Clopidogrel Versus Dipyridamole in Addition to Aspirin in Reducing Embolization Detected With Ambulatory Transcranial Doppler
A Randomized Trial

Alice King, BSc; Philip M.W. Bath, FRCP; Hugh S. Markus, FRCP

Background and Purpose—After stroke and transient ischemic attack there is a high early risk of recurrent stroke, particularly in large artery disease. It has been suggested more intensive antiplatelet regimens are required, but trial data are lacking. Treatment efficacy can be evaluated using transcranial Doppler detection of embolic signals. Ambulatory transcranial Doppler has recently been developed; prolonged recording may reduce subject numbers required to determine therapeutic efficacy. In a randomized trial (ISRCTN68019845) with blinded end point evaluation, we determined whether treatment with dipyridamole or clopidogrel, in addition to aspirin, was more effective at reducing embolization.

Methods—Consecutive patients with recent symptomatic carotid stenosis were recruited. Ambulatory transcranial Doppler and platelet aggregometry were performed at baseline and 48 hours. Patients, all on aspirin, were randomized to dipyridamole or clopidogrel. Recordings were analyzed offline masked to subject identity.

Results—Sixty patients were recruited, 30 in each arm. The primary end point of change in embolic signal frequency did not differ between groups ($P=0.36$). In patients with embolic signals at baseline, there was no difference in reduction in embolic signal frequency: dipyridamole (75.5; SD 17.7%) versus clopidogrel (77.5; SD 20.5%; $P=0.77$). Baseline platelet aggregation was not different between regimens, but at 48 hours, adenosine 5’-diphosphate aggregation rate (but not collagen) was lower with clopidogrel ($P<0.001$).

Conclusions—Both dipyridamole and clopidogrel reduced embolization to a similar extent. Embolic signals are strong predictors of future stroke rate in this patient group. Our results suggest these 2 treatment regimens have similar efficacy in early secondary prevention of stroke, although this now needs testing in large Phase III trials. (Stroke. 2011;42:650-655.)

Key Words: antiplatelet ■ carotid stenosis ■ embolism ■ prevention ■ stroke ■ ultrasound

There is a high risk of early recurrent stroke after minor stroke and transient ischemic attack (TIA), and patients with large artery stenosis are at particularly high risk.1 The mechanism of recurrence is believed to be primarily embolic, and frequent asymptomatic embolic signals (ESs) have been demonstrated using transcranial Doppler ultrasound (TCD).2–4 Antiplatelet agents reduce the risk of recurrent stroke, but most data in stroke prevention are from long-term secondary prevention trials. In this setting, therapy with aspirin and dipyridamole was more effective than aspirin alone5 and equivalent to clopidogrel alone.6 Clopidogrel and aspirin showed no benefit over clopidogrel alone, primarily due to an increased risk of hemorrhagic side effects with the clopidogrel and aspirin combination.7 However, optimal antiplatelet regimes for early secondary prevention may differ from those for long-term secondary prevention. This has been demonstrated for acute coronary artery disease in which more intensive regimes are used for a short period of a few months after the acute event. Due to the high early risk of recurrent stroke in the acute period after TIA and minor stroke, more intensive antiplatelet regimes given over a short period may be beneficial even if associated with increased hemorrhagic side effect risks.

There are no data from Phase III trials examining this issue. Such studies with an end point of clinical stroke require large sample sizes of thousands. One way of screening therapeutic combinations before such studies is to use TCD emboli detection. This noninvasive technique is highly sensitive and specific for detection of circulating emboli.8,9 Such ESs are frequent in the acute setting in patients with large artery disease allowing treatment effects to be evaluated in smaller sample sizes. Prospective studies have shown that ESs are an independent predictor of future stroke in symptomatic carotid stenosis.4 A number of studies have used this technique to...
evaluate antiplatelet therapy in patients with symptomatic large artery disease. The Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic carotid Stenosis (CARESS) trial recorded for 1 hour before and 1 week after treatment with either aspirin monotherapy or aspirin and clopidogrel. Dual therapy was more effective in abolishing emboli and resulted in a 66% reduction in ES frequency. The clopidogrel plus aspirin for infarction reduction in acute stroke or transient ischemic attack patients with large artery stenosis and microembolic signals (CLAIR) trial demonstrated similar results for intracranial stenosis.

