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REVIEW

Aspirin Resistance in Cardiovascular Disease: A Review

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Background. Aspirin is effective at reducing the cardiovascular event rate in defined patient groups. The introduction of antiplatelet therapies other than aspirin and the concept of aspirin resistance have led to critical reappraisal of current treatment. This review aims to clarify the evidence for aspirin resistance in patients with atherosclerosis.

Methods. Medline search was performed to identify publications concerned with antiplatelet effects of aspirin and failure of aspirin therapy. Manual cross referencing was also performed.

Results and conclusion. Wide variations in the rate of aspirin resistance (5.5–75%) have been reported. The lack of consensus on an appropriate definition and the number of different tests used to investigate aspirin resistance needs to be addressed. There are few studies where the primary aim was to document aspirin resistance or aspirin non-response. Further work should aim to investigate if aspirin resistance is clinically important and, if it is, what treatments may be beneficial to the at risk patient.

Key Words: Aspirin; Platelet; Platelet aggregation inhibitors; Aspirin resistance.

Introduction

Aspirin is commonly used to reduce the risk of ischaemic events in patients with cardiovascular disease. Aspirin inhibits platelets by irreversibly binding to cyclooxygenase and blocking the synthesis of thromboxane A₂. However, patients treated with aspirin still suffer ischaemic events,¹ and laboratory assessment of platelet function reveals persistent platelet aggregation despite regular aspirin therapy in a significant proportion of patients at high risk of ischaemic events.² The concept of aspirin resistance and aspirin non-response has highlighted an area where current antiplatelet treatment may be suboptimal. This collective review attempts to explain the definitions and mechanisms of aspirin resistance, to highlight studies of aspirin resistance and to suggest how deficiencies in our current understanding of this problem may be addressed.

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Methods

Medline search from January 1966 to January 2003 was performed using the terms 'aspirin', 'platelet', 'platelet aggregation inhibitors', to identify publications concerned with antiplatelet effects of aspirin. The terms 'failure', 'resistance', and 'non-response' were used to identify articles referring to aspirin resistance. Reference lists of major articles were also reviewed for further relevant publications.

Results

Aspirin and alternative antiplatelet medications in cardiovascular disease

Aspirin has been shown to be effective in both primary and secondary prevention of adverse cardiovascular events. Compared with placebo, aspirin treatment in middle aged men has been reported to reduce the risk of a first myocardial infarction (MI) by 44% over a 5-year period^{3,4} and has also been shown to reduce mortality in patients following MI by 23% when used in conjunction with thrombolytic therapy.⁵

Meta-analysis of randomised trials involving antiplatelet therapy in >100,000 patients and controls have demonstrated a 25% reduction in vascular death, MI and stroke in patients at high risk of vascular complications, with aspirin being the most widely studied antiplatelet agent.⁶ Antiplatelet therapy has also been shown to confer a 48% reduction in vascular graft and arterial occlusion.^{7,8} Aspirin exerts its antiplatelet effect by irreversibly acetylating the serine-530 in the active site of the cyclooxygenase 1 (COX1) enzyme and deactivating it for the life of the platelet (Figs. 1 and 2). This deactivation leads to

inhibition of thromboxane A2 (TXA2) production, a potent platelet agonist.^{9,10}

While the benefits of aspirin are widely accepted its side effects and the fact that a proportion of patients experience ischaemic events despite aspirin therapy has led to the development of other antiplatelet agents. From clinical observation recurrent ischaemic events despite treatment with aspirin is not uncommon. Of 10,948 patients suffering a non-ST elevation acute coronary syndrome enrolled in the PURSUIT (Platelet IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy) trial, 63.8% had been taking

