Aspirin failure in patients presenting with acute cerebrovascular ischaemia

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Introduction

Aspirin remains the most widely used agent for prevention of non-cardioembolic ischaemic stroke. The relative risk reduction for stroke in patients with a previous cerebrovascular event is around 22%, and so patients taking aspirin may still develop a new stroke or transient ischaemic attack (TIA) (1). This represents a significant treatment challenge. Possible reasons for recurrent ischaemic stroke in patients taking aspirin (‘aspirin treatment failures’) include inadequate inhibition of platelet reactivity due to inadequate dose or poor adherence to treatment, mechanisms of platelet activation which are not inhibited by aspirin and mechanisms of ischaemia which are not dependent on platelet activation.

Relative resistance to the inhibition of platelet cyclooxygenase by aspirin (“aspirin resistance”) has been described in aspirin treatment failure (2, 3). However, the reported prevalence of “aspirin resistance” varies widely. This may be due, at least in part, to variation in the laboratory techniques employed and the definitions used (3–6). Furthermore, poor adherence to aspirin therapy has not always been considered. Nevertheless, ex vivo measures of incomplete platelet inhibition by aspirin have been shown to be associated with risk of further vascular events (7, 8). Recently, Gengo et al. (9) reported an increased rate of recurrent ischaemic events in stroke patients who were poorly responsive to aspirin.

Lack of adherence to long-term therapy has long been recognised as a critical reason for the mismatch between evidence-based therapeutic recommendations and the actual care which patients receive. It has been estimated to cost the US healthcare system $100 billion a year and leads to a significant number of adverse events (10).

In order to investigate the prevalence and causes of aspirin failure in patients with stroke and TIA we have for the first time com-

Summary

Aspirin is the most commonly used antiplatelet drug for prevention of ischaemic stroke. In order to determine the prevalence and nature of aspirin failure, we studied 51 adults admitted with suspected ischaemic stroke and already prescribed daily aspirin. Within 48 hours (h) of onset, blood and urine samples were collected to assess platelet aggregation, activation and aspirin response by a range of methods. All tests were then repeated on a second sample taken 24 h after witnessed administration of 75 mg or 150 mg aspirin. At entry to the study, incomplete response to aspirin, measured by arachidonic acid (AA)-stimulated platelet aggregation, was found in 43% of patients. Following in-hospital aspirin administration, there was a significant decrease in AA-aggregation (p=0.001) suggesting poor adherence to therapy prior to admission. However, residual aggregation (10–15%) persisted in 11 subjects – suggesting alternative causes. In incomplete responders on admission, platelet aggregation with adenosine diphosphate (ADP) was significantly higher compared with responders (p<0.05) but there were no significant differences in collagen aggregation, platelet fibrinogen binding or P-selectin expression, plasma von Willebrand factor, fibrinogen, high-sensitivity C-reactive protein, or the urinary metabolite, 11-dehydro-TxB2. Incomplete platelet inhibition was common around the time of acute cerebrovascular ischaemic events in patients prescribed aspirin. Up to 50% of these observations appear due to incomplete adherence to aspirin therapy. Intervention studies are required to determine the clinical relevance of measured platelet response to aspirin in terms of outcome, and the effectiveness of improved pharmacotherapy for stroke prevention.

Keywords

Antiplatelet agents, aspirin resistance, platelet pharmacology, stroke prevention

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prehensively assessed platelet reactivity in the acute phase of cerebrovascular ischaemia, together with an assessment of adherence to aspirin therapy.

Materials and methods

Patients and study design

Fifty-one eligible consecutive adults admitted to Aberdeen Royal Infirmary or Woodend Hospital, Aberdeen, Scotland with suspected ischaemic stroke were recruited, following informed consent. Ethical approval, including permission to obtain consent from the nearest relative if the patient was unable to give informed consent, was obtained from the Scotland A Multi-centre research ethics committee (06/MRE00/53).

Only patients who had been prescribed aspirin before their admission to hospital were included. Medication use, including reported adherence to current therapy, was documented by a short questionnaire, interview of relatives and information from the General Practitioner.