A limitation of conventional TCD is that a nonportable system is used and therefore recording duration is limited. Recently an ambulatory TCD apparatus has been developed that allows recording for up to 8 hours. This uses a novel signal correction algorithm, which relocates the vessel signal when it is lost allowing automated long-term recordings. Early studies have demonstrated the technique is more sensitive to detecting embolization in patients with carotid artery stenosis. By performing longer duration recordings, it may be possible to reduce sample sizes further.

The AMBulatory Dual Anti-Platelet (AMBDAQ) study was designed to determine whether dual antiplatelet therapy with aspirin and clopidogrel was more effective than therapy with aspirin and dipyridamole in preventing embolization in patients with acute symptomatic carotid stenosis. The primary end point was ES frequency measured using ambulatory TCD.

**Methods**

**Study Design**

AMBDAQ was a randomized study with blinded end-point evaluation. Subjects with recently symptomatic carotid stenosis were randomized to dipyridamole or clopidogrel. All were on aspirin. Ambulatory TCD recordings were performed at baseline and 48 hours. The primary end point was the number of ESs. Data were also collected on platelet aggregation and recurrent TIA/stroke. The study was registered as a clinical trial with ISRCTN 68019845; EudraCT 2007-002681-34.

**Subjects**

Consecutive patients presenting to an acute stroke unit, or the rapid access TIA clinic in the same hospital, were screened for eligibility. Inclusion criteria included carotid stenosis ≥50% with symptoms of TIA or stroke within the last month and age >18 years. Exclusion criteria were taking antithrombotic medication other than aspirin and/or low-dose prophylactic subcutaneous heparin; prosthetic heart valves; contraindication to clopidogrel or dipyridamole; carotid endarterectomy planned within the next 48 hours; and pregnant and lactating women. The local ethics committee approved the study and all patients gave signed informed consent.

Baseline MRI or CT imaging was performed in all cases. Carotid stenosis ≥50% was established by color-coded carotid duplex ultrasound.

**Treatment Protocol**

If patients were not already taking aspirin, they were initially treated with a 300-mg aspirin loading dose and then 75 mg once a day. Immediately after the 6-hour baseline recording, patients were randomized to either 200 mg dipyridamole MR twice a day or clopidogrel with a 300-mg loading dose followed by 75 mg once a day. It was not possible to obtain placebo for the dipyridamole MR tables and therefore treatment was open. However, analysis of the TCD data, and therefore the primary end point, was masked to patient identity and time of recording. Patients remained on random-ized treatment for 1 month and were followed up for recurrent stroke and TIA for 1 month or until endarterectomy was performed.

**TCD Recordings**

The ambulatory TCD apparatus has previously been described. It consists of the Doppler unit, a 2-MHz transducer probe mounted on a glassless spectacle frame, which acts as a fixation device, and a separate lithium ion battery. The quadrature Doppler signal is recorded and stored on a flash disk. This is capable of storing up to 8 hours of data. For this study, 6-hour recordings were performed; a pilot study found ESs were detected in most patients with symptomatic carotid stenosis if recordings were continued for this duration.

The middle cerebral artery was initially insonated through the transtemporal window using a standard TCD system (Pioneer/Nicolet EME TC4040/Companion III). If an adequate window could be detected, the ambulatory TCD system was set up using a portable PC. An axial sample volume of 5.2 or 10.1 mm was used depending on the transtemporal window. The unit was then placed in a jacket/dressing gown worn by the patient. The software monitors the Doppler signal quality and has an autosave module that attempts to restore the vessel insonation during recording when the signal drops below a preset level. In addition, the researcher returned hourly to monitor signal quality. After recording was finished, the quadrature signal from the flash disk was transferred to the PC and subsequently stored on CD for subsequent analysis.

