cardiac transplant patients, restenosis, microvascular disease, hibernating myocardium, stunned myocardium, left ventricular hypertrophy, and pulmonary hypertension. Non-cardiovascular uses include treating renovascular, cerebrovascular, and peptic ulcer diseases and wound healing.

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Evidence based cardiology

Prevention of ischaemic stroke

Henry J M Barnett, Michael Eliasziw, Heather E Meldrum

Stroke is the second most common cause of death worldwide, exceeded only by heart disease.[1] Coincident with the emergence of prevention strategies, incidence of stroke is declining dramatically in developed countries. The prevention of stroke is an obligation facing everyone involved with delivering health care.

Summary points

- Managing the risk factors of hypertension, tobacco, and hyperglycaemia reduces the risk of stroke
- Managing hyperglycaemia will diminish the severity of strokes
- Warfarin prevents stroke in non-valvular atrial fibrillation
- Aspirin is the first choice of platelet inhibitors for stroke prevention
- Endarterectomy prevents stroke when symptoms are due to severe stenosis; with moderate stenosis the benefit is muted
- Endarterectomy is of uncertain benefit for asymptomatic carotid stenosis

Manageable risk factors for stroke

Prospective population studies and retrospective case series have identified modifiable risk factors important for ischaemic and haemorrhagic stroke.

The Four Horsemen of the Apocalypse of stroke display the banners of hypertension, tobacco, diabetes mellitus, and hyperlipidaemia.[2] All are responsible for cerebral arteriosclerosis. Transient ischaemic events are powerful predictors of stroke. Coronary artery disease and atrial fibrillation increase stroke risk. Compounds lowering cholesterol, the "statins," reduce the risk of myocardial infarction and stroke.[3]

At no age and in neither sex is a systolic blood pressure above 160 mm Hg and a diastolic pressure above 90 mm Hg acceptable. Even elderly subjects and heavy smokers reduce the risk of stroke by abandoning cigarettes.[4]

Control of insulin dependent diabetes has not been shown to reduce stroke.[5] A stroke in the presence of hyperglycemia is more disabling.

Family history of stroke requires the Four Horsemen be sought and managed in the early decades of life. Fatalistic attitudes are wrong. Genetics deals the cards. The play can be determined by environmental influences.

Coagulation abnormalities and homocysteinaemia add to the likelihood of early stroke but are manageable.[6]

Anticoagulants in stroke prevention

Seven randomised trials reported that adjusted doses of warfarin prevent stroke in patients with non-valvular atrial fibrillation.[7] From meta-analysis, a 64% relative

This is the last of four articles

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risk reduction of stroke favoured warfarin over placebo,[2] without increase in major bleeding.[8 9] (The target international normalised ratio is 2-3.)

Compared with aspirin, the overall relative risk reduction of 48% favours warfarin.[7] Compared with placebo, aspirin reduces the stroke risk by 22%.

Warfarin decreased the rate of stroke in all subgroups of non-valvular atrial fibrillation except in younger patients without risk factors.[8 9] Fixed dose therapy in patients with international normalised ratios 1.2-1.5 did not prevent strokes.[9]

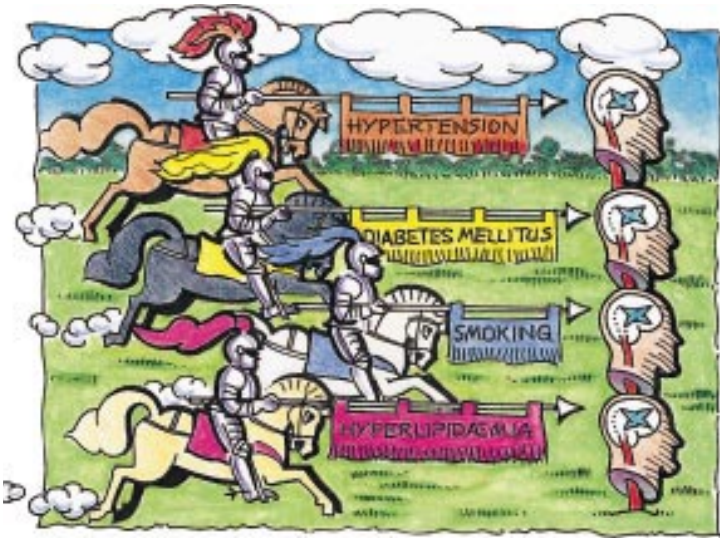
Under age 65, patients without a history of hypertension, cerebral ischaemic events, or diabetes are at lowest risk of stroke, and such patients should receive aspirin. Aspirin may be appropriate in other "low risk" patients without recent congestive heart failure or previous thromboembolism and whose systolic blood pressure is <160 mm Hg, and for women over 75 years.[8]

