REVIEW ARTICLE

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

Part II

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KEY WORDS

atrial fibrillation, carotid angioplasty, statins, stroke, stroke prevention, thrombolysis, tissue plasminogen activator, transient ischemic attack, venous thromboembolism

ABSTRACT

Six studies from 2006–2008 that have influenced clinical management of stroke and threatened stroke are presented. The ABCD2 score effectively stratifies the short-term risk of stroke following transient ischemic attack into those with a high (12%), moderate (6%), and low (1%) 7-day stroke risk. High-dose atorvastatin reduces recurrent stroke in patients with recent stroke, but probably slightly increases central nervous system hemorrhage (SPARCL). Intravenous tissue plasminogen activator is of overall benefit to selected patients when given 3 to 4.5 hours after ischemic stroke onset (ECASS III). Adjusted-dose warfarin is far superior to aspirin and is relatively safe for very old people with atrial fibrillation (BAFTA). Despite results from 3 recent randomized trials (SAPPHIRE, EVA-3S and SPACE) the optimal role of carotid angioplasty/stenting vs. endarterectomy remains unclear. Enoxaparin once daily is an efficacious alternative to unfractionated heparin twice daily for prevention of venous thromboembolism after acute ischemic stroke (PREVAIL). These recent studies add important pieces to the complex puzzle of optimal stroke prevention and treatment.

From the scores of randomized trials, observational cohort studies, and epidemiological surveys published between 2006 and 2008, the 10 studies that have most influenced my day-to-day clinical management of stroke and threatened stroke are reviewed (TABLE 1). In part I, the first 4 studies dealing with antithrombotic therapies for secondary prevention of noncardioembolic ischemic stroke were analyzed[1], while in part II the second 6 studies are considered.

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[3], and BAFTA[4] and as a secondary site investigator of PRoFESS [5] and PREVAIL[6].

5. The ABCD2 score predicts the short-term risk of stroke following transient ischemic attack Transient ischemic attacks (TIA) are "a falsely benign form of brain attack"[7] with about 1 patient in 20 suffering a stroke within the subsequent 48 hours.[8] Two investigator groups pooled their data to generate a unified score for prediction of short-term stroke risks among patients presenting within 0–2 days of experiencing a TIA (TABLE 2A).[9] The diagnosis of TIA was based on that of the initial treating physician so that results should be generalizable beyond experts in stroke. TIA patients with ABCD2 scores of 6–7 (high risk) had a 10-fold increase in the 7-day risk of stroke compared with those with scores of 0–3 (low risk)(TABLE 2B).

Clinical prediction rules seldom perform as well as in the original publication when subsequently tested by other investigators in different patient cohorts. Is the ABCD2 score ready for general clinical use? Recent editorialists think so.[10,11] Nevertheless, independent validation in separate cohorts would be reassuring. At present, it is reasonable to consider the ABCD2 score, along with other factors, in management decisions regarding patients with acute TIA.

Urgent outpatient evaluation of patients with TIA and minor stroke appears to substantially reduce the 90-day stroke recurrence rate. The

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Received: September 17, 2008.
Accepted: September 18, 2008.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2008; 118 (12): 747-755

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)[5]
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)[12]
4 Aspirin as good as anticoagulation after noncardioembolic brain ischemia (ESPRIT)[13]
5 The ABCD2 score predicts the short-term risk of stroke following TIA[9]
6 High-dose atorvastatin reduces stroke in patients with recent stroke, but possibly increases CNS hemorrhage (SPARCL)[3]
7 Intravenous tPA is of overall benefit when given 3 to 4.5 hours after ischemic stroke onset (ECASS III)[14]
8 Warfarin is efficacious and safe for very old people with atrial fibrillation (BAFTA)[4]
9 Carotid angioplasty/stenting vs. endarterectomy? (SAPPHIRE, EVA-3S and SPACE)[15-17]
10 Enoxaparin vs. unfractionated heparin for prevention of venous thromboembolism after acute ischemic stroke (PREVAIL)[6]

