Cañivano Petreñas, L.; García Yubero, C.
Resistance to aspirin: Prevalence, mechanisms of action and association with
thromboembolic events. A narrative review
Farmacia Hospitalaria, vol. 34, núm. 1, 2010, pp. 32-43
Sociedad Española de Farmacia Hospitalaria
Madrid, España

REVIEW

Resistance to aspirin: Prevalence, mechanisms of action and association with thromboembolic events. A narrative review

L. Cañivano Petreñas,[a],* and C. García Yubero[b]

[a]*Pharmacy Division, Guy's & St. Thomas Hospital NHS Foundation Trust, London, United Kingdom*
[b]*Pharmacy Division, Infanta Sofía Hospital, San Sebastián de los Reyes, Madrid, Spain*

Abstract
Objectives: The purpose of this study is to review the prevalence of aspirin resistance in patients with a high risk of cardiovascular events, and secondly, to investigate its epidemiology and mechanism of action, and the clinical consequences it can provoke.
Material and methods: A search was run on PubMed, EMBASE and Reviews Database for English or Spanish articles on aspirin resistance published up to November 2008. Additional studies were obtained by searching the reference lists in the selected articles for articles relevant to our secondary objectives.
Results: Aspirin resistance is described as affecting 0% to 57% of the population, and is related to a decreased protective effect against strokes and cardiovascular events. Many modifiable and unmodifiable factors can affect the efficacy of antiplatelet drugs. Possible strategies for overcoming this decreased antiaggregant effect include increasing the aspirin dosage or dual therapy with another antiplatelet agent.
Conclusions: Lack of response to aspirin decreases its protective effects. However, lack of a standard definition for aspirin resistance, the absence of diagnostic reference methods to identify resistant patients, and the different mechanisms of action involved in platelet aggregation call the clinical importance of this fact into question. Additional well-designed studies are needed to detect patients with real resistance in order to have more effective prevention of cardiovascular morbidity and mortality.
© 2009 SEFH. Published by Elsevier España, S.L. All rights reserved.

*Corresponding author.
E-mail addresses:* leti-27@hotmail.com, leticia.canivano-petrenas@gstt.nhs.uk (L. Cañivano Petreñas).

Resistencia a la aspirina: prevalencia, mecanismos de acción y asociación con eventos tromboembólicos. Revisión narrativa

Resumen

Objetivo: Revisar la prevalencia de resistencia a la aspirina en pacientes de alto riesgo cardio-vascular y, de forma secundaria, investigar la epidemiología, los mecanismos de acción de este fenómeno y las consecuencias clínicas que se derivan de ello.

Material y métodos: Se realizó una búsqueda en PubMed, EMBASE y Reviews Database de artículos publicados en inglés y en español hasta noviembre de 2008 referidos a resistencia a la aspirina. Se hizo también un seguimiento de las referencias para recuperar aquellas consideradas relevantes para los objetivos secundarios de esta revisión.

Resultados: La resistencia a la aspirina se describe entre un 0 y un 57%, lo que se traduce en una disminución de la eficacia protectora frente a eventos cerebrovasculares y cardiovasculares. Numerosos factores modificables, así como otros no modificables, influyen en la eficacia del efecto antiagregante. Las estrategias por seguir para contrarrestar esta antiagregación disminuida pueden dirigirse a un aumento de dosis de aspirina o a la terapia dual junto con otros agentes antiplaquetarios.

Conclusiones: La falta de respuesta a la aspirina disminuye su eficacia protectora. Sin embargo, la falta de una definición de resistencia a la aspirina universalmente consensuada y la inexistencia de un método diagnóstico de referencia que identifique con fiabilidad a pacientes resistentes, así como los diferentes mecanismos de acción implicados en la agregación plaquetaria, cuestionan la relevancia clínica de este fenómeno. Son necesarios más estudios clínicos adecuadamente diseñados para detectar pacientes con verdadera resistencia a la aspirina y así conseguir prevenir de manera más eficaz la morbimortalidad cardiovascular.

Introduction

Cardiovascular and cerebrovascular diseases are some of the main causes of morbidity and mortality in developed countries. Aspirin or acetylsalicylic acid (ASA) is the most common antiplatelet drug used as a prophylactic against thromboembolic events. In patients at a high risk for cardiovascular disease, treatment with ASA has been shown to reduce the risk of non-fatal acute myocardial infarction (AMI), non-fatal stroke or death due to vascular causes.[1,2]

The antiaggregant effect of ASA is achieved through permanent inhibition of the enzymes prostaglandin (PG) synthase or cyclooxygenase (COX).[3] The COX enzyme is present in two isoforms: COX-1, which is a constitutive enzyme present in most cells, and COX-2, which is only expressed in response to inflammatory stimuli. The irreversible inhibition of COX-1 blocks conversion of arachidonic acid (AA) to PG, such as PGH2, a precursor of thromboxane A2 (TXA_2).[3] This mediator, together with other biological mediators such as adenosine diphosphate (ADP) or fibrinogen, acts in a way that favours a prothrombotic state.

ASA is 170 times more effective at inhibiting the COX-1 enzyme than COX-2, and low doses (75-300 mg) will therefore only inhibit COX-1 (antiaggregant effect). Although ASA has a short half-life (approximately 30 min), a single daily dose is enough to inhibit 90% of the TXA_2 production since it irreversibly inactivates the COX-1 enzyme in blood platelets and only 10% of the platelets are renewed daily.

However, cases have been observed in which antiaggregant treatment is suboptimal, leading to certain patients suffering cardiovascular events despite proper administration of ASA.[4] This is called "aspirin resistance" or "failure to respond to ASA". These terms, although lacking a universally accepted definition, can be oriented from two different approaches. From a clinical viewpoint, resistance (or failure to respond) to ASA is defined as the appearance of thromboembolic cardiovascular events despite continued administration of ASA in therapeutic doses. However, due to the multi-factor nature of atherothrombotic processes,[5] it is not correct to speak only of resistance to ASA in this context. As a result, the biochemical definition is more generally used. It defines resistance as the failure of therapeutic doses of ASA to prolong bleeding time, which is a primary measurement of platelet function, or a failure to reduce TXA_2 production.[6]

The most common methods used to measure the degree of platelet inhibition are described below[7]:

- In vivo test:
  ○ *Urinary thromboxane B_2 concentrations:* 11-dehidro-tromboxane B_2, the stable metabolite of TXA_2, is measured in urine as a platelet activation marker, and therefore a marker of response to antithrombotic drugs.
  ○ *Bleeding time:* measures the length of a haemorrhage resulting from a puncture in the skin. This technique is not commonly used because it is only rarely reproducible.
- In vitro test: multiple laboratory techniques have been developed for measuring platelet activation. However, none of those used today is considered a reference

method, since they do not evaluate platelet aggregation as a whole; there are many channels for platelet activation. Nevertheless, these methods are much more widespread than in-vivo testing.

