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Secondary Prevention of Ischemic Stroke

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Stroke is the second commonest cause of death and disability in the developing world. The crude prevalence rate of stroke in India can be as high as 942/100,000 population, although the pooled data suggest a more moderate prevalence rate of 115-203/100,000 and the incidence from 105-124/100,000. Prevention is of utmost importance in lowering the public health impact of stroke, especially because of its high incidence. People at risk need to be identified in order to institute these stroke prevention strategies. Some risk factors, such as age, sex, race-ethnicity and heredity are not modifiable. These serve as markers for those at higher risk. However, there are also multiple modifiable risk factors with numerous options for intervention. The focus of this chapter is to discuss the common modifiable risk factors for stroke. This review will not cover stroke in young as the risk factors and management are more specified and will not fall in the present preview of the chapter.

HYPERTENSION[1-9]

Hypertension, the most important modifiable risk factor for stroke, affects approximately 50 million people in the USA, and probably even more in India. Because of the high prevalence of this condition, the population-attributable risk for stroke is up to 40% depending on the age group. The prevalence of hypertension also differs by race-ethnic groups, leading to a differential impact of hypertension on stroke risk by race-ethnicity.

Elevated blood pressure causes sheer stress predisposing to atheroma formation and arteriosclerosis. Vascular compromise results in end-organ damage in the myocardium, brain and kidneys. Cardiovascular risk doubles for every 20 mmHg systolic or 10 mmHg diastolic increase in blood pressure.

In the Framingham Study, hypertension defined as blood pressure greater than 160/95 mmHg was associated with an age-adjusted relative risk of stroke of 3.1 for men and 2.9 for women. Isolated systolic hypertension is also an independent risk factor for stroke. But the past definitions of hypertension (>160/90) may be too high. The risk of stroke has a direct and continuous relationship with the degree of elevation of blood pressure. This relationship holds to a blood pressure as low as 115/75 mmHg. Therefore, the blood pressure threshold for increased vascular risk is lower than previously thought and the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7) Report addressed this with redefined categories of hypertension. The current definition of normal blood pressure is < 120/80 mmHg. Furthermore, JNC-7 created a new category of "pre-hypertension". Patients with pre-hypertension have blood pressure ranges of 120-139/80-89 mmHg. This category identifies patients who are at a higher risk of developing hypertension.

The risk of stroke increases continuously above blood pressure levels of approximately 115/75 mmHg. Since the association is steep, and BP levels are high inmost adult populations, almost two-thirds of stroke burden globally is attributable to non-optimal BP (i.e., > 115/75 mmHg). Approximately 2/3 of this burden occurs in middle-aged subjects (45 to 69 years) and approximately 2/3 occur in developing regions. The strength of the associations was similar for men and women and for fatal and non-fatal events but attenuated with age.

Meta-analysis of randomized controlled trials confirm an approximate 30 to 40% stroke risk reduction with BP lowering. Detailed evidence-based recom-

mendations for the BP screening and treatment for persons with hypertension are summarized in the American Stroke Association Scientific Statement on the Primary Prevention of Ischemic Stroke and AHA Guidelines for primary prevention of CVD and Stroke: 2002 Update. The JNC-7 stresses the importance of life style modifications in the overall management of hypertension. Systolic BP reductions have been associated with weight loss; the consumption of a diet rich in fruits, vegetables, low fat dairy products; regular aerobic physical activity and limited alcohol consumption.

A systematic review focused on the relationship between BP reduction and the secondary prevention of stroke and other vascular events. The analysis included 7 published, non-confounded, randomized controlled trials with a combined sample size of 15527 participants with ischemic stroke, TIA or ICH randomized from 3 weeks to 14 months after the index event and followed up for 2 to 5 years. No relevant trials tested the effects of non-pharmacological interventions. Treatment with antihypertensive drugs has been associated with significant reductions in all recurrent strokes, non-fatal recurrent stroke, MI and all vascular events with similar, albeit non-significant, trends towards a reduction in fatal stroke and vascular death.

