REVIEW ARTICLE

What's new in stroke? The top 10 studies of 2006–2008

Part I

Robert G. Hart

Department of Neurology, University of Texas Health Science Center, San Antonio, TX, USA

KEY WORDS

anticoagulation, antiplatelet agents, aspirin, clopidogrel, dipyridamole, stroke, stroke prevention

ABSTRACT

Ten studies from 2006–2008 that have importantly influenced clinical management of stroke and threatened stroke are presented. In Part I, four randomized clinical trials testing antithrombotic agents for secondary prevention of noncardioembolic ischemic stroke are analyzed.

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.

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 patients[7,12]; 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 CHARISMA[2], SPARCL[6], and BAFTA[8], and as a secondary site investigator of PRoFESS[1] and PREVAIL[12].

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/aspirin have about equal benefits after ischemic stroke or transient ischemic attack (PRoFESS)

In the PRoFESS (Prevention Regimen For Effectively avoiding Second Strokes), 20,332 patients (mean age was 66 years, 64% were men) with recent (<120 days) ischemic stroke were randomized

Correspondence to:
Prof. Robert G. Hart, MD, Department of Neurology, University of Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, TX, USA, 78229, phone: 001-210-592-0404, fax: 001-210-592-0552, e-mail: hartr@uthscsa.edu
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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)[1]
2 Combination antiplatelet therapy with clopidogrel plus aspirin not better than either alone for prevention of vascular events and caused more serious bleeding (CHARISMA)[2]
3 Extended-release dipyridamole/low-dose aspirin better than low-dose aspirin alone for secondary stroke prevention (ESPRIT)[3]
4 Aspirin as good as anticoagulation after noncardioembolic brain ischemia (ESPRIT)[4]
5 The ABCD2 score predicts the short-term risk of stroke following transient ischemic attack[5]
6 High-dose atorvastatin reduces stroke in patients with recent stroke, but possibly increases CNS hemorrhage (SPARCL)[6]
7 Intravenous tissue plasminogen activator is of overall benefit when given 3–4.5 hours after ischemic stroke onset (ECASS III)[7]
8 Warfarin is efficacious and safe for very old people with atrial fibrillation (BAFTA)[8]
9 Carotid angioplasty/stenting vs. endarterectomy? (SAPPHIRE, EVA-3S and SPACE)[9-11]
10 Enoxaparin vs. unfractionated heparin for prevention of venous thromboembolism after acute ischemic stroke (PREVAIL)[12]

to extended-release dipyridamole (200 mg)/low-dose aspirin (25 mg) twice daily vs. clopidogrel 75 mg once daily in a double-blind design carried-out at 695 sites in 35 countries.[16] The trial was planned with a noninferiority design and, in addition to the antiplatelet comparison, participants were also randomized to receive telmistartan vs. placebo added to usual blood pressure care; this component is not discussed further here. About half (52%) of qualifying strokes were attributed to cerebral small-artery disease (i.e. "lacunar" strokes), median time from qualifying stroke to study entry was 15 days, and average follow-up was 2.3 years. The primary outcome was recurrent stroke (i.e. combined ischemic and hemorrhagic stroke) and was no different between treatment arms: the recurrent stroke rate was 3.6% per year for those assigned extended-release dipyridamole plus aspirin and 3.5% per year for those assigned clopidogrel (hazard ratio 1.01, 95% CI 0.92–1.11) (TABLE 2).[1] There were fewer major hemorrhages in those assigned clopidogrel (p = 0.05): about 1 fewer major hemorrhage per year for every 200 treated patients.

In summary, the large PRoFESS trial shows no difference for recurrent stroke or for major vascular events between clopidogrel and extended-release dipyridamole plus low-dose aspirin, with a narrow confidence interval around the hazard ratio that excludes a clinically important difference. Trends favor clopidogrel regarding fewer major hemorrhages and better tolerance, but absolute differences are small.

2 Clopidogrel plus aspirin is no better than either alone for prevention of vascular events and causes serious bleeding (CHARISMA) In the double-blind CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, 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.[2] The mean participant 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![17]

CHARISMA results are best considered in the context of the MATCH (Management of AThero-thrombosis with Clopidogrel in High-risk patients with transient ischemic attack [TIA] or stroke) randomized trial.[18] 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.[19] 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

TABLE 2 Main results of the PRoFESS trial antiplatelet comparison

Outcomes	Extended-release dipyridamole + aspirin (n = 10,181)	Clopidogrel (n = 10,151)	p
Recurrent stroke*	916 9% (3.6%/year)	898 8.8% (3.5%/year)	NS
Intracranial hemorrhage	147	103	<0.01
Myocardial infarct	178	197	NS
Stroke, myocardial infarct, or vascular death	1333 (13.1%)	1333 (13.1%)	NS
Life-threatening hemorrhage	128 (1.3%)	116 (1.1%)	NS
Major hemorrhage	419 (4.1%)	365 (3.6%)	0.05
Recurrent stroke or major hemorrhage	1194 (11.7%)	1156 (11.4%)	NS
All-cause death	739 (7%)	756 (7%)	NS
Discontinuation of meds – due to headache	29% 5.9%	23% 0.9%	<0.001 <0.01

*Primary outcome
All results based on intention-to-treat analysis unless otherwise specified.