- *Optical aggregometry:* this is a spectrophotometric technique which measures light transmission through a platelet-rich plasma sample. Aggregation is induced with a specific platelet agonist (AA, ADP, epinephrine, etc.) depending on the antiaggregant drug being tested, and considering the different action mechanisms they possess.
- *Verify Now (RPFA [Ultegra-Rapid Platelet Function Assay]):* turbidimetric study based on the same principle as the previous method, with the advantage of being faster and requiring a smaller sample size. The result is expressed in arbitrary units of response to the agonist.
- *PFA-100 (Platelet Function Analyzer):* analyser that provides an automatic evaluation of platelet aggregation caused by high flow velocity and by a mixture of platelet activators, collagen/epinephrine or collagen/ADP, which adhere to a capillary membrane. Platelets interact with the membrane and occlude the aperture. The haemostatic response is expressed as the time needed to obstruct the flow in the capillary interior, which would be least to most platelet aggregation.

The primary goal of this narrative study is to review the prevalence of ASA resistance in patients at high cardiovascular risk who are being treated with this antiaggregant drug for secondary prevention of cardiovascular and cerebrovascular events. Secondly, we will describe the possible action mechanisms explaining this phenomenon, the clinical consequences deriving from it, and the possible strategies for improving response to antiplatelet drugs in these patients.

Material and methods

Information sources: search strategy.

We performed a literature search in PubMed of all articles published up to November 2008 by entering the keywords *"aspirin"* AND *"drug resistance"* in MESH. We set our search limits for publications in English and Spanish. After recovering a high number of articles, we limited the search by using two different strategies: we first set limits to *"clinical trial"*, *"meta-analysis"*, and *"randomized controlled trial"*, after which we set limits to *"review"* and *"practice guidelines"*. In addition, we performed another bibliographical search in EMBASE which employed the terms *"aspirin"* AND *"drug resistance"* OR *"disease resistance"* OR *"resistance blood vessel"* OR *"therapy resistance"*.

We also reviewed Reviews Database-Cochrane Database of Systematic Reviews, American College of Physicians Journal Club, Database of Abstracts of Reviews of Effects and Cochrane Central Register of Controlled Trials.

We subsequently performed a manual search for articles of interest listed in the bibliographies of articles which had already been selected.

From the resulting articles, we excluded those that did not meet the following inclusion criteria:

- Patients older than 18 being treated with ASA for secondary prevention of cardiovascular or cerebrovascular events.
- Definition of ASA resistance.
- Definition of the methods for measuring platelet function.

Many of the excluded articles were considered for the description of this review's secondary objectives.

Results

We recovered a total of 190 references from PubMed and EMBASE, of which 43 were selected according to their abstracts and titles. In the other databases we reviewed, 110 new references appeared after duplicates were eliminated; of these, only two were selected based on their titles and abstracts. During the subsequent manual search, we added two articles in Hungarian and Polish for which only an abstract was available.

To perform the prevalence review, we selected 33 articles that met the inclusion criteria out of the pool of 47 previously chosen articles.

Prevalence of resistance

Using the selected clinical trials, we reviewed the prevalence of resistance to ASA in patients on antiaggregant treatment with different clinical situations. The large majority of these studies included at least one in vitro test to determine platelet aggregation.

The prevalence we found showed a very wide range of variation between 0.4% and 57%[8-40] (Table 1).

The meta-analysis by Hovensetal[41] established a mean prevalence of ASA resistance of 24% (95% CI: 20-28), that is, one in four patients was likely to be resistant to the treatment. A similar result was obtained by Crescente et al,[42] who showed a prevalence of 27% when platelet aggregation was measured using PFA-100.

Association of resistance to acetylsalicylic acid and prothrombotic events

The clinical relevance of this phenomenon has been investigated in patients with a history of stable cardiovascular disease,[23,39] coronary artery disease,[13,27,30,40,43,44] cerebrovascular events,[10,12,13,44] coronary artery bypass,[29,33,45] peripheral vascular disease[46] and percutaneous coronary interventions[34,35] (Table 2).

The large majority of these studies find a significant correlation between resistance to ASA and a larger risk of cardiovascular and cerebrovascular events among patients with this type of sensitivity: higher frequency of cerebrovascular events, cardiovascular death, fatal or non-fatal AMO, restenosis after a percutaneous transluminal angioplasty or coronary artery bypass.

Several meta-analyses, including both prospective and retrospective studies,[47-50] have been carried out to demonstrate the association between resistance to ASA and increased risk of vascular events. All of these studies confirm the increase in risk of new cardiovascular events appearing

Table 1 Prevalence of resistance to acetylsalicylic acid in secondary prevention

Study	Patient characteristics, n	mg ASA/day	Test used to measure R	Prevalence of R to ASA, %
Harrison et al[8]	Stroke (100)	75-150	Optical aggregometry PFA-100 RPFA	Aggregometry: 5 PFA-100: 22 RPFA: 17 R per all 3 tests: 2
Alberts et al[9]	Stroke (129)	81-650	PFA-100	37
Berrouschot et al[10]	Stroke (291)	300	Optical aggregometry	Primary R (24 h after beginning treatment): 7.2 Secondary R (3, 6 or 12 months after beginning treatment): 4.1
Grotemeyer[11]	Stroke (82)	50, 100 and 200 (in SD)	RP	Primary R (2 h after ingesting ASA): • 500 mg and 200 mg: 10 • 100 mg: 20 • 50 mg: 30
Grotemeyer et al[12]	Stroke (180)	1,500	RP	33
Grundmann et al[13]	Stroke (53) (controlled case study)	100	PFA-100	R in the case group (stroke at least 3 days before): 34 R in the control group (stroke at least 24 months before): 0
Helgason et al[14]	Stroke (113)	325 (gradually scaled doses up to 1,300 in non-responders)	Optical aggregometry	≤325 mg: 20.5, semi-R 650 mg: 3.7, semi-R 950 mg: 0.9, semi-R 1,300 mg: 0, R
Helgason et al[15]	Stroke (306)	325 (gradually scaled doses up to 1,300 in non-responders)	Optical aggregometry	≤325 mg: 25.4, semi-R 1,300 mg: 8.2
Macchi et al[16]	Stroke (37)	160	PFA-100	24.3
Tarján et al[17]	CAD (75)	200-325	Optical aggregometry	34
Coma-Canella et al[18]	Stable CVD (113)	100-300	PFA-100	32
Christiaens et al[19]	Stable CVD (50)	75-300	PFA-100	20 (at rest). In those who responded at rest, 22% were R after exercise
Dussaillant et al[20]	Stable CVD (99)	100-325	Optical aggregometry	11.1
Friend et al[21]	Stable CVD (56)	325	Optical aggregometry	25
Gum et al[22]	Stable CVD (325)	325	Optical aggregometry PFA-100	Aggregometry: 5.5-R 23, 8-semi-R PFA-100: 9.5
Gum et al[23]	Stable CVD (326)	325	Optical aggregometry	5.2
Kuliczkowski et al[24]	Stable CVD (205)	160	Optical aggregometry	20
Lee et al[25]	Stable CVD (468)	100	RPFA	27.4
Macchi et al[26]	Stable CVD (98)	160	PFA-100	29.6
Pamuku et al[27]	CAD (105)	100-300	PFA-100	19
Wang et al[28]	CAD (422)	81-325	RPFA	23
Buchanan et al[29]	CABG (289)	325	Bleeding time	54.7
Andersen et al[30]	AMI (202)	160	PFA-100	35
Schwartz et al[31]	AMI (190)	81-325 (normal treatment), followed by cleansing period and administration of ASA in doses of 325 (SD)	Optical aggregometry	R during habitual treatment with ASA: 9 R 2 h after ingesting 325 mg ASA in SD: 0.52

