STATE-OF-THE-ART PAPER

The Role of Aspirin in Cardiovascular Prevention

Implications of Aspirin Resistance

Armen Yuri Gasparyan, MD, PHD, Timothy Watson, MRCP, Gregory Y. H. Lip, MD, FRCP

Birmingham, United Kingdom

Aspirin is well recognized as an effective antiplatelet drug for secondary prevention in subjects at high risk of cardiovascular events. However, most patients receiving long-term aspirin therapy still remain at substantial risk of thrombotic events due to insufficient inhibition of platelets, specifically via the thromboxane A2 pathway. Although the exact prevalence is unknown, estimates suggest that between 5.5% and 60% of patients using this drug may exhibit a degree of "aspirin resistance," depending upon the definition used and parameters measured. To date, only a limited number of clinical studies have convincingly investigated the importance of aspirin resistance. Of these, few are of a sufficient scale, well designed, and prospective, with aspirin used at standard doses. Also, most studies do not sufficiently address the issue of noncompliance to aspirin as a frequent, yet easily preventable cause of resistance to this antiplatelet drug. This review article provides a comprehensive overview of aspirin resistance, discussing its definition, prevalence, diagnosis, and therapeutic approaches. Moreover, the clinical implications of aspirin resistance are explored in various cardiovascular disease states, including diabetes mellitus, hypertension, heart failure, and other similar disorders where platelet reactivity is enhanced.   (J Am Coll Cardiol 2008;51:1829–43) © 2008 by the American College of Cardiology Foundation

The fascinating history of aspirin-like remedies traces back to antiquity. The Assyrians and the Egyptians were well aware of the analgesic effects of a decoction of myrtle or willow leaves for joint pain (1). Since the times of Hippocrates, Celsus, Pliny the Elder, Dioscorides, and Galen, remedies made from willow bark were used as antipyretic and antirheumatic therapies (2). In 1838, the Italian chemist, Rafaelle Piria discovered the active ingredient in willow bark—salicylic acid (3). However, it was not until some 60 years later when in 1897, Felix Hoffman, who worked for the Bayer pharmaceutical company in Germany, synthesized the acetylated form of salicylic acid, which was named "aspirin," and became the most widely used drug of all time (4). Aspirin differed markedly from previous forms of salicylic acid, with improved tolerability and reduced gastrointestinal side effects, and remains widely used as both an anti-inflammatory and antirheumatic drug.

A new era of aspirin usage began in 1971 when Sir John Vane demonstrated that the main mechanism of action was the inhibition of prostaglandin synthesis (5). The critical importance of this discovery was underlined in 1982 when Vane was awarded the Nobel Prize for Medicine (1). Subsequent clinical and experimental studies have demonstrated that low-dose aspirin irreversibly acetylates a serine residue at position 530 on the cyclooxygenase-1 (COX-1)

enzyme in platelets, thus blocking synthesis of prostaglandin G2/H2 (Fig. 1). This reaction is the first in a series that allows transformation of arachidonic acid into the potent platelet agonist, thromboxane A_2, thereby leading to the beneficial clinical effect of aspirin in patients with coronary artery disease and stroke (6–9).

The importance of aspirin therapy in this setting is sealed by a large meta-analysis from the Antithrombotic Trialists' Collaboration (287 randomized trials of antiplatelet therapy of patients at high risk of occlusive vascular events), which demonstrated a 32% reduction of nonfatal myocardial infarction (MI), nonfatal stroke, and vascular death in patients treated with 75 to 150 mg aspirin daily (10). Despite such strong evidence, it is increasingly appreciated that some patients still fail to respond adequately to aspirin therapy. This is usually seen by the occurrence of further clinical (thrombotic) events despite aspirin treatment in "usual" prophylactic dosages. Such "aspirin resistance" has also been defined in the laboratory setting by the failure of aspirin to fully inhibit platelet aggregation.

This review provides an overview on the importance of aspirin therapy in primary and secondary prevention of vascular disease and explores the purported role of aspirin resistance and the implications of this for everyday clinical practice.

Search Criteria

We performed a comprehensive search of electronic bibliographic databases (e.g., MEDLINE, EMBASE, DARE)

for English-language sources using key words related to aspirin use in randomized clinical trials. In addition, several relevant full-text review articles were identified from ProQuest Medical Library. We hand searched bibliographies for important articles and reviewed abstracts from major conferences. We also searched the open databases of the Cochrane Collaboration and the Clinical Trials database for other relevant studies.

Aspirin in the Prevention of Vascular Disease

The role of aspirin in primary prevention of vascular disease has been investigated in 6 randomized controlled trials (11–16) and in several meta-analyses (17,18), as summarized in Table 1. Although 4 of these trials clearly indicate the importance of aspirin for primary prevention (11,13–15), a meta-analysis of all trials (n = 95,456 participants, 54% women) for an average follow-up period of 6.4 years surprisingly did not find a significant reduction in the risk of stroke, cardiovascular, or all-cause mortality (17,18), presumably because the majority of patients included were, in fact, at low risk for vascular disease.

Among the randomized trials, the Physicians' Health study (11) merits special attention. This prospective study not only demonstrated the important efficacy of aspirin in reducing vascular events, but also explored the link between chronic inflammation and atherothrombosis. The investigators found that levels of C-reactive protein (CRP) (a marker of inflammation) were predictive of future MI and stroke, and that the greatest and most statistically significant reduction in risk of a first MI associated with aspirin use was observed among men with baseline CRP levels in the highest quartile.

In contrast to the conflicting data for primary prevention, the majority of studies of aspirin for secondary prevention have clearly shown the positive efficacy of this drug. One important example is the ISIS-2 (Second International Study of Infarct Survival) study, where the benefits of early administration of 162.5 mg of aspirin after acute MI were clear. After 35 days follow-up from the index event, a 9.4% death rate was observed in the aspirin group compared with 12.0% in the placebo arm (risk ratio 0.78; 95% confidence interval [CI] 0.71 to 0.85; p < 0.0001) (19).

The inequity in efficacy for aspirin between primary and secondary prevention trials and the apparent failure of aspirin to suppress further events in some patients raises important questions. 1) In which patient group(s) does aspirin therapy have the greatest efficacy? 2) Which factors are implicated in aspirin treatment failure (aspirin resistance)? 3) Are laboratory assays available to reliably identify patients who will not sufficiently respond to aspirin? 4) Is combined antiplatelet therapy more advantageous than aspirin alone?

"Aspirin Resistance" and Its Implications

There has been a staggering increase in the volume of literature addressing the issue of so-called "aspirin resistance" in recent years. Terminology and definitions vary widely, some based on clinical observations and other based upon measurement of various laboratory parameters, defined from both in vivo and in vitro studies.

The term "aspirin resistance" has various synonyms, including "aspirin nonresponsiveness," "aspirin treatment failure," and "inadequate aspirin efficacy," but has also been sometimes defined as "biochemical or laboratory aspirin resistance" (20,21). Estimates of the prevalence of aspirin resistance vary widely (5.5% to 60%), reflecting the diversity of various laboratory assays and confounding from the broad range of disease states investigated (22–27).