Relative benefits of specific antihypertensive regimens for secondary stroke prevention are still being debated. A meta-analysis showed a significant reduction in recurrent stroke with diuretics and diuretics and ACE inhibitors combined but not with beta blockers or ACEIs used alone. The analysis included patients with ischemic stroke, TIA or hemorrhagic stroke. Whether a particular class of antihypertensive drug or a particular drug within a class offers a particular advantage for use in patients after ischemic stroke, remains uncertain. There has been a lot of focus on ACEIs for their presumed "class" effect. The Heart Outcomes Prevention Evaluation (HOPE) study compared the effects of the ACEI ramipril with placebo in high-risk persons and found a 24% risk reduction (95% CI, 5 to 40) for stroke, MI or vascular death among the 1013 patients with a history of stroke or TIA. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) was specifically designed to test the effects of a BP-lowering regimen, including an ACEI, in 6105 patients with stroke or TIA with in the previous 5 years. Randomization was stratified by intention to use single (ACEI) or combination (ACEI + the diuretic indapamide) therapy in both hypertensive (> 160 mmHg systolic or > 90 mmHg diastolic) and non-hypertensive patients. The combination (reducing BP by an average of 12/5 mmHg) resulted in a 43% (95% CI, 30 to 54) reduction in the risk of recurrent stroke and a 40% (95% CI, 29 to 49) reduction in the risk of major vascular events, with the effect present in both the hypertensive and normotensive groups. The JNC report concluded that "recurrent stroke rates are lowered by the combination of an ACEI and thiazide type diuretic".

Based on the considerable data available so far, antihypertensive treatment is recommended for both prevention and recurrence of stroke and prevention of other vascular events in persons who have had an ischemic stroke or TIA and are beyond the hyperacute period (Class I, Level of Evidence A). An absolute target BP level and reduction are uncertain and should be individualized, but benefit has been associated with an average reduction of 10/5 mmHg and normal BP levels have been defined as < 120/80 mmHg by JNC–7 (Class IIa, Level of Evidence B). Several lifestyle modifications have been associated with blood pressure reductions and should be included as part of a comprehensive antihypertensive therapy. Available data support the use of diuretics and the combination of diuretics and an ACEI (Class I, Level of Evidence A). The choice of specific drugs and targets should be individualized on the basis of reviewed data and consideration of specific patient characteristics (e.g. extra-cranial cerebrovascular occlusive disease, renal impairment, cardiac disease, and diabetes).

DIABETES MELLITUS[10-25]

Studies have demonstrated an independent effect of DM on stroke risk. For example, Japanese men with DM participating in the Honululu Heart Program had twice the risk of stroke than those who were not diabetic. This increased risk was independent of other factors. A large population-based study that included over 14,000 subjects found DM(> 140 mmHg) was associated with a relative risk of ischemic stroke of 2.26 after adjustment for other stroke risk factors. One study suggested that women with DM have a greater risk of stroke than men with DM. Racial or ethnic differences may exist as well in prevalence and risk from DM. In the Northern Manhattan Stroke Study, the prevalence of DM was as high as 22% among elderly Black and Hispanic subjects with a corresponding attributable risk of stroke of up to 20% in these populations.

Insulin resistance in the Atherosclerosis Risk in Communities Study, as measured by elevated fasting insulin levels in non-diabetic patients was also associated with increased risk of stroke (relative risk 1.19 per 50 pmol/l increase). The latest recommendations

from the American Diabetes Association have included new criteria for DM, defining fasting blood glucose over 110 mg% as indicative of DM and 100 mg% to 109 mg% as prediabetes.

Multifactorial approaches with intensive treatments to control hyperglycemia, hypertension, dyslipidemia and micoralbuminuria have demonstrated reductions in the risk of cardiovascular events.

Glucose control is recommended to near-normoglycemic levels among diabetes with ischemic stroke or TIA to reduce microvascular complications (Class I, level of Evidence A) and possibly macrovascular complications (Class IIb, Level of Evidence B). The goal for hemoglobin A1c should be d" 7% (Class IIa, Level of Evidence B).