Abbreviations: NS – not statistically significant (p >0.05)

TABLE 3 Main results of the CHARISMA trial

Outcomes	Clopidogrel + aspirin (n = 7802)	Aspirin (n = 7801)	p
Stroke, myocardial infarct or vascular death*	534	573	NS
All nonfatal strokes	149	185 (1%/year)	0.05
All deaths	371	374	NS
Primary intracerebral bleeds	26	27	NS
Severe hemorrhage	130	104	0.09
Moderate hemorrhage	164	101	<0.001

*Primary outcome
All results based on intention-to-treat analysis unless otherwise specified.

Abbreviations – see TABLE 2

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.[3] 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 counterintuitive.

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.[20]

TABLE 4 Main results of the ESPRIT antiplatelet comparison

Outcomes	Extended-release dipyridamole + aspirin (n = 1363)	Aspirin (n = 1376)	Relative risk reduction
Stroke, myocardial infarct, vascular death, or major hemorrhage[a]	173	216	20% (p <0.05)
First ischemic stroke	96 (2.1%/year)	116 (2.6%/year)	16% (32%–10%)[b]
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.

Abbreviations – see **TABLE 2**

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

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

[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**

5 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 (see below). Editorial commentaries by stroke experts [21-24] support the interpretation of the ESPRIT Study Group: "The ESPRIT results, combined with the results of the previous trials, provide sufficient evidence to prefer the combination regimen of aspirin plus dipyridamole over aspirin alone as antithrombotic therapy after cerebral ischemia of arterial 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 [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.[4] 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,

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

Trial	N	Study population/mean age	Aspirin dosage	Mean achieved INR	Intracranial bleeding	Key results
SPIRIT [25] (1993–1996)	1316	Non-CE; ~64 years, BP = 158/91 mmHg	30 mg/d	3.3	3.7%/year	Intolerable CNS bleeding during anticoagulation
WARSS [26] (1994–2000)	2206	Non-CE; 63 years, BP = NR	325 mg/d	2.0	NR	Equal considering ischemic stroke and death
WASID [27] (1999–2003)	569	Symptomatic intracranial stenosis; 64 years, BP = 140/77 mmHg	1300 mg/d	2.5	0.5%/year	Equal considering all stroke and death
ESPRIT [4] (1997–2005)	1068	Non-CE; 61 years, BP = 153/87 mmHg	30 mg/d*	2.6	0.8%/year	Equal considering stroke, myocardial infarct, vascular death or major hemorrhage

* 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 7 2008 Guidelines for Antithrombotic Therapy for Secondary Prevention of Noncardioembolic Ischemic Stroke

Acceptable antiplatelet therapies	
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).
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)."
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."
Preferred antiplatelet agents	
ESO	"Where possible, combined aspirin and dipyridamole, or clopidogrel alone, should be given."
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)"
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)."
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)"
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)"

Abbreviations: ESO – European Stroke Organization[28], AHA – American Heart Assocation[29], ACCP – American College of Chest Physicians[30]

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

prevention after TIA or minor stroke of arterial origin",[4] 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)[25-27], ESPRIT 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 noncardiembolic ischemic stroke and TIA? Updated versions of three major guidelines were published in 2008 by the European Stroke Organization (ESO)[28], the American Heart Association (AHA)[29] and the American College of Chest Physicians (ACCP)[30]. All three guidelines considered data from the CHARISMA trial (1, above) and from both components of ESPRIT (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 [28], 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 [31] 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.[32] 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 [31] will presumably strengthen the recommendation for clopidogrel over aspirin in future AHA and ACCP guidelines, bringing them into line with the current ESO recommendations.

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KOMUNIKAT

Dnia 23 października 2008 roku w Pałacu Staszica w Warszawie odbyło się nadzwyczajne posiedzenie Komisji Nefrologicznej Komitetu Patofizjologii Klinicznej Wydziału VI Nauk Medycznych PAN z udziałem luminarzy medycyny polskiej pt.

Życie i działalność naukowa Profesora Tadeusza Orłowskiego

dla uczczenia pamięci zmarłego 30 lipca 2008 roku Profesora Tadeusza Orłowskiego, wybitnego internisty, twórcy nefrologii, dializoterapii i transplantologii polskiej, wieloletniego Redaktora Naczelnego *Polskiego Archiwum Medycyny Wewnętrznej*, członka rzeczywistego Polskiej Akademii Nauk.

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5 Wacław Droszcz *Profesor Tadeusz Orłowski – również wielki internista*
6 Liliana Gradowska, Leszek Pączek *Wkład Profesora Tadeusza Orłowskiego w rozwój nowoczesnej nefrologii*
7 Joanna Klepacka *Wkład Profesora Tadeusza Orłowskiego w rozwój dializoterapii w Polsce*
8 Mieczysław Lao, Magdalena Durlik *Wkład Profesora Tadeusza Orłowskiego w rozwój polskiej transplantologii*