**TCD Data Analysis**

Data were double-blinded before analysis. The 12 hours of raw quadrature signal from each patient were pooled with other patients and then randomly split into 1-hour files blinded to hour, recording, patient, and treatment. Blinded data were played from a laptop through the conventional TCD machine with 128FFT (PRF 4629-Hz sweep speed 5.1 seconds). ES analysis was performed by a trained observer (A.K.) and potential ESs then reviewed by an experienced observer (H.S.M.). ESs were identified as short-duration, high-intensity unidirectional signals accompanied by a characteristic chirping or clicking sound using International Consensus Criteria and a threshold of 7 dB.

**Platelet Aggregometry**

The turbidimetry method of Born and Cross was used to determine platelet aggregation of platelet-rich plasma with collagen (at 5 μL, 25 μL, and 50 μL) and adenosine 5'-diphosphate (ADP) agonists (5 μL [2\times10^{-5}], 50 μL [2\times10^{-5}], 50 μL [4\times10^{-5}], and 50 μL [2\times10^{-9}]). A Platelet Aggregation Profiler (Model PAP-4; Bio Data Corporation, Alpha Laboratories) was used to generate aggregation intensity graphs of the percent light transmission from platelet-rich plasma with agonist using platelet-poor plasma as control. All the graphs were analyzed and standardized by the same 2 observers (A.K., P.M.W.B.).

**Sample Size Calculations**

These were based on data from a pilot study using ambulatory TCD monitoring, in which patients on aspirin and dipyridamole had a mean (SD) ES count of 22 (8) during a 6-hour recording. A sample size of 60, 30 in each arm, was calculated to detect a difference in the primary end point of 22% with power 80% and $P=0.05$.

**Statistical Methods**

The primary outcome measure was the change in ES count between baseline and 48 hours between the 2 treatment groups. An analysis was also performed limited to subjects with ES at baseline. The treatment groups were compared using Fisher exact test (frequency data) or Mann Whitney $U$ and $t$ tests (ordinal or continuous data) using SPSS software Version 16.0 (SPSS Inc, Chicago, IL).
Results

Study Population

Sixty patients were randomized, 30 to clopidogrel and 30 to dipyridamole. An additional 9 consented patients did not have an adequate temporal window for good-quality TCD recordings. Two randomized patients withdrew consent before recording, 2 patients’ medical condition deteriorated and did have a second recording, and in 1 subject, further MRI brain imaging revealed that the stroke was in the posterior, not anterior, circulation. Baseline and follow-up recordings were therefore available for 55 patients, 28 dipyridamole and 27 clopidogrel.

Demographic and Baseline Characteristics

The demographic and baseline characteristics are summarized in Table 1. The qualifying event was TIA (including amaurosis fugax) in 17 (28.3%) and stroke in 43 (71.7%). A total of 71.7% of patients had symptoms within the previous week. The degree of carotid stenosis was 50% to 69% in 13 (21.7%), 70% to 85% in 23 (38.3%), and 85% to 99% in 24 (40.0%). There were no significant differences in demographics between the 2 treatment groups. Hypertension and hypercholesterolemia were treated by the attending physician according to clinical guidelines. In the AD arm, 19 of 30 patients presented with hypercholesterolemia; 6 of these were untreated at presentation. Twenty-two of 30 patients in the AC arm presented with hypercholesterolemia; 8 of these were untreated at presentation. All patients with untreated hypercholesterolemia were treated with statins at 48-hour follow-up. In the AD arm, 28 of 30 patients presented with hypertension; 3 of these were untreated at presentation. Twenty-four of 30 patients in the AC arm presented with hypertension; 4 of these were untreated at presentation. All patients with untreated hypertension were treated at 48-hour follow-up.

Emboli Recordings

ES characteristics before and after treatment are summarized in Table 2. The baseline rate of ES/hour was higher in those receiving dipyridamole: mean±SD rate dipyridamole 4.55±6.09 (median, 2) and clopidogrel 1.48±2.81 (median,
Thirty-six (65.5%) of patients were ES-positive at baseline: dipyridamole 78.6% and clopidogrel 51.0% \((P=0.048)\). There were no other significant differences between baseline characteristics of the 2 groups.