LIPIDS[26-40]

Recent clinical trials suggest that stroke may be reduced by the administration of statin agents in persons with CAD. The risk reductions with statins were beyond that expected solely through cholesterol reductions and have led to the consideration of other potential beneficial mechanisms. These findings led to approval of simvastatin and pravastatin for the prevention of stroke in those with CAD.

A review of recent prevention guidelines concerning cholesterol lowering by statin use in stroke prevention suggests that the National Cholesterol Education Program (NCEP), Expert Panel on Detection, Evaluation and Treatment of High Cholesterol in Adults (Adult Treatment Panel III), is the most comprehensive guide for management of lipids in persons at risk for or who have cerebrovascular disease. NCEP emphasizes LDL-C lowering and 2 major modalities for LDL-C lowering: therapeutic life-style change and drug specific therapy. When there is a history of CAD and CAD risk equivalents, the target LDL-C goal is < 100 mg%. LDL-C lowering results in a reduction of total mortality, coronary mortality, major coronary events, coronary procedures, and stroke in persons with CAD. The recommendation in very-high-risk persons is to aim for an LDL-C of < 70 mg%. Very high-risk patients are those who have established cardiovascular disease plus (1). Multiple major risk factors (especially DM); (2) severe and poorly controlled risk factors (especially continued cigarette smoking); (3). Multiple risk factors of the metabolic syndrome (especially high triglycerides ≥ 200 mg% with low HDL cholesterol (≤ 40 mg%)) and (4). Patients with acute coronary syndromes. Other medications also used to treat dyslipidemia include niacin, fibrates and cholesterol absorption inhibitors. These agents can be used in stroke or TIA patients who cannot tolerate statins but data demonstrating their efficacy for prevention of stroke recurrence are scant.

CORONARY ARTERY DISEASE (CAD)

Patients with CAD have twice the stroke risk as patients with out CAD. The presence of left ventricular hypertrophy triples the risk and CHF is associated with 4 times the risk. For stroke, the attributable risk of coronary heart disease is approximately 12% and ranges from 2.3 to 6% for cardiac failure. Another study that examined the risk of stroke after myocardial infarction found the 5 year rate of stroke to be 8.1%. Post MI, older patients had a higher risk of stroke. Patients with ejection fraction less than 28% after MI also had a higher risk of stroke compared with patients with ejection fraction greater than 35% (relative risk 1.86).

OBESITY

The relationship of obesity and weight gain in adult years to stroke is complex. Obesity is strongly related to several major risk factors including hypertension, diabetes and dyslipidemia. In men, findings from the Physicians Health Study have shown that an increasing BMI is associated with a steady increase in ischemic stroke. Independently of the effects of hypertension, diabetes and cholesterol. Among women, data are in consistent, with some positive and others with no association.

Clinically, abdominal obesity is defined by a waist circumference > 120 cm (40 inches) in men, 88 cm (35 inches) in women. For stroke, a significant and independent association between abdominal obesity and ischemic stroke was found in all racial/ethnic groups in the Northern Manhattan Study. No study has demonstrated that weight reduction will reduce stroke recurrence. Because obesity is a contributory factor to other risk factors associated with recurrent stroke, promoting weight loss and the maintenance of a healthy weight is a high priority.

BEHAVIORAL RISK FACTORS

Cigarette Smoking[41-46]

Cigarette smoking is an independent risk factor for stroke. Smoking may increase stroke risk by contributing to acceleration of atherosclerosis. A marker of progressing atherosclerosis is carotid intimal-medial thickness, and current smoking status has been

associated with a 50% increase in progression of carotid intimal-medial thickness.

A meta-analysis of 32 studies found a relative risk of stroke for smokers of 1.5. A case-control study found a dose-response relationship with increased stroke risk in heavy smokers compared with light smokers. Even passive exposure to cigarette smoke increases the risk of progression of atherosclerosis.

Alcohol[47-53]

Increasing levels of alcohol consumption have been associated with an increased risk of hemorrhagic stroke. The relationship between alcohol and ischemic stroke has been less straightforward.

