 8% per year (11). What factors might contribute to recurrence?

Adherence

Many patients do not take medications as prescribed. Little evidence is available to assess what proportion of patients taking aspirin and experiencing recurrent vascular events were not taking aspirin as prescribed. Tarjan and colleagues' study of 75 coronary care patients found that 11% were nonadherent, according to results of urine tests for salicylate metabolites (12). More work is needed to assess the scale of the problem and to develop methods to improve adherence in aspirin-treated patients.

Dosage

At present, evidence from clinical trials suggests that daily aspirin doses of 75 mg to 150 mg are optimal for the best average benefit and the least harm. Clinical trials, meta-analyses, and meta-regression studies indicate that reduction in vascular events with high-dosage aspirin (500 to 1500 mg/d) may be no greater than with low-dosage aspirin (75 to 150 mg/d) (1, 2, 13). Aspirin-induced adverse effects (such as gastrointestinal bleeding) are dose dependent (14).

Some uncertainty remains about the optimal dose in specific circumstances. Dosages less than 75 mg/d have been suggested on theoretical grounds, but no empirical evidence supports this in practice (2). After coronary surgery, higher dosages of aspirin (around 325 mg/d) appear to be more effective than lower dosages, but this higher dosage requirement may simply reflect the unique conditions created by surgical interventions, which include increased platelet turnover by the bone marrow as a response to the stress of surgery (15, 16). These results may therefore not apply to other clinical contexts, although a similar effect has been observed in a study of patients undergoing percutaneous coronary interventions (17).

Comorbid Conditions

Other conditions, such as arteritis or cardiac embolism from prosthetic heart valves, rheumatic heart disease, or infective endocarditis, can independently cause recurrent events in patients taking aspirin. However, a much more common problem is cigarette smoking. A few small studies have compared the effect of aspirin on platelet aggregation in healthy smokers and nonsmokers and have found that

Table 1. **Labels Used in the Literature To Describe Aspirin's Effect**

Term	Usual Definition
Aspirin responsiveness	An individual's response to aspirin prescribed in a therapeutic dose, measured by various tests of platelet activation
Aspirin nonresponsiveness	A relative concept, based on the presence of persisting platelet activation despite prescription of a regular therapeutic dose of aspirin
Clinical aspirin resistance (or aspirin treatment failure)	The recurrence of coronary heart disease, stroke, and peripheral vascular disease syndromes, despite prescription of a regular therapeutic dose of aspirin
Biochemical aspirin resistance	A phenomenon of persistent platelet activation, measured by platelet function tests, despite prescription of a regular therapeutic dose of aspirin

smoking reduces the effect of aspirin on platelet aggregation (18–20).

Smoking, unstable angina, hyperlipidemia, and diabetes may also interfere with aspirin's effect on platelet activation by increasing the production of prostaglandin F_2–like compounds, known as isoprostanes (18, 21–25). Isoprostanes are produced from arachidonic acid, primarily through a non-COX process of lipid peroxidation catalyzed by oxygen free radicals, so their synthesis is unaffected by aspirin. F_2-isoprostanes induce vasoconstriction and have prothrombotic effects by amplifying the response of platelets to other agonists and through aspirin-insensitive thromboxane biosynthesis (26, 27). Studies in smokers have demonstrated that the production of F_2-isoprostanes increased with the number of cigarettes smoked and that 75 mg of aspirin per day failed to suppress production despite suppression of thromboxane metabolite excretion (19, 20). These mechanisms could lead to recurrent vascular events that are insensitive to the effect of aspirin at usual preventive doses.

Drug Interactions

Regular consumption of certain nonsteroidal anti-inflammatory drugs (NSAIDs), including ibuprofen and indomethacin, appears to antagonize the antiplatelet effects of aspirin and may worsen outcomes in patients who are also prescribed aspirin (7, 28–30). Aspirin irreversibly acetylates a serine residue at position 529 in COX-1, preventing arachidonic acid from reaching the binding site. However, certain NSAIDs can block the access of aspirin to the COX-1 binding site by occupying the nearby catalytic site, thus preventing aspirin from gaining access to its target serine (7). This interaction is potentially important because many patients taking aspirin may also take NSAIDs (prescribed or purchased over the counter) for other conditions. No studies to date have examined the proportion of patients experiencing recurrent vascular events who are taking NSAIDs as well as aspirin.

