

Review Article

Aspirin Resistance

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The development of adverse cardiovascular events despite aspirin use has established an interest in a possible resistance to the drug. Several definitions have been set and various laboratory testing modalities are available. This has led to a wide range of prevalence reports in different clinical entities. The etiologic mechanism has been related to clinical, genetic, and other miscellaneous factors. The clinical implications of this phenomenon are significant and warrant concern. Management strategies are currently limited to dosing alteration and introduction of other antiplatelet agents. However, these measures have not met the expected efficacy or safety.

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1. Introduction

Despite the development of newer antiplatelet drugs in the last decade, aspirin is still the most widely used antiplatelet agent across the world to prevent cardiovascular diseases [1–4]. In the 19th century, willow leaves became an attraction after their extract, salicylic acid, was found effective as an analgesic for arthralgias and an antirheumatic for a variety of rheumatic disease [5–7]. At the end of the 19th century the acetylated form of salicylic acid was manufactured [8], with less gastrointestinal side effects, and consequently became more widespread and commonly used. Long-term aspirin administration in patients at high risk of occlusive vascular events reduced up to 34% of nonfatal myocardial infarction (MI), 25% of nonfatal stroke, and 18% of all-cause mortality [4]. Ever since, several patients have reported developing adverse vascular events despite aspirin intake, an observation that was later coined the term “aspirin resistance” (AR) [9]. Nowadays, the term has been employed to express the occurrence of cardiovascular events in spite of regular intake of aspirin at recommended doses [10–13]. Recent advances in evaluating platelet function and the introduction of the point-of-care platelet function machinery made assessing the degree of platelet response to a certain antiplatelet drug more reasonable, accessible, and easier to perform [14].

In this paper, the prevalence, mechanism, and clinical implications of aspirin resistance will be highlighted. Moreover, the available laboratory tests used to assess this phenomenon and the possible ways to overcome it will be described.

2. Terminology

The lack of agreement on a standardized definition for “aspirin resistance” has contributed to the disparity in reports of its incidence among different studies. Whereas some use the term “aspirin treatment failure,” while others like to call it “aspirin nonresponsiveness.” The term “resistance” was assigned based on biochemical and laboratory findings in which aspirin was unable to inhibit one of the many available *in vitro* tests of platelet function [15, 16]. Hence, from a pharmacologic point of view, resistance to aspirin may be defined as lack of ability to attain the expected inhibition of platelet cyclooxygenase-(COX-)1 with avoidance of platelet thromboxane (TX) A₂ formation [17]. “Aspirin treatment failure” is defined based on clinical outcomes, when aspirin fails to prevent recurrent vascular ischemic events. However, reinfarction after aspirin use in the setting of an acute coronary event may be due to thrombus spread mediated by adenosine diphosphate (ADP) rather

TABLE 1: Prevalence of aspirin resistance.

Reference	Patients	Test used	Prevalence of AR N(%)	Comments
Christiaens et al. [32]	N = 97 Stable CAD patients already on aspirin	PFA-100 analyzer	29 (29.9)	♀ > ♂ (38 versus 15%) No clinical correlation with laboratory parameters after 2.5 years follow-up
Pamukcu et al. [33]	N = 234 Stable CAD	PFA-100 analyzer	52 (22.2)	Similar risk in resistant and nonresistant patients after 20.6 ± 6.9 months follow-up. Risk in aspirin resistant patients increased after cessation of clopidogrel
Pamukcu et al. [34]	N = 105 ACS	PFA-100 analyzer	20 (19)	Greater risk of MACE in patients resistant to aspirin
Akay et al. [35]	N = 280 Healthy Turkish volunteers	Optical platelet aggregometry (ADP, AA)	77 (27.5)	Large trial evaluating the frequency of AR in healthy subjects
Lee et al. [36]	N = 468 Stable CAD	VerifyNow-Aspirin	128 (27.4)	100 mg or less daily dose were associated with a higher incidence of AR in patients with CAD
Harrison et al. [30]	N = 100 Patients after TIA or Stroke	PFA-100 VerifyNow-Aspirin Optical platelet aggregometry	22 (22) 17 (17) 5 (5)	Poor agreement between the different tests leads to the conclusion that aspirin resistance is highly test-specific
Gum et al. [28]	N = 325 Stable CAD	Optical platelet aggregometry PFA-100 analyzer	18 (5.5) 31 (9.5)	Trend toward increased age in patients with AR

