Association of Aspirin Resistance With Increased Stroke Severity and Infarct Size

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Objective: To investigate the relationship between aspirin resistance and clinical and neuroimaging measures of stroke severity in acute stroke patients.

Design: Prospective single-center survey of acute ischemic stroke patients receiving aspirin therapy.

Setting: The Royal Melbourne Hospital, Parkville, Victoria, Australia.

Patients: Ninety acute stroke patients who previously received aspirin therapy were enrolled.

Main Outcome Measures: Clinical stroke severity was measured using the National Institutes of Health Stroke Scale (NIHSS) and stroke infarct size was measured using the Alberta Stroke Program Early CT Score (ASPECTS). Aspirin resistance was measured using the VerifyNow system.

Results: The mean (SD) age was 75 (9.9) years and 64.4% were male. The median NIHSS score and ASPECTS were 4 (interquartile range [IQR], 3-10) and 9 (IQR, 6-10), respectively. Aspirin resistance was detected in 28.9% (95% CI, 0.19 to 0.38) of all patients. The median aspirin reaction unit (ARU) was 486.0 (IQR, 432.3-557.0). Every 1-point increase in ARU was associated with a 0.03-point increase in NIHSS score (95% CI, 0.01 to 0.04; P < .001) and a 0.02-point decrease in ASPECTS (95% CI, -0.03 to -0.01; P < .001). This corresponded to an approximate median increase of 1 point in NIHSS score for every 33-point increase in ARU or a decrease of 1 point in ASPECTS for every 50-point increase in ARU.

Conclusions: Aspirin resistance is associated with increased clinical severity and stroke infarct volume in acute stroke patients. Our results support the need for a randomized controlled study to investigate alternative antiplatelet therapy in patients with aspirin resistance.


IMPROVING CLINICAL OUTCOME IS the cornerstone of both acute stroke treatment and prevention. In addition to intravenous recombinant tissue plasminogen activator,1 short-term aspirin therapy significantly reduces death and dependency at 6 months.2 Pooled analysis of the International Stroke Trial and Chinese Acute Stroke Trial showed significant relative risk reduction of 11% of nonfatal stroke or death in patients treated with short-term aspirin.3 Further, prior use of aspirin has also been associated with lower National Institutes of Health Stroke Scale (NIHSS) scores on hospital admission4,5 as well as lower modified Rankin Scale scores at discharge.6 Prior antiplatelet therapy has been shown to decrease infarct growth in both animal models7 and human studies.8

Aspirin inhibits the conversion of arachidonic acid into prostaglandin H2 by acetylation cycloxygenase-1,9 leading to decreased formation of thromboxane A2. The biological consequence is the inhibition of platelet aggregation and thrombus formation.9 This may reduce the size and extent of thromboses and emboli, leading to reduced infarct volume.10 Aspirin may also reduce stroke severity through anti-inflammatory11 and neuroprotective mechanisms12,13

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However, a proportion of patients treated with aspirin demonstrate poor clinical outcomes, which may be attributable to aspirin resistance,14 an increasingly recognized clinical phenomenon. Aspirin resistance is the failure of aspirin to reduce platelet production of thromboxane A2 and therefore platelet activation and aggregation.15 Approximately 30% of patients with cardiovascular disease do not achieve an expected level of platelet inhibition with aspirin.16 A similar prevalence is found in stroke populations.17 These “aspirin-resistant” patients exhibit
an increased risk of vascular events such as myocardial infarction, transient ischemic attack, or stroke.26-21

The effect of aspirin resistance on stroke severity has been previously investigated, but the findings were inconclusive.22,23 Schwammenthal and colleagues22 found a significant association with admission NIHSS score; however, less than half their cohort were receiving long-term aspirin therapy. A different study23 found that aspirin resistance was significantly associated with functional outcome (modified Rankin Scale score), but not stroke severity (NIHSS score), within 72 hours of onset.

