

# Aspirin resistance in coronary heart disease: Current understandings and strategies

Ya-ling Han

Department of Cardiology, General Hospital of Shenyang Military Command, Shenyang 110016, Liaoning Province, China

## INTRODUCTION

The use of antiplatelets is an important approach toward the management of cardiovascular diseases and prevention of thrombotic events. Responses to antiplatelet therapy may vary among individuals, referred to as the antiplatelet therapy response variability. Even with aspirin, a conventional antiplatelet, the treatment can sometimes appear ineffective. Alongside the continuous advances in interventional therapy and development of new antiplatelet agents, resistance to aspirin has attracted more and more clinical attention. This article reviews the definition, mechanism, clinical impacts, detection, and intervention of aspirin resistance.

## DEFINITION OF ASPIRIN RESISTANCE

The concept of aspirin therapy response variability is mainly based on specific pathophysiological mechanisms, pharmacokinetics, and/or pharmacodynamics by which aspirin works. Aspirin resistance may be simply one of potential causes leading to interindividual variability in the response to aspirin.<sup>[1]</sup> In 2009, the Working Group on Thrombosis of the European Society of Cardiology released a position paper on interindividual variability in the response to oral antiplatelets, in which, aspirin resistance was categorized as clinical resistance and laboratory resistance.<sup>[2]</sup> The clinical resistance is associated with occurrence of cardiovascular events when the patient is receiving aspirin, whereas the laboratory resistance is manifest by insufficiently suppressed platelet activity shown by *in-vitro* assays despite current use of aspirin.

## PROBABLE MECHANISM UNDERLYING ASPIRIN RESISTANCE

A number of studies have investigated the underlying mechanism of aspirin resistance. Multiple factors may affect aspirin inhibition of thromboxane A<sub>2</sub> (TXA<sub>2</sub>) production/activation and interfere with platelet aggregation, thereby causing laboratory aspirin resistance. There may also be many factors that lead to failed aspirin therapy (clinical aspirin resistance).

### *Patient compliance*

Poor compliance of patients is a most neglected albeit common reason for laboratory or clinical inefficacy of aspirin therapy. A study by Cuisset *et al.*<sup>[3]</sup> showed that, of 136 patients undergoing coronary artery stenting, nonresponse to aspirin therapy was identified in 19 patients (14%) at 1 month after they were discharged home. However, after commitment of aspirin use in the patients, all except one nonresponder became responsive to the treatment. Poor compliance, rather than virtually biological aspirin resistance, was thus recognized in these patients.

### *Dosage*

Laboratory studies have shown that aspirin may effectively inhibit the activities of platelet cyclooxygenase (COX)-1 even with low doses. Yet, extremely low-dose aspirin may be associated with aspirin resistance. A meta-analysis by Antithrombotic Trialists' Collaboration showed uncertain therapeutic efficacy of aspirin at doses below 75 mg/d.<sup>[4]</sup> A study also demonstrated that, among a total of 128 (27.4%) aspirin-resistant patients, mean dose of aspirin was significantly lower than that in patients

**Address for Correspondence:**  
Professor Ya-lin Han, Department of Cardiology, General Hospital of Shenyang Military Command, Shenyang 110016, Liaoning Province, China.  
Email: hanyaling@263.net

### Access this article online

**Website:**

www.intern-med.com

**DOI:**

10.1515/jtim-2016-0002

**Quick Response Code:**



without aspirin resistance; by multivariate analysis, aspirin dose <100 mg was an independent predictor of aspirin resistance (OR 2.23, 95%CI 1.12-4.44,  $P = 0.022$ ).<sup>[5]</sup>

### ***Drug interactions***

Concomitant use of aspirin and other therapeutic agents, such as nonsteroidal anti-inflammatory drugs or COX-2 inhibitors, may pharmacokinetically induce aspirin resistance due to drug interactions.<sup>[6]</sup> For example, Ibuprofen may antagonize the aspirin-induced irreversible platelet inhibition.<sup>[7]</sup> Naproxen may also interfere with the aspirin inhibition of platelet COX-1 activity and function.<sup>[8]</sup> Moreover, it was shown that the prevalence of aspirin resistance appears to be higher in patients who are on Statins.<sup>[9]</sup>

