Aspirin resistance: Fact or fiction? A point of view

Jawahar L Mehta, Bhavna Mohandas

Abstract
Aspirin is a wonder drug that has been used for well over 100 years for its analgesic and antipyretic effects. For the past three decades, it has increasingly been used for the prevention of primary and secondary cardiovascular events. Lately, it has been suggested that a significant number of individuals taking aspirin have become resistant to this drug. The phenomenon of “aspirin resistance” is based on the observation of clinical events in some patients taking aspirin, and/or a diminished platelet aggregation inhibitory response to aspirin therapy. Unfortunately, laboratory assays used to monitor the efficacy of aspirin are far from accurate and the results are not reproducible. Furthermore, results of different platelet function tests are often not congruent. In addition, platelet aggregation studies show marked inter-individual and intra-individual variability. Patients with coronary heart disease take many drugs that interfere with the effect of aspirin on platelet aggregation. Besides inhibiting formation of thromboxane A2 from arachidonic acid, aspirin has a host of platelet-independent effects that complement its platelet inhibitory effects. Laboratory assays designed to measure platelet function do not take into account these pleiotropic effects of aspirin. In our view, use of the term “aspirin resistance” based on inadequate knowledge of imperfect laboratory tests does a disservice to physicians and patients.

INTRODUCTION
A substance called salicilin was first isolated from the bark of willow tree by Reverend Edmund Stone in 1763[1]. In 1897, acetylsalicylic acid was marketed by the Bayer Company as Aspirin® as an analgesic[2,3]. When other non-steroidal anti-inflammatory drugs (NSAIDs) were introduced in the 1950s, the popularity of aspirin declined. In the 1970s and 1980s, research revealed potent anti-platelet and cyclooxygenase (COX) inhibitory actions of aspirin. Soon thereafter, aspirin started being used as a first-line drug in patients with a variety of cardiovascular disease states.

The Antithrombotic Trialists’ Collaboration[4] showed a 12% reduction in major vascular events in primary prevention trials. This was primarily driven by a reduction in myocardial infarction. There was no significant effect of aspirin on the incidence of stroke or vascular mortality. The reduction in major coronary events was similar in both primary and secondary prevention trials [relative risk (RR) 0.82 for primary prevention and RR 0.80 for secondary prevention]. The absolute benefit of aspirin in primary prevention trials was 0.06% per year and in secondary prevention trials was 1% per year. There was a significant 20% reduction in stroke in secondary prevention trials. In
a recent meta-analysis of six studies of aspirin in primary prevention in patients with diabetes mellitus[8], however, no significant reduction in the risk of cardiovascular or all-cause mortality was identified. Although there was a heterogeneity in the rate of myocardial infarction and stroke, aspirin reduced the risk of myocardial infarction in men [odds ratio (OR), 0.57; 95% confidence interval (CI): 0.34-0.94], but not in women (OR, 1.08; 95% CI: 0.71-1.65), and there was no benefit of aspirin against stroke in men or women. Nonetheless, it is now generally accepted that aspirin exerts a powerful effect against cardiovascular events in all secondary, and in some primary, prevention trials. Hence this drug is used in patients with known coronary heart disease and forms the background medication in all patients undergoing coronary, carotid, renal or peripheral artery revascularization.

This issue of “aspirin resistance” is of much interest to patients and physicians, since aspirin is perhaps the most widely used drug worldwide. Almost 30 million people, or 36% of the adult population in the United States, consume 10-20 billion aspirin tablets each year either alone or with other antiplatelet drugs to protect their hearts and brains from platelet-rich clots, the leading cause of heart attacks and strokes.

A recent Medline search by the authors using the words “aspirin-resistance” revealed 364 published articles between 1993 and 2009, 116 published articles using the words “aspirin-resistance coronary disease”, and 52 published article using the words “aspirin-resistance stroke”.

Antiplatelet therapy, whether it consists of aspirin, clopidogrel, other antiplatelet drugs, or their combination is essentially unmonitored for efficacy. Whether it should remain unmonitored or if the dose or type of drug/s should be tailored for the individual patient is subject to debate. In this context, “aspirin resistance”, if there is such a phenomenon, becomes very important.

**HOW DOES ASPIRIN WORK?**

Aspirin acts on platelets by acetyllating the COX enzyme at position serine 529 resulting in the reduced formation of cyclic endoperoxides [prostaglandin G2 (PGG2) and PGH2] from arachidonic acid[9]. The inhibition of the constitutive COX enzyme is irreversible[9]. Since platelets are anucleated cells and cannot generate a new COX enzyme, the action of aspirin lasts for the entire lifespan of the platelets which is 7-10 d. The COX enzyme is required for the production of the prostanoid thromboxane A2 (TXA2) from cyclic endoperoxides in platelets. TXA2 is a very potent stimulus for platelet aggregation.

Besides arachidonic acid, platelets are activated in response to epinephrine, collagen, thrombin, and adenosine diphosphate (ADP) (Figure 1). When there is injury to the vascular intima, circulating platelets are exposed to subendothelial collagen, proteoglycans, fibronectin and other adhesive proteins. The resulting changes in platelets can be divided into adhesion, secretion and aggregation. For adhesion, von Willebrand factor is necessary and serves as a bridge between collagen and platelets through its receptor glycoprotein (Gp) I b/IX[8]. This causes release of cytosolic Ca2+ which facilitates the second phase or sequestration. In this phase there is release of alpha and dense granules. P-selectin released from alpha granules causes adhesion of monocytes and neutrophils to activated platelets[9]. Dense granules release ADP, a potent mediator of the third phase of platelet aggregation, namely platelet aggregation. ADP acts through the platelet specific receptor P2Y1 and mediates the action of phospholipase A2 on membrane phospholipids[10]. This releases arachidonic acid, which is converted to endoperoxides via constitutive COX (COX-1); activation of TXA2 synthase enzyme then converts endoperoxides to TXA2 in platelets[10]. In addition to ADP and TXA2, other stimuli, such as 5-hydroxytryptamine and epinephrine can initiate aggregation via specific receptors. The cytosolic release of Ca2+ also causes a conformational change in platelet Gp II b/IIIa receptors which allows the platelets to bind to fibrinogen[10]. These stimuli lead to a build-up of Ca2+, which causes an autocatalytic reaction of platelet aggregation.