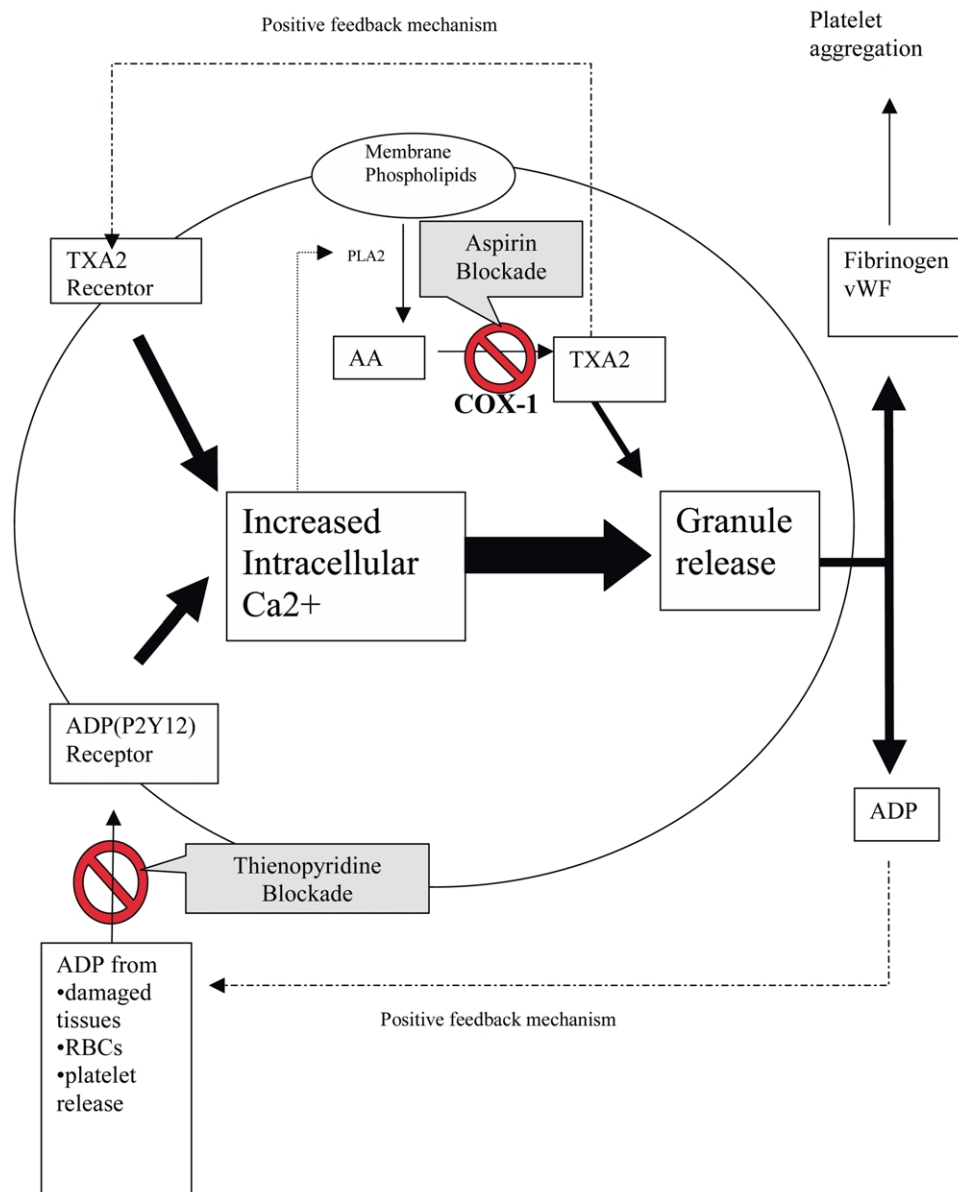


Fig. 1. Pathways of thienopyridine and COX-1 mediated inhibition of platelet activation. COX1 inhibition inhibits formation of TXA2, but does not inhibit feedback from TXA2 already generated. Thienopyridine blockade of ADP receptor inhibits both exogenous ADP dependent platelet activation and the feedback effect of ADP released from platelet granules.

