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Primary And Secondary Prevention Of Stroke

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Summary

Results from recent clinical trials have shown that stroke is preventable both before and after symptomatic cerebrovascular disease through a change in lifestyle, medical therapy and surgical procedures. Risk factor control, antiplatelet agents, anticoagulation, and carotid endarterectomy have been proven to be effective under appropriate clinical circumstances. In this update, we shall highlight the areas in which scientific evidence is available. (*HK Pract* 1998;20:67-77)

摘要

從最近臨床資料顯示，在腦血管疾病症狀發生前後，可以透過改善生活習慣及使用適當藥物及手術來預防中風之發生。在適當情況下，控制誘發中風之因素，抗血小板劑，抗血凝劑及頸動脈內膜切除術已證實有效。本文重點強調已有臨床科學證據之預防方法。

Introduction

Stroke is a major neurological disease and a leading cause of death and disability in Hong Kong. Some breakthrough has been achieved recently in acute stroke treatment,[1,2] but prevention remains the optimal strategy for reducing the burden of stroke in our community. Stroke is a heterogeneous syndrome with different causes, types, and severity. Ischaemic stroke is the most common, intracerebral haemorrhage the second, and subarachnoid haemorrhage the least common among the three major stroke types.[3] Therapy should be formulated according to the clinical characteristics and risk factor profile of individual patients. Primary stroke prevention refers to prevention of stroke in people with no history of cerebrovascular symptoms, and secondary prevention applies to patients who have had a stroke or transient ischaemic attack.

Epidemiological and cohort studies have identified many modifiable risk factors for stroke. Risk factors identification allows us not only to recognize people at risk of stroke but also to promote a healthy lifestyle in the general population. Antithrombotic therapy should be considered in people at risk of cerebral ischaemia, as thromboembolism is a major pathogenic mechanism for ischaemic stroke. Finally, corrective procedures are available for carotid artery stenosis. These measures in general apply to both primary and secondary stroke prevention (**Table 1**).

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Table 1: Approach to prevention of stroke

Category	Action
Modifiable risk factors	
1. Hypertension	Screen for hypertension; keep systolic and diastolic blood pressure around 140 and 85 mmHg, respectively
2. Cardiac diseases	Check potential cardioembolic source; screen for other causes of stroke; see **Tables 2** and **3**
3. Atrial fibrillation	Check ECG and echocardiography; see **Tables 3** and **4**
4. Diabetes mellitus	Screen for undiagnosed diabetes mellitus; aim at strict glycaemic control
5. Dyslipoproteinaemia	Screen and control dyslipoproteinaemia
6. Cigarette smoking	Advise to quit smoking; consider nicotine gum or pad
7. Alcohol abuse	Advise to reduce drinking
8. Obesity	Reduce weight
9. Lack of exercise	Practise regular exercise
Antithrombotic therapy	
1. Antiplatelet agents	Start oral aspirin for secondary prevention of stroke and other vascular events; consider ticlopidine as an alternative
2. Anticoagulation	See **Table 3**
Carotid artery stenosis	
1. Endarterectomy	See **Table 5**
2. Angioplasty and stenting	Await further studies

Modifiable Risk Factors

Hypertension

Both systolic and diastolic blood pressures are independently associated with a 4 to 5 times increased risk of stroke of all types.[4] Hypertension promotes atherosclerosis in large and medium-sized arteries, arteriosclerosis in small penetrating arteries, and cardiac diseases of ischaemic and hypertensive types. These pathological processes may, in turn, cause stroke through thrombosis, embolism, occlusion of small vessels, or arterial rupture. One meta-analysis revealed a 42% reduction in the incidence of stroke and a 45% reduction in the incidence of fatal stroke with only 5 to 6 mm Hg decrease in the mean diastolic pressure following treatment.[5] The Systolic Hypertension in the Elderly Program (SHEP) reported a 36% decline in stroke risk with 11 mm Hg reduction in the mean systolic pressure.[6] In a local study, 74% of patients presented with cerebral haemorrhage were hypertensive.[7] Thus, early detection and good control of hypertension is one of the most important factors in the primary prevention of stroke. The same applies to secondary prevention. The systolic and diastolic blood pressures should be kept around 140 mmHg and 85 mmHg, respectively, to minimise the risk of stroke and other complications.[8,9]

Cardiac diseases

About one in five ischaemic strokes are caused by cardioembolism.[10] **Table 2** summarises the clinical, topographical, and neuroradiological features of cardioembolic stroke. Nevertheless, the presence of a potential cardioembolic source in a patient with cerebral ischaemia may be co-incidental. Other possible causes of stroke, such as carotid artery stenosis and prothrombotic states, should also be considered. Different cardiac conditions have varying risks of causing strokes (**Table 3**), and the chance of detecting such conditions depends on thoroughness of the evaluation. Long-term antithrombotic therapy is available to reduce the risk of embolic stroke at the expense of an increased risk of systemic and cerebral haemorrhages.

