

## Aspirin resistance: Where are we now?

*Aspirin direnci: Şimdi biz neredeyiz?*

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### ABSTRACT

Aspirin is an effective antiplatelet drug for preventing thrombo-embolic vascular events. However, clinical and laboratory evidence demonstrates diminished or no response to aspirin in some patients that is called aspirin resistance. This situation has been reported to be independently associated with an increased risk of adverse cardiovascular events. The exact mechanism of aspirin resistance has not been established yet. The clinical, pharmacological and genetic factors may be associated with aspirin resistance. However, there is not currently standardized test to the diagnosis and no proven effective treatment of aspirin resistance. This article summarizes aspirin resistance, discussing its definition, clinical outcomes, laboratory tests, possible causes and therapeutic approaches. (*Anadolu Kardiyol Derg 2013; 13: 370-3*)

**Key words:** Aspirin resistance, clinical outcomes, laboratory tests, therapeutic approaches

### ÖZET

Trombo-embolik vasküler olayların engellenmesinde aspirin etkili bir antiplatelet ilaçtır. Bununla beraber bazı hastaların klinik ve laboratuvar bulguları aspirine cevabın azalmış veya hiç olmadığını gösterir. Bu durum aspirin direnci olarak adlandırılır ve artmış kardiyovasküler risk ile ilişkili olduğu bildirilmiştir. Aspirin direncinin mekanizması henüz tam olarak ortaya konulmamıştır. Klinik, farmakolojik ve genetik faktörler aspirin direnci ile ilişkili olabilir. Bununla birlikte aspirin direncinin günümüzde tanı için standardize testi ve kanıtlanmış tedavisi yoktur. Bu makale aspirin direncini tanımlama, klinik sonuçlar, laboratuvar testleri, olası nedenler ve tedavisel yaklaşımları tartışarak özetlemiştir. (*Anadolu Kardiyol Derg 2013; 13: 370-3*)

**Anahtar kelimeler:** Aspirin direnci, klinik sonuçlar, laboratuvar testleri, tedavi yaklaşımları

### Introduction

Atherothrombotic vascular diseases are the leading causes of mortality and morbidity in developed countries. Aspirin is an effective antiplatelet drug for preventing thrombo-embolic vascular events. In a meta-analysis of 287 studies demonstrated that efficacy of long-term use of aspirin in primary and secondary cardiovascular prevention (1). Hence, guidelines of both the American College of Cardiology (ACC) and European Society of Cardiology (ESC) recommend the use aspirin as a antiplatelet

drug in the treatment of patients with cardiovascular disease and at high risk patients for cardiovascular events. Despite strong evidence, there are still some patients that experience cardiovascular events under daily aspirin therapy. The clinical and laboratory evidences show diminished or absent response to aspirin therapy in these patients who were called unresponsive or aspirin resistant. The prevalence of aspirin resistance has been determined as 0.4-35% by various methods (2, 3). Nevertheless, there is also the limitation of extrapolating from ex vivo test result for nonresponsiveness and limited data suggest-

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ing nonresponsiveness with clinical outcomes. There is still needed to establish the definition of aspirin resistance, effective treatment and relationship between laboratory aspirin resistance and clinical outcome.

This paper reviews aspirin resistance, discussing its definition, clinical outcomes, laboratory tests, possible causes and therapeutic approaches.

### **The effect of aspirin**

Aspirin selectively and irreversibly acetylates the serine residue in cyclooxygenase-1 (COX-1) present in platelet, thereby blocking the synthesis of prothrombotic thromboxane A2 (TXA2). Aspirin is readily absorbed in the upper gastrointestinal tract. After indigestion, aspirin is observed in plasma in less than 30 minutes and reaches peak levels in about 1 hour (4). Aspirin is mainly metabolized by the liver and intestinal (5). Therefore, most platelet inhibition occurs in prehepatic circulation.

