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**Review**

## Aspirin resistance

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**Abstract:**

Aspirin protects many though not all patients from acute cardiovascular events. It is generally accepted that such prophylactic effect depends mainly on the antithrombotic action involving inhibition of thromboxane A<sub>2</sub> production and platelet aggregation. In many patients aspirin failure to protect against cardiovascular event is obvious, as their symptoms simply cannot be controlled by the administration of a single drug. Others do not adhere properly to the treatment regimen. There is, however, a group of subjects, in which aspirin fails to inhibit platelet function (measured by various *in vitro* tests) and thromboxane A<sub>2</sub> (TXA<sub>2</sub>) formation (measured either in whole blood or as urinary TXA<sub>2</sub> metabolite excretion). There is evidence that such impairment of biochemical aspirin effect may be of importance in predicting future cardiovascular events. Several factors can influence antiplatelet effectiveness of aspirin; among them: hypercholesterolemia, increased expression of the isoform 2 of cyclooxygenase, genetic factors (polymorphisms of β<sub>3</sub> integrin, and factor XIII A-subunit), use of other nonsteroidal anti-inflammatory use, and possibly others. Still, several questions remain unanswered. While biochemical aspirin resistance can predict major cardiovascular events we are still lacking a reliable test to predict such a risk in an individual patient. In addition, we do not know whether any alteration in therapy may improve clinical outcome in a subject identified as aspirin-resistant.

**Key words:**

aspirin, platelets, aggregation, cardiovascular disease

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### Introduction

Acetylsalicylic acid (aspirin, ASA) is the most widely prescribed drug all over the world with indications ranging from fever to clinical manifestations of arterial thrombosis.

Cyclooxygenase (COX)-1 and -2 are 72 kD luminal proteins of the endoplasmic reticulum and nuclear envelope, where they catalyze the conversion of arachidonic acid to prostanoids.

Aspirin inhibits COX-1, a constitutive enzyme, by acetylating a serine residue at position 529, which blocks the access of arachidonic acid to the catalytic site in the core of the enzyme molecule. Suppression

of prostaglandin PGH<sub>2</sub> formation results in decreased production of PGD<sub>2</sub>, PGE<sub>2</sub>, PGF<sub>2α</sub>, prostacyclin and thromboxane A<sub>2</sub> (TXA<sub>2</sub>). This latter compound acts as an platelet agonist, vasoconstrictor and vascular smooth muscle cell mitogen [21]. A capacity of the anucleate platelets for TXA<sub>2</sub> synthesis is restored only by newly released platelets. The effect of a single dose of aspirin disappears within 7–10 days. The COX-1 activity is present in most tissues, including the endothelium, that possess the capacity to generate the new enzyme molecules and recover their normal function within a few hours following aspirin administration. Therefore, a single dose of aspirin has only a transient systemic effect on COX-1 with the exception of the platelets [21].

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Aspirin is also able to acetylate COX-2 at serine 516. However, a modified form of this enzyme is capable of the arachidonic acid oxidation that result in the production of 15-hydroperoxide of eicosatetraenoic acid (15-HPETE), which is a potential substrate for other eicosanoids such as 15-epi-lipoxins. In contrast to COX-1, COX-2 is expressed in most tissues and cells at very low levels unless induced by mitogens or hormones at inflammation sites, including the vascular wall (predominantly endothelial cells and smooth muscle cells) by activation of several signal transduction pathways. Platelets do not contain detectable amounts of COX-2 under physiological conditions [21].

There is general consensus that a major antithrombotic action of aspirin *in vivo* involves its antiplatelet action, reflected by attenuation of platelet aggregation that is associated with inhibition of platelet TXA<sub>2</sub> biosynthesis.

