Platelet Response to Aspirin in Chinese Stroke Patients is Independent of Genetic Polymorphisms of COX-1 C50T and COX-2 G765C

Xingyang Yi¹, Qiang Zhou¹, Jing Lin¹, Lifen Chi¹ and Zhao Han²

¹Department of Neurology, 3rd Affiliated Hospital of Wenzhou Medical College, Wenzhou, China
²Department of Neurology, 1st Affiliated Hospital of Wenzhou Medical College, Wenzhou, China

Aim: Aspirin resistance (AR) is common in Chinese stroke patients taking antiplatelet medications; however, few studies have documented the role of cyclooxygenase (COX)-1 C50T and COX-2 G765C polymorphisms in AR. The aim of this study was to investigate the prevalence of AR in Chinese stroke patients and the relationships between AR and COX-1 C50T and COX-2 G765C polymorphisms, and to evaluate the effect of these polymorphisms on platelet response to aspirin.

Methods: We prospectively enrolled 634 Chinese stroke patients. Platelet aggregation testing was performed before and after aspirin administration. The pre- and post-aspirin levels of 11-dehydrothromboxane B2 (11-dTxB2) were determined in urine samples. COX-1 C50T and COX-2 G765C genotypes were determined by a polymerase chain reaction-allelic restriction assay.

Results: AR was detected in 129 patients (20.4%), aspirin semi-resistance (ASR) was detected in 28 patients (4.4%), and aspirin sensitivity (AS) was detected in 477 patients (75.2%). There was no association between COX-1 C50T or COX-2 G765C polymorphisms and ASR+AR. Aspirin could efficiently reduce 11-dTxB2 production by approximately 75%. In addition, platelet aggregation, both in response to arachidonic acid (AA) and adenosine 5’-diphosphate (ADP), was inhibited by more than 80% and 40%, respectively; however, the percentage reduction in platelet aggregation and 11-dTxB2 levels was not significantly different between the COX-1 C50T and COX-2 G765C genotypes (p > 0.05).

Conclusions: There was no association between COX-1 C50T and COX-2 G765C polymorphisms and AR in Chinese stroke patients. In addition, COX-1 C50T and COX-2 G765C polymorphisms had no effect on the platelet response to aspirin.


Key words: Aspirin resistance, Stroke, Platelet function tests, Cyclooxygenase, Polymorphism

Introduction

Aspirin is the most commonly used antiplatelet drug worldwide in both the primary and secondary prevention of cardiovascular disease and stroke¹-⁴. High-risk vascular patients treated with aspirin have a 34% reduction in nonfatal myocardial infarction (MI), 25% reduction in nonfatal stroke, and 18% reduction in all-cause mortality⁴; however, in some patients, the platelet anti-aggregating effect of aspirin may be sub-optimal⁵-⁶. From a biochemical point of view, aspirin resistance (AR) refers to patients who are taking aspirin but do not display an adequate degree of platelet inhibition⁷.

The principal mechanism proposed for the anti-thrombotic effect of aspirin is inhibition of platelet cyclooxygenase (COX), which decreases the production of thromboxane A2 (TXA2), a potent stimulator of platelet aggregation. The stable thromboxane metabolite 11-dehydrothromboxane B2 (11-DTXB2) reflects in vivo platelet activation⁸ and can be measured in plasma or urine. This metabolite is useful in...
monitoring platelet activity in patients not taking antithrombotic medications or in testing for AR.

The etiology of AR is likely to be multifactorial in origin. Reduced absorption and/or increased metabolism of aspirin may contribute to AR. In addition, the biosynthesis of TXA2 via pathways not inhibited by aspirin as well as alternative pathways involved in platelet activation not blocked by aspirin (e.g., those involving adenosine 5’-diphosphate (ADP), collagen, epinephrine, and thrombin) may play a role in AR. Moreover, the majority of AR reported in the literature may be the result of poor adherence.