Consequently, there is a need to further investigate the effect of aspirin resistance on clinical stroke severity. There is also increasing interest to measure stroke severity with additional neuroimaging tools. In particular, area of infarct is an alternate measure of stroke severity. The Alberta Stroke Program Early CT Score (ASPECTS) is widely used for measuring the area of infarct seen on admission computed tomography.24

We hypothesized that in patients receiving prior aspirin therapy with aspirin resistance stroke severity would be greater measured by a clinical impairment score and a radiological measure. We therefore aimed to investigate the association between aspirin resistance and stroke severity measure by NIHSS and infarct volume as measured by ASPECTS.

**METHODS**

We obtained ethics approval to prospectively recruit consenting acute stroke patients presenting to the Royal Melbourne Hospital stroke care unit. The inclusion criteria were at least 7 days of aspirin therapy (acetylsalicylic acid, 100 mg daily) prior to stroke onset, evidence of ischemic infarct on computed tomography or magnetic resonance imaging, and age older than 18 years. Compliance was determined by interviews of patients and patient relatives. Patients were excluded if there was evidence of hemorrhage on computed tomography or magnetic resonance imaging or they had platelet function disorders or were concurrently taking an additional antiplatelet, anticoagulant, or nonsteroidal anti-inflammatory medication.

Patient enrollment, blood sampling, and data collection occurred within 48 hours of hospital admission. Those who had aspirin withheld during this period were further excluded, as were those for whom an antiplatelet other than aspirin or anticoagulant medication was added. Demographic and clinical information including duration of aspirin therapy, stroke subtype according to the Oxfordshire Community Stroke Project and Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, and whether they were given tissue plasminogen activator were collected for all patients. History of myocardial infarction, ischemic stroke, and transient ischemic attack was assessed retrospectively over the previous 2 years.

Stroke severity was assessed using the NIHSS25 on admission by persons trained in the examination and blinded to the diagnosis of aspirin resistance. A severe stroke was defined as an NIHSS score of 16 or more and a mild to moderate stroke was defined as an NIHSS score less than 16. The size of infarction was measured on admission computed tomography scan using the ASPECTS24,26 scoring system by radiologists trained in the examination and blinded to the diagnosis of aspirin resistance. The ASPECTS scoring also relies on middle cerebral artery territory involvement; therefore, posterior infarctions were excluded from this analysis. A large area of infarction was defined as an ASPECTS less than 7 and a small area of infarction was defined as an ASPECTS of 7 or more.

Blood samples were taken no sooner than 2 hours and no later than 24 hours following last aspirin ingestion. A 2-mL blood sample was collected into a 3.2% sodium citrate vacuum-sealed tube. All patients were tested while receiving 100 mg of aspirin every morning as documented on ward records.

Aspirin resistance was measured using the VerifyNow system (Accumetrics), a type of rapid platelet function assay. The device measures the change in light transmission across a whole blood sample in response to agonist stimulation proportional to the level of platelet activation/aggregation in the sample. Results are produced in the form of an aspirin reaction unit (ARU). In line with previous definitions,27,28 a cutoff of 550 ARU was used to determine the presence of aspirin resistance. Raw ARU scores as continuous variables were also used to indicate the degree of platelet aggregation.

Statistical analysis was performed using statistical software SPSS version 16 (IBM SPSS) and Stata version 11IC (StataCorp). A Shapiro-Wilk test was used to assess the normality of distributions. Univariate analyses of sociodemographic and clinical variables, as well as vascular risk factors, were performed using the t test, Wilcoxon-Mann-Whitney rank sum test, or χ² test as appropriate depending on the nature of the underlying distributions. Independent association between aspirin resistance and both NIHSS score and ASPECTS was assessed using the Spearman rank correlation coefficient. The magnitude of the association between aspirin resistance and both NIHSS score and ASPECTS (both unadjusted and adjusted for vascular risk factors and cardioembolic stroke) was estimated using median regression. The difference in both NIHSS score and ASPECTS between aspirin-resistant and aspirin-sensitive groups (dichotomized using the 550-ARU threshold) was assessed using the Wilcoxon-Mann-Whitney rank sum test and median regression was used to estimate corresponding effects (both unadjusted and adjusted for vascular risk factors and cardioembolic stroke). The difference in proportions of severe strokes between the aspirin-resistant and aspirin-sensitive groups was assessed using the Fisher exact test and corresponding effect sizes were estimated using corresponding odds ratios (ORs). A 2-comparison Bonferroni-corrected (corresponding to NIHSS score and ASPECTS), 2-sided P <.025 was used as a statistical significance threshold for testing the main hypotheses. A Kruskal-Wallis equality of populations rank test was used to assess whether NIHSS score or ASPECTS differed by TOAST categories. Stroke etiology was then dichotomized into cardioembolic and noncardioembolic.

