Efficacy of Antiplatelet Therapy in Secondary Prevention Following Lacunar Stroke
Pooled Analysis of Randomized Trials

Chun Shing Kwok, MBBS*; Ashkan Shoamanesh, MD*; Hannah Charlotte Copley, MBChir; Phyo Kyaw Myint, MD; Yoon K. Loke, MD; Oscar R. Benavente, MD

Background and Purpose—Lacunar stroke accounts for ≈25% of ischemic stroke, but optimal antiplatelet regimen to prevent stroke recurrence remains unclear. We aimed to evaluate the efficacy of antiplatelet agents in secondary stroke prevention after a lacunar stroke.

Methods—We searched MEDLINE, Embase, and the Cochrane library for randomized controlled trials that reported risk of recurrent stroke or death with antiplatelet therapy in patients with lacunar stroke. We used random effects meta-analysis and evaluated heterogeneity with $I^2$.

Results—We included 17 trials with 42234 participants (mean age 64.4 years, 65% male) and follow up ranging from 4 weeks to 3.5 years. Compared with placebo, any single antiplatelet agent was associated with a significant reduction in recurrence of any stroke (risk ratio [RR] 0.77, 0.62–0.97, 2 studies) and ischemic stroke (RR 0.48, 0.30–0.78, 2 studies), but not for the composite outcome of any stroke, myocardial infarction, or death (RR 0.89, 0.75–1.05, 2 studies). When other antiplatelet agents (ticlodipine, cilostazol, and dipyridamole) were compared with aspirin, there was no consistent reduction in stroke recurrence (RR 0.91, 0.75–1.10, 3 studies). Dual antiplatelet therapy did not confer clear benefit over monotherapy (any stroke RR 0.83, 0.68–1.00, 3 studies; ischemic stroke RR 0.80, 0.62–1.02, 3 studies; composite outcome RR 0.90, 0.80–1.02, 3 studies).

Conclusions—Our results suggest that any of the single antiplatelet agents compared with placebo in the included trials is adequate for secondary stroke prevention after lacunar stroke. Dual antiplatelet therapy should not be used for long-term stroke prevention in this stroke subtype. (Stroke. 2015;46:1014-1023. DOI: 10.1161/STROKEAHA.114.008422.)

Key Words: antiplatelet agent ■ aspirin ■ lacunar stroke ■ mortality ■ stroke

Lacunar stroke or small vessel ischemic stroke represents ≈25% of all ischemic strokes.1 Although the functional prognosis of single episode of lacunar stroke is generally good, recurrence is not uncommon.2,3 The underlying pathogenesis is believed to be cerebral small vessel disease in the form of arteriolosclerosis of deep penetrating arteries. This mechanism is thought to be the most frequent cause of vascular cognitive impairment.4 Therefore, preventing progression of cerebral small vessel disease is extremely important. Current therapeutic options are, however, limited, and the comparative efficacy of available antiplatelet agents remains uncertain.

Until recently, all of the evidence supporting the use of antiplatelet agents as secondary prevention after lacunar stroke came from subgroup analysis from randomized controlled trials designed to assess the efficacy of these agents in all ischemic stroke subtypes. However, these subgroups generally have small sample sizes. The Secondary Prevention of Small Subcortical Strokes (SPS3) trial was the first to address the question at hand in a randomized controlled trial with a large (n=3020) well-defined population of magnetic resonance imaging-confirmed lacunar stroke, comparing aspirin monotherapy to dual antiplatelet therapy (DAPT) with aspirin and clopidogrel. This trial was, however, terminated early because of lack of efficacy and increased mortality among participants randomized to DAPT.3 In view of the paucity of data, differing vascular pathology underlying lacunar stroke, and the recent SPS3 trial results, the utility of antiplatelet monotherapy has been questioned in this population.5

References


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1014
The primary aim of this study is to evaluate the evidence for antiplatelet therapy as secondary stroke prevention in patients with lacunar stroke. We performed a systematic review and pooled meta-analysis of randomized controlled trials.

Methods

Eligibility Criteria
We included randomized controlled trials that evaluated the use of antiplatelet therapy as secondary prevention after acute stroke. Among these trials, only those which reported outcomes separate for lacunar stroke were included. For certain trials, additional data were obtained via personal correspondence from the authors.

Outcomes
Primary outcome of interest was any stroke recurrence (ischemic or hemorrhagic). Secondary outcomes of interest were (1) recurrent ischemic stroke and (2) composite of any stroke, myocardial infarction, and death. We accepted composite outcomes as specified by trial investigators so long as strokes and deaths were captured in the composite end point.

Search Strategy
MEDLINE and Embase searches with no date limitations or language restrictions were conducted in December 2013 using the broad search terms as shown in Supplementary Data I in the online-only Data Supplement. Furthermore, we reviewed the bibliography of included trials, Cochrane Reviews, and the most recent review by the antithrombotic trialist collaboration for additional studies.

Study Selection and Data Extraction
Two reviewers (C.S. Kwok and A. Shoamanesh) considered all titles and abstracts retrieved from the search for potential eligibility. Where there was disagreement, study inclusion or exclusion was agreed upon by consensus with the other authors. Two reviewers (C.S. Kwok and H.C. Copley) independently extracted information on study design, participant characteristics, types of interventions, outcomes, results, and risk of bias onto a spreadsheet. The 2 extractions were compared and differences were resolved by consensus. Where there was uncertainty, journal authors were contacted for clarification.

Assessment of Risk of Bias
Two reviewers (C.S. Kwok and H.C. Copley) independently assessed the individual studies' risks of bias in accordance with the recommendations of the Cochrane Collaboration, which included baseline differences, blinding, lost to follow up, exposure and outcome ascertainment, and conflicts of interest. We planned to assess publication bias using funnel plots if there were >10 studies included in the meta-analysis, and there was no significant statistical heterogeneity.

Statistical Analysis
Fixed effects meta-analysis of dichotomous events was performed using RevMan 5.3 (Nordic Cochrane Center, Copenhagen, Denmark) to estimate pooled risk ratios (RRs). Statistical heterogeneity was assessed using I² statistic, with values of 30% to 60% representing a moderate level of heterogeneity.

