腦中風的內科及外科的預防

馮清世

摘 要

腦中風是一常見與嚴重的疾病，大多數的腦中風並無有效的治療方式，故腦中風的預防是一個重要的課題。初級與次級腦中風預防試驗顯示降低高血壓病人的血壓可減少腦中風的危險。另有證據發現發生心肌梗塞後的病人服用 warfarin 或 statin 藥物可減少腦中風的發生率。在非瓣膜性心房顫動的病人若合併有其他的危險因子，需服用 warfarin。控制糖尿病病人的高血壓是必要的，且嚴格控制血糖可減少小血管的併發症。有高膽固醇血症的病人，降低血中的膽固醇可減少腦中風的發生。頸動脈高於百分之七十狹窄的症狀性病人接受頸動脈內膜切除術可減少腦中風的發生，然而頸動脈內膜切除術對於頸動脈狹窄而無症狀性的病人，在腦中風的預防效果尚不清楚。曾有腦缺血症狀的病人服用 aspirin 或 clopidogrel 可減少再發性腦中風的危險。抽煙與與飲酒過量應該避免，他們會增加腦中風的發生。不建議曾有腦中風病史或有腦中風危險因子的女性使用含有雌激素的荷爾蒙補充療法與服用口服避孕藥。

關鍵字：腦中風，預防

佛教大林慈濟綜合醫院神經科
受文日期：2003年3月18日。修改日期：2003年4月25日。
接受日期：2003年5月21日。

通訊作者：馮清世。佛教大林慈濟綜合醫院神經科，622 嘉義縣大林鎮民生路2號。
E-mail: csfong@tcts.seed.net.tw

Medical and Surgical Prevention of Stroke

Chin-Shih Fong

Abstract- Stroke prevention is an important subject because stroke is a frequent and severe disorder, and there are no effective treatments for most of stroke. Primary and secondary prevention trials have shown that reducing blood pressure in hypertensive individuals reduces stroke risk. Evidence for stroke reduction exists for using warfarin or statin agents for patients after myocardial infarction. Warfarin is indicated for patients with valvular heart disease and nonvalvular atrial fibrillation who have specific risk factors. Careful control of arterial hypertension in diabetics is recommended, together with a strict glycemic control to reduce systemic microvascular complication. Lowering serum cholesterol in patients with hypercholesterolemia reduces the risk of stroke. Carotid endarterectomy reduces the risk of stroke in symptomatic patients with at least 70 percent stenosis of carotid artery. The endarterectomy with perioperative stroke-related morbidity and mortality of 3% or less is considered for patients with asymptomatic carotid lesion of at least 60% stenosis. In patients with cerebral ischemic symptoms, aspirin or clopidogrel reduce the risk for recurrent stroke. Cigarette smoking and heavy drinking are associated with an increased risk of stroke, and should be avoided. Estrogen prescribed in hormone replacement or oral contraceptives therapies is not recommended in women with prior stroke events or with risk factors for stroke.

Key Words: Stroke, Carotid artery disease, Risk factor, Prevention

Acta Neurol Taiwan 2003;12:212-220

INTRODUCTION

Stroke is a heterogeneous disorder that includes cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhge. Cerebral infarction is the most common form of stroke, accounting for 71% of stroke in Taiwan[1]. In Taiwan, stroke is the second leading cause of mortality in recent decades. The average annual incidence rate of first-ever stroke for people aged 50 years or older is 527 per 100,000 populations. The 28-day case-fatality rate is 24.5% for first-ever stroke and 60% for recurrent stroke[2]. Less than 50% of stroke patients are independent one year after stroke and many of them have residual physical and behavior changes, leading to family burden. As the aging of the population and improved survival of patients with acute stroke, the health burden of stroke will probably increase during the next decades. The cost of acute and long-term care for stroke patients is approximately $30 billion per year in United States. Besides the health burden, stroke also