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## Clinical benefits of aspirin

Antiplatelet therapy results in a 25% reduced risk of nonfatal myocardial infarction (MI), nonfatal stroke, or vascular death in high-risk patients, regardless of sex, age, the presence of arterial hypertension or diabetes [2]. Aspirin is also effective in patients with acute MI, as demonstrated in the landmark study [37]. Administration of 162 mg aspirin within 24 h following the onset of acute coronary symptoms was associated with a decrease in the risk of cardiovascular mortality (by 23%), nonfatal reinfarction (by 49%), and nonfatal stroke (by 46%) in a short-term follow-up [37]. Based on the data from randomized trials, the American College of Cardiology/American Heart Association (ACC/AHA) Task Force recommends aspirin in an initial dose of 162 to 325 mg to all patients with ST elevation MI unless there is a contradiction [3]. In addition to improving clinical outcomes in patients with acute coronary syndromes, aspirin when given prior to new episodes likely reduces the risk of ST elevation MI, in-hospital mortality and acute heart failure [62]. In subjects who present with a non-ST elevation MI, prior aspirin use can predict adverse events [4]. The first randomized controlled trial, PPP (the Primary Prevention Project) [14], conducted in men and women aged 50 years or more, provided the direct evidence of aspirin's efficacy in prevention of cardiovascular events such as angina, peripheral ar-

tery disease, and transient ischemic attacks (TIA) and demonstrated a reduction in the relative risk of death to 0.56 among individuals taking 100 mg aspirin daily. However, the AHA guidelines recommend aspirin use in subjects who have a ten-year cardiovascular risk of at least 10%, though primary prevention trials have indicated that the use of low-dose aspirin is safe and effective in subjects with coronary event risk of at least 1.5% per year [60]. Moreover, the American Diabetes Association recommends that aspirin be used in primary prevention of cardiovascular disease in patients with diabetes having at least one extra risk factor [15]. Collectively, both European and American guidelines unanimously recommend low-dose aspirin administration in high-risk patients [51, 52, 63], while a small absolute benefit in terms of cardiovascular morbidity and mortality does not justify a routine use of aspirin among low-risk individuals.

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## Aspirin resistance – definition and frequency

The term aspirin resistance has been used to describe a clinical situation in which a subgroup of patients on therapeutic doses of aspirin experiences thrombotic vascular events [29, 33, 44]. The concept of “clinical aspirin resistance”, or rather treatment failure, is obviously based on a false assumption that major manifestations of atherothrombosis can be controlled by using a single pharmaceutical agent. Treatment failures occur with all drugs whenever used. Currently, the prevailing view is that aspirin resistance should be defined based on biochemical criteria which are, however, largely inconsistent.

The incidence of aspirin resistance in cardiovascular patients varies and ranges from below 1% to 50% or more. Aspirin resistance in stroke patients, assessed using *ex vivo* platelet function tests, has been estimated at 8 to 45% [23, 24, 32]. The frequency of aspirin resistance has been reported to be similar in patients with Coronary Artery Disease (CAD) [26]. In patients who underwent coronary artery bypass grafting (CABG), aspirin resistance seems the highest in the first days following operation [43, 75]. However, impaired aspirin responsiveness might be transient and infrequent following 1 month after CABG [22].

## Testing for aspirin resistance

*In vivo* tests used to detect aspirin resistance include:

1) evaluation of urinary concentrations of 11-dehydrothromboxane B<sub>2</sub>, a metabolite of TXA<sub>2</sub> [18] or serum TXA<sub>2</sub> [31].

2) determination of P-selectin expression on platelet membranes using flow cytometry or measurement of plasma P-selectin levels [48]; other activation-dependent platelet changes that can be monitored with regard to aspirin resistance include the expression of activated glycoprotein IIb–IIIa or formation of leukocyte-platelet aggregates induced by arachidonic acid.

3) assessment of bleeding time, since aspirin is well known to prolong it. It has been estimated that aspirin, in a dose-dependent manner, prolongs the bleeding time in 60% of healthy individuals [6]. However, the lack of prolongation of bleeding time is associated with inhibited TXA<sub>2</sub> production and platelet aggregation like in responders to aspirin, which speaks against the usefulness of bleeding time in identifying aspirin resistance [6].