To the practicing clinician, a definition and diagnosis of aspirin resistance based on clinical assessment of treatment outcomes (i.e., adverse vascular events) would seem preferable. Nevertheless, the major limitation to this approach is that it relies upon a retrospective review of clinical events. For this reason, most researchers are increasingly advocating the application of various laboratory tests.
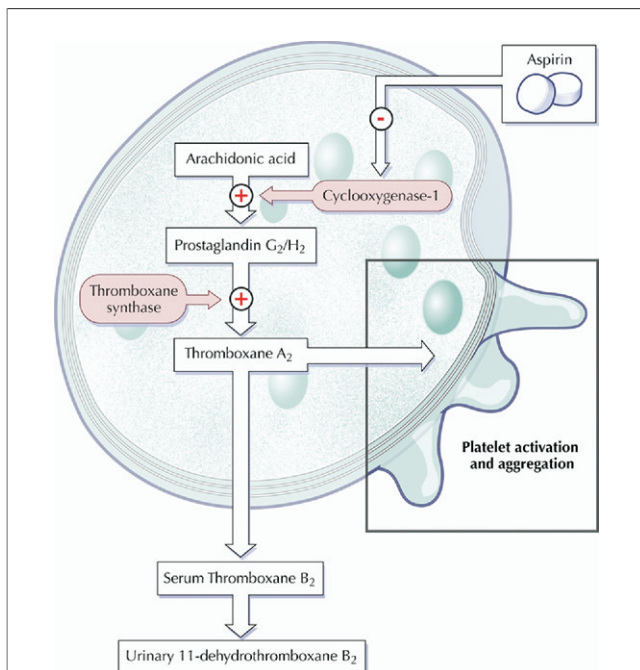
Figure 1   **Inhibition of Platelet Thromboxane A2 Pathways by Low-Dose Aspirin**

Figure illustration by Rob Flewell.

Table 1	Randomized Controlled Trials on Aspirin in Primary Prevention of CV Events		
Study	**Study Design**	**Benefits of Aspirin Use With Regard to End Points**	**Comments**
Physician's health study (11)	1,086 apparently healthy male physicians, age 40 to 84 yrs, were assigned to 325 mg of aspirin or placebo on alternate days.	44% reduction in the risk of first MI in the aspirin group; the greatest effect of aspirin was seen in those with the highest baseline CRP.	Data exclusively refer to primary prevention in men. There is no benefit of aspirin use in subjects with lower baseline CRP.
British doctors' trial (12)	A 6-yr randomized trial among 5,139 apparently healthy male physicians taking 500 mg aspirin daily. End point: incidence of and mortality from stroke, MI, or other vascular conditions.	Aspirin did not appear to have a beneficial impact on the death or incidence of MI and stroke.	Underpowered study, terminated due to ethical issues.
Thrombosis prevention trial (13)	5,499 men age 45 to 69 yrs at high risk of ischemic heart disease assigned to warfarin plus aspirin 75 mg, warfarin plus placebo aspirin, aspirin 75 mg plus placebo warfarin, or placebo warfarin plus placebo aspirin. Primary end point was all IHD defined as the sum of fatal and nonfatal events (coronary death and fatal and nonfatal MI).	Aspirin offered a 32% reduction in nonfatal events.	Data exclusively refer to primary prevention in men. Aspirin is not as effective in preventing fatal events as nonfatal. Combined treatment with warfarin and aspirin confer greater benefit, although potential hemorrhagic complications of the combined regimen should be considered.
Hypertension optimal treatment trial (14)	9,399 patients with hypertension (both men and women) were randomly assigned to aspirin 75 mg daily and 9,391 patients to placebo. The trial was designed to assess the efficacy of adding aspirin to antihypertensive therapy for primary prevention. End points were major CV events (nonfatal MI, nonfatal stroke, and CV death).	Acetylsalicylic acid significantly reduced major CV events by 15% (p = 0.03) and MI by 36% (p = 0.002).	No difference in stroke incidence between patients randomized to acetylsalicylic acid or placebo. Fatal bleeding did not differ between groups. However, nonfatal major and minor bleedings were 1.8 times more frequent among those treated with aspirin.
Primary prevention project (15)	4,495 patients (mean age 64.4 yrs) with at least 1 major CV risk factor were randomly allocated to receive 1 tablet of 100 mg enteric-coated aspirin daily or placebo. Mean follow-up period was 3.6 yrs. The end point was the cumulative rate of CV death, nonfatal MI, and nonfatal stroke.	Aspirin use significantly reduced CV death rate (from 1.4% to 0.8%; relative risk 0.56, 95% CI 0.31 to 0.99) and CV events (from 8.2% to 6.3%; relative risk 0.77, 95% CI 0.62 to 0.95).	Severe bleeding complications were 3 times more frequent in the aspirin group, but the benefit of aspirin therapy significantly outweighed this complication.
Women's health study (16)	39,876 healthy women age above 45 yrs randomized to receive 100 mg aspirin on alternate days or placebo and monitored for 10 years for a first major CV event.	No significant effect of aspirin on the risk of all MI or death from CV causes. Women above 65 yrs of age benefited most from aspirin therapy. In this subgroup, the risk of major CV events, ischemic stroke, and MI was significantly reduced.	First large trial assessing aspirin efficacy in women. Gastrointestinal bleeding requiring transfusion was more frequent in the aspirin group than in the placebo group.

CI = confidence interval; CRP = C-reactive protein; CV = cardiovascular; IHD = ischemic heart disease; MI = myocardial infarction.

Laboratory Assessment of Aspirin Resistance

Light or optical aggregometry, which is generally considered the "gold standard" of platelet function assessment, is the most widely used technique for defining aspirin resistance. The technique is based on the increase in light transmission through platelet-rich plasma as a result of aggregation of platelets and formation of clumps in response to various agonists. Although numerous agonists (e.g., arachidonic acid, adenosine diphosphate [ADP], epinephrine, collagen, thrombin) can be used, the most specific for detection of aspirin resistance appears to be arachidonic acid, which induces platelet aggregation through the thromboxane A_2 pathway. Using this method, the most widely accepted definition of aspirin resistance is $\geq$20% platelet aggregation with 1 mg/ml arachidonic acid and $\geq$70% aggregation with 10 μmol/l ADP (28).

Optical aggregometry generally correlates well with clinical outcomes (e.g., death, cardiovascular, and cerebrovascular events), but there is often a lack of agreement with other measures of platelet function; for example, the Platelet Function Analyzer-100 (PFA-100) (Dade Behring, Leiderbach, Germany) (29). Besides, optical aggregometry has several other limitations, including the necessity to run the assay rapidly (usually within 1 to 3 h of blood collection) and

a dependence upon operator and interpreter experience. In addition, difficulties in reproducing and comparing results obtained in the same and different laboratories are frequently reported (30). As an ex vivo test, optical aggregometry neglects to assess several important factors, such as the interactions between platelets, erythrocytes, neutrophils, and monocytes and also the high shear stress induced by vascular injury.

To overcome some of these limitations, the PFA-100 device (Dade Behring) was developed (31). This allows measurement of the closure time of a microscopic aperture in a membrane/cartridge coated with collagen/epinephrine or collagen/ADP using whole blood anticoagulated with sodium citrate. The system simulates injured artery, high shear stress conditions, and operates in the presence of erythrocytes. Thus, platelet function is assessed by the time taken to form a platelet plug occluding the aperture. Using this test, aspirin resistance is generally defined as a closure time for a collagen/epinephrine cartridge of <164 s despite regular aspirin intake.