From the Department of Neurology, Buddhist Dalin Tzu Chi General Hospital, Chia Yi, Taiwan.
Received March 18, 2003. Revised April 25, 2003.
Accepted May 21, 2003.
Reprint requests and correspondence to: Chin-Shih Fong, MD. Department of Neurology, Buddhist Dalin Tzu Chi General Hospital, No. 2, Min Sheng Road, Dalin, Chia Yi, Taiwan.
E-mail: csfong@tcts.seed.net.tw

exacts an enormous financial burden[3]. There are currently no effective treatments for most of forms of stroke, therefore, the best strategy for stroke remains prevention. Several conditions and lifestyle factors have been identified as risk factors for stroke. These include hypertension, myocardial infarction (MI), nonvalvular atrial fibrillation, valvular heart disease diabetes mellitus (DM), hyperlipidemia, carotid artery disease, smoking, alcohol use, and estrogen use. These risk factors for each stroke subtype are surprisingly similar. Recognition of these risk factors is important to reduce the incidence of stroke. The aim of this review is to address the medical and surgical measures to prevent stroke from available literature.

HYPERTENSION

Primary prevention trials

Hypertension is the most prevalent and controllable risk factor for stroke, and its treatment substantially reduces the risk of stroke. Epidemiological studies have shown a continuous, positive, linear relationship between systolic and diastolic blood pressure and the incidence of any subtype of ischemic or hemorrhagic stroke, at any age, and in both sexes. The risk of stroke doubles for every 7.5 mmHg increase in diastolic blood pressure[4]. A meta-analysis of 14 primary prevention randomized clinical trials shows that a decrease in diastolic blood pressure of 5 to 6 mm Hg reduces the risk for stroke by 42%[5]. The Systolic Hypertension in the Elderly Program (SHEP) study shows that treatment of isolated systolic hypertension in the elderly decreases the risk for stroke by 36%[6]. An overview of clinical trials suggests that diuretics are associated with a 39% odds reduction and beta-blockers a 25% odds reduction for stroke events in older persons with hypertension[7]. The studies of Syst-EUR indicate that in elderly subjects with isolated systolic arterial hypertension, a calcium antagonist, nitrendipine, reduces the risk of stroke by 42%[8]. The Heart Outcome Prevention Evaluation (HOPE) study shows that patients who receive angiotensin-converting enzyme inhibitors, ramipril have a relative risk of stroke of 0.68 when compared to those who receive placebo[9]. The LIFE study[10] includes 1,326 patients with isolated systolic hypertension and left ventricular hypertrophy, randomly assigned to receive angiotensin II antagonist, losartan or atenonol. The nonfatal and fatal stroke in losartan group is less than in atenolol group, 10.6 versus 18.9 events per 1,000 patients-years. However, a meta-regression across 27 trials including 136,124 patients, show that all antihypertensive drugs have similar long-term efficacy and safety that the most important action of antihypertensive drugs on stroke prevention is the direct consequence of blood pressure reduction[11]. The Arterial Hypertension Optimal Treatment (HOT) trial demonstrates that systolic and diastolic blood pressure should be lowered to 140-85 mmHg or lower[12].

Secondary prevention trials

There was no clear evidence until recently that reducing blood pressure after stroke reduces the rate of new vascular events or death. PROGRESS[13] has included 6,105 patients with a history of stroke or TIA within the past 5 years, randomly assigned perindopril alone, in combination with indapamide, or placebo and active treatment (perindopril alone or in combination) reduces blood pressure by 9/4 mmHg. In the active treatment group, after a 4-yers period, the rate of recurrent stroke is reduced by 28% and the rate of total major vascular event by 26%. The risk reduction is similar in normotensive and hypertensive patients. The effect is significant only with perindopril plus indapamide. The effect is present in all stroke subtypes, but greater in hemorrhagic strokes.

MYOCARDIAL INFARCTION

Following MI, approximate rate of ischemic stroke is 1-2%/ year. This risk is greatest in the first month after MI[14]. Most cardiogenic emboli occur from left ventricular thrombus. Stroke complicates about 6% of anterior MI during the acute course, but only about 1% of inferior MI. Treatment to prevent stroke after MI may include oral anticoagulants, antiplatelet agent, and lipid-lowering agents.