### **Definition of aspirin resistance**

There is no universal accepted definition of aspirin resistance. The definition of aspirin resistance may be performed as clinical and laboratory. Laboratory aspirin resistance has been used to describe the lack of an expected effect of aspirin on platelet function tests of its pharmacologic effect that may correlate independently with increasing risk of cardiovascular events (6). However, there is no still specific laboratory test that can be used as the ideal test to assess platelet antiaggregation. The clinical definition of aspirin resistance as the failure of drug to prevent a cardiovascular event despite continued administration of aspirin in therapeutic doses. The diagnosis of clinical resistance may only be performed retrospectively because a thrombotic event must occur after aspirin treatment.

### **Laboratory tests**

Laboratory aspirin resistance defines as the failure of the therapeutic doses of aspirin to prolong bleeding time, which is a primary measurement of platelet function or a failure to reduce TXA2. Serum thromboxane B2 is a stable metabolite of TXA2 and therefore can be reflected the pharmacological effect of aspirin. Although there is no specific laboratory test to assess platelet antiaggregation, the most common methods to evaluate the degree of platelet inhibition are below:

### **Optical aggregometry**

This spectrophotometric test measures light transmission through a platelet suspension that occurs when platelet response to specific platelet agonist (arachidonic acid, ADP, epinephrine etc.). Optical aggregometry test is not ideal for measuring platelet sensitivity to aspirin. Because it is an interpreter dependent, it is difficult to prepare platelet rich plasma and there is a lack of standardization of cut-off value. However, the prevalence of aspirin resistance by this test is lower than other assays.

### **Verify now**

This turbidimetric test based on the same principle as Optical aggregometry is a simple bedside test that measures the response of platelet aggregation to fibrinogen and arachidonic acid. Its advantages are: it is faster and requires smaller sample size. However agreement between "Verify now" and other test is poor and in some situation this test may not be specific (7).

### **PFA -100 (Platelet Function Analyzer)**

PFA-100 evaluates platelet aggregation caused by high flow velocity and platelet activators such collagen-epinephrine. The system is automatic and quick. It is sensitive to von Willebrand disease and platelet function abnormalities (8, 9).

### **Bleeding time**

This technique measures the length of bleeding time from a puncture in the skin but it is not commonly used.

However, the appropriate method for detecting aspirin resistance is still controversial and the absolute definition is not available.

### **Possible causes of aspirin resistance**

The exact mechanism of aspirin resistance has not been established yet. The clinical, pharmacological and genetic factors may be associated with aspirin resistance.

Considerable number of patients receiving aspirin does not use regularly their regimen that is the predominant cause of aspirin resistance (noncompliance). Schwartz et al. (10) evaluated one hundred ninety patients with a history of myocardial infarction using arachidonic acid-stimulated light aggregometry at 3 different time points: while receiving their usual daily aspirin, after not receiving aspirin for 7 days, and 2 hours after the observed ingestion of aspirin 325 mg. At the first time point, 17 patients (9%) failed to show aspirin inhibition of platelet aggregation, but 2 hours after observed aspirin ingestion, aspirin inhibition was observed in all but one patient.

Smoking may cause aspirin resistance as a result of its procoagulative properties. Gum et al. (11) showed that patients who were aspirin resistant or aspirin semi-responders were likely to be smokers compared with aspirin-sensitive patients.

Some previous studies suggested an association of aspirin resistance with diabetes, hypercholesterolemia, and age (11-13). We investigated the prevalence of aspirin resistance in patients with end-stage kidney disease (ESKD) and an association between biochemical aspirin resistance and clinical outcome. Our study included 78 end-stage renal disease patients. The primary end -point was the composite of death, myocardial infarction (MI), unstable angina or cerebrovascular accident (CVA). Mean follow-up was 20.7±6.1 months. Aspirin resistance was present in 34 (43.58%) of 78 patients with ESKD. Major events occurred in 20 (25.6%) of the 78 patients. Between the patients who were aspirin resistant, 13 of 34 (38.2%) experienced death, MI, or CVA compared with 7 of 44 (15.9%) patients who were not aspirin resistant (p=0.034). Our study demon-

strated that a significant number of ESKD patients are resistant to aspirin therapy and it to be significantly associated with major adverse events during long term follow-up (14, 15).