Results
We included a total of 17 randomized trials that included 42234 participants with lacunar stroke treated with antiplatelet therapy (mono or dual) or placebo. We did not include 4 trials (IST [International Stroke Trial], PERFORM [Prevention of Cerebrovascular and Cardiovascular Events of Ischaemic Origin With Terutroban in Patients With a History of Ischaemic Stroke or Transient Ischaemic Attack], S-ACCESS [Sarpogrelate-Aspirin Comparative Clinical Study for Efficacy and Safety in Secondary Prevention of Cerebral Infarction], and TRA 2P–TIMI 50 [Trial to Assess the Effects of Vorapaxar (SCH 530348; MK-5348) in Preventing Heart Attack and Stroke in Patients With Atherosclerosis]) in our pooled analysis. IST’s composite outcome of death and dependency did not match our criteria, and TRA 2P–TIMI50 did not provide number of events. Novel less-established agents were excluded from the analysis in an attempt to reduce the level heterogeneity between the different agents’ mechanisms of action, but their results are reported separately (Sarpogrelate [S-ACCESS] and Terutroban [PERFORM] trials). The process of study selection is shown in Figure I in the online-only Data Supplement. Table shows the summary characteristics of the study populations of included studies. Of these, 14 were double-blind randomized trials. The mean age was 64 years, and 65% of participants were male across 16 studies; one study (IST) reported 61% of participants >70 years of age and one study (CSPS2 [Cilostazol Stroke Prevention Study]) did not report the number of male and female participants. All the studies included participants with suspected ischemic stroke or transient ischemic attack, and neuroimaging was performed to confirm diagnosis in all but one study (CATS [Canadian American Ticlopidine Study]), which relied on neurological evaluation for diagnosis. Only 6 of the studies formally defined lacunar stroke using criteria, such as the TOAST Criteria, modified Fisher criteria, or other predefined criteria, and only 1 used magnetic resonance imaging to verify the diagnosis of lacunar stroke.

Table I in the online-only Data Supplement shows the quality assessment of the studies included. Sequence generation of randomization was described in 10 studies and allocation concealment was described in 13 studies. Fourteen trials were double blind trials, and some means to assess treatment exposure or compliance was considered in 8 trials. All but one study had some form of outcome ascertainment, and 4 studies had unclear participant lost to follow-up.

The treatments received, crude events rate, outcomes, and results are shown in Table II in the online-only Data Supplement. The follow-up of the studies ranged from 4 weeks to 3.5 years.