What Is Aspirin Resistance?

The incidence of recurrent vascular events in patients taking aspirin has been called *aspirin resistance* (4, 31–34). Confusingly, this term has been used interchangeably in the literature to describe biochemical as well as clinical phenomena (**Table 1**). Thus, aspirin resistance has been used to describe either persistent platelet activation, demonstrated by platelet function tests (biochemical aspirin resistance), or the recurrence of vascular events in patients prescribed usual therapeutic doses of aspirin (clinical aspirin resistance). The clinical concept is nonspecific and might be preferably labeled as *clinical treatment failure* (27).

We propose that the term *aspirin resistance* should be used cautiously. There are a number of competing explanations for recurrent vascular events in aspirin-treated patients. At present, no standardized definition or test can be used to quantify aspirin resistance, but we understand the term to best describe the phenomenon of measurable, persistent platelet activation that occurs in patients prescribed therapeutic doses of aspirin and may underlie an unknown proportion of clinical treatment failures. We therefore define *aspirin resistance* as a biochemical phenomenon that *may* have clinical consequences.

How Can Aspirin's Effects on Platelets Be Measured?

Platelet activation comprises a change in platelet shape; a change in platelet aggregation; and the release of platelet constituents, such as adenosine diphosphate, fibrinogen, factor V, hydrolytic enzymes, and catalase (35). Platelet activation may therefore be quantified by examining factors such as shape change and a tendency to aggregate or by measuring blood and urine levels of platelet metabolic products (3, 35). Biochemical aspirin resistance has been evaluated by using measures of platelet activation that fall into 2 main categories: those reflecting in vivo platelet activity and those reflecting ex vivo platelet activity. These tests are summarized in **Table 2**.

In Vivo Tests

Urinary Thromboxane B_2

As the end product of the arachidonic acid pathway, thromboxane B_2 indicates the level of platelet activity (**Figure**) (36, 37). The test is relatively simple and inexpensive and has been used in studies of aspirin resistance (38).

Expression of P-Selectin on Platelet Membranes

The selectins are adhesion proteins expressed on all blood cell types (39). P-Selectin moves to the plasma membrane when platelets are activated and degranulated. Increased P-selectin expression on the platelet surface thus indicates platelet activation (40). However, testing requires expensive equipment and carefully controlled test conditions (41).

Table 2. **Laboratory Tests Used To Investigate Platelet Function***

Test	Method	Advantages	Disadvantages
Platelet aggregation	Optical	Widely available Correlated with clinical events	Not specific Labor intensive Operator- and interpreter-dependent Assesses platelet function in the absence of erythrocytes and blood flow (shear stress)
	Semi-automated PFA-100, VerifyNow Aspirin Assay†	Simple Rapid Correlated with clinical events Assesses platelet function in presence of erythrocytes and high shear	Moderately expensive Uncertain sensitivity and specificity
Platelet membrane receptor expression	P-selectin flow cytometry	Expression indicates platelet activation	Uncertain sensitivity and specificity Uncertain reproducibility Uncertain correlation with clinical events Results highly dependent on flow models chosen Expensive Labor intensive
Platelet-release products	Soluble P-selectin	Simple Correlated with clinical events Long-term storage	Uncertain sensitivity and specificity Uncertain reproducibility
	Urinary thromboxane excretion	Simple Correlated with clinical events Long-term storage	Uncertain sensitivity and specificity Uncertain reproducibility

* Data from reference 4. PFA-100 = Platelet Function Analysis-100.
† PFA-100 is manufactured by Dade Behring, Leiderbach, Germany. VerifyNow Aspirin Assay is manufactured by Accumetrics, San Diego, California.

Soluble P-Selectin

Increased plasma levels of this protein indicate increased platelet activation (40, 42). This test is simple to perform but moderately expensive. Because it is stable and can be stored for many months, it may be a suitable test for use in large epidemiologic studies.

