Scores of randomized trials, observational cohort studies, and epidemiological surveys have altered the management of stroke and threatened stroke in recent years. Here 10 studies that have most influenced my day-to-day clinical management are analyzed, and selected methodological features relevant to their interpretation are discussed.

Randomized clinical trials provide the strongest evidence, and nine of the 10 are randomized trials (Table 1).1-12 Even “negative” randomized trials (i.e. those in which the randomized interventions are not shown to be statistically significantly different) can importantly impact clinical practice if they are methodologically sound, adequately powered, and testing widely-used treatments; half of the influential trials considered here reported no difference in treatment outcomes. Only two of the selected studies involve management of acute stroke patients7,12; several trials testing novel agents in acute stroke that were anticipated to be positive based on preliminary phase II studies were disappointingly negative (and not considered further).13-15

By way of disclosure, I had minor roles in several of the selected studies: serving on the external data monitoring committees of CHARISMA2, SPARCL6, and BAFTA8, and as a secondary site investigator of PRoFESS1 and PREVAIL12.

This paper analyzes the first four studies – randomized clinical trials together involving 39,742 participants testing antithrombotic agents for secondary prevention of noncardioembolic ischemic stroke – and then summarizes recent guideline recommendations. In Part II, the remainder of the “top 10” is considered.

1 Clopidogrel and extended-release dipyridamole/low-dose aspirin in patients with recent ischemic stroke are shown to be about equal for reducing recurrent stroke in the giant international PRoFESS trial. Combination antiplatelet therapy with clopidogrel plus aspirin is not better than either alone for prevention of vascular events and causes more serious bleeding based on the CHARISMA trial. Extended-release dipyridamole/low-dose aspirin is better than low-dose aspirin alone for secondary stroke prevention from ESPRIT. Based on the second component of ESPRIT, aspirin is as good as anticoagulation after noncardioembolic brain ischemia. These trials, together involving 39,742 participants, have influenced 2008 European and North American guidelines for secondary prevention of noncardioembolic stroke, and these guideline recommendations are reviewed.
Table 1: The top 10 stroke studies of 2006–2008

1. Clopidogrel vs. extended-release dipyridamole/low-dose aspirin about equal after ischemic stroke (PROFESS)

2. Combination antiplatelet therapy with clopidogrel plus aspirin not better than either alone for prevention of vascular events and caused more serious bleeding (CHARISMA)

3. Extended-release dipyridamole/low-dose aspirin better than low-dose aspirin alone for secondary stroke prevention (ESPRIT)

4. Aspirin as good as anticoagulation after noncardioembolic brain ischemia (ESPRIT)

5. The ABCD2 score predicts the short-term risk of stroke following transient ischemic attack

6. High-dose atorvastatin reduces stroke in patients with recent stroke, but possibly increases CNS hemorrhage (SPARCL)

7. Intravenous tissue plasminogen activator is of overall benefit when given 3–4.5 hours after ischemic stroke onset (ECASS III)

8. Warfarin is efficacious and safe for very old people with atrial fibrillation (BAFTA)

9. Carotid angioplasty/stenting vs. endarterectomy? (SAPPHIRE, EVA-3S)

10. Enoxaparin vs. unfractionated heparin for prevention of venous thromboembolism after acute ischemic stroke (PREVAIL)

Management, and Avoidance) randomized trial, the combination of clopidogrel 75 mg/day plus aspirin (dosage range 75 mg to 162 mg daily) was compared with aspirin alone in 15,603 patients with stable cardiovascular disease or multiple cardiovascular risk factors during 2.3 years mean follow-up. Two mean patient age was 64 years, 70% were men, and 42% had diabetes mellitus. The primary outcome constellation (stroke, myocardial infarct or vascular death) was not different between treatment arms, but bleeding was increased with combination therapy (Table 3). The stroke rate was low, averaging 1% per year, among all CHARISMA participants. Among the 3645 CHARISMA participants who had a prior ischemic stroke a mean of 3 months before study entry, the primary event constellation was reduced by 22% (p = 0.03) – but beware of accepting positive exploratory subgroup analyses from overall negative trials!