The Nurses' Health Study found a protective effect of mild alcohol consumption (up to 1.2 drinks per day) for ischemic stroke. In contrast to the Nurses' Health Study, which was comprised predominantly of white subjects, a study of Japanese subjects did not show a protective effect of alcohol. This may be due to a differential risk based on race/ethnicity. In Northern Manhattan, a J-shaped relationship between alcohol and ischemic stroke existed. A protective effect on stroke risk was seen with light to moderate alcohol use (two or fewer drinks per day) when compared with no alcohol use while heavy alcohol consumption was associated with an increased stroke risk. Drinking more than two drinks per day was not associated with a statistically significant protective effect.

The various mechanism through which alcohol may increase the risk of stroke include hypertension, increased coagulability, cardiac arrhythmias, and cerebral blood flow reductions. However, evidence also shows that light-to-moderate drinking can increase HDL cholesterol, reduce the risk of coronary artery disease and increase endogenous tissue plasminogen activator.

Antiplatelet Agents[54-73]

A systematic review by the Antiplatelet Trialists' Collaboration showed that among high risk patients, antiplatelet drugs reduced the odds of nay serious vascular event (non-fatal myocardial infarction, non-fatal stroke, or death from vascular causes) by about 25%. The review determined that among people with a prior ischemic stroke, antiplatelet drugs avoided 38 serious vascular events for every 1,000 people treated for about three years. The risk of intra-cranial bleeding with antiplatelet treatment is small, at most one or two per 1,000 people per year in trials of long-term treatment. In general, the benefits of antiplatelet therapy in high risk individuals outweigh any hazards.

Medium dose aspirin (75-325 mg per day) is the dose that has been most thoroughly evaluated bur direct randomized comparisons provide no clear evidence that nay one dose of aspirin is more effective than another. Gastrointestinal side effects (dyspepsia, constipation) are clearly dose related.

Clopidogrel is more effective than aspirin in preventing a combined end-point of ischemic stroke, MI or vascular death, but it has not been shown to be superior to aspirin in preventing recurrent stroke in transient ischemic attack or stroke patients. Several subgroups such as stroke patients with additional peripheral artery disease, patients with prior coronary artery bypass, patients with insulin-dependent diabetes, and patients with recurrent vascular events, were identified, in whom the benefit of clopidogrel is amplified. In patients with higher co-morbidity, clopidogrel may be more effective for the individual patient compared with aspirin, and might also be cost-effective. Furthermore, in patients with aspirin intolerance, clopidogrel is a useful but inexpensive alternative.

Combination Antiplatelet Therapy

Aspirin plus extended release dipyridamole:

In the European Stroke Prevention Study-2 (ESPS-2), the safety and efficacy of low-dose aspirin (50 mg), modified release dipyridamole (400 mg), and the two agents in combination for secondary prevention of ischemic stroke were investigated. Primary end points were stroke, death or both. TIA and other vascular events were secondary end points. Patients were followed on treatment for two years. Data from 6,602 patients were analyzed. Factorial analysis demonstrated a highly significant effect for aspirin and for dipyridamole in reducing the risk of stroke ($p \leq 0.001$) and stroke or death combined ($p < 0.01$). In pairwise comparisons, stroke risk in comparison to placebo was reduced by 18% with aspirin alone, 16% with dipyridamole alone and 37% with combination therapy. Headache was the most common side effect occurring in dipyridamole treated patients. The investigators concluded that aspirn (25 mg) twice daily and dipyridamole in a modified release form at a dose of 200 mg twice daily when co prescribed the protective effects are additive, the combination therapy being significantly more effective than either agent prescribed singly.

Results from the European/Australasian Stroke Prevention in Reversible Ischemica Trial (ESPRIT) published recently, confirm that extended release dipyridamole plus aspirin is superior to aspirin as an antithrombotic prevention treatment for stroke patients.