Abbreviations: CNS – central nervous system, TIA – transient ischemic attack, tPA – tissue plasminogen activator

TABLE 2A ABCD2 score for TIA patients

	Score	Feature
Age	1	≥60 years
BP	1	SBP >140 or DBP ≥90 mmHg
Clinical features	2	Unilateral weakness
	1	Speech impairment without weakness
Duration	2	>60 minutes
	1	10–59 minutes
	0	<10 minutes
Diabetes	1	

Abbreviations: BP – blood pressure, DBP – diastolic blood pressure, SBP – systolic blood pressure, TIA – transient ischemic attack

TABLE 2B Early stroke rates in acute TIA patients stratified by the ABCD2 score[a]

ABCD2 score	2-day risk	7-day risk	90-day risk
0–3 (low risk)	1.0%	1.2%	3.1%
4–5 (moderate risk)	4.2%	5.9%	9.8%
6–7 (high risk)	8.1%	11.7%	17.8%

a based on combined analysis of 6 cohorts with 4799 TIA patients seen within 48 hours of TIA[9]

Abbreviations: see TABLE 2A

OXVASC investigators compared early stroke rate in 2 sequential eras during which the median delay from event to outpatient evaluation decreased from 3 days to 1 day and the median delay to prescription of treatment decreased from 20 days to 1 day.[18] Strokes rates at 90 days were much lower in those undergoing early outpatient evaluation and treatment in the second era (2%) compared with the 1st era (10%) (p <0.0001). While this was not a randomized trial, most of the usual biases in non-randomized comparisons were minimized, and the results seem credible. A "round-the-clock" TIA urgent access center in Paris, France reported similarly low stroke rates.[19]

6. High-dose atorvastatin reduces subsequent stroke in patients with recent stroke, but possibly increases central nervous system hemorrhage (SPARCL) Although the benefits of HMG-CoA reductase inhibitors (i.e. "statins") for reducing vascular events have been demonstrated in many randomized trials involving patients with coronary artery disease and coronary risk factors, specific assessment of the risks and benefits in patients with recent stroke/TIA was lacking. Because of the established benefits of statins in those with coronary artery disease, patients with known coronary artery disease were excluded from the SPARCL trial (Stroke Prevention by Aggressive Reduction in Cholesterol Levels).[3] The SPARCL trial recruited 4731 participants from 205 sites on 5 continents with stroke or TIA 1–6 months prior to entry (lacunar infarcts predominated, and 93 participants (2%) had intracerebral hemorrhage as their qualifying event), assigned them to atorvastatin 80 mg/day vs. placebo (double-blind), and followed them for a median of 4.9 years.[3]

All stroke was reduced by 16% (p = 0.05), with a 21% (p = 0.01) reduction in ischemic stroke partially offset by an increase in intracerebral hemorrhage (TABLE 3)(p = 0.02). High-dose atorvastatin was well tolerated with mildly increased liver function tests in 2% of atorvastatin patients vs. 0.5% of placebo patients (p <0.001); there were no cases of serious liver toxicity/failure and no excess cases of myopathy.

Several findings prompt comment.

1 There was no apparent reduction in stroke in those assigned atorvastatin until after 12 months of treatment, and hence the effect on stroke appears to be delayed.

2 The 16% stroke reduction in SPARCL was identical to that seen from pooled analysis of the effect of statins on stroke from "non-stroke" trials (16%), [20] but less than predicted for aggressive cholesterol lowering. An exploratory analysis of SPARCL participants with >50% reduction in low density lipoproteins (LDL) cholesterol compared with those with no reduction (i.e. eliminating cross-overs/noncompliant participants) showed a 31% reduction in stroke.[21]

3 There was a statistically significant increase in intracerebral hemorrhage among those assigned to statins in an exploratory analysis. This is similar to another exploratory analysis from the UK Heart Protection Study of patients with cerebrovascular disease in which 40 mg of simvastatin was compared with placebo (LDL reduced from 136 mg/dl to 97 mg/dl).[22,23] In patients without cerebrovascular disease, statins have not been associated with increased intracerebral hemorrhage.[20]