Any Single Antiplatelet Agent Versus Placebo
Overall, patients on antiplatelet monotherapy had significantly lower rates of any stroke as compared with placebo (RR 0.77, 0.62–0.97, 2 trials, CATS, ESPS-2 [European Stroke Prevention Study]). There was a significant reduction in ischemic stroke (RR 0.48, 0.30–0.78, 2 trials, AICLA [Accidents Ischémiques Cérébraux Lies a L’Atherosclerose], Matsumoto14) but not in the composite outcome (RR 0.89, 0.75–1.05, 2 trials CAST [Chinese Acute Stroke Trial], ESPS-2). Results of these analyses are shown in Figure 1A–1C.
### Table: Study Design and Participant Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Midyear of Study</th>
<th>Years of Study</th>
<th>Design; Country</th>
<th>No. of Patients With Lacunar Stroke (%)</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>AICLA</td>
<td>1976</td>
<td>Oct 1975 to Dec 1978</td>
<td>Double blind, multicenter randomized trial; 4 centers in France.</td>
<td>98 (16%)</td>
<td>ASA/ASA+dipyridamole/placebo</td>
</tr>
<tr>
<td>CATS</td>
<td>Before 1989</td>
<td>Before 1989</td>
<td>Double blind, multicenter randomized controlled trial; 25 centers in Canada.</td>
<td>274 (26%)</td>
<td>Ticlopidine/placebo</td>
</tr>
<tr>
<td>ESPS-2</td>
<td>1992</td>
<td>Feb 1989 to Mar 1995</td>
<td>Double blind, multicenter randomized controlled trial; 16 centers, 6 countries.</td>
<td>2600 (59%)</td>
<td>ASA+dipyridamole/ASA+dipyridamole/placebo</td>
</tr>
<tr>
<td>IST</td>
<td>1993</td>
<td>Jan 1991 to May 1996</td>
<td>Open randomized trial; international 467 hospital from 36 countries.</td>
<td>4616 (24%)</td>
<td>ASA/control</td>
</tr>
<tr>
<td>Matsumoto 2005</td>
<td>1994</td>
<td>Apr 1992 to Mar 1996</td>
<td>Double blind randomized control trial; 183 institutes in Japan.</td>
<td>794 (74%)</td>
<td>Cilostazol/placebo</td>
</tr>
<tr>
<td>CAST</td>
<td>1995</td>
<td>Nov 1993 to Mar 1997</td>
<td>Multicenter randomized controlled trial; 413 hospitals in China.</td>
<td>6263 (30%)</td>
<td>ASA/placebo</td>
</tr>
<tr>
<td>Uchiyama 2009</td>
<td>1999</td>
<td>July 1996 to Nov 2003</td>
<td>Double blind, multicenter randomized trial; Japan.</td>
<td>1341 (73%)</td>
<td>Clopidogrel/ticlopidine</td>
</tr>
<tr>
<td>MATCH</td>
<td>2001</td>
<td>Dec 2000 to Apr 2002</td>
<td>Double blind, multicenter randomized controlled trial; International 507 centers in 28 countries.</td>
<td>3148 (53%)</td>
<td>ASA+clopidogrel/clopidogrel</td>
</tr>
<tr>
<td>ESPRIT</td>
<td>2001</td>
<td>Jul 1997 to Dec 2005</td>
<td>Multicenter randomized controlled trial; International 79 hospital from 14 countries.</td>
<td>1377 (50%)</td>
<td>ASA+dipyridamole/ASA</td>
</tr>
<tr>
<td>S-ACCESS</td>
<td>2002</td>
<td>Apr 2001 to Nov 2003</td>
<td>Double blind, multicenter randomized trial; 113 institutes in Japan.</td>
<td>963 (64%)</td>
<td>Sarpogrelate/ASA</td>
</tr>
<tr>
<td>PrOFESS</td>
<td>2005</td>
<td>Sept 2003 to Feb 2008</td>
<td>Double blind, multicenter randomized controlled trial; International, 695 centers in 35 countries.</td>
<td>10578 (52%)</td>
<td>ASA+dipyridamole/clopidogrel</td>
</tr>
<tr>
<td>CSPS2</td>
<td>2005</td>
<td>Dec 2003 to Oct 2006</td>
<td>Double blind, multicenter randomized trial; 278 sites in Japan.</td>
<td>1743 (65%)</td>
<td>Cilostazol/ASA</td>
</tr>
<tr>
<td>AAASPS</td>
<td>2006</td>
<td>Dec 1992 to Oct 2001</td>
<td>Double blind, multicenter randomized trial; 62 centers in the United States</td>
<td>1221 (68%)</td>
<td>Ticlopidine/ASA</td>
</tr>
<tr>
<td>SPS3</td>
<td>2007</td>
<td>2003 to 2011</td>
<td>Double blind, multicenter randomized trial; international, 8 countries.</td>
<td>3020 (100%)</td>
<td>ASA+clopidogrel/ASA</td>
</tr>
<tr>
<td>Mean Age</td>
<td>% Male</td>
<td>Participant Selection</td>
<td>Stroke Ascertainment</td>
<td>Definition of Lacunar Stroke Specified</td>
<td></td>
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<tr>
<td>63</td>
<td>70%</td>
<td>Participants had ≥1 cerebral or retinal atherothrombotic ischemic event whether transient or complete.</td>
<td>Neurological assessment with history and CT scan and cerebral angiography was optional.</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>66</td>
<td>61%</td>
<td>Participants with minor ischemic stroke or TIA.</td>
<td>Ischemic vascular accident is defined as neurological deficit because of involvement of the brain or brain stem without symptoms or signs of hemorrhage or tumor.</td>
