Aspirin Resistance: Is it Real and Does it Matter?

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Abstract

Platelets play a pivotal role in the pathophysiology of ischaemic complications of atherosclerotic cardiovascular disease. Aspirin is an oral antiplatelet drug that has been shown to reduce adverse clinical events across the wide spectrum of patients with atherothrombotic disease. However, recurrent ischaemic events still occur in a significant proportion of patients despite aspirin treatment. The concept of aspirin resistance therefore emerges. Although uniformed definitions and standardised assays are not yet available, numerous studies have documented the inter-individual variability in platelet responsiveness to aspirin. Evidence is also accumulating to demonstrate that hypo-responsiveness to aspirin in the laboratory (i.e. resistance) is associated with adverse clinical events in different patient populations. Clinical application of aspirin resistance will require proof from prospective randomised trials that modifications of antiplatelet therapy based on tests of antiplatelet responsiveness will improve the outcomes of patients with aspirin resistance.

Introduction

Platelets play a pivotal role in mediating thrombotic complications of atherosclerotic vascular disease and percutaneous coronary intervention (PCI). Platelets adhere to the subendothelium via interaction with collagen and von Willebrand factor at sites of spontaneous or iatrogenic plaque disruption. After adhesion, platelets undergo conformational changes and release agonists with prothrombotic and/or vasoactive properties such as thromboxane A2 (TxA2) and adenosine diphosphate (ADP), which result in amplification and propagation of platelet activation and aggregation, eventually leading to thrombus formation in combination with coagulation factors. Aspirin is the cornerstone of oral antiplatelet therapy for preventing ischaemic events of atherothrombotic disease. Aspirin inhibits platelet cyclooxygenase-1 by irreversible acetylation of a serine residue at position 530, which prevents the conversion of arachidonic acid to TxA2. The antithrombotic effect of aspirin is resulting from the decreased production of TxA2, a potent vasoconstrictor and platelet agonist. The Antithrombotic Trialists’ Collaboration reported that aspirin therapy was associated with 15% reduction in vascular mortality, 34% reduction in myocardial infarction (MI), and 25% reduction in stroke among high-risk patients with atherothrombotic disease.1 Aspirin has also been shown to reduce the acute ischaemic complications of coronary angioplasty.2,4

Although the effectiveness of aspirin in reducing ischaemic events is well established, there are still a significant proportion of patients experiencing recurrent events despite aspirin treatment. Together with the recognition of laboratory variability in the response to aspirin, the concept of aspirin resistance emerged and has aroused attention in recent years. Despite the lack of universal agreement, the term aspirin resistance generally refers to the inability of aspirin to prevent ischaemic vascular events or the laboratory phenomenon of reduced effect of aspirin on one or more tests of platelet function. In addition to disagreement regarding definition(s), the clinical relevance of aspirin resistance is also uncertain. The remainder of this article is devoted to examine the evidence concerning the relationship of aspirin resistance and adverse clinical events among patients treated with aspirin.

Aspirin Resistance and Clinical Relevance

Variability in the response to aspirin has been recognised for decades. Aspirin’s antiplatelet effect is usually quantified by assays of platelet aggregation or measurements of markers of platelet activation. Using different methodologies and varied definitions, the prevalence of hypo-responsiveness (i.e. resistance) to aspirin has been reported to vary from 5% to 60% among patients with atherosclerotic diseases involving different vascular beds.5-16 The mechanisms of aspirin resistance are not clearly defined. Multiple clinical, pharmacodynamic, cellular, and genetic factors alone or in combination are likely to be involved.17,18 A number of prospective studies relating laboratory measures of aspirin resistance to adverse clinical outcomes have been reported and are summarised in Table 1. Grottemeyer et al10 determined aspirin responsiveness in 180 stroke patients 12 hours after an oral intake of 500 mg aspirin. Patients with a platelet reactivity index >1.25 were categorised as aspirin responders while those with an index >1.25 were defined as secondary aspirin non-responders (i.e. aspirin-resistant). All patients were prescribed aspirin 500 mg three times daily and were followed for 24 months. Stroke, MI, or vascular death were major outcome measures. Complete follow-up was obtained in 174 patients (96%). One-third of the patients were noted to be aspirin-resistant. Major events were noted in 29 patients: 5 (4.4%) in the aspirin responder group versus 24 (40%) in the aspirin-resistant group (p < 0.0001).
Mueller et al\textsuperscript{9} evaluated 100 patients with intermittent claudication undergoing elective percutaneous balloon angioplasty. Aspirin was prescribed at a dose of 100 mg daily. They utilised the method of corrected whole blood aggregometry to define a normal response to aspirin as at least 50% reduction in platelet function with both ADP and collagen as agonists. Aspirin responsiveness was noted to fluctuate among the studied population on repeated monitoring. The incidence of aspirin resistance was 60% at each time point of measurement. At 52-week follow-up, 8 patients in the aspirin-resistant group were found to have reocclusion at the angioplasty site, compared with none of the patients with a normal response to aspirin (87% increase in risk, \( p = 0.0093 \)).