The primary end point of the change in ES number did not differ between treatment groups \((P=0.36)\). An analysis was performed in those patients with ES at baseline to compare the change in ES frequency in the 2 groups. Twelve of 55 (21.8%) patients were ES-negative at both time points, dipyridamole 4 of 28 and clopidogrel 8 of 27, and were excluded from this analysis. There was no difference in reduction in ES frequency: dipyridamole \((75.5\%\pm17.7\%)\) and clopidogrel \((77.5\%\pm20.5\%\); \(P=0.77)\).

There was no difference in whether a patient became ES-negative: dipyridamole 11 of 24 and clopidogrel 8 of 19 \((P=0.81)\). Twelve patients (6 in each arm) who were ES-negative at baseline became ES-positive at 48 hours.

The mean intensity of ES at baseline was 11.06\pm3.61 dB. The mean baseline intensity of ES with dipyridamole \((10.8\pm3.4\ dB)\) was lower than with clopidogrel \((11.8\pm4.0\ dB; \(P=0.011\); Table 3). There was no difference between the 2 arms at 48 hours: dipyridamole 10.2\pm3.0 dB and clopidogrel 10.6\pm3.0 dB \((P=0.43)\). The change in mean ES intensity in those 18 patients who were consistently ES-positive was not different between the 2 groups: dipyridamole \(-0.08\pm4.19\ dB\) and clopidogrel \(1.00\pm3.29\ dB\) \((P=0.59)\). The percentage change in intensity was not different between the 2 groups: dipyridamole \(-1.41\%\pm40.6\%\) and clopidogrel \(5.02\%\pm28.5\%\) \((P=0.73)\).

### Platelet Studies

There was no difference in baseline aggregation rate between the clopidogrel and dipyridamole groups with ADP \((P=0.83)\) or 50 \(\mu\)L collagen \((P=0.32\); Table 4). At 48 hours, the aggregation rate to ADP was lower with clopidogrel than dipyridamole \((P<0.001)\). In contrast, at 48 hours, there was difference in aggregation to collagen \((50\ \mu\)L): dipyridamole 48.4\pm38.8 and clopidogrel 40.6\pm22.5 \((P=0.06)\). There was a correlation between ES number at baseline and ADP aggregation rate at baseline \((P=0.005)\) but not after treatment. There was no correlation between change in ES and change in ADP aggregation rate \((P=0.37)\).

### Clinical Outcome Events and Major Side Effects

There was no difference in the length of follow-up between the 2 treatment arms: mean\pmSD with AC 17.8\pm10.5 versus AD 13.4\pm10.7 \((P=0.131)\). In addition, there was no difference between the 2 groups in the number of carotid interventions with 15 in the AC arm versus 19 in the AD arm \((P=0.412)\). Four patients had ipsilateral TIA during follow-up, 1 in the clopidogrel arm and 3 on dipyridamole. There were no recurrent strokes. One patient on dipyridamole had a gastrointestinal bleed requiring 4 U of blood transfusion. There we no major, life-threatening, or intracerebral bleeding events in the clopidogrel arm.

### Discussion

This study suggests that in patients with acute symptomatic large artery disease, both dipyridamole and clopidogrel reduce embolization to a similar extent when added to aspirin. In patients with ES at baseline, both resulted in an approximately 75% reduction in ES frequency, which is similar to the 65% reduction seen in the CARESS trial10 when clopidogrel was added to aspirin. In contrast, over the same time period in CARESS, ES frequency in the aspirin alone arm was reduced by only 18%. ESs have been shown to be a strong independent predictor of future stroke rate in patients with symptomatic large artery disease.4 Therefore, our results suggest these 2 treatment regimens will have similar efficacy in early secondary prevention of large artery stroke, although to ensure the reduction in ES can be translated into clinical events, it now needs testing in a large Phase III trial with the end point of stroke.