The genetic etiology of AR has also been proposed. Many studies have examined the association of AR with single nucleotide polymorphisms (SNPs) in COX-1 genes and in several receptors on the surface of platelets. In addition, numerous studies have investigated the role of genetic factors that contribute to the resistance or augmented response to aspirin, however, they have conflicting results. A systematic review revealed that the PLA1/A2 variant is significantly associated with AR, but no significant association was found with AR in polymorphisms of COX-1, GP Ib, P2Y1, or P2Y12 genes. Aspirin leads to COX-1 inactivation and decreased TXA2 production, achieving the goal of antithrombotic therapy. A study revealed that the frequencies of minor alleles in COX-1 C50T and COX-2 G765C were 8.6% and 21.3%, respectively, in Caucasians, which suggested that the variation of either gene affected the effect of aspirin. Similarly, Colaizzo et al. revealed an association between the COX-2 G765C polymorphism and cerebrovascular ischemia, suggesting that the COX-2 gene is a susceptibility locus for the risk of cerebrovascular ischemic disease; however, Cipollone et al. found that the COX-2 G765C polymorphism could reduce urine 11-dehydro-thromboxane B2 (11-dTxB2) and was a protective factor against myocardial infarction and ischemic stroke. In addition, Frelinger et al. have shown that AR in a number of subjects may be independent of both COX-1 and COX-2; however, Maree et al. showed that genetic variability in COX-1 appears to modulate both arachidonic acid (AA)-induced platelet aggregation and thromboxane generation. Heterogeneity in the way patients respond to aspirin may in part reflect COX-1 genotype variations. Nevertheless, these studies have been too small to allow reliable conclusions to be drawn, and they have rarely taken into account the various biochemical and functional methodologies available, thus giving rise to conflicting results.

Several laboratory tests are currently used to assess the response to aspirin, including (i) optical platelet aggregometry (OPA), (ii) bleeding time, (iii) platelet function analysis (PFA), (iv) the VerifyNow Aspirin system, and (v) determination of serum TXB2 or urinary 11-DTXB2 levels. Each method has its own advantages and disadvantages.

**Aims and Hypothesis**

Due to the inhibitory action of aspirin on COX, this enzyme is the most obvious gene to study with regard to AR. Despite suggested associations with AR, few studies have documented the role of COX-1 C50T and COX-2 G765C polymorphisms in Chinese stroke patients. We therefore hypothesized that COX-1 C50T and COX-2 G765C polymorphisms may affect COX activation and TXA2 production, and they may contribute to AR and affect the platelet response to aspirin. In the present study, the COX-1 C50T and COX-2 G765C polymorphisms, platelet aggregation, and urinary 11-dTxB2 levels were measured to evaluate the association of COX-1 C50T and COX-2 G765C polymorphisms with platelet response to aspirin in Chinese stroke patients.

**Methods**

**Study Populations**

We prospectively enrolled 634 patients, including 332 men (52.4%), who had suffered their first stroke between August 2008 and August 2010. The inclusion criteria were as follows: 1) age ≥ 18 years; 2) diagnosis of ischemic stroke as defined by the WHO criteria; and 3) the mechanism of stroke was atherosclerosis or small artery disease according to the Trial of ORG 10172 in the Acute Stroke Treatment (TOAST) classification system. Exclusion criteria included the following: 1) any clinically relevant arrhythmia on admission, including atrial fibrillation; 2) any major concurrent illness, including renal failure and malignancies; 3) fever, hypoxia, alterations in consciousness, or any relevant hemodynamic compromise on admission; 4) ingestion of ticlopidine, dipyridamole, or other nonsteroidal anti-inflammatory drugs, or the use of other drugs containing aspirin within 1 week prior to admission; 5) the administration of heparin or low molecular weight heparin within 24 h before enrollment in the study; 6) family or personal history of bleeding disorders; 7) platelet count < 100 × 10^9/L or > 450 × 10^9/L and hemoglobin < 8 g/dL; and 8) other conditions, such as asthma or severe cardiovascular, liver, or renal disease. The study was reviewed and approved by the ethics committee of our hospital. All participants signed an informed consent form.

**Exclusion Criteria**

- History of bleeding disorders
- Platelet count < 40 × 10^9/L or > 600 × 10^9/L
- Hemoglobin < 7 g/dL
- Creatinine > 2 mg/dL
- Age < 18 years
- Pregnancy
- Recent trauma

**Inclusion Criteria**

- Age ≥ 18 years
- Diagnosis of ischemic stroke as defined by the WHO criteria
- Mechanism of stroke was atherosclerosis or small artery disease according to the Trial of ORG 10172 in the Acute Stroke Treatment (TOAST) classification system
- No history of bleeding disorders
- Platelet count between 40 and 600 × 10^9/L
- Hemoglobin ≥ 7 g/dL
- Creatinine ≤ 2 mg/dL
- Age ≥ 18 years
- Not pregnant
- No recent trauma
form before enrollment.