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Table 2: Features of cardioembolic stroke

Clinical features	Topographical features	Neuro-radiological features
1. Presence of a cardioembolic source	1. Posterior division of the middle cerebral artery	1. Superficial cortical location in the above territories
2. Non-progressive onset	2. Anterior cerebral artery	2. Multi-focal infarcts
3. Non-lacunar stroke	3. Cerebellar arteries	3. Haemorrhagic transformation in computed tomography of the brain
4. Isolated hemianopia, aphasia, or ideomotor apraxia	4. Multiple territories	4. Embolic occlusion without atherosclerosis or normal findings in angiography
5. Lack of vascular risk factors		
6. No other cause of stroke		

Table 3: Causes and management of cardioembolic stroke*

Category	Underlying cause	Management
Valvular heart diseases	1. Rheumatic heart disease	Anticoagulation
	2. Prosthetic valves	Anticoagulation
	3. Infective endocarditis	Antibiotics, anticoagulation?
	4. Calcific aortic stenosis	Aspirin?
	5. Mitral annulus calcification	Anticoagulation, surgery
	6. Non-bacterial thrombotic endocarditis	Aspirin, anticoagulation?
	7. Mitral valve prolapse	Aspirin?
	8. Inflammatory valvulitis	Treat underlying cause
Coronary artery disease	1. Acute myocardial infarction	Anticoagulation
	2. Left ventricular aneurysm	Anticoagulation?
	3. Left ventricular dyskinesia	Anticoagulation?
Arrhythmias	1. Atrial fibrillation (see **Table 4**)	Anticoagulation, aspirin
	2. Sick sinus syndrome	Pacemaker
Nonischaemic CMP	1. Dilating CMP	Anticoagulation
	2. Hypertrophic CMP	β-blocker, surgery
Intracardiac tumours	1. Primary atrial myxoma	Surgery
	2. Metastatic	Surgery?
Paradoxical emboli	1. Atrial septal defects	Surgery, anticoagulation?
	2. Patent foramen ovale	Anticoagulation?
	3. Ventricular septal defects	Surgery, anticoagulation?

*CMP = cardiomyopathy; ? = controversial

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Atrial fibrillation (AF) affects 1% of the general population, 6% of people aged above 65 years, and 10% of those over 75 years of age.[11] AF increases the risk of ischaemic stroke through systemic embolization of stasis-induced left atrial thrombi. The continued decline in the frequency of rheumatic heart disease will make non-valvular atrial fibrillation (NVAF) the commonest cause of this arrhythmia. Silent cerebral infarcts on computed tomography of the brain are present in about 25% of patients with NVAF, and are often multiple or bilateral.[12] Nevertheless, the associated cardiac abnormalities, coexistent cardiovascular diseases and intrinsic cerebrovascular diseases may account for 25 to 33% of all strokes associated with AF.[13] Recent randomised trials have revealed an increased risk of stroke (about 5% per year or 5 to 7 times as controls) in patients with NVAF and have proved the safety and benefit of long-term anticoagulation with warfarin.[4] Nevertheless, the actual risk of stroke is affected by a number of clinical and echocardiographic factors (**Table 4**). Using meta-analysis, the overall relative risk reduction in stroke among patients treated with warfarin as compared with placebo is 64%, and the corresponding benefit of aspirin is 22%.[14] For patients with AF due to rheumatic heart disease, the benefit of long-term anticoagulation is proven.[14]

Long-term anticoagulation (with warfarin) is therefore an established practice for secondary stroke prevention in patients with AF due to valvular heart disease or non-valvular causes (**Table 3**), and is increasingly employed in primary prevention. However, it must be emphasised that careful consideration of compliance and other factors must be given before starting treatment and that adequate instructions be communicated to patients and their relatives in order to reduce the risk of haemorrhagic complications. Low-intensity anticoagulation (with international normalized ratios between 2 to 3) carries an extra 1 to 2% risk of severe bleeding, including an 0.3% annual incidence of intracerebral haemorrhage.[15] Older patients (more than 75 years) have a higher risk of stroke but manifest greater toxicity to warfarin. Patients at lower risks for cardioembolism and those with contraindications for warfarin should be given low-dose aspirin at 325 mg per day to achieve stroke prevention.[4,14,15] Other medical and surgical therapies are also useful in individual cardiac diseases.