Drug interactions are important causes for aspirin resistance. A higher percentage of aspirin resistance was observed among patients who take statin (16), non-steroidal anti-inflammatory drugs (17) and proton pump inhibitors (2).

Genetic factors may play an important role in aspirin resistance. Faraday et al. (18) did a study of 500 patients. They showed a genetic cause for aspirin resistance. Several candidate genes might be responsible for aspirin resistance. COX -1 enzyme gene, P2Y1 and P2Y12 platelet receptor genes and glycoprotein (GP) IIb/IIIa genes are most studied genes in aspirin resistance, but there are conflicting results regarding association of aspirin non-response and gene polymorphism (19-21). A meta-analysis of 31 studies examining 50 polymorphisms in 11 genes showed that only GPIIIa gene polymorphism was associated with aspirin resistance (22).

#### Clinical outcomes of aspirin resistance

Several published studies have been shown correlating aspirin resistance with adverse clinical outcomes. Gum et al. (23) made a 2 years follow-up study with stable cardiovascular patients receiving aspirin therapy that they found higher serious vascular events who were aspirin resistance and their study revealed that aspirin resistance is a significantly independent predictor of future adverse outcomes in multivariate analysis. Eikelboom et al. (24) reported higher risk for MI (2-fold) and cardiovascular death (3.5-fold) in patients with aspirin resistance. Grottemeyer et al. (25) assessed post-stroke patients for two years and showed that among 174 patients, aspirin non-responders had a 10-fold increase in the risk of ischemic vascular events compared with aspirin responders (40 vs 4.4%  $p < 0.0001$ ). An Australian study found that arterial re-occlusion in aspirin nonresponsive men was 87% higher than in the aspirin-sensitive group who underwent peripheral arterial balloon angioplasty for peripheral vascular disease (26).

#### Treatment of aspirin resistance

Aspirin resistance is clinically defined and determined with laboratory techniques. However, the exact mechanisms of aspirin resistance are still not understood and there is no standard test for diagnosis. Therefore, specific treatment of aspirin resistance is unknown. There are a few studies investigating treatment of aspirin resistance. Higher doses of aspirin, combination of the aspirin therapy with ADP receptor antagonists, or P2Y12 antagonists are potential choices of therapy. Higher doses of aspirin may eliminate aspirin resistance. In one study, lower dose of aspirin were associated with higher rate of aspirin resistance (27). Recent trials have demonstrated the superior clinical benefit of the combination of clopidogrel with aspirin compared with aspirin alone in patients with acute coronary syndrome (28) or after coronary stenting (29). The PCI-CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) study showed that

the combination of aspirin and clopidogrel had significant benefit in death, stroke, nonfatal MI compared with aspirin (30). But CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance) and MATCH (Management of Atherothrombosis with Clopidogrel in High-risk patients) large randomized clinical trials could not show any difference between dual antiplatelet therapy (aspirin and clopidogrel) and aspirin alone in primary end-point in high risk cardiovascular patients (31, 32). Furthermore, the ASCET (Aspirin Non-Responsiveness and Clopidogrel Endpoint Trial) trial demonstrated that aspirin non-responder patients with stable coronary artery disease randomized to clopidogrel, there was a 40% reduction in the combined end-point compared with aspirin responders to continue aspirin (33). These results suggest that aspirin non-responder patients may benefit from clopidogrel therapy. However, another study showed that clopidogrel was less sensitive in patients with aspirin resistance and some patients had resistance for both drugs (34). It may be plausible to use prasugrel in patients with aspirin resistance. Further studies are needed to determine the treatment of aspirin resistance.

#### Conclusion

Although aspirin is an effective antiplatelet agent with proven benefits in both secondary prevention and high risk primary prevention of adverse cardiovascular events, interindividual variation in platelet response to aspirin is still high and there is no universal accepted definition of aspirin resistance, no specific laboratory test to assess platelet antiaggregation and correct treatment of aspirin resistance. Further randomized, multicenter, large-scale studies are required to better define the effect of aspirin, to establish a universal definition of aspirin resistance, its clinical relevance and correct treatment.

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