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Review of aspirin and clopidogrel resistance in peripheral arterial disease

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ABSTRACT

Objective: Aspirin resistance (AR) and clopidogrel resistance (CR) are terms used to describe a reduction in the medication's efficacy in inhibiting platelet aggregation despite regular dosing. This review gives context to the clinical role and implications of antiplatelet resistance in peripheral arterial disease (PAD).

Methods: A review of English-language literature on AR and CR in PAD involving human subjects using PubMed and MEDLINE databases was performed in April 2017. A total of 2075 patients in 22 relevant studies were identified. To give this issue context, a review of the larger, more established literature on antiplatelet resistance in coronary disease was undertaken, identifying significant research associating resistance to major adverse cardiovascular events (MACEs).

Results: Studies in the coronary arterial disease literature have strongly associated antiplatelet resistance with increased MACE. Prevalence of AR or CR in coronary disease appears to be >55% for each in some studies. Meta-analyses of >50 studies revealed that AR and CR are significantly associated with MACE (relative risk of 2.09 and 2.8, respectively). This adds further weight to the literature reporting antiplatelet resistance as an independent predictor of and a threefold risk factor for major adverse cardiovascular events. The prevalence of resistance in PAD in this review was comparable to that in the coronary disease literature, with AR and CR prevalence up to 60% and 65%, respectively. There is evidence that the adverse effects of antiplatelet resistance are significant in PAD. In fact, research directly studying stent thrombosis populations with either coronary arterial disease or PAD revealed more significantly impaired platelet responsiveness to clopidogrel and aspirin in PAD compared with similar individuals with coronary disease. AR in PAD was found in studies to be a significant risk factor for iliofemoral stent reocclusion ($P = .0093$) and stroke in patients with symptomatic carotid disease ($P = .018$). CR was found to be a significant, independent risk factor in predicting ischemic outcomes in several recent PAD studies ($P < .0001$). Loss-of-function carriers of enzyme CYP2C19, important in clopidogrel metabolism, have a 30% greater risk of ischemic events ($P < .001$). Importantly, less antiplatelet drug resistance may be encountered with newer antiplatelet agents, including ticagrelor and prasugrel, because of reduced enzymatic polymorphisms.

Conclusions: The limited research addressing AR and CR in PAD suggests that further research is required to clarify the role of platelet assays and potential for individualized antiplatelet therapy. (J Vasc Surg 2017;66:1576-86.)

Platelet activation and aggregation, mediated by a variety of agonists, play a primary role in organ ischemia. Thrombin generation, platelet-platelet interactions, and vessel wall inflammation lead to mechanical obstruction of the artery lumen.[1] Antiplatelet therapy is the mainstay of treatment in coronary artery disease (CAD), ischemic cerebrovascular disease (CVD), and peripheral arterial disease (PAD), and its efficacy is well established.[2] Aspirin and clopidogrel are by far the most studied and used antiplatelet medications in arterial disease, whether as dual therapy or monotherapy.[3] However, despite adhering to antiplatelet therapy, a significant proportion of patients will suffer ischemic events.[4] The concept of aspirin resistance (AR) and clopidogrel resistance (CR) is used to describe those patients who have higher platelet reactivity than the reference range despite taking antiplatelet therapy and are therefore at greater risk of ischemic events. Increasing evidence is showing that in CAD, antiplatelet resistance is associated with more ischemic events, including after percutaneous coronary interventions (PCIs).[5,6] Highlighting the potential magnitude of antiplatelet resistance in CAD, the prevalence of AR or CR appears to be >55% in some studies. Meta-analyses of >50 studies revealed that AR and CR are significantly associated with cardiovascular events (relative risk of 2.09 and 2.8, respectively).[3] This adds further weight to the literature reporting antiplatelet resistance as an independent predictor of and a threefold risk factor for major adverse cardiovascular events (MACEs; $P = .009$ to $P = .037$).[7,8] However, a clear role for platelet

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function testing in the management of patients having PCI has not yet been supported.[9,10]

Importantly, there is extensive research into the significance of AR and CR in CAD and CVD patients.[11-13] More recently, there appears to be an emerging, limited body of literature analyzing a relationship between AR and CR and ischemic events in PAD.[14-16] However, almost all studies and reviews into AR or CR in PAD analyze only one antiplatelet in isolation rather than both.[16,17] Current research shows that more and more PAD patients are being treated with dual antiplatelet therapy.[18,19] Furthermore, dual antiplatelet therapy appears to reduce the risk of MACEs in symptomatic PAD[20] and is beneficial in patients with reduced platelet response to aspirin monotherapy.[21] Therefore, in light of this, it is imperative to address the issue of AR and CR in PAD simultaneously. This review is the first to examine the evidence currently available on AR and CR and their association with ischemic events in PAD.