<td>Yes. Small vessel disease had signs and symptoms of 1 of the classical lacunar syndromes (pure motor stroke, pure sensory stroke, ataxic hemiparesis or dysarthria clumsy hand syndrome).</td>
<td></td>
</tr>
<tr>
<td>65 61% &gt;70 years</td>
<td>54%</td>
<td>Participants with acute stroke with onset &lt;48 h previously and no evidence of intracranial hemorrhage.</td>
<td>All patients were CT scanned and eligibility was based on view of responsible physician. Classification of stroke type was based on neurological deficits.</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>65</td>
<td>66%</td>
<td>Participants aged &lt;80 years with onset of cerebral infarction between 1 and 6 months confirmed on CT or MRI scan and no serious complications were present.</td>
<td>Diagnosis confirmed on CT or MRI imaging.</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>63</td>
<td>64%</td>
<td>Participants were within 48 h of onset of symptoms of suspected acute ischemic stroke and had no clear indication for or contraindications to aspirin.</td>
<td>Patient judged to be within 48 h of onset of symptoms of suspected acute ischemic stroke and had CT scan.</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>65</td>
<td>71%</td>
<td>Participants had recent ischemic stroke (must have occurred &gt; 8 days before enrollment).</td>
<td>Brain infarcts were documented by computed tomography or MRI.</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>66</td>
<td>63%</td>
<td>Participants had ischemic stroke or TIA in the previous 3 months with ≥1 of 5 additional risk factors within 3 years.</td>
<td>Diagnosis and stroke type according to TOAST criteria with MRI or CT imaging.</td>
<td>Yes. Small vessel occlusion defined as one of the traditional clinical lacunar syndromes and should not have evidence of cerebral cortical dysfunction. Small vessel disease was used as lacunar stroke but not defined.</td>
<td></td>
</tr>
<tr>
<td>63</td>
<td>65%</td>
<td>Participants had TIA within 6 months or minor stroke of arterial origin.</td>
<td>Data collected by checklist and classification was on basis of CT or MR scan and clinical features.</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>65</td>
<td>72%</td>
<td>Participants with cerebral infarction based on NINDS criteria.</td>
<td>Symptoms, signs, and evidence on CT or MR imaging.</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>66</td>
<td>64%</td>
<td>Participants had recent ischemic stroke (within 90 days of randomization) with symptoms lasting &gt;24 h or evidence of cerebral infarction on CT or MRI scan, clinical and neurological stability before randomization and age ≥55 years. Excluded were those with contraindication for antplatelet agents.</td>
<td>Symptoms of ischemic stroke with evidence of a recent brain infarction on CT or MRI scan.</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>63</td>
<td>NA</td>
<td>Participants with noncardioembolic cerebral infarction (NINDS-III classification) with evidence on CT or MRI scan and age 20–79 years.</td>
<td>NINDS-III classification with evidence on CT or MRI scan of noncardioembolic cerebral infarction.</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>61</td>
<td>53%</td>
<td>Participants were black race of age 29–85 years of age with noncardioembolic ischemic stroke with onset ≥7 days but not &gt;90 days with neurological imaging and measurable neurological deficits consistent with cerebral infarction.</td>
<td>Cranial computed tomographic scan or MRI of the brain consistent with cerebral infarction.</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>63</td>
<td>63%</td>
<td>Participants had recent lacunar stroke.</td>
<td>Clinical diagnosis with investigations, including an MRI, ECG, ECHO, standard blood tests, and imaging of cervical and intracranial arteries.</td>
<td>Yes. Clinical lacunar syndrome that corresponded to an ischemic lesion measuring ≤2.0 cm in diameter on MRI on DWI or &lt;1.5 cm on FLAIR/T1.</td>
<td></td>
</tr>
</tbody>
</table>
Cilostazol, Ticlopidine, Dipyridamole, Terutroban, Sarpogrelate Versus Aspirin Alone

Overall, the meta-analysis shows no significant advantage of other single agents above aspirin alone. These analyses are shown in Figure 2A and 2B. Two trials, PERFORM\(^{21}\) and S-ACCESS,\(^{15}\) evaluating terutroban and sarpogrelate also found no significant benefit above aspirin alone (terutroban HR 0.90, 0.62–1.31; sarpogrelate HR 1.31, 0.84–2.04).

