Aspirin resistance can be defined as the lack or decreased antiplatelet effect despite therapeutic doses of aspirin or the incidence of recurrent vascular events in patients taking aspirin. This term has been used interchangeably in the literature to describe biochemical as well as clinical phenomenon (Sanderson et al., 2005).

Failure of aspirin to suppress thromboxane production and therefore to inhibit platelet aggregation in vitro has been linked to inadequate protection against atherothrombotic events. Millions of people with heart disease who take aspirin need to know whether it is effective for them. Not finding out whether the patient is aspirin resistant would be comparable to diagnosing someone with high blood pressure, giving him medication and then not monitoring his blood pressure.

However aspirin resistance, also called 'aspirin non-responsiveness' or simply treatment failure, is a heterogeneous phenomenon still without a generally accepted definition and with unclear clinical implications.

**Classification**

Aspirin resistance may be classified as (Patrono, 2003).

i. Laboratory resistance (the failure of aspirin to inhibit platelet thromboxane-A2 production or inhibit platelet aggregation or persistent platelet activation, demonstrated by platelet function tests (biochemical aspirin resistance)

ii. Clinical resistance (the failure of aspirin to prevent clinical thromboembolic ischemic events in patients prescribed aspirin) or the recurrence of vascular events in patients prescribed usual therapeutic doses of aspirin (clinical aspirin resistance). The clinical concept is nonspecific and might be preferably labeled as clinical treatment failure.

**Postulated mechanisms for aspirin resistance**

**Possible postulated mechanisms** for aspirin resistance as reviewed by Cambria-Kiely and Gandhi (2002):

- Concurrent intake of certain NSAIDs
- Inadequate dose of aspirin
- Poor compliance
- Reduced bioavailability
- Enhanced platelet function
Biosynthesis of TXA2 by pathways that are not blocked by aspirin, e.g. by COX-2 in monocytes and macrophages

- Increased platelet sensitivity to ADP and collagen
- Hypercholesterolemia, usually accompanied by increased thrombin generation
- Hypercoagulable states following MI and unstable angina
- Increased release of platelets from bone marrow in response to stress, i.e. after coronary artery bypass surgery, introducing to blood newly formed platelets unexposed to aspirin
- Genetic polymorphisms
- Transcellular arachidonate metabolism between aspirinated platelets and endothelial cells
- Inadequate blockade of red cell-induced platelet activation
- Polymorphism of platelet glycoprotein IIb/IIIa; carriers of PlA2 allele are less sensitive to antithrombotic action of aspirin in vivo
- Polymorphisms of platelet collagen receptors
- COX-2 variants in patients after coronary artery bypass surgery
- FXIII Val34Leu polymorphism leading to variable inhibition of FXIII activation by low-dose aspirin
- Increased platelet turnover
- Upregulation of non-platelet pathways of thromboxane production

Other probable factors

- Increased levels of norepinephrine (excessive physical exercise, mental stress)
- Smoking
- Oxidant stress and biosynthesis of 8-iso-PGF2a

The potential benefit of aspirin therapy may be significantly reduced in patients with aspirin resistance, creating a clinical and economic burden on the healthcare system. It is estimated that 29 billion aspirin tablets are consumed each year by Americans, with the most popular use of aspirin being the prevention of cardiovascular disease. However studies have estimated that 5% to 45% of patients taking aspirin are experiencing suboptimal antiplatelet effects (Gum et al., 2001). The potential impact of aspirin resistance is highly significant since large populations of patients are taking aspirin and therapeutic failure due to aspirin resistance can have a major impact on the cost of treating patients with coronary heart disease and stroke.

The American Heart Association (AHA) estimates that $112 billion per year is spent on direct costs, including hospital, nursing home, physician and drug cost on these diseases. The cost on society adds another $88 billion per year in lost productivity and loss of future earnings. AHA also estimates that 2.4 million procedures, including angioplasty, PCI (percutaneous intervention) and cardiac revascularization are performed yearly. Since aspirin resistance prevalence is estimated to be between 5% and 45%, the cost of treatment and the number of interventions can be significantly reduced if patients can be identified with validated laboratory tests and treated appropriately according to their resistance to aspirin (Gum et al., 2001).

There is growing evidence that patients with laboratory evidence of aspirin resistance are at a greater risk of thromboembolic events than aspirin sensitive or aspirin responders.

Clinical Studies

A number of clinical studies have been done in an attempt to explain the phenomenon of aspirin resistance, but they seem to be insufficient in explaining the phenomena of aspirin resistance. Same research may yield different results and, the characteristics in different population exhibiting aspirin resistance may add to the complexity. Aspirin resistance cannot be explained by only one pathway. More studies are required to investigate the mechanisms in different population (Zhang and Zhang, 2007).

The first study to demonstrate variability in response to aspirin was published nearly 50 years ago. Since then numerous trials evaluating responsiveness to aspirin in a variety of different settings, have been undertaken. No trial till date has ever found a uniform response to aspirin despite using a wide range of techniques.