ESPRIT an independent investigator initiated prospective, multicenter randomized, open label blinded endpoint study, was conducted in 79 centers in 15 countries and randomized a total of 2739 patients with transient ischemic attacks or minor ischemic strokes or presumed arterial origin. Patients were randomized to aspirin (30 mg to 325 mg daily) or extended release dipyridamole (200 mg twice daily) plus aspirin (30 mg to 325 mg daily). The primary outcome event was the composite of death from all vascular causes, non-fatal stroke, non-fatal MI or major bleeding complication, whichever happened first.

The study showed a statistically significant 20% relative risk reduction of primary outcome events in patients treated with extended release dipyridamole plus aspirin compared with patients treated with aspirin alone. Dipyridamole-induced headache typically occurred during treatment initiation and is in most cases transient.

The study results were consistent with the outcome of the earlier ESPS-2 trial. The ESPRIT results reinforce the place of combination of aspirin and dipyridamole in current guidelines. Its use as a first line treatment for secondary stroke prevention is recommended in many international guidelines such as those issued by the European Stroke Initiative (EUSI), the National Institute of Health and Clinical Excellence (NICE) and the American College of Chest Physicians (ACCP).

Results of the PRoFESS (Prevention Regimen For Effectively Avoiding Second Strokes) study, the largest secondary stroke prevention trials are expected in 2008. 20,000 patients from 35 countries would participate in the trials, which aims to demonstrate that extended release dipyridamole plus aspirin is superior in preventing secondary strokes compared with clopidogrel.

ASPIRIN PLUS CLOPIDOGREL

The MATCH (Management of Atherothrombosis with Clopidogrel In High Risk Patients with Recent Transient Ischemic Attack Study) trial evaluated the efficacy and safety of combined aspirin plus clopidogrel therapy to clopidogrel alone in high-risk patients with completed stroke or transient ischemic attack and who also had 1 or more of 5 additional risk factors. The combined end point of ischemic stroke, myocardial infarction, vascular death, or recurrent hospitalization for an ischemic event was used. The study demonstrated an insignificant trend for greater efficacy with the combination therapy on the primary endpoint, but a highly significant increased risk for life-threatening bleeding side effects.

Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) was a prospective, multicenter, randomized double-blind, placebo-controlled study of the safety and efficacy of clopdogrel plus aspirin compared to aspirin alone in stable patients at high risk for a cardiovascular event. The CHARISMA study included 15,603 patients with either diagnosed cardiovascular disease (80% of the study population) or multiple risk factors for cardiovascular disease (20% of tthes tudy population). Patients were randomly assigned to receive clopidogrel (75 mg per day) plus low dose aspirin (75 to 162 mg per day) or placebo plus low dose aspirin for a mediain period of 28 months. The primary endpoint was measured as a combination of heart attack, stroke, or death from cardiovascular causes.

The findings of CHARISMA suggest a significant benefit of dual antiplatelet therapy in patients with established cardiovascular disease, while demonstrating a lack of benefit and increased bleeding in patients only having multiple risk factors.

Taking economical aspects into account, the fixed combination of aspirin and extended release dipyridamole can be recommended for secondary stroke prevention as a first-line alternative to aspirin inpatients with out major co-morbidity.

ANTICOAGULANTS FOR PATIENTS IN ATRIAL FIBRILLATION[74-78]

Anticoagulants are the drugs of choice for preventing stroke in high risk patients with atrial fibrillation. A systematic review evaluated six trials comparing anticoagulants (target international normalized ratio [INR] about 2-3) with placebo in 2900 patients with atrial fibrillation. Anticoagulants reduced the relative risk of stroke by 62% corresponding to a reduction in the absolute risk of stroke of 2.7% per year for primary prevention and 8.4% per year for secondary prevention. The rate of intra-cranial hemorrhage averaged 0.3% per year in the group receiving anticoagulants and 0.1% in the placebo group.

Warfarin (target INR 2.2 to 3.1) has been compared with aspirin for stroke prevention in 2837 patients with atrial fibrillation in five trials. Both agents were effective but warfarin especially. Overall, warfarin reduced the relative risk of stroke by 36% compared to aspirin.