AR: aspirin resistance; CAD: coronary artery disease; ACS: acute coronary syndrome; MACE: major adverse cardiac events; ADP: adenosine diphosphate; AA: arachidonic acid; TIA: transient ischemic attack.

than continuing TX-induced platelet aggregation; which may render the terminology “failure” improper [18]. Some suggested that until the various possible reasons of treatment failure with aspirin have been recognized, the more suitable term may be “aspirin nonresponsiveness” [15].

3. How Prevalent Is Aspirin Resistance?

Due to the lack of standardized testing for AR, prevalence rates of nonresponders to aspirin among adults differ according to the platelet function test used and the threshold of response, with a wide range reported (5.5 to 60%) [19–22]. For instance, there are up to seven different thresholds for defining aspirin response using the PFA-100 [23–29]. When using the combination of different laboratory tests to define resistance (VerifyNow-Aspirin, optical aggregometry, and PFA-100), a lower resistance rate (2%) was reported as compared to using each test alone [30].

The majority of studies on AR were conducted on adult patients, but recently the prevalence of AR was studied in 44 children aged 1 to 17 years taking aspirin for different indications, by using different laboratory tests. Six out of 44 were considered aspirin resistant according to at least

one laboratory test (5 by PFA-100, 1 by aggregometry, and urinary 11dhTxB2), which leads to the conclusion that, as with adults, the incidence of AR is also assay-dependent in the pediatric population [31]. Table 1 summarizes the main studies investigating AR prevalence in different clinical entities [28, 30, 32–36].

4. Proposed Etiology

4.1. Pharmacology of Aspirin. Low-dose aspirin (as low as 81 mg) irreversibly inhibits the COX-1 enzyme, by acetylating the serine residue at position 529, consequently impairing the transformation of arachidonic acid to prostaglandin (G2/H2), and TX A2, which is a potent mediator of platelet aggregation and activation. This effect explains the clinical benefit of aspirin in patients with high risk vascular disease [37–39]. Aspirin’s effect on COX-2 is minimal in doses <1200 mg [40, 41].

4.2. Mechanism of Resistance. The different mechanisms by which AR might take place are not yet well understood [10, 12, 13, 19]. Medication compliance is one preventable and important contributor to the phenomenon of resistance

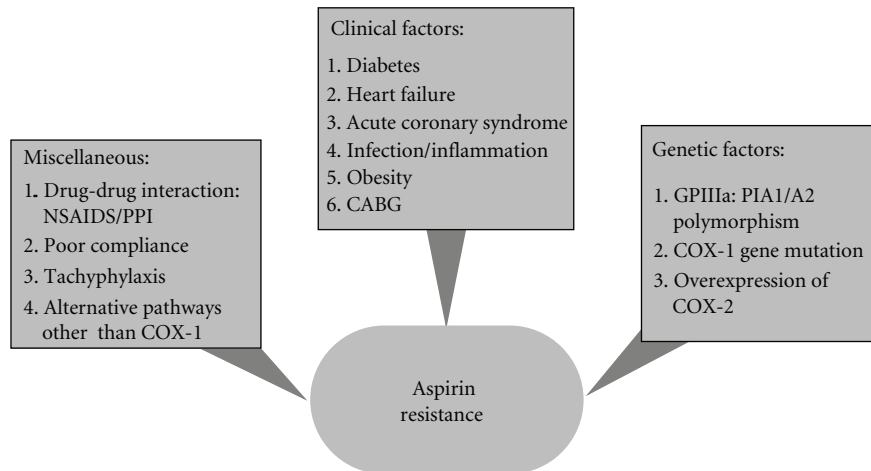


FIGURE 1: Proposed factors contributing to aspirin resistance (CABG: coronary artery bypass grafting; COX: cyclooxygenase; NSAIDs: nonsteroidal anti-inflammatory drugs; PPI: proton pump inhibitors).

and to the overreporting of aspirin nonresponsiveness [42]. To stress the importance of this factor, a recent meta-analysis including 50 000 patients at high risk of ischemic coronary disease found that noncompliance or early discontinuation of the drug carried a 3 times higher risk of cardiac events (odds ratio [OR] 3.14, 95% confidence interval [CI] 1.75–5.61; $P = .0001$) [43]. Thus, explaining the benefits of antiplatelet therapy to the patient may help improving compliance [44].