Untreated patients over 75 years face the worst prognosis and potentially should benefit most from anticoagulant therapy but have the highest risk of haemorrhagic complications. Patients must be carefully monitored to keep the international normalised ratio below 3.0.

Risk evaluation will determine the need for a lifetime of warfarin therapy. Randomised trials, case series, and a meta-analysis favour the use of heparin and warfarin to prevent stroke after acute myocardial infarction.[10–12] For patients with cerebral ischaemia after myocardial infarction, 3-6 months of anticoagulant therapy is recommended. For patients without cerebral ischaemia, use of anticoagulants is discretionary.

In patients with arterial disease causing ischaemic events, when platelet inhibitors fail it is common practice to switch to anticoagulants. Ongoing trials may confirm this empirical indication.[13] At present it cannot be recommended.

Anticoagulants have been evaluated in patients immediately after acute strokes. One acute stroke trial (n=308) compared two doses of low molecular weight heparin with placebo within 48 hours of onset of stroke.[14] A significant dose dependent reduction in death and dependency was reported at six months. These observations were not confirmed in a factorial, 19 435 patient trial of low or medium unfractionated heparin.[15] The higher dose of heparin led to more transfusions, fatal extracranial bleeds, and haemorrhagic strokes. Another acute stroke trial of low molecular weight heparin versus placebo had negative results.[16]



SUE SHARPLES

High rates of bleeding complications (particularly intracerebral haemorrhage) led to termination of a trial comparing anticoagulant therapy (ratio 3.0-4.5) with low dose aspirin in patients with recent (less than six months) ischaemic events.[17] Major bleeding complications increased steeply with the intensity of anticoagulation.

The routine use of anticoagulants in non-cardiac ischaemic stroke patients is not recommended.

Platelet inhibitors in stroke prevention

Six platelet inhibitors have been evaluated in stroke prevention. Suloctidil and sulphinpyrazone were ineffective.

Dipyridamole

Dipyridamole was evaluated first. Negative benefit was reported in 169 patients. In three subsequent trials 1575 patients with transient ischaemic attacks or minor stroke were randomised to receive either aspirin in doses of 900-1300 mg or dipyridamole with aspirin. The combination was not superior to aspirin alone. A recent study claims benefit for the combination of dipyridamole and 50 mg of aspirin daily over aspirin or dipyridamole alone.[18] The investigation has been criticised and its acceptance was not enthusiastic.[19–21] The previously compared dose of aspirin was reduced 20-fold, lower than any dose proven useful in a placebo controlled, stroke prevention trial. The placebo arm raised ethical concerns.

Dipyridamole is not recommended, alone or with aspirin.

Aspirin

A seminal trial of factorial design (n=585) gave either 1300 mg aspirin, sulphinpyrazone, both, or double placebo. A 31% relative risk reduction of stroke and death favoured aspirin. Subsequently 15 trials have utilised aspirin against placebo in patients with transient ischaemic attacks and stroke.[22 23]

Aspirin prevents stroke in both sexes. The relative risk reduction averages 25%.

Minimal complications after 11 000 patient years of aspirin administration indicate a satisfactory tolerance and safety for enteric coated aspirin (North American symptomatic carotid endarterectomy trial, unpublished data). Haemorrhagic side effects are not dose related. These observations mute the importance of the uncertainty about dosage.

The optimum dose for stroke prevention has not been determined by direct comparisons. Indirect comparisons provide no evidence that low or high doses are superior to each other. From indirect evidence we recommend 650-900 mg of aspirin daily for patients threatened by stroke.