A recent consensus statement based on the available evidence recommends warfarin both for patients of any age who have atrial fibrillation and specific risk factors for stroke (previous transient ischemic attack, stroke, other systemic embolism, hypertension, left ventricular

dysfunction) and for patients older than 75 years with AF and no risk factors. Either warfarin or antiplatelet therapy is suggested for patients aged 65-75 with AF and no risk factors, depending on the status of the patient. Anticoagulation increases the risk of serious bleeding for patients in normal sinus rhythm. Warfarin (target INR 2-3) is also recommended for patients after myocardial infarction who also have other risk factors, including non valvular atrial fibrillation, a decreased left ventricular ejection fraction or left ventricular thrombosis.

Aspirin is a reasonable option for patients with atrial fibrillation who cannot tolerate anticoagulants. In general, moderate intensity anticoagulation (target INR 2-3) is recommended. Therapy should be tailored to the individual, depending not only on the risk of recurrent stroke but also on bleeding risks (for example, a tendency to fall, recent gastrointestinal bleeding, liver disease, dementia, uncontrolled hypertension) and the potential to benefit from treatment. The best time to start anticoagulation after an ischemic stroke is unclear. At present, data are sparse with regard to the efficacy of alternative antiplatelet agents for stroke prevention in AF patients who are allergic to aspirin. An ongoing study, Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE), is evaluating the safety and efficacy of the combination of clopidogrel and aspirin in AF patients.

CAROTID REVASCULARIZATION[79-103]

Among patients with TIA or stroke and documented carotid stenosis, a number of randomized trials have compared endarterectomy plus medical therapy with medical therapy alone. For patients with symptomatic atherosclerotic carotid stenosis >70%, as defined using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria, the value of carotid endarterectomy (CEA) has been clearly established from the results of 3 major prospective randomized trials: the NASCET, the European Carotid Surgery Trial (ECST), and the Veterans Affairs Cooperative Study Program. Among symptomatic patients with TIAs or minor strokes and high-grade carotid stenosis, each trial showed impressive relative and absolute risk reductions for those randomized to surgery.

For patients with carotid stenosis <50%, these trials showed that there was no significant benefit of surgery. In ECST, no benefit of surgery was demonstrated among those with <50% ipsilateral carotid stenosis.Among those patients with <50% stenosis in NASCET, there was no significant reduction in the ipsilateral stroke risk among those treated with endarterectomy compared with those treated medically. Although not specifically addressed by these trials, patients with nonstenosing ulcerative plaque generally would have been included in the groups with carotid stenosis <50% and would not have been found to benefit from endarterectomy.

For those with symptomatic carotid stenosis in the moderate category (50% to 69% stenosis), there is some uncertainty. The results from NASCET and ECST demonstrated less impressive benefits for CEA in this moderate group compared with medical therapy.In NASCET, the 5-year risk of fatal or nonfatal ipsilateral stroke over the 5-year period was 22.2% in the medically treated group and 15.7% in patients treated surgically ($P = 0.045$). The relative and absolute risk reductions for surgery were less impressive than those observed for more severe degrees of stenosis.

Various comorbid features altered the benefit-to-risk ratio for CEA for moderate carotid stenosis. Benefit from surgery was greatest in men, patients ≥75 years of age, and those randomized within 2 weeks after their last ischemic event and fell rapidly with increasing delay.

Extracranial-intracranial (EC/IC) bypass surgery was not found to provide any benefit for patients with carotid occlusion or those with carotid artery narrowing distal to the carotid bifurcation. New efforts using more sensitive imaging to select patients with the greatest hemodynamic compromise for RCTs using EC/IC bypass surgery are ongoing.

Data on carotid artery balloon angioplasty and stenting (CAS) for symptomatic patients with internal carotid artery stenosis in stroke prevention consist primarily of a number of individual published case series but few controlled randomized multicenter comparisons of CEA and CAS. The Wallstent Trial randomized 219 symptomatic patients with 60 to 90% stenosis to CEA or CAS. CAS was performed without distal protection and currently accepted antiplatelet prophylaxis. Study design allowed operators with limited experience to participate. The risk of peri-operative stroke or death was 4.5% for CEA and 12.1% for CAS, and the risk of major stroke or death at 1 year was 0.9% for CEA and 3.7% for CAS. The trial was halted because of poor results from CAS.