**Treatment**

Aspirin (Bayer Healthcare Company Ltd., Beijing, China) was administered daily from the day of admission (200 mg/day for 14 days and 100 mg/day thereafter).

**Blood and Urine Samples**

Blood and urine samples were collected before aspirin intake and again 7 to 10 days after aspirin intake. When needed, platelet-rich plasma and platelet-poor plasma were obtained from citrated blood samples (0.129 mol/L citrate-containing tubes; Vacutainer, Becton Dickinson, Meylon, France). Functional studies were performed with platelet-rich plasma or whole blood within 2 h of extraction. Urine and platelet-poor plasma samples were stored at −70°C until analysis. For cell counts, biochemical determinations, and genotyping, additional blood samples were obtained in EDTA-containing tubes (Vacutainer; Becton Dickinson).

**Platelet Aggregation Testing**

Platelet aggregation was measured by OPA methods. In brief, whole-blood specimens were centrifuged at 200 g for 10 min to obtain platelet-rich plasma. Platelet-poor plasma was obtained from the remaining specimens by centrifugation at 4,000 g for 10 min. A platelet count was measured on the platelet-rich plasma and was adjusted to between 200 × 10^3/μL and 300 × 10^3/μL with platelet-poor plasma. The baseline optical density (OD) was set with platelet-rich plasma or whole blood within 2 h of extraction. Urine and platelet-poor plasma samples were stored at −70°C until analysis. For cell counts, biochemical determinations, and genotyping, additional blood samples were obtained in EDTA-containing tubes (Vacutainer; Becton Dickinson).

**Urine 11-dTxB₂ Levels**

Pre- and post-aspirin 11-dTxB₂ levels were determined in urine samples using a commercially available ELISA kit (11-Dehydro-thromboxane B₂: EIA Kit; Cayman Chemical, San Antonio, TX, USA) following the manufacturer’s instructions. All urine samples were assayed in duplicate, and the mean intra-assay coefficient of variation (CV, %) was determined.

**Genotyping**

Determination of COX-1 C50T and COX-2 G765C genotypes was performed by a polymerase chain reaction-allelic restriction assay. Genomic DNA was isolated with the AxyPre Blood Genomic DNA Maxiprep Kit (Axogen Biosciences, Union City, CA, USA) using cell lysis and a hemoglobin/protein precipitation technique in combination with selective DNA adsorption to the membrane. Double-distilled water was added to dissolve the isolated DNA, and the concentration was determined using a nucleic acid spectrometer. The DNA was stored at −80°C.

PCR was performed using two pairs of primers that were synthesized by Sangon Biotech Co., Ltd (Shanghai, China). The forward primer for COX-1 C50T was 5′-GGTGCCCGGTGGGGAATTTTC-3′ and the reverse primer was 5′-GAGGGGAAGGA-GGGGTTG-3′. The forward primer for COX-2 G765C was 5′-CCGCTTCTTTGTCATCAG-3′ and the reverse primer was 5′-GGCTGTATATCT- GCTCTATATGC-3′. PCR amplification was performed in a final reaction volume of 50 μL containing 0.1 μg DNA, 12.5 μL Premix Ex Taq, 0.5 μL ROX Reference Dye II, 2 μL of each primer, 8 μL template DNA, and 25 μL double-distilled water. The following protocol was used for PCR: initial denaturation at 94°C for 5 min, followed by 35 cycles of denaturation at 94°C for 45 sec, annealing at 55°C for 45 sec, and 72°C for 45 sec, and final extension at 72°C for 10 min. The amplification product was identified with 2% agarose gel electrophoresis followed by ethidium bromide (EB) staining and observation under ultraviolet light.