The Anticoagulant Secondary Prevention of Events in Coronary Thrombosis (ASPECT) Research Group[15]

recruits 3,404 patients who had MI. They are randomized and double-blinded to treatment with anticoagulation therapy or placebo. The likelihood of recurrent MI is reduced by 53%, risk of stroke reduced 42% and risk of mortality reduced 10%. Long-term warfarin is indicated for patients with MI plus persistent atrial fibrillation, decreased left ventricular function or left ventricular thrombi. An INR range of 2.0 to 3.0 with a target goal of 2.5 is recommended.

The Antiplatelet Trialists' Collaboration[16] concluded in 1994 that in patients with previous MI, antiplatelet agents reduce the odds of nonfatal MI by 31%, nonfatal stroke by 39%, and vascular death by 15%. A pooled analysis of 11 trials performed by the North of England Aspirin Guideline Development Group[17] demonstrates that aspirin use in patients with previous MI results in a risk difference of 3.2% for the combined end point of MI, stroke, or vascular death. However, the American College of Physician (ACP)[18] reports that aspirin use in patients with previous MI results in only a small absolute stroke risk reduction and this is not substantial enough evidence to conclude that antiplatelet agents are useful in preventing a first stroke after MI.

Current evidence suggests that cholesterol-lowering agents, in particular the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statin agents), decrease the risk of stroke after MI. The Cholesterol and Recurrent Events (CARE)[19] Trial (n=4,159) shows that in patients with previous MI and average cholesterol levels (<240 mg/dL), pravastatin sodium is associated with a 31% risk reduction for stroke compared with placebo. The effects of the statin agents except the lipid-lowering properties come from nonlipid mechanisms that modify endothelial function, inflammatory responses, plaque stability, and thrombus formation. The Scandinavian Simvastatin Survival Study (4S) (n=4,444)[20] assesses patients with coronary heart disease and high cholesterol levels from 213-309 mg/dL and demonstrates a 37% reduction in stroke and transient ischemic attack for patients taking simvastatin. In a larger study, the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial (n=9,014)[21], patients with coronary heart disease and normal to high cholesterol levels, from 155-270 mg/dL who took pravastatin experiences a 20% risk reduction for stroke.

NONVALVULAR ATRIAL FIBRILLATION

Nonvalvular atrial fibrillation (NVAF) is an important risk factor for stroke. It increases the risk of stroke by about 6 times. About 36% of strokes in patients between the ages of 80 and 89 years are attributed to this condition[22]. The ACP[18] recommends that oral anticoagulation with warfarin be given for patients with NVAF who have specific risk factors for stroke, including age >60 years, previous transient ischemic attack or stroke, hypertension, heart failure, and DM. However, patients with NVAF who do not have specific risk factors are treated with aspirin[23].

VALVULAR HEART DISEASE

Valvular heart disease of which the most common variety causes stroke is rheumatic mitral value disease (RMVD)[24]. The incidence of embolic stroke increases dramatically in the setting of atrial fibrillation. It has be reported that up to 80% of the RMVD patients suffering cerebral emboli occur in the presence of atrial fibrillation. Atrial fibrillation associated with rheumatic mitral valve disease has the highest stroke risk (about 17 times greater than unaffected controls). The stroke risk is greater with chronic than with paroxysmal atrial fibrillation and is highest in the first year after onset of the arrhythmia. Rheumatic mitral valve disease requires long-term anticoagulant therapy whether or not the lesion is accompanied by atrial fibrillation.