Some drugs may compete with aspirin at the COX-1 receptor site; of those, the most commonly encountered are nonsteroidal anti-inflammatory drugs such as ibuprofen which can offset the clinical benefit of aspirin in a variety of vascular diseases [45]. The bioavailability of a drug is dependent on numerous factors, absorption being the most relevant. Lower doses of acetylsalicylic acid may be hydrolyzed to a higher extent into an inactive form, by gastrointestinal mucosal esterases when given with proton pump inhibitors due to acid suppression, thus reducing the absorption of the active drug. However, current evidence failed to confirm this argument [46, 47].

Another hypothesis considers resistance at the target site of the drug's action. This may highlight the role of genetic studies to determine the potential contribution of some genetic polymorphisms in AR. Polymorphisms in the COX-1 gene have been implicated in the partial nonresponse to low-dose aspirin [48, 49]. However, a recent large systematic review addressing the role of different genetic polymorphisms did not find a clear association between COX-1 gene polymorphisms (specifically C50T/A842G polymorphism) and AR [50]. Another major genetic contributor to biological AR is thought to be the PlA1/A2 polymorphism in the GPIIIa platelet receptor [51–53], which is according to the same systematic review, the most frequently investigated parameter (19 studies involving 1389 subjects) [50]. This variant was noticeably associated with AR when measured in the healthy population (OR 2.36, 95% CI 1.24–4.49;

$P = .009$), but combining data from both healthy individuals and those with cardiovascular disease reduced the size of the observed effect (OR 1.14, 95% CI 0.84–1.54; $P = .40$) [50].

Poor glucose control and body weight are also proposed to contribute to AR, where in a recent study assessing 48 patients with type 2 diabetes mellitus using the PFA-100 assay, AR was significantly associated with HbA1c $\geq 8\%$ ($P = .002$) and obesity (BMI ≥ 30 kg/m²; $P = .01$) [54]. Although this might implicate that better glucose control leads to less incidence of AR, the clinical significance of such findings should be carefully inspected, since in two of the largest trials [55, 56] assessing the role of aspirin on primary prevention of cardiovascular events in patients with type2 diabetes, low-dose aspirin did not decrease the risk of cardiovascular events when compared to placebo (13.6 per 1000 person-year in the aspirin group versus 17.0 per 1000 person-year in the placebo group, hazard ratio [HR] 0.80; 95% CI 0.58–1.10 in the JPAD trial [55]; 116 of 638 primary events in the aspirin group compared with 117 of 638 in the no aspirin group, HR 0.98; 95% CI 0.76–1.26 in the POPADAD trial [56]). In the JPAD trial both groups (aspirin versus no aspirin) had similar baseline characteristics in terms of glycosylated hemoglobin (7.0 versus 7.1, resp.). On the other hand, the aspirin group in the POPADAD trial had a mean HbA1c of 8.0 compared to 7.9 in the no aspirin group. The lack of beneficial effect of aspirin in the latter study may be partly explained by the fact that AR is significantly associated with HbA1c levels $\geq 8\%$ [54].

Finally in all conditions associated with a high platelet turnover (coronary artery bypass grafting, acute coronary syndrome (ACS), acute or chronic infection, or inflammation), low-dose aspirin is associated with a short half-life (15 to 20 minutes) and might not be able to suppress COX-1 in fresh platelets that are continuously and quickly released into the circulation in such stressful circumstances, leading to higher platelet reactivity (Figure 1) [57–60].