**Dual Antiplatelet Therapy Versus Aspirin Alone**

The results of DAPT versus aspirin are shown in Figure 3. Overall, DAPT may possibly have a modest advantage over aspirin, but this is driven mainly by the aspirin/dipyridamole data from ESPS-2.\(^{19}\) The pooled risk ratio for any stroke, ischemic stroke, and the composite outcome were RR 0.83, 0.68 to 1.00; RR 0.80, 0.62 to 1.02; and RR 0.95,0.85 to 1.07, respectively.

**Dipyridamole/Aspirin, Clopidogrel/Aspirin, and Ticlopidine Versus Clopidogrel Alone**

We observed no significant advantage of DAPT versus clopidogrel or ticlopidine versus clopidogrel. For this analysis, aspirin/dipyridamole did not seem to be superior to clopidogrel alone. Results are shown in Figure 4. Finally, DAPT using vorapaxar in addition to aspirin or clopidogrel use showed no significant benefit on vascular end points (HR 0.99,0.75–1.31).\(^{22}\)

**Discussion**

The current American Heart Association guidelines\(^{24}\) state that 4 antiplatelet regimens (aspirin, clopidogrel, ticlopidine, or the combination of dipyridamole and aspirin) have been shown to reduce the risk of ischemic stroke after stroke or TIA. The guidelines further suggest that several factors should be considered, such as patient comorbidities, side effects, and costs, when choosing an agent at an individual level. Suitably, our findings suggest that antiplatelet monotherapy (ie, aspirin, dipyridamole, clopidogrel, cilostazol, and ticlopidine) should be recommended as secondary prevention of stroke among patients with lacunar stroke. Aspirin seems to be as good as any other antiplatelet agents and is likely the appropriate first line in most because it is less expensive and generally well tolerated, which may increase long-term adherence to therapy.\(^{24}\) Cilostazol showed a nonsignificant trend in reducing strokes when compared with aspirin; however, further larger studies are needed to validate these findings and ensure generalizability to non-East Asian populations.

Unfortunately, in view of the limited number of studies which evaluate the role of DAPT, we are unable to separate out individual agents and maintain a meaningful pooled analysis. Accordingly, we identified substantial heterogeneity in the effects of DAPT, which may depending on the choice of the combination and the comparator drugs. Only one trial shows DAPT to be favorable (ESPS-2), but the superiority of dipyridamole and aspirin was not replicated when clopidogrel was used as the control rather than aspirin. Moreover, long-term DAPT with clopidogrel/aspirin led to significantly higher rates of major bleeding in MATCH (Management of Atherothrombosis With Clopidogrel in High-Risk Patients) and all-cause mortality in SPS3. Therefore, current evidence does not justify the use of long-term DAPT in patient with lacunar stroke.

Our results are in line with those of the SPS3 trial regarding the lack of benefit from clopidogrel and aspirin therapy in lacunar stroke patients. We, however, did not notice...
any significant increase in our composite outcome of any stroke, myocardial infarction, and death. Limited by the available published data, we were unable to consider mortality rates in isolation; however, long-term DAPT (mean 3.4 years) led to increased all-cause mortality (HR 1.52, 1.14–2.04, \( P = 0.004 \)) in comparison to monotherapy with aspirin within SPS3.3.

Our study has limitations. There were a limited number of trials, and there was insufficient data to investigate particular outcomes, such as hemorrhagic stroke or all-cause mortality in isolation. Additionally, lacunar stroke was defined in a heterogeneous manner among the trials, with only one study using a strict clinical criteria and magnetic resonance imaging verification of the infarct,3 and we were unable to consider the effect-specific DAPT regimens in isolation. A final limitation is that our analysis is unable to account for possible differences in treatment-effects between the acute/semiacute phase after stroke and the chronic phase.

In conclusion, our results suggest that at present, antiplatelet monotherapy of the agents included in the trials should be indicated for secondary stroke prevention after a lacunar stroke. Furthermore, current data are insufficient to justify using one antiplatelet agent over another in this particular population.

Acknowledgments
C.S. Kwok and A. Shoamanesh was involved in design, screening, study selection, data extraction, data analysis, and preparation of article. H.C. Copley was involved in screening and data extraction. P.K. Myint was involved in the design, screening, and preparation of the article. Y.K. Loke was involved in the design, study selection, data extraction, data analysis, and preparation of the article. O.R. Benavente was involved in design and preparation of the article.

Disclosures
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References
11. International Stroke Trial Collaborative Group. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both,
Figure 1. Risk of outcome with antiplatelet versus placebo. AICLA indicates Accidents Ischémiques Cérébraux Liés à l’Atherosclérose; CAST, Chinese Acute Stroke Trial; CATS, Canadian American Ticlopidine Study; and ESPS-2, European Stroke Prevention Study.


Figure 3. Risk of outcome with dual antiplatelet therapy versus aspirin. AICLA indicates Accidents Ischémiques Cérébraux Lies a l'Atherosclerose; ECLIPse, Effect of Cilostazol in Acute Lacunar Infarction Based on Pulsatility Index of Transcranial Doppler; ESPRIT, European/Australasian Stroke Prevention in Reversible Ischaemia Trial; ESPS-2, European Stroke Prevention Study; and SPS3, Secondary Prevention of Small Subcortical Strokes.
Figure 4. Risk of outcome with other antiplatelet regimens versus clopidogrel. MATCH indicates Management of Atherothrombosis With Clopidogrel in High-Risk Patients; and PROFESS, Prevention Regimen for Effectively Avoiding Second Strokes.
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Supplementary Figure I: Flow diagram of study selection

431 potentially relevant studies found on search of MEDLINE and EMBASE.

386 studies had titles and abstracts screened and were deemed to be not relevant based on inclusion criteria and were excluded.

41 studies were retrieved and full publications reviewed for potential inclusion.

24 studies were excluded because 5 did not evaluate antiplatelet therapy, 10 did not report lacunar stroke outcomes, 5 were reviews and 4 were duplicates.

