Antiplatelet Therapy for Secondary Prevention of Noncardioembolic Ischemic Stroke
A Critical Review

Martin J. O'Donnell, MB; Graeme J. Hankey, MD, FRACP; John W. Eikelboom, MB, BS, MSc

Abstract—For patients with ischemic stroke or transient ischemic attack caused by atherothromboembolism, immediate and long-term aspirin reduces the relative risk of recurrent stroke, MI, and death attributable to vascular causes. Oral anticoagulation is not more effective than aspirin. Long-term clopidogrel reduces the relative risk of stroke, MI, or vascular death by about 9% (0.3% to 16.5%) compared with aspirin. Any long-term benefits of clopidogrel combined with aspirin, compared with aspirin or clopidogrel alone, appear to be offset by increased major bleeding. The combination of aspirin and extended-release dipyridamole reduces the relative odds of stroke, MI, or vascular death by about 18% (odds ratio 0.82, 0.74 to 0.91) compared with aspirin alone without causing more bleeding. Cilostazole reduces the risk of stroke, MI, or vascular death by 39% compared to placebo. A large clinical trial comparing clopidogrel with the combination of aspirin and dipyridamole, in >20,000 patients with recent (<120 days) atherothrombotic ischemic stroke, is expected to report in 2008. Emerging antiplatelet therapies presently being evaluated for secondary prevention of atherothromboembolism include other P2Y12 ADP receptor antagonists (prasugrel, cangrelor, AZD 6140), thromboxane receptor antagonists (eg, S18886 - terutroban), and thrombin receptor (PAR-1) antagonists (eg, SCH530348). (Stroke. 2008;39:1638-1646.)

Key Words: antiplatelet drugs ■ aspirin ■ therapy ■ Clopidogrel

Stroke is a leading cause of adult disability and death worldwide.1 A key aim to management of patients with ischemic stroke and transient ischemic attack (TIA) is to reduce the high early risk of recurrent stroke2 and long-term risk of all serious nonfatal and fatal vascular events.3

Randomized trials have established antiplatelet therapy as a cornerstone for secondary stroke prevention.4 The Antiplatelet and Antithrombotic Trialists’ collaborations4 reported that random assignment to any antiplatelet therapy compared with control (placebo or no antiplatelet therapy) was associated with an 11% reduction in odds of stroke, myocardial infarction, or death attributable to vascular causes (serious vascular events) among patients with acute ischemic stroke (n=40,821) and a 22% reduction for long-term secondary prevention in patients with prior ischemic stroke or TIA (n=23,020).4

Aspirin was the first antiplatelet agent to be used for secondary stroke prevention and remains the most commonly prescribed agent. However, over the past 2 decades, a number of other antiplatelet agents and combinations of antiplatelet drugs have been evaluated in an attempt to improve on the effectiveness and safety of aspirin.5

In this article, we review the evidence from randomized trials for the effectiveness and safety of established and emerging antiplatelet therapies for secondary prevention of serious vascular events among patients with ischemic stroke and TIA and provide recommendations for their use.

Methods

Search Strategy
We identified randomized trials and meta-analyses of randomized trials that compared antiplatelet therapy with placebo or no antiplatelet therapy or that compared different antiplatelet therapies with each other by searching electronic databases (PUBMED, Cochrane Database of Clinical Trials) between 1966 and April 2007 using the following MeSH terms: stroke, antiplatelet therapy, aspirin, clopidogrel, ticlopidine, dipyridamole, novel antiplatelet therapy, glycoprotein IIb/IIa inhibitor, bleeding, intracranial hemorrhage, clinical trial, and methodology. We examined the “relevant articles” links in

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From McMaster University (M.J.O., J.W.E.), Hamilton, ON, Canada; and the School of Medicine and Pharmacology (G.J.H.), University of Western Australia, Perth, Australia.

Correspondence to Dr Martin O’Donnell, McMaster Clinic Bld, Hamilton General Hospital, 237 Barton St East, Ontario, L8V 1C3, Canada. E-mail odonnmm@mcmaster.ca