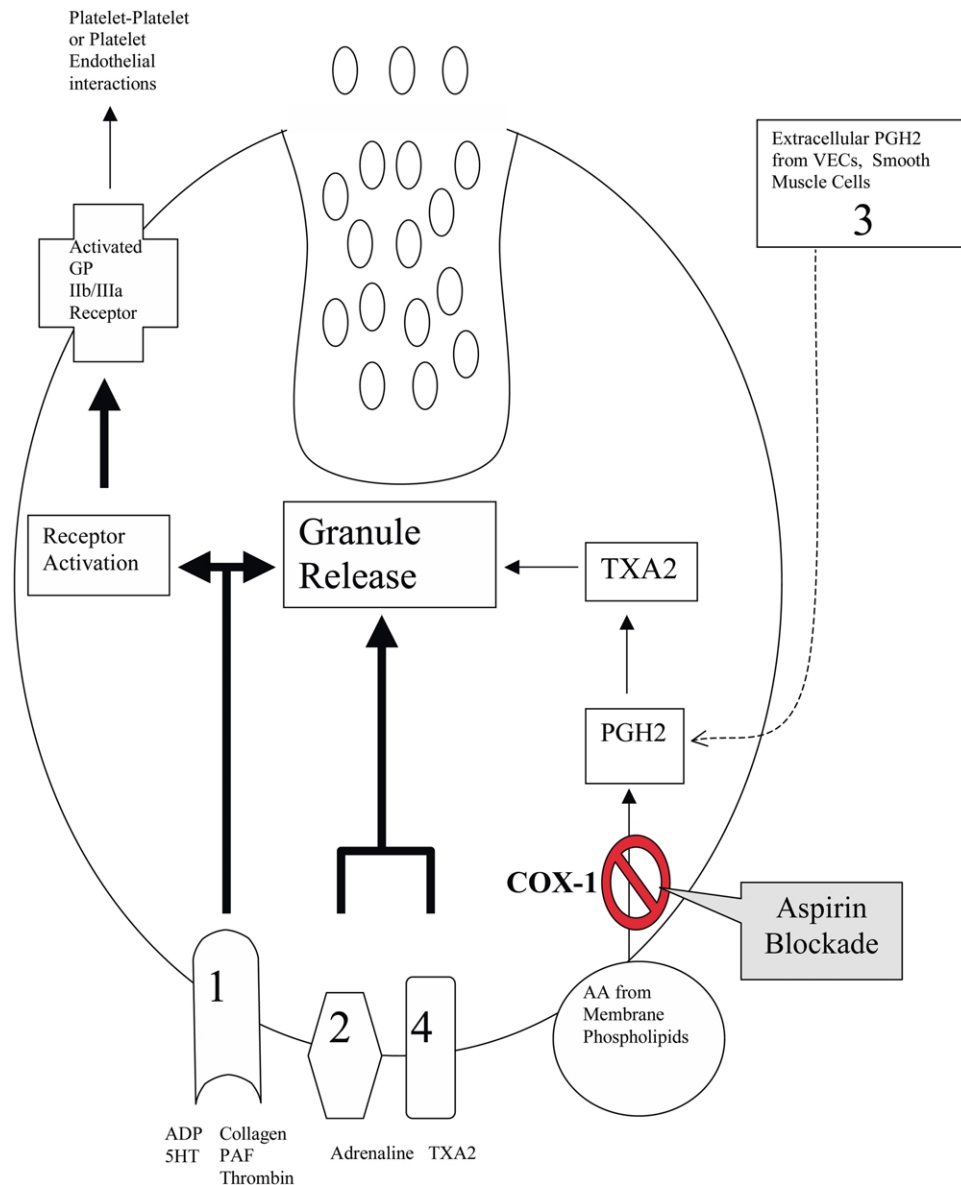


Fig. 2. Non-COX-1 mediated pathways of platelet activation. There are multiple non-COX1 mediated pathways of platelet activation (indicated 1–3) that may account for aspirin resistance. COX1 inhibition of TXA2 production may be overcome by movement of exogenous PGH2 into the affected platelet and its conversion to TXA2. Decreased COX1 based TXA2 production limits platelet activation via path 4, but persistent activation may occur via TXA2 produced via path 3.

aspirin for 2 weeks prior to infarction.¹ Relative or complete resistance to the antiplatelet effect of aspirin might have contributed to the poor outcomes seen in this patient group.¹

Alternative antiplatelet medications have been shown to provide benefits with regard to reduction of recurrent events compared to aspirin.¹¹ Thienopyridines, such as ticlopidine and clopidogrel, inhibit platelets by selectively and irreversibly binding to the adenosine diphosphate (ADP) receptor on platelet membranes thus blocking the ADP dependent activation of the Glycoprotein IIb/IIIa (GP IIb/IIIa)

complex which is the major receptor for fibrinogen on the platelet surface¹² (Fig. 1). Ticlopidine has been shown to reduce the rate of recurrence of transient ischaemic attacks and stroke in patients in whom aspirin therapy has failed clinically.¹³ Clopidogrel, in two large prospective randomised trials,¹¹ achieved a 7–8% decrease in relative risk of recurrent stroke, MI or vascular death over aspirin when taken alone,¹⁴ and a 20% relative risk reduction in vascular events defined as cardiovascular death, non-fatal MI and stroke when taken in combination with aspirin, compared with aspirin alone.¹⁵ Although combination

therapy was associated with a significant increase in the risk of major bleeding (3.7% vs. 2.7%), there was no difference in the risk of life-threatening bleeding or haemorrhagic strokes.¹⁵

The beneficial effects of thienopyridines observed may be multifactorial. Aspirin resistance secondary to lack of compliance with aspirin medication and/or the presence of TXA2 independent mediators of platelet activation, such as thrombin and serotonin, have been suggested as possible reasons (Fig. 2). Thrombin mediated platelet activation may be important in this patient group since serum fibrinogen levels and thrombin generation are thought to be important in pathophysiology of atherothrombosis.¹⁶ Other factors such as high levels of ADP and collagen at sites of atherothrombosis may also contribute to this observed effect.¹⁷ Platelets from aspirin resistant subjects have been found to be more sensitive to ADP¹⁸ and this may contribute to the proposed advantage of clopidogrel.