17 studies met the inclusion criteria.
### Supplementary Table I: Quality of included trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding</th>
<th>Treatment; exposure; ascertainment</th>
<th>Outcome; outcome ascertainment</th>
<th>Follow up; lost to follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>AICLA [1]</td>
<td>Patients were randomized using a established randomization schedule, balanced for every 6 patients.</td>
<td>Unclear.</td>
<td>Double-blind.</td>
<td>330 mg ASA, placebo, 330 mg ASA and 75 mg dipyridamole, three times a day; exposure for duration of study; at each follow up patients were asked about drug habits and urine salicylate measurements were performed.</td>
<td>Ischemic stroke; clinical diagnosis with CT scan.</td>
<td>3 years; 11% withdrew from study not related to health problems, 41% discontinued treatment, and 8% withdrew from study.</td>
</tr>
<tr>
<td>CATS [2]</td>
<td>Randomization code used for randomization.</td>
<td>Unclear.</td>
<td>Double-blind.</td>
<td>500 mg ticlopidine, placebo; ascertained by pill counting.</td>
<td>Any stroke; events were classified by steering committee.</td>
<td>2 years; 4 patients loss to follow up.</td>
</tr>
<tr>
<td>ESPS-2 [3]</td>
<td>Treatment group allocation was determined by a randomization system based on the minimization technique and taking into account various factors.</td>
<td>Unclear.</td>
<td>Double-blind.</td>
<td>Aspirin 50 mg, modified-release dipyridamole 400 mg, aspirin and dipyridamole combined and placebo; exposure for 2 years; unclear ascertainment.</td>
<td>Any stroke. Unclear ascertainment.</td>
<td>Up to 2 years; unclear loss to follow up.</td>
</tr>
<tr>
<td>IST [4]</td>
<td>Computer allocated the study treatments using a minimization algorithm which reduced any imbalance in recorded prognostic features between treatment groups.</td>
<td>Adequate allocation concealment where patients were allocated by telephoning the central randomization service at Clinical Trial Service Unit, Oxford, UK.</td>
<td>Not fully double-blind.</td>
<td>300 mg ASA or control (avoid aspirin); exposure for study duration: medication in hospital so compliance not an issue.</td>
<td>Death or dependence; outpatient collection of data, coordinating centre mail a validated questionnaire, or telephone call interview (coordinated centrally).</td>
<td>6 months (0.5 years); 74 lost at 6 months.</td>
</tr>
<tr>
<td>Matsumoto 2005 [5]</td>
<td>Randomization was performed by the dynamic balancing method adjusted for several variables.</td>
<td>Adequate allocation concealment by central Registration and Analysis Center, an independent organization set up at Tokyo University for the present study.</td>
<td>Double-blind.</td>
<td>100 mg cilostazol twice daily vs. placebo; exposure duration of study; unclear ascertainment.</td>
<td>Ischemic stroke; Evaluation Committee classified all events.</td>
<td>2 years (1.8 years in cilostazol, 1.6 years in placebo); unclear lost to follow up.</td>
</tr>
<tr>
<td>CAST [6]</td>
<td>Randomization was by prepacked, sequentially numbered trial envelopes.</td>
<td>Adequate allocation concealment with prepacked sealed envelopes produced centrally.</td>
<td>Unclear blind.</td>
<td>160 mg ASA, placebo; exposure duration of study; compliance not an issue because nurse administered medication.</td>
<td>Death or non-fatal stroke; clinical diagnosis with CT scan.</td>
<td>4 weeks (0.08 years); unclear loss to follow up.</td>
</tr>
<tr>
<td>Uchiyama 2009 [7]</td>
<td>Unclear.</td>
<td>Unclear.</td>
<td>Double-blind.</td>
<td>75 mg clopidogrel or ticlopidine 200 mg; exposure for 26 weeks or Combined ischemic stroke, MI and vascular</td>
<td>26 and 52 weeks; 7 excluded from</td>
<td></td>
</tr>
<tr>
<td>Trial</td>
<td>Description</td>
<td>Allocation</td>
<td>Randomization</td>
<td>Outcome</td>
<td>Notes</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>-------------</td>
<td>------------</td>
<td>---------------</td>
<td>---------</td>
<td>-------</td>
<td></td>
</tr>
<tr>
<td>MATCH [8]</td>
<td>Sequence generation was based on a computer-generated list of treatment numbers.</td>
<td>Adequate allocation concealment which was done centrally, with an interactive voice response system (by phone).</td>
<td>Double-blind.</td>
<td>Ischemic stroke; follow-up visit and telephone calls.</td>
<td>1.5 years; 13 participants were lost to follow up.</td>
<td></td>
</tr>
<tr>
<td>ESPRIT [9]</td>
<td>Treatment allocation was by means of computer generated randomization codes stratified by hospital before the start of the trial.</td>
<td>Adequate allocation concealment with randomization by means of a telephone call, fax, or email to the central trial office.</td>
<td>Non-blinded.</td>
<td>Ischemic stroke and all cardiac events (MI, sudden death and death from cardiac causes); 3 member committee audited outcome events and independently classified events.</td>
<td>3.5 years; 106 participants were lost to follow up, 554 discontinued treatment.</td>
<td></td>
</tr>
<tr>
<td>S-ACCESS [10]</td>
<td>Patients were randomly assigned according to an allocation table that was generated by using random numbers by a person who was not part of this study.</td>
<td>Adequate allocation concealment with web-based randomization.</td>
<td>Double-blind.</td>
<td>Ischemic stroke; diagnosis by clinical evaluation with Efficacy End Point Committee.</td>
<td>1.59 years; 11 not included in efficacy analysis.</td>
<td></td>
</tr>
<tr>
<td>PROFESS [11]</td>
<td>Unclear.</td>
<td>Adequate allocation concealment by a central telephone randomization system.</td>
<td>Double-blind.</td>
<td>Any stroke; ascertained by central committee using TOAST criteria to classify event.</td>
<td>2.5 years; 0.6% were lost to follow up in each arm.</td>
<td></td>
</tr>
<tr>
<td>CSPS2 [12]</td>
<td>The randomization table was generated with SAS and random allocation was done with a dynamic balancing method to minimize differences in the distribution of baseline variables between the two groups.</td>
<td>Adequate allocation concealment with remote randomization by contract research organisation at the registration centre.</td>
<td>Double-blind.</td>
<td>Any stroke; independent data monitoring committee.</td>
<td>2.42 years; 85 not included in analysis, 793 discontinued drug and 4 lost to follow up.</td>
<td></td>
</tr>
<tr>
<td>AAASPS [13]</td>
<td>Patients were randomized using a algorithm using a length of block varying from 2 to 8 with a ratio of patients receiving ticlopidine to aspirin of 1:1.</td>
<td>Adequate allocation concealment with automated phone registration.</td>
<td>Double-blind.</td>
<td>Any stroke; blinded adjudication committee.</td>
<td>1.54 years; 522 participants withdrew from study but all were included in analysis.</td>
<td></td>
</tr>
<tr>
<td>SPS3 [14]</td>
<td>Randomization assignments were</td>
<td>Adequate allocation concealment</td>
<td>Double-blind.</td>
<td>Any stroke, ischemic</td>
<td>3.4 years; no loss to</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Allocation</td>
<td>Randomization</td>
<td>Adherence</td>
<td>Events</td>
<td>Follow up</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>------------</td>
<td>---------------</td>
<td>-----------</td>
<td>--------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td><strong>PERFORM [15]</strong></td>
<td>The allocation sequence was generated by the sponsor through in-house application software. The randomization was balanced, non-adaptive, and stratified by country, with blocks of size four.</td>
<td>Adequate allocation concealment by a central interactive response system (telephone or internet).</td>
<td>Double-blind.</td>
<td>Ischemic stroke, MI, vascular death. Independent Data Monitoring Committee.</td>
<td>28.3 months; 20 excluded, 58 lost to follow up and 382 withdrew consent.</td>
<td></td>
</tr>
<tr>
<td><strong>ECLIPSE [16]</strong></td>
<td>A blocked randomization procedure generated by a statistician was used by the central trial pharmacist randomized patients.</td>
<td>Adequate allocation concealment with randomization by central trial pharmacist who produced identical study kits.</td>
<td>Double-blind.</td>
<td>Any stroke (ischemic stroke data also provided); follow up with transcranial doppler and examination.</td>
<td>90 days; no lost to follow up.</td>
<td></td>
</tr>
<tr>
<td><strong>TRA 2P-TIMI 50 [17]</strong></td>
<td>Unclear.</td>
<td>Adequate allocation concealment by a central computerized telephone system.</td>
<td>Double-blind.</td>
<td>Cardiovascular death, MI or stroke; ascertained by a Clinical Events Committee blinded to treatment allocation.</td>
<td>Median 24 months (up to 3 years). 32 lost to follow up and 532 withdrew consent for follow up.</td>
<td></td>
</tr>
</tbody>
</table>
Supplementary Table II: Treatments, outcomes, crude events and follow up of studies included