Table 4: Risk factors for stroke in non-valvular atrial fibrillation

Category	Factor
Clinical	1. Older than 65
	2. Hypertension
	3. Diabetes mellitus
	4. Recent heart failure
	5. Previous history of stroke
	6. Transient ischaemic attack
Echocardiographic	1. Enlarged left atrium
	2. Left ventricular dysfunction

Glucose tolerance

Diabetes mellitus is associated with cerebrovascular disease (including atherosclerosis and/or small vessel disease) directly and indirectly via coronary artery disease, hypertension, abnormal lipids, and obesity.[16] The relative risks of ischaemic stroke and stroke of all types are elevated by two-folds in both diabetic men and women.[4] In a local study of 176 Chinese patients with acute stroke, the overall prevalence of diabetes mellitus and impaired glucose tolerance was 33.5% and 21.0% respectively, with a higher prevalence being found in patients with cerebral infarction.[17] Forty percent of those with diabetes mellitus were previously undiagnosed.

Since undiagnosed diabetes mellitus is a distinct health problem in our elderly population, it may be important to screen for diabetes mellitus as part of primary health care of the elderly particularly those who are at a higher risk. Treatment should aim at both strict glycaemic control as well as control of all risk factors for cardio- and cerebrovascular diseases, although the influence of the former on the risk of stroke remains unknown.

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Cigarette smoking

Cigarette smoking increases the risk of ischaemic stroke by 2 to 3 times through the induction of atherosclerosis and ischaemic heart disease.[4] In addition, cigarette smoking increases blood levels of fibrinogen and other clotting factors, promotes platetet aggregation, elevates the haematocrit, reduces the level of high-density lipoprotein cholesterol, produces acute rise in arterial blood pressure, and enhances the breakdown of elastic tissue within arteries.[16] The latter two effects may lead to arterial rupture and intracerebral or subarachnoid haemorrhage.[18] The risk of stroke for smokers is higher in women than men, becomes less with increasing age, and is proportional to the number of cigarettes smoked per day.[19] The risk of stroke of all types decreases promptly towards the level of non-smokers within five years of quitting in both men and women.[19]

Alcohol abuse

Recent studies have clarified the role of alcohol consumption in stroke. Low levels of alcohol intake (one to two drinks per day) appears to reduce the risk for ischaemic stroke via reducing the risk of ischaemic heart disease, improving the lipid pattern, increasing the level of prostacyclin, and activating the fibrinolytic system.[16] Higher levels of drinking, especially following acute intoxication, increases the risk for ischaemic and haemorrhagic strokes by 3 to 4 times via haemoconcentration (producing hyperviscosity), hypertension (increasing the risk for intracerebral bleeding), rebound thrombocytosis (causing a prothrombotic state), cardiac arrhythmias (generating thromboemboli or hypoperfusion), and interactions with smoking (as smoking is more frequent among heavy drinkers).[16]

Blood lipids

High level of total and low-density lipoprotein cholesterols, reduced level of high-density lipoprotein cholesterol, and increased ratio of low- to high-density lipoprotein cholesterols constitute dyslipoproteinaemia, which is associated with premature atherosclerosis and ischaemic heart disease.[20] The association between dyslipoproteinaemia and stroke has been established recently. Lipid lowering agents have been found to reduce the risk of fatal and non-fatal strokes as well as retard the progression of carotid atherosclerosis.[4]

Obesity

Obesity is probably not an independent factor but related to dyslipoproteinemia, hypertension, hyperinsulinaemia, glucose intolerance, and lack of exercise.[16] In experimental animal studies, caloric restriction prolongs survival.[21]

Lack of exercise

Exercise reduces blood pressure, body weight, and platelet aggregation but improves lipid pattern and sensitivity to insulin.[16] These effects may explain the association between sedentary lifestyle and strokes of all types in both men and women.