Definition of aspirin resistance

In defining aspirin resistance, it is important to distinguish clinical aspirin resistance to resistance demonstrated by laboratory testing of platelet activity. Clinical aspirin resistance, where patients suffer atherothrombotic events despite the use of aspirin, is a relatively common problem as demonstrated in the PURSUIT trial.¹ Some patients will suffer vascular events in spite of adequate platelet inhibition due to the severity of underlying arterial disease. The assessment of aspirin resistance by laboratory methods is potentially of greater therapeutic importance as their results would allow identification of patients at risk of clinical events and allow intervention to prevent subsequent morbidity or mortality.

Laboratory definitions of aspirin resistance have involved either detecting the failure of aspirin's pharmacological effect, or the failure of aspirin to prevent inhibition of platelet aggregation. Aspirin resistance, defined by its pharmacological action, is persistent production of thromboxane A2 despite therapy, measured by the presence of thromboxane A2 metabolites in serum or urine.¹⁹ In contrast, persistent platelet aggregation despite aspirin treatment defines failure of aspirin mediated platelet inhibition, and this may occur via non-thromboxane mediated pathways of platelet activation. It has been suggested that aspirin resistance is a misleading term since in some situations, aspirin successfully inhibits thromboxane synthesis but platelet aggregation persists. The term aspirin 'non-response' encompasses the failure of aspirin to both inhibit thromboxane syn-

thesis and reduce platelet aggregation.¹⁹ In an attempt to clarify different patterns of aspirin resistance in patients Weber *et al.*²⁰ demonstrated three distinct groups with regard to pharmacological behaviour (Table 2). This relatively complex definition attempts to objectively classify the difference between aspirin resistance and aspirin non-response, but is limited to collagen agonist based aggregometry as the method of platelet function testing and is therefore associated with limitations of this methodology.

Laboratory assessment of aspirin resistance is problematic since definitions of aspirin resistance or non-response vary according to the method of platelet function testing employed. Different techniques define levels of platelet aggregation in units that cannot be directly compared.² Definitions of aspirin resistance within a particular technique are also subject to variation. The setting of criteria defining aspirin resistance is often arbitrary, and there is no standard protocol in administering tests. Using the same technique of optical aggregometry, Helgason *et al.* and Gum *et al.* reported rates of complete aspirin resistance of 75%²¹ and 5.5%,² respectively. The considerably different platelet aggregation criteria and different concentration of agonists used for platelet activation in the two studies probably contributed to this disparity.

Definitions of aspirin resistance need to incorporate an understanding of pathophysiological conditions and outcomes to have clinical significance. Defining aspirin resistance by assessing the inhibition of TXA2 production considers the pharmacological action of aspirin but does not consider platelet aggregation, which is arguably a more clinically relevant outcome. Measurement of the metabolites of thromboxane A2 in serum and urine, thromboxane B2 and urinary 11-dehydro thromboxane B2, have been used extensively to investigate aspirin resistance.¹⁹ However, urinary 11-dehydro TXB2 levels can be influenced by recent acute thrombotic events such as MI or stroke which may increase secretion and cause variation in the levels of this urinary marker.¹⁹

Laboratory definitions of aspirin non-response based on platelet function rather than the measurements of metabolites, and preferably based on techniques that are suitable for use and interpretation in the wider medical community, are most likely to have clinical utility. However, documentation of laboratory defined aspirin non-response cannot be presumed to have clinical significance before correlation with patient outcomes is established. There is a need to define levels of failure of platelet inhibition that have high positive and negative predictive values for subsequent clinical events.