The first blood sample was taken within 48 hours (h) of onset of the ischaemic event, and before aspirin was given in hospital. A single-void urine sample was also obtained. Samples were taken directly to the laboratory for platelet testing. Patients with contraindications to continued use of aspirin (including those who had suffered a haemorrhagic stroke) were excluded from the study.

Patients with ischaemic stroke or TIA were prescribed aspirin – 75 mg or 150 mg daily – as part of their routine care. In order to assess adherence to therapy, blood and urine samples were taken for repeat measurements 24 h after the first in-hospital dose of aspirin.

Methods

Blood sampling

Venous blood was obtained by clean venepuncture with a 21 G needle and syringes. The first 5 ml was discarded; then 18 ml collected into 3.8% trisodium citrate (9:1 vol:vol). Fifty μl blood was diluted in 450 μl HEPES-Mg buffer for flow cytometry. The remaining blood sample was centrifuged at 250 x g for 10 minutes (min) at room temperature to obtain platelet-rich plasma (PRP), then at 2,500 x g for 15 min to obtain platelet-poor plasma (PPP).

Platelet aggregometry

Platelet aggregometry was performed on a PAP-4 aggregometer using arachidonic acid (AA) 1.5 mM, collagen 2 mg/ml (Alpha Laboratories, Eastleigh, UK) and adenosine diphosphate (ADP) 5 and 10 μM (Sigma Aldrich Chemical Company Ltd, Dorset, UK, equine muscle adenosine diphosphate). Platelet-rich plasma (PRP) was kept at room temperature and the platelet count adjusted to 300 x 10^9/l. Briefly, 450 μl PRP was incubated at 37°C for

Table 1: Patient demographics.

<table>
<thead>
<tr>
<th></th>
<th>All subjects n=51</th>
<th>Responder to aspirin n=29</th>
<th>Incomplete responder n=22</th>
<th>Incomplete responders vs. responders p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years): Median (IQR)</td>
<td>75 (67 – 83)</td>
<td>74 (65 – 81)</td>
<td>76.5 (67–85)</td>
<td>0.351</td>
</tr>
<tr>
<td>Male (%)</td>
<td>25 (49)</td>
<td>14 (48)</td>
<td>11 (50)</td>
<td>1.0</td>
</tr>
<tr>
<td>Female (%)</td>
<td>26 (51)</td>
<td>15 (52)</td>
<td>11 (50)</td>
<td></td>
</tr>
<tr>
<td>Blood glucose (mM)</td>
<td>6.25 (5.50–7.80)</td>
<td>6.2 (5.5–8.2)</td>
<td>6.3 (5.2–7.8)</td>
<td>0.658</td>
</tr>
<tr>
<td>Cholesterol (mM)</td>
<td>4.55 (3.60–5.25)</td>
<td>4.6 (3.6–5.8)</td>
<td>3.9 (3.5–4.9)</td>
<td>0.436</td>
</tr>
<tr>
<td>HDL (mM)</td>
<td>1.40 (1.02–1.50)</td>
<td>1.3 (1.0–1.5)</td>
<td>1.4 (1.1–1.6)</td>
<td>0.452</td>
</tr>
<tr>
<td>LDL (mM)</td>
<td>2.40 (1.7 – 3.3)</td>
<td>2.6 (1.7–3.5)</td>
<td>2.3 (1.7–2.8)</td>
<td>0.478</td>
</tr>
<tr>
<td>Triglycerides (mM)</td>
<td>1.36 (1.06–1.72)</td>
<td>1.3 (1.0–1.6)</td>
<td>1.5 (0.9–1.9)</td>
<td>0.481</td>
</tr>
<tr>
<td>Statin use: number (%)</td>
<td>33 (67.3)</td>
<td>17 (63)</td>
<td>16 (76)</td>
<td>0.505</td>
</tr>
<tr>
<td>Other antiplatelet medication</td>
<td>5 (9.8)</td>
<td>4 (14)</td>
<td>1 (4.5)</td>
<td>0.368</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>16 (31.4)</td>
<td>7 (24)</td>
<td>9 (40.9)</td>
<td>0.330</td>
</tr>
<tr>
<td>Previous TIA</td>
<td>9 (17.6)</td>
<td>3 (10)</td>
<td>6 (27)</td>
<td>0.150</td>
</tr>
<tr>
<td>Previous MI</td>
<td>13 (25.5)</td>
<td>9 (31)</td>
<td>4 (18)</td>
<td>0.472</td>
</tr>
<tr>
<td>Previous Angina</td>
<td>16 (31.4)</td>
<td>8 (28)</td>
<td>8 (36)</td>
<td>0.716</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11 (21.6)</td>
<td>5 (17)</td>
<td>6 (27)</td>
<td>0.498</td>
</tr>
<tr>
<td>Hypertension</td>
<td>27 (52.9)</td>
<td>14 (48)</td>
<td>13 (59)</td>
<td>0.629</td>
</tr>
<tr>
<td>Current or ex-smoker</td>
<td>36 (71)</td>
<td>20 (69)</td>
<td>16 (73)</td>
<td>1.0</td>
</tr>
<tr>
<td>History of alcohol consumption</td>
<td>18 (35)</td>
<td>9 (31)</td>
<td>9 (41)</td>
<td>0.664</td>
</tr>
</tbody>
</table>
Platelet function testing: From bench to bedside