A number of current or planned large Phase III trials are examining the use of more intensive treatment regimens in

### Table 3. ES Intensities in the 2 Treatment Arms

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intensity, dB</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td><strong>Total ES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>10.8</td>
<td>3.44</td>
<td>10</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>11.8</td>
<td>4</td>
<td>11.5</td>
</tr>
<tr>
<td><strong>ES-positive patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>9.92</td>
<td>1.62</td>
<td>10</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>10.3</td>
<td>2.73</td>
<td>11</td>
</tr>
</tbody>
</table>

### Table 4. Platelet Aggregation With ADP and Collagen Agonists in the 2 Treatment Arms

<table>
<thead>
<tr>
<th>Rate of Platelet Aggregation</th>
<th>Pre</th>
<th>Post</th>
<th>(P)</th>
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</thead>
<tbody>
<tr>
<td>Collagen 25 (\mu)L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>21.7 (34.1)</td>
<td>17.6 (23.0)</td>
<td>21.8 (30.7)</td>
</tr>
<tr>
<td>Collagen 50 (\mu)L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>48.4 (23.1)</td>
<td>48.4 (38.8)</td>
<td>52.6 (26.9)</td>
</tr>
<tr>
<td>ADP 50 (\mu)L (2\times10^{-5})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>53.8 (17.4)</td>
<td>49.4 (16.9)</td>
<td>54.1 (20.6)</td>
</tr>
<tr>
<td>ADP 50 (\mu)L (4\times10^{-5})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>81.8 (18.1)</td>
<td>84.5 (22.9)</td>
<td>79.8 (15.5)</td>
</tr>
<tr>
<td>ADP 50 (\mu)L (2\times10^{-6})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>94.7 (13.1)</td>
<td>101.7 (13.0) *</td>
<td>97.2 (19.0)</td>
</tr>
</tbody>
</table>

*\(P<0.0001\).*
the early secondary prevention of stroke. Our results have important implications for treatment regimens in this context. The use of clopidogrel with aspirin in acute cardiac ischemia, combined with the results of Phase II studies in early prevention after stroke and TIA, have suggested that clopidogrel and aspirin may be the favored option in early secondary prevention after stroke and TIA. Our results suggest that dipyridamole, when combined with aspirin, has a similar effect on reducing embolization.

Previous randomized trials using TCD emboli detection have shown that the combination of aspirin and clopidogrel is more effective than aspirin alone at reducing embolization in recently symptomatic patients with both extracranial large artery disease and intracranial large artery disease. The combination of aspirin and dipyridamole has not been previously compared with aspirin and clopidogrel in this setting. However, consistent with our results, a single study comparing aspirin and dipyridamole with aspirin and clopidogrel on rates of embolization postcardiotomy endarterectomy could not detect a difference between the regimens.

In contrast to the lack of difference between the 2 treatment regimens on embolization, we found expected differences in platelet aggregation. Platelet aggregation studies, measuring ex vivo platelet aggregation, showed clopidogrel is more effective than dipyridamole at inhibition of ADP (but not collagen) -mediated platelet aggregation. Clopidogrel is a prodrug that selectively and irreversibly inhibits the platelet ADP P2Y12 receptor and therefore inhibits ADP-mediated aggregation. In contrast, the mechanism of dipyridamole in stroke prevention is less clear. Dipyridamole has multiple actions, including inhibition of uptake of adenosine by red cells and of adenosine deaminase, which both raise extracellular adenosine levels, inhibition of phosphodiesterases raising platelet cyclic guanosine monophosphate and adenosine 3',5'-cyclic monophosphate levels, and reduction of circulating von Willebrand factor levels. Therefore, dipyridamole stimulates several endogenous platelet antagonists (adenosine, guanosine 3’,5’-cyclic monophosphate, adenosine 3’,5’-cyclic monophosphate). These mechanisms of action explain the platelet results seen in the present trial, namely that clopidogrel was superior at inhibiting ADP-invoked platelet aggregation, whereas the 2 pairs of agents did not differ in their response on collagen-induced aggregation. It has been suggested that clopidogrel is probably a more potent antiplatelet agent than dipyridamole as measured by overall platelet activity ex vivo, for example, the effect on cutaneous bleeding time. This, combined with the equivalence in reducing ES in our study, suggests that nonplatelet effects of dipyridamole such as reducing white cell and endothelial activity (reduction of von Willebrand factor) may also be important in reducing emboli.