Ex Vivo Tests

Optical Platelet Aggregation Tests

These tests measure optical changes in plasma caused by platelet aggregation, induced by the addition of various substrates (including adenosine diphosphate and collagen) in the absence of erythrocytes and blood flow (43). Although historically these tests have been the most widely used, they are time-consuming and do not correlate well with other indicators of platelet function. They do not reflect in vivo platelet activity as well as other tests, such as the Platelet Function Analysis-100 (PFA-100) test (35).

PFA-100

The PFA-100 system (Dade Behring, Leiderbach, Germany) uses a disposable test cartridge that simulates an injured blood vessel (44–46). Whole blood passes through an aperture cut into a collagen-coated membrane, which is infused with adenosine diphosphate or epinephrine at high shear stress. Activated platelets adhere to this membrane surface and aggregate to form a platelet plug. This plug eventually closes the aperture, and blood flow ceases; the closure time reflects platelet function in the sample. Measurement of platelet function in the PFA-100 is performed in the presence of erythrocytes and at a high shear rate. Therefore, it might be considered more clinically relevant than platelet aggregometry, which is conducted in the absence of erythrocytes and blood flow. One of the main determinants of platelet adhesion is transport of platelets toward the vessel wall (47). In flowing blood, high shear forces in capillaries result in erythrocytes migrating to the middle of the blood flow stream, pushing platelets toward the vessel wall. Thus, the concentration of platelets near the vessel wall increases with increasing shear, allowing platelet membrane receptors to interact with adhesive proteins in the blood vessel wall. However, the PFA-100 test is moderately expensive, and testing must occur within 4 hours after blood collection. This may make it less suitable for large epidemiologic studies.

There is no consensus reference standard for measuring platelet activation, so most studies investigating biochemical aspirin resistance have used a battery of different tests (35). Because of the complexity of the platelet activation process, one single test is unlikely to adequately reflect all aspects of platelet function that are relevant to clinical events. This makes assessment of relative test performance difficult. However, without validation, the clinical importance of the phenomenon of biochemical aspirin resistance will remain in question.

How Common Is Biochemical Aspirin Resistance?

We identified 5 studies investigating the prevalence of biochemical aspirin resistance (12, 48–51) (**Table 3**). The range of prevalence estimates for biochemical aspirin resistance varied from 5.5% to 56.8%, depending on the

Table 3. **Studies Reporting the Prevalence of Biochemical Aspirin Resistance***

Study, Year (Reference)	Sample Size, *n*	Patient Characteristics	Intervention	Men/Women, *n/n*	Mean Age, *y*
Gum et al., 2001 (48)	325	Stable cardiac patients	Aspirin, 325 mg/d, for ≥7 d; no other antiplatelet agents	252/73	61.5
Sane et al., 2002 (49)	88	Outpatients with heart failure (ejection fraction <0.4)	Aspirin, 325 mg/d, for ≥1 mo; no other antiplatelet agents	34/54	65
Helgason et al., 1994 (50)	306	Patients with past ischemic stroke already taking aspirin (any dose)	Aspirin, 325 mg/d, increased by 325 mg/d to 1300 mg/d or until complete inhibition of platelet aggregation	NR	NR
Roller et al., 2002 (51)	26	Previously untreated outpatients with peripheral vascular disease who were not taking other antiplatelet agents or NSAIDs	Aspirin, 100 mg/d, for 7 d followed by 300 mg/d if nonresponsive	17/9	62
Tarjan et al., 1999 (12)	75	Patients admitted to coronary care unit with an acute coronary syndrome previously treated with aspirin	–	44/31	61.3

* ADP = adenosine diphosphate; MI = myocardial infarction; NR = not reported; NSAID = nonsteroidal anti-inflammatory drug; PFA-100 = Platelet Function Analysis-100.
† Dade Behring, Leiderbach, Germany.

method of assessing platelet function, the definition of biochemical aspirin resistance, and the patients tested. These studies suggest that biochemical aspirin resistance is a measurable phenomenon in a substantial proportion of patients prescribed aspirin. However, the studies have several limitations (**Table 3**), including small sample sizes, lack of agreement between different platelet function tests, different dose regimens and nonadherence, and little information about measurement stability over time.