1 min. Maximum light transmission was set to 100% with autologous PPP. PRP was stirred at 1,000 rpm for 3 min to establish a baseline and to monitor for spontaneous aggregation. Fifty μl of agonist was added and light transmission was recorded for a further 4 min.

Definition of incomplete response
Maximum aggregation greater than or equal to 10% in response to 1.5 mM AA was used to define an incomplete response to aspirin, derived from a reference range using the same method in our laboratory (unpublished data): In 15 healthy subjects tested after a single dose of 150 mg aspirin, AA-stimulated platelet aggregation ranged from 0% to 8% (mean 4.46, standard deviation [SD] 2.11).

Soluble P-selectin and soluble CD40 ligand were measured in plasma by commercial ELISA (Bender Medsystems, Vienna, Austria). D-dimer was measured by automated immunoassay (VIDAS® D-Dimer Exclusion™ Kit, BioMérieux, Marcy l’Etoile, France).

Statistical analysis
Statistical analysis was performed using SPSS (Chicago, IL, USA). Wilcoxon signed rank test was used to compare paired admission and post-aspirin results; Mann-Whitney U-test was used for differences between groups. Logistic regression was performed on the significant variables.

Results
Patients
From a total of 63 patients recruited, 12 were excluded following a diagnosis of haemorrhagic stroke. A total of 51 (25 male : 26 female) patients took part. The final diagnosis was ischaemic stroke in 41 and TIA in 10. Demographics are shown in Table 1.

According to information received from the general practitioners, all participants were prescribed daily aspirin before their admission to hospital. Interview of the patient or nearest relative confirmed this. Of the 51 patients, only one admitted to not taking aspirin regularly.

Platelet aggregation response to AA on admission
There was no spontaneous aggregation in any sample. Maximum AA aggregation (1.5 mM) on the admission sample ranged from 0 to 73% (median 7, interquartile range [IQR] 4–12%). Incomplete response (maximum AA aggregation ≥10%) was found in 22 patients (43%) (Fig. 1).
Platelet response to AA after aspirin in hospital

After supervised aspirin administration in hospital, median AA aggregation was 7% (IQR 4–10%). This represented a significant decrease in aggregation response for the 22 incomplete responders when compared with the admission sample (p <0.001) (Fig. 1). Maximum AA aggregation was lower in 16 of the 22 originally incomplete responders, and was less than 10% in 11 of these subjects. However, according to our criterion, 11 of the incomplete responders remained incompletely responsive, with residual aggregation of between 10% and 15%, suggesting the influence of factors other than poor adherence to therapy in around 20% of subjects.

There were four responders on admission whose aggregation response changed to an incomplete response (10–13%) after in-hospital dosing. In one subject, AA-aggregation changed from 10% on admission to 60% after aspirin in hospital; this was unexplained, but it was speculated that the effects of co-administration of other drugs – the patient was commenced on low-molecular-weight heparin and clopidogrel between the two sampling points – may have been contributory (12).