Incidence

Aspirin resistance has been detected by laboratory methods in both healthy individuals^{22,23} as well as those with vascular disease. Studies have variably documented aspirin resistance in 5.5–60% of patients, but platelet activation is notoriously difficult to study and the variations are likely due to different methods of platelet investigation, different definitions of aspirin resistance and small sample sizes (Table 1).²⁴ Failure of aspirin effect may be more significant in those with known cardiovascular disease (Table 2) since atherosclerosis is associated with a prothrombotic state.^{21,23,25,26} In a prospective trial of patients with vascular disease Gum *et al.*² found that aspirin non-responders and aspirin semi-responders were more likely to be women, and tended to be older. Rates of aspirin resistance were not affected by race, diabetes, platelet count or presence of renal and hepatic disease.² Smokers have raised fibrinogen levels²⁷ and smoking has been associated with an increased level of aspirin resistance²⁸ but these findings have not been consistent.²

Mechanism

A mechanism of resistance has not been firmly established, but is almost certainly multifactorial. Issues such as inadequate dose and poor drug compliance may contribute to the failure of aspirin to inhibit platelet aggregation. Other factors contributing to aspirin resistance can be classified into these three broad groups:

Non-COX1 mediated pathways of platelet activation

Aspirin exerts its antiplatelet effect by blocking the COX1 enzyme that produces the potent platelet agonist TXA₂ from arachidonic acid. Non-COX1 mediated pathways of platelet activation, such as platelet activation mediated by serotonin and thrombin, may contribute to aspirin resistance (Fig. 2).

Persistent TXA₂ production despite adequate COX1 inhibition can occur via an alternative COX2 pathway, found in vascular endothelial cells (VECs) and smooth muscle cells. COX2, which is strongly induced in vascular disease²⁵ is able to convert arachidonic acid to prostaglandin H₂ (PGH₂) which can be transported into platelets for the production of TXA₂.^{29,30} COX1 regeneration in nucleated cells such as macrophages or VECs can also lead to persistent TXA₂ production.^{19,31}

Increased levels of catecholamines associated with stress and exercise have a significant prothrombotic

effect that may also contribute to apparent aspirin resistance.

Increased platelet reactivity

Erythrocyte interactions with platelets, polymorphisms in the IIIa subunit of platelet GPIIb/IIIa receptors, increased levels of prostaglandin F_{2α} (PGF_{2α}) and increased platelet sensitivity to collagen may all contribute to increased platelet reactivity and platelet aggregation despite aspirin therapy.

Erythrocytes have been shown to induce the production of factors by platelets that are central to thrombus formation, including thromboxane B₂, serotonin, β-thromboglobulin and ADP.^{32,33}

Carriers of the A2 polymorphism of the GP IIb/IIIa fibrinogen receptor subunit have platelets that are associated with enhanced thrombin formation and a lower threshold for activation with alpha granule release and fibrinogen binding.³⁴ Such individuals are therefore less responsive to the antithrombotic effects of aspirin.³⁴ This polymorphism is reported to have a frequency of 20–30% in European populations.³⁵

Other factors associated with increased platelet reactivity include increased production of PGF_{2α}, an isoprostane that can amplify the response of human platelets to agonists and cause vasoconstriction,³⁶ and an increased sensitivity of platelets in aspirin resistant patients to low dose collagen, a physiological platelet agonist.³⁷

Increased platelet turnover

Increased platelet turnover in response to haemorrhage and surgical intervention may lead to the generation of an increased fraction of platelets still able to form thromboxane within the daily dosing intervals.³⁸

Measurement

Techniques that have been employed to investigate aspirin resistance include bleeding time,²² whole blood and platelet aggregometry,^{2,21,26} measurement of platelet aggregation ratios,³⁹ the platelet reactivity index,²⁴ thromboxane A₂ metabolites,¹⁹ flow cytometry⁴⁰ and PFA-100™.^{2,41,42} Different methods have reported a wide range of estimates of aspirin resistance in study populations with poor concordance between different methods.²

There is growing evidence that constituents of blood other than platelets and plasma are important in the coagulation process, such as vascular endothelial factors and shear stress. Production of nitric oxide, an important inhibitor of platelet activation, by

Table 1. Rate of aspirin resistance in vascular disease

| Patient population | Platelet analysis technique | Sample size | Dose of aspirin | Rate of aspirin resistance | Author | Year |
|---------------------------|--|-------------|-----------------|----------------------------|---------------------------|------|
| Poststroke | Platelet reactivity ²⁴ | 82 | 200–500 mg/day | 30% | Grottemeyer <i>et al.</i> | 1991 |
| Coronary artery disease | PFA-100, Optical aggregometry | 325 | 325 mg/day | 9.5% (PFA) 5.5% (agg) | Gum <i>et al.</i> | 2001 |
| Coronary artery disease | Bleeding time, ²² PFA-100 ⁴¹ | 40 | 325 mg/day | 30–40% | Buchanan <i>et al.</i> | 1995 |
| Intermittent claudication | Corrected whole blood aggregometry ²⁶ | 71 | 160 mg/day | | Andersen <i>et al.</i> | 2003 |
| | | 100 | 100 mg/day | 60% | Mueller <i>et al.</i> | 1997 |

vascular endothelial cells (VECs) and aspirin inhibition of endothelial prostacyclin production, a vasodilator and platelet antiaggregant, cannot be accounted for by *ex vivo* tests.^{21,43} Use of platelet rich plasma in tests such as optical aggregometry cannot account for the prothrombotic effects of erythrocyte–platelet interactions, and may not accurately replicate physiological platelet aggregation.