CHARISMA results are best considered in the context of the MATCH (Management of Atherosclerosis with Clopidogrel in High-risk patients with transient ischemic attack [TIA] or stroke) randomized trial. The MATCH trial was designed to assess the value of adding aspirin to clopidogrel (rather than adding clopidogrel to aspirin as in CHARISMA) for secondary stroke prevention. In the MATCH trial, clopidogrel 75 mg daily alone was compared to clopidogrel 75 mg daily plus aspirin 75 mg daily in 7,599 patients with recent ischemic stroke or transient ischemic attack (TIA). All strokes were nearly equal (347 clopidogrel, 339 clopidogrel plus aspirin). There was an excess of 32 nonCNS life-threatening hemorrhages among those assigned combination antiplatelet therapy (an absolute increase of 0.5% per year, p <0.05). In short, MATCH does not demonstrate benefits of adding aspirin 75 mg/d to clopidogrel, and serious bleeding was significantly increased among those given the combination.

Considered together, the relatively consistent results of MATCH and CHARISMA show that combined antiplatelet therapy with clopidogrel and aspirin offers uncertain, minimal benefits for longterm treatment of patients after TIA or ischemic stroke compared with single therapy with either drug alone and that serious bleeding is clearly increased by the combination.

3. Extended-release dipyridamole plus low-dose aspirin better than low-dose aspirin alone for secondary stroke prevention (ESPRIT) 12 years ago, the double-blind European Stroke Prevention Study-2 randomized trial reported that addition of extended-release dipyridamole (200 mg twice daily) to low-dose aspirin (25 mg twice daily) reduced recurrent stroke by 23% in patients with initial TIA/stroke relative to aspirin alone based on 3299 participants followed for two years with 363 stroke events. Involvement of the sponsoring pharmaceutical company in all aspects of the trial, exclusion of substantial numbers of randomized patients from one site, and the low
The on-treatment results (i.e. excluding participants who were not taking the assigned medication) were not better than the intention-to-treat results, with trends in the opposite direction. In most clinical trials, on-treatment results, while potentially biased, magnify treatment differences. While the investigators suggest that this could be due to chance, the opposite-to-expected trend was evident for each of nine individual outcomes.

Major bleeding was less with dual therapy (although not quite statistically significant). Considering the primary event constellation, the largest effect of dual antiplatelet therapy was an unexpected reduction in major hemorrhage, but there was no effect on minor bleeding. That combination antiplatelet therapy reduces major bleeding (but with no effect on minor bleeding) is counter-intuitive.

There was no reduction in ischemic events until after two years of follow-up, with all benefit accruing later. The investigators postulate play-of-chance. Does this imply another mechanism is operative to explain the benefit of dipyridamole?

Blood pressures did not differ between the treatment groups.

Aspirin dosage led to skepticism on the part of some about the incremental value of extended-release dipyridamole plus aspirin over aspirin alone for secondary stroke prevention.

The long-awaited ESPRIT (European/Australasian Stroke Prevention in Reversible Ischemia Trial) comparing these same agents was led by experienced, independent clinical trialists from the Netherlands. In an open-label design, 2739 patients with minor ischemic stroke or TIA were randomized and followed for a mean of 3.5 years. The results were “positive” for the specified primary outcome constellation of stroke, myocardial infarct, vascular death or major hemorrhage, but the reduction in ischemic stroke was not statistically significant (Table 4).

Several aspects prompt comment:

1. The dosage of aspirin averaged 75 mg daily, and about 40% of participants took only 30 mg daily. Subgroup analysis did not suggest that participants taking the lower dosages had more benefit from addition of dipyridamole. Even so, 30 mg daily of aspirin is less than the usual dosage for stroke prevention used in North America and below the dosage that endorsed by the U.S. Food and Drug Administration (50–325 mg daily).

2. The on-treatment results (i.e. excluding participants who were not taking the assigned medication) were not better than the intention-to-treat results, with trends in the opposite direction. In most clinical trials, on-treatment results, while potentially biased, magnify treatment differences. While the investigators suggest that this could be due to chance, the opposite-to-expected trend was evident for each of nine individual outcomes.

3. Major bleeding was less with dual therapy (although not quite statistically significant). Considering the primary event constellation, the largest effect of dual antiplatelet therapy was an unexpected reduction in major hemorrhage, but there was no effect on minor bleeding. That combination antiplatelet therapy reduces major bleeding (but with no effect on minor bleeding) is counter-intuitive.