Determination if platelets from incomplete responders can be inhibited by aspirin added directly in vitro

When PRP was incubated with acetylsalicylic acid (ASA) (10⁻⁵mol/l and/or 10⁻⁴mol/l) in vitro, ASA failed to abolish AA-aggregation in five out of the 18 incomplete responders who were tested at admission. In the post-aspirin samples, 10⁻⁵mol/L and/or 10⁻⁴mol/L failed to abolish AA-aggregation in six of the 11 persistently incomplete responders, indicating that their platelets were resistant to complete inhibition in vitro as well as in vivo.

Differences between responders and incomplete responders to aspirin, and changes after aspirin administration in hospital

Platelet aggregometry with other agonists

Aggregation with both 5 μM ADP and 10 μM ADP was significantly greater in incomplete responders on admission when compared with responders. Maximum aggregation with 5 μM ADP: incomplete responders median 54 (IQR 49–67), n=22; responders median 40 (IQR 34–48), n=29; (p<0.01). Maximum aggregation with 10 μM ADP: incomplete responders median 63 (IQR 57–70),
n=22; responders median 55 (IQR 48–61), n=29; p<0.05 (Fig. 2B). Collagen-induced aggregation was not significantly different between the groups: incomplete responders median 63 (IQR 56–70)%; responders median 62 (IQR 52–68)% (Fig. 2C). There was a significant decrease in aggregation stimulated by 5 μM ADP in the post-aspirin sample (p=0.002).

**Platelet activation markers**

There were no statistically significant differences between responders and incomplete responders in platelet fibrinogen binding or P-selectin expression in unstimulated samples or after stimulation with 10 μM ADP (Table 2).

After aspirin dosing in hospital, there was a significant decrease in resting platelet P-selectin expression (p=0.023) and a trend towards decreased ADP-stimulated P-selectin expression (p=0.068) (Table 3).

**11-dehydro-TxB2**

There were no statistically significant differences between responders and incomplete responders in urine 11-dehydro-TxB2 (Fig. 2D), and no significant change after aspirin administration in hospital (Table 3).

**Markers of coagulation, endothelial activation and inflammation**

There were no statistically significant differences between responders and incomplete responders in plasma vWF, fibrinogen, D-dimer, sCD40L, sP-selectin or hsCRP (Table 2).

There were statistically significant increases in plasma hsCRP levels (p=0.013) and plasma fibrinogen (p=0.026) between the first and second samples (Table 3).

**Other factors associated with incomplete response to aspirin**

There were no statistically significant differences between responders and incomplete responders in any of the demographics, lipids, blood glucose, co-morbidity, or documented medication use (Table 1).
Logistic regression

The only significant association with AA-aggregation was ADP-induced aggregation, and we found that for each 1% increase in 5 μM ADP-induced platelet aggregation, the odds of being an incomplete responder is 1.2 times higher (95% confidence interval: 1.07–1.29).

Discussion

This study examines platelet reactivity in subjects on aspirin at the time of acute cerebrovascular ischaemia and makes a quantitative assessment of incomplete adherence to therapy. Incomplete platelet inhibition by aspirin was present in 43% of patients. However we found that the platelet response was improved in the majority of cases following a single aspirin dose in hospital, compatible with incomplete adherence to treatment prior to admission. Nevertheless, platelets remained incompletely responsive in half of these subjects, suggesting that factors other than poor adherence to therapy exist in around a quarter of patients. This may represent some degree of true resistance to the platelet inhibitory effect of aspirin in this cohort. We hypothesise that aspirin resistance and incomplete adherence to therapy may both contribute to recurrent cerebral ischaemia in some subjects.

Most previous studies of aspirin treatment failure and aspirin resistance have been in coronary heart disease. Substantial variability exists in the reported prevalence of aspirin resistance in the literature (3, 6). In patients with cerebrovascular disease, it ranges from 5% to 75% (13–15) and seems to depend largely on the methods and criteria used (16).