Gum and colleagues (48) found little agreement between optical aggregometry findings and PFA-100 results ($\kappa = 0.1$). Biochemical aspirin resistance was more common in nonsmokers, conflicting with evidence presented earlier about smoking and platelet aggregation. The study

Table 3—**Continued**

Design	Study Labels and Definition of Biochemical Aspirin Resistance	Main Results	Comments
Cross-sectional prevalence	Aspirin resistant if PFA-100† closure time was ≥193 s	Aspirin resistant, 9.5%	Poor level of agreement between the 2 testing methods (κ = 0.1 [95% CI, 0.0450 to 0.246]) Aspirin resistance more common in women and nonsmokers
	Aspirin resistant if mean aggregation was ≥70% with ADP AND ≥20% with epinephrine	Aspirin resistant, 5.5%	
	Aspirin semi-responder if mean aggregation was ≥70% with ADP OR ≥20% with epinephrine	Semi-responders, 23.8%	
Cross-sectional prevalence	Patients were considered aspirin nonresponsive when 4 of the 5 following variables were fulfilled: 1) collagen-induced aggregation > 70%; 2) ADP-induced aggregation > 60%; 3) whole-blood aggregation > 18 ohm; 4) expression of glycoprotein IIa/IIIa > 220 log mean fluorescence units; 5) P-selectin membrane receptor positivity > 8%	Aspirin nonresponsive, 56.8%	Highly selected patient sample with limited applicability Nonresponders were more likely to have had previous MI, more severe heart failure, diabetes, hyperlipidemia, and hypertension
Prospective cohort over 33 mo, plus nonrandomized intervention study of dose escalation; aggregation results interpreted according to previously published criteria	Aspirin treatment fully effective if platelet aggregation was completely inhibited, arachidonic acid response was absent, ADP response was reduced, epinephrine response was absent or markedly decreased, collagen response was absent or markedly decreased, and spontaneous aggregation was absent	Baseline (n = 306): complete responders, 74.5%; partial responders, 25.5%	Confounding factors not explored, especially age, sex, drug interactions Nonrandomized intervention Only 55.8% of the sample had had a repeated test at time of publication Interpretation of aggregation nonstandard
	Aspirin treatment partially effective if platelet aggregation was partially inhibited, arachidonic acid caused aggregation, ADP response was normal, epinephrine response was normal or decreased, and collagen response was normal or decreased	≥1 repeated test (n = 171): complete responders, 69.5%; partial responders, 30.5%	
	Aspirin resistant if unable to achieve complete inhibition of platelet aggregation despite aspirin dosage of 1300 mg/d	Aspirin resistant, 8.1%	
Before and after 7 d of treatment with aspirin, 100 mg/d Nonrandomized intervention: nonresponsive patients' daily dose increased to 300 mg	Aspirin nonresponder if PFA-100 closure time was ≤165 s	Nonresponders, 38.5%; of these, 16% remained nonresponsive despite increase to 300 mg/d	Small sample size; 5 patients excluded from original 31 patients recruited (1 lost to follow-up, 1 with von Willebrand disease, 3 taking NSAIDs)
Cross-sectional prevalence	Aspirin nonresponder if typical aggregation curves above final concentration of inducers were as follows: ADP >5 μmol, epinephrine >5 μmol, arachidonic acid >250 μmol, and collagen >2 μg/mL	Nonresponders, 34%	11% deemed nonadherent on the basis of testing urine for salicylate metabolites on admission

by Roller and associates (51) found that the response to aspirin could be improved by increasing the dosage from 100 mg/d to 300 mg/d in one fifth of patients with biochemical aspirin resistance. Tarjan and colleagues (12) found that 11% of patients with biochemical aspirin resistance were not adherent, based on baseline assessment of urinary salicylates. The study by Helgason and coworkers (50) suggests that biochemical aspirin resistance is not a static phenomenon. The prevalence of biochemical aspirin resistance increased over time from stroke: Thirty percent of the 75% of patients who demonstrated complete inhibition of platelet aggregation at the baseline assessment did not maintain the effect. The reported prevalence of biochemical aspirin resistance was 8.1%. Because these results were not stable over time, it is

Table 4. **Studies Investigating Biochemical Aspirin Resistance and Clinical Outcomes***