5. Platelet-Function Testing

Multiple assays for platelet function and response to aspirin have emerged in the past decade. The test that is considered gold standard for assessment of the degree of aspirin response is light transmittance aggregometry (LTA) [61]. This assay measures the increase in light transmittance across platelet-rich plasma as a consequence of aggregation of platelets and development of clumps in response to different agonists (ADP, collagen, arachidonic acid). Several drawbacks limit the use of this assay. However, it has been described as time consuming, operator dependent, and of high cost. Inability to reproduce results, even in the same laboratory, has also been reported [62]. According to this assay, the most accepted definition of AR is $\geq 20\%$ platelet aggregation with 1 mg/mL arachidonic acid and $\geq 70\%$ aggregation with 10 $\mu\text{mol/l}$ ADP despite regular intake of aspirin [63].

The point-of-care platelet function analyzer PFA-100 device (Dade Behring, Leiderbach, Germany) acts like an injured artery, where high shear stress conditions are present, and works in the presence of erythrocytes; unlike LTA where there is no interaction between platelet and other blood components. Hence, platelet function is evaluated by the time needed to form a platelet plug to occlude the gap present in this device. Using this test, AR is generally defined as a closure time of < 164 s despite regular aspirin intake. The device is easy to use and requires only a small amount of blood. The test is also fast and reproducible. Unfortunately, correlation between clinical outcomes with the PFA-100 is poor [64]. The lack of correlation with clinical outcome was also demonstrated in a recent prospective study assessing the prevalence of resistance in 97 patients with stable coronary artery disease on 160 mg aspirin for at least one month using the PFA-100 and a follow-up of 2.5 years for the composite of death, MI, and ischemic cerebral infarction or acute limb ischemia. It was found that aspirin resistant patients (29.9%) did not have a higher risk of death, MI, or ischemic vascular event compared with aspirin-sensitive patients [65]. Moreover, the reliance upon hematocrit and plasma von Willebrand factor, along with high cost, limits the use of PFA-100.

Another point-of-care newly introduced assay is the VerifyNow-Aspirin (the Ultegra Rapid Platelet Function Assay, Accumetrics Inc., San Diego, Calif, USA) which correlates well with light transmittance aggregometry [66]. Results from the VerifyNow-Aspirin were highly reproducible in 21 healthy volunteers and 40 patients with stable coronary artery disease [67]. It also showed poor sensitivity and good specificity with a cut-off value at 550 aspirin reaction units (ARU), compared to LTA, which makes the significance of the cut-off level at 550 ARU for detecting AR controversial [67].

Other test measures consider the end products of the TX A2 pathway such as serum TX B2 [68], or urine 11-dehydroTX B2 [49], for assessing aspirin activity [49]. In fact, these two tests may better reflect the amount of TX A2 derived from sources other than platelets such as macrophages and monocytes, and on the COX-2 linked

pathway of arachidonic acid, which is blocked by aspirin at very high doses (1200 mg) only [40, 41]. Urinary 11-dehydroTX B2 concentration is affected by kidneys production of this substance; however, measurement of this metabolite is still commonly used in trials assessing AR due to its low cost and ease to carry out [49, 69].

A relevant question is the extent to which these laboratory methods correlate with one another. The various laboratory assays used to identify AR are compared weakly with each other. This was demonstrated in a study using six different platelet function tests in 201 patients with stable coronary artery disease who were on daily aspirin use. The encounter of AR varied according to the assay used, being uppermost for the PFA-100 (60%) and lowermost using LTA (4%) [70]. Workup of a patient with suspected aspirin resistance, eventually leading to appropriate platelet-function testing, is highlighted in Figure 2.

6. Clinical Implication

Another significant question to consider is whether this phenomenon is confined to laboratory findings or affects the expected clinical outcome. A recent meta-analysis on 2930 patients with cardiovascular disease, who were on aspirin (75–325 mg daily) alone or in combination with other antiplatelet therapy, found resistance to be more prevalent in females as well as in patients with renal impairment. These populations were found to carry a fourfold higher risk of death due to vascular events and higher risk of nonfatal cerebrovascular and cardiovascular events compared to aspirin sensitive patients (39% of AR patients versus 16% of aspirin sensitive patients had a cardiovascular event, OR 3.85, 95% CI 3.08–4.80; $P < .001$), regardless of the assay used to assess resistance [71]. The authors conclusions are reinforced by a previous meta-analysis evaluating clinical outcome in AR, where again, resistant patients had considerably higher risk of recurrent vascular events compared to aspirin sensitive patients [72].