What are the advantages of the PFA-100? The device is simple to use and requires only a small volume of blood (800 μl). The test is also quick and has good sensitivity and reproducibility. Nonetheless, there are several limitations, including dependence upon plasma von Willebrand factor and hematocrit, the necessity to test blood samples within 3 to 4 h after blood collection, and expense: all factors that restrict the widespread and practical applicability of this test.

Another point-of-care, easy-to-use, and rapid test for defining aspirin resistance is the VerifyNow-Aspirin (the Ultegra Rapid Platelet Function Assay, Accumetrics Inc., San Diego, California), which is a turbidimetric-based optical detection system for measuring platelet-induced aggregation (32). The VerifyNow-Aspirin assay correlates well with optical aggregometry, and uses an aspirin cartridge with fibrinogen-coated beads and a platelet activator (metallic cations, propyl gallate, arachidonic acid) to stimulate the COX-1 pathway and to measure aspirin reaction units (32). The most important limitation of this test relates to its diagnostic criteria, as these were set in comparison with optical aggregation in response to adrenaline, after only a single 325-mg dose of aspirin.

Other laboratory measures of aspirin resistance are also available. These include in vivo measurement of thromboxane A_2 pathway end products, such as serum thromboxane B2 (33) and urinary 11-dehydrothromboxane B2 (34). Neither test specifically reflects platelet activity, but instead may reflect the contribution of monocytes/macrophages to thromboxane A_2 synthesis and also the COX-2 linked pathway of arachidonic acid, which is only partially blocked by aspirin. In addition, ex vivo platelet activation during blood sample collection, storage, and processing may also interfere with the results of these tests. Urinary 11-dehydrothromboxane B2 concentrations are also highly dependent on renal production of this metabolite, further complicating interpretation of this test. Nevertheless, as a

relatively straightforward and inexpensive in vivo test that can be performed on stored samples, the measurement of urinary 11-dehydrothromboxane B2 is frequently used in large trials on aspirin resistance (34,35).

Measurement of platelet membrane-bound P-selectin expression by flow cytometry and the level of soluble P-selectin in plasma by enzyme-linked immunoadsorbent assay has also been employed in some studies of platelet activation in disease states (22,36). However, the fact that this molecule may be expressed on cells other than platelets has resulted in conflicting data when this marker is used to assess aspirin efficacy (37,38).

How Prevalent Is Aspirin Resistance?

Many of the tests proposed to define the prevalence of aspirin resistance lack sensitivity, specificity, and reproducibility. Indeed, a recent systematic review by Hovens et al. (39) reiterated this point, emphasizing that the prevalence of aspirin resistance as defined by each test varied widely: the lowest figure seen with optical aggregometry using arachidonic acid (6%; 95% CI 0% to 12%) and the highest prevalence with the PFA-100 analyzer (26%; 95% CI 21% to 31%).

Given the complexity of pathways of platelet activation and poor correlation between assays, some have advocated using a combination of criteria for aspirin resistance based on multiple parameters. In a recent study by Sane et al. (40), for example, aspirin resistance was considered to be present if 4 of the following 5 criteria were met: collagen-induced aggregation >70%; ADP-induced aggregation >60%; whole-blood aggregation >18 Ohm; expression of glycoprotein IIa/IIIa >220 log mean fluorescence units; or P-selectin membrane receptor positivity >8%. Even with this (very) strict definition, Sane et al. (40) reported that the incidence of aspirin resistance in heart failure patients was shown to be 55%. In contrast, another study screening for aspirin resistance in patients receiving low-dose aspirin after transient ischemic attack or ischemic stroke found the prevalence of the aspirin resistance to be 17% using the VerifyNow-Aspirin assay, 22% by the PFA-100, 5% by optical aggregometry, and only 2% by the combination of these tests (31).

Prospective Studies

Although there are numerous studies of aspirin resistance, only 4 studies to date are of sufficiently large scale and well-designed, using doses of aspirin frequently prescribed in clinical practice (34,41–43) (Table 2). In each, the sample size was >100, and follow-up was for at least 1 year. Such study design is important when assessing the relative prognostic value of each test used to define aspirin resistance.

In these prospective studies, the lowest prevalence of aspirin resistance was defined using aggregometry (between 5.2% and 8%) (41,42), while the PFA-100 analyzer yielded the highest frequency of aspirin resistance (22.2%) (43). The

Table 2	Prospective Follow-Up Studies on Aspirin Resistance in Patients Treated With Low-Dose Aspirin		
Reference	**Patients**	**Study Description**	**Results**
Eikelboom et al. (34)	976 patients at high risk of cardiovascular events treated with aspirin (75 to 325 mg/day). Aspirin resistance was defined at baseline. 488 patients had MI, stroke, or cardiovascular death during a follow-up period (cases) and 488 patients had no event (age- and gender-matched control subjects). Mean age in the case group, 67.3 yrs.	Patients enrolled in the HOPE trial were followed-up over 5 yrs. Nested case-control design was used and baseline urinary 11-dehydrothromboxane B2 levels were measured. Aspirin resistance was defined as elevated urinary 11-dehydrothromboxane B2.	Composite outcome of MI, stroke, or cardiovascular death increased with each increasing quartile of 11-dehydrothromboxane B2. Patients in the upper quartile had a 2 times greater risk of MI (OR 2.0; 95% CI 1.2 to 3.4; p = 0.006) and a 3.5 times greater risk of cardiovascular death (OR 3.5; 95% CI 1.7 to 7.4; p < 0.001) than those in the lower quartile.
Gum et al. (41)	326 stable cardiovascular patients taking aspirin 325 mg/day for at least 7 days. Mean age 60.5 yrs.	Mean follow-up period was 679 ± 185 days. Aspirin resistance was defined by optical aggregometry as a mean aggregation of ≥70% with 10 μM ADP and ≥20% with 0.5 mg/ml arachidonic acid.	5.2% of patients were aspirin resistant at baseline and had increased risk of death, MI, or cerebrovascular accidents compared with patients who were aspirin sensitive (24% vs. 10%, hazard ratio 3.12, 95% CI 1.10 to 8.90; p = 0.03).
Mueller et al. (42)	100 patients with intermittent claudication after elective percutaneous balloon angioplasty in iliac-femoral arteries, treated with 100 mg/day aspirin. Mean age 62.5 yrs.	Aspirin response was monitored over a period of 12 months by corrected whole blood aggregometry response to arachidonic acid, ADP, and collagen.	Reocclusion at the site of angioplasty occurred in 8% of patients (in male patients in whom aggregometry failed to prove an inhibition of aggregation upon ADP and collagen).
Pamukcu et al. (43)	234 patients with stable CAD treated with 100 to 300 mg/day aspirin. Mean age 57 yrs.	The mean follow-up period was 20.6 ± 6.9 months. Aspirin resistance was defined by the Platelet Function Analyzer-100 as having a normal closure time of collagen/ epinephrine cartridge (<186 s).	The baseline prevalence of aspirin resistance was 22.2%. In the follow-up period, major adverse cardiac events occurred in 8 aspirin-resistant (15.4%) and 20 aspirin-sensitive (11.0%) patients (p = 0.269). No relation was found between aspirin resistance and age, gender, hypertension, diabetes, or hyperlipidemia.

