



# The dilemma of aspirin resistance in obese patients

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**Abstract:** Aspirin resistance (AR) commonly refers to the concept of reduced aspirin efficacy in preventing cardiovascular disease and platelet inhibition. Obesity increases the risk of heart disease three- to four-fold and has been associated with AR. Aspirin is used as a tool for both primary and secondary prevention, but recent studies suggest that its lack of efficacy for primary prevention is partly attributable to obesity. Several mechanisms have been described that contribute to AR in obese patients using pharmacokinetics and pharmacodynamics. AR may be attenuated through weight loss, alternative dosing regimens, and different drug formulations. With the global rise of obesity, it is imperative to find preventive therapies that adequately address atherosclerotic cardiovascular disease (ASCVD) risk in this population.

**Keywords:** Aspirin resistance (AR); obesity; aspirin

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## Introduction

Aspirin has long been considered a stalwart for the prevention of atherosclerotic cardiovascular disease (ASCVD) due to its prominent antiplatelet effects (1). While the benefit of aspirin in secondary prevention remains salient (1,2), more recent studies have called into question the role of aspirin in the primary prevention of ASCVD (3-5). In fact, the American Association of Family Physicians, American Heart Association, and American College of Cardiology have all recently changed their guidelines to recommend against aspirin use for primary prevention because the bleeding risk outweighs the net clinical benefit of decreased ASCVD events (1,6). While numerous studies performed in 1990s showed that aspirin is beneficial in the primary prevention of cardiovascular event (2,7), more recent studies have failed

to demonstrate as profound of a benefit, especially with bleeding risk is considered (8,9). One theory for the lack of benefit is that obesity affects aspirin efficacy. The prevalence of obesity in United States skyrocketed from 12% to 19.8% between 1991 and 2000 (10,11), and as an estimated 58% of world population are projected to be overweight or obese by the year 2030 (12,13). Thus, understanding the role of obesity in aspirin is paramount.

## Aspirin resistance (AR)

Defined as the occurrence of ASCVD events despite consistent use of aspirin at recommended doses, AR may explain some degree of therapy failure in the primary prevention of heart disease (14-16). Studies have found that diabetes mellitus, female gender, post-acute coronary

syndrome (ACS) or post-coronary artery bypass grafting, history of stent thrombosis, and obesity are all associated with AR (15,17-22). Obesity confers a three- to four-fold increased risk of secondary ASCVD events and a six-fold higher risk of death (23,24). Obesity affects aspirin metabolism in several ways that reduce its suppression of platelet function (15). Increased platelet reactivity combined with obesity-specific metabolic changes creates a prothrombotic state that warrants treatment. Laboratory studies are attempting to quantify AR by multiple mechanisms, including the suppression of thromboxane B2 (TXB2), assays that detect platelet aggregation in whole blood (e.g., the VerifyNow assay), and flow cytometric analysis for various clusters of differentiation (15,25,26). These studies have found that between 2% and 57% patients do not respond to aspirin optimally (15,25-29).

AR in obesity was first described by Cox *et al.* in 2006 wherein 71 patients taking enteric coated (EC) aspirin showed treatment failure [relative risk (RR) 2.2; 95% confidence interval (CI), 1.7-3.0] and incomplete TXB2 inhibition (RR 1.3; 95% CI, 1.2-1.5) for each 10 kg increase in bodyweight (30). This study paved the way for subsequent trials evaluating the efficacy of aspirin in obesity and highlights the importance of AR in this population who may need adjusted aspirin therapy to be better protected from primary ASCVD events.

### Disruption of primary hemostasis

Aspirin is unique in its ability to prevent atherothrombotic events compared to other nonsteroidal anti-inflammatory drugs (31). Aspirin exerts its cardio-protective effects by acting as an antiplatelet drug. During clot formation, arachidonic acid (AA) is converted to TXA2, which then activates platelets by upregulating fibrinogen receptors on platelet surface which allows the primary platelet plug to be formed (29,31). Aspirin, unlike other non-steroidal anti-inflammatory drugs, irreversibly acetylates cyclooxygenase-1 (COX-1) thereby decreasing TXA2 levels (31,32). Lower levels of TXA2 do not activate platelets as effectively and thus thrombus formation is impeded (15,33).