**ASPIRIN CAN ACT THROUGH COX-INDEPENDENT PATHWAYS BEIDES A COX-DEPENDENT PATHWAY**

Aspirin has a myriad of effects that are not limited to platelet inhibition through COX enzymes (Table 1). In platelets, there is residual arachidonic acid-induced platelet activation in aspirin treated patients even after controlling for

| Table 1 | Cyclooxygenase-independent effects of aspirin |
|---------|---------------------------------------------|
| On platelets | Partially inhibits ADP2Y12 receptor activation responsible for residual arachidonic acid induced platelet activation[12] |
|          | Blocks NF-kB activation that facilitates platelet inhibition by neutrophils[13] |
|          | Anti-inflammatory effect |
|          | Inhibits release of reactive oxygen species[14] |
|          | Inhibits release of elastase and soluble ICAM-1[15] |
|          | Inhibits formation of malondialdehyde[16] |
|          | Inhibits formation of oxidized LDL antibodies[17] |
|          | Reduces inflammatory cell activity[17] |
|          | Anti-oxidant effect |
|          | Inhibits oxidized LDL formation[18] |
|          | Blocks transcription of LOX-1[19] |
|          | Scavenges hydroxyl radicals[18] |
|          | Induces synthesis of ferritin[19] |
|          | Inhibits nitric oxide synthase[20,21] |
|          | Inhibits expression of redox sensitive transcription factor NF-κB[22,23] |
|          | Acetylates proteins and prevents their oxidation[22,23] |
|          | Endothelial function modification |
|          | Prevents adhesion of neutrophils and monocytes[24] |
|          | Induction of VCAM-1, ICAM-1 and E-selectin[25,26] |
|          | Miscellaneous effects |
|          | Inhibits vascular smooth muscle cell function[26] |
|          | Inhibits angiogenesis[27-29] |
|          | Inhibits γ-carboxylation of coagulation factors[24] |

ADP: Adenosine diphosphate; NF-kB: Nuclear factor-kB; ICAM-1: Intracellular adhesion molecule-1; LDL: Low density lipoprotein; LOX-1: Oxidized LDL receptor.
non-compliance and under-dosing. This platelet activation is independent of the COX pathway and is dependent on ADP P2Y1 and P2Y2 receptors\[^{[14]}\]. Through the nitric oxide/nuclear factor-κB (NF-κB) pathway aspirin facilitates the inhibition of platelet activation by neutrophils\[^{[15]}\].

Other agents that inhibit COX expression or activity, such as NSAIDs, or the direct TXA\(_2\) synthase and receptor inhibitors inhibit platelet aggregation, but do not show the same beneficial effect against vascular disease as aspirin, suggesting unique vascular properties of aspirin, independent of the COX-TXA\(_2\) pathway\[^{[16]}\].

Activation of inflammatory pathways is intimately related to the pathogenesis of atherosclerosis as well as the precipitation of acute vascular events. Aspirin reduces inflammatory cell activity, release of elastase and soluble intracellular adhesion molecule-1 (ICAM-1), and formation of malondialdehyde and oxidized low density lipoprotein (LDL) antibodies\[^{[17]}\].

Aspirin has significant antioxidant properties. Accordingly, it protects LDL-cholesterol from oxidation. Oxidized LDL is now recognized to be a more potent mediator of vascular disease as well as the pathogenesis of atherosclerosis as well as the precipitation of acute vascular events. Aspirin reduces inflammatory cell activity, release of elastase and soluble intracellular adhesion molecule-1 (ICAM-1), and formation of malondialdehyde and oxidized low density lipoprotein (LDL) antibodies\[^{[17]}\].

Aspirin inhibits cytokine-inducible nitric oxide synthase gene expression, an effect that involves the activation of redox-sensitive transcription factor NF-κB\[^{[18]}\]. In vivo its acetyl moiety, aspirin can acetylate ε-amino groups of lysine residues in proteins and prevent their oxidation\[^{[19]}\]. This effect of aspirin on proteins is important in limiting both lipoprotein and fibrinogen oxidation\[^{[20]}\], with resultant reduction in inflammation in patients with vascular disease\[^{[21]}\].

Aspirin improves the dysfunctional state of the endothelium\[^{[22]}\] and prevents the adhesion of neutrophils and monocytes to the activated vascular endothelium. This effect is mediated via inhibition of NF-κB activation and induction of various adhesion molecules, such as vascular cell adhesion molecule-1, ICAM-1 and E-selectin\[^{[23]}\]. In clinical disease states, aspirin has been shown to normalize nicotine-induced endothelial dysfunction\[^{[24]}\] and to restore the forearm vasodilatory effect of acetylcholine in hypercholesterolemic patients\[^{[25]}\].

Aspirin, in high concentrations, inhibits growth of human vascular smooth cells in culture\[^{[26]}\]. This property of aspirin may have a salutary effect after percutaneous intervention in terms of restenosis at the site of angioplasty or stent placement. Aspirin can reverse hypoxia-induced coronary vasoconstriction\[^{[27]}\], a mechanism that contributes to aspirin’s effect on vascular tone following percutaneous coronary intervention.
Aspirin also has a modest anticoagulant effect. Salicylate, a metabolite of aspirin, can inhibit γ-carboxylation of coagulation factors II, VII, IX and X[27-29]. The fibrinolytic activity of blood increases with aspirin and is mediated by acetylation of the ε-amino groups of lysine residues.