ADP = adenosine diphosphate; CAD = coronary artery disease; HOPE = Heart Outcomes Prevention Evaluation; OR = odds ratio; other abbreviations as in Table 1.

number of major adverse events during the follow-up period was relatively low in each study, and, thus, it became inappropriate to draw firm conclusions on the significance of aspirin resistance from these studies. Furthermore, each was limited by failure to correct for confounding factors (particularly age and gender) and the failure to assess adherence to aspirin by measurement of serum salicylate levels. Certainly, it is possible and plausible that hypertension, diabetes, peripheral vascular disease, smoking, and various other confounding factors may contribute to aspirin resistance, while also enhancing vascular risk (and thereby often necessitating aspirin therapy) in their own right. Such potential confounders clearly need to be elucidated, as does the effect of race and gender on the efficacy of aspirin therapy.

Recently, researchers have even highlighted the dynamic nature of aspirin resistance, the extent of which may vary, as blood pressure and various biochemical markers do, throughout the day and with sickness and health (24,25,44). Consequently, the value of a single point estimate measure of aspirin resistance at baseline only is questionable, and certainly more advanced study designs are required.

Possible Causes of Aspirin Resistance

As the main antiplatelet mechanism of aspirin relates to irreversible inhibition of COX-1 enzyme in mature platelets, the possible causes of aspirin resistance might be divided into

2 main groups: those related to the COX-1 pathway of thromboxane A2 production and those unrelated (Table 3).

In a series of small studies, an interesting hypothesis of the PlA polymorphism (Leu33Pro, PlA1/A2) of the platelet membrane glycoprotein IIIa gene as the main genetic background of biological aspirin resistance has been suggested (45–47). Carriers of the PlA2 allele, particularly in the homozygous state, have been considered more resistant to the antiplatelet action of aspirin and, thus, may require treatment with alternative or additional agent(s).

Unfortunately, no prospective studies have investigated the prognostic significance of glycoprotein IIIa gene polymorphisms, and only conflicting data are available (48,49). Also, there is speculation that polymorphism of COX-1 gene, overexpression of COX-2 messenger ribonucleic acid on platelets, and endothelial cells and polymorphism of platelet glycoprotein Ia/IIa collagen-receptor gene might be equally plausible causes for aspirin resistance (50). Clearly, more research is required to address these factors.

Based on a number of large trials and meta-analyses (10), low doses of aspirin (75 to 150 mg/day) are comparatively safe and sufficient to inhibit platelet COX-1 and are as effective in preventing vascular events as higher aspirin doses (500 to 1,500 mg/day). In some patients, the failure to suppress platelet COX-1 may be due to an inadequate dosage and reduced bioavailability of aspirin. In some cases, this may well relate to poor patient adherence (compliance),

| Table 3	**Possible Causes of Aspirin Resistance**
COX-1–Related Causes	**COX-1–Nonrelated Causes**
Poor patient compliance	Up-regulation of COX-2 pathway of thromboxane A2 production by platelets, monocytes, macrophages and endothelial cells
Failure to prescribe aspirin properly (premature discontinuation of therapy)	Increased production of prostaglandin F2-like compounds by lipid peroxidation of arachidonic acid
Concurrent administration of nonsteroidal anti-inflammatory drugs competing with aspirin for binding with COX-1	Conditions associated with activation of platelets by collagen Ia/IIa receptors, von Willebrand factor, ADP receptors, thrombin, serotonin, catecholamines, and shear stress
Reduced absorption of active acetylsalicylic acid due to inadequately low dose of aspirin, intake of proton pump inhibitors, advanced age and weight	
Increased platelet turnover in response to stress conditions	
Polymorphisms of COX-1 gene	Polymorphisms of glycoprotein IIIa (PlA1/A2), glycoprotein Ia/IIa collagen receptor genes

ADP = adensine diphosphate; COX = cyclooxygenase.

concurrent administration of nonsteroidal anti-inflammatory drugs (e.g., ibuprofen, indomethacin) and COX-2 inhibitors (which may compete with aspirin for platelet COX-1), or even a reduced absorption (or increased metabolism) of aspirin (24,51,52). Such concerns have been highlighted in a recent meta-analysis of 6 studies focusing either on nonadherence or premature discontinuation of aspirin in over 50,000 patients at high risk of coronary artery disease, where a 3-fold increased risk of cardiac events (odds ratio 3.14; 95% CI 1.75 to 5.61; p = 0.0001) was related to nonadherence or the unjustified withdrawal of aspirin (53).

Nonetheless, poor compliance is not unique to aspirin and occurs to a certain extent with all prescribed medications. Various factors that increase nonadherence rates have been identified and include polypharmacy (4 or more drugs, including aspirin and coadministration of other nonsteroidal anti-inflammatory drugs), poor patient understanding of the benefits of antiplatelet therapy, and side effects (54). Obviously, to overcome nonadherence to aspirin, it is quite important to educate patients about the mechanism of action of this agent, as well as its difference from common cardiovascular drugs (e.g., angiotensin-converting enzyme [ACE] inhibitors, beta-blockers, calcium antagonists, antidiabetic drugs, and statins), which demonstrate their effect within relatively short periods of time, and in clinical practice, their effects can be easily quantified (e.g., blood pressure, heart rate, glucose, and lipid levels). To further explore the role of nonadherence and its relevance to the studies of aspirin resistance, Schwartz et al. (55) tested platelet function by arachidonic acid-induced light aggregometry in patients with a prior MI. Measurements were taken while patients were receiving their usual daily aspirin, after stopping aspirin for 7 days, and then 2 h after ingestion of aspirin, 325 mg; at the first time point, laboratory nonresponsiveness to aspirin was observed in 17 patients (9%), whereas at the third time point only in 1 patient (0.5%).

Age, weight, and intake of proton pump inhibitors may also reduce the bioavailability of low-dose aspirin, mainly due to increased inactivation of acetylsalicylic acid by gastrointestinal mucosal esterases and reduced absorption of active acetylsalicylic acid (24). Although low-dose aspirin may potentially be a cause of apparent aspirin resistance through reduced absorption, the use of higher doses of aspirin seems unjustifiable and is outweighed by an increased risk of gastrointestinal bleeding (56). However, in conditions accompanied by increased platelet turnover (e.g., acute coronary syndromes, coronary artery bypass grafting and other surgical procedures, acute or chronic infection, inflammation), a temporary increase of aspirin dose seems reasonable, albeit unproven. Under these circumstances, low-dose aspirin, given its short half-life (15 to 20 min), is unable to inhibit COX-1 in platelets rapidly released into the circulation (57–60). However, although COX-1-dependent mechanisms are suggested to be responsible for aspirin resistance in these conditions, it is more likely that more complex pathways and proinflammatory/thrombogenic molecules are also involved. Circumstantial evidence for this claim is available as aspirin resistance (as defined by PFA-100) is twice as common in acute coronary syndromes complicated by pneumonia compared with those cases without infectious complications (90% vs. 46%) (60). In addition, there appears to be an independent association between CRP and aspirin resistance in these patients.