4. There was no reduction in ischemic events until after two years of follow-up, with all benefit accruing later. The investigators postulate play-of-chance. Does this imply another mechanism is operative to explain the benefit of dipyridamole?

Blood pressures did not differ between the treatment groups.
dipyridamole over aspirin alone as antithrombotic therapy after cerebral ischemia of arteri
al origin."

3 4 Aspirin as good as anticoagulation following noncardioembolic ischemic stroke and TIA (ESPRIT) The ESPRIT included a second component comparing adjusted-dose anticoagulation (target \([\text{international normalized ratio – INR}] 2–3\)) with aspirin (30–325 mg daily), given open-label, in 1068 patients within 6 months of TIA or minor ischemic stroke of arterial origin. Notably, patients with major cardioembolic sources (e.g. atrial fibrillation), patients over age 75 years, and those with severe “leukoariosis” detected by computer tomography or magnetic resonance imaging (who are at high risk of anticoagulation-related intracerebral hemorrhage) were excluded. The mean participant age was 61 years, and half of ischemic events were attributed to small-vessel disease. The mean follow-up was 4.6 years, the median aspirin dosage was 30 mg per day, the absolute magnitude of benefit conferred by combination antiplatelet therapy to ESPRIT participants was small: the number-needed-to-treat (NNT) for one year with dual therapy over aspirin alone to prevent one ischemic stroke is 240 patients. Using on-treatment results, the estimated NNT is about 430 patients. While the NNT for the event constellation making up the primary outcome was 100 patients treated for one year, a portion of this benefit was accounted for by the implausible reduction in major hemorrhage by dual antiplatelet therapy. The influential ESPRIT antiplatelet trial has impacted recent major guidelines for secondary stroke prevention, strengthening the recommendation for use of extended-release dipyridamole/ aspirin over aspirin alone as antithrombotic therapy after cerebral ischemia of arterial origin.3

4

Table 4 Main results of the ESPRIT antiplatelet comparison

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Extended-release dipyridamole + aspirin (n = 1363)</th>
<th>Aspirin (n = 1376)</th>
<th>Relative risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke, myocardial infarct, vascular death, or major hemorrhage</td>
<td>173</td>
<td>216</td>
<td>20% (p &lt;0.05)</td>
</tr>
</tbody>
</table>
| First ischemic stroke | 96 (2.1%/year) | 116 (2.6%/year) | 16% (32%–10%)
| All deaths | 93 | 107 | 12% (p = NS) |
| Major hemorrhages | | | |
| All | 35 | 53 | 33% (p = −0.07) |
| Intracranial | 12 | 21 | 43% (p = NS) |
| Minor hemorrhages | 171 | 168 | −3% (p = NS) |
| Stroke, myocardial infarct, or vascular death | 140 | 174 | 19% (p = −0.06) |

a Primary outcome
b On-treatment analysis: 9% reduction (95% CI from 32.0 to −22)
All results based on intention-to-treat analysis unless otherwise specified.

Table 5 Main results of the ESPRIT aspirin vs. anticoagulant comparison

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Aspirin (n = 532)</th>
<th>Anticoagulant (n = 536)</th>
<th>Hazard ratio (95% CI)/p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke, myocardial infarct, vascular death or major hemorrhage</td>
<td>98</td>
<td>99</td>
<td>1.02 (0.77–1.35)</td>
</tr>
<tr>
<td>All stroke</td>
<td>62 (2.8%/year)</td>
<td>59 (2.7%/year)</td>
<td>0.76 (0.51–1.15)</td>
</tr>
<tr>
<td>first ischemic stroke</td>
<td>53</td>
<td>41</td>
<td>0.76 (0.51–1.15)</td>
</tr>
<tr>
<td>intracranial hemorrhage</td>
<td>9</td>
<td>18</td>
<td>p = NS</td>
</tr>
<tr>
<td>Major extracranial hemorrhage</td>
<td>9</td>
<td>27</td>
<td>p &lt;0.01</td>
</tr>
<tr>
<td>Cardiac event: MI, sudden death, cardiac death</td>
<td>33</td>
<td>25</td>
<td>p = NS</td>
</tr>
<tr>
<td>All deaths</td>
<td>44</td>
<td>59</td>
<td>p = NS</td>
</tr>
</tbody>
</table>

a Primary outcome
b All strokes not specifically reported and was estimated as the sum of first ischemic stroke and intracranial hemorrhage; it is possible that there was some patients with both who would have been double-counted.
c 5 patients in warfarin arm and 3 patients in aspirin arm did not have brain imaging; strokes assumed to be ischemic.