Both COX-1 and COX-2 are important in the regulation of angiogenesis. Aspirin inhibits angiogenesis, which is an essential step in the growth of atherosclerosis. This inhibitory effect of aspirin is mediated via inhibition of mitogen-activated protein kinase activity on endothelial cells[30].

**WHAT IS “ASPIRIN RESISTANCE”?**

There is no consensus definition of “aspirin resistance”. This phenomenon has been described based on clinical assessment or on the results of laboratory tests that assess platelet activation. A recent article in the European Heart Journal has aimed at obtaining a consensus definition for aspirin resistance. The clinical definition of “aspirin resistance” relates to the occurrence of thromboembolic events despite aspirin intake. In the laboratory, “aspirin resistance” has been defined as the failure to inhibit platelet reactivity despite taking antiplatelet drugs. However clinical resistance to aspirin has often been termed ‘treatment failure’. Not all patients with ‘treatment failure’ have laboratory evidence of aspirin resistance and vice versa[30].

The reported prevalence of “aspirin resistance” is variable[39-74] with a rate of approximately 8.3% in healthy adults (Table 2). In subjects with one or more risk factors its prevalence ranges from 0.7% to 23.4%. In patients with stable coronary artery disease, again a wide range has been noted, with the prevalence as high as 29%. In patients with acute myocardial infarction, congestive heart failure and peripheral vascular disease, and in others undergoing coronary artery bypass grafting or percutaneous coronary intervention, the reported prevalence of “aspirin resistance” has been as high as 50%-70%. However, based on the results from a combination of three of the most commonly used laboratory tests (VerifyNow®, optical aggregometry, PFA-100®), the prevalence rate is approximately 2% in patients with transient ischemic attacks and stroke[40].

**Laboratory evaluation of platelet activation**

Most of the variability in the prevalence of “aspirin resistance” is due to different platelet function tests that are used to assess platelet activation. The tests used include light transmission aggregometry, whole blood aggregation, flow cytometry and point-of-care tests. Indirect measurement of TXA2 formation include serum TXB2 and urinary 11-dehydro-TXB2. However, measurement of TXA2 metabolites does not take into account formation of TXA2 by non-platelet sources, such as endothelial cells, leukocytes and renal tissue[11].

Light transmission and impedance aggregometry have been the gold standard for measuring platelet aggregation function. Many point-of-care assays have been developed to study platelet activation. Some of these assays assess COX-dependent pathways and others include COX-independent pathways. The most common of these point-of-care assays are VerifyNow® and PFA-100®. A comparison between PFA-100®, platelet aggregometry and Gp IIb/IIIa flow cytometry found little correlation between the results obtained from these three methods[75]. Some investigators have also used measurement of aspirin metabolites and bleeding time to assess the efficacy of aspirin.

**PFA-100® assay**

This test uses cartridges coated with platelet agonists (either collagen/ADP or collagen/epinephrine). The time for platelet plug to close the central opening (closing time) is used as a measure of platelet reactivity[46]. This test is thought to simulate platelet function in vivo and can be considered an *in vitro* equivalent of bleeding time[76]. “Aspirin resistance” is defined as: closing time < 193 s using collagen/epinephrine, and < 121 s using collagen/ADP as agonists[46]. This test is unfortunately not aspirin-specific. It correlates well with light transmission aggregometry.

**VerifyNow® assay**

This is a point-of-care platelet aggregation test that correlates with the results obtained with light transmission aggregometry. Response to aspirin is reported in aspirin resistance units. The extent of COX inhibition is believed to be measured by this assay[77,78]. “Aspirin resistance” is usually taken as ≥ 550 units[80].

**Light transmission and impedance aggregometry assays**

Light transmission aggregometry measures optical density of plasma after platelet aggregation with an agonist. The problem with this test is lack of standardization as to the choice of agonist/s and their concentration. For example, platelet aggregation in a given person may be abnormal in response to ADP 1-5 μmol/L, but completely normal using higher concentrations. Furthermore, there is a marked variability in aggregation response to different agonists. Impedance aggregometry has the same principle, but utilizes whole blood instead of plasma and measures

---

**Table 2** Reported prevalence of “aspirin resistance”

| Prevalence (%) | Ref. |
|---------------|-----|
| Healthy adults | 8.3 | [39] |
| Risk factors   | 0.7-23.4 | [41-48] |
| Stable CAD     | 0.4-29.2 | [41-48] |
| CVD           | 12.5-56 | [49-52] |
| CABG          | 7.1-54 | [53-56] |
| PCI           | 12.7-26.2 | [53-56] |
| MI            | 0.5-70.1 | [53-56] |
| CHF           | 55.0 | [57] |
| PVD          | 9.6-60 | [72,73] |

CAD: Coronary artery disease; CVD: Cardiovascular disease; CABG: Coronary artery bypass grafting; PCI: Percutaneous coronary intervention; MI: Myocardial infarction; CHF: Congestive heart failure; PVD: Peripheral vascular disease.
electrical impedance instead of light transmission\cite{78}. This test assesses the role of blood components including leu-
koocytes and clotting factors besides platelets in thrombus formation as a mild electrical current is passed through the whole blood. Again, the ideal agonist for thrombus formation has not been defined.

**TXA\(_2\): metabolites**

Serum TXB\(_2\) and urinary 11-dehydro-TXB\(_2\) are metabol-
ites of TXA\(_2\). They have been used to assess “aspirin resistance”. These are COX-1 dependent tests and are not platelet specific and do not necessarily reflect platelet reac-
tivity. Serum TXB\(_2\) reflects TXA\(_2\) formation by en-
dothelial cells and leukocytes in addition to platelets. Urini-
ary 11-dehydro-TXB\(_2\): usually requires 24 h urine collec-
tion and reflects TXA\(_2\) formation by renal tissues besides platelets and leukocytes\cite{79}. These tests were initially quite popular, but have lost their popularity because of the time delay between aspirin intake and measurement in the laboratory.