Thus, in conditions that are associated with both infection and inflammation, nonplatelet sources of thromboxane A_2 production (e.g., monocytes, macrophages, endothelial cells) and up-regulation of the COX-2 enzyme coupled with increased levels of F2-isoprostanes may lead to uncontrolled thromboxane synthesis. Such COX-1-independent mechanisms are especially relevant to patients with diabetes mellitus (61–63), hyperlipidemia (64), smoking (65), and heart failure (66–68), all of which are associated with augmented lipid peroxidation of arachidonic acid and consequent overproduction of isoprostanes. Again, these issues
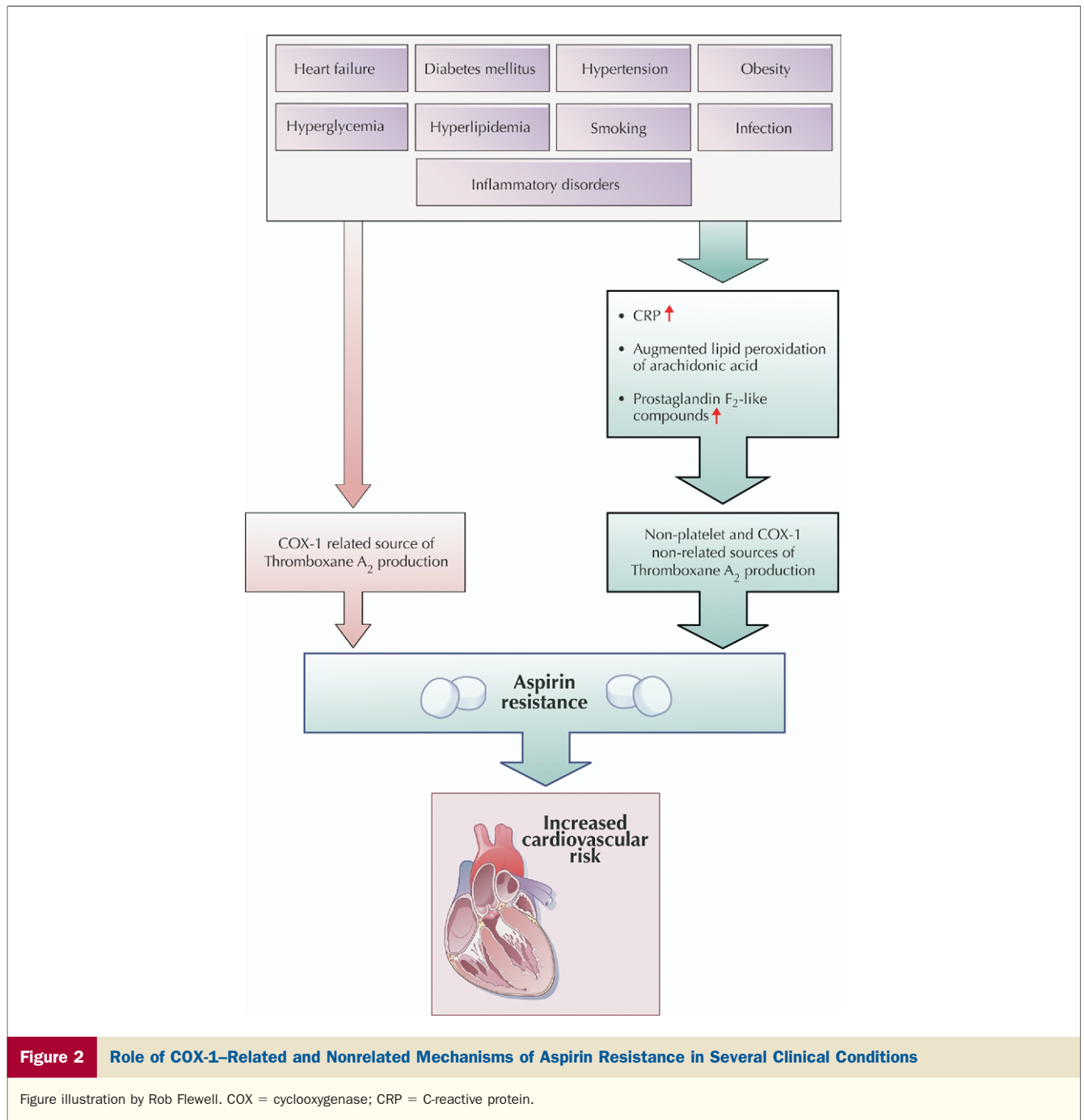
Figure 2   **Role of COX-1–Related and Nonrelated Mechanisms of Aspirin Resistance in Several Clinical Conditions**

Figure illustration by Rob Flewell. COX = cyclooxygenase; CRP = C-reactive protein.

have implications for defining aspirin resistance, as well as its assessment.

Studies defining the causes of aspirin resistance suggest that the mechanistic approach to this phenomenon have relied largely on COX-1 pathway studies, and the use of "more specific" laboratory tests employing arachidonic acid–induced platelet activation and aggregation is often far from being pathophysiologically justifiable, pragmatic, or practical (69,70). To predict the risk of atherothrombotic events in patients on aspirin, a comprehensive approach to measure residual platelet reactivity caused by the arachidonic acid

pathway (and perhaps, multiple pathways), which are "nonblocked" by aspirin, seems more important, albeit significantly less straightforward and poorly explored (71) (Fig. 2).

Aspirin Resistance in Cardiovascular Disorders

Heart failure. Many of the complications associated with heart failure are thrombus related. Given the high mortality and morbidity associated with heart failure, aspirin resistance may play a role. To date, only 1 study has found a high

prevalence of aspirin resistance in heart failure. In this study, Sane et al. (40) examined 88 patients with congestive heart failure treated with aspirin (325 mg/day) for more than 1 month and found aspirin resistance to be present in as much as 55% of patients.

Is this clinically significant? Indeed, there is conflicting evidence regarding the benefits of aspirin in reducing the high incidence of vascular events in patients with chronic heart failure (72), and aspirin may possibly attenuate the efficacy of ACE inhibitors in heart failure patients (73). In 1 large study of 24,012 patients age 65 years or older with heart failure secondary to coronary artery disease, those taking aspirin (54%) only had modestly lower risk of death (risk ratio 0.94; 95% CI 0.90 to 0.99) and were relatively free of a negative interaction with ACE inhibitors (74). Other observational studies (e.g., patients with ischemic cardiomyopathy, age over 75 years) found no difference in all-cause mortality and hospitalization within 1 year of index hospitalization regardless of aspirin usage (75).

To date, the efficacy of aspirin in heart failure has been assessed in 3 controlled prospective trials. In the WASH (Warfarin/Aspirin Study in Heart failure) trial, patients with heart failure were recruited and randomized to placebo, aspirin 300 mg/day, or warfarin. Within the follow-up period (27 ± 1 months), patients taking aspirin had more hospitalizations due to heart failure (p = 0.044). However, there was no difference in primary outcomes of the study (death, nonfatal MI, or stroke) between the 3 study arms (76). In a larger trial, the WATCH (Warfarin and Antiplatelet Therapy in Chronic Heart failure) trial, patients were randomized to aspirin (162 mg), clopidogrel, or warfarin (77). Unfortunately, this trial was underpowered and terminated prematurely due to poor patient recruitment. Again, there was no detectable difference in primary outcome between 3 arms, but hospitalization rate in the aspirin arm was significantly higher (22.2% vs. 16.1% and 18.3% for aspirin, warfarin, and clopidogrel, respectively; p = 0.01). Finally, the HELAS (Heart Failure Long-term Antithrombotic Study) was initially aimed at recruiting 6,000 patients with chronic heart failure of New York Heart Association functional class II to IV (78). Patients were randomized to aspirin 325 mg daily, warfarin, or placebo and followed for 2 years to determine the rate of thromboembolic, hemorrhagic, and lethal events. Again, this trial was terminated prematurely because of recruitment difficulties, and only 197 patients with left ventricular ejection fraction <35% were enrolled, with no significant difference shown in the incidence of MI, hospitalization, heart failure decompensation, death, and hemorrhage rate between the groups (79).