TABLE 3 Main results of the SPARCL trial

	Atorvastatin (n = 2365)	Placebo (n = 2366)	Relative risk reduction (p)
Change in LDL cholesterol (mg/dl)	133 to 73 –45%	134 to 129 –4%	–
Strokes	265 (2.3%/year)	311 (2.7%/year)	–16% (p = 0.05)
all fatal strokes	24	41	–43% (p = 0.03)
all ischemic strokes[a]	225	286	–21% (p = 0.01)
intracerebral hemorrhages	55	33	+66% (p = 0.02)
Acute coronary events	101	151	–35% (p = 0.001)
Deaths – all	216	211	0%
vascular deaths	78	98	–22% (NS)
nonvascular deaths	138	113	+22% (NS)

All results based on intention-to-treat analysis unless otherwise specified.
a Includes 19 unclassified strokes

Abbreviations: LDL – low density lipoproteins

TABLE 4 Main results of ECASS III

	tPA (n = 418)	Placebo (n = 403)	Statistical significance
Favorable outcomes[a]	52%	45%	p = 0.04[c]
Symptomatic CNS bleeds[b]	2.4%	0.2%	p = 0.008
All deaths	7.7% (n = 32)	8.4% (n = 34)	NS

a modified Rankin score of 0–1 (no neurological disability) after 90 days
b secondary hemorrhage causing >4 points worsening on the NIH Stroke Scale or leading to death
c per-protocol subgroup of 730 participants who met all eligibity criteria and received treatment, p=0.01

Abbreviations: see TABLE 1

The overall benefit of statin therapy in patients with ischemic stroke/TIA should not be neglected because of concerns about a potential small absolute increase in intracerebral hemorrhage. Based on the SPARCL trial, both European[24] and American[25] guidelines recommend the use of statins for secondary prevention in patients with noncardioembolic stroke. From a recent analysis of magnitude of benefit: "On average, a poststroke/TIA individual will gain one more month of high quality life during each year of statin therapy."[26]

7. Intravenous tissue plasminogen activator is of overall benefit when given 3 to 4.5 hours after ischemic stroke onset (ECASS III) Intravenous tissue plasminogen activator (tPA) within 3 hours of onset offers substantial benefit to victims of ischemic stroke. In 2004 an important analysis of pooled data concerning 2775 patients with acute ischemic stroke randomized tPA vs. placebo participating in 6 randomized clinical trials showed the likelihood of a favorable 3-month outcome was 2.8 times that of controls when tPA was given within 90 minutes of stroke onset.[27] The benefit of intravenous tPA declined as the time to treatment lengthened; with decreasing benefit apparent for treatment up to 4.5 hours after stroke onset.[27]

The ECASS (European Cooperative Acute Stroke Study) investigators tested the hypothesis that treatment with intravenous tPA given 3 to 4.5 hours after stroke onset was of overall benefit in the randomized, double-blinded ECASS III trial carried-out in 130 sites in 19 European countries.[14] Tissue plasminogen activator was administered in the standard stroke dosage (0.9 mg/kg over 1 hour) after a CT excluded brain hemorrhage and hypodensity involving >1/3rd of the middle cerebral artery (MCA) territory. Other important exclusion criteria included age over 80 years, NIH Stroke Scale score >25 (i.e. severe strokes), previous stroke within 3 months prior to randomization or any other stroke with persistent ipsilateral deficits, and patients with diabetes mellitus and prior stroke with residual neurological deficits. The primary outcome was "favorable outcome after 90 days" defined as a modified Rankin score of 0–1 (no neurological disability). Among the 821 participants, mean participant age was 65 years, the mean NIH Stroke Scale score was 11, and the mean time from stroke onset to the start of tPA infusion was 4 hours.