**Thromboelastogram and impact cone and platelet analyzer**

The thromboelastogram platelet mapping system is a point-of-care system that measures clot formation and lysis. This uses whole blood and requires pipetting. The impact cone and platelet analyzer is a point-of-care test that assesses shear-induced platelet adhesion\cite{80}.

**Flow cytometric analysis**

Monoclonal antibodies against platelet surface antigens, such as Gp II b/III a, P-selectin, platelet monocyte ag-
gregates, thrombospondin and CD-40 ligand can be used to measure expression of certain antigens. Expression of these antigens has been found to be lower in patients treated with aspirin than controls\cite{81}.

**Rapid platelet function assay**

In this test, blood is run through a transparent fibrinogen-
coated cartridge with platelet agonists. When a thrombus forms on the surface, light transmission changes and reflects platelet aggregation\cite{82}. This test is not aspirin-
specific.

**Platelet reactivity**

Venous blood is mixed with either EDTA-buffer or EDTA-formaldehyde buffer; activated platelets are dis-
persed in the former and fixed in the latter. The mixture is then centrifuged and only non-activated platelets remain in the supernatant. Platelet count in the supernatant (\(pt\) the platelet count in blood) is a reflection of adherent platelets\cite{83}.

**Bleeding time**

This is the only in vivo test that measures platelet activa-
tion. It is independent of coagulation factors and is a reasonably good index of platelet function\cite{84}.

A recent consensus statement by the Working Group for antiplatelet drug resistance\cite{85} states that the term laboratory resistance should be reserved for pharmaco-
dynamic resistance resulting from changes in enzyme or receptor. Aspirin hyporesponsiveness is defined as more than 10\%–20\% with light transmittance aggregometry and more than 0 ohms with impedance aggregometry. For determining aspirin-specific effects, the recommend-
ed test is arachidonic acid-induced aggregation or serum TXB\(_2\): levels. However, it should be noted that there is no evidence that any of these laboratory values are asso-
ciated with an adverse cardiovascular outcome.

**DOES “ASPIRIN RESISTANCE” REALLY EXIST?**

The phenomenon of “aspirin resistance” is characterized by attenuated inhibition of platelet aggregation in some patients taking aspirin. The term “aspirin resistance” came into use because some patients manifesting this phenomenon had cardiovascular events, presumably on the basis of platelet activation\cite{86}. However, a direct correlation between evolution of cardiovascular events and ex vivo platelet activation has never been demonstrated. Also, the reduced platelet response (aggregation inhibition) in studies showing “aspirin resistance” was identified by different methods in different studies; some used platelet-
rich plasma, others used whole blood to assess platelet ag-
gregation, and yet others used serum TXB\(_2\): measurement. The concentration of agonists used for inducing platelet aggregation varied widely in different studies, and the ago-
nists were different in different studies. Pitfalls in studying platelet activation with different stimuli have been de-
scribed earlier. Some investigators have shown that “aspirin resistance” may be present in some individuals using one particular stimulus, but not another. In addition, a person with “aspirin resistance” may not have “aspirin resistance” a week or two later.

As mentioned earlier, there is residual platelet activa-
tion (primary wave of aggregation) which is unaffected by aspirin treatment and is independent of non-compliance and under-dosing of aspirin. The residual platelet aggre-
gation may be quite marked in some individuals. As stated earlier, there are multiple pathways of platelet aggregation (Figure 1) and most laboratory tests assess only one or two of these pathways. Most of these pathways are not entirely TXA\(_2\)-dependent and, therefore, not aspirin-spe-
cific. Further, most studies on “aspirin resistance” did not measure baseline platelet function (i.e. before aspirin treat-
ment). In our opinion, the wide variation in the prevalence of “aspirin resistance” reflects the underlying heteroge-
nity in platelet response from patient to patient.

There are multiple reasons for the phenomenon of diminished inhibition of platelet aggregation in patients taking aspirin (Table 3). Non-compliance is perhaps the most likely cause of “aspirin resistance”\cite{86,87}. Use of concomitant medications, such as NSAIDs and proton pump inhibitors (PPIs), which affect COX enzyme kinetics, can contribute to “aspirin resistance”. Age, gender
and smoking also reduce the platelet inhibitory effect of aspirin[47]. Hormonal changes in women have been shown to enhance platelet activation, and thus women may be more prone to show “aspirin resistance”[85], others have disputed the presence of this phenomenon[41]. There is also a diurnal as well as a seasonal increase in platelet aggregation related to catecholamine surge in the morning hours and during the winter months which may manifest as a diminished response to aspirin. Variation in pharmacokinetics is another cause of “aspirin resistance”. Clinical conditions, such as diabetes mellitus, advanced coronary disease, chronic kidney disease, acute coronary syndromes, inflammation, obesity and bypass surgery, are characterized by an increased platelet aggregatory response to different stimuli, which may be characterized as “aspirin resistance”. We have observed serum TXB2 levels to rise with continued use of aspirin (unpublished data), perhaps a response to the increase in platelet turnover and/or activation of alternate sources of TXA2 generation.

Genetic polymorphisms have been noted to contribute to the diminished effect of aspirin on platelet biology. Genetic polymorphisms involving GpIIb-IIIa (PLA1/A2 polymorphisms)[85,86] and COX-1 and COX-2[85,87] can lead to a variable effect of aspirin on platelet function. It is also important to recognize that in conditions that are associated with infection and inflammation, non-platelet sources such as monocytes, macrophages and endothelial cells, activate the COX-2 enzyme, resulting in increased formation of TXA2 and increased levels of F2-isoprostanes. Such COX-1-independent mechanisms are especially relevant to patients with diabetes mellitus, hyperlipidemia, smoking and heart failure, all of which are associated with augmented lipid peroxidation of arachidonic acid and consequent overproduction of isoprostanes. Failure of usual doses of aspirin to completely inhibit TXA2 may be misinterpreted as aspirin resistance.

