Secondary Prevention of Atherothrombotic Events After Ischemic Stroke

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Atherosclerotic vascular disease is the leading cause of ischemic stroke, resulting in occlusive or severely stenotic lesions of major intracranial or extracranial arteries and narrowing of small penetrating arteries of the brain. Atherosclerosis of the coronary arteries (ie, coronary artery disease) is an indirect cause of cardioembolic stroke secondary to myocardial infarction. Ischemic heart disease may also be complicated by atrial fibrillation and cardioembolic stroke. Prevention of recurrent stroke and other ischemic events, including myocardial infarction, is a key component of treatment for patients with symptomatic ischemic cerebrovascular disease. Prevention of recurrent stroke involves controlling those factors that promote the course of atherosclerosis, including hypertension, hyperlipidemia, diabetes mellitus, and smoking, as well as such local interventions as carotid endarterectomy and endovascular treatment. Nevertheless, administration of antiplatelet agents remains the core of management for preventing recurrent stroke and other cardiovascular events in at-risk patients.

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ACE = angiotensin-converting enzyme; AHA = American Heart Association; ARB = angiotensin II receptor blocker; ASA = American Stroke Association; CAD = coronary artery disease; CEA = carotid endarterectomy; ESPRIT = European/Australasian Stroke Prevention in Reversible Ischaemia Trial; ESPS-2 = European Stroke Prevention Study 2; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; PAD = peripheral arterial disease; PRoFESS = Prevention Regimen for Effectively Avoiding Second Strokes; TIA = transient ischemic attack

Stroke is a leading cause of death and disability in the United States. The economic consequences of stroke, including health care costs and lost economic productivity, are substantial. Of the approximately 780,000 strokes that occur annually in the United States, 87% are secondary to brain ischemia.[1] Although ischemic stroke and transient ischemic attack (TIA) may be secondary to a broad spectrum of underlying diseases, atherosclerosis is the leading etiologic factor, especially among those aged 50 years or older.[2] Disruption of an advanced atherosclerotic plaque may lead to ischemia secondary to thromboembolic occlusions, and occlusion or severe stenosis of an atherosclerotic artery may lead to hypoperfusion of the brain.

In addition to affecting major extracranial (eg, the aorta) and intracranial arteries, atherosclerotic disease affects the smaller penetrating arteries of the brain. Atherosclerotic disease in these smaller arteries may cause lacunar infarctions. Cardiogenic embolism leading to ischemic stroke, most commonly occurring among persons with atrial fibrillation, is often the indirect result of ischemic heart disease secondary to atherosclerosis.

Because of the diffuse nature of atherosclerosis, patients with TIA or stroke often have symptomatic disease or advanced asymptomatic disease affecting the coronary or peripheral arteries. As a result, patients with ischemic neurologic symptoms are also at risk of symptomatic peripheral vascular disease, myocardial infarction, and vascular death.[3,4] Thus, managing the underlying atherosclerotic vascular disease is important when treating patients with ischemic cerebrovascular disease and is crucial for preventing recurrent stroke or ischemic events in other arterial sites.[5-7] In recognition of the importance of managing atherosclerotic vascular disease, evidence-based guidelines for the treatment of patients with recent stroke or TIA have been developed by the American Heart Association (AHA)/American Stroke Association (ASA) and the American College of Chest Physicians.[8-11]

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MANAGEMENT OF RISK FACTORS FOR ADVANCED ATHEROSCLEROSIS AND ISCHEMIC VASCULAR DISEASE

Some risk factors associated with increased likelihood of advanced atherosclerosis and ischemic disease are not modifiable. These risk factors include age, sex, ethnicity, family history, and premature vascular disease. However, several conditions that augment the course of atherosclerosis can be effectively addressed across the continuum of care. Among these risk factors, hypertension, hyperlipidemia, diabetes mellitus, and smoking are especially important, and their control is fundamental to management strategies for lowering the likelihood of recurrent ischemic events among patients with ischemic heart disease, ischemic stroke, or peripheral arterial disease (PAD). Management in such cases includes lifestyle changes and use of prescription medications, to be coordinated by a primary care physician in order to achieve optimal control.

HYPERTENSION

Arterial hypertension (ie, systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg) is the most

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TABLE 1. **Management of Hypertension in Patients With Ischemic Stroke**

Hypertension stage	Blood pressure (mm Hg)		Usual treatment
	Systolic	Diastolic	
Prehypertension	120-139	80-89	Lifestyle changes[a]
Stage 1	140-159	90-99	Lifestyle changes,[a] 1 medication[b]
Stage 2	>159	>99	Lifestyle changes,[a] 2 or more medications[b]

[a] Lifestyle changes include weight reduction, increased exercise, limited alcohol use, reduced dietary salt intake, increased consumption of potassium-containing foods, and smoking cessation.

[b] Medications include thiazide diuretic, angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, β-blocker, and/or calcium channel blocker.