Table 1 *(continuation)*

Study	Patient characteristics, n	mg ASA/day	Test used to measure R	Prevalence of R to ASA, %
Golanski et al[32]	CABG (24)	325	Optical aggregometry PFA-100	10th day post-op: *Incomplete response:* 25 *Weak response:* 46 *No response:* 16.5 1 month post-op: *Incomplete response:* 21 *Weak response:* 4 *No response:* 0
Yilmaz et al[33]	CABG (28) (controlled case study)	Case group: 189 ± 100 Control group: 214 ± 90	PFA-100	R in case group: 50 R in control group: 7.1
Chen et al[34]	PCI (151)	80-325	RPFA	19.2
Chen et al[35]	PCI (117)	80-325	RPFA	18.8
Tantry et al[36]	PCI (203) and thrombosis with a stent (20)	325	Optical aggregometry Thromboelastography	0.4
Roller et al[37]	PAD (31)	100	PFA-100	40
Sane et al[38]	CHF (88)	325	Optical aggregometry PFA-100 Flow cytometry	56.8
Christiaens et al[39]	CVD (97)	160	PFA-100	29.9
Stejskal et al[40]	CAD (103)	100	Optical aggregometry	55

AMI indicates acute myocardial infarction; ASA, acetylsalicylic acid; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; CVD, cardiovascular disease; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PFA, Platelet Function Analyser; R, resistance; RPFA, Ultegra-Rapid Platelet Function Assay; SD, single dose; semi-R, semi-resistance.

in patients who do not respond to ASA treatment. We also observe that this association is higher in non-prospective studies than in prospective ones (OR: 3.12; 95% CI: 2.40-4.06 vs OR: 1.75; 95% CI: 1.35-2.28; *P*=.005).[50]

Mechanisms related to the phenomenon of acetylsalicylic acid resistance

Specific factors exist which can modify response to ASA. These can be classified as factors that cause an insufficient blood levels of ASA to be reached (pharmacokinetic mechanisms) and factors that cause a change in the metabolic pathways or pharmacological targets by which ASA exerts its antiplatelet effect (pharmacodynamic mechanisms).

The type of pharmaceutical formulation may have an effect on different ASA bioavailabilities. Alberts et al[9] relate galenic formulation of ASA with a lower response to ASA. In patients who received the enteric formulation, resistance was found in 65%, while only 25% of patients on the normal formulation demonstrated resistance.

Drug interactions are another important factor having to do with decreased treatment effectiveness. A higher percentage of resistance was found among patients who take statins.[18] Feher et al[51] observed that a higher percentage of patients in whom ASA resistance was found were being treated with that class of hypolipaemic drugs than in the group of patients who responded to ASA (52% vs 38%; *P*<.05). They therefore established that taking statins concomitantly with ASA was considered an independent risk factor for developing resistance to ASA (OR: 5.9; 95% CI: 1.83-16.9; *P*<.005).

Other drug families such as NSAIDs compete with ASA and block ASA's access to where it binds with the COX-1 enzyme, decreasing its antiaggregant effect. This interaction has been demonstrated with ibuprofen, but not with diclofenac and certain selective COX-2 inhibitors, such as rofecoxib.[52] It has also been shown that ingesting proton pump inhibitors decreases the bioavailability of ASA due to increasing the action by esterases in the gastrointestinal mucosa on ASA, which leads to less ASA absorption.[53] However, another study[54] performed subsequently observed that omeprazol did not have a significant effect on ASA's bioavailability or its antiaggregant effect. As a result, it seems that we are witnessing an interaction with little clinical relevance, although concomitant use of both drugs is very frequent in clinical practice.

Table 2 Association between resistance to acetylsalicylic acid and appearance of cardiovascular events

Study	Patient characteristics, n, mg of ASA/day Type of Study Duration	Measured clinical variables	Frequency of clinical events in patients with R and demonstrated response to ASA	Association between R to ASA and cardiovascular events: OR (95% CI); *P*-value
Berrouschot et al[10]	Stroke (240) 300 mg (+clopidogrel for R) Prospective 1 year	Recurrent stroke	R to ASA: 3.3% S to ASA: 3.8%	0.8 (0.1-7.2); ns
Grotemeyer et al[12]	Stroke (180) 1,500 mg Prospective 2 years	CV/CB events	R to ASA: 40% S to ASA: 4.4%	14.5 (5.2-40.9); <.001
Grundmann et al[13]	Stroke (53) 100 mg Case-control group >2 years	Stroke, TIA	R to ASA: 100% S to ASA: 56.1%	19.7 (1.1-354.7); <.05
Andersen et al[30]	AMI (71) 160 mg Prospective 4 years	CV/CB events	R to ASA: 36% S to ASA: 24%	1.8 (0.6-5.2); ns
Christiaens et al[30]	Stable CVD (97) 160 mg Prospective 2.5 years	CV/CB events	R: 17% S: 13%	1.6 (0.8-1.7); ns
Pamukcu et al[27]	CAD (105) 100-300 mg Prospective 1 year	CV/CB events	R to ASA: 45% S to ASA: 11.7%	6.1 (2.0-18.5); <.001
Pamucku et al[43]	CAD (234) 100-300 mg Prospective 2 years	CV/CB events	R to ASA: 15.4% S to ASA: 11%	1.4 (0.6-3.6)
Gum et al[23]	Stable CVD (326) 325 mg Prospective 679 ± 137 d	CV/CB events	R patients: 24% S patients: 10%	2.9 (0.9-9.3)
Stejskal et al[40]	CAD (103) 100 mg Prospective 4 years	CV/CB events	R to ASA: 88% S to ASA: 46%	8.5 (3.2-22.7)