Others

Higher-dose oral contraceptives have been found to increase the risk of stroke in women over 35 years of age, smokers, hypertensives, and migraineurs.[16] Although low-dose oral contraceptives do not increase the risk of stroke,[22] oral contraceptives should be avoided in women at high risk for stroke. Post-menopausal oestrogen replacement may reduce cardio- and cerebrovascular events and prevent osteoporosis, but there is an increased risk of endometrial and breast cancer.[22] Prospective randomised trials are awaited to clarify the benefits of oestrogen replacement, antioxidant vitamins, dietary potassium, or polyunsaturated fatty acids in stroke prevention.[16]

Antithrombotic therapy

Anticoagulation

Prophylactic anticoagulation for patients with a high risk of cardioembolism has been discussed (see **Table 3**).

Antiplatelet agents

Use of aspirin in the primary prevention of stroke remains controversial among healthy subjects. Studies of healthy subjects taking aspirin of various doses have reported

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no benefit in the risk of ischaemic stroke, strokes of all types, fatal stroke, or fatal vascular events.[4,14] While low-dose aspirin protects against first myocardial infarctions, there may be a small increase in the risk of intracerebral haemorrhage.

Meta-analysis of data from large clinical trials on antiplatelet agents shows that aspirin reduces vascular mortality by 15% and non-fatal vascular events (stroke and myocardial infarction) by 30%.[23,24] The dosage is less important; 300 mg daily is as effective as 1.3 gm daily, but produces less gastrointestinal upset.[25]

Two major multicentre trials[26,27] have shown that ticlopidine 250 mg twice daily is as effective as aspirin in secondary stroke prophylaxis. It is not ulcerogenic but may cause skin rash, leucopenia, aplastic anaemia and bleeding tendency, and rarely cholestatic jaundice or raised transaminases. In general, it is given to patients who cannot tolerate aspirin.

Carotid artery stenosis

Extracranial carotid artery stenosis is an established risk factor for symptomatic and silent stroke. The immediate pathogenic mechanisms for cerebrovascular ischaemic symptoms and/or signs in carotid artery stenosis are two: thromboembolic (especially with an ulcerated plaque) and haemodynamic (when there is near or total occlusion, especially with poor collaterals and/or systemic hypotension). The risk for stroke is non-uniform but affected by factors such as occurrence of symptoms, degree of stenosis, presence of ulceration, contralateral occlusion, presence of collaterals, number of other risk factors and cerebral infarction on computed tomography of the brain.[28] Standard contrast angiography remains the gold standard for providing accurate images of the carotid arteries, the proximal vessels and the intracranial vasculature. Diameter stenosis (comparing the diameter of the internal carotid artery above the stenosis as the denominator with the diameter of the narrowest part as the numerator) should be used.[29] This is the method used in the North American Symptomatic Carotid Endarterectomy Trial. Contemporary data on the prevalence of carotid artery stenosis is not available in Hong Kong Chinese. In addition, the risk of first and recurrent strokes is unknown in local patients with moderate or severe carotid artery stenosis.

Carotid artery stenosis can be corrected by carotid endarterectomy or percutaneous transluminal angioplasty with or without stenting. Carotid endarterectomy carries a significant perioperative risk of morbidity and mortality of 5 to 7% or more.[29] The preoperative carotid arteriography also contributes an additional risk to the procedure.

Patients with severe asymptomatic carotid artery stenosis have a 1.5 to 2% annual stroke rate.[4] Results of four randomised clinical trials of carotid endarterectomy in patients with severe asymptomatic carotid disease were published.[14,30] Only the Asymptomatic Carotid Atherosclerosis Study found a marginal benefit from surgery in asymptomatic stenosis of 60% or more by diameter: 1% per year absolute reduction in stroke risk over a five-year projected period despite a remarkably low perioperative risk of 2.3%.[30] Nevertheless, there was no reduction in the major strokes or deaths. There was no benefit in females, and there was no relation between the benefit and the degree of stenosis. At present, scientific data do not unequivocally support carotid endarterectomy as an effective way of primary stroke prevention in patients with asymptomatic carotid artery stenosis of any severity so the prophylactic measures are antithrombotic therapy with low-dose aspirin and modification of risk factors.[29]

In general, patients with transient ischaemic attacks related to severe (70 to 99% by diameter) carotid artery stenosis have a 12 to 13% rate of stroke in the first year and a cumulative rate of 30 to 35% in five years, whereas those presenting with strokes have a 5 to 9% annual rate of recurrence and a five-year rate of 25 to 45%.[29] After successful carotid endarterectomy, patients who presented with transient ischaemic attacks continue to have a 1 to 2% annual risk of recurrent stroke, while a presenting history of stroke carries a 2 to 3% per year rate of subsequent stroke. Surgery has been proven to be inferior to the best medical management if the symptomatic stenosis is less than 30%.[29] Contemporary guidelines of carotid endarterectomy are summarised in **Table 5**.