Between October 1, 2006, and April 7, 2011, 710 acute ischemic stroke patients who were receiving aspirin therapy were screened. A total of 90 patients were enrolled. The mean (SD) age was 75 (9.9) years and 64.4% were male. Participants had been taking aspirin for a median duration of 5 years (interquartile range [IQR], 2-10 years). Demographic and clinical characteristics of the patient population are presented in Table 1.

Raw ARUs ranged from 385 to 655, with a median of 486.0 (IQR, 432.3-557.0). A total of 26 of 90 enrolled patients (28.9%; 95% CI, 0.19 to 0.38) were aspirin resistant, defined by more than 550 ARU. Demographic and clinical characteristics of the aspirin-resistant and aspirin-sensitive groups are given in Table 2. Aspirin-resistant patients were significantly more likely to have sustained
a myocardial infarction, transient ischemic attack, or stroke within the last 2 years (OR, 8.04; 95% CI, 2.89 to 22.3; *P* = .001). The Oxfordshire Community Stroke Project classification significantly varied with aspirin-resistance status. Five percent of aspirin-sensitive patients sustained a total anterior circulation infarct compared with 35% of the aspirin-resistant patients (OR, 0.093; 95% CI, 0.023 to 0.38; *P* = .001). Patients who did not respond to aspirin were significantly more likely to have a history of smoking (OR, 3.08; 95% CI, 1.17 to 8.13; *P* = .02). No other vascular risk factors differed significantly between the aspirin-sensitive and aspirin-resistant groups. Aspirin response status, NIHSS score, and ASPECTS did not differ significantly between patients with and without cardioembolic stroke.

The Spearman rank correlation indicated a significant association between raw NIHSS and raw ARU scores (ρ = 0.36; *P* < .001). Median regression estimated a statistically significant increase in NIHSS score of 0.03 point for every 1-point increase in ARU (95% CI, 0.01 to 0.04; *P* = .001). This corresponds to an approximate median increase of 1 point in NIHSS score for every 33-point increase in ARU or 8 points in NIHSS score over the entire range of ARUs observed in the present study. This association remained significant after adjusting for vascular risk factors. A Kruskal-Wallis rank test found no significant difference in NIHSS score between stroke etiology defined by TOAST criteria (*H* = 7.09, *P* = .07). The NIHSS score did not differ significantly when etiology was dichotomized into cardioembolic and noncardioembolic strokes (*P* = .62).

Aspirin resistance (>550 ARU) was significantly associated with stroke severity (**Figure 1**). Observed median NIHSS score was 11 (IQR, 4-16) in the aspirin-resistant group compared with 4 (IQR, 2-6) in the aspirin-sensitive group, resulting in a statistically significant median difference of 7 (95% CI, 4.69 to 9.31; *P* < .001), with the aspirin-resistant group having higher NIHSS scores. Adjustment for cardioembolic strokes did not alter the results (median difference, 7; 95% CI, 4.6 to 9.4; *P* < .001). This difference increased further when adjusted for vascular risk factors (median difference, 8; 95% CI, 5.0 to 11.0; *P* < .001). Aspirin-resistant patients were significantly more likely to sustain a severe stroke, defined as an NIHSS score of 16 or more (OR, 7.49; 95% CI, 1.49 to 48.0; *P* = .002).