Eikelboom et al\textsuperscript{20} performed a nested case-control study on 976 aspirin-treated patients, with documented or at high-risk of cardiovascular disease, from the Heart Protection Prevention Evaluation (HOPE) trial. Aspirin responsiveness was divided into quartiles by urinary 11-dehydrothromboxane B\(_2\) levels, a marker of in vivo thromboxane generation. After 5 years of follow-up, those patients in the upper quartile had 1.8-fold increase in risk for the composite of MI, stroke, or cardiovascular death (odds ratio [OR] 1.8; 95% confidence intervals [CI] 1.2 to 2.7; \( p = 0.0099 \)) when compared to those in the lower quartile, and the association was independent of traditional risk factors. There was a 2-fold increase in the risk of MI and 3.5-fold increase in the risk of cardiovascular death as well. Gum et al\textsuperscript{21} enrolled 326 stable patients with cardiovascular disease treated with aspirin 325 mg daily for 2.7 days and defined aspirin resistance as a mean aggregation of ≥70% with 10 M ADP and a mean aggregation of ≥20% with 0.5 mg/ml arachidonic acid by optical platelet aggregation. Aspirin resistance was noted in 17 patients (5.2%). After a mean follow-up of 1.8 years, major events (death, MI, or stroke) occurred in 4 (24%) patients in the aspirin-resistant group, compared with 30 (10%) patients in the aspirin-sensitive group (\( p = 0.13 \)). The Kaplan-Meier time-to-event curves for event-free survival showed late divergence of the event curves that remained to be explained. Multivariate analysis demonstrated that, in addition to other risk factors like increasing age, history of congestive heart failure, and elevated platelet count, aspirin resistance was an independent predictor of adverse outcomes (hazard ratio [HR] 4.14, 95% CI 1.42 to 12.06, \( p = 0.009 \)).

Chen et al\textsuperscript{22} examined aspirin responsiveness in patients undergoing elective PCI treated with aspirin at 80-300 mg daily for at least 7 days, clopidogrel pretreatment with a loading dose of 300 mg at least 12 hours before intervention, and procedural anticoagulation using heparin. Using the aggregation-based point-of-care VerifyNow Aspirin, 29 (19.2%) out of the 151 enrolled patients were found to be aspirin-resistant, as defined by an aspirin reaction unit (ARU) ≥ 550. Patients with aspirin resistance were at increased risk of myocardial necrosis (OR 2.9; 95% CI 1.2 to 6.9; \( p = 0.015 \)) determined by creatine kinase-myocardial band elevation, when compared with aspirin-sensitive patients. The mechanism was explored in a sub study by the same group, showing an inverse linear relationship between coronary flow reserve measured by the corrected Thrombolysis In Myocardial Infarction frame count and log-dosed ARU (\( r = 0.28 \); \( p = 0.015 \)). This observation implies that insufficient aspirin-induced platelet inhibition is associated with increased propensity of platelet thrombus formation during iatrogenic plaque rupture by PCI. The attendant distal embolization with or without local platelet-dependent thrombosis will lead to microvascular obstruction which is measurable by reduced CFR. After reporting the predictors and prevalence of aspirin resistance among 468 stable patients with coronary artery disease (CAD) using VerifyNow Aspirin, Chen et al followed this cohort prospectively and found that after a mean follow-up of 379 ± 200 days, patients with aspirin resistance (n=128; 27.4%) were at increased risk of the composite outcome of cardiovascular death, MI, unstable angina requiring hospitalisation, stroke, and transient ischaemic attack compared with patients who were aspirin-sensitive (15.6% vs 5.3%, HR 3.12, 95% CI 1.65 to 5.91, \( p < 0.001 \)).

Cox proportional hazard regression modelling identified aspirin resistance, diabetes, prior MI, and a low haemoglobin to be independently associated with major adverse long-term outcomes (HR for aspirin resistance 2.46; 95% CI 1.27 to 4.76, \( p = 0.007 \)).