### ***Gene polymorphisms***

Genetic factor may be playing an important role in aspirin resistance. In a study of 124 patients with acute myocardial infarction, COX1-A1 mutation was significantly correlated with aspirin resistance.<sup>[10]</sup> Glycoprotein IIIa (GPIIIa) gene polymorphism was also linked to aspirin resistance in 450 Chinese elderly patients treated with aspirin.<sup>[11]</sup>

### ***Increased platelet turnover***

Increased platelet turnover is noted during coronary artery bypass grafting, infections, and inflammation. Given the very short half-life of aspirin, the high platelet turnover may lead to, during the 24 h dosing interval, an increase in the proportion of non-aspirin-inhibited platelets, as reflected by insufficient inhibition of platelet COX-1 activity.<sup>[12]</sup>

### ***Other potential causes***

A recent study showed significantly up-regulated expression of platelet glycoprotein IIIa receptor in aspirin-resistant patients, which was not found in patients responsive to aspirin. This finding offers new clues to the mechanism of aspirin resistance, and also suggests that platelet GPIIIa receptor may become a novel biomarker for aspirin resistance.<sup>[13]</sup> In another study, aspirin resistance was found to correlate with age, and the incidence of aspirin resistance was high in patients with coronary heart disease (CHD) aged 75 years or above.<sup>[14]</sup> It was also shown that enteric-coated aspirin may cause aspirin resistance, and therefore low-dose enteric-coated aspirin as a medication for secondary prevention of cardiovascular diseases may not achieve complete inhibition of platelet COX due to inadequate bioavailability. However, pharmacologists argue that this may be the “pseudo-resistance” to aspirin resulting from enteric coating-induced delay and decrease of drug absorption.<sup>[15]</sup> aspirin resistance may occur in smoking patients owing to the procoagulant effect of cigarettes. Other factors, such as thromboxane of nonplatelet

sources and nonatherosclerotic lesions, may also be correlated with aspirin resistance.

## **CLINICAL IMPACTS OF ASPIRIN RESISTANCE**

In patients with stable cardiovascular disease, aspirin resistance has been shown to be associated with a threefold or greater risk of major adverse cardiovascular events (MACEs).<sup>[16]</sup> In 2014, a meta-analysis including 1889 CHD patients showed that 622 were confirmed to have aspirin resistance; in these patients, the risk of adverse events was significantly higher compared with those who were sensitive to aspirin (OR 2.44, 95% CI 1.81-3.30,  $P < 0.01$ ). Even in CHD patients who were well-compliant to aspirin therapy, aspirin resistance can increase the risk for MACEs by 2.4 times.<sup>[17]</sup>

## **DETECTION OF ASPIRIN RESISTANCE**

### ***Optical aggregometry***

Light transmission aggregometry (LTA) is used to measure the transmission of light through a sample of aggregating platelet. This method is considered not only as the “gold standard” to measure platelet aggregation function, but also as one of the most common laboratory monitoring indicators for antiplatelet therapy and aspirin resistance. However, low specificity, high demand for sample volume, and technical challenges with LTA could frequently lead to measurement errors.<sup>[18]</sup>

### ***VerifyNow***

VerifyNow is a device that works by the same principle of measurement as optical aggregometry does, while measuring the agglutination response of platelets to fibrinogen and arachidonic acid. The advantages include smaller sample volume, simple and fast manipulation, and suitability for point-of-care detection. VerifyNow is currently preferred for its considerably high sensitivity and specificity in monitoring aspirin resistance, yet it is more costly as well.<sup>[19]</sup>

### ***Platelet function analyzer (PFA-100)***

PFA-100 can measure the platelet aggregation induced by high blood flow and platelet activators, such as collagen/epinephrine. Measurement with this test system is automatic and rapid. PFA-100 is now considered as one of ideal methods to diagnose platelet anomalies, and the most reliable and effective in indicating aspirin resistance. PFA-100 requires rigorous processing of blood specimens so that the test should be completed within 4–6 h after blood sampling.

**Bleeding time**

Dermal puncture is used to measure the bleeding time, the earliest method to examine platelet function and so far the only approach to do so in-vivo. Test of bleeding time is simple and easy to operate, and does not require preparation of blood, but is not commonly used.

Owing to certain individual disadvantages, the above-mentioned measurements are mainly used for laboratory research, not yet justified for widespread use in clinical practice.