The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) trial randomly compared angioplasty with surgical therapy among 504 symptomatic carotid patients, in whom only 26% received stents.Major outcome events within 30 days did not differ between endovascular treatment and surgery groups, with a 30-day risk of stroke or death of 10.0%

and 9.9%, respectively. Despite the increased risk of severe ipsilateral carotid stenosis in the endovascular group at 1 year, no substantial difference in the rate of ipsilateral stroke was noted up to 3 years after randomization.

The Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial randomized 334 patients to endarterectomy or stenting with the use of an emboli-protection device, testing the hypothesis that stenting was not inferior to endarterectomy. Only 30% of the study population was symptomatic. Qualified CAS operators had a periprocedural stroke, death or MI complication rate of 4%. The primary end point of the study (the cumulative incidence of death, stroke, or MI within 30 days after the intervention, or death or ipsilateral stroke between 31 days and 1 year) occurred in 20 stent patients and 32 endarterectomy patients (30-day risk, 5.8% versus 12.6%; P=0.004 for noninferiority). Most of the benefit was detected in the lower risk of MI for the stent compared with the high-surgical risk endarterectomy cases.

The National Institute of Neurological Diseases and Stroke (NINDS)–funded Carotid Revascularization With Endarterectomy or Stent Trial (CREST) is currently comparing CEA and CAS in patients with symptomatic severe stenosis (70% by ultrasonography or 50% by NASCET angiography criteria). The primary objective is to compare the efficacy of CAS versus CEA in preventing stroke over a follow-up period of up to 4 years. Other randomized trials are ongoing in Europe and Australia.

At present, CAS has been used in selected patients in whom stenosis is difficult to access surgically, medical conditions that greatly increase the risk for surgery are present, or other specific circumstances exist such as radiation-induced stenosis or restenosis after CEA. CAS has also been used in selected cases after arterial dissection, fibromuscular hyperplasia, or Takayasu's arteritis. More definitive evidence is needed before we can advocate the widespread use of angioplasty plus stent as routine care for patients with extracranial carotid stenosis.

For patients with recent TIA or ischemic stroke within the last 6 months and ipsilateral severe (70 to 99%) carotid artery stenosis, CEA by a surgeon with a perioperative morbidity and mortality of <6% (Class I, Level of Evidence A) is recommended. For patients with recent TIA or ischemic stroke and ipsilateral moderate (50 to 69%) carotid stenosis, CEA is recommended, depending on patient-specific factors such as age, gender, comorbidities, and severity of initial symptoms (Class I, Level of Evidence A). When the degree of stenosis is <50%, there is no indication for CEA (Class III, Level of Evidence A)

When CEA is indicated for patients with TIA or stroke, surgery within 2 weeks is suggested rather than delaying surgery (Class IIa, Level of Evidence B).

Among patients with symptomatic severe stenosis (>70%) in whom the stenosis is difficult to access surgically, medical conditions are present that greatly increase the risk for surgery, or other specific circumstances exist such as radiation-induced stenosis or restenosis after CEA, CAS is not inferior to endarterectomy and may be considered (Class IIb, Level of Evidence B). CAS is reasonable when performed by operators with established periprocedural morbidity and mortality rates of 4% to 6%, similar to that observed in trials of CEA and CAS (Class IIa, Level of Evidence B).

Among patients with symptomatic carotid occlusion, EC/IC bypass surgery is not routinely recommended (Class III, Level of Evidence A).

EXTRACRANIAL VERTEBROBASILAR DISEASE

Revascularization procedures can be performed on patients with extracranial vertebral artery stenosis who are having repeated vertebrobasilar TIAs or strokes despite medical therapy. Atherosclerotic plaques of both the vertebral and carotid arteries that are concentric, smooth, fibrous lesions without ulceration are amenable to endovascular therapy, which has generally moved from simple angioplasty to stenting to prevent recoil and restenosis. Retrospective case series have shown that the procedure can be performed with a high degree of technical success. Long-term follow-up data are limited, and further randomized studies are needed to more clearly define evidence-based recommendations in this setting.