Such data have led to the conclusion that aspirin therapy may possibly attenuate the efficacy of ACE inhibitors and, therefore, explain the increased hospitalization rate in heart failure patients taking aspirin in these trials (73). Given the paucity of evidence for use of aspirin in heart failure and the apparent high rate of aspirin resistance, further prospective trials are required in this setting

(72). The WARCEF (Warfarin versus Aspirin in patients with reduced Cardiac Ejection Fraction) trial, a large multinational randomized trial with a target enrollment of 2,860 patients, is ongoing and will randomize patients with systolic heart failure to aspirin or warfarin (80).

Diabetes mellitus. As is the case with other diseases that contribute to cardiovascular risk, many advocate the use of aspirin in patients with diabetes mellitus, even in the absence of strong evidence from major prospective clinical trials. One prime example is a subgroup analysis of patients with type 2 diabetes mellitus from the PPP (Primary Prevention Project) trial, one-half of whom were taking aspirin (81). This drug failed to reduce global cardiovascular events in diabetic patients, but did appear to confer a significant reduction in stroke events.

Despite the lack of prospective studies to support the use of low-dose aspirin in diabetic patients, this agent is considered a cornerstone of primary and secondary prevention of thrombotic cardiovascular, cerebral, and peripheral arterial events in both type 1 and type 2 diabetes mellitus (82–85). Much of the evidence for this argument stems directly from the Antiplatelet Trialists' Collaboration meta-analysis (10), which found a significant reduction in ischemic vascular events by use of aspirin in a subgroup of patients with diabetes mellitus.

There are only limited direct data on the prevalence of aspirin resistance in diabetes mellitus. Given the complex pathophysiology of diabetes mellitus and the frequent association with other disorders (e.g., hyperlipidemia, hyperglycemia, hypertension, endothelial dysfunction, chronic inflammation, accelerated atherogenesis, hypercoagulable state, micro- and macro-vasculopathy, and so on) all of which may significantly up-regulate COX-1–independent pathways of platelet activation and aggregation, it is considered that the prevalence of aspirin resistance is likely to be substantial (86,87). In a cohort of 488 patients with aspirin resistance in the HOPE (Heart Outcomes Prevention Evaluation) trial, 32.6% had diabetes mellitus (34). In a group of type 2 diabetic patients treated with aspirin 100 mg daily, the prevalence of aspirin resistance was estimated at 21.5% using the PFA-100 analyzer with collagen/epinephrine cartridges (88). However, the authors did not find any association between aspirin resistance and cardiovascular events after 1-year follow-up, nor any association between aspirin resistance and confounding factors (hyperlipidemia, hyperglycemia, hypertension, obesity, or smoking). This study was small, and further prospective long-term studies are required to assess the real clinical significance of aspirin resistance in diabetes.

Hypertension. For secondary prevention, the benefit of antiplatelet therapy with aspirin in subjects with hypertension is well established and supported by strong trial data (89). For primary prevention, however, the evidence is less robust. In the large HOT (Hypertension Optimal Treatment) trial, the efficacy of aspirin in reducing major cardiovascular events (in particular, MI, not stroke) was evident, but aspirin increased the risk of major and minor nonfatal

bleedings, and there was no major effect on mortality (14). Perhaps this may, in part, relate to aspirin resistance, as a significant proportion of patients (45% to 63.5%) with this phenomenon do, in fact, have hypertension (34,45). Nonetheless, little is known about aspirin response and its prognostic value in patients with arterial hypertension.

As appears to be the case with heart failure and with diabetes mellitus, a number of factors may contribute to altered platelet reactivity and lead to relatively high frequency of aspirin resistance among subjects with hypertension. As already discussed, this presumably occurs predominantly through activation of COX-1–independent mechanisms. In the case of hypertension, this is likely not only related to altered production of thromboxane A2, but also, given the pleiotropic function of aspirin, may be related to the activation of nitric oxide (NO) synthase and an increase in NO production by platelets (90). The increased NO may then counteract various prothrombotic and hypertensive factors, and, thereby, may be implicated in the clinical efficacy of aspirin.

In a recent study, Feher et al. (91) investigated the presence of hypertension and aspirin resistance among patients with cardiovascular and cerebrovascular disease who were taking aspirin 100 to 325 mg daily. They found a significantly higher prevalence of hypertension among aspirin-sensitive patients compared with that seen in aspirin-resistant patients (80% vs. 62%; p < 0.05). However, there was also a significantly higher rate of beta-blocker and ACE inhibitor usage among aspirin-sensitive patients; these drugs may exert an additive antiplatelet action when combined with aspirin. Oddly, the use of statins was shown to be an independent predictor of aspirin resistance.

Rheumatic diseases. Autoimmune, inflammatory, and thrombotic reactions may be enhanced by various rheumatic diseases, and—in conjunction with classic cardiovascular risk factors—may accelerate the course of atherosclerosis, leading to premature manifestation(s) of cardiovascular disease (92–94). In this context, both the anti-inflammatory and the antiplatelet properties of aspirin may be crucial for primary and secondary prevention.

In a study of almost 9,000 cases of a first-time MI among patients registered on the British General Practice Research Database, the highest risk of MI was found in patients with rheumatoid arthritis or systemic lupus erythematosus (adjusted odds ratio 3.68; 95% CI 2.36 to 5.74) and in those following cessation of nonsteroidal anti-inflammatory drugs after long-term use (adjusted odds ratio 2.60, 95% CI 1.84 to 3.68) (95). In a post-mortem study of patients with rheumatoid arthritis, atherosclerosis was less prevalent among those subjects with a prolonged course of arthritis (more than 8 years) and regular aspirin use (96). An inverse relationship was found between the prevalence of symptomatic atherosclerosis and duration of aspirin intake.

Such findings should be considered carefully with evidence from a number of small studies suggesting that the efficacy of antiplatelet therapy with aspirin may be diminished by persistent inflammation (e.g., from rheumatic disease) and concurrent use of other nonsteroidal anti-inflammatory drugs, and may even be negated by the potential risk of major gastrointestinal hemorrhage (97,98). Large-scale, prospective studies investigating the relationship between low-dose aspirin usage, aspirin resistance, inflammation, and cardiovascular risk are awaited.

Therapeutic Opportunities for Aspirin Resistance

Aspirin resistance is a multifactorial phenomenon, and treatment should, therefore, be directed to a number of COX-1–dependent and –independent factors, some of which may be modifiable (e.g., patient compliance, aspirin dosage, drug–drug interactions, and increased platelet turnover). Adequate treatment of confounding clinical conditions such as smoking, hyperlipidemia, hyperglycemia, hypertension, heart failure, infection, and inflammation may further increase efficacy of antiplatelet treatment with aspirin.