Table 3 Underlying causes of “aspirin resistance”

| Abnormal pharmacokinetics                  |
|--------------------------------------------|
| Non-compliance                             |
| Inadequate dosing                          |
| Tachyphylaxis                              |
| Interaction with other drugs, such as NSAIDs and PPIs |
| Clinical conditions                        |
| Advanced coronary artery disease, acute coronary syndromes, CABG |
| Diabetes mellitus                          |
| Heart failure                              |
| Infection/inflammation                     |
| Obesity                                    |
| Genetic                                    |
| COX-1 gene mutation                        |
| COX-2 overexpression                       |
| Gp IIb-IIIa polymorphisms                  |
| Molecular                                  |
| Increased turnover of platelets            |
| PGII-substrate is provided to platelets by monocytes or endothelial cells |
| Incomplete inhibition of TXA2 formation    |
| Increased platelet sensitivity to ADP and collagen |
| Increased COX-2 expression on platelets    |

COX: Cyclooxygenase; NSAIDs: Non-steroidal anti-inflammatory drugs; PPIs: Proton pump inhibitors; Gp: Glycoprotein; TXA2: Thromboxane A2; PGII: Prostaglandin H2; ADP: Adenosine diphosphate.

**REFERENCES**

1 Stone E. An account of the success of the bark of the willow in the cure of agues. In a letter to the Right Honourable George Earl of Macclesfield, President of R. S. from the Rev. Mr. Edmund Stone, of Chipping-Norton in Oxfordshire. Phil Trans 1763; 53: 195-200
2 Jack DB. One hundred years of aspirin. Lancet 1997; 350: 437-439
3 Sneader W. The discovery of aspirin: a reappraisal. BMJ 2000; 321: 1591-1594
4 Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, Buring J, Hennekens C, Kearney P, Meade T, Patrono C, Roncaglioni MC, Zanchetti A. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009; 373: 1849-1860
5 De Berardis G, Sacco M, Strippoli GF, Pellegrini F, Graziano G, Tognoni G, Nicolucci A. Aspirin for primary prevention of coronary heart disease: a clinical guideline. BMJ 2009; 339: b2003
6 Mehta JL et al. Aspirin resistance

**MANAGEMENT OF DIMINISHED RESPONSE TO ASPIRIN**

The 2005 position paper of the working group on aspirin resistance concluded that there was not enough evidence of clinical improvement in changing treatment in aspirin resistance[85]. Some experts have recommended increasing the dose of aspirin to overcome “aspirin resistance”[85,89], others have refuted the usefulness of this approach[8]. We believe that while most patients have adequate inhibition of platelet aggregation with low doses of aspirin, others need higher doses. Which patients are in the latter group is not known. Accordingly, we tend to prescribe a 325 mg daily dose to patients with multiple risk factors with evidence of ongoing vascular injury and inflammation, and to those who show evidence of repeated coronary artery occlusion. Addition of other antiplatelet agents such as clopidogrel and prasugrel to aspirin therapy might also help. A recent study shows that addition of an omega-3 fatty acid can overcome “aspirin resistance”[90].

In general, the use of NSAIDs and PPIs in patients needing aspirin should be curtailed or kept at a minimum as these agents tend to reduce the availability of aspirin. There may well be other agents that influence the pharmacokinetics of aspirin. Point-of-care tests, in our view, are not helpful in defining who is “aspirin resistant” and who is not.

**CONCLUSION**

Aspirin is a remarkable drug that reduces cardiovascular events and limits atherogenesis and perhaps development. This drug works through a host of mechanisms which are complementary to its platelet inhibitory effect. As such, use of the term “aspirin resistance” based on imperfect test-tube measurements is a disservice to the legacy of this very useful compound.
cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials. BMJ 2009; 339: b5531

6 Roth GJ, Calverley DC. Aspirin, platelets, and thrombosis: theory and practice. Blood 1994; 83: 895-898

7 Brunton L, Lazo J, Parker K, Goodman and Gilman's The Pharmacological Basis of Therapeutics. 11th ed. New York: McGraw-Hill Professional, 2005

8 Furie B, Furie BC. Mechanisms of thrombus formation. N Engl J Med 2008; 359: 938-949

9 Palabrica T, Lobb R, Furie BC, Aronovitz M, Benjamin C, Hsu YM, Sajer SA, Furie B. Leukocyte accumulation promoting fibrin deposition is mediated in vivo by P-selectin on adherent platelets. Nature 1992; 359: 848-851

10 Hankey GJ, Elkeboom JW. Aspirin resistance. Lancet 2006; 367: 606-617

11 Frelinger AL 3rd, Furman MI, Linden MD, Li Y, Fox ML, Barnard MR, Michelson AD. Residual arachidonic acid-induced platelet activation via an adenosine diphosphate-dependent but cytochrome-c and cytochrome-c2-independent pathway: a 700-patient study of aspirin resistance. Circulation 2006; 113: 2888-2896

12 López-Farre A, Caramelo C, Esteban A, Alberola ML, Millás L, Montón M, Casado S. Effects of aspirin on platelet-neutrophil interactions. Role of nitric oxide and endothelin-1. Circulation 1995; 91: 2080-2088

13 Egger G, Burda A, Obnerester A, Mitterhammer H, Kager G, Jürgens G, Hofer HP, Fabjan JS, Pilger E. Blood polymorphonuclear leukocyte activation in atherosclerosis: effects of aspirin. Inflammation 2001; 25: 129-135

14 Steer KA, Wallace TM, Bolton CH, Hartog M. Aspirin protects low density lipoprotein from oxidative modification. Heart 1997; 77: 333-337

15 Mehta JL, Chen J, Yu F, Li DY. Aspirin inhibits ox-LDL-mediated LOX-1 expression and metalloproteinase-1 in human coronary endothelial cells. Cardiovasc Res 2004; 64: 243-249