### Mechanisms of AR in obesity

Laboratory studies focus on two major approaches to AR: pharmacokinetic and pharmacodynamic. Pharmacodynamic explanations revolve around how obesity creates a prothrombotic state that aspirin is unable to suppress.

Laboratory experiments performed by Bordeaux *et al.* quantified platelet reactivity by measuring COX-1 pathway metabolites in response to triggers for thrombosis such as collagen, adenosine diphosphate, and AA (19). Results showed that obese individuals had greater baseline platelet reactivity compared to non-obese controls. After low-dose aspirin treatment, platelet function tests still showed greater activation in obese individuals compared to non-obese patients. Higher-dose aspirin, to account for the increased volume of distribution in obese patients, also did not reduce platelet reactivity in obese patients (19). It is worth noting that aspirin only inhibits one of the many pathways of platelet activation and atherothrombosis; therefore, patients may continue to have ASCVD events while taking this medication (8). Obesity is associated with increased concentrations of leptin, a hormone that regulates hunger (15). Studies have showed that leptin increases platelet reactivity and produces a prothrombotic environment (34). This shows that obesity intrinsically affects platelet reactivity and makes it more resistant to aspirin. Further, obesity is associated with higher platelet turnover. Thus, the daily 10-15% of newly added platelets remain activated despite optimal aspirin effect and can be perceived as AR (35,36).

Pharmacokinetic explanations focus on reduced concentration of aspirin in the body. A one-dose-fits-all approach to aspirin causes variations in serum aspirin concentrations (37). Among obese patients, aspirin does not reach therapeutic levels in bloodstream and is, therefore, less effective (37). Additionally, aspirin acetylates plasma proteins, such as albumin, hemoglobin, and fibrinogen, which all act as competitive antagonists to COX-1 (37). By non-specifically acetylating these proteins, aspirin's ability to acetylate COX-1 is reduced, thereby lowering platelet reactivity. Aspirin is deacetylated and deactivated by enzymes found in the intestinal epithelium, liver, plasma, and red blood cells (RBCs) (38). Obese patients have higher volumes of plasma and RBCs, which can be associated with elevated concentrations of deacetylating enzymes. Thus, aspirin is more readily deactivated in obese individuals, leading to reduced bioavailability (37). By understanding these mechanisms of AR in obesity, overcoming AR becomes possible.

### Overcoming AR

AR may be overcome by modulating weight, aspirin dose, dosing frequency, and medication formulation. Some studies suggest that weight loss reverses the metabolic

changes associated with obesity-related AR (39,40). Weight loss was associated with reduced baseline platelet reactivity and improved response to aspirin (39,40). In fact, bariatric surgery has also been associated with improved aspirin responsiveness, which suggests that adipocytes may predispose obese patients to a prothrombotic state (40). Therefore, weight loss can reduce baseline platelet reactivity and decreases AR. This reduction in AR can reverse the increased cardiovascular risks associated with AR.

Most studies evaluating aspirin for cardiovascular benefits have looked at low-dose aspirin because it was believed that aspirin does not display a dose-responsiveness in its antithrombotic effect (15,41). It has come to attention recently that a one-dose-fits-all approach could have led to some biases on its effectiveness (37). When higher doses of aspirin (300 mg, 325 mg, 500 mg) were compared to lower doses (75–100 mg) in obese patients, higher doses were found to have lower risk of all cardiovascular events (37). At the same time, higher doses of aspirin were associated with an increased risk of gastrointestinal bleeding (15,37,41). This highlights how aspirin dosage plays a role in AR, and modulating dosage can impact AR.

Bleeding risk, especially gastrointestinal, is the major risk of aspirin, and alternate drug formulations have been tried to reduce this risk. Enteric-coating, has not been shown to decrease gastrointestinal (GI) bleeding (35), is associated with increased AR, which highlights the role of drug absorption in AR (30,35,42). A randomized, single-blinded, triple-crossover study analyzed the trends in aspirin non-responsiveness via TXB2 generation when treated with plain aspirin, EC aspirin and lipid-based formulation of aspirin (PL2200) (42). The study tested 325mg aspirin on the forty enrolled patients who had non-insulin dependent diabetes and BMI between 30 and 40 kg/m<sup>2</sup>. Aspirin non-responsiveness was lowest in PL2200 (8.1%) compared to plain aspirin (15.8%) and EC aspirin (52.8%) (42). Another study conducted by Peace *et al.* stratified aspirin formulations according to weight for overcoming AR (43). They concluded that patients <90 kg respond well to 75 mg of EC aspirin while patients >90 kg have better benefit with 75 mg of plain aspirin (43). These studies demonstrate how the formulation of aspirin affects AR.