Adapted from *Hypertension*,[24] with permission.

important modifiable factor associated with increased risk of stroke. Both diastolic and isolated systolic hypertension are important predictors of primary or recurrent stroke.[12] Hypertension predisposes patients to atherosclerotic disease of the intracranial and extracranial arteries, most commonly at sites of vascular bifurcation. Hypertension also contributes to disease of the small penetrating arteries that perfuse deep brain structures.[13,14]

Management of hypertension is important both during the acute phase of ischemic stroke and throughout the long-term course of this condition. Both low blood pressure and high blood pressure in the setting of acute stroke are associated with poor outcomes. However, the optimal treatment of patients with hypertension in the first few hours or days after stroke has not been established.[15] Some research has focused on antihypertensive therapy initiated in the first few days after stroke, but additional evaluation of the safety and efficacy of such therapy is needed.[15-19] In the absence of definitive clinical data, current evidence-based guidelines suggest pursuing a cautious approach to reducing blood pressure in the acute stroke setting.[20] In many cases, the patient's blood pressure will decrease spontaneously during the first few hours after stroke, and no medical intervention will be needed.

An exception to the cautious approach involves aggressive management of patients who are at high risk for hemorrhagic transformation. In addition, the blood pressure of patients who are to be treated with thrombolytic agents needs to be lower than 185 mm Hg systolic and less than 110 mm Hg diastolic in order to receive this medication.[20]

When short-term management of hypertension evolves into a strategy for longer-term treatment, the patient's condition will most likely be monitored by primary care physicians. The efficacy of antihypertensive therapy is confirmed by meta-analyses and randomized trials, which have shown that a 30% to 40% reduction in risk of recurrent stroke can be achieved by reducing blood pressure in patients.[21-23] Although a major benefit may be achieved with only a 5- to 10-mm Hg reduction in blood pressure, the goal of long-term management is to reduce blood pressure to normal levels (ie, <120/80 mm Hg).[24] Blood pressure is affected favorably by such lifestyle changes as reduced alcohol consumption, weight loss, increased exercise, restricted salt intake, increased consumption of fruits and vegetables, and smoking cessation. Nevertheless, most patients with high blood pressure will require treatment with antihypertensive medications (Table 1).

The optimal medical regimen for managing hypertension after stroke has not yet been established. Clinical trials have tested, both singly and in combination, the efficacy of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), β-blockers, calcium channel blockers, and diuretics.[22,23] In addition to lowering blood pressure, evidence suggests that ACE inhibitors and ARBs may slow progression of arterial disease.[25,26] This effect may partially explain the reduction in recurrent vascular events observed with the use of a perindopril-based blood pressure–lowering regimen among patients with a history of stroke or TIA but without hypertension.[27] Although these data are interesting, they have not yet led to the widespread use of antihypertensive medications for prevention of recurrent stroke in patients who are not hypertensive.

On the basis of current evidence, guidelines for prevention of recurrent stroke suggest that a diuretic or the combination of a diuretic and an ACE inhibitor may be the most appropriate choice for initial antihypertensive therapy. However, guidelines also recommend consideration of the severity of arterial disease and the presence of concomitant renal disease, renal artery stenosis, heart disease, and diabetes mellitus when selecting a therapeutic antihypertensive regimen.[10]

Hyperlipidemia

Although hyperlipidemia causes an increased risk of stroke secondary to atherosclerosis, especially among younger patients, its association with recurrent stroke is less clear. However, because hyperlipidemia is a strong predictor of myocardial ischemia, a fasting lipid profile should be obtained from all patients who have had recent ischemic stroke. If levels of low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) fall outside the target range (LDL-C <70-100 mg/dL, HDL-C >50 mg/dL; to convert to mmol/L, multiply by 0.0259), a comprehensive management program consisting of lifestyle modifications and medications should be initiated in the hospital and maintained on a long-term basis for patients with hyperlipidemia[10] (Table 2).

Several clinical trials have shown the efficacy of statins for reducing the risk of recurrent cardiovascular events in patients with ischemic stroke.[28-31] The results of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial,[29] which included 4731 participants with a history of TIA or stroke but no history of coronary artery disease (CAD), indicated that, in comparison with placebo, atorvastatin reduced the relative risk of recurrent stroke by 16% during 5 years of follow-up (95% confidence interval, 1%-29%; *P*=.03). The recently updated AHA/ASA guidelines[9] for secondary stroke prevention recommend the use of statin therapy for all patients with atherosclerotic stroke or TIA. In addition to lowering lipid levels, statins appear to stabilize the vasculature and to slow the progression of atherosclerosis.[32,33]

Concern has recently been expressed that statins may increase the patient's risk of hemorrhagic stroke.[29,34,35] However, the observed increases in hemorrhagic stroke have been minimal, so the benefits of statins in preventing ischemia outweigh the risk of bleeding.[34] Thus, statin therapy should not be withheld from patients who have had ischemic stroke.

In addition to using statins, patients with hypertriglyceridemia or low HDL-C levels may be treated with ezetimibe, niacin, or gemfibrozil.[36-38] These medications also may be administered to patients who are unable to tolerate statins.

