# Stroke Prevention — Current Trends

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Strokes are common in Sri Lanka. In a WHO collaborative study[1] done in 1974 the age adjusted annual incidence rate for stroke was found to be about 1.9 per 1000 population. The study involved a population of 562 thousand in Colombo and this would amount to around 1068 strokes per year. The real incidence has to be more as some strokes in the community may have been not reported and also as the population has increased since. In the last three decades significant progress has been made in the understanding of the pathophysiology of strokes, identification of risk factors, in diagnostic techniques and treatment. Still there are many controversies concerning incidence, risk factors, prevention and treatment of stroke.

Stroke is the commonest cause of serious physical disability and is the third commonest cause of death after heart attacks and cancer. Age and sex specific annual incidence rates show higher rates for Myocardial infarctions (MI) than for Ischaemic strokes. MI affects a relatively younger population group when compared to the strokes[2]. (Figure 1)

Sudden vascular events such as myocardial infarction, cerebral infarction, transient ischaemic attacks (TIAs) and the appearance of unstable angina are all thought to be due to arterial thrombosis. In all these atherosclerosis is the basic problem but the final event being arterial thrombosis following fissuring or rupture of a palaque. The apparent similarity of the process that leads to such clinically different events makes one wonder why MIs begin at an earlier age than ischaemic strokes. No explanation is available for this so far.

**Figure 1**

**Age-adjusted average annual incidence rates from Framingham Study**

| | *Age 35 — 63* | *Age 65 — 94* |
|---|---|---|
| Myocardial infarction | 6/1000 | 13/1000 |
| Cerebral infarction | 1/1000 | 5/1000 |

Stroke prevention can be considered under two categories — primary and secondary prevention. As far as we understand the situation today the best strategy for prevention will be the early detection of hypertension and it's effective control as hypertension is the most significant proven risk factor.

Hypertension increased the risk of stroke 4 — 8 times that of age matched controls[3] and control of hypertension is shown to decrease the risk[4]. Hypertension causes stroke by—

1. promoting atherosclerotic occlusive vascular disease,

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2. causing changes such as lipohyalinosis in small vessels leading to lacunar infarcts[5].

3. intracerebral haemorrhage due to weakening of small vessel walls.

4. increasing the embolic risk as a result of hypertensive heart disease which leads to MIs and heart failure.

Other risk factors are not easily modifiable. These are TIAs, valvular heart and disease with or without arrhythmias, diabetes. Discretionary risk factors include cigarette smoking and heavy alcohol ingestion. The incidence of subarachnoid haemorrhage is particularly increased in women who used oral contraceptives and also smoked.

Although blood lipids and lipoproteins are strongly related to coronary atherosclerosis, their association with cerebrovascular atherosclerosis and strokes are less clear. Most of the studies where a relation was sought between plasma lipids and cerebral vascular disease have led to the conclusion that such a relation exists and that it is stronger in older than younger individuals[6].

The influence of diet upon stroke incidence remains controversial. Diet-induced hyperlipidaemia is a potent risk factor for IHD, but seems to have less influence on the cerebral arteries. A study on Japanese men living in Hawaii suggests that diets high in animal protein saturated fats are protective against stroke[7]. This finding requires confirmation in further studies but focuses attention on the gaps in our understanding of the influence of diet.

About 20% of patients with strokes have histories of TIAs prior to the infarction[8]. Risk of stroke after TIAs is about 5% during the first year and is 5 times that of normal population[9]. The mortality rate of patients with TIAs is about 6% per year, which is higher than the mortality rate for patients with angina which is about 3—4%[10]. Patients with TIAs are at a higher risk of dying of a MI whether or not they have symptoms of IHD or an abnormal ECG. It can be assumed from these data that the most important implication of a TIA is that the patient should be assessed with a view to prevent a stroke occuring as well as a MI. Similarly asymptomatic carotid bruits (ACB) are an indication of generalised arterio sclerosis and these patients are also at an increased risk from dying of a MI. Their risk of having stroke is low but the risk of cardiac death is more[11]. In other words patients surviving a MI often die of a stroke, carotid bruits are as much a marker of coronary artery disease as cerebro vascular disease.