**TREATMENT STRATEGIES FOR ASPIRIN RESISTANCE****Dose escalation**

In light of individual variation in responses to aspirin therapy, the dose of aspirin may differ among single patient to achieve optimal platelet inhibition. In a study on aspirin-resistant patients with unstable angina or non-ST segment elevated myocardial infarction (NSTEMI), a dose of 300 mg/d aspirin was shown to make a statistically significant difference in adenosine diphosphate (ADP) induced platelet aggregation rate, percentage of collagen-induced platelet aggregation, and the level of thromboxane B2 (TXB2) compared with 150 mg/d aspirin, suggesting that dose escalation may improve aspirin resistance.<sup>[20]</sup> In 2013, a study recruiting 40 CHD patients noted that all the patients were resistant to 75 mg/d aspirin as indicated by VerifyNow. Subsequently, an escalation in aspirin dose to 150 mg/d caused successful reversion of aspirin resistance in 62.5% of the patients, as with re-evaluation by VerifyNow at 4 weeks later.

It should be noted that, with the introduction of novel, powerful P2Y12 receptor blockers, findings from several studies (eg. PLATO) show that escalating aspirin dose could not reduce clinical events, but rather, increase the risk of bleeding.<sup>[21]</sup> Therefore, dose escalation is not recommended when aspirin is administered in combination with P2Y12 inhibitors, even if platelet function test suggests poor response to the therapy. Consistent with this finding, recent guidelines propose that for patients undergoing percutaneous coronary intervention (PCI) and receiving dual antiplatelet therapy with aspirin plus P2Y12 inhibitor, the dose of aspirin should be reduced to 75–100 mg/d from the initial loading dose of 150–300 mg/d.<sup>[22]</sup> Apparently, the majority of current studies on dose escalation to improve aspirin resistance target at patients given aspirin for antiplatelet monotherapy or those who have discontinued dual antiplatelet therapy, and does not apply to the combination therapy using aspirin and P2Y12 receptor blocker.

**Improving patient compliance to medication**

The incidence of aspirin resistance can be as well reduced by increasing patient compliance to the medication. An observational study, which included a total of 212 patients with a history of myocardial infarction, revealed that improving patient compliance and escalating aspirin dose (up from 100 mg to 200–300 mg) could reduce the rate of aspirin resistance from 18.4% to 1.4%.

**Increasing the frequency of medication**

Studies have also confirmed that increasing the frequency of medication with aspirin is effective toward lowering the rate of aspirin resistance. A single-center crossover study on 92 patients suggested that, in diabetics complicated with and coronary artery disease, twice-daily oral aspirin performed better in suppressing platelet aggregation than the once-daily aspirin regimen with the same daily dose.

**Use of other antiplatelet agents**

Recently, it has been found that using Clopidogrel in dual antiplatelet therapy can be feasible in averting aspirin resistance. In a study, the investigators included 60 patients who underwent off-pump coronary artery bypass grafting. All patients were randomized into two groups, given antiplatelet monotherapy with aspirin 100 mg/d or dual antiplatelet therapy with aspirin 100 mg/d and Clopidogrel 75 mg/d. At 1 and 2 days after medication, platelet aggregation testing revealed that patients on dual therapy were less likely to have aspirin resistance compared with those on monotherapy (32.1% *vs.* 62.1%, 10.7% *vs.* 34.5%, both  $P < 0.05$ ).

**Other strategies**

More other strategies to reduce aspirin resistance have been proposed, such as avoiding drug interactions, addressing complications, and selecting proper dosage forms. However, these need validation in further clinical trials.

In conclusion, aspirin resistance is a clinical entity that can lead to failed treatment, and significantly affect the clinical prognosis of CHD. Due to the lack of suitable laboratory diagnostic tools and the inadequately understood mechanisms of aspirin resistance, limitations and controversies remain regarding the current approaches for diagnosis and treatment. Therefore, more studies are needed to provide a clear definition and proper management of this condition in the future.

**Conflicts of Interest**

None declared.