DIABETES MELLITUS

Diabetes mellitus has an increased risk for stroke through multiple and potentially synergistic mechanisms. These include acceleration of large artery atherosclerosis, adverse effects on both low-density lipoprotein and high-density lipoprotein cholesterol levels, and promotion of plaque formation through hyperinsulinemia. Despite epidemiological and basic science evidence that links DM to stroke, studies have not conclusively shown that tight control of serum glucose levels reduces the risk

for stroke. Randomized controlled trials have demonstrated that tight control of blood sugars with intensive insulin therapy in patients with type 1 DM and intensive sulfonylurea and/or insulin therapy in patients with type 2 DM result in a reduction in the number of microvascular complications (retinopathy, nephropathy, neuropathy) but not macrovascular complications such as stroke[25]. However, tight control of blood pressure (<150/85 mm Hg) in patients with hypertension and type 2 DM reduces the risk of fatal and nonfatal stroke by 44% compared with the group with less tight control[26].

SERUM CHOLESTEROL

The positive relationship between total serum cholesterol and incidence of coronary heart disease (CHD) has been well established. However, the relationship between serum cholesterol levels and the risk of stroke remain a matter of debate. A U-shaped relation between the serum level of total cholesterol and the risk of stroke of all types has been proposed, derived from an inverse association with hemorrhagic stroke and a direct association with ischemic stroke. An increase in serum cholesterol could lead to atherosclerosis of the internal carotid artery and the larger cerebral arteries and to subsequent ischemic stroke. Conversely, low serum cholesterol levels could involve the weakening of the endothelium of smaller intracerebral arteries and lead to hemorrhagic stroke. In a meta-analysis, an increase in the risk of fatal stroke (odds ratio, 1.32) and a decrease in the risk of nonfatal stroke (odds ratio, 0.88) are observed among men in intervention to lower lipid levels through clofibrate or diet[27]. An overview of 41 trials[28] find lowering serum cholesterol with statins or gemfibrozil reduces the nonfatal and fatal stroke incidence in patients with hypercholesterolemia or CHD, but it is unknown whether there is any benefit from lowering cholesterol levels in normo-cholesterolemic stroke patients.

EXTRACRANIAL CAROTID ARTERY DISEASE

Randomized clinical trials have evaluated carotid endarterectomy (CEA) and extracranial-intracranial anastomosis to prevent stroke in patients with extracranial carotid artery disease. Stroke risk increases with the degree of carotid artery stenosis[29]. The European Carotid Surgery Trialists Collaborative (ECST) finds that the 3-year risk of ipsilateral stroke is 5.7% for asymptomatic carotid stenosis of 70-99% but only 1.8% for stenosis of 0-29%[30]. Four randomized controlled trials have been published in this area[31-34]. The CASANOVA (Carotid Artery Stenosis with Asymptomatic Narrowing: Operation versus Aspirin)[31] trial include 410 patients with asymptomatic stenosis (50-90%) of the internal carotid artery. No benefit is found for endarterectomy. Mayo Asymptomatic Carotid Endarterectomy randomized trial[32] is discontinued 71 patients have been enrolled, because myocardial infarctions and cerebral ischemic events have occurred in endarterectomy group, as compared with none in the aspirin group. The third trial is the Department of Veterans Affairs study of 444 patients[33]. The incidence of transient ischemic attacks (TIAs) is reduced in the surgical group. When TIAs are omitted from the analyses, endarterectomy does not improve the occurrence of death or long-term stroke survival. The fourth trial, Asymptomatic Carotid Atherosclerosis Study (ACAS)[34] finds a benefit from CEA as compared with medical treatment in 1662 patients with 60% to 99% asymptomatic stenosis followed for an average of 2.7 years. The five-year risk of stroke is 10.6% in the medical group and 4.8% in the surgical group. This reflects a 5.8% absolute risk reduction in five years. The American Heart Association[35] guideline recommends CEA for asymptomatic lesions of at least 60% stenosis and a perioperative complication rate of less than 3%.

Randomized clinical trials have also proved benefit for CEA in cerebral symptoms associated with arteriosclerotic stenosis of the carotid artery. ECST and North American Symptomatic Carotid Endarterectomy Trial (NASCET)[36] indicate that for symptomatic patients with stenosis of 70% or more, medical treatment alone is inferior to CEA. In NASCET the risk of ipsilateral stroke at two years is 26% for patients treated medically and 9% for those treated surgically. In ECST the absolute difference between the risk of stroke among patient receiving medical treatment alone and the risk

among those undergoing surgery is 17%. In both NASCET and ECST surgery is not beneficial in patients with less than 70% stenosis.