Various studies have reported a prevalence of aspirin resistance in healthy volunteers and in patients with various manifestations of atherosclerosis in frequencies ranging from 5.5% to 60%. So far only a few published papers have provided knowledge on the clinical relevance of aspirin resistance. Overall these trials support the hypothesis of an association between aspirin resistance and an increased risk of suffering future thrombotic complications.

In 2004, the New York Times reported that up to 40% of aspirin users are resistant to aspirin. Patients prescribed aspirin to prevent atherothrombotic vascular disease need to know if they are resistant to aspirin and if so, what the implications are.
Friend et al., (2003) defined aspirin resistance as poor platelet responsiveness to aspirin and therefore aggregation of ≥ 50% of platelets. Gum et al., (2001), defined aspirin resistance based on the aggregating agents used. The percentage aggregation by using different stimulating agents was measured. Aggregation of ≥ 70% with 10 μM ADP, and of ≥ 20% with 0.5 mg/ml arachidonic acid, constituted aspirin resistance. This study shows that the aggregating or the stimulating agents also need to be considered while defining aspirin resistance.

Weber et al. (1999, 2002) classified aspirin resistance into three main categories. Type-1 (pharmacokinetic type) entails the inhibition of platelet thromboxane formation in vivo but not in vitro. Type-2 (pharmacodynamic type) is characterized by the inability of aspirin to inhibit platelet thromboxane formation both in vivo and in vitro. Type-3 (pseudoresistance) involves thromboxane-independent platelet activation. The results also suggested that the inducible isoform of cyclooxygenase in platelets, COX-2, confers aspirin resistance, although this opinion was challenged by Patrignani et al. (1999).

It is clear that further large prospective studies are needed to further clarify the clinical significance of aspirin resistance. Hence aspirin resistance and aspirin non-responsiveness are the terms used for describing both the failure of aspirin to

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**Table 1. Prevalence of aspirin resistance reported in selected studies (Modified from Poulsen et al., 2005).**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sample size</th>
<th>Aspirin dose mg/day</th>
<th>Platelet analysis method used</th>
<th>% aspirin resistant</th>
<th>Aggregating agent used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grottemeyer et al., (1993)</td>
<td>180</td>
<td>1500</td>
<td>Platelet reactivity index</td>
<td>33</td>
<td>Aggregation induced by blood collection</td>
</tr>
<tr>
<td>Helgason et al., (1994)</td>
<td>306</td>
<td>325</td>
<td>Optical</td>
<td>25</td>
<td>AA, ADP, Collagen, Epinephrine</td>
</tr>
<tr>
<td>Mueller et al., (1997)</td>
<td>100</td>
<td>100</td>
<td>Whole blood aggregometer</td>
<td>60</td>
<td>ADP, Collagen</td>
</tr>
<tr>
<td>Buchan et al., (2000)</td>
<td>289</td>
<td>325</td>
<td>Bleeding time</td>
<td>55</td>
<td>Collagen, ADP, Epinephrine</td>
</tr>
<tr>
<td>Peters et al., (2001)</td>
<td>19</td>
<td>100</td>
<td>PFA-100</td>
<td>63</td>
<td>Collagen, ADP, Epinephrine</td>
</tr>
<tr>
<td>Macchi et al., (2002)</td>
<td>72</td>
<td>160</td>
<td>PFA-100</td>
<td>29</td>
<td>Collagen/Epinephrine</td>
</tr>
<tr>
<td>Andersen et al., (2002)</td>
<td>129</td>
<td>75-160</td>
<td>PFA-100</td>
<td>37</td>
<td>Epinephrine, ADP</td>
</tr>
<tr>
<td>Christensen et al., (2002)</td>
<td>50</td>
<td>&gt;75</td>
<td>PFA-100</td>
<td>20</td>
<td>Collagen/Epinephrine</td>
</tr>
<tr>
<td>Hezard et al., (2002)</td>
<td>50</td>
<td>75-300</td>
<td>PFA-100, optical</td>
<td>52</td>
<td>ADP</td>
</tr>
<tr>
<td>Ziegler et al., (2002)</td>
<td>52</td>
<td>100</td>
<td>PFA-100</td>
<td>10</td>
<td>Collagen/Epinephrine</td>
</tr>
<tr>
<td>Sane et al., (2002)</td>
<td>88</td>
<td>325</td>
<td>Flow cytometry,</td>
<td>57</td>
<td>Collagen, ADP</td>
</tr>
<tr>
<td>Macchi et al., (2003)</td>
<td>72</td>
<td>160</td>
<td>PFA-100</td>
<td>29</td>
<td>Collagen/Epinephrine</td>
</tr>
<tr>
<td>Gum et al., (2003)</td>
<td>326</td>
<td>325</td>
<td>PFA-100, optical</td>
<td>9.5, 5.5</td>
<td>AA, ADP</td>
</tr>
<tr>
<td>Wang et al., (2003)</td>
<td>422</td>
<td>81-325</td>
<td>Ultegra RPFA</td>
<td>23</td>
<td>ADP</td>
</tr>
<tr>
<td>Grundmann et al., (2003)</td>
<td>53</td>
<td>100</td>
<td>PFA-100,</td>
<td>34</td>
<td>Collagen/Epinephrine</td>
</tr>
<tr>
<td>Chen et al., (2004)</td>
<td>151</td>
<td>80-325</td>
<td>Ultegra RPFA</td>
<td>19</td>
<td>Incidence of myonecrosis measured</td>
</tr>
<tr>
<td>Cotter et al., (2004)</td>
<td>82</td>
<td>100</td>
<td>TxB2</td>
<td>12</td>
<td>Measured health outcome</td>
</tr>
<tr>
<td>Alberts et al., (2004)</td>
<td>129</td>
<td>&lt;162</td>
<td>PFA-100</td>
<td>56</td>
<td>Analysed mean closure time</td>
</tr>
<tr>
<td>Prabhakaran et al., (2008)</td>
<td>71</td>
<td>Median dosage</td>
<td>RPFA</td>
<td>4.2</td>
<td>Aspirin reaction measured</td>
</tr>
<tr>
<td>Lim et al., (2009)</td>
<td>63</td>
<td>75</td>
<td>Urinary 11</td>
<td>14.8</td>
<td></td>
</tr>
<tr>
<td>Thomson et al., (2009)</td>
<td>100</td>
<td>75</td>
<td>Urinary 11</td>
<td>38.1</td>
<td></td>
</tr>
<tr>
<td>Jian Cao et al., (2012)</td>
<td>304</td>
<td>&gt;75</td>
<td>LTA</td>
<td>8.2</td>
<td></td>
</tr>
<tr>
<td>Liu et al., (2013)</td>
<td>246</td>
<td>&gt;75</td>
<td>LTA</td>
<td>9.3</td>
<td>AA, ADP</td>
</tr>
<tr>
<td>Ibrahim et al., (2013)</td>
<td>74</td>
<td>5 doses total</td>
<td>Multiplate</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Azmin et al., (2013)</td>
<td>50</td>
<td>900mg</td>
<td>Multiplate</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Yaturu et al., (2014)</td>
<td>142</td>
<td>81</td>
<td>Urinary TxB2</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Chadha et al., (2015)</td>
<td>126</td>
<td>150</td>
<td>LTA</td>
<td>2</td>
<td>ADP, AA</td>
</tr>
<tr>
<td>Maleki et al., (2016)</td>
<td>370</td>
<td>80,81,100,325</td>
<td>Bleeding Time (IVY method)</td>
<td>37.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Urinary TXB2</td>
<td>64</td>
<td></td>
</tr>
</tbody>
</table>