## REFERENCES

1. Rocca B, Petrucci G. Variability in the responsiveness to low-dose aspirin: pharmacological and disease-related mechanisms. *Thrombosis* 2012; 212: 376721.
2. Kuliczowski W, Witkowski A, Polonski L, Watala C, Filipiak K, Budaj A, *et al.* Interindividual variability in the response to oral antiplatelet drugs: a position paper of the Working Group on antiplatelet drugs resistance appointed by the Section of Cardiovascular Interventions of the Polish Cardiac Society, endorsed by the Working Group on Thrombosis of the European Society of Cardiology. *Eur Heart J* 2009; 30: 426-435.
3. Cuisset T, Frere C, Quilici J, Gaborit B, Bali L, Poyet R, *et al.* Aspirin noncompliance is the major cause of "aspirin resistance" in patients undergoing coronary stenting. *Am Heart J* 2009; 157: 889-893.
4. 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: 71-86.
5. Lee PY, Chen WH, Nq W, Cheng X, Kwok JY, Tse HF, *et al.* Low-dose aspirin increases aspirin resistance in patients with coronary artery disease. *Am J Med* 2005; 118:723-727.
6. Stitham J, Vanichakarn P, Ying L, Hwa J. Cardiovascular pharmacogenetics of anti-thrombotic agents and non-steroidal anti-inflammatory drugs. *Curr Mol Med* 2014; 14:909-931.
7. Catella-Lawson F, Reilly MP, Kapoor SC, Cucchiara AJ, DeMarco S, Tournier B, *et al.* Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med* 2001; 345: 1809-1817.
8. Capone ML, Sciulli MG, Tacconelli S, Grana M, Ricciotti E, Renda G, *et al.* Pharmacodynamic inter-action of naproxen with low-dose aspirin in healthy subjects. *J Am Coll Cardiol* 2005; 45: 1295-1301.
9. 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 haemorrhological variables. *Drugs Aging* 2006; 23: 559-567.
10. lehlova J, Slavik L, Kucerova J, Krcova V, Vaclavik J, Indrak K. Genetic polymorphisms of platelet receptors in patients with acute myocardial infarction and resistance to antiplatelet therapy. *Genet Test Mol Biomarkers* 2014; 18: 599-604.
11. Wang BY, Tan SJ. Platelet glycoprotein IIIa gene polymorphism (Leu-33Pro) and aspirin resistance in a very elderly Chinese population. *Genet Test Mol Biomarkers* 2014; 18: 389-393.
12. Zimmermann N, Wenk A, Kim U, Kienzle P, Weber AA, Gams E, *et al.* Functional and biochemical evaluation of platelet aspirin resistance after coronary artery bypass surgery. *Circulation* 2003; 108: 542-547.
13. Floyd CN, Goodman T, Becker S, Chen N, Mustafa A, Schofield E, *et al.* Increased platelet expression of glycoprotein IIIa following aspirin treatment in aspirin-resistant but not aspirin-sensitive subjects. *Br J Clin Pharmacol* 2014; 78: 320-328.
14. Vaturi M, Vaduganathan M, Bental T, Solodky A, Kornowski R, Lev EI. Relation of aspirin response to age in patients with stable coronary artery disease. *Am J Cardiol* 2013; 112: 212-216.
15. Maree AO, Curtin RJ, Dooley M, Conroy RM, Crean P, Cox D, *et al.* Platelet response to low-dose enteric-coated aspirin in patients with stable cardiovascular disease. *J Am Coll Cardiol* 2005; 46: 1258-1263.
16. 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: 961-965.
17. Li J, Song M, Jian Z, Guo W, Chen G, Jiang G, *et al.* Laboratory aspirin resistance and the risk of major adverse cardiovascular events in patients with coronary heart disease on confirmed aspirin adherence. *J Atheroscler Thromb*, 2014, 21: 239-247.
18. Zhang LW, Wang XF, Wang HL. Aspirin resistance and its experimental monitoring. *Theory Pract Diagn* 2006; 21: 239-442.
19. Wang Xiaodong. Research advances in monitoring platelet function and efficacy of antiplatelet drugs. *J Tongji Univ (Med Sci)* 2011; 32: 120-124.
20. Salama MM, Morad AR, Saleh MA. Resistance to low-dose aspirin therapy among patients with acute coronary syndrome in relation to associated risk factors. *J Clin Pharm Ther* 2012; 37: 630-636.
21. Mahaffey KW, Wojdyla DM, Carroll K, Becker RC, Storey RF, Angiolillo DJ, *et al.* Ticagrelor compared with clopidogrel by geographic region in the Platelet Inhibition and Patient Outcomes (PLATO) trial. *Circulation* 2011; 124: 544-554.
22. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC)1, Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, *et al.* ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012; 33: 2569-2619.

**How to cite this article:** Han Y. Aspirin resistance in coronary heart disease: Current understandings and strategies. *J Transl Intern Med* 2016; 4: 7-10.