The PFA-100™ is a promising technique for the rapid assessment of aspirin resistance. Benefits of this technique include ease of use, speed of analysis and reproducibility of results.^{42,44} It also attempts to replicate the shear stress found *in vivo* by passing the sample of whole blood through a capillary tube (Fig. 3). These advantages enable the PFA-100™ to be widely used and rapidly interpreted outside tertiary institutions, in contrast to aggregometric techniques. PFA-100™ has been found to be more sensitive than optical aggregometry in detecting aspirin resistance.²

The need to accurately diagnose and monitor treatment of aspirin resistance demands a test to be rapid, reproducible, easily operated and interpreted, and should involve the use of whole blood samples to best replicate the physiological conditions of platelet aggregation. Most platelet function techniques used in researching aspirin resistance have limited clinical application due to their complexity and cost, and definitions of aspirin resistance and their clinical utility are therefore limited. Potential point of care techniques such as the PFA-100™ are promising,⁴¹ with some studies suggesting that the technique may assist in guiding dose of aspirin to account for inter and intra-patient variability,⁴⁵ but its insensitivity to the action of thienopyridines may limit its use.⁴⁶ Other point of care techniques that may be promising but yet to be used in researching aspirin resistance include the Ultegra Rapid Platelet Function Assay (Accumetrics)⁴⁷ and the Thromboelastogram.⁴⁸

Dose of aspirin

Non-standardised doses of aspirin may contribute to aspirin resistance. Current studies demonstrate that 80–325 mg of aspirin daily is both pharmacologically effective at inhibiting 95% of COX1⁴⁹ and clinically beneficial, with higher doses associated with a greater incidence of gastrointestinal side effects without any additional clinical benefit.^{8,50,51} However, *ex vivo* studies of platelet function suggest that anti-aggregatory effects of aspirin are dose dependent. An increase in aspirin dosage from 325 to 1300 mg/day has been shown to reduce rates of aspirin resistance from 25 to 8%.²¹ The reported difference may be related to the

Table 2. Types of aspirin resistance²⁰

| | | |
|---------------------|------------------|---|
| Type I resistance | Pharmacokinetic | Platelet aggregability successfully inhibited by <i>in vivo</i> addition of aspirin. This may be due to patient non-compliance or a range of dose-response effect between patients |
| Type II resistance | Pharmacodynamic | Platelet aggregability continued when <i>in vitro</i> aspirin was added, with the persistent formation of TXA2. This suggests that platelet activation persists despite inhibition of COX1, possibly due to COX2 production of PGH2, which can be converted to TXA2. An alternative explanation is defective COX1 binding of aspirin due to polymorphisms in the gene encoding Ser529 or Arg120 |
| Type III resistance | Pseudoresistance | Platelet aggregability was continued even when <i>in vitro</i> aspirin was added, but there was successful inhibition of TXA2 formation. The likely mechanisms are non-TX mediated pathways of thrombosis and an increased sensitivity to collagen. ^{37,38} |

inhibition of COX2. While 95% of COX1 is inhibited by 80–325 mg of aspirin, inhibition of COX2 requires doses of aspirin in excess of 500 mg daily.⁴⁹ PGH2 can be formed from COX2 conversion of arachidonic acid (AA), and can be transported to platelets for the production of TXA2 without platelet COX1. Higher doses of aspirin may inhibit both COX1 and COX2, inhibiting both possible sources of TXA2. Higher doses of aspirin (500 mg) have also been shown to inhibit the prothrombotic interactions between erythrocytes and platelets.³³ While aspirin dosage above 325 mg daily is probably inappropriate in clinical practice, dose related changes in aspirin resistance

within recommended aspirin prescription guidelines have also been observed in patients assessed by aggregometry⁵² and assays of TXA2 metabolites.⁵³ While there is no clinical evidence to suggest that doses higher than 325 mg daily are beneficial,⁸ there is a clear dose-response relationship between aspirin and the inhibition of platelet function in *ex vivo* laboratory tests, even within the usual range of 75–325 mg which may contribute to the variability of aspirin resistance rates reported.