Table 2 *(continuation)*

Study	Patient characteristics, n, mg of ASA/day Type of Study Duration	Measured clinical variables	Frequency of clinical events in patients with R and demonstrated response to ASA	Association between R to ASA and cardiovascular events: OR (95% CI); *P*-value
Buchanan et al[29]	CABG (289) 325 mg Prospective 2 years	Thrombotic events or graft reocclusion	R to ASA: 9.5% S to ASA: 6.9%	1.4 (0.6-3.4)
Poston et al[45]	CABG (225) 325 mg Prospective 1 month	Graft reocclusion	R to ASA: 14.3% S to ASA: 6.2%	2.5 (0.9-7.2)
Yilmaz et al[33]	CABG (36) Case group: 189 ± 100 mg; Control group: 214 ± 90 mg Case-control group Case group: 7.5 ± 3.9 years; control group: 6.2 ± 2.5 years	Graft reocclusion	R to ASA: 87% S to ASA: 35%	9.0 (1.3-64.4)
Chen et al[34]	PCI (151) 80-325 mg (+clopidogrel) Prospective 6-8 hours after PCI	Incidence of myocardial myonecrosis: CK-MB elevations after the PCI	R to ASA: 51.7% S to ASA: 24.6%	3.3 (1.4-7.6)
Chen et al[35]	PCI (117) 80-325 mg (+clopidogrel) Prospective 6-8 hours after PCI	Incidence of myocardial myonecrosis: CK-MB elevations after the PCI	R to ASA: 45.5% S to ASA: 17.9%	3.8 (1.4-10.3)
Mueller et al[46]	PAD with angioplasty (100) 100 mg Prospective 1.5 years	Reocclusion in angioplasty	R to ASA: 12.3% S to ASA: 0%	10.5 (0.6-187.5)
Eikelboom et al[44]	CVE (976) Dose range for ASA unknown 5-year case-control group	CV/CB events	NR	1.8 (1.2-2.7)[a]

ASA indicates acetylsalicylic acid; CABG, coronary artery bypass graft; CAD, coronary artery disease; CI, confidence interval; CK-MB, creatinine kinase subtype MB; CV/CB events, cardiovascular and cerebrovascular events (fatal or not fatal); CVD, cardiovascular disease; d, days; NR, not revealed; OR, odds ratio; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; R, resistance; S, sensitivity; TIA, transitory ischaemic attack.

[a]OR from the highest and lowest quartiles of 11 urinary dehydro-TXB2 values.

"Alternative TXA$_2$ formation pathways" by means of the COX-2 enzyme have been described, in addition to the platelet pathway in which the COX-1 enzyme intervenes.[56,57] The COX-2 enzyme is mainly synthesised in nucleate cells, such as monocytes, macrophages and new platelets formed in response to inflammatory stimuli, which are able to synthesise this enzyme rapidly.[44] Higher doses of ASA and a higher administration frequency are needed to inhibit this isoenzyme and thereby produce an anti-inflammatory, analgesic and antipyretic effect. It is believed that in certain inflammatory situations, nucleate cells may be able to synthesise certain amounts of PGH2, a precursor of TXA$_2$, by means of the COX-2 enzyme. This enzyme is not inhibited by the ASA doses normally used to achieve an antiaggregant effect.[44,55] This same synthesis process may occur with the COX-2 enzyme expressed in the platelets.[56]

On the other hand, PGH2 is a precursor of PGD2, PGF$_2\alpha$ and PGI23. PGI2 produces a vasodilator, antiaggregant action. It has been hypothesised that high doses of ASA could inhibit PGI2 production in such a way as to weaken its antiaggregant effect, but this has not yet been demonstrated conclusively.[58]

Zimmermann et al[59] also showed induction of the isoform of the COX-2 immunoreactive platelet enzyme in patients who had undergone coronary artery bypass and were treated with 100 mg of ASA. Another previous trial showed that an "increase in platelet turnover"[60] following coronary artery bypass could explain the ineffectiveness of low doses of ASA, since platelet TXA$_2$ synthesis must be blocked by at least 10% for platelet inhibition to be efficient. Therefore, ASA, with its short plasma half-life, would not be able to inhibit this synthesis in newly formed platelets.

In the same way, it is postulated that genetic mutations exist that could explain the phenomenon of ASA resistance. Polymorphisms or mutations in the COX-1 enzyme gene have been described which could favour resistance to ASA.[61]

Furthermore, authors have described differences in GPIIb/IIIa fibrinogen receptor activity having to do with polymorphism of the P1^{A1,A2} allele[62] that codifies the GPIIIa subunit of that receptor. In this way, platelets that are homozygous for the P1^{A1} allele have been linked to greater resistance to ASA[62,63] unlike platelets that have at least one P1^{A2} allele. However, other authors question these conclusions due to finding a greater resistance to the effects of ASA in patients bearing at least one P1^{A2} allele, as well as a higher risk of thrombotic events.[64-67]

Other studies relate high blood levels of the Von Willebrand factor,[68] P-selectin[30] or ADP[69] with increased resistance to ASA. Increased platelet sensitivity to collagen[70] may also be related to ASA resistance.

On the other hand, high levels of the isoprostane 8-iso-PGF$_{2\alpha}$ have been found in patients with unstable angina[71] and in smokers.[72,73] These compounds, which are similar to PGF2, originate from AA through lipid peroxidation catalysed by oxygen free radicals. These powerful vasoconstrictors increase platelet response, and could therefore be involved in cardiovascular disease pathogenesis. In this way, many studies show a significant association,[18,20,40,74-76] or a non-significant tendency[37] between resistance to ASA and the smoking habit. However, contradictory results have been found. Davis et al[74] carried out a randomised, double-blind trial in 30 smokers with coronary artery disease in which the effects of 150 mg ASA, 300 mg ASA and a placebo were compared on the platelet aggregation ratio before and after smoking. In the placebo group, the platelet aggregation ratios were 0.77 and 0.72 respectively before and after smoking, and these values did not change after administering both doses of ASA.

With regard to possible non-modifiable risk factors, the female sex has been correlated with ASA resistance.[9,21,25,35,39] Other authors have found a potential correlation with age.[9,22,25]

Certain clinical situations have been described in which there is a higher level of platelet reactivity. Therefore, both dyslipidaemia and obesity,[18,21,37,38,40] as well as type I and II diabetes,[37,38,40,77-80] may be accompanied by a more moderate response to the antiaggregant effect. In some of these studies, the tendency is not statistically significant. This may be caused by the small sample size, which makes it difficult to reach conclusive results. These data suggest that there may be an association between metabolic syndrome and resistance to anti-platelet treatment.

Arterial hypertension[16,38] has also been listed as a risk factor, and nearly twice the rate of resistance to ASA has been described in patients with acute coronary syndromes complicated by pneumonia than in those without respiratory complications.[81]

Likewise, catecholamine release in certain situations, such as stress or exercise[19,82,83] produces platelet activity and decreases the effectiveness of ASA.