The anastomosis of the superficial temporal artery to a cortical branch of the middle cerebral artery seems logical as a prophylaxis for patients with occlusion of the extrcranial carotid artery. An international randomized trial fails[37] to find benefit from the procedure. Recent some studies[38,39] have reported unchanged resting cerebral blood flow (CBF) and improved cerebrovascular reactivity after extracranial-intracranial (EC-IC) bypass surgery in patients with reduced cerebrovascular reserve due to internal carotid artery occlusion or Moyamoya disease.

Several small series of patients with symptomatic and asymptomatic stenosis in either vertebrobasilar or carotid arteries have undergone percutaneous transluminal angioplasty. This procedure carries the risk of dislodging emboli that can be carried to the brain. Angioplasty should be delayed until it passes the stage of experimental use and randomized clinical trials.

PRIOR TIA OR STROKE

Patients suffering from a transient ischemic attack (TIA) or stroke are particularly vulnerable to subsequent stroke. Estimates indicate that as many as 40% of those who survive a first TIA or stroke will have a subsequent stroke within 5 years. Most of these individuals are candidates for antiplatelet treatment to prevent a recurrence. Available antiplatelet therapies include aspirin, sulfinpyrazone, dipyridamole, ticlopidine, and clopidogrel. Aspirin has proven value in the prevention of ischemic stroke when given to individuals experiencing TIA or minor stroke. In a meta-analysis, there is 25% relative risk reduction of stroke and vascular death in a total of 14,400 patients studied in 15 randomized clinical trials using aspirin alone[40]. Neither sulfinpyrazone plus aspirin nor dipyridamole plus aspirin proves more beneficial than aspirin alone in stroke prevention. However, European Stroke prevention Study in 6,602 patients[41] demonstrates that aspirin 20mg twice daily and dipyridamole at a dose of 200mg twice daily have each been equally effective for the secondary prevention of ischemic stroke, and the combined therapy is more effective than either agent prescribed singly. The Ticlopidine Aspirin Stroke Study[42] concludes that ticlopidine is somewhat more effective than aspirin, but more patients in the ticlopidine group have side effects. CAPRIE[43] is a randomized, blinded international trial designed to assess the relative efficacy of clopidogrel and aspirin in reducing the risk of ischemic stroke, myocardial infarction, or vascular death, as well as to assess their relative safety. The analysis shows that clopidogrel is more effective than aspirin in the prevention of vascular events (5.32% versus 5.83%) and the overall safety profile of clopidogrel is similar to that of aspirin.

ASPIRIN IN HEALTHY SUBJECTS

Despite conclusive evidence of the benefits of aspirin in the secondary prevention of stroke, only three clinical trials for primary prevention been have conducted. The American Physician Health Study in 22,071 male physicians demonstrates a reduction in first myocardial infarction, but not in the incidence of stroke[44]. The British study in 5,139 male physicians finds no significant difference in the incidence of stroke between the treatment and control group[45]. In a study involving 87,678 women, use of aspirin does not reduce the risk of stroke either[46].

LIFESTYLE FACTORS

Cigarette smoking

The effects of smoking are multifactorial, affecting both vessels and coagulation. The vascular effects of smoking are the consequence of reduced vessel distensibility and increased arterial wall stiffness, leading to atheroma. The blood effects consist of increased fibrinogen levels, platelet aggregation and decreased HDL levels. A meta-analysis of 22 studies[47] indicates that smoking doubles the risk of ischemic stroke. Passive exposure to cigarette smoke also increases the risk of progression of atherosclerosis[48].

Alcohol use

Alcohol consumption has a direct dose-dependent

effect on the risk of hemorrhagic stroke[49]. Studies[50] have suggested a J-shaped dose-response curve between alcohol use and ischemic stroke risk, with protection for those drinking up to 2 drinks a day and an increased risk for those drinking more than 5 drinks a day. The deleterious effects of alcohol for stroke may occur through increasing arterial hypertension, hypercoagulable states, cardiac arrhythmia and reduced cerebral blood flow. However, a light alcohol intake may act as a protector by increasing HDL cholesterol and endogenous tissue plasminogen activator.