This is the first study to use ambulatory TCD to compare therapies. Ambulatory recordings have shown that ESs show temporal clustering. This means that short recordings of 30 to 60 minutes may not provide a true representation of the embolic load. The ambulatory apparatus is small and portable and allows continuous monitoring to be performed at the time the patient continues with daily activities. We were able to obtain good-quality recordings aided by an autosearch and correction device, which monitors and automatically corrects a poor-quality TCD signal.

Despite the randomized study design, we observed an imbalance in baseline ES frequency. Previous studies using ambulatory TCD in carotid stenosis found ES in almost all patients. Our power calculations were based on this assumption. However, in this study, in a number of patients, no ESs were detected at baseline. Therefore, we also performed an analysis in subjects who had ES at baseline to allow comparison with other studies such as CARESS and CLAIR, which only recruited patients with ES present on a screening baseline recording. This analysis showed no difference in the reduction of ES frequency between the 2 regimens (75.5% versus 77.5%) confirming a similar treatment effect with the 2 regimens. This reduction was of a similar magnitude to that seen in the clopidogrel and aspirin arms of the CARESS and CLAIR studies. With this difference in treatment effect, a sample size of 1280 in each arm would be required to show any difference between groups suggesting we have not missed a significant treatment difference. Consistent with these results, there was no difference in the change in mean ES intensity between the 2 treatment arms.

In summary, we found both aspirin and clopidogrel and aspirin and dipyridamole reduced embolization to a similar extent. Our results suggest these 2 treatment regimens have similar efficacy in early secondary prevention of large artery stroke, although this now needs testing in large Phase III trials.

Acknowledgments

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Source of Funding

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Disclosures

None.

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Abstract

应用动态经颅多普勒超声监测阿司匹林联合双嘧达莫或氯吡格雷对减少栓子的作用：一项随机对照试验

Clopidogrel Versus Dipyridamole in Addition to Aspirin in Reducing Embolization Detected With Ambulatory Transcranial Doppler

A Randomized Trial

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背景和目的: 近年来,随着动态经颅多普勒超声的发展,使得研究的监测时间得以不断延长,从而减少了能够判断抗血小板治疗疗效所需样本例数。我们设计了一项盲法评估终点事件的随机试验,旨在评估对减少栓子方面阿司匹林联合双嘧达莫或氯吡格雷,哪种治疗更有效。

方法: 连续纳入了近期发生症状性颈动脉狭窄的患者。分别在基线和入组后 48 小行动态经颅多普勒超声检查和血小板聚集率的测定。所有入组患者均在服用阿司匹林的基础上,再随机给予双嘧达莫或氯吡格雷。经颅多普勒超声检测的记录在脱机后进行盲法分析。

结果: 本研究共纳入了 60 例患者,每组各 30 例。两组间主要终点事件栓子信号的频率无明显差别 (P=0.36)。在基线检测存在栓子信号的患者中,两组间栓子信号减少的频率无明显差别: 双嘧达莫(75.5, 标准差 17.7%), 氯吡格雷 (77.5, 标准差 20.5%, P=0.77)。两种治疗组基线检测的血小板聚集率没有差别,但氯吡格雷组在治疗 48 小时检测的5'-二磷酸腺苷诱导的血小板聚集率(非胶原蛋白诱导的聚集率)更低(P<0.001)。

结论: 双嘧达莫和氯吡格雷在减少栓子方面作用相当。栓子信号是近期症状性颈动脉狭窄患者再发卒中的强有力的预测因子。本研究结果表明,两种抗血小板治疗方案对卒中患者早期的二级预防疗效相近,但尚需大样本的 III 期临床试验进一步验证。

关键词: 抗血小板制剂, 颈动脉狭窄, 栓塞, 预防, 卒中, 超声

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