In a recent trial evaluating the relationship between AR (assessed by thrombelastography) and stroke in 45 patients with ischemic stroke, it was found that AR was more frequent in the stroke than the control arm (67% versus 40%; $P = .028$). Within the stroke group, the AR arm had more severe stroke (assessed by Rankin score). In addition AR was greater in lacunar than embolic strokes [73]. In a follow-up of 468 patients with stable coronary artery disease and/or a high risk for vascular events (diabetic and/or hypertensive) for a mean period of 379 ± 200 days, cardiovascular death and/or nonfatal events were more frequent among patients with AR [74]. Moreover, after measuring urinary 11-dehydroTX B2 levels in 976 high-risk patients (half of them had sustained previous vascular events) who were initially enrolled in the heart outcomes prevention evaluation (HOPE) trial (on aspirin for 5 years), it was demonstrated that patients with levels in the highest quartile sustained more MI and cardiovascular death versus those in the lowest quartile [49], the drawbacks of this nested case control study were the issue of compliance which was not verified adequately by objective laboratory methods.

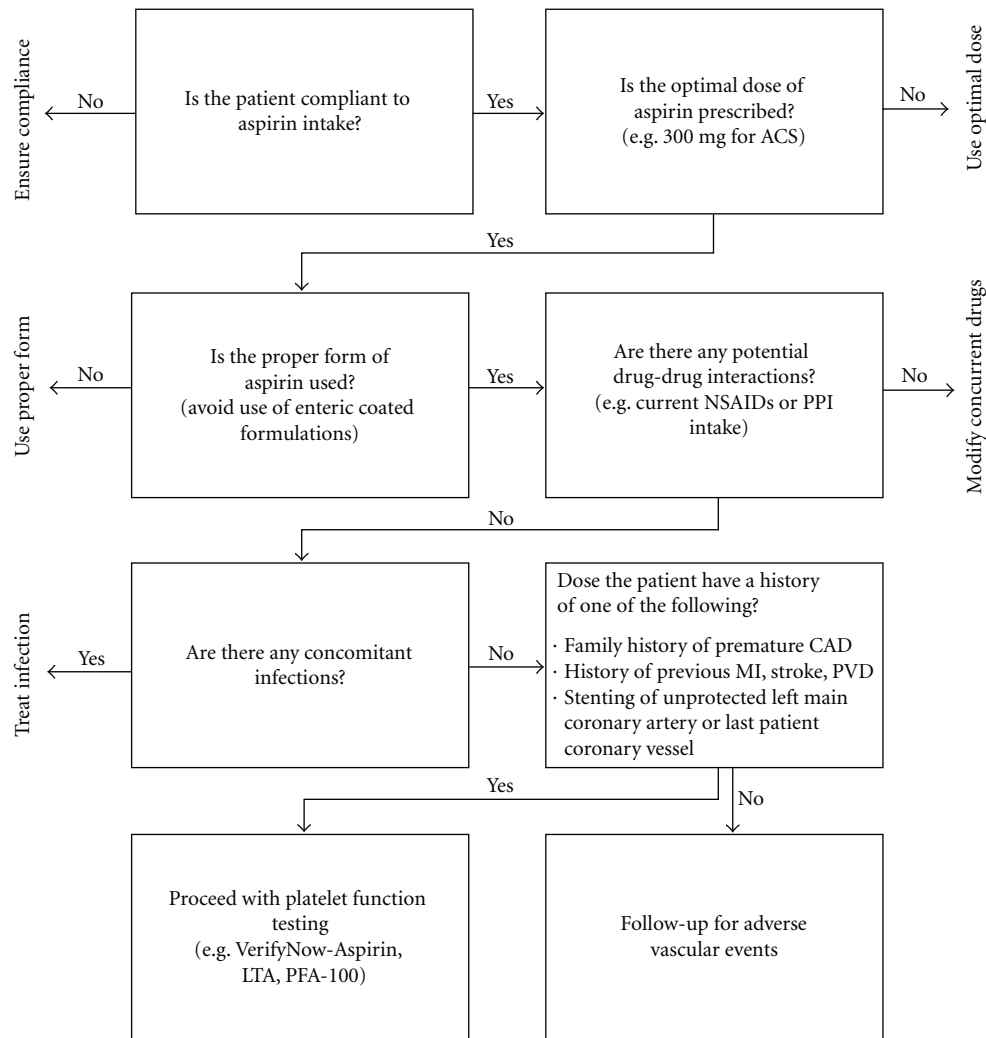


FIGURE 2: Algorithm highlighting approach to a patient with suspected aspirin resistance. ACS: acute coronary syndrome; NSAIDs: nonsteroidal antiinflammatory drugs; PPI: proton pump inhibitors; CAD: coronary artery disease; MI: myocardial infarction; PVD: peripheral vascular disease; LTA: light transmittance aggregometry; PFA: platelet function analyzer.

The clinical correlation of AR was also elucidated in patients undergoing percutaneous coronary intervention (PCI) in a recent study that measured the cardiac biomarkers (CK-MB and Troponin I) in 151 patients who underwent nonurgent PCI and who were already on various doses of aspirin and a 300 mg loading dose of clopidogrel. The study demonstrated that patients with AR, assessed using the VerifyNow-Aspirin test, sustained a considerably higher incidence of post-PCI elevation in cardiac biomarkers [75]. Furthermore, in 216 patients with ST elevation myocardial infarction (STEMI), enhanced platelet activity assessed with PFA-100, was an independent predictor of markers of cardiac