**Presumed decrease in stroke incidence**

During the last ten years many studies have demonstrated a decreasing frequency in strokes both ischaemic and haemorrhagic[12 13]. To what extent this decline in incidence and mortality is real and related to better control of hypertension and other risk factors remains unknown. But the possible reasons for the decline are (1) availability of better diagnostic techniques resulting in more accurate diagnosis (2) decrease in case fatality due to better care including intensive care units (3) better control of hypertension.

According to most recent information from North America decline in

stroke incidence was from 1950s to 1979 when the incidence came down by 46%. In 1980s the incidence has started to go up again and the decline is attributed to the better control of hypertension and the more recent rise to improved diagnosis by newer techniques like computerised tomographic scanning.[14]

**Prevention**

Current treatment to prevent strokes in high risk patients include antiplatelet drugs, anticoagulants and vascular surgery. The value of these therapies remain controversial. Two randomised trials of carotid endarterectomy [15 16] did not show a significant reduction in morbidity and mortality. No benefit has been shown from the often performed extra cranial-intra cranial by-pass operation in the USA.[17] The value of anticoagulants in the prevention of strokes in patients with atherosclerotic disease is also unproved. The possible role of aspirin in the prevention of cardiovascular disease has been recognised only recently. Since the first report in 1956[18] of the value of aspirin in preventing stroke numerous clinical trials have evaluated aspirin's effects. Despite the publication of over 25 trials, no two studies were identical in methodology causing problems in coming to definitive conclusions. As various doses of aspirin were used in these trials the ideal dose of aspirin for these patients is also still not known but low doses 80, 160 and 320 mg are more effective and less gastrotoxic. A current Dutch TIA trial is using 80 mg of aspirin. The benefits of aspirin observed in the Second International Study of Infarct Survival were using 160 mg daily.

Anti platelet trialists collaboration study[19] — a mega analysis reviewing over 25 trials done on aspirin for secondary prevention reported in an analysis of 29,000 patients, that aspirin reduced vascular mortality by 15% and non fatal vascular events — strokes and MI by 30%. British physicians study[20] and the American ongoing physicians health study[21] for primary prevention produced conflicting results. American study showed a 44% reduction in the risk of MI in the aspirin group using a dose of 325 mg every other day. The British study using 500 mg of aspirin failed to show any risk reduction in non fatal MI or stroke. Taken together these two studies demonstrated a significant reduction in non fatal MI of about 30%. However there was no reduction in the overall risk of stroke, indeed these two studies suggested an increased risk of disabling or fatal stroke in aspirin treated patients.

The Second International Study of Infarct Survival (ISIS-2),[22] a landmark in aspirin trials evaluated the role of aspirin in evolving MI on 17,187 patients. This demonstrated a 49% reduction in non fatal MI, 46% decrease in non fatal stroke and 23% decrease in cardiovascular deaths after 5 weeks. The value of aspirin in reducing the incidence of subsequent stroke have been shown conclusively in survivors of MI, stroke and in patients with unstable angina.

The findings of primary prevention trials are suggestive of an increase in the number of all strokes although not significant statistically, among aspirin users. In view of this it may be appropriate to distinguish between ischaemic stroke, in which aspirin may

be beneficial, from a haemorrhagic stroke in which aspirin may be hazardous. Larger trials with sample sizes adequate to distinguish between ischaemic stroke and haemorrhagic stroke are required to settle this controversy. According to our present knowledge it can be said that aspirin should not be used in the prophylaxis of strokes in low risk patients and that it is probably indicated in low doses in patients at high risk for strokes. Most recent addition to the anti platelet armoury is a new drug known as Ticlopidine hydrochloride which acts primarily by inhibiting the adenosine diphosphate pathway of platelet aggregation. Ticlopidine does not inhibit the cyclo oxygenase pathway. In a recent trial[23] this drug was found to be somewhat more effective than aspirin in preventing strokes in high risk patients though the side effects with this drug were more than with aspirin.

The use of anticoagulant therapy for prevention of thrombotic strokes or treatment of progressive strokes cannot be justified on evidence available so far. Still some believe there may be special situations in which anticoagulants may be useful, such as Heparin in progressing stroke, though the precise nature and pathology of a progressing stroke is ill understood.

**Place of Surgery**

The surgical procedures are available for patients at a high risk of developing a stroke. These are 1) Carotid endarterectomy 2) Extra cranial to intracranial by-pass operation.