In some patients, an increased dose of administered aspirin may prove useful to overcome resistance (e.g., acute coronary syndromes, infections, inflammation, and so on). This approach is unjustifiable and even unsafe in diabetes, chronic heart failure, and rheumatic heart disease. In addition, the available evidence does not consider aspirin doses higher than 81 mg as either effective or safe (56).

The most logical and promising approach, therefore, seems to be the addition of other antiplatelet or antithrombotic drugs to aspirin therapy rather than replacement of aspirin in clinical conditions where aspirin resistance is anticipated. In several studies, platelet sensitivity to ADP and levels of this agonist in patients with aspirin resistance were shown to be significantly increased (99,100). In addition, those patients with the least sensitivity to the effect of aspirin on the arachidonic acid pathway appeared to be highly sensitive to the P2Y12 platelet ADP receptor antagonist clopidogrel (101). Such data suggest the potential for dual antiplatelet therapy, and, consequently, this approach has been addressed by several large randomized trials (Table 4) (102–108).

Dual antiplatelet therapy with clopidogrel and aspirin demonstrates statistically significant additive benefit (in terms of primary end points and bleeding rate) over aspirin monotherapy in various clinical trials (COMMIT [ClOpidogrel and Metoprolol in Myocardial Infarction Trial], CURE [Clopidogrel in Unstable angina to prevent Recurrent Events], PCI-CURE [substudy of CURE], CREDO [Clopidogrel for the Reduction of Events During Observation]) (Table 4) (102–105).

In two large trials, the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial and the MATCH (Management of ATherothrombosis with Clopidogrel in High-risk patients) trial, with 15,603 and 7,599 high-risk

Table 4	Randomized Prospective Trials of Dual Antiplatelet Therapy With Clopidogrel and Aspirin		
Trial	**Patients**	**Antiplatelet Treatment**	**Results**
The COMMIT trial (102)	45,852 patients with suspected acute MI.	Clopidogrel 75 mg/day plus 162 mg/day aspirin versus placebo plus aspirin.	In the follow-up period (up to 4 weeks), in the clopidogrel group there was a 9% reduction in the composite of death, reinfarction, or stroke (95% CI 3% to 14%; p = 0.002) and a 7% reduction in all-cause mortality (95% CI 1% to 13%; p = 0.03).
The CURE trial (103)	12,562 patients with non–ST-segment elevation acute coronary syndromes followed up to 1 yr (mean 9 months).	Clopidogrel (300-mg loading dose followed by 75 mg/day) plus 75 to 325 mg/day aspirin versus placebo plus aspirin.	Dual therapy reduced by 20% the relative risk of cardiovascular death, nonfatal MI, and stroke (p = 0.001). Although the incidence of major bleeding was comparatively high in the clopidogrel-treated group, there was no difference in the incidence of life-threatening bleeding and hemorrhagic stroke.
The PCI-CURE trial (CURE substudy) (104)	2,658 patients with non–ST-segment elevation ACS undergoing PCI.	Pre-treatment with clopidogrel or placebo plus aspirin for a median of 10 days before intervention. After PCI, more than 80% in both groups received ADP antagonist (clopidogrel or ticlopidine) for 4 weeks. Then patients continued to receive clopidogrel or placebo for an average of 8 months.	Dual therapy (clopidogrel-aspirin) reduced by 30% the relative risk of cardiovascular death, MI, and urgent target vessel revascularization within a month after PCI (p = 0.03). In the follow-up period, there was no significant difference in major bleedings between the groups.
The CREDO trial (105)	2,116 patients who were either scheduled to undergo PCI or were at high likelihood of undergoing PCI.	Clopidogrel (300-mg loading dose followed by 75 mg/day) plus 325 mg/day aspirin versus placebo plus aspirin. From 29th day through 12 months: clopidogrel 75 mg/day plus aspirin or placebo plus aspirin.	In the follow-up period, dual antiplatelet therapy reduced by 26.9% the relative risk of death, MI, and stroke (95% CI 3.9% to 44.4%, p = 0.02).
The CARESS trial (106)	107 patients with symptomatic carotid stenosis with asymptomatic microembolic signals detected by transcranial Doppler ultrasound.	Clopidogrel (300-mg loading dose followed by 75 mg/day for 7 days) plus 75 mg/day aspirin versus placebo plus aspirin.	On day 7 microembolic signals were detected in 43.8% of patients in the dual antiplatelet therapy group and in 72.7% in the monotherapy with aspirin group (relative risk reduction 39.8%, 95% CI 13.8% to 58.0%; p = 0.0046).
The CHARISMA trial (107)	15,603 patients with a history of symptomatic CAD, cerebrovascular disease, or peripheral arterial disease or at high cardiovascular risk.	Clopidogrel 75 mg/day plus aspirin 75 to 162 mg/day versus placebo plus aspirin.	In the 28-month follow-up period, there was no difference in the rate of cardiovascular death, MI, and stroke between the groups (relative risk 0.93; 95% CI 0.83 to 1.05; p = 0.22). In the clopidogrel plus aspirin group, hospitalization rate for ischemic events was 16.7% versus 17.9% in the aspirin group (relative risk 0.92, 95% CI 0.86 to 0.995; p = 0.04). The rate of severe bleeding was 1.7% and 1.3%, correspondingly (relative risk 1.25, 95% CI 0.97 to 1.61%; p = 0.09).
The MATCH trial (108)	7,599 patients with recent ischemic stroke or transient ischemic attack and at least 1 additional vascular risk factor.	Aspirin 75 mg/day plus clopidogrel 75 mg/day versus placebo plus clopidogrel 75 mg/day.	After 18 months, dual antiplatelet treatment was associated with 1% nonsignificant absolute reduction of major ischemic events and a significant 1.3% absolute risk increase of the life-threatening bleeding (95% CI 0.6 to 1.9). The rates of fatal bleeding and all-cause mortality were not different between the groups.

ACS = acute coronary syndromes; ADP = adenosine diphosphate; CAD = coronary artery disease; CARESS = Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic carotid Stenosis; CHARISMA = Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; COMMIT = Clopidogrel and Metoprolol in Myocardial Infarction; CREDO = Clopidogrel for the Reduction of Events During Observation; CURE = Clopidogrel in Unstable angina to prevent Recurrent Events; MATCH = Management of ATherothrombosis with Clopidogrel in High-risk patients; PCI = percutaneous coronary intervention; other abbreviations as in Table 1.

cardiovascular and cerebrovascular patients, respectively, there was no difference in the primary end points between the dual and monotherapy arms of the trials. Importantly, of the broad range of high-risk atherothrombosis patients enrolled in the CHARISMA trial, a subgroup of 9,478 patients with prior MI, stroke, and symptomatic peripheral arterial disease did appear to benefit from dual antiplatelet therapy (109). In this subgroup analysis, the composite end point of cardiovascular death, MI, and stroke was lower in the clopidogrel plus aspirin arm compared with the placebo plus aspirin arm (7.3% vs. 8.8%; hazard ratio 0.83, 95% CI 0.72 to 0.96; p = 0.01). With regard to secondary end

points, hospitalization rate over the mean follow-up period of 27.6 months was significantly lower in the clopidogrel plus aspirin arm (11.4% vs. 13.2%; hazard ratio 0.86, 95% CI 0.76 to 0.96; p = 0.008), and there was no difference in the rate of severe bleeding. This subgroup analysis of the CHARISMA trial stressed the importance of identifying selected patients who would benefit from dual antiplatelet therapy.