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Ultegra RPFA=Ultegra Rapid Platelet Function Assay, PFA-100=Platelet Function Analyser-100 MEA=Multiple electrode platelet aggregometry.
Conflict of Interests – None Declared

Several studies utilizing a broad range of platelet function tests have shown that some subgroups of individuals exhibit a reduced or completely missing antiplatelet response to aspirin. The clinical significance of aspirin non-responsiveness for the prediction of clinical endpoints remains, however, to be determined. Thus far, only a few prospective clinical trials have demonstrated a possible relationship between aspirin non-responsiveness and subsequent vascular events. Most platelet function tests used in respective clinical studies cannot be reliably performed in clinical routine and are not interchangeable for monitoring antiplatelet treatment. There is a need for a simple and reliable assay for predicting the clinical efficacy of antiplatelet therapy (Patrono, 2003; Sanderson et al., 2005).

Several studies have demonstrated, using various platelet function tests (PFTs) that subgroups of patients taking acetylsalicylic acid (ASA) failed to produce the desired antiplatelet effect. Several different methods like optical aggregometry, platelet aggregation in whole blood, platelet function analyzer (PFA-100), platelet reactivity test or platelet aggregate ratio, flow cytometry and thromboxane B2 generation have been used to determine platelet function and hence aspirin resistance. The widespread clinical use of these platelet function tests is substantially limited due to complex preanalytic factors, reduced specificity and poor reproducibility and hence, there is a need for a simple and reliable assay for predicting the clinical efficacy of antiplatelet therapy (Haubelt et al., 2005).

Although formal diagnostic criteria are lacking, aspirin resistance generally describes the failure of aspirin to produce an expected biological response or the failure of aspirin to prevent atherothrombotic events. Aspirin resistance has been reported to occur in 5% to 60% of the general population, therefore, its detection is potentially of clinical importance (Benedek et al., 1995; Buchanan et al., 1995).

Conclusion

Estimates suggest that the prevalence of aspirin resistance is between 5.5% and 60% depending upon the definition used and parameters measured and also the methods used to measure platelet aggregation. Only a limited number of clinical studies which are of a sufficient scale, well designed, and prospective, with aspirin used at standard doses have convincingly investigated the importance of aspirin resistance. Also, most studies do not sufficiently address the issue of non-compliance to aspirin as a frequent, yet easily preventable cause of resistance to this antiplatelet drug. The clinical implications of aspirin resistance needs to be explored in various cardiovascular disease states, including diabetes mellitus, hypertension, heart failure, and other similar disorders where platelet reactivity is enhanced.

Conflict of Interests – None Declared

References


Circulation, 72:1177-1184.