necrosis [76]. The laboratory response to glycoprotein (GP) IIB/IIIA inhibitors and the clinical outcome in 70 patients with STEMI undergoing PCI correlated well with baseline platelet reactivity (PR) (assessed with the PFA-100) before intervention. High-baseline PR was associated with a 5–11 times increase in the risk of death, reinfarction, and target vessel revascularization (HR 11, 95% CI 1.5–78; $P = .02$

when the PFA-100 was used and HR 5.2, 95% CI 1.1–23; $P = .03$ using the LTA) [77].

Finally, aspirin resistance has been implicated recently as a potential cause of the rare but very serious complication of drug eluting stents thrombosis. This was demonstrated in a prospective systematic analysis of platelet aggregation in four subsequent cases of late thrombosis, where all four cases showed resistance to either aspirin (evaluated with the PFA-100) or clopidogrel, and two cases showed dual resistance to both of these platelet antiaggregants [78].

7. Management

After correlating AR with incidence of more adverse cardiovascular events many investigators are trying to find solutions to overcome this poor response. The idea of increasing aspirin dose in order to overcome resistance has been assayed in many studies, since there is some evidence that response to aspirin may be dose-dependent

[27]. Laboratory and genetic inconsistency as well as dose dependence is seen when agonists other than arachidonic acid (the most specific in assessing AR), such as (ADP, collagen, epinephrine), are used for in vitro assessment of platelet inhibition by aspirin. This inconsistency and dose-dependence may be explained by the fact that those agonists maybe only in part reliant upon, or even independent of, the COX-1 pathway which is the main target of aspirin [79–82]. More solid evidence that reflects on the appropriate dosage of aspirin was portrayed by the antithrombotic trialists collaboration. It showed that the most effective aspirin dose with the fewest adverse consequences is 75 to 150 mg once daily with similar efficacy as doses up to 1500 mg daily [8, 83]. Even though low-aspirin doses might relate to resistance by reducing absorption, administration of higher doses looks unwarranted and is outweighed by a higher risk of gastrointestinal bleeding [84].