Carotid endarterectomy — This operation removes atheromatous plaques from the origin of the internal carotid artery (ICA) to try to prevent thrombi forming and embolishing to the cerebral circulation. About 40% of carotid distribution TIA patients have significant stenosis at the origin of the symptomatic ICA in the neck. Removal of such a stenosis seems logical as it would remove the source of thrombosis and embolisation and also may improve the cerebral blood flow. However, we do not know if this operation really does reduce the risk of subsequent stroke as there are no properly conducted trials on this subject[24]. Also the benefit achieved by the operation may be offset by the morbidity and mortality associated with the surgery which can be around 2 — 8% in the best of centres. The operation is considered suitable for patients with TIA or minor strokes who have significant stenosis in the relevant proximal ICA. There are two multicentre trials one in USA and the other in Europe being carried out now to evaluate this operation and compare with aspirin.

Extra cranial to Intra cranial bypass — This operation fashions a bypass around surgically inaccessible stenosis of the ICA or middle cerebral artery (MCA) by anastomosing the superficial temporal artery with the MCA. Recent studies[17] have shown that this operation offers no benefit and has no part to play in preventing strokes. This appealing operation therefore remains in search of an indication.

**Cerebral emboli**

The use of anticoagulants for the management of cerebral emboli of cardiac origin is generally accepted. With the decline of Rheumatic valvular disease in developed countries the major

cardiac cause of cerebral embolism today are nonvalvular atrial fibrillation (NVAF) and mural thrombi following MI. Incidence of cerebral embolism following MI is highest during the first two weeks and anticoagulation reduces the incidence of cerebaal embolism in patients with recent MI by 75%[25]. It is believed that the risk of stroke in patients with NVAF is about five times that of age matched controls and the risk is more at the onset of AF. Recent evidence from Minnesota, USA[26] shows that lone AF (AF in the absence of overt cardiovascular disease or precipitating illness) in patients under 60 years of age at diagnosis is associated with a very low risk that anticoagulants for this group is not justified. AF per se may not be a risk factor, but it's association with cardiac and vascular disease and hypertension is the reason for the high incidence of stroke in NVAF. European multicentre trial being carried out now on patients with AF and strokes will shed more light on these issues and determine the place of aspirin and anticoagulants in these patients.

Recurrence rate of cardiogenic embolism is high (15%[27]) and early anticoagulation may be advisable. Problem with early anticoagulation is the risk of cerebral haemorrhage or development haemorrhagic infarction if the infarct is large. Haemorrhagic infarction is common with embolic strokes — upto 20%[28]. Early CT scanning to exclude haemorrhagic infarction is not foolproof as bleeding into the infarct can occur upto 48 hours. Therefore large infarcts should not be anticoagulated for the first 2 weeks and the CT scanning may be delayed for 48 hours after a stroke to detect any late bleeding[29].

In conclusion future research in stroke prevention will provide the answers to the following uncertainities. The best effective dose of aspirin in the prevention of vascular events, the value of aspirin in primary prevention of vascular disease, mainly strokes, availability of better drugs than aspirin — eg. Ticlopidine, the value of endarterectomy, the value of lowering cholesterol in preventing progression of cerebrovascular disease, the value of long term anticoagulants in cardiogenic embolism and in lone AF. Most of all why some older men who smoke heavily and are liberal about the fats in their diet go through life without suffering a stroke or MI while some middle aged men who do not smoke and have normal cholesterol levels do get MIs and strokes need explanation.

## REFERENCES

1. Aho K, Harmsen P, Hatano S, et al. Cerebrovascular disease in the community: results of a WHO Collaborative study. *Bulletin of the World Health Organization*, 58(1): 113–130 (1980).
2. Shurteff D. Some characteristics related to the incidence of cardiovascular disease and death. Framingham study, 18 year follow-up, in W B Kennel and T Gordon (eds). "The Framingham study. An epidemiologic investigation of cardiovascular disease", DHEW Publication (NIH) 74-599 Sec 30, 1974.
3. Kannell W B, Wolf P A, Verter J, et al. Epidemiologic assessment of the role of blood pressure in stroke. *JAMA*, 1970; 214: 301–311.
4. Whisnant J P. Indications for medical and surgical therapy for ischaemic stroke. *Adv. Neurol.* 1977; 16: 133–144.
5. Fisher C M. Lacunes: small deep cerebra infarcts. *Neurology*, 1965; 15: 774–784.