These findings suggest that there may be some benefit to increasing aspirin dosage based on lab tests within the recommended range of 75–325 mg daily,

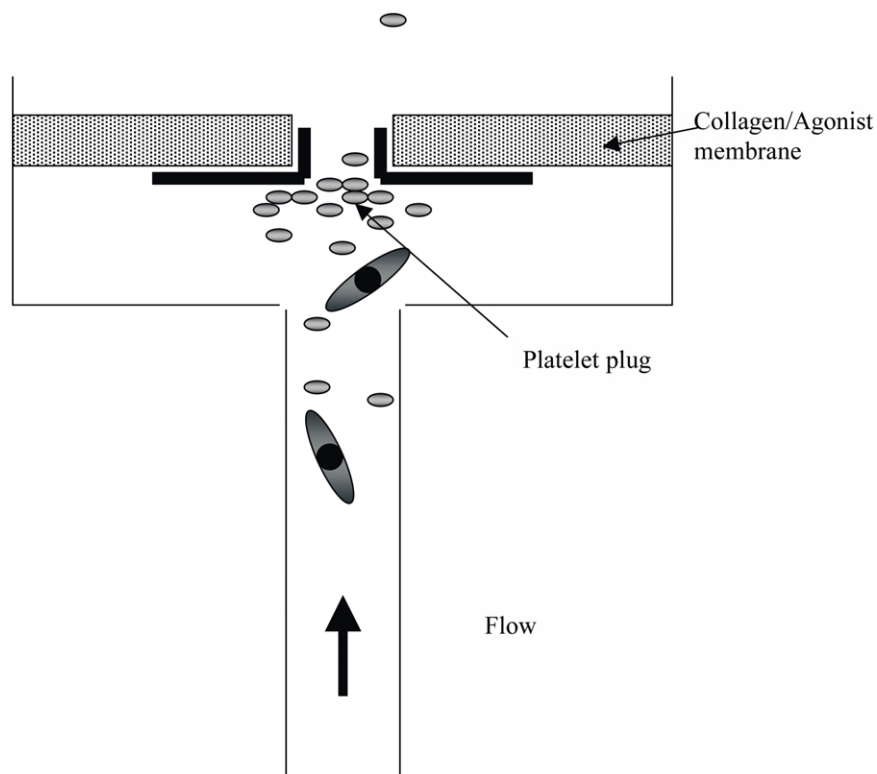


Fig. 3. Platelet function analyser. Whole blood 'flows' through an aperture in a collagen/agonist membrane. A platelet plug forms causing flow to stop. This is the outcome measure; closure time.

but the clinical benefits of this are unclear. There is currently no clinical indication for doses higher than this range. In some circumstances, aspirin dosing above the recommended range may be appropriate due to either evidence of clinical or laboratory aspirin resistance, but given the increasing morbidity related to doses of aspirin higher than 325 mg daily, alternative antiplatelet therapy should be considered. More work is needed to clarify the clinical significance of dose dependent aspirin resistance, and given the present circumstantial clinical correlation of aspirin resistance and clinical outcomes, a recommendation to change current practice is not appropriate.

Other factors affecting aspirin resistance

Aspirin resistance in the postoperative period

Increased platelet turnover may contribute to inadequate inhibition of platelet aggregation in the post-surgical patient treated with aspirin. Patients receiving daily aspirin after coronary artery bypass grafting showed only 30–50% inhibition of thromboxane production compared to 94% in healthy volunteers receiving the same dose of aspirin. The increased platelet turnover in response to surgical intervention may lead to the generation of an increased fraction of platelets still able to form thromboxane within the daily dosing intervals.³⁸ Such patients may need more frequent doses of antiplatelet medication to account for increased platelet generation.

Aspirin resistance over time

Differences in platelet response with time on a fixed dose of aspirin treatment has been reported by Helgason *et al.*²¹ who found that some patients changed from complete to partial platelet inhibition during a constant dose of ASA over 6 months. Andersen *et al.*⁴¹ found that 10% of patients converted from aspirin responder to non-responder over 5 months follow-up. Variability in response can also be measured on a shorter time scale with a larger effect of aspirin at 2 h postdose compared to 12 and 24 h.^{24,39} This time dependent effect may also explain, in part, the range of reported incidence of aspirin resistance.

Consideration needs to be given to the time after administration of aspirin that analysis of platelet function is performed. The variability of aspirin effect over time may be relevant in the need for repeated testing for aspirin resistance over months to ensure long-term drug efficacy and continued protection against ischaemic events.