Abbreviations – see Table 2
unethical in the wake of results of the antiplatelet comparison favoring extended-release dipyridamole/low-dose aspirin (see 3, above).

No overall benefit was evident in those assigned to adjusted-dose anticoagulation (Table 5), but the 95% CI did not exclude a clinically important benefit because the trial was stopped with only about half of the planned number of primary events. A trend toward fewer ischemic strokes among those assigned to anticoagulation was counterbalanced by more intracranial hemorrhages. The investigators conclude that “Oral anticoagulants (target INR range 2.0–3.0) are not more effective than aspirin for secondary and the mean achieved INR was 2.6 (with about 70% falling within the target range). Analysis of results was intention-to-treat and hence included those “off assigned therapy”: 19% and 32% of those assigned to anticoagulation and 6% and 15% of those assigned to aspirin at 1 year and 5 years, respectively. The mean blood pressure was high at trial entry (153/87 mmHg); blood pressures during follow-up were not reported. The trial was terminated before accumulation of the planned number of primary events (the constellation of stroke, myocardial infarct, vascular death, or major hemorrhage) because continuance of aspirin was believed by the investigators to be unethical in the wake of results of the antiplatelet comparison favoring extended-release dipyridamole/low-dose aspirin (see 3, above).

No overall benefit was evident in those assigned to adjusted-dose anticoagulation (Table 5), but the 95% CI did not exclude a clinically important benefit because the trial was stopped with only about half of the planned number of primary events. A trend toward fewer ischemic strokes among those assigned to anticoagulation was counterbalanced by more intracranial hemorrhages. The investigators conclude that “Oral anticoagulants (target INR range 2.0–3.0) are not more effective than aspirin for secondary

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Study population/mean age</th>
<th>Aspirin dosage</th>
<th>Mean achieved INR</th>
<th>Intracranial bleeding</th>
<th>Key results</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPIRIT 25 (1993–1996)</td>
<td>1316</td>
<td>Non-CE; −64 years, BP = 158/91 mmHg</td>
<td>30 mg/d</td>
<td>3.3</td>
<td>3.7%/year</td>
<td>Intolerable CNS bleeding during anticoagulation</td>
</tr>
<tr>
<td>WARSS 26 (1994–2000)</td>
<td>2206</td>
<td>Non-CE; 63 years, BP = NR</td>
<td>325 mg/d</td>
<td>2.0</td>
<td>NR</td>
<td>Equal considering ischemic stroke and death</td>
</tr>
<tr>
<td>WASID 27 (1999–2003)</td>
<td>569</td>
<td>Symptomatic intracranial stenosis; 64 years, BP = 140/77 mmHg</td>
<td>1300 mg/d</td>
<td>2.5</td>
<td>0.5%/year</td>
<td>Equal considering all stroke and death</td>
</tr>
<tr>
<td>ESPRIT 4 (1997–2005)</td>
<td>1088</td>
<td>Non-CE; 61 years, BP = 153/87 mmHg</td>
<td>30 mg/d*</td>
<td>2.6</td>
<td>0.8%/year</td>
<td>Equal considering stroke, myocardial infarct, vascular death or major hemorrhage</td>
</tr>
</tbody>
</table>

* Median aspirin dosage = 30 mg/24 h, but dosages up to 325 mg/24 h permitted.

Abbreviations: BP – average blood pressure at study entry, INR – international normalized ratio, N – number of participants, non-CE – noncardioembolic stroke etiology, NR – not reported.