6. Tell G S, Crouse J R, Furberg C D. Relation between blood lipids, lipoprotein and cerebrovascular atherosclerosis. *Stroke*, 1988; 19: 423-430.

7. Takeya Y, Popper J S, Shimuzu Y, et al. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: Incidence of stroke in Japan and Hawaii. *Stroke*, 1948; 15: 15-23.

8. Matsumoto N, Whisnant J P, Kurland L J, et al. Natural history of stroke in Rochester, Minnesota 1955-1969: an extension of a previous study. *Stroke*, 1973; 4: 20-29.

9. Baker R N, Ramseyer J C, Schwartz W S. Prognosis in patients with TIAs. *Neurology*, 1968; 18: 1157-1185.

10. Heydens S, Heiss G, Heyman A, et al. Cardiovascular mortality in TIAs. *Stroke*, 1980; 11: 252-255.

11. Chambers B R, Norris J W. Outcome in patients with asymptomatic neck bruits. *N. Eng. J. Med.* 1986; 315: 860-865.

12. Whisnant J. The decline of stroke. *Stroke*, 1984; 15: 160-168.

13. Garraway W M, Whisnant J P, Furlan A J, et al. The declining incidence of stroke, *N. Eng. J. Med.* 1979; 300: 449-452.

14. Broderick J P, Phillips S J, Whisnant J P et al. Incidence rates of stroke in the eighties: The end of the decline in stroke? *Stroke*, 1989; 20: 577-582.

15. Fields W S, Maslenikov V, Meyer J S, et al. Joint study of extra-cranial arterial occlusion. Progress report of prognosis following surgery or non-surgical treatment for TIAs and cervical carotid artery lesion. *JAMA*, 1970; 211: 1993-2003.

16. Shaw D A, Venables G S, Cartlidge N E F, et al. Carotid endarterectomy inpatients with TIA. *J. Neurol. Sciences*, 1984; 64: 45-53.

17. EC-IC Bypass Study Group. Failure of extracranial-intracranial arterial bypass to reduce the risk of ischaemic stroke. Results of an international randomised trial. *N. Eng. J. Med.* 1985; 313: 1191-1200.

18. Craven L L. Prevention of coronary and cerebral thrombosis. *Miss. Val. Med. J.* 1956; 78: 213-215.

19. Antiplatelet Trialists Collaboration. Secondary prevention of vascular disease by prolonged antiplatelet treatment. *Br. Med. J.* 1988; 296: 320-331.

20. Peto R, Gray R, Collins R, et al. Randomised trial of prophylactic daily aspirin in British male doctors. *Br. Med. J.* 1988 296: 313-316.

21. Final report on the aspirin component o. the ongoing physicians health study. *N Eng. J. Med.* 1989; 321: 129-135.

22. Second International Study of Infarct Survival (ISIS-2). Collaborative group randomised trial of intravenous Streptokinase, oral aspirin, both or neither among 17, 187 case of suspected acute myocardial infarction. *Lancet*, 1988; 2: 349-60.

23. Hass W K, Easton J D, Adams H P. et al. A randomised trial comparing Ticlopidine Hydrochloride with aspirin for the prevention of stroke in high risk patients. *N. Eng. J. Med.* 1989; 32: 501-507.

24. Warlow C. Carotid Endarterectomy; Does it work? *Stroke*, 1984; 15: 1068-1076.

25. Ebert R V. Anticoagulants in acute MI. Results of a cooperative clinical trial *JAMAs* 1973; 225: 724-729.

26. Kopecky S L, Gersh B J, McGoon M D. et al. The natural history of lone atrial fibrillation. A population based study over three decades. *N. Eng. J. Med.* 1987; 317: 669-674.

27. Cerebral Embolism Task Force. Cardiogenic brain embolism *Arch. Neurol.* 1986; 43: 71-84.

28. Hart R G, Easton J D. Haemorrhagic infarcts. *Stroke*, 1986; 17: 586-589.

29. Cerebral Embolism Task Force. Cardiogenic Brain Embolism. The second report of the cerebral embolism task force. *Arch. Neurol.* 1989; 46: 727-743.