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Table 1. Summary of the Effects of Early Antiplatelet Therapy Versus Control in Acute Ischemic Stroke*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>Absolute Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death/dependency</td>
<td>0.94</td>
<td>0.91 to 0.98</td>
<td>-1.3%</td>
<td>-0.4 to -2.2%</td>
</tr>
<tr>
<td>Complete recovery</td>
<td>1.06</td>
<td>1.01 to 1.11</td>
<td>+1.0%</td>
<td>+0.2 to +1.9%</td>
</tr>
<tr>
<td>Death</td>
<td>0.92</td>
<td>0.87 to 0.98</td>
<td>-0.8%</td>
<td>-0.2 to -1.4%</td>
</tr>
<tr>
<td>Recurrent ischemic stroke</td>
<td>0.77</td>
<td>0.69 to 0.87</td>
<td>-0.7%</td>
<td>-0.4 to -1.0%</td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td>1.23</td>
<td>1.0 to 1.5</td>
<td>+0.2%</td>
<td>+0.0 to +0.4%</td>
</tr>
<tr>
<td>Any recurrent stroke</td>
<td>0.88</td>
<td>0.79 to 0.97</td>
<td>-0.5%</td>
<td>-0.1 to -0.9%</td>
</tr>
<tr>
<td>Major ECH</td>
<td>1.68</td>
<td>1.34 to 2.09</td>
<td>+0.4%</td>
<td>+0.2 to +0.6%</td>
</tr>
<tr>
<td>DVT</td>
<td>0.78</td>
<td>0.36 to 1.67</td>
<td>-4.9%</td>
<td>Not significant</td>
</tr>
<tr>
<td>PE</td>
<td>0.71</td>
<td>0.53 to 0.96</td>
<td>-0.1%</td>
<td>-0.0 to -0.3%</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; DVT, deep vein thrombosis; ECH, extracranial hemorrhage; ICH, intracranial hemorrhage; PE, pulmonary embolism.

Table derived from Hankey GJ. Stroke Treatment and Prevention: An Evidence-Based Approach. Cambridge University Press 2005. Data derived from Sandercock et al.16

*Includes 9 trials, n=41 399.

Acute Ischemic Stroke

There have been 11 trials comparing antiplatelet therapy to control involving 42 648 patients with acute ischemic stroke. Four of these trials compared aspirin to control,7–10 1 compared aspirin plus dipyridamole to control,11 3 trials compared ticlopidine to control,12–14 1 trial compared thomboxane synthase inhibitor to control,15 and 2 trials compared abciximab to control.16,17 Two trials (International Stroke Trial and Chinese Acute Stroke Trial) evaluating aspirin 160 to 300 mg once daily started within 48 hours of onset. The maximum duration of follow-up was 6 months (Table 1).

Aspirin Versus Placebo or Untreated Control

Trials

Four trials have compared aspirin to control in a total of 41 291 patients with acute ischemic stroke.7–10 More than 98% of data came from 2 trials (IST and CAST), which followed patients for a total of 1 and 6 months.7,8

Efficacy

Meta-analysis18 of the data from 3 trials7,8,10 indicate that random assignment to aspirin 160 to 300 mg daily, started within 48 hours of onset of symptoms of ischemic stroke, and continued for about 2 to 4 weeks, compared with control, was associated with a 23% reduction in odds of recurrent ischemic stroke (3.1% [control] versus 2.4% [aspirin]; OR 0.77, 95% CI: 0.69 to 0.87), 12% reduction in recurrent stroke of any type (3.9% [control] versus 3.4% [aspirin]; OR 0.88, 95% CI: 0.79 to 0.97), 29% reduction in pulmonary embolism (0.48% [control] versus 0.34% [aspirin], OR 0.71, 95% CI 0.53 to 0.97), 8% reduction in death (12.9% [control] versus 12.1% [aspirin], OR 0.92, 95% CI 0.87 to 0.98), and 5% reduction in death or dependency at the end of follow-up (46.4% [control] versus 45.3% [aspirin], OR 0.95, 95% CI 0.91 to 0.99).18 Subgroup-specific analyses found no significant heterogeneity of the benefit of early aspirin over 2 to 4 weeks among 28 subgroups examined, which included the elderly, gender, and ischemic stroke subtypes.

Safety

Against these benefits, random assignment to aspirin was associated with a 22% increase in odds of symptomatic intracranial hemorrhage (0.8% [control] versus 1.0% [aspirin], OR 1.22, 95% CI 1.00 to 1.50) and 69% increase in major extracranial hemorrhage during the treatment period (0.6% [control] versus 1.0% [aspirin], OR 1.69, 95% CI 1.35 to 2.11; Table 1).18

Abciximab Versus Aspirin

Trials

Two trials have compared intravenous abciximab (a long-acting glycoprotein IIb/IIIa antagonist) to placebo in aspirin-treated patients with stroke.16,17

Efficacy

A phase IIb trial (AbESTT) randomized 400 patients within 5 hours of onset of ischemic stroke to abciximab 0.25 mg/kg intravenous bolus followed by a 12-hour infusion of 0.125 µg/kg per minute or placebo. At 3 months, there was no significant difference in death or dependency, defined as a modified Rankin Scale (mRS) of 2 to 6 (60% [placebo] versus 52% [abciximab], OR: 0.71, 95% CI: 0.48 to 1.05). AbESTT-II aimed to randomize 1800 patients within 5.5 hours of ischemic stroke to receive abciximab or placebo (all patients were treated with aspirin), but the trial was terminated early after 808 patients were enrolled because of an excess of bleeding (see below).

Safety

The AbESTT study did not report a significantly increased risk of symptomatic intracranial hemorrhage (1.0% [placebo] versus 3.5% [abciximab], OR: 3.11, 95% CI: 0.8 to 11.6), but the larger Phase III AbESTT-II trial was terminated early because of an excess of symptomatic or fatal intracranial hemorrhage at 5 days (0.5% [placebo] versus 5.5% [abciximab]) (P=0.002).