Less ASA resistance is also observed in patients with ischaemic heart disease[18,40] and congestive heart failure.[38]

Managing patients resistant to acetylsalicylic acid

Clinical management of this phenomenon is still being investigated. Although measuring platelet aggregation using biochemical tests is one option for initial detection of patients who do not respond to ASA treatment, it has not yet been determined which of the methods is the most appropriate for identifying these patients, or how the results obtained correlate with the appearance of cardiovascular events and their cost-effectiveness ratio. As a result they are not currently recommended as a diagnostic strategy in daily clinical practice.

However, where there is a suspected case of ineffective treatment with ASA, the first step is to rule out faulty treatment adherence before diagnosing a patient as resistant, even if the platelet aggregation tests seem to indicate this is the case.[17,31,84] If, on the contrary, the patient complies well, and other reasons for treatment ineffectiveness are discarded (such as the presence of drug interactions), we can contemplate the following options for working against this phenomenon and the clinical consequences arising from it.

Increasing the acetylsalicylic acid dose

Evidence exists that doses of 75 to 150 mg are just as effective at inhibiting platelet aggregation and decreasing cardiovascular events[2] as higher doses are, with the advantage of creating fewer gastrointestinal side effects, since these are dose-dependent.

However, several studies suggest that an increased dose[5,9,11,14,15,25,40,85] may be sufficient for clinical management of treatment-resistant patients or patients with risk factors that lead us to suspect a possible case of resistance.

One important aspect to keep in mind is that increasing the dose is accompanied by an increase in side effects, particularly gastrointestinal ones, and therefore by a higher possibility of abandoning treatment. Prescribing the minimum effective dose is therefore always recommended.[2]

Adding other antiaggregant drugs

Adding a thienopyridine, such as clopidogrel, ticlopidine (currently in disuse due to producing a higher incidence of neutropoenia and bone marrow suppression) or new oral GPIIb/IIIa antagonists, acts by blocking other alternative platelet aggregation pathways different from those of ASA.

Thienopyridines inhibit the union of ADP to its platelet receptor, thus inhibiting activation of the ADP-mediated GPIIb/IIIa complex. In this way, platelet aggregation is inhibited by a different pathway from that used by ASA. Adding clopidogrel to ASA has been shown to be better than ASA monotherapy in indications of non-ST segment elevation acute coronary syndrome,[86] including patients who have undergone percutaneous coronary surgery with stent placement[87] and ST-elevation acute coronary syndrome.[88] As a result, adding another antiplatelet to ASA treatment may be a treatment strategy for ASA-resistant patients.

However, this double antiplatelet treatment option has not been specifically evaluated in any clinical trials. On the other hand, we cannot overlook the fact that resistance to clopidogrel, associated with increased risk of atherothrombotic events,[89-91] has also been observed, and there may be resistance to both drugs (clopidogrel and ASA).[92]

Discussion

We have encountered considerable variability in the prevalence of ASA resistance in the reviewed studies. These discrepancies can be explained in part by the lack of a uniform method for defining ASA resistance; here, we see it measured using different platelet aggregation tests. Furthermore, even when we use the same technique, there is no uniformity in the reference value used for classifying patients as resistant or not responding to ASA treatment.

The main methods used for measuring in vitro aggregation are as follows: Optical aggregometry, PFA-100 and RPFA. Harrison et al[8] observed greater sensitivity for detecting resistant patients when using the PFA-100 and RPFA methods. However, they stressed the lack of correlation found between these tests and optical aggregometry ($\kappa = 0.16$; 95% CI: −0.8 to 0.39; P=.11 and $\kappa = 0.09$; 95% CI: −0.12 to 0.30; P=.32, respectively), and between the two tests themselves ($\kappa = 0.14$; 95% CI: −0.08 to 0.36; P=.15). Other studies also confirmed the scant agreement between the results from different methods and the diagnostic capacity of the phenomenon called resistance to ASA.[93,94]

We must also consider that diagnosing a patient as ASA resistant according to a technique that measures the effects of ASA on AA is not completely precise, since there are hypotheses about the existence of other cardioprotective mechanisms in ASA that are independent on this platelet activation pathway.[5]

However, despite having found many difficulties in defining whether or not a patient is ASA resistant from a biochemical standpoint, according to most studies, this lack of response leads to a decrease in its ability to protect the patient from cerebrovascular and cardiovascular events.

While this association seems logical, the clinical relevance of this phenomenon has not been completely established. We must also take into account the following limitations of the clinical trials: small sample size, different times elapsed between ASA ingestion and collecting the sample to perform the resistance study, and population heterogeneity, including individuals who may require a different degree of platelet aggregation in order to experience the protective effect of ASA. Within this context, we are aware of the prothrombotic state that may arise in different clinical situations, such as acute coronary syndrome, in which more antiplatelet action is needed to counteract this clinical situation.

Another factor we must take into account is treatment adherence in clinical trials. In the studies in which this variable was not controlled[13,23,27,40,43-45] the association between decreased antiaggregant activity and the phenomenon of resistance to ASA and the appearance of clinical events may be overstated in many cases.

Furthermore, we must ask ourselves if resistance to ASA is variable, or if it is an absolute value in time.

Lastly, we must consider the possibility that thrombosis caused by platelets is not the only mechanism involved in atherothrombotic processes. It has been shown that chronic treatment with ASA is associated with a progressive decrease in platelets' sensitivity to that drug, and thus less treatment effectiveness.[95]

Identifying patients resistant to antiaggregant treatment may be recommendable in clinical practice. But since there is no diagnostic method of reference, we cannot yet recommend routine use of these techniques.

Likewise, identifying factors that may have to do with decreasing treatment effectiveness is important so that we may work toward optimising treatment on a personal basis. Strategies that we may use to counteract this decrease in antiaggregant action are as follows: increasing the ASA dose, dual treatment with other antiplatelet drugs or modifying certain risk factors, such as obesity, diabetes and smoking habits. However, these measures have not been rigorously investigated in the population of ASA-resistant patients.

More studies must be developed to clarify all of the questions listed above. In this way, we can establish clearer recommendations for clinical management of ASA resistance in order to reach the goal of using this antiplatelet drug to treat all patients at a high cardiovascular risk.

Conflict of interest

The authors affirm that they have no conflicts of interest.

References

1. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy-I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ.1994;308:81-6.

2. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients.BMJ.2002;324:71-6.

3. Vane JR, Bakhle YS, Botting M. Cyclooxygenases 1 and 2. Annu Rev Pharmacol Toxicol. 1998;38:97-120. Health & Medical Complete. p. 97.

4. Gum PA, Kottke-Marchant K, Poggio E, Gurm H, Welsh PA, Brooks L, et al. Profile and prevalence of aspirin resistance in patients with cardiovascular disease. Am J Cardiol. 2001;88:230-5.