Major disadvantages of these methods represent sample preparation, uncertain sensitivity and specificity, low reproducibility.

As an optimal method of platelet function testing to identify individuals with aspirin resistance, most investigators have used platelet aggregometry even if this method assesses platelet function in a static system in the absence of erythrocytes and at least for this reason it barely simulates the *in vivo* arterial flow conditions. In studies on aspirin resistance, adenosine diphosphate (ADP) (mostly 5 μmol/l), collagen (mostly 1–5 μg/ml), and arachidonic acid (mostly 0.5 mmol/l) have been used as platelet agonists. In citrated platelet-rich plasma or whole blood milieus with very low calcium levels, the aspirin's effect evaluated by platelet aggregation, does not reflect the actual impact of this agent on platelet function and has to be considered as an approximation that is practical, but fraught with disadvantages such as high sample volume and time-consuming procedure.

When arachidonic acid-induced whole blood platelet aggregation has been used to define aspirin resistance, a single patient out of 122 subjects (0.8%) with preserved platelet reactivity following administration of low-dose aspirin has been found [34]. It is not clear whether arachidonic acid, indeed, is the best agonist for measuring aspirin resistance.

An alternative to optical platelet aggregation tests is the Platelet Function Analyzer (PFA-100), which has been designed as an *in vitro* measure of primary hemostasis at a high shear rate, mimicking flow conditions in the arteries. The PFA-100 system activates platelets by aspirating a blood sample through a capillary to a membrane through an aperture coated with collagen either ADP (50 μg), or epinephrine (10 μg). The closure time is a time needed to stop citrated whole blood flow. This method is dependent on plasma von Willebrand factor and hematocrit [10]. Aspirin prolongs the closure time in the collagen-epinephrine cartridge, and has a negligible effect on this time when the collagen-ADP cartridge is used. The PFA-100 system is rather expensive and all measurements should be done within 4 h after blood collection. Aspirin resistance is often defined as normal closure times (mostly between 150–193 s) based on the 90% or 95% central interval in a normal population [26]. Another whole blood assay for the detection of aspirin resistance, the Ultegra Rapid Platelet Function Assay-ASA (Verify Now Aspirin), measures platelet aggregation with arachidonic acid or propyl gallate cartridges [42]. An aspirin reaction unit (ARU) ≥ 550 indicates decreased sensitivity to aspirin based on the correlation with epinephrine-induced light transmission aggregometry.

Using the PFA-100 system aspirin nonresponsiveness has been described in 35% of patients with CAD [1] and in 34% in subjects suffering from recurrent cerebral ischemic attacks [25]. A slightly smaller proportion (23–27%) of patients with stable angina who were non-responsive to aspirin has been found by means of the Ultegra RPFA-ASA system Wang et al. [40, 72]. A recent comparison of both whole blood tests with conventional light transmission aggregometry using ADP and arachidonic acid revealed that the use of PFA-100 as well as Ultegra RPFA-ASA systems results in much higher incidence of aspirin resistance (22% and 17% vs. 5% for aggregometry, respectively) [30]. Only 2% of patients with cerebrovascular disease taking low-dose aspirin were resistant to aspirin by all 3 tests studied, with poor correlation of results obtained using both whole blood systems [30].

The lack of one adopted definition of aspirin resistance accounts largely for marked differences in the its frequency reported by various investigators. At present, aspirin nonresponsiveness appears to be highly specific for the test used and evaluation of whole blood TXA<sub>2</sub> formation and its urinary metabo-

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lite is widely considered now the best methodological approach. It should be stressed that until now there is no standard method to detect aspirin resistance and it is unlikely that a single platelet test might be a much-desired standard.

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## Mechanisms of aspirin resistance

Several mechanisms underlying aspirin resistance have been proposed:

1) low adherence in aspirin-treated subjects.