ECASS III results verified independently those of the previous pooled analysis showing benefit of intravenous tPA extending to treatment 4.5 hours after stroke onset (TABLE 4)[14]. The odds ratio of a favorable outcome was 1.34 with a number needed to treat of 14 for 1 additional patient with a favorable outcome.[14]

Can clinicians now extend the limit for intravenous tPA treatment to 4.5 hours based on the ECASS III results? Given that ECASS III confirms

TABLE 5 Main results of the BAFTA trial

Outcomes	Aspirin n = 485	Warfarin n = 488	Relative risk reduction (95% CI)
All strokes	62 (5.0%/year)	35 (2.7%/year)	46%, p = 0.002
Ischemic strokes + unknowns	56	27	56%, p <0.001
Intracerebral hemorrhage[a]	6	8	–
Disabling or fatal strokes	44	21	54%, p = 0.003
Non-CNS emboli	3	1	–
Major extracranial hemorrhages	20 (1.6%/year)	18 (1.4%/year)	–
Myocardial infarcts	15	15	–
All-cause mortality	108	107	5% (–26.28)
Nonvascular deaths	51	51	–
Vascular deaths	57	56	–

All results based on intention-to-treat analysis unless otherwise specified.
a Includes subdural hematomas: 2 with warfarin, 1 with aspirin

the previous pooled analysis, this seems reasonable, with important caveats. Patients and families should be informed that guideline statements have not yet addressed the ECASS III results, and that the absolute benefit of tPA is less than for those treated earlier (but still substantial), while the serious risks remain the same.[28] Further, the restricted ECASS III eligibility criteria should be followed carefully: excluding patients over 80 years old, those whose NIH Stroke Scale score exceeds 25, patients with >1/3rd MCA territory hypodensity on CT, patients with previous stroke within 3 months or any other stroke with persistent ipsilateral deficits, or with diabetes and previous clinical stroke.

The results of ECASS III should not be an excuse to treat patients later: time is brain, and minutes count when treating acute stroke patients. For a typical stroke, it has been estimated that 1.9 million neurons are lost each minute in which the stroke is untreated.[29] Run, don't walk, to the emergency department to give tPA to appropriate stroke patients!

8. Warfarin is efficacious and relatively safe for very old people with atrial fibrillation (BAFTA) The superiority of adjusted-dose warfarin over antiplatetelet therapy for prevention of stroke in patients with atrial fibrillation has been firmly established by consistent results of 11 randomized trials.[30] However, participants in these trials have typically been younger (averaging about 70 years old) than atrial fibrillation patients commonly encountered in clinical practice (averaging in their late 70s and with a substantial fraction of octogenarians), and the efficacy and safety of adjusted-dose warfarin in the very elderly is less clear. In the Birmingham Atrial Fibrillation Treatment in the Aged trial, primary care physicians in the English Midlands undertook to address this issue, randomizing 973 atrial fibrillation patients age ≥75 years (mean age 81.5) to adjusted-dose warfarin (target international normalized ratio [INR] 2–3) vs. aspirin 75 mg/day given open-label and followed for a mean of 2.7 years.[4] Anticoagulation management was "real-life" by the standard of UK general practices; 67% of INRs were within the therapeutic range with median INR 2.3 and mean INR 2.4 during follow-up.

The stroke rate was 5% per year on aspirin and nearly halved by adjusted-dose warfarin (TABLE 5). Surprisingly, major extracranial hemorrhages very similar in those assigned warfarin and aspirin. Of note, 40% of participants had previously received warfarin prior to study entry, likely biasing toward lower bleeding rates than expected in warfarin-naïve patients. The investigators conclude that "these data lend support to the use of anticoagulation for all people >75 years who have atrial fibrillation, unless there are contraindications or the patient decides that the size of the benefit is not worth the inconvenience of treatment."[4] The BAFTA trial results provide welcome reassurance about the efficacy and safety of adjusted-dose warfarin in very elderly patients with atrial fibrillation managed in a primary care setting with the caveat of probably underestimating the early bleeding risk in warfarin-naïve patients.