5. Patrono C, Coller B, FitzGerald GA, Hirsh J, Roth G. Platelet-active drugs: The relationships among dose, effectiveness, and side effects. Chest. 2004;126:234S-64S.

6. Pamuckcu B. A review of aspirin resistance; definition, possible mechanisms, detection with platelet function tests, and its clinical outcomes. J Thromb Thrombolysis. 2007;23:213-22.

7. Michelson AD. Methods for the measurement of platelet function. Am J Cardiol.2009;103:20A-6A.

8. Harrison P, Segal H, Blasbery K, Furtado CH, Silver L, Rothwell PM. Screening for aspirin responsiveness after transient isquemic attack and stroke: Comparison of 2 point-of-care platelet function test with optical aggregometry. Stroke. 2005; 36:1001-5.

9. Alberts MJ, Bergman DL, Molner E, Jovanovic BJ, Ushiwata I, Teruya J. Antiplatelet effect of aspirin in patients with cerebrovascular disease. Stroke. 2004;35:175-8.

10. Berrouschot J, Schwetlick B, Von Twickel G, Fisher C, Uhlemann H, Siegemund T, et al. Aspirin resistance in secondary stroke prevention. Acta Neurol Scand. 2006;113:31-5.

11. Grotemeyer KH. Effects of acetylsalicylic acid in stroke patients evidence of non responders in a subpopulation of treated patients. Thromb Res.1991;63:587-93.

12. 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.

13. Grundmann K, Jaschonek K, Kleine B, Dichgans J, Topka H. Aspirin non-responder status in patients with recurrent cerebral ischemic attacks. J Neurol.2003;250:63-6.

14. Helgason CM, Tortorice KL, Winkler SR, Penney DW, Schuler JJ, McClelland TJ, et al. Aspirin response and failure in cerebral infarction. Stroke. 1993;24:345-50.

15. Helgason CM, Bolin KM, Hoff JA, Winkler SR, Mangat A, Tortorice KL, et al. Development of aspirin resistance in persons with previous ischemic stroke. Stroke. 1994;25:2331-6.

16. Macchi L, Petit E, Brizard A, Gil R, Neau P. Aspirin resistance in vitro and hypertension in stroke patients. J Thromb Haemost. 2003;1:1710-3.

17. Tarján J, Salamon A, Jáger R, Poór F, Barczi V, Dinnyés J, et al. The rate of acetylsalicylic acid non-respondents among patients hospitalized for acute coronary disease, previously undergoing secondary salicylic acid prophylaxis. Orv Hetil. 1999;140:2339-43 [article in Hungarian] Summary.

18. Coma-Canella I, Velasco A, Castano S. Prevalence of aspirin resistance measured by PFA-100. Int J Cardiol. 2005 71-6.

19. Christiaens L, Macchi L, Herpin D, Coisne D, Duplantier C, Allal J, et al. Resistance to aspirin in vitro at rest and during exercise in patients with angiographically proven coronary artery disease. Thromb Res.2003;108:115-9.

20. Dussaillant G, Zapata M, Fardella P, Conte G, Cuneo MV. Frequency and characteristics of aspirin resistance in Chilean cardiovascular patients. Rev Med Chile. 2005;133:409-17.

21. Friend M, Vucenik I, Miller M. Platelet responsiveness to aspirin in patients with hyperlipidaemia. BMJ. 2003;326:82-3.

22. Gum PA, Kottke-Marchant K, Poggio E, Gurm H, Welsh PA, Brooks L, et al. Profile and prevalence of aspirin resistance in patients with cardiovascular disease. Am J Cardiol. 2001;88:230-5.

23. Gum PA, Kottke-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;41:961-5.

24. Kuliczkowski W, Halawa B, Korolko B, Mazurek W. Aspirin resistance in ischaemic heart disease. Kardiol Pol. 2005;62:14-25 [Article in Polish]. Summary.

25. Lee P-Y, Chen W-H, Ng W, Cheng X, Kwok JY-Y, Tse H-F, et al. Low-dose aspirin increases aspirin resistance in patients with coronary artery disease. Am J Med. 2005 723-7.

26. Macchi L, Christiaens L, Brabant S, Sorel N, Ragot S, Allal J, et al. Resistance in vitro to low dose aspirin is associated with platelet P1A1 (GP IIIa) polymorphism but not with C807T (GPIa/IIa) and C-5T Kozak (GPIba) polymorphisms. J Am Coll Cardiol. 2003;42:1115-9.

27. Pamucku B, Oflaz H, Oncul A, Umman B, Mercanoglu F, Ozcan M, et al. The role of aspirin resistance on outcome in patients with acute coronary syndrome and the effect of clopidogrel therapy in the prevention of major cardiovascular events. J Thromb Thrombolysis.2006;22:103-10.

28. Wang JC, Aucoin-Barry D, Manuelian D, Monbouquette R, Reisman M, Gray W, et al. Incidence of aspirin non responsiveness using the Ultegra Rapid Platelet Function Assay-ASA. Am J Cardiol. 2003;92:1492-4.

29. Buchanan MR, Schwartz L, Bourassa M, Brister SJ, Peniston CM, BRAT investigators. Results of the BRAT study: A pilot study investigating the possible significance of ASA non responsiveness on the benefits and risks of ASA on thrombosis in patients undergoing coronary artery bypass surgery. Can J Cardiol. 2000;16:1385-90.

30. Andersen K, Hurlen M, Arnesen H, Seljeflot I. Aspirin non-responsiveness as measured by PFA-100 in patients with coronary artery disease. Thromb Res. 2003;108:37-42.

31. Schwartz KA, Schwartz DE, Ghosheh K, Reeves MJ, Barber K, De Franco A. Compliance as a critical consideration in patients who appear to be resistant to aspirin after healing of myocardial infarction. Am J Cardiol. 2005;95:973-5.

32. Golanski J, Chlopicki S, Golanski R, Gresner P, Iwaszkiewicz A, Watala C. Resistance to aspirin in patients after coronary artery bypass grafting is transient. Ther Drug Monit. 2005;27:484-490.

33. Yilmaz MB, Balbay Y, Caldir V, Ayaz S, Guray Y, Guray U, et al. Late saphenous vein graft occlusion in patients with coronary bypass: Possible role of aspirin resistance. Thromb Res. 2005;115:25-9.

34. Chen W-H, Lee P-Y, Ng W, Tse H-F, Lau Ch-P. Aspirin resistance is associated with a high incidence of myonecrosis after non-urgent percuatneous coronary intervention despite clopidogrel pretreatment. J Am Coll Cardiol. 2004;43:1122-6.

35. Chen W-H, Lee P-Y, Ng W,Kwok Y-T,Cheng X,Lee SW-L, et al. Relation of aspirin resistance to coronary flow reserve in patients undergoing elective percutaneous coronary intervention. Am J Cardiol. 2005;96:760-3.