16 Marwali MR, Hu CP, Mohandas B, Dandapat A, Deonkar P, Chen J, Cawich I, Sawamura T, Kaviad M, Mehta JL. Modulation of ADP-induced platelet activation by aspirin and prasugrel: role of lectin-like oxidized low-density lipoprotein receptor-1, nitric oxide, oxidative stress, and inside-out integrin signaling. J Pharmacol Exp Ther 2007; 322: 1324-1332

17 Betts WH, Whitehouse MW, Cleland LG, Vernon-Roberts B. In vitro antioxidant properties of potential biotransformation products of salicylate, sulphasalazine and amidopyrine. J Free Radic Biol Med 1985; 1: 273-280

18 Obele S, Potte E, Aabe A, Podhaisky HP, Schröder H. Aspirin increases ferritin synthesis in endothelial cells: a novel antioxidant pathway. Circ Res 1998; 82: 1016-1020

19 Farivar RS, Brecher P. Salicylate is a transcriptional inhibitor of the inducible nitric oxide synthase in cultured cardiac fibroblasts. J Biol Chem 1996; 271: 31585-31592

20 Kimura A, Roseto J, Suh KY, Cohen AM, Bing RJ. Effect of acetylsalicylic acid on nitric oxide production in infarcted heart in situ. Biochem Biophys Res Commun 1998; 251: 874-878

21 Pinckard RN, Hawkins D, Farr RS. In vitro acetylation of plasma proteins, enzymes and DNA by aspirin. Nature 1968; 219: 68-69

22 Ezratty A, Freedman JE, Simon D, Loscalzo J. The antithrombotic effects of acetylation of fibrinogen by aspirin. J Med Vet Biol Med 1994; 5: 152-159

23 Husain S, Andrews NP, Mulcahy D, Panaza JA, Quyyumi A A. Aspirin improves endothelial dysfunction in atherosclerosis. Circulation 1998; 97: 716-720

24 Weber C, Earl W, Pietsch A, Weber PC. Aspirin inhibits nuclear factor-kappa B mobilization and monocyte adhesion in stimulated human endothelial cells. Circulation 1995; 91: 1914-1917

25 Voisard R, Fischer O, Ovsshad M, Voglic S, Baur R, Susa M, Koenig W, Hombach V. Aspirin (5 mmol/L) inhibits leukocyte attack and triggered reactive cell proliferation in a 3D human coronary in vitro model. Circulation 2001; 103: 1688-1694

26 Bernhardt J, Rogalla K, Lüscher TF, Bührler FR, Resnik TJ. Acetylsalicylic acid, at high concentrations, inhibits vascular smooth muscle cell proliferation. J Cardiovasc Pharmacol 1993; 21: 973-976

27 Loew D, Vaznizer H. Dose-dependent influence of acetylsalicylic acid on platelet functions and plasmatic coagulation factors. Haemostasis 1976; 5: 239-249

28 Owens MR, Cimino CD. The inhibitory effects of sodium salicylate on synthesis of factor VII by the perfused rat liver. Thromb Res 1980; 18: 839-845

29 Roncaglioni MC, Ulrich MM, Muller AD, Soute BA, de Boer van den Berg MA, Vermeer C. The vitamin K-antagonism of salicylate and warfarin. Thromb Res 1986; 42: 727-736

30 Jones MK, Wang H, Peskar BM, Levin E, Itani RM, Sarfey IJ, Tarnawski AS. Inhibition of angiogenesis by nonsteroidal anti-inflammatory drugs: insight into mechanisms and implications for cancer growth and ulcer healing. Nat Med 1999; 5: 1418-1423

31 Mehta JL, Nichols WW. The potential role of thromboxane inhibitors in preventing myocardial ischaemic injury. Drugs 1990; 40: 657-665

32 Mehta JL. Oxidized or native low-density lipoprotein cholesterol: which is more important in atherogenesis? J Am Coll Cardiol 2006; 48: 980-982

33 Fields M, Lewis CG, Bureau I. Aspirin reduces blood cholesterol in copper-deficient rats: a potential antioxidant agent? Metabolism 2001; 50: 559-561

34 Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997; 336: 973-979

35 Blache D, Bouthillier D, Davignon J. Acute influence of smoking on platelet behaviour, endothelium and plasma lipids and normalization by aspirin. Atherosclerosis 1992; 93: 179-188

36 Noon JP, Walker BR, Hand MF, Webb DJ. Impairment of forearm vasodilatation to acetylcholine in hypercholesterolaemia is reversed by aspirin. Cardiovasc Res 1998; 38: 480-484

37 Toda N, Matsumoto T, Yoshida K. Comparison of hypoxia-induced contraction in human, monkey, and dog coronary arteries. Am J Physiol 1992; 262: H678-H683

38 Kulickowski W, Witkowski A, Polorosi L, Watala C, Filipiak K, Budaj A, Golanek J, Sitkiewicz D, Pregowski J, Gorski J, Zembala M, Orloński G, Huber K, Arnesen H, Kristensen M, Jürgens G, Hofer HP, Fabjan JS, Pilger E. Blood polymorphonuclear leukocyte activation in atherosclerosis: effects of aspirin. Inflammation 2001; 25: 129-135

39 Marshall PW, Williams AJ, Dixon RM, Growcott JW, Warburton S, Armstrong J, Moores J. A comparison of the effects of aspirin on bleeding time measured using the Simplate method and closure time measured using the PFA-100, in healthy volunteers. Br J Clin Pharmacol 1997; 44: 151-155

40 Malinin A, Spergling M, Muhlestein B, Steinshlub S, Serebruy V. Assessing aspirin responsiveness in subjects with multiple risk factors for vascular disease with a rapid platelet function analyzer. Blood Coagul Fibrinolysis 2004; 15: 295-301