Study, Year (Reference)	Sample Size, *n*	Description	Intervention	Men/Women, *n/n*	Mean Age, *y*
Grundmann et al., 2003 (52)	53	Symptomatic patients: recurrent stroke/TIA; 100 mg of aspirin > 5 mo Asymptomatic patients: no recurrent stroke/TIA in preceding 24 months; receiving long-term aspirin therapy	–	39/14	67.5
Eikelboom et al., 2002 (38)	976	Case-patients: treated with aspirin and had MI, stroke, or cardiovascular death during 5 y of follow-up Controls: age- and sex-matched; were not experiencing an event End point: composite of MI, stroke, and death from vascular disease	–	23%/77%	67.3
Andersen et al., 2002 (53)	129	Post-MI patients Mean follow-up was 4 y End points were nonfatal MI or thromboembolic stroke, revascularization	Random assignment to receive aspirin, 160 mg/d; aspirin, 75 mg/d, plus warfarin; or warfarin alone	76.5%/23.5%	Aspirin group: 65.8‡ Aspirin plus warfarin group: 67.3‡
Grotemeyer et al., 1993 (54)	180	Stroke in internal carotid territory (CT scan); followed for 24 mo End points were stroke, MI, or vascular death	500 mg of aspirin 3 times/d	106/74	58
Mueller et al., 1997 (55)	100	Patients with intermittent claudication after elective angioplasty in iliac–femoral arteries; followed for 18 mo End point: reocclusion at the site of angioplasty, detected by clinical assessment, Doppler, and angiography	Aspirin, 100 mg/d	70/30	62.5
Gum et al., 2003 (56)	326	Cardiac patients taking aspirin who had not experienced a cardiac event before enrollment followed for a mean of 679 d End points: composite of death (all causes), MI, and cerebrovascular accident	Aspirin, 325 mg/d, for ≥7 d; no other antiplatelet agents	253/73	60.5

* ADP = adenosine diphosphate; CT = computed tomography; HDL = high-density lipoprotein; HOPE = Heart Outcomes Prevention Evaluation; MI = myocardial infarction; PFA-100 = Platelet Function Analysis-100; PRI = Platelet Reactivity Index; TIA = transient ischemic attack; WARIS II = Warfarin–Aspirin Reinfarction Study.
† Dade Behring, Leiderbach, Germany.
‡ Median age.

possible that biochemical aspirin resistance could be caused by vascular disease. However, no clear mechanism has been proposed for this effect, which could also be related to other factors, such as adherence.

Does Biochemical Aspirin Resistance Matter Clinically?

We identified 6 studies that investigated biochemical aspirin resistance and its association with clinical outcomes (38, 52–56) (**Table 4**). The data from these studies suggest that biochemical aspirin resistance increases the risk for vascular events. The study by Grundmann and colleagues (52) reported that 35% of patients with recurrent strokes had evidence of biochemical aspirin resistance, compared with 0% of patients without recurrent strokes. Eikelboom and coworkers (38) found that patients in the highest quartile of urinary thromboxane B_2 excretion had a relative risk of 3.5 (95% CI, 1.7 to 7.4) for cardiovascular death com-