Of note, in a subgroup analysis of participants with atrial fibrillation in the randomized PROGRESS blood pressure trial, modest reduction in blood pressure using perindopril and indapamide resulted in ~25% reduction in stroke and major vascular events.[31] Control of blood pressure in atrial fibrillation patients is doubly important, reducing both ischemic strokes and intracerebral bleeding (the most feared complication of antithrombotic therapy in the elderly).

9. Carotid angioplasty/stenting vs. endarterectomy? (SAPPHIRE, SPACE, and EVA-3S) 3 recent randomized comparisons of carotid angioplasty/stenting vs. endarterectomy have helped clarify and focus (but not settle) the controversies surrounding the relative benefits and risks of these 2 re-vascularization procedures. Important differences in inclusion criteria, use of emboli-protection devices, and experience level require critical comparison of their designs and results.

TABLE 6 Main results of three randomized trials comparing carotid angioplasty/stenting vs. endarterectomy

	SAPPHIRE (n = 334) 2000–2002	EVA-3S (n = 520) 2000–2005	SPACE (n = 1200) 2001–2006
Key inclusion criteria	High risk for CEA: coronary artery disease, age >80 years	Stenosis >60%	Stenosis >50%
Symptomatic stenosis	29%	100%	100%
Use of cerebral protection device(s)	100% single type	92% multiple types	27% multiple types
Stroke at 30 days			
CEA	3% (n = 5)	3% (n = 9)	6% (n = 36)
angioplasty/stenting	4% (n = 6)	10% (n = 25)[a]	8% (n = 45)
Myocardial infarct at 30 days			
CEA	6% (n = 10)	0.8% (n = 2)	not reported
angioplasty/stenting	2% (n = 4)	0.4% (n = 1)	
Mortality at 30 days			
CEA	2% (n = 4)	1% (n = 3)	1% (n = 5)
angioplasty/stenting	1% (n = 2)	1% (n = 2)	1% (n = 4)
Stroke – longer follow-up	at 3 years[b]	at 4 years	at 2 years
CEA	9% (n = 15)	7% (n = 19)	10% (n = 57)
angioplasty/stenting	9% (n = 15)	13% (n = 34)	11% (n = 64)
Mortality – longer follow-up	at 3 years	at 4 years	at 2 years
CEA	21% (n = 35)	14% (n = 37)	5% (n = 28)
angioplasty/stenting	19% (n = 31)	14% (n = 38)	6% (n = 32)
Cranial nerve injury			
CEA	5% (n = 8)	8% (n = 20)	not reported
angioplasty/stenting	0	1% (n = 3)	

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

a with use of cerebral protection device = 8% (n = 18)

b ipsilateral stroke: 11 stenting, 9 endarterectomy

Abbreviations: CEA – carotid endarterectomy

The SAPPHIRE trial (Stenting and Angioplasty with Protection in Patients at HIgh Risk for Endarterectomy) enrolled 334 patients at 28 sites with cervical carotid occlusive disease and who were high-risk for carotid surgery into a randomized trial comparing carotid surgery to angioplasty/stenting using the Accunet cerebral protection device.[15,32] The main reasons for being considered "high risk" were clinically manifest coronary artery disease and age >80 years. Most (71%) had asymptomatic stenosis >80%, while the remainder had symptomatic stenosis >50%. The primary outcome measure was death, stroke or myocardial infarction in the first 30 days plus death and ipsilateral stroke between 30 days and 1 year. Considering a 3% absolute rate difference as clinically relevant "noninferiority," stenting was shown to be non-inferior to endarterectomy (TABLE 6). The main difference between the 2 treatments was on myocardial infarctions within 30 days. In the recently published 3-year follow-up from the SAPPHIRE trial, 15 patients in both treatment groups had experienced stroke (TABLE 6).[15] 10 strokes in the endarterectomy group and 9 strokes in the angioplasty/stenting group occurred between 30 days and 3 years for an estimated annualized stroke rate of 2.3%/year.