Compared with other studies where aggregometry was used to define aspirin resistance, we found a higher proportion of patients with an incomplete response to aspirin (13–15). This is not unexpected, as our patients had all suffered very recent cerebrovascular ischaemia despite having been prescribed aspirin. Indeed the study group was intentionally chosen to represent patients in whom aspirin therapy had ostensibly failed to protect against ischaemic stroke. After patients had taken aspirin in hospital the incidence of incomplete aspirin response was similar to or lower than in previous studies. This is consistent with inadequacy of dose or poor adherence to aspirin treatment in our group prior to admission. In most previous stroke studies, it was not possible to determine the effect of adherence to treatment, since aspirin resistance was assessed only after aspirin had been administered in hospital. Komiya et al. estimated that non-compliance contributed to poor platelet response to aspirin in 10% of cerebrovascular disease outpatients (17). Our results indicate that non-adherence to aspirin therapy could be a major reason for aspirin failure in patients with stroke and TIA, and that true biochemical aspirin resistance is relatively uncommon.

It has been suggested that poor aspirin response may be due to inadequate dose, but 81 mg per day is generally sufficient to block AA-induced aggregation (18). Higher doses of aspirin are, however, associated with inhibition of platelet response to other agonists including ADP (18). The effects of aspirin on platelet aggregation response to agonists other than AA are, not surprisingly, variable but could nevertheless be important in prevention of cardiovascular disease. The association between residual AA-aggregation and higher platelet responses to ADP possibly reflects intrinsic platelet hyper-activity as well as incomplete inhibition of thromboxane (Tx)A2 production. In support of this, residual platelet activation in aspirin-treated coronary artery disease patients was shown to be independent of cyclooxygenase (COX) pathways (19). Inherent variability in individual baseline platelet activation levels and responsiveness is probably one of the most important determinants of response to antiplatelet drugs (20), and this can only be tested in studies that have included a pre-aspirin baseline.

In the present study, AA-induced aggregation in PRP was our primary measure. True aspirin resistance is the inability of aspirin

Table 3: Markers of platelet activation, endothelial function and inflammation on admission compared with post-aspirin in hospital, by Wilcoxon signed rank test. Median (IQR).

<table>
<thead>
<tr>
<th></th>
<th>On admission</th>
<th>Post aspirin in hospital</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet P-selectin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(% positive platelets)</td>
<td>1.02 (0.66–1.79)</td>
<td>0.73 (0.41–1.18)</td>
<td>0.023 *</td>
</tr>
<tr>
<td>ADP-platelet P-selectin (% positive platelets)</td>
<td>39.3 (25.4–53.4)</td>
<td>33.0 (22.0–43.6)</td>
<td>0.068</td>
</tr>
<tr>
<td>Platelet fibrinogen binding (% positive platelets)</td>
<td>2.76 (1.36–5.39)</td>
<td>2.74 (1.05–5.60)</td>
<td>0.88</td>
</tr>
<tr>
<td>ADP-platelet fibrinogen binding (% positive platelets)</td>
<td>40.1 (29.8–55.3)</td>
<td>39.60 (32.9–56.0)</td>
<td>0.29</td>
</tr>
<tr>
<td>hs CRP (mg/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=51</td>
<td>3.50 (1.5–6.4)</td>
<td>6.60 (1.6–13.7)</td>
<td>0.013 *</td>
</tr>
<tr>
<td>Plasma vWF (IU/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=51</td>
<td>1.69 (1.39–2.46)</td>
<td>1.74 (1.31–2.48)</td>
<td>0.94</td>
</tr>
<tr>
<td>Plasma Fibrinogen (g/l)</td>
<td>3.3 (2.9 – 4.0)</td>
<td>3.6 (3.1 – 4.1)</td>
<td>0.026*</td>
</tr>
<tr>
<td>Plasma sP-selectin (ng/ml)</td>
<td>107.2 (86.4 – 144.7)</td>
<td>103.5 (78.0 – 127.5)</td>
<td>0.223</td>
</tr>
<tr>
<td>Plasma sCD40L (ng/ml)</td>
<td>0.9 (0.4 – 3.9)</td>
<td>0.8 (0.4 – 3.8)</td>
<td>0.409</td>
</tr>
<tr>
<td>D-dimer (ng/ml)</td>
<td>902.7 (525.1 – 1875.3)</td>
<td>869.2 (507.7 – 1338.9)</td>
<td>0.168</td>
</tr>
<tr>
<td>Urine 11-dehydro-TxB2 (μg/mmol creatinine)</td>
<td>77.22 (50.13–175.5)</td>
<td>69.65 (40.15–122.41)</td>
<td>0.234</td>
</tr>
<tr>
<td>Urine salicylate (g/mol creatinine)</td>
<td>11.7 (6.9–15.8)</td>
<td>14.5 (10.2–25.1)</td>
<td>0.001 **</td>
</tr>
</tbody>
</table>
to inhibit its platelet target, the COX pathway (3, 21). Inhibition can be measured most directly by platelet aggregometry with AA stimulation, or assay of TXB2, a stable metabolite of TXA2. The criterion we used for complete inhibition by aspirin was derived from our laboratory ranges which show a maximum AA-induced platelet aggregation between 0% and 8% following a single dose of aspirin in 15 healthy subjects. Previous studies have used 20% AA-aggregation as the cut-off (22). The clinical significance of low-level residual AA-aggregation between 10% and 20% is unclear. Had we applied similar criteria to Gum et al. (22) however, eight patients (16%) would still have been deemed incomplete responders on admission, and 98% of all subjects would have become “good responders” after receiving aspirin in hospital.