The PCR amplification product (5 μL) was sampled and digested at 37°C for 16 h in a final reaction volume of 15 μL, containing 1 μL (1 U) of Smu I (Fermentas, Glen Burnie, MD, USA) for COX-1 C50T and COX-2 G765C, 1 μL of 10× Buffer1 Tango, and 8 μL sterile, deionized, double-distilled water. The digested product was identified using 2% agarose gel electrophoresis at 100 V followed by EB staining and observation under ultraviolet light, and was photographed. PCR products of some gene loci were identified using sequencing with an ABI3730 DNA Analyzer (Perkin-Elmer Applied Biosystems, Carlsbad, CA, USA).

**Statistical Analysis**

SPSS 16.0 (SPSS, Chicago, IL, USA) was used to perform statistical analysis. Results are expressed as the...
AA and ADP (mean percentage of aggregation, 92.3 ± 11.5 and 88.5 ± 13.6, respectively). This AA-induced response was inhibited by more than 80% after aspirin intake for 7 to 10 days (mean percentage of aggregation, 16.2 ± 8.4). Meanwhile, this ADP-induced response was inhibited by more than 40% after aspirin intake for 7 to 10 days (mean percentage of aggregation, 51.7 ± 9.4).

**Urine 11-dTxB2 Levels**

The pre-aspirin urine 11-dTxB2 levels were highly variable among patients (mean, 156.3 ± 101.2; range, 52.24-534.8 ng/mmol creatinine; CV = 74%). After aspirin administration, we still observed significant heterogeneity in the 11-dTxB2 levels (mean, 39.6 ± 21.7; range, 8.2-88.1 ng/mmol creatinine; CV = 45%). In contrast, all patients displayed a high and rather uniform reduction in their 11-dTxB2 levels (mean percentage of reduction, 75.2 ± 14.2; range, 56.2-88.6%; CV = 13%).

**Distribution of COX-1 C50T and COX-2 G765C Polymorphisms in Stroke Patients in the ASR + AR and AS Groups**

Among the 634 stroke patients, 597 were homozygous for the 50C haplotype (94.2%) and 37 were heterozygous for the C50T haplotype (5.8%); however, no patients were homozygous for the 50T haplotype in our sample. In addition, 442 stroke patients were homozygous for the 765G haplotype (69.7%), 156 were heterozygous for the G765C haplotype (24.6%), and 36 were homozygous for the 765C haplotype (5.7%). The genotype and allele frequency distributions of COX-1 C50T and COX-2 G765C in

### Table 1. Comparison between patients with AS and those with ASR or AR

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AS</th>
<th>AR + ASR</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 477</td>
<td></td>
<td>n = 157</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>69.3 ± 10.22</td>
<td>70.2 ± 10.51</td>
<td>0.36</td>
</tr>
<tr>
<td>Gender (female, %)</td>
<td>215 (45.1%)</td>
<td>87 (55.41%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Smoking (n, %)</td>
<td>127 (26.62%)</td>
<td>47 (29.94%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Hypertension (n, %)</td>
<td>325 (66.04%)</td>
<td>108 (68.79%)</td>
<td>0.94</td>
</tr>
<tr>
<td>Diabetes (n, %)</td>
<td>66 (13.85%)</td>
<td>61 (38.85%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.96 ± 4.76</td>
<td>5.01 ± 1.05</td>
<td>0.83</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>1.79 ± 0.91</td>
<td>1.80 ± 0.81</td>
<td>0.88</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.29 ± 0.38</td>
<td>1.28 ± 0.36</td>
<td>0.78</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>2.85 ± 0.75</td>
<td>3.13 ± 0.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Platelet count (×10^9/L)</td>
<td>196.51 ± 17.97</td>
<td>195.05 ± 15.66</td>
<td>0.95</td>
</tr>
</tbody>
</table>

*Statistical significance was based on Student’s t-test and the chi-square (χ²) test. Results are expressed as the mean ± standard deviation (SD). AS, aspirin resistance; ASR, aspirin semi-resistance; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

### Occurrence Rate of AR

According to the platelet aggregation test results, among the 634 stroke patients, AR was detected in 129 patients (20.4%), ASR was detected in 28 patients (4.4%), and aspirin sensitivity (AS) was detected in 477 patients (75.2%). Table 1 compares the parameters between patients with AS and those with ASR + AR. The rate of diabetes and the LDL were higher in patients with ASR + AR than in those with AS (p < 0.05, respectively), and more women were found in the ASR + AR group (p < 0.05).