Aspirin and Clopidogrel Versus Aspirin

One trial (FASTER), reported in abstract only, compared combination aspirin and clopidogrel (300 mg loading followed by 75 mg/d) to aspirin alone in patients presenting within 24 hours of a minor ischemic stroke or TIA (factorial design with simvastatin 40 mg/d).20 The pilot study was terminated early after 392 patients were randomized because of slow recruitment, and it reported a nonsignificant reduction in the primary outcome of all-stroke at 90 days in the combination antiplatelet therapy group (ARR 3.8%; P=0.19).20

Antiplatelet Therapy Versus Anticoagulation

Trials

Five clinical trials have compared aspirin to parenteral anticoagulants.7,21–23 A meta-analysis24 has pooled the results...
of 4 RCTs\textsuperscript{7,11,21,22} involving a total of 16,558 patients that assessed the effectiveness and safety of anticoagulants (unfractionated heparin [UFH] or low molecular-weight heparin) compared with aspirin. Patients were recruited within 48 hours of presentation and received therapy for 10 to 14 days. Clinical follow-up in individual trials ranged from 10 days to 6 months.

Subsequent to this meta-analysis,\textsuperscript{24} another clinical trial has been published,\textsuperscript{23} comparing the efficacy and safety of early administration, within 48 hours of onset of ischemic stroke, of subcutaneous nadroparin calcium 3800 antifactor Xa IU/0.4 mL twice daily with oral aspirin 160 mg daily for 10 days, followed by aspirin 80 to 300 mg once daily for 6 months, among 603 Asian patients with acute ischemic stroke attributable to large artery occlusive disease.

### Efficacy

The meta-analysis of the 4 earlier RCTs\textsuperscript{7,11,21,22} indicates that random allocation to parenteral anticoagulation compared with aspirin was associated with no significant difference in recurrent ischemic stroke (OR 1.09, 95% CI: 0.89 to 1.33), recurrent stroke of any type (OR 1.20, 95% CI: 0.99 to 1.46), pulmonary embolism (OR 0.85, 95% CI 0.55 to 1.32), and death or dependency (62.0% [aspirin] versus 63.4% (heparin), OR 1.07, 95% CI 0.99 to 1.15) but significantly increase the odds of death by 10% (OR 1.10, 95% CI 1.01 to 1.21) at the end of follow-up (Table 2).\textsuperscript{24} The results of the recent trial in Asian patients\textsuperscript{23} are consistent with those of the meta-analysis; the proportion of good outcomes (Barthel index ≥85) was 73% among 180 patients assigned LMWH and 69% among 173 patients assigned aspirin (adjusted OR 1.21, 95% CI: 0.74 to 1.99; absolute risk benefit 4%, 95% CI: −5% to 13%).

### Safety

In the meta-analysis,\textsuperscript{24} allocation to anticoagulation was associated with an increase in symptomatic intracranial hemorrhage (0.6% [aspirin] versus 1.2% [heparin], OR 2.27, 95% CI 1.49 to 3.46) and an increase in major extracranial hemorrhage during the treatment period (0.4% [aspirin] versus 0.9% [heparin], OR 1.94, 95% CI 1.20 to 3.12) compared with aspirin, at 14 days (Table 2).

### Antiplatelet Therapy for Long-Term Secondary Prevention

#### Aspirin Versus Control

**Trials**

A meta-analysis\textsuperscript{25} has pooled data from 11 RCTs of long-term aspirin versus control in 9469 patients with previous ischemic stroke or transient ischemic attack.\textsuperscript{26–36}

**Efficacy**

Random allocation to long-term aspirin therapy reduced the risk of all serious vascular events by 13% (ie, stroke, myocardial infarction and vascular death; RR: 0.87%, 95% CI: 0.81 to 0.94).\textsuperscript{25} The dose of aspirin ranged from 50 mg/d to 1500 mg/d but there was no evidence of heterogeneity in treatment effect by aspirin dose (Table 3).

**Safety**

A meta-analysis of 22 randomized controlled trials of low-dose aspirin (75 to 325 mg/d) administered for vascular prevention, including 30,496 patients, reported that aspirin increased the relative risk of major bleeding by 71% (RR: 1.71, 95% CI: 1.41 to 2.08) but the absolute annual increase was modest (ARI; 0.13%, 95% CI: 0.08 to 0.20).\textsuperscript{37} The increased risk of bleeding was mainly attributable to an increase in major gastrointestinal (GI) bleeding (RR: 2.07, 95% CI: 1.61 to 2.66) and intracranial bleeding (RR: 1.65, 95% CI: 1.06 to 5.9). This review did not find evidence of an increased risk of bleeding with moderate-dose aspirin (162.5 to 325 mg daily) compared to low-dose aspirin (75 to 162.5 mg daily). A more recent systematic review\textsuperscript{38} reported an increased risk of gastrointestinal bleeding with doses of aspirin greater than 75 to 81 mg/d.