The Spearman rank correlation indicated a significant association between raw ARU scores and raw ASPECTS (ρ = −0.48; *P* < .001). Median regression estimated a statistically significant decrease of 0.02 in ASPECTS for every 1-point increase in ARU (95% CI, −0.03 to −0.01; *P* < .001). This corresponds to an approximate median decrease of 1 point in ASPECTS for every 50-point increase in ARU or a median decrease of 5.4 points in ASPECTS over the entire range of ARUs observed in the study sample. This association remained significant after adjusting for vascular risk factors and cardioembolic stroke.

Aspirin resistance status was significantly associated with infarct size (**Figure 2**). Observed median ASPECTS was 5.5 (IQR, 4-6.5) in the aspirin-resistant group compared with a median ASPECTS of 10 (IQR, 8-10) in the aspirin-sensitive group, resulting in a statistically significant median difference of −5 (95% CI, −7.0 to −3.0; *P* < .001). While remaining highly statistically significant, this difference decreased slightly when adjusted for vascular risk factors and cardioembolic stroke (median difference, −4.0; 95% CI, −4.8 to −3.3; *P* < .001). The aspirin-resistant group was also significantly more likely to sustain a large stroke defined by an ASPECTS of 7 or less (OR, 60.0; 95% CI, 10.5 to 343.2; *P* = .001).

### Comment

Aspirin is widely used in the treatment of stroke. It significantly reduces the risk of recurrence and the severity of stroke. Long-term aspirin therapy has been estimated to have a cost-effectiveness ratio of $11 000 per quality-adjusted year of life gained. Resistance to aspirin could translate into a significant increase in health burden.

Aspirin resistance is the inability to decrease thromboxane A2 levels after aspirin therapy. It has been associated with increased risk of recurrent stroke and poor outcome after stroke. Drug interactions and compliance, which may fall to 75% at 3 months, have been previously proposed but not substantiated. Genetic polymorphisms in genes encoding collagen, glycoprotein, von Willebrand receptors, or enzymes of the platelet arachidonic acid cascade have also been suggested.
The present study shows that aspirin resistance is prevalent (28.9%; 95% CI, 0.19 to 0.38) in the ischemic stroke population. This is comparable with most previous reports in ischemic stroke populations. The wide range of prevalence may be due to use of different tests of platelet function as well as clinical and demographic differences.

Our study showed that aspirin resistance was significantly associated with a higher median NIHSS score on admission. This was expected because aspirin therapy has previously been found to reduce stroke severity. Schwammenthal et al found that aspirin resistance was associated with a lower NIHSS score on admission. However, less than half their cohort was receiving long-term aspirin therapy prior to the index event and aspirin doses varied between participants. Englyst et al found aspirin resistance to be significantly associated with modified Rankin Scale score but not NIHSS scores. Their failure to find significance with clinical stroke severity can be attributed to small sample size within which only a subset took aspirin prior to the index event. The 72-hour time window to collect stroke severity scores may also have influenced their results; a score collected on