An effect on platelet reactivity of the acute ischaemic event itself cannot be ruled out. It is also possible that absorption or metabolism of aspirin could be affected by the event. Harrison et al. reviewed the stroke patients from a study of aspirin resistance after one year (16, 23) and reported that reproducibility of platelet testing over time was poor and thereby likely to undermine the predictive value. Previous work from our own group shows that platelets are activated at the time of acute stroke and remain so in convalescence, despite increasing aspirin use between the two samples (24).

In the current study, there was a significant increase in plasma fibrinogen and hsCRP from the first to the second sample, which probably reflects the acute phase and inflammatory response during the progression of acute stroke, while developing infection may also contribute to increased levels. No association was found between fibrinogen or hsCRP and the platelet response to aspirin.

Some authors have suggested that aspirin may not provide a complete inhibition of platelet aggregation during the usual 24 h dosing interval (25), and this phenomenon could contribute to the residual platelet aggregation found in some of our subjects even after aspirin dosing in hospital. It has also been suggested that increased platelet turnover due to platelet consumption might conceivably shorten the effective half-life of aspirin inhibition (26–28).

There is growing evidence for an association between degree of inhibition of platelet aggregation by aspirin and clinical outcome in patients with cardiovascular disease and stroke (9, 29, 30). The use of 11-dihydroTXB2 as a marker of aspirin resistance was given prominence by the association of increased levels with stroke, myocardial infarction or cardiovascular death outcomes in 976 cardiac patients in the HOPE study (31). The association was confirmed by analysis of the CHARISMA trial subjects (32). However, we found no significant differences in urine 11-dihydroTXB2 in our study. Lack of agreement between 11-dehydroTXB2 and AA-induced platelet aggregation is consistent with the results of previous studies in coronary artery disease patients (4, 5), and with those of Fitzgerald et al. (33). Therefore, this measurement may not be a good marker of impaired platelet response to aspirin or, alternatively, residual aggregation as measured by aggregometry is not related to the degree of inhibition of thromboxane by aspirin (34). TX metabolites can derive from other sources, such as vessel wall and leukocytes, reflecting inflammatory processes. In support of this, lower levels of 11-dihydroTXB2 in the CHARISMA trial were associated with, inter alia, history of treatment with non-steroidal anti-inflammatory drugs or statins (32).

In conclusion, incomplete platelet inhibition by aspirin is commonly found in acute cerebrovascular ischaemia. A significant proportion is due to incomplete adherence to aspirin therapy and is therefore easily amenable to intervention. It would be helpful to know an individual’s response to antiplatelet treatment, particularly as emerging evidence shows that the degree of platelet inhibition, whether or not directly associated with COX inhibition, correlates with the incidence of recurrent ischaemic events (29, 30). Unfortunately no single test has yet emerged as clinically informative (35). The data from the current study support the growing body of opinion that true biochemical resistance to aspirin is uncommon. However, poor adherence to aspirin therapy and reduced bioavailability are evident in patients presenting with cerebrovascular ischaemia and contribute to incomplete platelet inhibition by current therapy. Intervention studies are therefore required to determine the clinical relevance of measured platelet response to aspirin in terms of outcome, and the effectiveness of improved pharmacotherapy for stroke prevention.

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Conflict of interest

None declared.

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