Ticlopidine

Two trials of ticlopidine showed benefit. Though ticlopidine is an effective drug in stroke prevention, its superiority to aspirin is modest, and it has serious disadvantages. It causes diarrhoea in up to 20% of

Number needed to treat by endarterectomy to prevent one stroke in 2 years in patients with carotid stenosis

	No of patients in specified trial	Medical risk (%) at 2 years	Surgical risk (%) at 2 years	Risk difference (%)	Relative risk reduction (%)	No need to treat*	Perioperative stroke and death rate (%)
Symptomatic patients:							
70-99% (NASCET)[33]	659	21.4	8.6	12.8	60	8	5.8
70-99% (ECST)[31]**	501	19.9	7.0	12.9	65	8	5.6
50-69% (NASCET)[32]	858	14.2	9.2	5.0	35	20	7.1
50-69% (ECST)[31]**	684	9.7	11.1	–1.4	–14	—	9.8
<50% (NASCET)[32]	1368	11.6	10.1	1.5	13	67	6.5
<50% (ECST)[31]**	1882	4.3	9.5	–5.2	–109	—	6.1
Asymptomatic patients:							
⩾50% VA, men only[45]	444	7.7†	5.6†	2.1	27	48	4.4
ACAS[35]	1662	5.0	3.8‡ (actual)	1.2	24	83	2.6
ACE[43]	2848	5.0§ (assumed)	5.8	–0.8	—	—	4.6

NASCET=North American symptomatic carotid endarterectomy trial; ECST=European carotid surgery trial; ACAS=asymptomatic carotid atherosclerosis study; ACE=aspirin and carotid endarterectomy trial; VA=Veterans Administration.
*Number of patients needed to treat by endarterectomy to prevent one stroke in 2 years after the procedure, compared with medical treatment alone.
**By NASCET measurement. Additional data supplied by Dr P Rothwell.
†Extrapolated from results.
‡Assigning a perioperative risk of 2.6% based on 724 of 825 patients who actually received endarterectomy in the surgical arm of ACAS, and utilizing the 0.6% risk of stroke in each of the two years after endarterectomy. The same 1.2% risk is assumed for the ACE patients and VA patients.
§No medical arm—assumed from ACAS data.

subjects, and 5% or more cannot tolerate this side effect. Complicating bone marrow suppression has been fatal in 16% of the patients in which it was reported.[24] Despite appropriate monitoring, 33% of 60 patients with complicating thrombotic thrombocytopenic purpura died.[25]

Clopidogrel

Clopidogrel is a chemical relative to ticlopidine. In a trial of 19 185 patients it was tested against 325 mg of aspirin daily for patients with stroke, myocardial infarction, or peripheral vascular disease.[26] The relative risk reduction of combined vascular events was 8.7% favouring clopidogrel. The absolute risk reduction of 0.5% due to clopidogrel is narrowly better than that of aspirin.

Clopidogrel must be given to 200 patients to prevent one end point per year more than with aspirin.[27 28] Reduction for the combination of stroke and death was not statistically significant.[28] Two thirds of the patients in the trial had not experienced recent cerebral ischaemia. The inclusion of 6452 patients with symptoms of peripheral arterial disease seemed to tip the scales towards marginal benefit for the combination of mixed system end points.

There was less diarrhoea than with ticlopidine. Reversible bone marrow suppression occurred in 0.2% of patients.

The daily cost in the United States of $2.40 (£1.50) compares with a cost of $0.17 for aspirin. Clopidogrel does not replace aspirin as the drug of first choice. Because of the serious and fatal side effects from ticlopidine, clopidogrel becomes the drug of second choice if symptoms persist despite aspirin or if aspirin is not tolerated.

Carotid endarterectomy in stroke prevention

In 1954 a patient with transient ischaemic attacks responded to segmental resection of a stenosed carotid artery.[29] Subsequently, endarterectomy was performed with increasing frequency. By 1985, 107 000 endarterectomies were done in the United States. Questions were raised about the appropriateness of the extensive use of this procedure.[30] Complication rates ranged from low to unacceptably high.