DEFINITION AND MEASUREMENT OF ANTIPLATELET RESISTANCE

The definitions of AR and CR are not uniform in the literature because of several key reasons. First, there is discordance in the terminology assigned to the clinically measurable outcome of undesirably high platelet reactivity despite regular antiplatelet therapy. Terms such as *high on-treatment platelet reactivity*, *nonresponsiveness*, and *resistance* have been used in trials, reviews, and meta-analyses to describe a high platelet reactivity measurement or ischemic clinical outcome despite regular antiplatelet treatment.[13,22] Frequently, these terms are interchangeably used. This review uses the term *antiplatelet resistance* to mean that which is the result of high antiplatelet reactivity or is associated with undesirable ischemic clinical outcomes.

Measurement of platelet reactivity highlights another area of discordance in determining resistance. Some of the tests initially developed (such as optical aggregometry) are now less used because of their time-intensive and user-dependent nature in sample preparation and procedure, leading to variability in results.[23] As there is currently no "gold standard" to measure in vivo receptor occupancy in the presence of the antiplatelet agent, surrogate assays have been used to measure platelet reactivity under different circumstances. Not surprisingly, there is discordance between different assays in correlating AR or CR to ischemic events. This is the case with AR-measuring assays, for which in the same cohort of stable CAD patients, there was poor correlation among six different assays, with an AR rate varying from 6.7% to 59.5%.[24] To add further complexity to platelet function tests, the majority of assay-specific resistance cutoff values are determined arbitrarily.[4] Table I summarizes the most common platelet function assays and their characteristics.[24,25]

The historical gold standard platelet function test, light transmittance aggregometry, requires a skilled technician, is time-intensive, and is poorly standardized. These limitations have largely led to a shift toward point-of-care assays.[24] Currently, there is no gold standard point-of-care platelet assay because of the difficulty in defining normal and abnormal ranges to delineate what would be considered antiplatelet resistance from normal values. Furthermore, value interpretation differs between each test as determined by either the clinician's interpretation or arbitrary biochemical results.[24] We are also not aware of any new tests in their infancy to date.

Despite these discrepancies, many assay manufacturers assigned antiplatelet resistance values on the basis of trials involving higher risk vascular patients who suffered MACE while taking antiplatelets. One trial used multiple electrode aggregometry to analyze CR and drug-eluting stent thrombosis involving 1608 CAD patients undergoing PCI. The patients with the highest quartile of multiple electrode aggregometry platelet reactivity were found to be at a statistically significant risk of early stent thrombosis (2.2% vs 0.2%; $P < .0001$).[26] Whereas this 2% absolute difference would appear to be a small percentage difference, it is a highly statistically significant result in a large number of patients and therefore should be regarded seriously. The value assigned to CR in this study has since been used by the assay manufacturer (Dynabyte, Germany) as well as in the 2010 "Consensus and Future Directions on the Definition of High On-Treatment Platelet Reactivity to Adenosine Diphosphate" document.[27] Separate trials using the same platelet function assay showed that similar cutoff points used in previous trials continued to yield significant prognostic value among similar populations using clopidogrel.[27] However, further work is required in platelet reactivity testing to determine which is the most effective test and what the normal and abnormal ranges are before clinical inferences can be relied on.

AR IN PAD

AR is defined as lower than normal ability to inhibit platelet aggregation after standard aspirin dosing.[28] Despite the obvious discordances explained before, a large body of evidence points to a significant correlation between AR and increased risk of ischemic events in at-risk populations. Most of these studies, however, have been in the CAD population.

Prevalence of AR and discordance among platelet function tests. Prevalence of AR in patients with CAD is unsurprisingly variable, ranging from 1% to almost 60%.[7] These results are highly dependent on assay technique and study design.[7,29] Two systematic reviews of 20 studies (95% CAD or CVD populations) and 42 studies (34 full-text articles and 8 meeting abstracts, 85% CAD or CVD disease populations) revealed an AR