#### Dipyridamole Versus Control

**Trials**

One large clinical trial compared dipyridamole to no antiplatelet therapy.\textsuperscript{32}

**Efficacy**

In ESPS-2, among patients assigned extended-release dipyridamole 200 mg twice-daily day, the annual relative risk of stroke or death was reduced by 15% compared with placebo.
(22.9% [placebo] versus 19.4% [dipyridamole]; ARR 3.5% over 24 months, \(P\) = 0.02; NNT 29 over 24 months).

**Safety**
Dipyridamole was not associated with an increased risk of any bleeding compared with placebo. However, dipyridamole was associated with an increased frequency of headache, compared with placebo (37.1% dipyridamole versus 32.3% control). Headache was sufficiently severe to lead to discontinuation of study drug in 8.0% of patients in the ESPS-2 trial who were assigned dipyridamole compared with 2.4% discontinuation among those assigned placebo (RR: 3.20; 95% CI: 2.25 to 4.54).³² Dipyridamole also caused gastrointestinal upset leading to discontinuation of study drug (RR: 1.65; 95% CI: 1.21 to 2.26).

**Thienopyridine (Ticlopidine) Versus Control**

**Trials**
One trial compared ticlopidine (250 mg twice-daily) to placebo in 1072 patients with ischemic stroke in the preceding 4 months.³⁹

**Efficacy**
After a mean follow-up of 24 months, assignment to ticlopidine was associated with a 23% lower relative risk of the composite outcome of stroke, myocardial infarction, or vascular death compared with placebo (14.8% [placebo] versus 11.3% [ticlopidine]; RR: 0.77, 0.60 to 0.99).³⁹

**Safety**
Ticlopidine (250 mg twice daily) doubled the risk of major bleeding (0.2% versus 0.4%) and minor bleeding episodes (6.5% versus 3.0%) compared with placebo. Ticlopidine also increased the risk of severe neutropenia (≤450 neutrophils per mm³), occurring in 0.8% of patients in the ticlopidine group compared to 0.2% in placebo group.

Ticlopidine was also associated with an increased risk of thrombotic thrombocytopenic purpura (TTP), affecting about 1 in 5000 patients primarily during the first 3 months of treatment.⁴⁰

**Cilostazol Versus Control**

**Trials**
One RCT compared cilostazol (inhibitor of cAMP phosphodiesterase) with placebo in 1095 patients with recent (1 to 6 months ago) ischemic stroke.⁴¹

**Efficacy**
Among patients assigned cilostazol 100 mg twice daily, the annual relative risk of serious vascular events was reduced by 39% compared with placebo (6.8% [control] versus 4.2% [cilostazol], RR 0.61, 95% CI: 0.41 to 0.91).⁴¹

**Safety**
Adverse effects of cilostazol included headache, tachycardia, and palpitations, which are probably related to its vasodilatory properties.

**Thienopyridine Versus Aspirin: Ticlopidine Versus Aspirin**

**Trials**
Two clinical trials have compared ticlopidine to aspirin.⁴¹

**Efficacy**
Among 3069 Caucasian patients with recent (<3 months) ischemic stroke, random assignment to ticlopidine (250 mg daily twice-daily) compared with aspirin (650 mg twice-daily) did not reduce the odds of serious vascular events compared with aspirin (25.6% [aspirin] versus 24.2% [ticlopidine], OR 0.93, 95% CI: 0.79 to 1.09) during up to 3 years of follow-up.²² Likewise, among 1809 blacks with ischemic stroke, ticlopidine compared with aspirin did not reduce the risk of serious vascular events (12.3% [aspirin] versus 14.7% [ticlopidine], HR 1.22, 95% CI: 0.94 to 1.57).²³

**Safety**
Compared with aspirin, ticlopidine is associated with an almost 3-fold excess of neutropenia (<1.2×10⁹/l) (2.3% [ticlopidine] versus 0.8% [aspirin]; OR: 2.7; 95% CI 1.5 to 4.8) and a 2-fold increase in the odds of skin rash (11.8% [ticlopidine] versus 5.5% [aspirin]; OR 2.2; 95% CI: 1.7 to 4.9).

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**Table 3. Summary of the Effects of Each Antiplatelet Regimen on the Composite Outcome of Stroke, MI or Vascular Death (Serious Vascular Events) Among Patients With TIA and Ischemic Stroke for Chronic Secondary Prevention**