The SPACE trial (Stent-supported Percutaneous Angioplasty of the Carotid artery versus Endartertectomy) enrolled 1200 patients at 35 centers in Germany, Austria, and Switzerland with ischemic stroke (about half) or TIA.[16] Ipsilateral carotid stenosis of >50% was required, with the average degree of stenosis between 80% and 89%. The primary outcome was ipsilateral ischemic stroke or death within 30 days of randomization, and these were nearly equal, as were the occurrence of stroke or death after 2 years (TABLE 6). Multiple types of stents were used, and multiple types of cerebral protection devices were allowed, although the latter was employed in only 27% of endovascular procedures.

The EVA-3S trial (Endarterectomy Versus Angioplasty in Symptomatic Severe carotid Stenosis) enrolled 520 patients at 30 sites in France with ischemic stroke (about half) or TIA/transient monocular blindness.[17] Ipsilateral carotid stenosis of >60% was required; the average degree of stenosis was about 85%. The primary outcome was any stroke or death within 30 days of randomization, seeking non-inferiority within a 2% margin; the trial stopped early due to futility and safety concerns. Of note, a higher risk of stroke was seen early in the trial

TABLE 7 Main results of the PREVAIL trial: Efficacy population analysis[a]

	Unfractionated heparin 5000 IU SC twice daily	Enoxaparin 40 mg SC once daily	Relative risk (p)
Number randomized	878	884	–
Number analyzed[a]	669	666	–
Asymptomatic and symptomatic VTE	121 (18%)	68 (10%)	0.57 (p = 0.001)
Symptomatic VTE only	7 (1%)	2 (<1%)	
Intracranial hemorrhage or major extracranial hemorrhage	6 (1%)	11 (2%)	–
Intracranial hemorrhage	6 (1%)	4 (1%)	–
Deaths at 90 days	103	100	–

a About 130 participants in each treatment group did not undergo venography or ultrasonography to assess for asymptomatic VTE and were not included in the reported analysis that was restricted to the efficacy population

Abbreviations: SC – subcutaneously, VTE – venous thromboembolism

when cerebral protection devices were not used, and the protocol was amended to recommend their use. The rate of stroke or death at 30 days was significantly lower among those assigned carotid endarterectomy vs. angioplasty/stenting (4% vs. 10%, p <0.01, respectively), and a difference in stroke persisted after 4 years of follow-up (p = 0.05). The high rate of early stroke with angioplasty/stenting brought the experience of the trial interventionalists into question (at some sites, procedures were performed under supervision of a tutor because of inexperience), but the importance of the relative inexperience of those performing angioplasty/stenting on EVA-3S has been disputed.[33]

Despite over 2000 participants these 3 randomized trials, the optimal role of angioplasty/stenting vs. endarterectomy of occlusive cervical carotid artery disease remains unsettled. One trial was restricted to those at high-risk for endarterectomy[15], another did not employ emboli--protection devices[16], and the 3rd was carried-out by those relatively inexperienced with angioplasty/stenting[17]. Following the first 30 days, the long term ipsilateral stroke rate was <1% annually with either procedure, a consistent finding in all 3 trials. A recent meta-analysis of randomized trials (including early trials that did not use emboli-protection devices) offered that "if one considers the two procedures equivalent if the absolute difference in events is <2%, these results provide moderate quality evidence for equivalence with respect to death and nonfatal myocardial infarction, (...) but only low-quality evidence of equivalence in stroke."[34]

Clinical trials beget better clinical trials. Large, multi-center trials involving a broad range of patients, using modern emboli-protection in the hands of experienced investigators, and with unbiased outcomes are ongoing. But further complicating comparison is the evolution in stent-related technology that potentially could improve safety over that from ongoing trials.