36. Tantry US, Bliden KP, Gurbel PA. Overestimation of platelet aspirin resistance detection by thrombelastograph platelet mapping and validation by conventional aggregometry using arachidonicacid stimulation. J Am Coll Cardiol. 2005;46:1705-9.

37. Roller RE, Dorr A, Ulrich S, Pilger E. Effect of aspirin treatment in patients with peripheral arterial disease monitored with the platelet function analyzer PFA-100. Blood Coagul Fibrinolysis. 2002;13:277-81.

38. Sane DC, McKee SA, Malinin AI, Serebruany VL. Frequency of aspirin resistance in patients with congestive heart failure treated with antecedent aspirin. Am J Cardiol. 2002;90:893-5.

39. Christiaens L, Ragot S, Mergy J, Allal J, Macchi L. Major clinical vascular events and aspirin-resistance status as determined by the PFA-100 method among patients with stable coronary artery disease: A prospective study. Blood Coagul Fibrinolysis. 2008;19:235-9.

40. Stejskal D, Václavík J, Lacnák B, Proskova J. Aspirin resistance measured by cationic propylgallate platelet aggregometry and recurrent cardiovascular events during 4 years of follow-up. Eur J Intern Med. 2006;17:349-54.

41. Hovens MMC, Snoep JD, Eikenboom JCJ, Vander Bom JG, Mertens BJA, Huisman MV. Prevalence of persistent platelet reactivity despite use of aspirin: A systematic review. Am Heart J. 2007;153:175-81.

42. Crescente M, Di Castelnuovo A, Iacoviello L, Vermylen J, Cerletti C, De Gaetano G. Response variability to aspirin as assessed by the platelet function analyzer (PFA)-100. Thromb Haesmost. 2008;99:14-26.

43. Pamucku B, Oflaz H, Onur I, Oncul A, Ozcan M, Umman B, et al. Clinical relevance of aspirin resistance in patients with stable coronary artery disease: A prospective follow-up study (PRO-SPECTAR). Blood Coagul Fibrinolysis. 2007;18:187-92.

44. Eikelboom JW, Hirsh J, Weitz JI, Johnston M, Yi Q, Yusuf S. Aspirin-resistant thromboxane biosynthesis and the risk of miocardial infarction, stroke, or cardiovascular death in patients at high risk for cardiovascular events. Circulation. 2002;105:1650-5.

45. Poston RS, Gu J, Brown JM, Gammie JS, White C, Nie L, et al. Endothelial injury and acquired aspirin resistance as promoters of regional thrombin formation and early vein graft failure after coronary artery bypass grafting. J Thorac Cardiovasc Surg. 2006;131:122-30.

46. Mueller MR, Salat A, Stangl P, Murabito M, Pulaki S, Boehm D, et al. Variable platelet response to low-dose ASA and the risk of limb deterioration in patients submitted to peripheral arterial angioplasty. Thromb Haemost. 1997;78:1003-7.

47. Snoep JD, Hovens MMC, Eikenboom JCJ, Vander Bom JG, Huisman MV. Association of laboratory-defined aspirin resistance with a higher risk of recurrent cardiovascular events. Arch Intern Med.2007;167:1593-9.

48. Krasopoulos G, Brister SJ, Beattie WS, Elliot RF, Buchanan MR. Aspirin ''resistance'' and risk of cardiovascular morbidity: Systematic review and meta-analysis. BMJ. 2008;336:195-8.

49. Reny JL, De Moerloose P, Dauzat M, Fontana P. Use of the PFA-100 closure time to predict cardiovascular events in aspirin-treated cardiovascular patients: A systematic review and meta-analysis. J Thromb Haemost. 2008;6:444-50.

50. Crescente M, Di Castelnuovo A, Iacovello L, De Gaetano G, Cerletti CH. PFA-110 closure to predict cardiovascular events in aspirin-treated cardiovascular patients: A meta-analysis of 19 studies comprising 3,003 patients. Thromb Haemost. 2008;99:1129-31.

51. Feher G, Koltai K, Papp E, Alkonyi B, Solyom A, Kenyeres P, et al. Aspirin resistance: Possible roles of cardiovascular risk factors, previous disease history, concomitant medications and haemorrheological variables. Drugs Aging. 2006;23:559-67.

52. Catella-Lawson F, Reilly M, Kapoor SC, Cucchiara AJ, De Marco S, Tournier B, et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. N Eng J Med. 2001;345:1809-17.

53. Hankey GJ, Eikelboom JW. Aspirin resistance. Lancet. 2006;367:606-617.

54. Iñarrea P, Esteva F, Cornudella R, Lanas A. Omeprazole does not interfere with the antiplatelet effect of low-dose aspirinin man. Scand J Gastroenterol. 2000;35:242-6.

55. Halushka MK, Halushka PV. Why are some individuals resistant to the cardioprotective effects of aspirin?: Could it be thromboxane A2? Circulation. 2002;105:1620-2.

56. Weber AA, Zimmermann KC, Meyer-Kirchrath J, Schör K. Cyclooxigenase-2 in human platelets as a possible factor in aspirin resistance. The Lancet. 1999;353:9156.

57. Cipollone F, Patrignani P, Greco A, Panara MR, Padovano R, Cuccurullo F, et al. Differential suppression of thromboxane biosynthesis by indobufen and aspirin in patients with unstable angina. Circulation. 1997;96:1109-16.

58. Patrono C, Bachmann F, Baigent C, Bode Ch, De Caterina R, Charbonnier B, et al. Documento de consenso de expertos sobre el uso de agentes antiplaquetarios. Rev Esp Cardiol. 2004;57:963-80.

59. Zimmermann N, Wenk A, Kim U, Kienzle P, Weber A-A, Gams E, et al. Functional and biochemical evaluation of platelet aspirin resistance after coronary artery bypass surgery. Circulation. 2003;108:542-7.

60. Zimmermann N, Kienzle P, Weber A-A, Winter J, Gams E, Schör K, et al. Aspirin resistance after coronary artery bypass grafting. J Thorac Cardiovasc Surg. 2001;121:982-4.

61. Halushka MK, Walker LP, Halushka PV. Genetic variation in cyclooxygenase 1: Effects on response to aspirin. Clin Pharmacol Ther.2003;73:122-30.

62. Cooke GE, Bray PF, Hamlington JD, Pham DM, Goldschmidt-Clermont PJ. P1A2 polymorphism and efficacy of aspirin. The Lancet. 1998;351:1253.

63. Michelson AD, Furman MI, Goldschmidt-Clermont P, Mascelli MA, Hendrix C, Coleman L, et al. Platelet GPIIIa PI(A) polymorphisms display different sensitivities to agonists. Circulation. 2000;101:1013-8.

64. Undas A, Sanak M, Musial J, Szczeklik A. Platelet glycoprotein IIIa polymorphism, aspirin, and thromb in generation. The Lancet. 1999;353:982-3.