INTRACRANIAL ATHEROSCLEROSIS

Data from prospective studies show that patients with symptomatic intracranial atherosclerosis have a relatively high risk of recurrent stroke. The Warfarin Aspirin Symptomatic Intracranial Disease (WASID) study evaluated 569 patients with symptomatic intracranial stenoses who were prospectively randomized to aspirin or warfarin. This study, which was stopped for safety reasons, showed no significant difference between groups in terms of the primary end point (ischemic stroke, brain hemorrhage, and nonstroke vascular death). In addition, retrospective data indicate that patients with symptomatic intracranial stenosis who fail antithrombotic therapy may have even greater rates of recurrent stroke.

Intracranial angioplasty and/or stenting provide an opportunity to rapidly improve cerebral blood flow. Results from single-center experiences suggest that the procedure can be performed with a high degree of technical success. These studies have generally been performed among patients who have hemodynamically significant intracranial stenoses and symptoms despite medical therapy. More long-term follow-up has been lacking, but available data raise the possibility that angioplasty may improve the natural history compared with medical therapy.

It is not clear that stenting confers any improvement in the long-term clinical or angiographic outcome compared with angioplasty alone in this setting. One prospective trial has evaluated stenting in a mixed group of patients with intracranial and/or extracranial disease. The Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA) Trial, a corporate-sponsored multicenter, nonrandomized, prospective feasibility study, evaluated 1 stent for treatment of vertebral or intracranial artery stenosis. Forty-three intracranial arteries (70.5%) and 18 extracranial vertebral arteries (29.5%) were treated. Successful stent placement was achieved in 58 of 61 cases (95%). Thirty-day stroke incidence was 6.6%, with no deaths. Four of 55 patients (7.3%) had strokes later than 30 days, 1 of which was in the only patient not stented. Recurrent stenosis >50% within 6 months occurred in 12 of 37 intracranial arteries (32.4%) and 6 of 14 extracranial vertebral arteries (42.9%). Seven recurrent stenoses (39%) were symptomatic. Although a few different stents have been approved by the Food and Drug Administration (FDA) for use in patients with arterial stenoses, further studies are necessary to determine whether these interventional procedures have short-term and long-term efficacy.

UNCONVENTIONAL/EMERGING RISK FACTORS

Hyperhomocysteinemia[104-108]

Cohort and case-control studies have consistently demonstrated a 2-fold-greater risk of stroke associated with hyperhomocysteinemia.The Vitamin Intervention for Stroke Prevention (VISP) study randomized patients with a noncardioembolic stroke and mild to moderate hyperhomocysteinemia (>9.5 μmol/L for men, 8.5 μmol/L for women) to receive either a high- or low-dose vitamin therapy (e.g., folate, B6, or B12) for 2 years.The risk of stroke was related to level of homocysteine; the mean reduction in homocysteine was greater in the high-dose group, but there was no reduction in stroke rates in the patients given high-dose vitamin. The 2-year stroke rates were 9.2% in the high-dose and 8.8% in the low-dose arms. Although there is no proven clinical benefit to high-dose vitamin therapy for mild to moderate hyperhomocysteinemia, patients should be encouraged to take a daily standard multivitamin preparation, given the low risk and cost associated with vitamin therapy. Additional research is needed to determine whether there are subgroups that might benefit from more aggressive vitamin therapy, particularly over the long term.

For patients with ischemic stroke or TIA and hyperhomocysteinemia (levels >10 μmol/L), daily standard multivitamin preparations with adequate B6 (1.7 mg/d), B12 (2.4 μg/d), and folate (400 μg/d) are reasonable to reduce the level of homocysteine, given their safety and low cost (Class IIa, Level of Evidence B). However, there is no evidence that reducing homocysteine levels will lead to a reduction in stroke recurrence.

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