<table>
<thead>
<tr>
<th>Study</th>
<th>Midyear of study</th>
<th>Treatment experimental/contr ol</th>
<th>Outcome</th>
<th>Experimental events</th>
<th>Total (outcome/yr)</th>
<th>Control events</th>
<th>Total (outcome/yr)</th>
<th>Trial follow-up duration (mean)</th>
<th>Reported HRs (95% CI) for outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>AICLA [1]</td>
<td>1976</td>
<td>ASA/placebo</td>
<td>Ischemic stroke</td>
<td>30</td>
<td>3.33%</td>
<td>34</td>
<td>8.82%</td>
<td>3 years</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>1976</td>
<td>ASA+dipyridamole/ASA</td>
<td>Ischemic stroke</td>
<td>34</td>
<td>1.96%</td>
<td>30</td>
<td>3.33%</td>
<td>3 years</td>
<td>-</td>
</tr>
<tr>
<td>CATS [2]</td>
<td>Prior to 1989</td>
<td>Ticlopidine/placebo</td>
<td>Any stroke</td>
<td>137</td>
<td>5%</td>
<td>27</td>
<td>10%</td>
<td>2 years</td>
<td></td>
</tr>
<tr>
<td>ESPS-2 [3]</td>
<td>1992</td>
<td>ASA/placebo</td>
<td>Any stroke</td>
<td>609</td>
<td>6.4%</td>
<td>681</td>
<td>7.9%</td>
<td>1.7-1.8 years</td>
<td>0.82 (0.60-1.11)</td>
</tr>
<tr>
<td></td>
<td>1992</td>
<td>Dipyridamole/placebo</td>
<td>Any stroke</td>
<td>651</td>
<td>6.3%</td>
<td>681</td>
<td>7.9%</td>
<td>1.7 years</td>
<td>0.80 (0.59-1.08)</td>
</tr>
<tr>
<td></td>
<td>1992</td>
<td>ASA+dipyridamole/placebo</td>
<td>Any stroke</td>
<td>659</td>
<td>4.4%</td>
<td>681</td>
<td>7.9%</td>
<td>1.7-1.8 years</td>
<td>0.56 (0.40-0.78)</td>
</tr>
<tr>
<td></td>
<td>1992</td>
<td>ASA+dipyridamole/ASA</td>
<td>Any stroke</td>
<td>659</td>
<td>4.4%</td>
<td>609</td>
<td>6.4%</td>
<td>1.8 years</td>
<td>0.68 (0.48-0.97)</td>
</tr>
<tr>
<td></td>
<td>1992</td>
<td>ASA/placebo</td>
<td>Composite vascular events*</td>
<td>609</td>
<td>9.4%</td>
<td>681</td>
<td>11.0%</td>
<td>1.7-1.8 years</td>
<td>0.86 (0.66-1.11)</td>
</tr>
<tr>
<td></td>
<td>1992</td>
<td>Dipyridamole/placebo</td>
<td>Composite vascular events*</td>
<td>651</td>
<td>9.5%</td>
<td>681</td>
<td>11.0%</td>
<td>1.7 years</td>
<td>0.86 (0.67-1.12)</td>
</tr>
<tr>
<td></td>
<td>1992</td>
<td>ASA+dipyridamole/placebo</td>
<td>Composite vascular events*</td>
<td>659</td>
<td>7.0%</td>
<td>681</td>
<td>11.0%</td>
<td>1.7-1.8 years</td>
<td>0.64 (0.48 – 0.84)</td>
</tr>
<tr>
<td></td>
<td>1992</td>
<td>ASA+dipyridamole/ASA</td>
<td>Composite vascular events*</td>
<td>659</td>
<td>7.0%</td>
<td>609</td>
<td>9.4%</td>
<td>1.8 years</td>
<td>0.74 (0.55-0.99)</td>
</tr>
<tr>
<td>IST [4]</td>
<td>1993</td>
<td>ASA/control</td>
<td>Death or dependence</td>
<td>2308</td>
<td>-</td>
<td>2308</td>
<td>-</td>
<td>6 months = 0.5 years</td>
<td>-</td>
</tr>
<tr>
<td>Matsumoto 2005 [5]</td>
<td>1994</td>
<td>Cilostazol/placebo</td>
<td>Ischemic stroke</td>
<td>400</td>
<td>2.97%</td>
<td>394</td>
<td>5.25%</td>
<td>2 years (1.8 years in cilostazol, 1.6 years in placebo)</td>
<td>-</td>
</tr>
<tr>
<td>CAST [6]</td>
<td>1995</td>
<td>ASA/placebo</td>
<td>Any (non-fatal) stroke or death</td>
<td>3117</td>
<td>-</td>
<td>3146</td>
<td>-</td>
<td>4 weeks = 0.08 years</td>
<td></td>
</tr>
<tr>
<td>Uchiyama 2009 [7]</td>
<td>1999</td>
<td>Clopidogrel/ticlopidine</td>
<td>Ischemic stroke, MI, vascular death</td>
<td>677</td>
<td>2.8%</td>
<td>664</td>
<td>3.3%</td>
<td>Up to 1 year.</td>
<td></td>
</tr>
<tr>
<td>MATCH [8]</td>
<td>2001</td>
<td>ASA-clopidogrel/clopidogrel</td>
<td>Ischemic stroke</td>
<td>1590</td>
<td>7.70%</td>
<td>1558</td>
<td>8.10%</td>
<td>18 months = 1.5 years</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Treatment</td>
<td>Outcomes</td>
<td>Event Rate</td>
<td>p-value</td>
<td>Follow-up</td>
<td>HR (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>------</td>
<td>------------</td>
<td>-----------------------------------</td>
<td>------------</td>
<td>---------</td>
<td>-----------</td>
<td>-------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESPRIT [9]</td>
<td>2001</td>
<td>ASA+dipyridamole/ASA</td>
<td>Ischemic stroke and all cardiac events (MI, sudden death and death from cardiac causes)</td>
<td>96</td>
<td>687</td>
<td>3.99%</td>
<td>106</td>
<td>690</td>
<td>4.39%</td>
</tr>
<tr>
<td>S-ACCESS [10]</td>
<td>2002</td>
<td>Sarpogrelate/ASA</td>
<td>Ischemic stroke</td>
<td>46</td>
<td>484</td>
<td>5.95%</td>
<td>35</td>
<td>479</td>
<td>4.53%</td>
</tr>
<tr>
<td>PROFESS [11]</td>
<td>2005</td>
<td>ASA+dipyridamole/clopidogrel</td>
<td>Any stroke</td>
<td>418</td>
<td>5292</td>
<td>3.16%</td>
<td>437</td>
<td>5286</td>
<td>3.31%</td>
</tr>
<tr>
<td>CSPS2 [12]</td>
<td>2005</td>
<td>cilostazol/ASA</td>
<td>Any stroke</td>
<td>59</td>
<td>869</td>
<td>3.06%</td>
<td>85</td>
<td>874</td>
<td>4.07%</td>
</tr>
<tr>
<td>AAASPS [13]</td>
<td>2006</td>
<td>Ticlodipine/ASA</td>
<td>Any stroke</td>
<td>55</td>
<td>600</td>
<td>6%</td>
<td>48</td>
<td>621</td>
<td>5%</td>
</tr>
<tr>
<td>SPS-3 [14]</td>
<td>2007</td>
<td>ASA+clopidogrel/ASA</td>
<td>Ischemic stroke</td>
<td>100</td>
<td>1517</td>
<td>2.00%</td>
<td>124</td>
<td>1503</td>
<td>2.40%</td>
</tr>
<tr>
<td>2007</td>
<td>ASA+clopidogrel/ASA</td>
<td>Any stroke</td>
<td>125</td>
<td>1517</td>
<td>2.50%</td>
<td>138</td>
<td>1503</td>
<td>2.70%</td>
<td>3.4 years</td>
</tr>
<tr>
<td>2007</td>
<td>ASA+clopidogrel/ASA</td>
<td>Any stroke, MI, death.</td>
<td>269</td>
<td>1517</td>
<td>-</td>
<td>253</td>
<td>1503</td>
<td>-</td>
<td>3.4 years</td>
</tr>
<tr>
<td>PERFORM [15]</td>
<td>2007</td>
<td>Tetroban/ASA</td>
<td>Ischemic stroke, MI and vascular death.</td>
<td>54</td>
<td>856</td>
<td>2.55%</td>
<td>61</td>
<td>877</td>
<td>2.98%</td>
</tr>
<tr>
<td>ECLIPSE [16]</td>
<td>2007</td>
<td>ASA+cilostazol/ASA</td>
<td>Any stroke (all events ischemic)</td>
<td>1</td>
<td>100</td>
<td>-</td>
<td>1</td>
<td>103</td>
<td>-</td>
</tr>
<tr>
<td>TRA 2P-TIMI 50 [17]</td>
<td>2009</td>
<td>Vorapaxar/placebo and concomitant medications</td>
<td>Any stroke, MI, cardiovascular death.</td>
<td>-</td>
<td>2262 (total)</td>
<td>3.80%</td>
<td>-</td>
<td>2262 (total)</td>
<td>3.77%</td>
</tr>
</tbody>
</table>