The scale of non-adherence is unclear. Based on urine tests for salicylate metabolites, it has been estimated that about 10% in patients with CAD did not take aspirin as prescribed [68]. Recently, Schwartz et al. [62] demonstrated that 9% MI survivors on long-term aspirin therapy appeared resistant to aspirin based on the results of arachidonic acid-induced light aggregometry, while 2 h after observed aspirin ingestion only one patient out of 190 met the criteria of the lack of platelet response to aspirin.

2) underdosing or poor absorption, especially in case of the use of enteric coated aspirin.

3) comorbid conditions.

Cigarette smoking attenuates significantly aspirin-induced inhibition of platelet aggregation [36]. Hypercholesterolemia, defined as total cholesterol above 6.5 mmol/l, has been found to be associated with weaker response to 300 mg aspirin that was measured at the site of microvascular injury [65, 66]. Elevated total cholesterol is likely to be linked to lower clinical effects of aspirin administration for the prevention, as evidenced in the Physician's Health Study [20] and the Thrombosis Prevention Trial [45].

A common mechanism of aspirin resistance in subjects with hypercholesterolemia or in smokers would be increased response to other platelet agonists and aspirin-insensitive thromboxane production related to enhanced isoprostane production from arachidonic acid through lipid peroxidation [54, 55].

4) transient increase of platelet COX-1/COX-2 expression in newly formed and drug-unaffected platelets when platelet turnover is accelerated [13, 57].

In CABG patients after the procedure, aspirin resistance has been reported to be associated with the appearance of COX-2 immunoreactivity in platelet pro-

tein lysates, without any concurrent alterations in the COX-1 protein expression [9].

5) augmented COX-2 expression in monocyte/macrophages or in platelets, especially in response to stress [12]; upregulation of COX-2 has been demonstrated in atherosclerotic plaque that might suggest that atherosclerotic burden can have an impact on the occurrence of aspirin resistance in patients with atherothrombosis affecting several vascular beds.

6) simultaneous regular administration of other non-steroidal anti-inflammatory drugs, especially ibuprofen, that interfere with aspirin-mediated COX-1 inhibition in platelets [8, 38, 41], which highlights a role of pharmacodynamic interactions of drugs given in conjunction with aspirin. Clinical aspirin resistance associated with Nonsteroidal Anti-inflammatory Drugs (NSAIDs) is particularly apparent in MI survivors [38]. There is no data regarding the proportion of patients with recurrent cardiovascular events on combined therapy with aspirin and NSAIDs, though the magnitude of this effect is now hard to estimate.

7) platelet interactions with monocytes or endothelial cells that can provide PGH<sub>2</sub> to platelets and are capable of the own TXA<sub>2</sub> synthesis.

8) genetic mutations affecting activity enzymes, including COX-1, COX-2, or TXA<sub>2</sub> synthase [7, 28]. Some studies, however, does not support the concept that common variants of the COX-1 gene lead to different patterns of platelet aggregation or granule content release [35].

9) genetic polymorphisms of platelet receptors, especially  $\beta_3$  integrins [27, 58], or also collagen and thromboxane receptors [73]. Until now, there is no evidence that any platelet polymorphisms are relevant to clinical outcomes in patients with cardiovascular disease either responsive or nonresponsive to aspirin.

The most compelling evidence regarding genetic determinants of aspirin-related changes in thrombus formation is focused on a common polymorphism of the  $\beta_3$  integrin gene, termed PIA1A2. A single nucleotide transition at position 1565 in exon 2 of the gene encoding  $\beta_3$  integrins results in the substitution of leucine to proline at position 33 of the protein. The PIA2 allele, present in approximately 20% of Caucasians, has been reported to increase cardiovascular risk [35], though available data are inconsistent [74]. The same is true for platelet reactivity in the presence of the PIA2 allele [19, 39, 47]". While studying platelet response to aspirin, [16] demonstrated impaired aggregability of platelets obtained from subjects carry-