### Platelet Aggregation

All patients displayed maximal platelet aggregation in the pre-aspirin samples, both in response to AA and ADP (mean percentage of aggregation, 92.3 ± 11.5 and 88.5 ± 13.6, respectively). This AA-induced response was inhibited by more than 80% after aspirin intake for 7 to 10 days (mean percentage of aggregation, 16.2 ± 8.4). Meanwhile, this ADP-induced response was inhibited by more than 40% after aspirin intake for 7 to 10 days (mean percentage of aggregation, 51.7 ± 9.4).

### Urine 11-dTxB2 Levels

The pre-aspirin urine 11-dTxB2 levels were highly variable among patients (mean, 156.3 ± 101.2; range, 52.24-534.8 ng/mmol creatinine; CV = 74%). After aspirin administration, we still observed significant heterogeneity in the 11-dTxB2 levels (mean, 39.6 ± 21.7; range, 8.2-88.1 ng/mmol creatinine; CV = 45%). In contrast, all patients displayed a high and rather uniform reduction in their 11-dTxB2 levels (mean percentage of reduction, 75.2 ± 14.2; range, 56.2-88.6%; CV = 13%).
COX-1 C50T and COX-2 G765C Polymorphisms

uniform reduction in 11-dTxB2 and AA- or ADP-induced platelet aggregation after aspirin intake. The percentage of reduction in platelet aggregation and 11-dTxB2 was not significantly different between the COX-1 C50T and COX-2 G765C genotypes ($p > 0.05$) (Table 4).

**Discussion**

The definition of the AR phenomenon is controversial, and thus the reported range varies broadly, from 5% to 40%, depending on the assay used for identification and the population studied.$^{32-34}$ In our study, the prevalence of AR and ASR by the historical gold standard of OPA was 20.4% and 4.4%, respectively, somewhat lower than that found in other studies.$^{35, 36}$ OPA was performed to evaluate AR, which is a widely available method routinely used to assess platelet function. This traditional test, however, is highly dependent on sample preparation and technical procedures. Eikelboom $^{37}$ et al. considered the variability between different laboratory measurements of platelet activity and estimated that aspirin therapy does not achieve adequate efficacy in 5%-60% of patients with vascular disease. Variance between different measurements of AR has been further confirmed by Lordkipanidze $^{38}$ et al.

Although previous studies$^{18}$ have suggested a correlation between AR and COX-1 C50T and COX-2 G765C polymorphisms, the present study showed

<table>
<thead>
<tr>
<th>Table 2. Comparison of genotype and allele frequency distribution of COX-1 C50T between the ASR+AR and AS groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>ASR + AR</td>
</tr>
<tr>
<td>AS</td>
</tr>
<tr>
<td>p-value*</td>
</tr>
</tbody>
</table>

*Statistical significance was based on the chi-square ($\chi^2$) test.

AS, aspirin resistance; ASR, aspirin semi-resistance.

<table>
<thead>
<tr>
<th>Table 3. Comparison of genotype and allele frequency distribution of COX-2 G765C between the ASR+AR and AS groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>ASR + AR</td>
</tr>
<tr>
<td>AS</td>
</tr>
<tr>
<td>p-value*</td>
</tr>
</tbody>
</table>

*Statistical significance was based on the chi-square ($\chi^2$) test.

AS, aspirin resistance; ASR, aspirin semi-resistance.
that the frequencies of genotype and alleles in COX-1 C50T and COX-2 G765C were not significantly different between the ASR + AR and AS groups. Therefore, these results indicated that there was no association between COX-1 C50T and COX-2 G765C polymorphisms and AR in Chinese stroke patients. The etiology of AR is likely to be multifactorial in origin. Reduced absorption and/or increased metabolism of aspirin may contribute to AR. Frelinger et al.\(^\text{12}\) reported that AR is caused by underdosing and/or noncompliance in approximately 2% of patients; in the remaining patients, AR occurs via COX-1- and COX-2-independent pathways in direct proportion to the degree of baseline platelet activation, and is mediated in part by adenosine diphosphate-induced platelet activation. Therefore, we conclude that alternative pathways involved in platelet activation and not blocked by aspirin (e.g., those involving adenosine 5'-diphosphate (ADP), collagen, epinephrine, and thrombin) may play a role in AR. This theory needs further investigation.