* Composite vascular events defined as nonfatal stroke, nonfatal MI, a nonfatal vascular events (DVT, PE, peripheral artery occlusion, venous retinal vascular event) or vascular death.
Supplementary Data I: Search Strategy

Database: Embase <1974 to 2013 Week 50>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

1. Aspirin or Clopidogrel or Ticlopidine or Dipyridamole or Prasugrel or Ticagrelor or Cilostazol or Dipyridamole [No Related Terms] (6084)
2. Platelet aggregation inhibitors or Antiplatelet [No Related Terms] (69182)
3. Platelet Aggregation Inhibitors [No Related Terms] (5716)
4. Stroke or cerebrovascular disease or cerebrovascular accident [No Related Terms] (8654)

5. Stroke/ (186298)
6. Brain Ischemia/ (112183)
7. Cerebrovascular Disorders/ (91210)
8. randomised controlled trial or randomized controlled trial or randomised controlled study or randomized controlled study [No Related Terms] (9836)
9. Randomized Controlled Trial/ (755711)

10. 1 or 2 or 3 (77570)
11. 4 or 5 or 6 or 7 (355197)
12. 8 or 9 (755716)
13. 10 and 11 and 12 (536)
14. remove duplicates from 13 (431)

***************************
References


ラクナ梗塞後の二次予防に対する抗血小板療法の有効性
無作為化試験のプール解析

Abstract

Chun Shing Kwok, MBBS1,2 ; Ashkan Shoamanesh, MD3 ; Hannah Charlotte Copley, MBBChir4 , et al.

Institute, Hamilton, Ontario, Canada; and  4  Department of Surgery, Addenbrooke's Hospital, Cambridge, UK.

各種脳卒中

表

リスク比

試験名あるいはサブグループ  インペクト  合計  香料

リスク比

ホエイポイド救済モデル  95%信頼区間 (CI)

AAASPS

各脳卒中

スイ・ノ・ポ・シ

ジン・レ・モ・モ・ポ・シ

アスピリンと比較した単剤抗血小板療法の転帰のリスク。AAASPS：American African Antiplatelet Stroke Prevention Study (アフリカ系アメリカ人抗血小板療法予防試験)，CSPS 2：Cilostazol Stroke Prevention Study (シロスタゾール脳卒中予防試験)，ESPS 2：European Stroke Prevention Study (欧州脳卒中予防試験)。Stroke 語の版を一部省略して掲載。
Abstract 2

열공뇌졸중 후 이차예방으로 항혈소판제 치료의 효능
무작위 임상시험의 종합 분석

Efficacy of Antiplatelet Therapy in Secondary Prevention Following Lacunar Stroke
Pooled Analysis of Randomized Trials

Chun Shing Kwok, MBBS*; Ashkan Shoamanesh, MD*; Hannah Charlotte Copley, MBChir;
Phyo Kyaw Myint, MD; Yoon K. Loke, MD; Oscar R. Benavente, MD

(Stroke. 2015;46:1014-1023.)

Key Words: antiplatelet agent ■ aspirin ■ lacunar stroke ■ mortality ■ stroke

배경과 목적
열공뇌졸중은 허혈뇌졸중의 ≈25%를 구성한다. 하지만, 뇌졸중 재발을 예방하기 위한 최적의 항혈소판제 요법은 여전히 불명확하다. 우리는 열공뇌졸중 후 이차뇌졸중 예방을 위한 항혈소판제 효능을 평가하고자 하였다.

방법
연구자들은 MEDLINE, Embase, the Cochrane library에서 열공뇌졸중 환자에서 항혈소판제를 사용하고 뇌졸중 재발 또는 사망 위험도를 보고한 무작위 대조군 시험을 찾았다. 랜덤회 효과 메타분석 모델을 사용하였고, I2를 이용한 이질성을 평가하였다.

결과
42234 참가자(평균 나이 64.4세, 65% 남성)를 대상으로 한 17개의 임상시험을 포함하였고 추적관찰 기간은 4주에서 3.5년이었다. 위약과 비교하여 단일 항혈소판제는 모든 종류의 뇌졸중 재발(RR 0.77, 0.62-0.96, 2개 연구) 및 허혈뇌졸중의 재발(RR, 0.48, 0.30-0.78, 2개 연구)의 유의한 감소를 보였고, 반면 모든 종류의 뇌졸중, 심근경색 또는 사망의 복합 결과(RR 0.89, 0.75-1.05, 2개 연구)에 대해서는 유의한 감소를 보이지 않았다. 아스피린과 다른 항혈소판제(티클로피딘, 실로스타졸, 디피리다는)를 비교했을 때 뇌졸중 재발에 유의한 감소는 없었다(RR 0.91, 0.75-1.10, 3개 연구). 이중 항혈소판제 치료는 단일 항혈소판제 치료에 비해 확실한 이익을 보이지 않았다(모든 뇌졸중 RR 0.83, 0.68-1.00, 3개 연구; 허혈뇌졸중 RR 0.80, 0.62-1.02, 3개 연구; 복합 결과 RR 0.90, 0.80-1.02, 3개 연구).

결론
본 연구는 어떤 종류의 단일 항혈소판제 치료라도 위약에 비해서 열공뇌졸중 후 이차뇌졸중 예방으로 적절함을 제안한다. 하지만 이중 항혈소판제 치료는 열공뇌졸중에서 장기간 뇌졸중 예방을 위해서 사용되어서는 안 된다.

Abstract 3

심방세동 환자에서 와파린 치료 중 허혈뇌졸중의 발생률

Rates of Ischemic Stroke During Warfarin Treatment for Atrial Fibrillation

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(Stroke. 2015;46:1120-1122.)

Key Words: anticoagulants ■ epidemiology

배경과 목적
와파린 투여 시작 직후의 허혈뇌졸중의 위험이 증가한다는 보고가 최근 발표되었다. 이 연구는 새롭게 와파린 치료를 시작하는 심방세동 환자에서 허혈뇌졸중의 발생률을 조사하였다.

방법
1997년 4월 1일부터 2010년 3월 31일의 기간 동안 66세 이상의 심방세동 환자로 온타리오 주(Ontario)에 거주하는 사람을 대상으로 한 코호트 연구를 시행하였다. 각 환자들을 30일 간격으로
5-year exposure to fine particulate matter, residential proximity to major roads and measures of brain structure.

Abstract 4

Long-Term Exposure to Fine Particulate Matter, Residential Proximity to Major Roads and Measures of Brain Structure

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(Stroke. 2015;46:1161-1166.)

Key Words: air pollution ■ brain infarcts ■ neuroimaging