41 Wang JC, Aucocin-Barry D, Manuelian D, Monbouquette R, Reisman M, Gray W, Block PC, Block EH, Ladenheim M, Simon DI. Incidence of aspirin nonresponsiveness using the Ultegra Rapid Platelet Function Assay-ASA. Am J Cardiol 2003; 92: 1492-1494

42 Pampucu B, Ofaz H, Nisanci Y. The role of platelet glycoprotein IIa polymorphism in the high prevalence of in vitro aspirin resistance in patients with intracoronary stent restenosis. Am Heart J 2005; 149: 675-680
Macchi I, Christiaens L, Brabant S, Sorel N, Ragot S, Allal J, Mauco G, Brizard A. Resistance in vitro to low-dose aspirin is associated with platelet PAI1 (GIa) polymorphism but not with C807T (GPAIa/Ia) and C-5T Kozak (GPGalba) polymorphisms. J Am Coll Cardiol 2003; 42: 1115-1119.

Friend M, Vucenik I, Miller M. Research pointers: Platelet responsiveness to asparin in patients with hyperlipidaemia. BMJ 2003; 326: 82-83.

Christiaens L, Macchi L, Herpin D, Coisne D, Duplantier C, Allal J, Mauco G, Brizard A. Resistance to aspirin in vitro at rest and during exercise in patients with angiographically proven coronary artery disease. Thromb Res 2002; 108: 115-119.

Macchi I, Christiaens L, Brabant S, Sorel N, Allal J, Mauco G, Brizard A. Resistance to aspirin in vitro is associated with increased platelet sensitivity to adenosine diphosphate. Thromb Res 2002; 107: 45-49.

Lee PY, Chen WH, Ng W, Cheng X, Kwok JY, Tse HF, Lau CP. Low-dose aspirin increases aspirin resistance in patients with coronary artery disease. Am J Med 2005; 118: 723-727.

Gum PA, Kotke-Marchant K, Welsh PA, White J, Topol EJ. A prospective, blinded determination of the natural history of aspirin resistance among stable patients with cardiovascular disease. J Am Coll Cardiol 2003; 41: 961-965.

Tanty US, Bidden KP, Gurbel PA. Overestimation of platelet aspirin resistance detection by thrombelastograph platelet mapping and validation by conventional aggregometry using arachidonic acid stimulation. J Am Coll Cardiol 2005; 46: 1705-1709.

McCabe DJ, Harrison P, Mackie IJ, Sidhu PS, Lawrie AS, Purdy G, Machin SJ, Brown MM. Assessment of the anti-platelet effects of low to medium dose aspirin in the early and late phases after ischaemic stroke and TIA. Platelets 2005; 16: 269-280.

Grundmann K, Jaschonek K, Kleine B, Dichtangs J, Topka H. Aspirin non-responder status in patients with recurrent cerebrovascular ischemic attacks. J Neurol 2003; 250: 65-66.

Alberts MJ, Bergman DL, Molner E, Jovanovic BD, Ushiwata I, Teruya J. Antiplatelet effect of aspirin in patients with cerebrovascular disease. Stroke 2004; 35: 175-178.

Grotemeyer KH, Scharafinski HW, Husstedt IW. Two-year follow-up of aspirin responder and aspirin non responder. A pilot-study including 180 post-stroke patients. Thromb Res 1993; 71: 397-403.

Grotemeyer KH. Effects of acetylsalicylic acid in stroke patients. Evidence of nonresponders in a subpopulation of treated patients. Thromb Res 1991; 63: 587-593.

Berrouschot J, Schwlicht B, von Twickel G, Fischer C, Uhlmann M, Siegemund T, Siegemund A, Roessler A. Aspirin resistance in patients who appear to be resistant to aspirin after healing of coronary artery disease. J Am Coll Cardiol 2003; 41: 961-965.

Hobikuoglo GF, Norgaz T, Akuo H, Ozer O, Erturk M, Nukalem Z, Narin A. High frequency of aspirin resistance in patients with acute coronary syndrome. Thorok J Exp Med 2005; 207: 59-64.

Faraday N, Braunstein JB, Heldman AW, Bolton ED, Chiles KA, Gerenstibith G, Schulan SP. Prospective evaluation of the relationship between platelet-leukocyte conjugate formation and recurrent myocardial ischemia in patients with acute coronary syndromes. Platelets 2004; 15: 9-14.

Sane DC, McKee SA, Malinin AI, Serebrayu VL. Frequency of aspirin resistance in patients with congestive heart failure treated with antecedent aspirin. Am J Cardiol 2002; 90: 893-895.

Mueller MR, Salat A, Stangl P, Murahito M, Pulaki S, Boehm D, Koppensteiner R, Ergun E, Mittboeck M, Schreiner W, Losert U, Woller E. Variable platelet response to low-dose ASA and the risk of limb deterioration in patients submitted to peripheral arterial angioplasty. Thromb Haemost 1997; 78: 1003-1007.

Ziegler S, Maca T, Alt E, Speiser W, Schneider B, Minar E. Monitoring of antiplatelet therapy with the FPA-100 in peripheral angioplasty patients. Platelets 2002; 13: 493-497.

Harrison P, Segal H, Blasbery K, Furtado C, Silver L, Rothwell PM. Screening for aspirin responsiveness after transient ischemic attack and stroke: comparison of 2 point-of-care platelet function tests with optical aggregometry. Stroke 2005; 36: 1001-1005.

Hézard N, Metz D, Nazyerolla P, Drouillé C, Potron G, Nguyen P. FPA-100 and flow cytometry: can they challenge aggregometry to assess antiplatelet agents, other than GPlIb/IIa blockers, in coronary angioplasty? Thromb Res 2002; 108: 43-47.

Homocnik M, Jilma B, Hergovich N, Stohlavetz P, Panzer S, Speiser W. Monitoring of aspirin (ASA) pharmacodynamics and early vein graft failure after coronary artery bypass grafting. J Thorac Cardiovasc Surg 2006; 131: 122-130.