Table 4—**Continued**

Design	Study Labels and Definition of Biochemical Aspirin Resistance	Main Results	Comments
Cross-sectional	Aspirin nonresponder if PFA-100† closure times were within normal range (74–165 s)	Nonresponders: 35% of symptomatic patients, 0% of asymptomatic patients	Sample size and designation of disease-free period were arbitrary Convenience sample Unable to assess whether observed results were the cause or effect of stroke event Adherence was not assessed
Nested case–control in HOPE trial Urine sample from baseline assessment	Relative aspirin response was determined by using quartiles of urinary 11-dehydrothromboxane B_2 (indicating failure of suppression of thromboxane synthesis by aspirin)	Odds ratios were 1.8, 1.2, and 3.5 for composite outcome, MI, and cardiovascular death, respectively (upper vs. lower quartile)	Subgroup analysis Difference in distribution of confounders Low power to demonstrate effect for stroke incidence Single assessment of aspirin resistance may not be stable over time Adherence was not assessed
Retrospective cohort Subset of patients from WARIS II trial	Aspirin nonresponders if PFA-100 closure time was <95th percentile of normal Supporting assays were urinary thromboxane B_2 (not specified) and soluble P-selectin levels (not specified)	Aspirin nonresponders: aspirin alone group, 35%; aspirin plus warfarin group, 40% No statistically significant difference in outcomes between responders and nonresponders	Subgroup analysis Dead patients selected out by study design Small number of events Adherence was not assessed
Prospective cohort	Aspirin response based on PRI measured 12 h after oral intake of 500 mg of aspirin; responders, PRI ≥ 1.25; secondary nonresponders, PRI > 1.25	Major end points: aspirin responders, 4.4%; secondary aspirin nonresponders, 40% Relative risk, 9.1	Very high aspirin maintenance dose Arbitrary assignment of time to assess aspirin response 6 patients lost to follow-up 36 patients discontinued treatment because of side effects (20%) Adherence was not assessed
Prospective cohort	Aspirin response based on corrected whole-blood aggregometry response to arachidonic acid, ADP, and collagen: group A, expected effect; group B, no effect; group C, unexpected effect	Reocclusion in 8% of patients: men only in groups B and C, no re-occlusions in women or in group A	Only 100 of the 145 originally recruited were analyzed (no reasons given for exclusion) Confounding variables in men, high levels of smoking, lower levels of HDL cholesterol (no female patients were smokers) Adherence was not assessed
Prospective cohort	Aspirin resistance: mean aggregation ≥70% with ADP and ≥20% with arachidonic acid	Aspirin resistance at baseline, 5.2% Hazard ratio, 4.1 for composite outcome in aspirin-resistant vs. aspirin-sensitive patients	11 patients lost to follow up (3.1%, 5.9% in aspirin-resistant group) Single assessment of aspirin resistance may not be stable over time Small total number of events Adherence was not assessed

pared with those in the lowest quartile. Andersen and associates (53) noted a trend of increased vascular events in patients with biochemical aspirin resistance, although the results were not statistically significant. Grotemeyer and colleagues (54) reported that vascular events occurred in 40% of patients with biochemical aspirin resistance compared with 4.4% of aspirin-sensitive patients (relative risk, 9.1). Mueller and coworkers (55) reported that 8% of patients experienced reocclusion after percutaneous angioplasty for intermittent claudication. Of these 8%, all were men who exhibited biochemical aspirin resistance. The study by Gum and associates (56) showed a hazard ratio of 4.1 (CI, 1.4 to 12.1) for serious vascular events in patients with biochemical aspirin resistance.

The findings from these studies should be treated with caution (**Table 4**). Grundmann and colleagues (52) used a cross-sectional design with a convenience sample of only 53 patients and arbitrary definitions of disease-free periods.

Thus, it is impossible to determine whether the observed biochemical aspirin resistance was the cause or the effect. The studies by Eikelboom and coworkers (38) and Andersen and associates (53) were essentially subgroup analyses from randomized trials designed for other purposes (57, 58). The study by Grotemeyer and colleagues (54) used a very high dose of aspirin (1500 mg/d). Not surprisingly, 20% of the sample stopped treatment because of side effects, and these patients were not followed or appropriately included in the results. The results of the study by Mueller and coworkers (55) are potentially confounded by variables such as sex and smoking, which the authors did not include in their analysis.

No study assessed adherence to treatment. Most included only a single assessment of biochemical aspirin resistance, making it difficult to assess stability over time. Most used composite primary end points, limiting the power of the studies to show associations with individual outcomes. For example, the study by Eikelboom and coworkers (38) reported an overall increased risk for the composite outcome measure but did not show an increased risk for stroke alone; the authors attributed this to the low number of stroke events in their sample. Similarly, in other studies, the number of vascular events was low compared with the prevalence of biochemical aspirin resistance. This suggests that aspirin resistance may not necessarily be causally associated with clinical outcomes, at least in the shorter term, or may be best seen as a continuous rather than a categorical phenomenon. However, conclusions cannot be drawn when there is no standardized definition of or quantitative test for biochemical aspirin resistance and when the reported prevalence varies so widely, suggesting heterogeneity in the test results, the samples, or both.