This notion is further supported by recent analysis of excess cardiovascular death rate in the CHARISMA trial of asymptomatic patients treated with dual antiplatelet therapy (110), and by results of 2 small studies, the PLUTO-CHF (PLavix Use for Treatment Of Congestive Heart Failure) (111) and prospective follow-up study of aspirin resistance by Pamukcu et al. (43). In the latter small studies, patients meeting criteria of laboratory aspirin resistance were randomly selected to receive clopidogrel plus aspirin therapy. In the PLUTO-CHF study, dual aspirin-clopidogrel therapy over 1 month resulted in significant changes in a number of platelet activation laboratory parameters in a small cohort (n = 25) of heart failure patients. Pamukcu et al. (43) reported 28 patients with coronary artery disease who were followed-up over a 6- to 12-month period, and those who received additional clopidogrel therapy over 12 months had less cardiovascular events than those who did not use or stopped clopidogrel at 6 months.

Although dual aspirin-clopidogrel therapy may seem to be the most beneficial therapeutic approach to aspirin resistance, a rapidly increasing number of publications recognize the existence of "clopidogrel resistance" (25,111–114) and even "dual aspirin-clopidogrel resistance" (115). These observations necessitate further search for new, more potent antiplatelet agents suitable for long-term cardiovascular prevention. Among these agents are thienopyridine compound, prasugrel (CS-747, LY 640315), which provides 10 times more potency, rapid and sustained antiplatelet effect, when compared with clopidogrel (111,116), and an oral reversible inhibitor of P2Y12 receptor AZD6140 (117).

Another approach to enhance antiplatelet effect of aspirin is an addition of dipyridamole. Combination therapy with aspirin and dipyridamole is used in the setting of secondary prevention after stroke. The evidence for this comes from the ESPS (European Stroke Prevention Study)-2 trial with 4 treatment arms (50 mg/day aspirin, 400 mg/day dipyridamole, dual therapy and placebo) (118). This trial showed 22% relative risk reduction of major vascular events in patients with dual aspirin-dipyridamole therapy compared with that seen with aspirin alone, but no significant effect on vascular death rate. Additionally, the ESPRIT (European/Australasian Stroke Prevention in Reversible Ischaemia Trial) study compared efficiency of aspirin (30 to 325 mg/day) with or without dipyridamole (400 mg/day) in patients with transient ischemic attack or minor stroke (119). The composite of vascular death, nonfatal stroke, nonfatal MI, and major bleeding was evaluated over a mean follow-up period of 3.5 years; superiority of clinical efficacy

of combined therapy was demonstrated (absolute annual risk reduction 1.0%, 95% CI 0.1 to 1.8) (119). Nevertheless, it is noteworthy that meta-analysis by Antithrombotic Trialists' Collaboration showed no difference in efficacy between aspirin plus dipyridamole and aspirin alone in high vascular risk patients (10). These results were reiterated by a recent systematic review of 29 trials with more than 23,000 patients with arterial vascular disease (120). No evidence was found that dipyridamole alone or in combination with aspirin significantly reduced the risk of vascular death, although it was efficacious in secondary prevention of cerebrovascular ischemic events.

In patients undergoing percutaneous coronary angioplasty, significant improvement of clinical efficacy of aspirin alone or in combination with clopidogrel may be achieved by addition of cilostazol, a phosphodiesterase type 3 inhibitor with potent antiplatelet, vasodilative, antiproliferative, endothelial function, and lipid profile improving effects (121,122). In the CREST (Cilostazol for RESTenosis) trial, addition of cilostazol to aspirin and clopidogrel therapy reduced the rate of restenosis by 36% after successful bare-metal stenting (123). It proved to be efficient in patients with peripheral arterial disease as well (124).

Whether addition of new inhibitors of P2Y12 receptor, dipyridamole, or cilostazol to aspirin is an effective intervention for subjects with aspirin resistance remains to be elucidated in future studies.

Conclusions

Despite the emergence of "aspirin resistance" as a clinical phenomenon, aspirin still remains the most commonly prescribed drug for prevention of atherothrombotic events. This is due not only to its potent inhibition of the thromboxane A_2 pathway, which is undoubtedly crucial for platelet activation and aggregation, but also because of a number of pleiotropic effects (suppression of acute phase reactants and subclinical inflammation, stimulation of NO synthesis, immunomodulatory effect on activated macrophages and lymphocytes, and so on) (125–127). Furthermore, aspirin has proved complementary to—and seems to potentiate—the effects of other antiplatelet agents (such as clopidogrel, dipyridamole, cilostazol) in the case of combined therapy. In addition, aspirin seems to be generally well tolerated by most patients, and relatively few have contraindications to this drug or develop major bleeding. Such characteristics mean that aspirin is likely to remain the cornerstone of antiplatelet therapy for long-term cardiovascular prevention.

As discussed in this review, numerous modifiable and nonmodifiable factors may interfere with aspirin therapy, preventing its targeted action on the thromboxane A2 pathway, thereby attenuating the effect of this drug on platelet activation and aggregation and limiting its role in cardiovascular prevention. The terms "biochemical or laboratory" and "clinical" aspirin resistance have been suggested

to better characterize those patients who do not benefit from long-term aspirin use. Despite this, relatively few well-designed prospective studies have been conducted thus far, yielding some evidence that is suggestive of a possible link between the inefficient inhibition of thromboxane A2 pathway and adverse cardiovascular events over long-term follow-up. Unfortunately, these studies lack a standardized definition of aspirin resistance based on validated and widely available methods of platelet function assessment. As a matter of fact, studies comparing main laboratory tests for detection of aspirin resistance (optical and whole blood aggregometry, PFA-100, VerifyNow-Aspirin, level of urinary 11-dehydro-thromboxane B2) found poor agreement between these tests (128) and left unresolved the issue of utility of these tests for routine measurements of aspirin resistance.

The available evidence does not adequately address the issue of dynamic changes in platelet function and whether aspirin resistance persists over a period of time when multiple intrinsic and extrinsic factors may exert their effect on platelet function in multiple directions. To address this issue, design of future prospective studies should include baseline and follow-up measurements of platelet function in patients with accurately monitored compliance to long-term aspirin use.

Actually, future studies of aspirin resistance should also consider complex interactions between age, gender, and ethnicity, as it is becoming more obvious that these factors may have an impact on the extent of inhibition of COX-1 pathway by aspirin (129–131). Finally, the issue of aspirin resistance should be considered separately for those who may not benefit from aspirin due to COX-1–related and –nonrelated genetic factors (131). Until further studies are available to investigate aspirin resistance in more depth, a balanced approach is required when assessing patients for antiplatelet therapy. Certainly, comorbidities that may enhance aspirin resistance (e.g., diabetes mellitus, hypertension, heart failure, inflammatory disorders, and so on) should be actively sought, as this may aid the practicing clinician in deciding between monotherapy with aspirin or coprescription with other more potent antiplatelet drugs.

Reprint requests and correspondence: Prof. Gregory Y. H. Lip, Haemostasis Thrombosis and Vascular Biology Unit, University Department of Medicine, City Hospital, Birmingham B18 7QH, United Kingdom. E-mail: g.y.h.lip@bham.ac.uk.

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