65. Weiss EJ, Bray PF, Tayback M, Schulman S, Kickler T, Becker LC, et al. A polymorphism of a platelet glycoprotein receptor as an inherited risk factor for coronary thrombosis. N Engl J Med. 1996;334:1090-4.

66. Bray PF. Platelet glycoprotein polymorphisms as a risk factors for thrombosis. Curr Opin Hematol. 2000;7:284-9.

67. Szczeklik A, Sanak M, Undas A. Platelet glycoprotein IIIa P1A polymorphism and effects of aspirin on thrombin generation. Circulation. 2001;103:E33-4.

68. Chakroun T, Gerotziafas G, Robert F, Lecrubier CH, Samama MM, Hatmi M, et al. In vitro aspirin resistance detected by PFA-100TM closure time: Pivotal role of plasma Von Willebrand factor. Br J Hematol. 2004;124:80-5.

69. Borna C, Lazarowski E, Van Heusden C, Öhlin H, Erlinge D. Resistance to aspirin is increased by ST-elevation myocardial infarction and correlates with adenosine diphosphate levels. Thrombosis Journal.2005;3:10.

70. Kawasaki T, Ozeki Y, Igawa T, Kambayashi J. Increased platelet sensitivity to collagen in individuals resistant to low-dose aspirin. Stroke. 2000;31:591-5.

71. Cipollone F, Ciabattoni G, Patrignani P, Pasquale M, Di Gregorio D, Bucciarelli T, et al. Oxidant stress and aspirin-insensitive thromboxane biosynthesis in severe unstable angina. Circulation. 2000;102:1007-13.

72. Morrow JD, Frei B, Longmire AW, Gaziano M, Lynch SM, Shyr Y, et al. Increase in circulating products of lipid peroxidation (F2-isoprostanes) in smokers. N Engl J Med. 1995;332:1198-1203.

73. Reilly M, Delanty N, Lawson JA, FitzGerald GA. Modulation of oxidant stress in vivo in chronic cigarette smokers. Circulation. 1996;94:19-25.

74. Davis JW, Hartman CR, Lewis Jr HD, Shelton L, Eigenberg DA, Hassanein KM, et al. Cigarette smoking: Induced enhancement of platelet function: Lack of prevention by aspirin in men with coronary artery disease. J Lab Clin Med. 1985;105:479-83.

75. Hung J, Lam J, Lacoste L, Letchacovski G. Cigarette smoking acutely increases platelet thrombus formation in patients with coronary artery disease taking aspirin. Circulation. 1995;92:2432-6.

76. Weber AA, Liesener S, Schanz A, Hohlfeld T, Schrör K. Habitual smoking causes an abnormality in platelet thromboxane A2

metabolism and results in an altered susceptibility to aspirin resistance. Platelets. 2000;11:177-82.

77. Watala C, Golanski J, Pluta J, Boncler M, Rozalski M, Luzak B, et al. Reduced sensitivity of platelets from type 2 diabetic patients to acetylsalicylic acid (aspirin): Its relation to metabolic control. Thromb Res. 2004;113:101-13.

78. Fateh-Moghadam S, Plöckinger U, Cabeza N, Htun P, Reuter T, Ersel S, et al. Prevalence of aspirin resistance in patients with type 2 diabetes. Acta Diabetol. 2005;42:99-103.

79. Mori TA, Vandongen R, Douglas AJ, Mc Culloch RK, Burke V. Differential effect of aspirin on platelet aggregation in IDDM. Diabetes. 1992;41:261-6.

80. Tamminen M, Lassila R, Westerbacka J, Vehkavaara S, Yki-Järvinen H. Obesity is associated with impaired platelet-inhibitory effect of acetylsalicylic acid in non diabetic subjects. Int J Obes Relat Metab Disord. 2003;27:907-11.

81. Modica A, Karlsson F, Mooe T. Platelet aggregation and aspirin non-responsiveness increase when an acute coronary syndrome is complicated by an infection. J Thromb Haemost. 2007;5:507-11.

82. Larsson PT, Wallén NH, Hjemdahl P. Norepinephrine-induced human platelet activation in vivo is only partly counteracted by aspirin. Circulation. 1994;89:1951-7.

83. Pamukcu B, Oflaz H, Acar RD, Umman S, Koylan N, Umman B, et al. The role of exercise on platelet aggregation in patients with stable coronary artery disease: Exercise induces aspirin platelet activation. Journal of Thrombosis and Thrombolysis. 2005;20:17-22.

84. Cotter G, Shemesh E, Zehavi M, Dinur I, Rudnick A, Milo O, et al. Lack of aspirin effect: Aspirin resistance or resistance to taking aspirin? Am Heart J. 2004;147:293-300.

85. Tohgi H, Cono S, Tamura K, Kimura B, Kawano K. Effects of low-to-high doses of aspirin on platelet aggregability and metabolites of thromboxane A2 and prostacyclin. Stroke. 1992;23:1400-3.

86. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrelin addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med.2001;345:494-502.

87. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, et al. Effects of pre-treatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: The PCI-CURE study. Lancet. 2001;358:527-33.

88. Sabatine MS, Cannon CP, Gibson CM, López-Sendón JL, Montalescot G, Theroux P, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med. 2005;352:1179-89.

89. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CHM. Response variability, drug resistance, and the effect of pretreatment platelet reactivity. Circulation. 2003;107:2908-13.

90. Matetzky S, Shenkman B, Guetta V, Schechter M, Bienart R, Goldenberg I, et al. Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. Circulation. 2004;3171-5.

91. Müller I, Besta F, Schulz CH, Massberg S, Schönig A, Gawaz M. Prevalence of clopidogrel non-responders among patients with stable angina pectoris scheluded for elective coronary stent placement. Thromb Haemost. 2003;89:783-7.

92. Lev EI, Patel RT, Maresh KJ, Guthikonda S, Granada J, De Lao T, et al. Aspirin and clopidogrel drug response in patients undergoing percutaneous coronary intervention: The role of dual drug resistance. Am Coll Cardiol. 2006;47:27-33.

93. Lordkipanidzé M, Pharand C, Schampaert E, Turgeon J, Palisaitis DA, Diodati JG. A comparison of six major platelet function tests to determine the prevalence of aspirin resistance in patients with stable coronary artery disease. Eur Heart J. 2007;28:1702-8.

94. Frelinger AL, Li Y, Linden MD, Tarnow I, Barnard MR, Fox ML, et al. Aspirin 'resistance': Role of pre-existent platelet reactivity and correlation between tests. J Thromb Haemost. 2008;6:2035-44.

95. Pulcinelli FM, Pignatelli P, Celestini A, Riondino S, Gazzaniga PP, Violi F. Inhibition of platelet aggregation by aspirin progressively decreases in long-term treated patients. J Am Coll Cardiol. 2004;43:979-84.