What Genetic Factors Are Involved in Aspirin Resistance?

Several single nucleotide polymorphisms have been linked to changes in platelet function, thrombosis, and increased risk for coronary heart disease (59–64). These include polymorphism PLA1/A2 of the gene encoding glycoprotein IIIa, a relatively common variant in white persons. A recent small study has suggested that a polymorphism in the COX-1 gene is associated with increased sensitivity to aspirin (65). More research is needed to confirm these associations, to establish the prevalence of these polymorphisms in relevant populations, and to elucidate the underlying functional mechanisms.

Conclusions and Implications

There are many reasons why aspirin may not prevent recurrent vascular events, including nonadherence, variable response to different doses, comorbid conditions, and drug interactions. The evidence presented in this review suggests that some patients exhibit persistent platelet activation, based on a range of measures of platelet function, despite being prescribed aspirin in therapeutic doses (biochemical aspirin resistance). This in turn may increase risk for recurrent vascular events.

Research in this area is currently hampered by the lack of a standardized definition of aspirin resistance. We have proposed a definition that is based on tests of platelet activation. This will enable reliable descriptive epidemiology, including changes in measures of biochemical aspirin resistance over time in different patient groups with both acute and chronic events. Future analytic epidemiologic studies investigating the association of biochemical aspirin resistance with clinical events must account quantitatively for potential confounders (such as age, sex, ethnicity, and clinical conditions) as well as for hematologic and biochemical factors (such as hyperlipidemia, platelet count, and hemoglobin level) and nonadherence. A key question for future work is to compare the extent to which different measures of platelet function, either alone or in combination, independently predict cardiovascular events in patients prescribed defined therapeutic doses of aspirin. Only once the definition, measurement, and epidemiology of aspirin resistance are clarified can studies usefully begin to assess the clinical utility (if any) of testing for aspirin resistance to inform cost-effective prescribing decisions for prevention of cardiovascular disease.

Testing for biochemical aspirin resistance cannot be recommended as a diagnostic strategy because of the uncertainty about its existence, measurement, and interpretation. We do not know the extent to which biochemical aspirin resistance translates into clinical events or what to do about it when it is found. We can only speculate that if aspirin resistance could be reliably identified by using tests of platelet function (or, in the future, genetic tests), patients might benefit from alternative or additional antiplatelet drugs.

Effective alternatives to aspirin, including clopidogrel and ticlopidine, act by blocking adenosine diphosphate–dependent platelet activation (8). Randomized trials and meta-analyses have shown that clopidogrel and ticlopidine can reduce the risk for serious vascular events by an additional 10% and 12%, respectively, compared with aspirin alone in patients with a history of myocardial infarction, stroke, or peripheral vascular disease (2, 66, 67). However, these newer drugs have potentially serious adverse effects and are also associated with treatment failure (68). No current evidence shows that patients with biochemical aspirin resistance would respond better to alternative antiplatelet treatment regimens. Identifying such patients directly may be less cost-effective than prescribing aspirin to everyone at risk and accepting some treatment failures. We do not want to risk depriving some patients of a treatment that may benefit them, even though the effect may be small.

Despite treatment failures, aspirin remains the single

most cost-effective drug for the secondary prevention of atherothrombotic disease. To optimize its clinical effectiveness, clinicians should be aware of the potential causes of aspirin treatment failure, prescribe aspirin in appropriate doses, and encourage patients to take aspirin, stop smoking, and avoid regular use of NSAIDs.

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Potential Financial Conflicts of Interest: None disclosed.

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Appendix: MEDLINE Search Terms

Group 1: Aspirin

Aspirin
Acetylsalicylic acid
Antiplatelet
Aspirin resistance
*Aspirin resp**
*Aspirin non(-)resp**
Cyclo(-)oxygenase
COX
Polymorphisms

Group 2: Platelets and Platelet Function Testing

Platelet function
Platelet activation
Adhesion molecules
PFA(0-0)100
Flow cytometry
Aggregometry
Polymorphisms

Group 3: Vascular Disease

Thrombosis
Atherosclerosis
Unstable angina
Peripheral vascular disease
Myocardial infarction
Stroke

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