ing the PIA2 allele. In contrast, Undas et al. [70] have reported that carriers of the Pro33 allele showed a tendency to higher thrombin formation and in contrast to subjects homozygous for the Leu33 allele, 75 mg/d aspirin did not affect this reaction. Detailed analysis of blood coagulation at the site of microvascular injury revealed that in subjects homozygous for the Leu33 allele, there were significant reductions in the velocity of thrombin formation (by about 30%), factor Va generation (by about 30%), fibrinogen cleavage (by about 40%) and also thrombin-mediated factor XIII activation (by about 20%) [69]. HPLC analysis of fibrinopeptide (FP) release during fibrinogen proteolysis showed that at the end of bleeding, FPA and FPB levels were significantly lower following aspirin administration for 7 days only in men with the PIA1A1 genotype [69]. Moreover, at 4 h after ingestion of 300 mg aspirin, bleeding time, an indirect marker of aspirin-induced alterations in hemostasis, became significantly less prolonged in healthy young men positive for the PIA2 allele as compared to individuals homozygous for the PIA1 allele [67]. Mechanisms of aspirin-mediated effects on the  $\beta_3$  integrin activity is unknown yet. Dominguez-Jimenez et al. [17] have suggested that non-steroidal anti-inflammatory drugs alter  $\beta_3$  integrin activation in a COX-independent manner by interfering with intracellular signaling pathways. Aspirin has also been found to acetylate GPIIb and GPIIIa molecules [61], which are crucial for platelet aggregation at high shear stress. However, it remains to be established how this effect might modulate thrombin generation in subjects receiving aspirin. A link between platelet GPIIIa PIA2 polymorphism and aspirin resistance has been shown in a few clinical studies [49, 50], but clinical relevance of these reports remains obscure.

10) genetic polymorphisms in the genes coding coagulation proteins such as factor (F)XIII.

A novel mechanism of ASA resistance might be related to the common Leu34 polymorphism of FXIII A-subunit mutation, which actually is not directly associated with platelet function. We have demonstrated that inhibition of FXIII activation following a 7-day aspirin treatment, evaluated at the site of microvascular injury, was enhanced in the Leu34-positive comparing with Leu34-negative subjects [71]. Results of our further studies on fibrin clot permeability and turbidity, performed in healthy subjects with all three allelic variants of FXIII Val34Leu mutation at baseline and 4 h after aspirin ingestion, revealed that after aspi-

rin intake, permeability increased significantly by 25% in Val34Val, 40% in Val34Leu, and 49% in Leu34Leu samples compared to pretreatment values and this effect was larger in Leu34-positive vs. Leu34-negative subjects [5]. Moreover, aspirin ingestion was associated with shorter fibrinolysis time compared to baseline in Leu34-positive (by about 2.5 min) vs. Leu34-negative subjects (by 1.5 min). Our experiments might suggest that in Leu34 carriers aspirin modifies fibrin cross-linking to greater extent than in Val34Val subjects, which may lead to the formation of clots more porous and more sensitive to fibrinolysis (A. Undas, unpublished data).

Concluding, aspirin resistance from the mechanistic point of view remains an enigma. In light of available evidence, this phenomenon is multifactorial [56]. In a proportion of the affected subjects, environmental modifiable factors such as lipid disorders or cigarette smoking play a major role. On the other hand, common genetic polymorphisms, most likely those affecting platelet function, modulate the aspirin's effects to some extent.