In a number of studies, sensitivity of platelets to ADP and levels of this agonist in patients with AR revealed to be considerably amplified [25, 85]. Moreover, in a randomized cross-over trial, patients with AR turned out to be highly responsive to platelet ADP receptor antagonist [86]. One could argue, based on the above that replacing or adding a different antiplatelet could cancel out the incidence of adverse events resulting from resistance to aspirin. This theory was refuted by a recent meta-analysis of 20 studies (6 of them had an additional antiplatelet used) which found that concomitant treatment with additional antiplatelet (namely, clopidogrel or tirofiban) provided no clinical benefit to those patients identified as aspirin resistant (OR 2.52, 95% CI 1.79–3.56 for aspirin alone versus OR 3.06, 95% CI 1.99 to 4.70 for the dual antiplatelet group) [71]. To elaborate on the issue of dual antiplatelet therapy, an analysis of asymptomatic low-risk patients on both aspirin and clopidogrel in the CHARISMA trial revealed a higher incidence of death due to cardiovascular disease [87], and that dual antiplatelet therapy should be reserved for patients with high risk for vascular events [88]. The addition of dipyridamole to aspirin has also been subject to much debate [4, 89, 90]. In a recent review involving 23 019 patients with vascular disease [91], dipyridamole alone or in combination with aspirin did not lessen the risk of vascular death (relative risk [RR] 0.99, 95% CI 0.87–1.12), though the risk of vascular events was lowered (RR 0.88, 95% CI 0.8–0.95).

In particular, dealing with some patients who develop adverse vascular events (e.g., cerebrovascular accidents (CVA) and ACS) despite being on aspirin remains challenging, and many questions persist without clear cut answers. There is no clear evidence and no consensus yet on whether using different laboratory assays to detect aspirin resistance would guide therapy in those patients, especially after a recent report assessing AR status with PFA-100 in 129 patients with transient ischemic attack (TIA), stroke, or vascular cognitive impairment failed to predict new thrombotic events in patients found to be AR during mean follow-up of 56 months, as new thrombotic events occurred in 15.4% of AR patients and in 14.6% of those without resistance ($P = 1.00$) [92].

Although the subgroup analysis of the CAPRIE trial failed to show a significant beneficial effect of clopidogrel over aspirin in patients with history of recent stroke or MI [93], the recommendations issued by the American Heart Association/American Stroke Association (AHA/ASA) in 2006 on stroke prevention [94] supported initial antiplatelet therapy with the combination of aspirin and extended-release dipyridamole (ER-DP), 25 mg/200 mg twice a day (aggrenox), rather than aspirin (Grade 2A evidence) or the use of clopidogrel for those not treated with aggrenox (Grade 2B evidence) in patients with a history of noncardioembolic stroke or TIA of atherothrombotic, lacunar (small vessel occlusive type), or cryptogenic type. Hence, adding an additional antiplatelet such as (ER-DP) or substituting aspirin by another potent antiplatelet (namely, clopidogrel) would be a logical alternative to patients who develop CVA despite using aspirin on a daily basis. The addition of clopidogrel to aspirin for secondary stroke prevention has fallen out of favor since the combination of the two drugs does not offer better benefit for stroke prevention than either drug alone but does considerably amplify the risk of bleeding complications [95]. Unlike patients who develop stroke, those being on aspirin and develop ACS (unstable angina and non-STEMI) would benefit from adding clopidogrel to aspirin as per the famous CURE trial [96].

8. Conclusion

Aspirin resistance is a true phenomenon that needs to be further elucidated. A single definition should be provided when describing resistance or nonresponse to aspirin. Moreover, consensus should be made about the optimal laboratory method that allows objective assessment of response to aspirin. These points, if achieved, may normalize the wide range of prevalence reported among different studies. The correlation between AR and higher incidence of adverse vascular events is established by a considerable number of well-designed trials. On the other hand, despite the absence of optimal methods to overcome this phenomenon of resistance, physicians must emphasize on proper patients compliance, as well as avoidance of potential drug-drug interactions. Finally one should always keep in mind that no single platelet activation pathway is responsible for all thrombotic complications, and a single treatment strategy directed against a specific receptor/target cannot overcome all thrombotic complications.

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