Table 2. Baseline Demographic and Clinical Characteristics of Aspirin-Resistant and Aspirin-Sensitive Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Aspirin Resistant (n = 26)</th>
<th>Aspirin Sensitive (n = 64)</th>
<th>P Value</th>
<th>Group Difference (95% CI)α</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, median (IQR)</td>
<td>76 (70.8-85)</td>
<td>76.5 (72.3-86.5)</td>
<td>.88</td>
<td>0 (−3.53 to 3.53)</td>
</tr>
<tr>
<td>Female</td>
<td>20 (77)</td>
<td>38 (59)</td>
<td>.12</td>
<td>0.18 (−0.26 to 0.38)</td>
</tr>
<tr>
<td>Duration of aspirin therapy, y, median (IQR)</td>
<td>4.5 (2-10)</td>
<td>5 (2-10)</td>
<td>.77</td>
<td>0 (−3.50 to 3.50)</td>
</tr>
<tr>
<td>Vascular risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking (current and past)</td>
<td>18 (69)</td>
<td>27 (42)</td>
<td>.02</td>
<td>0.27 (0.06 to 0.49)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9 (35)</td>
<td>27 (42)</td>
<td>.51</td>
<td>−0.08 (−0.29 to 0.14)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>11 (42)</td>
<td>17 (27)</td>
<td>.14</td>
<td>0.16 (−0.06 to 0.38)</td>
</tr>
<tr>
<td>Carotid stenosis</td>
<td>8 (31)</td>
<td>13 (20)</td>
<td>.29</td>
<td>0.10 (−0.10 to 0.31)</td>
</tr>
<tr>
<td>Previous MI, TIA, or stroke</td>
<td>18 (69)</td>
<td>14 (22)</td>
<td>.001</td>
<td>0.47 (0.27 to 0.68)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>24 (92)</td>
<td>60 (94)</td>
<td>.80</td>
<td>−0.01 (−0.13 to 0.10)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>13 (50)</td>
<td>52 (81)</td>
<td>&lt;.001</td>
<td>0.31 (−0.53 to −0.10)</td>
</tr>
<tr>
<td>Stroke subtype</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCSP</td>
<td>9 (35)</td>
<td>3 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TACI</td>
<td>11 (42)</td>
<td>36 (56)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>LACI</td>
<td>3 (11.5)</td>
<td>12 (19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOAST</td>
<td>5 (11.5)</td>
<td>13 (20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCSP</td>
<td>3 (11)</td>
<td>9 (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PACI</td>
<td>9 (35)</td>
<td>17 (27)</td>
<td>.47</td>
<td></td>
</tr>
<tr>
<td>LAA</td>
<td>7 (27)</td>
<td>11 (17)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CE, cardioembolic; IQR, interquartile range; LAA, large artery atherosclerosis; LACI, lacunar infarction; LI, lacunar infarction; MI, myocardial infarction; OCSP, Oxfordshire Community Stroke Project; OE, other determined etiology; PACI, partial anterior circulation infarction; POCI, posterior circulation infarction; TACI, total anterior circulation infarction; TIA, transient ischemic attack; TOAST, Trial of Org 10172 in Acute Stroke Treatment; UE, undetermined etiology.

αGroup difference for continuous variables is reported as median difference. Group difference for binary variables is reported as risk difference.

Figure 1. Variation of baseline National Institutes of Health Stroke Scale (NIHSS) scores with aspirin reaction unit. The asterisks and circle represent individual participants who were outliers. They had a particularly high NIHSS score for aspirin-sensitive patients.

Figure 2. Variation of Alberta Stroke Program Early CT Score (ASPECTS) between aspirin-sensitive and aspirin-resistant patients.
Aspirin resistance should therefore have a larger influence on patients with noncardioembolic stroke than those with cardioembolic stroke. Previous studies have reported a higher prevalence of aspirin resistance in lacunar stroke compared with embolic stroke. However, the current study found no significant association with stroke etiology defined by TOAST criteria. The NIHSS score did not differ between patients with cardioembolic and non-cardioembolic stroke. Atrial fibrillation also did not differ significantly between aspirin-sensitive and aspirin-resistant groups.

Our study has several strengths. First, to our knowledge, the association between aspirin resistance and ASPECTS has not previously been reported. Second is the prospective data collection, assessment of all patients within 48 hours of admission, and the strict inclusion and exclusion criteria. Third, ASPECTS is highly sensitive and specific for functional outcome, 0.78 and 0.96, respectively. However, our findings and conclusions should be interpreted in light of a small sample size. There was also a slight selection bias for patients with relatively milder symptoms. Furthermore, we are limited by the possible insensitivity of ASPECTS for early ischemic changes. Because ASPECTS was determined using admission computed tomography, allocated scores may not accurately represent the total area of ischemia.

The results of our study suggest that patients with aspirin resistance are more likely to sustain a more severe stroke than patients without. We recommend a randomized controlled study to compare alternative antiplatelet agents in patients with aspirin resistance.

References


3. Chen ZM, Sandercoc P, Pan HC, et al. Indications for early aspirin use in acute ischemic stroke: a combined analysis of 40,000 randomized patients from the