## Practical aspects of aspirin resistance

Rapidly growing evidence indicates that aspirin resistance might have important practical implications. In 976 patients who reported aspirin use (a dose being taken has not been specified) in the Heart Outcomes Prevention Evaluation (HOPE) study, urinary levels of 11-dehydrothromboxane B<sub>2</sub> in the highest quartile has been associated with a significantly higher odds (1.8; 95% CI, 1.2 to 2.7) for a composite end point of nonfatal MI, nonfatal stroke, or cardiovascular death after 5 years of follow-up, as compared to subjects in the lowest quartile of urinary TXB<sub>2</sub> levels [24]. In this case-control study, patients in the highest quartile had a 3.5-times higher risk (95% CI, 1.7 to 7.4) of cardiovascular death than those in the lower quartile [18]. Risk factors for aspirin resistance that have been identified include female sex, obesity, current cigarette smoking and a history of peripheral vascular disease [18]. Moreover, aspirin resistance detected by the Ultegra system has been implicated in increased risk for myocardial necrosis in patients after percutaneous coronary interventions [11].

How to abrogate aspirin resistance? There are few studies addressing this vital issue. Zimmermann et al. [76] showed that in CABG patients who did not re-

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respond to aspirin, the *in vitro* addition of a thromboxane synthase inhibitor and thromboxane receptor inhibitor inhibit platelet aggregation, which suggests that persisted thromboxane production is involved in aspirin resistance. The inhibition of COX-2 had no effect on platelet reactivity [76]. It is, however, unlikely that any of the known agents affecting thromboxane actions would be helpful in patients with aspirin resistance in clinical practice. Addition of ticlopidine, though clinically effective, does not influence significantly platelet reactivity towards aspirin.

Interestingly, it has been suggested that platelet sensitivity to aspirin reduces over time, resulting in a complete restoration of collagen-induced platelet aggregation in about 40% patients [53]. Fluctuations of platelet sensitivity to aspirin have been shown also in patients with previous ischemic stroke [32]. It is unclear to what extent this change is related to thromboxane production, however the concept of a dynamic nature of aspirin resistance could be of practical importance.

Worthy of note, the current evidence for the significance of aspirin resistance under various clinical settings comes largely from studies with rather hardly reliable and diverse methodology. The drawbacks of currently available trials include study design (series of cases or case-control studies), small number of patients and/or cardiovascular events during a follow-up, single method to identify aspirin-resistant individuals usually at one time point during the observation. First of all, without developing standard laboratory tests to define aspirin resistance, clinical significance of this phenomenon remains elusive [59]. Moreover, large prospective studies are required to determine the prognostic value of multiple assays currently used for measuring aspirin resistance.

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## Conclusions

Aspirin remains the mainstay of therapy in patients with atherothrombotic vascular disease. Aspirin resistance could be defined as the occurrence of cardiovascular events despite aspirin administration as recommended, or alternatively, impaired platelet sensitivity to aspirin detected by laboratory tests that might affect the clinical effectiveness of this agent. Aspirin resistance is environmentally and/or genetically determined, although a relative contribution of these two

sets of mechanisms is unknown. For example, the stability of the aspirin resistance phenotype has not been shown yet that points to the minor role of genetic factors of low responsiveness to this drug.

Now the evidence indicates that there is aspirin resistance, confirmed by biochemical tests, that can predict major cardiovascular events, however clinical relevance of aspirin resistance needs to be more convincingly established. Given the widespread use of aspirin in prevention of thrombotic manifestations of atherosclerosis, elucidation of the actual impact of aspirin resistance on the outcomes in high-risk patients might be of importance in clinical practice. Future regimens of antithrombotic therapy, including aspirin administration, are likely to be tailored to the individual patient following identification of patients who may require higher doses of this drug or other antiplatelet agents. However, a recent position paper of the Working Group of the International Society on Thrombosis and Hemostasis states that “the correct treatment, if any, of aspirin’s ‘resistance’ is unknown” [46], and it remains an open question whether any alterations in therapy are beneficial in terms of results of any of tests for aspirin resistance currently available and may improve clinical outcomes in subjects identifying as nonresponsive to this antiplatelet drug.

At present tests aimed at detecting aspirin resistance based on its diverse biochemical criteria cannot be recommended in any clinical setting. Clinical effectiveness of aspirin administration still rely predominantly on its appropriate dose, good adherence, treatment of cardiovascular risk factors and avoidance of regular use of NSAIDs.

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