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Table 5: Contemporary guidelines of carotid endarterectomy*

Category	Carotid endarterectomy
Symptomatic	1. Indicated in patients with 70 to 99% stenosis if peri-operative morbidity and mortality rate <6%
	2. Not indicated in patients with < 70% stenosis even if surgical risk <6%
	3. Not indicated when surgical risk approaches 10% irrespective of degree of stenosis
	4. Considered acceptable in patients with < 70% stenosis in an ongoing prospective contemporary randomized trial plus <6% surgical risk
Asymptomatic	1. Not definitely indicated in any patients
	2. Considered acceptable in patients with ≥ 75% stenosis plus < 3% surgical risk
	3. Not indicated when surgical risk is ≥ 3% irrespective of degree of stenosis

* degree of stenosis as defined by the North American Symptomatic Carotid Endarterectomy Trial

The optimal strategy for managing patients with combined coronary artery and carotid disease remains unresolved. Meta-analysis of the available reports indicates that combined carotid and coronary surgery carries the same peri-operative stroke rate (6.2%) as when carotid endarterectomy precedes coronary artery bypass grafting (stroke rate = 5.3%) and that the stroke rate is highest (10.0%) if carotid surgery follows coronary surgery.[29] Nevertheless, the probability of myocardial infarction (11.5%) and death (9.4%) is greater when carotid surgery precedes coronary artery bypass grafting than when the order is reversed (myocardial infarction rate = 2.7% and death rate = 3.6%). Simultaneous surgery has a 4.7% probability of myocardial infarction and a 5.6% probability of death. Thus, a prospective randomised trial is needed to resolve the controversy. Meanwhile, combined carotid and coronary surgery appears to be acceptable for patients in whom both procedures are of proven benefit.

Percutaneous transluminal angioplasty with or without stenting in cerebral artery stenosis is at the experimental stage.[14] This procedure carries the risk of cerebral or retinal embolization. While prospective data are being collected to build up our experience on the procedure, randomised control trials are awaited to confirm its usefulness.

Conclusion

Recent clinical studies have provided important data to guide primary and secondary prevention of stroke. Family physicians can therefore play an important role in stroke prevention. They are in a better position than specialists in screening and identifying risk factors of stroke, promoting a healthy lifestyle and providing routine management of modifiable risk factors. In most patients with ischaemic stroke, the pathogenic mechanism is atherothrombosis, and antiplatelet therapy is useful in secondary prevention. Family physicians should be able to monitor the long-term antiplatelet therapy, whereas complicated or unusual cases should be referred to neurologists. Anticoagulation is indicated for prevention of cardioembolic stroke provided contraindications are absent. Since long-term anticoagulation is a complex issue, it would be better handled by specialists. If the perioperative risk is acceptable, carotid endarterectomy for severe stenosis is beneficial for symptomatic patients but is controversial in asymptomatic patients. Patients with symptomatic carotid artery stenosis should be referred to specialists for assessment as carotid endarterectomy or angioplasty may have to be considered. Finally, ongoing clinical trials will help clarify the uncertain areas in stroke prevention. ■

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Key messages

1. Stroke is a major neurological disease and a leading cause of death and disability. Family physicians play an important role in stroke prevention.
2. Stroke is a heterogeneous syndrome, and specific therapy varies according to the clinical setting and risk factor profile of individuals.
3. Epidemiological and cohort studies have identified hypertension, atrial fibrillation and other types of cardiac diseases, diabetes mellitus, dyslipoproteinaemia, smoking and alcohol abuse, obesity and lack of exercise as the modifiable risk factors for stroke.
4. Antithrombotic therapy should be considered in people at risk of cerebral ischaemia. Antiplatelet therapy is effective in secondary prevention of atherothrombotic stroke. Anticoagulation prevents cardioembolic stroke, but contraindications should be noted.
5. Corrective procedures are available for carotid artery stenosis. If the perioperative risk is acceptable, carotid endarterectomy for severe stenosis is beneficial for symptomatic patients but is controversial in asymptomatic patients.
6. Complicated or unusual cases should be referred to neurologists.

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