Considering the results of these 3 trials, the European Stroke Organization (2008) published that "carotid angioplasty, with or without stenting, is not recommended for patients with asymptomatic carotid stenosis."[24] Further, "Carotid percutaneous transluminal angioplasty and/or stenting is only recommended in selected patients. It should be restricted to the following subgroups of patients with severe symptomatic carotid artery stenosis: those with contra-indications to CEA, stenosis at a surgically inaccessible site, re-stenosis after earlier CEA, and post-radiation stenosis."[24]

10. Enoxaparin vs. unfractionated heparin for prevention of venous thromboembolism after acute ischemic stroke (PREVAIL) In patients with acute ischemic stroke who have substantial leg weakness, antithrombotic therapy is recommended by most guidelines for prevention of venous thromboembolism (VTE).[24,35] Subcutaneous (SC) unfractionated heparin in dosages of 5000 IU 3 times daily and 12,500 IU twice daily have been demonstrated to reduce VTE in patients with acute ischemic stroke, but 5000 IU twice daily has not. Low-molecular-weight heparins (e.g. enoxaparin) and heparinoids (e.g. danaparoid) appear to be equally or more efficacious than unfractionated heparin for VTE prophylaxis in stroke patients.[36,37] Combined analysis of 2 large randomized trials reported a 29% reduction (p <0.05) in pulmonary embolism by aspirin 160–300 mg daily given a mean of 22 hours after ischemic stroke onset.[38] In the large randomized International Stroke Trial, SC heparin 5000 IU twice daily alone was associated with only an 11% (p >0.05) reduction in pulmonary embolism, but when combined with aspirin this dose of SC heparin resulted in a 42% reduction (p = 0.10) in pulmonary embolism.[39]

On this background, the PREVAIL trial investigators conducted a randomized, open-label trial of enoxaparin 40 mg SC once daily vs. unfractionated heparin (UFH) 5000 IU SC twice daily in patients within 48 hours of acute ischemic stroke who were unable to walk unassisted.[6] The primary outcome was asymptomatic or symptomatic

VTE up to day 14 after stroke. The study population was generally typical of patients with acute ischemic stroke; 22% were Asians and 91% of participants received concomitant antiplatelet therapy. There was blinded review of scans and blinded adjudication of major bleeding events. The frequency of symptomatic VTE was low (1%) in both treatment arms (TABLE 7). Considering all VTE (asymptomatic and symptomatic), there was a 43% reduction by enoxaparin compared with UFH. The investigators conclude: "Our results suggest that for patients with acute ischemic stroke, enoxaparin is preferable to unfractionated heparin for venous thromboembolism prophylaxis in view of its better clinical benefits to risk ratio and convenience of once daily administration."[6]

Three caveats are worth considering:

1 The bulk of outcomes were asymptomatic VTE. Symptomatic VTE were infrequent and not significantly different between treatments (although the 7 vs. 2 trend favored enoxaparin).

2 A large number of randomized patients were excluded from the primary analyses due to lack of assessment for asymptomatic VTE (i.e. the primary analysis was not intention-to-treat). While the number excluded was about equal in each treatment arm, the open-label design makes this worrisome.

3 The dosage of UFH chosen for comparison was 5000 IU twice daily, which alone has never been shown to be efficacious for VTE prevention in stroke patients (in contrast to 5000 IU 3 times daily, which has been shown efficacious, but its safety when combined with aspirin is unclear) The investigators defend their choice of this dosage based on safety concerns.

What should be the standard antithrombotic prophylaxis against VTE for patients with acute ischemic stroke and substantial leg weakness? Based on the PREVAIL trial results, we can do better than UFH 5000 IU twice daily, although the numbers needed-to-treat to prevent clinically evident VTE are large. The European Stroke Organization (2008) recommends prophylaxis with SC low-dose heparin (5000 IU twice daily) or low molecular weight heparins for patients at high risk of VTE or pulmonary embolism (e.g. due to immobilization, obesity, diabetes, previous stroke).[24] The cost to hospitals of the drugs varies widely. Given potential for medication error and convenience for patients and nursing staff, enoxaparin once daily is a reasonable choice if not excessively expensive. The Cochrane Collaboration's systematic review concluded that data were insufficient to recommend one over another.[37]

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