Diet

Dietary factors may be risk factors for stroke. Increased sodium intake is associated with hypertension, and reduction in salt consumption may significantly lower blood pressure and may reduce stroke mortality. Elevated plasma levels of total homocysteine are inversely related to dietary intake of folic acid and vitamin B6. Case-control studies have shown an association between moderately elevated homocysteine levels and stroke, but this relationship is less robust in prospective studies[51]. Finally, the role of fat intake as a stroke risk factor remains uncertain, whereas fruits and vegetables may contribute to prevention of stroke through antioxidant mechanisms or through the elevation of potassium levels.

Postmenopause estrogen replacement therapy

Postmenopausal therapy with exogenous estrogen is widely used to relieve the symptoms of menopause and prevent osteoporosis. Moreover, the use of exogenous estrogen has been associated with a 44% reduction in the risk of coronary heart disease. The beneficial effect might be mediated by reducing total and low-density lipoprotein cholesterol, increasing high-density lipoprotein cholesterol, inhibition of endothelial hyperplasia, and increased production of prostacyclin. A meta-analysis has demonstrated that the relative risk of stroke for stroke-free postmenpausal women who take either estrogen or estrogen plus progestin, as compared with those who do not take hormones is 0.96[52]. However, the Women Estrogen for Stroke Trial (WEST) has shown an increased risk of stroke and an increased severity of stroke in postmenopausal ischemic stroke women under estrogen replacement therapy[53].

Oral contraceptives

An increased risk of stroke is reported in users of high dose formulation of oral contraceptives after the introduction of oral contraceptives in the 1960s. Those at particular risk are women over 35 years of age, cigarette smokers, women with hypertension, and women with a history of migraine headaches. In the Royal General Practitioners' Study of more than 40,000 women, there is an increased incidence of fatal subarachnoid hemorrhage in women taking oral contraceptives[54]. Since the amounts of estrogen and progestogen in oral contraceptives have been reduced, recent studies have disclosed little or no increase in stroke incidence among user of oral contraceptives.

CONCLUSION

Basic research is leading to an improved understanding of the pathogenesis of stroke, and a number of therapeutic strategies of stroke are now being tested in clinical trials. These approaches must overcome both the extreme susceptibility of brain cells to the ischemia and the delays that occur before patients with stroke come to hospital. The outcome of patient with stroke may never be as good as that of someone in whom a stroke is prevented. Prevention is the key to alleviating the enormous burden of stroke. An optimal management of risk factors for stroke is crucial to reduce the risks of first-ever stroke, recurrent stroke, and any vascular event. One of the major public health issues for the coming years will be to focus more on risk factor recognition and management.

REFERENCES

1. Hu HH, Sheng WY, Chu FL, et al. Incidence of stroke in Taiwan. Stroke 1992;23:1237-41.
2. Fuh JL, Wang SJ, Liu HC, et al. Incidence of stroke on Kinmen, Taiwan. Neuroepidemiology 2000;19:258-64.
3. Hankey GJ, Warlow CP. Treatment and secondary prevention of stroke: evidence, cost, and effects on individuals