Prothrombotic effects of exercise and catecholamine release

Increased levels of catecholamines associated with stress and exercise have a significant prothrombotic effect, and may be relevant in antagonising the antiplatelet activity of aspirin in patients with atherosclerotic vascular disease. Catecholamine induced platelet aggregation was not inhibited by aspirin pretreatment of patients, despite adequate inhibition at rest.⁵⁴ Similarly in exercise, aspirin does not prevent an exercise induced rise in platelet activation and subsequent aggregation.⁵⁵ In both exercise and stress, the effect of serotonin release and shear induced aggregation due to increased cardiac output and changes in blood flow may combine with the increased catecholamine release to create a prothrombotic state.^{56,57} This may have bearing on the current advice regarding exercise programs given to patients with intermittent claudication and undergoing cardiac rehabilitation. While exercise has undoubted benefits in both patient groups close observation of response to antiplatelet therapy may prove interesting.

Clinical impact of aspirin resistance

It is clear that clinically defined aspirin resistance is a major concern, and there is growing evidence that patients with laboratory evidence of aspirin resistance are at a greater risk of thromboembolic events than aspirin responders.^{19,26,58} To date there has been only one prospective study associating suboptimal platelet response to aspirin to a higher risk of adverse clinical outcomes. In a 2-year follow up of 326 stable cardiovascular patients from 1997 to 1999 on 325 mg daily aspirin, 17 (5.2%) aspirin resistant patients defined by optical aggregometry had an increased risk of death, MI, or CVA compared with patients who were aspirin sensitive (24% vs. 10%).⁵⁸ However, aggregometry has significant methodological limitations and the small sample size studied likely contributed to an inexact estimation of hazard ratio suggested by the wide confidence interval reported (hazard ratio 4.1, 95% CI 1.4–12.1).⁵⁸ In a nested case control study of 488 aspirin treated patients, significantly higher concentrations of urinary thromboxane A2 metabolites were found in patients suffering cardiovascular events despite aspirin treatment compared to age and sex matched controls who did not suffer events.¹⁹ Patients in the upper quartile of urinary metabolite concentration ($n = 122$), suggesting greater failure of aspirin in reducing TX synthesis, had a two times higher risk of MI and a 3.5 times higher risk of cardiovascular death.¹⁹ Retrospective analysis of patients with prior atherosclerotic disease showed a

34% aspirin non-responder rate by PFA-100™ in patients who had suffered a cerebrovascular event in prior 24 months compared to 0% in asymptomatic patients.⁵⁹ In patients with POAD 60 of 100 patients undergoing peripheral artery angioplasty demonstrated inappropriate platelet inhibition after 100 mg of aspirin, with these non-responders having an 87% increased risk of arterial reocclusion during 2-year follow-up.²⁶ It is clear that further large prospective studies are needed to further clarify the clinical significance of aspirin resistance.

Some studies show statistically non-significant differences in subsequent clinical outcomes. Andersen *et al.* only demonstrated a tendency toward higher event rates in the non-responders as compared to the responders in 4 years follow up (36% vs. 24%)⁴¹ and Buchanan *et al.*⁶⁰ could not demonstrate a difference between responders and non-responders in thrombotic events after 2 years of follow up.

Conclusion

The current limitations in our understanding of aspirin resistance are in part due to the difficulties in assessing platelet function and aspirin resistance. A lack of consensus on a definition of aspirin resistance, variability on aspirin dosages between studies and the use of numerous platelet assessment techniques each with their own limitations, have all contributed to the variable reporting of aspirin resistance. However, it is clear that clinical aspirin resistance is a significant problem. While aspirin resistance can be detected with current laboratory techniques, a test with high positive and negative predictive values for important clinical end points remains elusive.

Developing a technique of platelet analysis that is affordable, rapid, widely available, easily performed and interpreted is a priority. The PFA-100™ needs further evaluation in the investigation of aspirin non-response, and expansion on its current insensitivity to thienopyridines which may limit its utility as a point of care test. Prospective trials using and comparing point of care testing techniques such as PFA and TEG are needed to clarify the significance of clinical outcomes associated with detected levels of aspirin non-response. Standardising both the dose of aspirin and the current array of tests for measuring aspirin non-response is required to achieve consistent results and allow further investigation of clinical outcomes. Better detection of aspirin resistance will allow improved investigation of the use and cost effectiveness of other antiplatelet therapies in patients with proven aspirin resistance.

Although there is no level 1 evidence on which to recommend a change in clinical practice, antiplatelet medication in patients suffering recurrent clinical events while prescribed low dose aspirin may be inadequate, and there may be a role for either increasing the aspirin dose to the upper range of the recommended 75–325 mg guide or prescribing an alternative antiplatelet agent.

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