<table>
<thead>
<tr>
<th>Antiplatelet Comparator</th>
<th>No. of Trials</th>
<th>n</th>
<th>Follow-Up</th>
<th>Serious Vascular Event Risk Reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin Control</td>
<td>11</td>
<td>9469</td>
<td>17 to 50 months</td>
<td>RR 0.87 (0.81 to 0.94)²⁵</td>
</tr>
<tr>
<td>Dipyridamole Control</td>
<td>1</td>
<td>3303</td>
<td>2 years</td>
<td>OR 0.81 (0.67–0.99)³²</td>
</tr>
<tr>
<td>Ticlopidine Control</td>
<td>1</td>
<td>1072</td>
<td>24 months</td>
<td>RR 0.77 (0.66 to 0.99)³³</td>
</tr>
<tr>
<td>Cilostazol Control</td>
<td>1</td>
<td>1095</td>
<td>~2 years</td>
<td>RR 0.61 (0.41–0.91)³¹</td>
</tr>
<tr>
<td>Ticlopidine Aspirin</td>
<td>1</td>
<td>4878</td>
<td>2 to 3 years</td>
<td>OR 0.93 (0.79 to 1.09)³²</td>
</tr>
<tr>
<td>Clopidogrel Aspirin</td>
<td>1</td>
<td>6431</td>
<td>1.91 years</td>
<td>RR 0.93 (0.81 to 1.06)³⁵</td>
</tr>
<tr>
<td>Triflusal Aspirin</td>
<td>4</td>
<td>2944</td>
<td>6 to 47 months</td>
<td>OR 1.02 (0.83–1.26)³⁵</td>
</tr>
<tr>
<td>Clopidogrel + Aspirin</td>
<td>1</td>
<td>3245</td>
<td>28 months</td>
<td>RR 0.78 (0.62 to 0.98)³³</td>
</tr>
<tr>
<td>Dipyridamole + Aspirin</td>
<td>6</td>
<td>7795</td>
<td>15 to 36 months</td>
<td>OR 0.82 (0.74 to 0.91)³⁵</td>
</tr>
<tr>
<td>Clopidogrel + Aspirin</td>
<td>1</td>
<td>7599</td>
<td>18 months</td>
<td>RR 0.94 (0.84 to 1.05)³⁵</td>
</tr>
</tbody>
</table>

*Subgroup analysis of stroke population within larger clinical trial; †median duration. RR indicates risk ratio; OR, odds ratio; HR, hazard ratio.
2.9) and diarrhea (20.4% [ticlopidine] versus 9.9% [aspirin]; OR 2.3; 95% CI: 1.9 to 2.8).44

**Clopidogrel Versus Aspirin**

**Trials**

One trial compared clopidogrel (75 mg/d) to aspirin (325 mg/d) in 19,195 patients with previous history of ischemic stroke (within 3 months), myocardial infarction, or established peripheral vascular disease.45

**Efficacy**

After mean follow-up of 2.1 years, clopidogrel reduced the relative risk of serious vascular events by 9% (10.7% [aspirin] versus 9.8% [clopidogrel], RR 0.91, 95% CI: 0.84 to 0.97). Within the subgroup of participants with previous ischemic stroke, there was a consistent reduction in risk of serious vascular events (14.4% [aspirin] versus 13.4% [clopidogrel], RR 0.93, 95% CI: 0.81 to 1.06).

**Safety**

Aspirin increased the risk of GI bleeding (RR: 1.45; 95% CI 1.0 to 2.1) compared with clopidogrel, but not other types of bleeding. Clopidogrel was associated with a significant one-third increased odds of skin rash (OR: 1.32; 95% CI, 1.2 to 1.5) and diarrhea (OR 1.34; 95% CI, 1.2 to 1.6) compared with aspirin. The yearly rate of symptomatic intracranial hemorrhage was comparable in both groups (0.49% [aspirin] versus 0.35% [clopidogrel]; NS).

**Triflusal Versus Aspirin**

**Trials**

Four randomized trials have compared triflusal (a selective cyclooxygenase-2 that is structurally related to aspirin) with aspirin among patients with stroke or TIA (2944 patients; followed for 6 to 47 months).46–49

**Efficacy**

A meta-analysis of these trials reported no significant difference between aspirin and triflusal in the risk of serious vascular events (OR 1.02, 95% CI 0.83 to 1.26).50

**Safety**

Random assignment to aspirin was associated with a higher risk of hemorrhage, both minor (OR 1.62, 95% CI 1.31 to 2.01) and major (OR 2.42, 95% CI 1.56 to 3.77), and lower risk of nonhemorrhagic gastrointestinal adverse events (OR 0.76, 95% CI 0.65 to 0.89).50

**Oral Glycoprotein IIb/IIIa Inhibitors Versus Aspirin**

**Trials**

The BRAVO trial (n=9190) compared lotrafiban, an oral GPIIa/IIa inhibitor, to placebo in aspirin-treated patients with cardiovascular and cerebrovascular disease (41% had a previous history of ischemic stroke), for secondary prevention of major vascular events.51

**Safety**

At interim review, the trial was terminated early because of an excess of vascular deaths in the lotrafiban group.