and populations. Lancet 1999;354:1457-63.
4. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22:983-8.
5. Collins R, Peto R, MacKahon S, et al. Blood pressure, stroke, and coronary heart disease, part 2: short-term reductions in blood pressure; overview of randomized drug trials in their epidemiological context. Lancet 1990;335:827-38.
6. SHEP Cooperative Reasearch Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA 1991;265:3255-64.
7. Messerli F, Grossmann E, Goldbourt U. Are beta-blockers efficacious as first-line therapy for hypertension in the elderly ? A systematic review. JAMA 1998;279:1903-7.
8. Staessen JA, Fagard R, Thijs L, et al. Randomized double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Sys-Eur) Trial Investigators. Lancet 1997;350:757-64.
9. Yusurf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcome Prevention Evaluation Study Investigators. N Engl J Med 2000;342:145-53.
10. Kjeldsen SE, Dahlof B, Devereux RB, et al. Effects of losartan on cardiovascular morbidity and mortality in patients with isolated systolic hypertension and left ventricular hypertrophy: a Losartan Intervention for Endpoint Reduction (LIFE) substudy. JAMA 2002;288:1491-8.
11. Staessen JA, Wang JG, Thijs L. Cardiovascular protection and blood pressure reduction: a meta-analysis. Lancet 2001;358:1305-15.
12. Hansson L, Zanchetti A, Carruthrers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. HOT Study Group. Lancet 1998;351:1755-62.
13. PROGRESS Collaborative Group Randomized trial of a perindopril-based blood-pressure-lowering regiment among 6105 individuals with previous stroke or transient ischemic attack. Lancet 2001;358:1033-41.
14. Tanne D, Goldbourt U, Zion M, et al, for the SPRINT Study Group. Frequency and prognosis of stroke/TIA among 4808 survivors of acute myocardial infarction. Stroke 1993;24: 1490-5.
15. Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) Research Group. Effect of long-term oral anticoagulant treatment on mortality and cardiovascular morbidity after myocardial infarction. Lancet 1994;343:499-503.
16. Antiplatelet Trialist' Collaboration. Collaborative overview of randomized trials of antiplatelet therpy, I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 1994;308:81-106.
17. Eccles M, Freemantel N, Mason J, for the North of England Aspirin Guideline Development Group. North of England evidence based guideline development project: guideline on the use of aspirin as secondary prophylaxis for vascular disease in primary care. BMJ 1998;316:1303-9.
18. Matchar DB, McCrory DC, Banett HJ, et al. Medical treatment for stroke prevention. Ann Intern Med 1994;121:41-53.
19. Sacks FM, Pfeffer MA, Moye LA, et al. for the Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patietrns with average cholesterol levels. N Engl J Med 1996;335:1001-9.
20. Randomized trial of cholesterol lowering in 4,444 patietns with coronary heart disease: the Scandinavian Simavastatin Survival Study (4S). Lancet 1994;344:1383-9.
21. The LIPID Study Group. Design features and baseline characteristics of the LIPID (Long-Term Intervention with Pravastatin in Ischemic Disease) Study: a randomized trial in patients with previous acute myocardial infarction and/or unstable angina pectoris. Am J Cardiol 1995;76:474-9.
22. Wolf PA, D'Agostino RB, Belanger AJ, et al. Probability of stroke: a risk profile from the Framinhham Study. Stroke 1991;22:312-8.
23. Hart RG, Sherman DG, Easton JD, et al. Prevention of stroke in patients with nonvalvular atrial fibrillation. Neurology 1998;51:674-81.
24. Wipf JE, Lipsky BA. Atrial fibrillation. Thromboembolic risk and indication for anticoagulation. Arch Intern Med 1990;150:1598-603.
25. UK Prospective Diabetes Study Group. Intensive blood-