**TABLE 6** Modern randomized trials of anticoagulant vs. aspirin after noncardioembolic stroke

<table>
<thead>
<tr>
<th>Table 7</th>
<th>2008 Guidelines for Antithrombotic Therapy for Secondary Prevention of Noncardioembolic Ischemic Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acceptable antiplatelet therapies</strong></td>
<td><strong>Prefered antiplatelet agents</strong></td>
</tr>
<tr>
<td>ESO “patients (…) should receive antiplatelet therapy (Class I, Level A)” Aspirin (50–1,300 mg/24 h), clopidogrel, dipyridamole, triflusal, or dipyridamole (200 mg extended release twice daily) combined with aspirin (30–300 mg/24 h).</td>
<td>ESO “Where possible, combined aspirin and dipyridamole, or clopidogrel alone, should be given.”</td>
</tr>
<tr>
<td>AHA “Aspirin (50–325 mg/24 h), the combination of extended-release dipyridamole, and clopidogrel monotherapy are all acceptable options for initial therapy (Class I, Level A).”</td>
<td>AHA “the combination of aspirin and extended-release dipyridamole is recommended over aspirin alone (Class I, Level B) (...). Clopidogrel may be considered over aspirin alone (Class IIb, Level B)”</td>
</tr>
<tr>
<td>ACCP “aspirin, the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily, and clopidogrel 75 mg/24 h are all acceptable options for initial therapy.”</td>
<td>ACCP “we recommend using the combination of aspirin and extended-release dipyridamole (25/200 mg twice daily) over aspirin (Grade 1A) and suggest clopidogrel over aspirin (Grade 2B).”</td>
</tr>
</tbody>
</table>

**Antiplatelet agents vs. anticoagulants**

| ESO “anticoagulation should not be used (…) except in some specific situations (…)” | AHA “antiplatelet agents rather than oral anticoagulants are recommended (Class I, Level A).” |
| ACCP “we recommend antiplatelet agents over oral anticoagulation (Grade 1A)” | ACCP “we recommend avoiding long-term use of the combination of aspirin and clopidogrel (Grade 1B)” |

**Combination of clopidogrel plus aspirin**

| ESO “The combination of aspirin and clopidogrel is not recommended (…) except in patients with specific indications (e.g. unstable angina or non-Q-wave MI, or recent stenting)” | AHA “combination therapy of aspirin and clopidogrel is not routinely recommended unless [...] a specific indication [...] (i.e. coronary stent or acute coronary syndrome).” |
| ACCP “we recommend avoiding long-term use of the combination of aspirin and clopidogrel (Grade 1B)” | |

prevention after TIA or minor stroke of arterial origin," but the trial is underpowered to firmly support this conclusion.

While not sufficient in itself, taken in the context of other modern randomized trials (Table 6), ESPIRIT contributes to the body of randomized evidence favoring antiplatelet therapy over oral vitamin K antagonists for secondary prevention in patients with noncardioembolic ischemic stroke and TIA. No benefit of anticoagulation emerged from these trials despite testing a wide range of achieved INRs and aspirin dosages.

Recommendations from recent guidelines regarding antithrombotic therapy for secondary stroke prevention

In the wake of the four trials discussed above, what is the current status of antithrombotic therapy for secondary prevention in patients with noncardioembolic ischemic stroke and TIA? Updated versions of three major guidelines were published in 2008 by the European Stroke Organization (ESO), the American Heart Association (AHA) and the American College of Chest Physicians (ACCP). All three guidelines considered data from the CHARISMA trial (1, above) and from both components of ESPIRIT (3 and 4, above), but none could consider the subsequently published PROFESS trial results (1, above). Their recommendations are similar (and the two American guidelines are virtually identical), with the main difference a stronger endorsement of clopidogrel by the ESO (Table 7).

How will the PROFESS trial results modify the next iteration of the guidelines? The current ESO guideline advocates either dipyridamole plus aspirin or clopidogrel as preferred antiplatelet agents, and hence the PROFESS results may not alter this recommendation.

Integration of the PROFESS trial results into recommendations for antiplatelet therapy requires weighing indirect comparisons between trial results. Clopidogrel was only slightly superior to aspirin 325 mg per day in the earlier CAPRIE trial and narrowly comparable to extended-release dipyridamole plus low-dose aspirin in PROFESS.1 Hence, by one interpretation of indirect comparisons, clopidogrel, dipyridamole plus low-dose aspirin, and aspirin 325 mg per day should all be of approximately similar efficacy.2 More likely, weighing the two trials supporting superiority of extended-release dipyridamole plus low-dose aspirin over low-dose aspirin alone 3,19 more heavily than the CAPRIE trial results will presumably strengthen the recommendation for clopidogrel over aspirin in future AHA and ACCP guidelines, bringing them into line with the current ESO recommendations.

REFERENCES
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