**Clopidogrel+Aspirin Versus Aspirin**

**Trials**

One trial compared clopidogrel (75 mg/d) plus low-dose aspirin (75 to 162 mg) to aspirin (75 to 162 mg/d) alone in 15,603 patients at high-risk of cardiovascular disease, which included 4320 patients with a previous ischemic stroke or TIA within the preceding 5 years.52

**Efficacy**

After a median follow-up of 28 months; the rate of serious vascular events was not significantly different between the treatment groups (7.3% [aspirin] versus 6.8% [clopidogrel plus aspirin], RR: 0.93; 95% CI: 0.83 to 1.05).54 In the subgroup of patients with previous ischemic stroke (n=3245), combination of aspirin and clopidogrel reduced the risk of serious vascular events by 22% (10.7% [aspirin] versus 8.4% [clopidogrel plus aspirin], RR: 0.78; 95% CI: 0.62 to 0.98).53

**Safety**

Clopidogrel plus aspirin was associated with no significant increase in the primary safety outcome of severe bleeding (1.3% [aspirin] versus 1.7% [aspirin+clopidogrel], RR: 1.25; 95% CI: 0.97 to 1.61) but a significant increase in the secondary safety outcome of moderate bleeding (1.3% [aspirin] versus 2.1% [aspirin+clopidogrel], RR: 1.62; 95% CI: 1.27 to 2.08).52

**Dipyridamole and Aspirin Versus Aspirin**

**Trials**

Six clinical trials (n=7795) have compared combination dipyridamole and aspirin to aspirin alone.50,52,34,54–56; the 2 most recent and largest trials52,55 evaluated extended release dipyridamole primarily (85% in ESPRIT used extended-release preparation), in contrast to the 4 earlier and smaller trials that evaluated immediate release dipyridamole.

**Efficacy**

A meta-analysis55 of all 6 trials revealed that random assignment to the combination of aspirin-DPD was associated with an 18% lower relative risk of serious vascular events compared to aspirin alone (RR 0.82; 95% CI 0.74 to 0.91).

**Safety**

A meta-analyses of 5 clinical trials that did not include the recently published ESPRIT trial reported no increase in bleeding with the aspirin-DPD regimen compared to aspirin alone. ESPRIT reported an unexpected 42% reduction in the risk of major bleeding with aspirin/E-DPD compared to aspirin (HR 0.58; 95% CI 0.35 to 0.97).57

**Clopidogrel+Aspirin Versus Clopidogrel**

**Trials**

One trial (MATCH) compared the combination clopidogrel (75 mg/d) and aspirin (75 to 162 mg/d) with clopidogrel (75 mg/d) among 7599 for high vascular risk patients within 3 months of TIA or minor ischemic stroke.58

**Efficacy**

At the end of 18-months follow-up, the addition of aspirin to clopidogrel did not significantly reduce the risk of serious
vascular events compared with clopidogrel alone (16.7% [clopidogrel] versus 15.7% [clopidogrel plus aspirin], RR: 0.94, 95% CI: 0.84 to 1.05).58

Safety
The addition of aspirin to clopidogrel was associated with a significant increase in life-threatening hemorrhage (1.3% [clopidogrel] versus 2.6% [aspirin+clopidogrel]). Life-threatening hemorrhage was intracranial (0.7% [clopidogrel versus 1.1% [clopidogrel+aspirin]) and gastrointestinal (0.6% [clopidogrel] versus 1.4% [clopidogrel+aspirin]).58

The risk of bleeding was cumulative over time. The Kaplan–Meier survival curves for survival free of primary intracerebral hemorrhage for each treatment group did not separate until at 3 to 4 months after randomization.

Antiplatelet Therapy Versus Warfarin Therapy

Trials
Seven randomized controlled trials have compared warfarin therapy to antiplatelet therapy for prevention of recurrent major vascular events after transient ischemic attack or minor stroke in patients with noncardioembolic stroke.59–65

Efficacy
A meta-analysis66 of 5 of these trials (n=4076) did not show superiority of warfarin over antiplatelet therapy. In trials evaluating medium intensity anticoagulation (INR of 2.1 to 3.6), warfarin did not reduce the risk of major vascular events compared to antiplatelet therapy (RR 0.96; 95% CI 0.38 to 2.42).

Since this meta-analysis, a second arm of the ESPRIT trial61 evaluated whether oral anticoagulation with medium intensity (INR 2.0 to 3.0) is more effective than aspirin (30 to 325 mg/d) in preventing future vascular events in patients with TIA or minor stroke of presumed arterial origin.61 A total of 1068 patients with recent TIA or minor stroke of presumed arterial origin were randomly assigned within 6 months of onset to open label therapy with either warfarin (n=536) or aspirin (n=532). After mean follow-up of 4.6 years (SD 2.2), the primary composite of vascular death, nonfatal stroke, nonfatal myocardial infarction, or major bleeding complication occurred in 19% of patients on anti-coagulants and 18% patients on aspirin (HR 1.02, 95% CI 0.77 to 1.35).