Symptomatic disease

The European carotid surgery trial and the North American symptomatic carotid endarterectomy trial involved 5909 patients.[31 32] Best medical care was randomly assigned to 2662 patients and carotid endarterectomy to 3247 patients. In patients with retinal or hemisphere symptoms attributable to "severe" (70-99%) carotid stenosis, endarterectomy was superior to medical care alone. The number of patients requiring endarterectomy to prevent one stroke in 2 years is 6-8 (table).

In published results, different methods were used to calculate the degree of stenosis.[31 32] "Severe" is 70% by North American measurements and 85% by European measurements. Patients with moderate stenosis (North American 50-69%, European 75%-84%) benefit less. The number needed to treat by endarterectomy in the North American symptomatic carotid endarterectomy trial becomes 19.[32] Symptomatic patients with minimal degrees of stenosis (North American below 50%; European below 75%) receive no benefit from endarterectomy, or perhaps even harm.

The best results from endarterectomy for patients with moderate (50-69%) stenosis were observed with hemisphere rather than retinal symptoms, non-disabling strokes rather than transient events, and male sex.[32] The operative risk doubles with occlusion of the artery opposite to the symptoms, thrombus visible in the artery, a history of diabetes, an appropriate lesion on computerised tomography, or diastolic blood pressure above 90 mm Hg.

The benefit from endarterectomy relates to complication rates. Reported benefits were predicated on operative risks of stroke or death of 7.5% in the European trial and 6.5% in the North American trial. If the endarterectomy rate exceeds the disabling stroke and death rate by as little as 2%, benefit disappears. Evidence is lacking to support the performance of endarterectomy for so called non-specific or non-hemisphere symptoms.

Both trials used conventional angiography. The identification of comparably "severe" or "moderate"

stenosis by non-invasive methods is imperfect. Screening will include ultrasound or magnetic resonance arterial imaging.

In capable hands, angiography carries a risk of disabling stroke of 0.1%. With expert surgeons endarterectomy carries a 2.0% risk of disabling stroke and death.[33] A 20-fold increase of risk from endarterectomy compared with angiography persuades us that angiography is an essential prelude. In many centres ultrasonography alone probably leads to inappropriate endarterectomy in as many as 30% of patients.[34]

Asymptomatic disease

Endarterectomy for asymptomatic patients remains controversial. Asymptomatic disease carries a substantially lower risk of stroke than when symptoms develop. Three negative trials and one positive trial have been published. A fifth is ongoing.

To benefit asymptomatic individuals the perioperative risk of endarterectomy must be no higher than 3%. In three of the four randomised trials this limit was exceeded. The largest of the completed trials (n = 1662), the asymptomatic carotid atherosclerosis study, had a low (2.6%) perioperative risk of stroke and death.[35] The five year risks were 11% in the medical group and 5.1% in the endarterectomy group. The absolute reduction of stroke favouring endarterectomy was 1% annually. Disabling strokes were not prevented.

Subgroup analysis found no benefit for women. The numbers were small, and outcome events were few. The perioperative risk of stroke or death was 3.3% for women.

In all trials with asymptomatic subjects the numbers needed to receive endarterectomy to prevent one stroke in two years are unacceptably high (table). The large observational studies of asymptomatic disease have identified that below 80% stenosis the annual stroke risk is 1% or less.[36 37]

Despite the modest reported benefits some observers believe that it is appropriate to operate on any asymptomatic patient with a stenosis above 60%. An American Heart Association consensus statement supports this liberal approach.[38] Statistical significance has been equated with clinical importance. We believe a conservative approach is in order and that future disciplined research, including the study of the impact of risk factors, is needed.[39–42]

Patients with asymptomatic stenosis on one side and a complete carotid occlusion on the other may benefit from endarterectomy. Validation of this practice requires careful data from future randomised studies.

Endarterectomy is commonly performed for asymptomatic stenosis as a prelude to coronary artery bypass grafting. The risks are additive. No convincing data are available to validate this practice.