glucose contril with sulphonylureas or insulin compared with conventional treatment and risk of complication in patients with type 2 diabetes. UKPDS 33. Lancet 1998;352: 837-53.
26. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998: 317:703-13.
27. Atkins D, Psaty BM, Koepsell TD, et al. Cholesterol reduction and the risk for stroke in men: a meta-analysis of randomized, controlled trials. Ann Intern Med 1993;119:136-45.
28. Di Mascio R, Marchioli R, Tognoni G. Cholesterol reduction and stroke occurrence: an overview of randomized clinical trials. Cerebrovasc Dis 2000;10:85-92.
29. Sacco RL, Benjamin EJ, Borderick JP, et al. American Heart Association Prevention Conference, IV: prevention and rehabilitation of stroke, risk factors. Stroke 1997; 28:1507-17.
30. The European Carotid Surgery Trialists Collaborative Group. Risk of stroke in the distribution of an asymptomatic carotid artery. Lancet 1995;345:209-12
31. The CASANOVA Study Group. Carotid surgery versus medical therapy in asymptomatic carotid stenosis. Stroke 1991;221:1229-35.
32. Mayo Asymptomatic Carotid Endarterectomy Study Group. Results of a randomized controlled trial of carotid Endarterectomy for asymptomatic carotid stenosis. Mayo Clin Proc 1992;67:513-8.
33. Hobson RW 2nd, Weiss DG, Fields WS, et al. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. N Engl J Med 1993;328:221-7.
34. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterctomy for asymptomatic carotid artery stenosis. JAMA 1995;273:1421-8.
35. Biller J, Feinberg WM, Castaldo JE, et al. Guidelines for carotid endarterectomy: a statement for healthcare professionals from a Special Writing Group of the Stroke Council, American Heart Association. Circulation 1998;97: 501-9.
36. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 1991;325:445-53.
37. The EC/IC Bypass Study Group. Failure of extracrania-intracranial arterial bypass to reduce the risk of ischemic stroke: results of an international randomized trial. N Engl J Med 1985;313:1191-200.
38. Schmiedek P, Piepgras A, Leinsinger G, et al. Improvement of cerebrovascular reserve capacity by EC-IC bypass surgery in patients with ICA occlusion and hemodynamic cerebral ischemia. J Neurosurg 1994;81:236-44.
39. Kuwabara Y, Ichiya Y, Sasaki M, et al. Cerebral hemodynamic and metabolism in moyamoya disease poitron emission tomography study. Clin Neurol Neurosurg 1997;99 Suppl 2:S74-8.
40. Barnett HJ, Eliasziw M, Meldrum HE. Drugs and surgery in the prevention of ischemic stroke. N Engl J Med 1995; 332:238-48.
41. Diener HC, Cunha L, Forbes C, et al. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci 1996; 143:1-13.
42. Hass WK, Easton JD, Adams HP Jr, et al. A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high risk patients. N Engl J Med 1989;321:501-7.
43. CAPRIE Steering Committee. A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996;348:1329-39.
44. Steering Committee of the Physicians' Health Study Research Group. Final report of the aspirin component of the ongoing Physician' Health Study. N Engl J Med 1989; 321:129-35.
45. Peto R, Gray R, Collins R, et al. Randomized trial of prophylactic daily aspirin in British male doctors. BMJ 1988; 296:313-6.
46. Manson JE, Stampfer MJ, Colditz GA, et al. A prospective study of aspirin use and primary prevention of cardiovascular disease in women. JAMA 1991;266:521-7.
47. Shinton R, Beevers G. Meta-analysis of relation between cigarette smoking and stroke. BMJ 1989;298:789-94.
48. Howard G, Wagenknecht LE, Burke GL, et al, for The Atherosclerosis Risk in Communities (ARIC) Study. Cigarette smoking and progression of atherosclerosis. JAMA 1998;279:119-24.
49. Donahue RP, Abbott RD, Reed DM, et al. Alcohol and hemorrhagic stroke. The Honolulu Heart Program. JAMA

1986;255:2311-4.

50. Sacco RL, Elkind M, Boden-Albala B, et al. The protective effect of moderate alcohol consumption on ischemic stroke. JAMA 1999;281:53-60.
51. Boushey CJ, Beresford SA, Omenn GS, et al. A quantitative assessment of plasma homocystein as a risk factor for vascular disease: probable benefits of increasing folic acid intakes. JAMA 1995;274:1049-57.
52. Grady D, Rubin SM, Petitti DB, et al. Hormone therapy to prevent disease and prolong life in post menopausal women. Ann Intern Med 1992;117:1016-37.
53. Viscoli CM, Brass LM, Kernan WN, et al. A clinical trial of replacement-replacement therapy after ischemic stroke. N Engl J Med 2001;345:1243-9.
54. Hannaford PC, Croft PR, Kay CR. Oral contraception and stroke: evidence from the Royal College of General Practitioners' Oral Contraception Study. Stroke 1994;25: 935-42.