Interestingly, we observed that 200 mg aspirin caused a rather uniform 75% reduction in urine 11-dTxB\(_2\) levels. The platelet aggregation, both in response to AA and ADP was inhibited by more than 80% and 40%, respectively. Moreover, both COX-1 C50T and COX-2 G765C genotypes had similar effects on platelet aggregation and 11-dTxB\(_2\) levels. The percentage of reduction in platelet aggregation and 11-dTxB\(_2\) was not significantly different between the COX-1 C50T or COX-2 G765C genotypes. These results indicated that there was no relationship between the studied polymorphisms and the response to aspirin in Chinese stroke patients.

However, we observed that the COX-1 C50T and COX-2 G765C variants were associated with significantly higher 11-dTxB\(_2\) and AA-induced platelet aggregation (both before and after aspirin intake), and there was a statistical association between 11-dTxB\(_2\) levels and AA-induced platelet aggregation, both pre-aspirin and post-aspirin. These results indicate that the COX-1 C50T and COX-2 G765C variants may increase the activity of COX, lead to too much thromboxane production, initiate the AA cascade, and be involved in the pathogenesis of cerebral infarction\(^{39}\).

In summary, AR is common in Chinese stroke patients and is likely to be multifactorial in origin. Aspirin could efficiently reduce 11-dTxB\(_2\) production

### Table 4. The influence of different polymorphisms on platelet aggregation and on urine 11-dTxB\(_2\) levels before and after aspirin intake

<table>
<thead>
<tr>
<th>Assay</th>
<th>COX-1 C50T</th>
<th>COX-2 G765C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CC (n=597)</td>
<td>GG (n=442)</td>
</tr>
<tr>
<td>11-dTxB(_2) pre-aspirin (ng/mmol creat)</td>
<td>128.3±54.5</td>
<td>142.3±78.8</td>
</tr>
<tr>
<td>11-dTxB(_2) inhibition, %</td>
<td>74.1±10.8</td>
<td>74.9±12.7</td>
</tr>
<tr>
<td>AA-induced platelet aggregation pre-aspirin, %</td>
<td>88.6±10.2</td>
<td>90.6±10.8</td>
</tr>
<tr>
<td>AA-induced platelet aggregation post-aspirin, %</td>
<td>14.6±7.5</td>
<td>15.6±8.6</td>
</tr>
<tr>
<td>ADP-induced platelet aggregation pre-aspirin, %</td>
<td>80.2±11.6</td>
<td>81.3±9.5</td>
</tr>
<tr>
<td>ADP-induced platelet aggregation post-aspirin, %</td>
<td>50.9±8.4</td>
<td>51.9±8.7</td>
</tr>
<tr>
<td>ADP-induced platelet aggregation inhibition, %</td>
<td>42.7±8.7</td>
<td>41.5±7.6</td>
</tr>
</tbody>
</table>

*Statistical significance was based on Student's t-test. Results are expressed as the mean ± standard deviation (SD). AA, arachidonic acid; ADP, adenosine 5'-diphosphate; COX, cyclooxygenase; Creat, creatine; 11-dTxB\(_2\), 11-dehydro-thromboxane B\(_2\).*
by approximately 75%, AA-induced platelet aggregation by more than 80%, and ADP-induced platelet aggregation by more than 40%. Thus, the 11-dTxB2 level and AA-induced platelet aggregation might be influenced by genetic characteristics; however, the present study indicated that there was no association between COX-1 C50T or COX-2 G765C polymorphisms and AR or response to aspirin in Chinese stroke patients.

**Acknowledgments**

This study was supported by the Scientific Research Foundation of the Zhejiang Provincial Health Department (2007A178). The authors thank Medjaden Bioscience Limited for assisting in the preparation of this manuscript.

**Conflict of Interest**

None.

**References**


2) Antithrombotic Trialists' Collaboration: Collaborative overview of randomised trials of antiplatelet therapy - II: maintenance of vascular graft or arterial patency by antiplatelet therapy. BMJ, 1994; 308: 159-168


30) Michelson AD, Frelinger AL, III, Furman MI: Current options in platelet function testing. Am J Cardiol, 2006; 98: S4, 10


39) Rink C, Khanna S: Significance of brain tissue oxygenation and the arachidonic acid cascade in stroke. Antioxid Redox Signal, 2011; 14: 1889-1903