Most asymptomatic patients are probably best treated by medical care. The aspirin and carotid endarterectomy trial (n = 1521) records a stroke and death rate of 4.6% in asymptomatic subjects (unpublished data). Comparable rates from recent randomised trials or community observations range from 4.0% to 6.9%.[43 44] When the risk is this high there is negative benefit (table).

Conclusions

- A lifetime commitment to managing risk factors is the pre-eminent therapeutic requirement for all patients threatened with stroke.
- Aspirin is the platelet inhibitor of first choice for patients experiencing transient ischaemic attacks or minor stroke related to cerebral arteriosclerosis.
- Clopidogrel is recommended for patients with a known intolerance to aspirin or if symptoms recur despite use of aspirin.
- Should clopidogrel fail, the cautious administration of ticlopidine is an acceptable alternative.
- Long term warfarin therapy should be considered for patients with non-valvular atrial fibrillation. Patients at lower risk should receive aspirin.
- Carotid endarterectomy is recommended for patients with severe carotid stenosis producing focal symptoms.
- Careful selection will allow some patients with symptoms and moderate stenosis to be considered for endarterectomy.
- In many institutions, endarterectomy will not benefit asymptomatic patients. Current guidelines about its usefulness are unduly optimistic.
- Institutions should make available the results of independent audits of surgical complications of stroke and death from endarterectomy.[45] The line between success and failure is a narrow one.

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When I use a word …

X marks the spot

The ℞ symbol is well known as the sign of a prescription, and it is often said that it is R_x, a shortened version of the Latin word recipe, take. But ℞ is not R plus x; it is a corruption of a symbol that was once used by the ancient Egyptians to signify the utchat, the eye of Horus.

As with so many ancient gods, Horus had several manifestations, which are often confused with each other. Originally he was Horus the Elder, the falcon headed god of the sky. Other manifestations included a war god, two different forms of sun god, and various children of Isis and Osiris, also known as Harsiesis, Harpakhrad, Harpokrates, and Horus the Younger.

Horus the Elder had two eyes, the sun and the moon. Set, the god of night and darkness, evil and death, stole the sun, but Thoth made a treaty between them and allotted the day to Horus and the night to Set. Set was not content, however, and continued to make war on Horus by regularly cutting off parts of the moon, while Thoth renewed it each month. An interesting explanation of a natural phenomenon.

In *Finnegans Wake* James Joyce created a cod book title, "How to Pull a Good Horuscoup even when Oldsire is Dead to the World" (105.28). This alludes to another version of the story. Set killed Osiris and cut his body into pieces. Isis, the wife of Osiris, found all the pieces (except the penis, for which she fabricated a replacement), put them together, and conceived Horus the Younger. To avenge his father, Horus made war on Set, and during a battle lost an eye, which was then miraculously restored by Thoth.

Because of these restorations, the eye of Horus became a potent symbol of good fortune and healing, later adopted by the Greeks, Arabs, and others.

In the drawing on the left it is represented in a form that is recognisable as the source of the ℞ symbol, although more often it was drawn as shown on the right—for example, on the Rosetta stone.

Horus had other medical connections. His four sons were guardians, each with one of the goddesses, of the enurned organs of the dead:

- Amset, the human headed god of the south, was guardian of the liver with Isis
- Hapi, the dog headed god of the north, was guardian of the lungs with Nephtys
- Duamutef, the jackal headed god of the east, was guardian of the stomach with Net
- Qebhsneuf, the hawk headed god of the west, was guardian of the intestines with Selqet.

Prior to embalming, these organs were removed, wrapped in linen, and placed in so called Canopic jars, the lids of which were shaped as the heads of the gods who guarded them. Examples are to be seen in the Louvre.

In recent years the belief that the sign ℞ is formed from R (= recipe) plus x (somehow indicating an abbreviation) has led to the proliferation of numerous similar abbreviations, used as shorthand in case notes: H_x for history, S_x for symptoms, I_x for investigations, D_x for diagnosis, M_x for management, Ab_x for antibiotics. I expect that before long we shall be seeing E_x for examination and perhaps even X_x for *x* ray.

Jeff Aronson, *clinical pharmacologist, Oxford*

We welcome articles up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake,* or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk. Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.