Interpretation of the Evidence

Acute Ischemic Stroke
Aspirin (160 to 300 mg) should be given as soon as possible (and continued as a once daily dose) in patients with suspected acute ischemic stroke, and reduced to lower doses (50 to 150 mg) after 10 to 14 days. In patients who are unable to swallow safely, aspirin may be given per rectum as a suppository or via a nasogastric tube. Antiplatelet drugs are no net advantage over antiplatelet drugs in acute ischemic stroke. It is usually recommended that patients who have been treated with thrombolytic therapy should probably not be started on aspirin for 24 to 48 hours. This is because nonrandomized comparisons suggest an adverse hemorrhagic interaction between thrombolytic and concomitant antithrombotic therapies, and increased risk of death, in randomized controlled trials of thrombolysis compared to control in acute ischemic stroke.57,68

Although many clinicians start clopidogrel or combination dipyridamole/aspirin in preference to aspirin alone during the acute period (particularly in patients already treated with aspirin before onset of stroke symptoms), no large clinical trials have evaluated the effectiveness and safety of this practice.

Long-Term Secondary Prevention
Aspirin (50 to 150 mg) remains the cornerstone antithrombotic therapy, with an expected 13% relative risk reduction in serious vascular events. The addition of extended release dipyridamole (400 mg/d) to aspirin is expected to contribute a further 18% (9% to 26%) reduction in relative risk of serious vascular events. Clopidogrel appears to be marginally but significantly more effective that aspirin, based on the CAPRIE trial. The combination of aspirin and clopidogrel is not more effective than clopidogrel alone, but may be more effective than aspirin alone. As the latter observation is based on a posthoc subgroup analysis of CHARISMA, the combination of aspirin and clopidogrel is not usually indicated for long-term secondary prevention of recurrent vascular events among patients with TIA and ischemic stroke, unless there is another indication for use of the combination ie, recent acute coronary syndrome or percutaneous coronary intervention (particularly after insertion of a drug-eluting coronary stent).69

Although indirect comparisons between trials of clopidogrel and combination aspirin/DPD suggest that aspirin/DPD may be more effective for secondary prevention, the 2 regimens are being compared directly in the ongoing large PROFESS trial, which should report its results in 2008 (Table 4).70

Future Directions
Present Antiplatelet Drugs
In the acute phase after ischemic stroke or TIA, a high priority is a dedicated evaluation, by means of an adequately powered clinical trial, of the safety and efficacy of adding clopidogrel, given as a loading dose of 300 or 600 mg, to aspirin in patients at high risk for early recurrent ischemic stroke (eg, with symptomatic large artery atherothromboembolism), and continued for a short period of about 3 months (during this time the benefits are likely to be greatest and the cumulative risks for bleeding lessened). Ongoing research also aims to identify the independent risk factors for bleeding complications associated with combination antiplatelet therapy, and the optimal antiplatelet regimens.

Novel Antiplatelet Drugs
At least 2 novel antiplatelet drugs are currently being evaluated for long-term management of patients with recent stroke or TIA.

The Prevention of cerebrovascular and cardiovascular Events of ischemic origin with terRutroban in patients with a history of ischemic strOKe or tRansient ischeMic attack (PERFORM) trial is underway and aims to randomize 18 000
patients with ischemic stroke or TIA of atherothrombotic origin to long-term treatment with aspirin or terutroban (S18886, a thromboxane receptor antagonist).

The Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TR 2P-TIMI 50) trial aims to randomize 19,500 high vascular risk patients with previous ischemic stroke, MI, or PAD (ABI <0.85 or prior revascularization or amputation) within the previous 2 weeks to 12 months to long-term treatment with aspirin 81 to 162 mg daily or SCH 530348 (a thrombin receptor antagonist) 2.5 mg per day.

Antiplatelet drugs that target the P2Y₁₂ receptor (eg, AZD-6140, prasugrel) are being evaluated as alternatives to clopidogrel or ticlopidine in patients with acute coronary syndromes or undergoing percutaneous coronary intervention but have not been evaluated in stroke. Other antiplatelet drugs that may have potential for the acute and long-term management of stroke include thromboxane receptor antagonists (eg, S18886), combined thromboxane synthase/thromboxane receptor inhibitors, and drugs that selectively block the platelet ADP receptor P2Y₁, glycoprotein Ib, Ia/Ila, and VI; HT2, and the thrombin (protease activated) receptor.

Disclosures

Dr Martin O'Donnell holds the William Walsh Endowed Research Chair in Internal Medicine and a Mentor-Mentee Award from the Canadian Institutes of Health Research. Dr John Eikelboom holds a Tier II Research Chair from the Canadian Institutes of Health Research. John Eikelboom has received honoraria for speaking at scientific symposia and serving on advisory boards sponsored by Bayer, Boehringer-Ingelheim, Sanofi-Aventis, and Bristol Myers Squibb. He was also a member of the Steering Committees of the CHARISMA and ESPRIT trials.