Lev EI, Patel RT, Maresch KJ, Gurtikhonda S, Granada J, DeLao T, Bray PF, Kleiman NS. Aspirin and clopidogrel drug response in patients undergoing percutaneous coronary intervention: the role of dual drug resistance. J Am Coll Cardiol 2006; 47: 27-33.

Chen WH, Lee PY, Ng W, Kwok JY, Cheng X, Lee SW, Tse HF, Lau CP. Relation of aspirin resistance to coronary flow reserve in patients undergoing elective percutaneous coronary intervention. Am J Cardiol 2005; 96: 768-763.

Zhang Y, Liang J, Zhou YF, Yuan H, Zhang YZ, Dong L. [Study on the relationship between aspirin resistance and incidence of myonecrosis after non-emergent percutaneous coronary intervention] Zhonghua Xin Xue Gao blood Zazhi 2005; 33: 695-699.

Gurbel PA, Bidden KP, Hiatt BL, O’Connor CM. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. Circulation 2003; 107: 2908-2912.

Stejskal D, Prosková J, Lacnáč B, Horalík D, Hamplová A, Oral I, Hrabovská I, Ochmanová R, Adamovská S, Juráková R, Ozanová G, Juchelka J, Kulisková O, Pěnkavová H. [Use of assessment of aggregation of thrombocytes induced by cationic propyl gallate to estimate recurrence of cardiovascular complications] Vnitř Lék 2004, 50: 591-599.

Borna C, Lazarowski E, van Heusden C, Ohln H, Erlinge D. Resistance to aspirin is increased by ST-elevation myocardial infarction and correlates with adenosine diphosphate levels. Thromb J 2005; 3: 10.

Schwartz KA, Schwartz DE, Ghosheh K, Reeves MJ, Barber K, DeFranco A. Compliance as a critical consideration in patients who appear to be resistant to aspirin after healing of myocardial infarction. Am J Cardiol 2005; 95: 973-975.

Andersen K, Hurlen M, Arnesen H, Seljeflot I. Aspirin non-responsiveness as measured by FPA-100 in patients with coronary artery disease. Thromb Res 2002; 108: 37-42.

Mehta JL et al. Aspirin resistance
with the platelet function analyzer PFA-100. *Thromb Haemost* 2000; 83: 316-321

78 Paniccia R, Antonucci E, Gori AM, Marcucci R, Giglioli C, Antonucci D, Gensini GF, Abbate R, Prisco D. Different methodologies for evaluating the effect of clopidogrel on platelet function in high-risk coronary artery disease patients. *J Thromb Haemost* 2007; 5: 1839-1847

79 Kasotakis G, Pipinos II, Lynch TG. Current evidence and clinical implications of aspirin resistance. *J Vasc Surg* 2009; 50: 1500-1510

80 Gurbel PA, Becker RC, Mann KG, Steinhubl SR, Michelson AD. Platelet function monitoring in patients with coronary artery disease. *J Am Coll Cardiol* 2007; 50: 1822-1834

81 Serebruany VL, Malinin AI, Oshrine BR, Sane DC, Takserman A, Atar D, Hennekens CH. Lack of uniform platelet activation in patients after ischemic stroke and choice of antiplatelet therapy. *Thromb Res* 2004; 113: 197-204

82 Freedman JE. The aspirin resistance controversy: clinical entity or platelet heterogeneity? *Circulation* 2006; 113: 2865-2867

83 Michelson AD, Cattaneo M, Eikelboom JW, Gurbel P, Kottke-Marchant K, Kunicki TJ, Pulcinelli FM, Cerletti C, Rao AK. Aspirin resistance: position paper of the Working Group on Aspirin Resistance. *J Thromb Haemost* 2005; 3: 1309-1311

84 Chen WH, Lee PY, Ng W, Tse HF, Lau CP. Aspirin resistance is associated with a high incidence of myocardial infarction after non-urgent percutaneous coronary intervention despite clopidogrel pretreatment. *J Am Coll Cardiol* 2004; 43: 1122-1126

85 Szczeklik A, Undas A, Sanak M, Frołow M, Wegrzyn W. Relationship between bleeding time, aspirin and the PLA1/A2 polymorphism of platelet glycoprotein IIa. *Br J Haematol* 2000; 110: 965-967

86 Papp E, Havasi V, Bene J, Komlosi K, Czopf L, Magyar E, Feher C, Feher G, Horvath B, Marton Z, Alexy T, Habon T, Szabo L, Toth K, Melegh B. Glycoprotein IIIA gene (PIA) polymorphism and aspirin resistance: is there any correlation? *Ann Pharmacother* 2005; 39: 1013-1018

87 Dropinski J, Musial J, Sanak M, Wegrzyn W, Nizankowski R, Szczeklik A. Antithrombotic effects of aspirin based on PLA1/A2 glycoprotein IIa polymorphism in patients with coronary artery disease. *Thromb Res* 2007; 119: 301-303

88 Halushka MK, Halushka PV. Why are some individuals resistant to the cardioprotective effects of aspirin? Could it be thromboxane A2? *Circulation* 2002; 105: 1620-1622

89 Eikelboom JW, Hirsh J, Weitz JJ, Johnston M, Yi Q, Yusuf S. Aspirin-resistant thromboxane biosynthesis and the risk of myocardial infarction, stroke, or cardiovascular death in patients at high risk for cardiovascular events. *Circulation* 2002; 105: 1650-1655

90 Lev EI, Solodky A, Harel N, Mager A, Brosh D, Assali A, Roller M, Battler A, Kleiman NS, Kornowski R. Treatment of aspirin-resistant patients with omega-3 fatty acids versus aspirin dose escalation. *J Am Coll Cardiol* 2010; 55: 114-121

S- Editor Cheng JX L- Editor Cant MR E- Editor Zheng XM