### Conclusions

It is incontrovertible that inter-individual variability in platelet responsiveness to oral antiplatelet drugs exists. Analogous to biological responses to other pharmacological agents, the response to clopidogrel has been shown to display a continuous distribution\textsuperscript{23} while similar response to aspirin may exist. On the basis of the aforementioned studies, there is substantial evidence illustrating hypo- or non-responsiveness to aspirin measured in the laboratory (i.e. resistance) is associated with adverse spontaneous (cardiovascular death, acute coronary syndromes, stroke or peripheral arterial occlusion) or procedure-related (myocardial necrosis after PCI or reocclusion after peripheral angioplasty) clinical events in diverse populations of patients with atherothrombotic disease in stable or unstable phase. Nevertheless, the currently available data are flawed by some major limitations. The samples size of these reports is small. Confounding variables are not adequately controlled by the study designs. Different definitions of aspirin resistance are used. Variable aspirin dosage, uncertain treatment compliance, and lack of pretreatment platelet activity assessment are noted in aspirin studies. Clinical application of aspirin resistance will require studies on larger populations that define aspirin resistance using consistent and reproducible assays, and correlate the measurements with clinical outcomes which can be improved by alterations in antiplatelet strategy (e.g., increasing dose of antiplatelet agent, adding or substituting second antiplatelet agent). Such prospective randomised trials are currently underway. The Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilisation, Management, and Avoidance (CHARISMA) trial comparing clopidogrel and aspirin versus placebo and aspirin for high-risk primary or secondary prevention was reported recently. Urinary 11-dehydrothromboxane B\(_2\) levels were checked in a substudy, enabling prospective assessment of the addition of clopidogrel to aspirin in reducing adverse events associated aspirin resistance.\textsuperscript{24} The ASPIrin non-responsiveness and Clopidogrel Endpoint Trial (ASCET) evaluates whether adding to clopidogrel will be superior to continued aspirin therapy in improving clinical outcomes among aspirin-resistant patients with angiographically documented CAD.\textsuperscript{27} The Research
Evaluation to Study Individuals who Show Thromboxane Or P2Y12 Receptor Resistance (RESISTOR) trial will investigate whether modifying antiplatelet regimens could prevent myonecrosis post-PCI in patients with aspirin and clopidogrel resistance. The practice of antiplatelet therapy tailored to individual response may usher soon upon validation by these trials.

References

Table 1. Prospective Studies on Clinical Relevance of Aspirin Resistance

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Population studied</th>
<th>ASA dose (mg/day)</th>
<th>Definition of ASA resistance</th>
<th>Incidence of ASA resistance</th>
<th>Adverse Clinical Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grottemeyer et al</td>
<td>Stroke patients (n=180)</td>
<td>1500</td>
<td>Platelet reactivity index &gt;1.25</td>
<td>33%</td>
<td>~10-fold increased risk of vascular death, MI, or stroke at 2 years</td>
</tr>
<tr>
<td>Mueller et al</td>
<td>PAD patients (n=100)</td>
<td>100</td>
<td>≥20% reduction in platelet function using CWBA</td>
<td>~60%</td>
<td>87% increased risk of reocclusion at angioplasty site at 1 year</td>
</tr>
<tr>
<td>Eikelboom et al</td>
<td>Patients with CAD, stroke, PAD, or DM plus ≥1 CV risk factor(s) (n=976)</td>
<td>Not specified</td>
<td>Quartiles of urinary 11-dehydro-thromboxane B2 levels</td>
<td>Not specified</td>
<td>1.8-fold increased risk of cardiovascular death, MI, or stroke at 5 years</td>
</tr>
<tr>
<td>Gum et al</td>
<td>Patients with stable CV disease (n=325)</td>
<td>325</td>
<td>≥70% ADP-induced and ≥20% AA-induced optical platelet aggregation</td>
<td>5.2%</td>
<td>4-fold increased risk of death, MI, or stroke at 1.8 years</td>
</tr>
<tr>
<td>Chen et al</td>
<td>Patients undergoing elective PCI (n=151)</td>
<td>80-300</td>
<td>ARU ≥550 in point-of-care platelet aggregation assay</td>
<td>19.2%</td>
<td>2.9-fold increased risk of CK-MB elevation after PCI</td>
</tr>
<tr>
<td>Chen et al</td>
<td>Patients with CAD (n=468)</td>
<td>80-300</td>
<td>ARU ≥550 in point-of-care platelet aggregation assay</td>
<td>27.4%</td>
<td>2.5-fold increased risk of death, MI, stroke, TIA, or UA hospitalisation at 1.0 years</td>
</tr>
</tbody>
</table>

AA = arachidonic acid; ADP = adenosine diphosphate; ARU = aspirin reaction unit; ASA = aspirin; CK = creatine kinase; CV = cardiovascular; CWBA = corrected whole blood aggregometry; DM = diabetes mellitus; MI = myocardial infarction; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention; TIA = transient ischaemic attack; UA = unstable angina

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