References

6. Deleted in proof.

Table 4. Antiplatelet Drugs Currently Approved for Use or in Advanced Stages of Evaluation for the Secondary Prevention of Noncardioembolic Ischemic Stroke

| Drug Target Prodrug Reversible Route Dosing Stroke Phase Nonbleeding Toxicity* |
|-------------------------------|-----------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Approved                      | ASA/Clodipogrel                  | COX-1            | No              | Oral o.d.       | Acute/chronic   | Asthma, GI intolerance |
|                               | ASA                              | COX-1            | No              | Oral b.i.d.     | Chronic         | Asthma, headache, GI intolerance |
|                               | Clopidogrel                      | P2Y₁₂            | Yes             | Oral o.d.       | Acute           | Allergy, rash, GI intolerance |
|                               | Ticlopidine                      | P2Y₁₂            | Yes             | Oral b.i.d.     | Chronic         | Rash, GI intolerance, cytoopenias, TTP |
|                               | ASA/dipyridamole*               | COX-1/PDE        | No              | Oral b.i.d.     | Chronic         | Asthma, headache, GI intolerance |

Phase 3 Trials

| Drug Target Prodrug Reversible Route Dosing Stroke Phase Nonbleeding Toxicity* |
|-------------------------------|-----------------------------------|-----------------|-----------------|-----------------|-----------------|
| Approved                      | ASA                              | COX-1/PDE       | No              | Oral b.i.d.     | Acute           | Asthma, headache, GI intolerance |
|                               | Clopidogrel                      | P2Y₁₂/COX-1     | No              | Oral o.d.       | Acute           | Allergy, rash, GI intolerance |
|                               | Cilostazol                      | PDE              | No              | Oral b.i.d.     | Acute/chronic   | Headache, GI intolerance |

| Drug Target Prodrug Reversible Route Dosing Stroke Phase Nonbleeding Toxicity* |
|-------------------------------|-----------------------------------|-----------------|-----------------|-----------------|-----------------|
| Approved                      | Abciximab                        | GPIIb/IIIa      | No              | i.v. Infuse     | Acute           | Thrombocytopenia |

*Trade name Aggrenox.

b.i.d. indicates twice daily; COX, cyclooxygenase; GI, gastrointestinal; o.d., once daily; PDE, phosphodiesterase; TTP, Thrombotic thrombocytopenic purpura.

Table 3. Estimates of the absolute benefits and risks of antiplatelet drugs currently used for the management of stroke.

b.i.d. indicates twice daily; COX, cyclooxygenase; GI, gastrointestinal; o.d., once daily; PDE, phosphodiesterase; TTP, Thrombotic thrombocytopenic purpura.

| Drug Target Prodrug Reversible Route Dosing Stroke Phase Nonbleeding Toxicity* |
|-------------------------------|-----------------------------------|-----------------|-----------------|-----------------|-----------------|
|Approved                      | ASA                              | COX-1            | No              | Oral o.d.       | Acute/chronic   | Asthma, GI intolerance |
|                               | Clopidogrel                      | P2Y₁₂            | Yes             | Oral o.d.       | Chronic         | Allergy, rash, GI intolerance |
|                               | Ticlopidine                      | P2Y₁₂            | Yes             | Oral b.i.d.     | Chronic         | Rash, GI intolerance, cytoopenias, TTP |
|                               | ASA/dipyridamole*               | COX-1/PDE        | No              | Oral b.i.d.     | Chronic         | Asthma, headache, GI intolerance |

Phase 3 Trials

| Drug Target Prodrug Reversible Route Dosing Stroke Phase Nonbleeding Toxicity* |
|-------------------------------|-----------------------------------|-----------------|-----------------|-----------------|-----------------|
| Approved                      | ASA                              | COX-1/PDE       | No              | Oral b.i.d.     | Acute           | Asthma, headache, GI intolerance |
|                               | Clopidogrel                      | P2Y₁₂/COX-1     | No              | Oral o.d.       | Acute           | Allergy, rash, GI intolerance |
|                               | Cilostazol                      | PDE              | No              | Oral b.i.d.     | Acute/chronic   | Headache, GI intolerance |

| Drug Target Prodrug Reversible Route Dosing Stroke Phase Nonbleeding Toxicity* |
|-------------------------------|-----------------------------------|-----------------|-----------------|-----------------|-----------------|
|Approved                      | Abciximab                        | GPIIb/IIIa      | No              | i.v. Infuse     | Acute           | Thrombocytopenia |


Antiplatelet Therapy for Secondary Prevention of Noncardioembolic Ischemic Stroke: A Critical Review

Martin J. O'Donnell, Graeme J. Hankey and John W. Eikelboom

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An erratum has been published regarding this article. Please see the attached page for:
/content/39/9/e147.full.pdf
In the article entitled “Antiplatelet Therapy for Secondary Prevention of Noncardioembolic Ischemic Stroke: A Critical Review” by O’Donnell et al., the authors report two errors. First, in Table 3, under Cilostazol’s Serious Vascular Event Risk Reduction (95% CI) column, the values should be “(0.41–0.91)” instead of “(0.41–0.01).” Second, on page 1641, the reference number of the “Efficacy” category under the “Cilostazol Versus Control” Section should be “41” instead of “42.” The authors regret these errors.

The corrected version can be viewed online at http://stroke.ahajournals.org.