In addition to higher dose and formulations, frequency of aspirin dosing has also been shown to affect AR (44,45). In a study of 36 patients with coronary artery disease and type 2 diabetes mellitus, the VerifyNow assay determined that greater platelet inhibition was achieved with twice daily low dose aspirin compared to once daily administration (44).

This study did not, however, assess bleeding risk associated with twice-daily dosing.

Finally, and perhaps most obviously, nonadherence to prescribed therapy is a leading cause of AR. A study by Hennekens *et al.* noted noncompliant patients do not have a reduced risk of myocardial infarction (MI) with aspirin therapy, and use of other nonsteroidal anti-inflammatory drugs combined with aspirin nonadherence actually increases the risk of MI (16). Without good, standardized means of measuring outpatient compliance, this mechanism of AR may be the most difficult to overcome. Overall, physicians should consider dose, formulations, and frequency of dosing before prescribing low-dose aspirin to all patients, and weight loss should be a strong, concomitant recommendation.

### Adjunctive therapies to improve AR

While AR can be overcome, there are adjunctive medicines that can be added to aspirin to reduce cardiovascular risks in high-risk patients. Omega-3-fatty acids inhibit COX-1 pathway and decrease platelet AA and TXA2 synthesis (45). In a randomized controlled trial, 30 patients with coronary artery disease treated with low-dose aspirin (75–162 mg) were found to have AR screened with VerifyNow aspirin assay. The patients were divided to receive either 325 mg daily aspirin or their original low-dose of aspirin plus omega-3-fatty acids. The VerifyNow aspirin assay showed that 80% of omega-3-fatty acid patient were no longer resistant, and no bleeding events occurred with either group. The study found that omega-3-fatty acids are a good addition to aspirin monotherapy since it reduces platelet reactivity and decreases AR (45).

When aspirin is used in combination with other antiplatelet agents, such as dipyridamole, ticlopidine, intravenous glycoprotein IIb/IIIa antagonists, or P2Y12 agents there is variable reduction in ASCVD events (46,47). Rothwell *et al.* reports that among individuals weighing at least 70 kg, dual antiplatelet therapy (DAPT) is more effective at reducing stroke in patients with a history of ASCVD events, compared to an isolated regimen of low-dose aspirin alone (37). However, adjunctive medications as part of DAPT were not described. It remains to be determined the effect of adjunctive antiplatelet therapy in a specifically obese population.

A recent meta-analysis evaluated the role of Chinese herbal medicine (CHM) on AR (48). After evaluating 1,460 patients from 18 studies, the main conclusions were that CHM

could reduce platelet aggregation and would not increase the risk of bleeding, but this is primarily based on trials with short courses (approximately four weeks) of therapy. The applicability outside China and to obese patients remains limited, especially since Chinese patented drugs were also included.

## Conclusions

AR is an emerging concept of interest as global use of aspirin has increased. Obesity not only increases ASCVD risk but also generally decreases aspirin efficacy, based on pharmacokinetic and pharmacodynamic studies. Obesity creates a prothrombotic state secondary to increased serum leptin levels, reduced serum aspirin concentrations, and greater aspirin inactivation. Despite multiple mechanisms of resistance, there are numerous ways to counteract AR in obese patients. These include modulating aspirin dose based on a patient's weight, increasing dose frequency, using different formulations, and combining other medications with aspirin to increase its effect. It is also important to recommend weight loss and highlight the importance of medication adherence. Ultimately, a one-dose-fits-all aspirin regimen may not be optimal in obese patients and requires tailored therapy to best reduce ASCVD events in this growing population.

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## Footnote

*Conflicts of Interest:* Dr. Cave discloses that he serves on the speaker's bureau for Portola pharmaceuticals. The other authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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