Diabetes Mellitus

Approximately 25% of patients who have had ischemic stroke also have diabetes mellitus, the presence of which is associated with an increased likelihood of recurrent stroke.[39,40] Patients with metabolic syndrome, which includes lipid disturbances, insulin resistance, hypertension, and truncal obesity, also have an increased risk of stroke and other ischemic events.[41] Because adequate glycemic control reduces the frequency of microvascular complications and lowers the risk of small-artery atherosclerotic disease, current secondary prevention guidelines recommend a goal of near normoglycemic levels (ie, glycated hemoglobin <7%) for patients with diabetes mellitus and recent stroke[10] (Table 2).

Because of the increased prevalence of hypertension and hyperlipidemia among patients with type 2 diabetes mellitus, aggressive management of these risk factors is crucial to reducing the risk of vascular events in these patients.[41-47] Most patients with diabetes mellitus will need more than a single antihypertensive agent to successfully reduce their blood pressure. Because ACE inhibitors and ARBs lessen the risk of renal dysfunction, these medications may be the best choices for patients with diabetes mellitus and recent stroke.[10] To reduce the high risk of ischemic events in patients with diabetes mellitus, the recommended target LDL-C level in these patients is less than 70 mg/dL.[10]

TABLE 2. **Management of Hyperlipidemia and Diabetes Mellitus in Patients With Ischemic Stroke**[a]

Treatment goal	Usual treatment
Hyperlipidemia	
LDL-C <100 mg/dL[b]	Lifestyle changes[c]
HDL-C >50 mg/dL[b]	Statins, ezetimibe, niacin, gemfibrozil
Diabetes mellitus	
Normoglycemia	Lifestyle changes[c]
HbA_{1c} <7%	Oral medications (eg, sulfonylureas, biguanides, thiazolidinediones, meglitinides), insulin
Normal blood pressure	ACE inhibitor, ARB
LDL-C <70 mg/dL	Lifestyle changes[c]

[a] ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; HbA_{1c} = glycated hemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.
[b] SI conversion factors: To convert LDL-C and HDL-C values to mmol/L, multiply by 0.0259.
[c] Lifestyle changes include weight reduction, increased exercise, and low-fat diet.
Adapted from *Stroke*,[10] with permission.

Smoking

Compelling evidence suggests that smoking is an important risk factor for ischemic stroke and that even passive exposure to smoking may increase stroke risk.[48-50] Cessation of smoking results in rapid reduction in the likelihood of recurrent ischemia, and within 5 years after smoking cessation, the risk of stroke drops to that found among persons who have never smoked. Because patients cannot smoke while hospitalized, this is the ideal time to start a smoking cessation program. Successful programs include a combination of counseling and the use of nicotine replacement products or such medications as bupropion and varenicline.[51]

Other Risk Factors

Several other measures to reduce the risk of stroke also are recommended in current prevention guidelines. These measures include the consumption of a diet rich in fruits and vegetables, increased potassium intake, decreased sodium intake, weight loss, regular exercise, and avoidance of heavy alcohol consumption.[10] In addition, guidelines include recommendations that women avoid postmenopausal hormone replacement therapy because such therapy may be associated with an increased risk of ischemic events, including stroke.[52,53]

ANTITHROMBOTIC THERAPY AND SURGICAL/ENDOVASCULAR INTERVENTIONS

Antithrombotic Therapy

Guidelines for antithrombotic therapy for secondary prevention of stroke in patients who have had ischemic stroke

TABLE 3. **American Heart Association/American Stroke Association Guidelines for Antithrombotic Therapy in Patients With Ischemic Stroke of Noncardioembolic Origin (Secondary Prevention)**

Guideline	Recommendation, level of evidence[a]
Antiplatelet agents recommended over oral anticoagulants	I, A
For initial treatment, aspirin (50-325 mg/d),[b] combination of aspirin and extended-release dipyridamole, or clopidogrel	I, A
Combination of aspirin and extended-release dipyridamole recommended over aspirin alone	I, B
Clopidogrel may be considered instead of aspirin alone	IIb, B
For patients hypersensitive to aspirin, clopidogrel is a reasonable choice	IIa, B
Addition of aspirin to clopidogrel increases risk of hemorrhage	III, A

[a] Recommendation: I = treatment is useful and effective; IIa = conflicting evidence or divergence of opinion regarding treatment usefulness and effectiveness; IIb = usefulness/efficacy of treatment is less well established; III = treatment is not useful or effective. Level of evidence: A = data from randomized clinical trials; B = data from a single randomized clinical trial or nonrandomized studies.
[b] Insufficient data are available to make evidence-based recommendations about antiplatelet agents other than aspirin.
Data from *Stroke*.[9]

of noncardioembolic origin have been developed by both the AHA/ASA (Table 3)[9,10] and the American College of Chest Physicians (Table 4).[11] Antithrombotic medications, including oral anticoagulants and antiplatelet agents, are key to strategies to reduce recurrent stroke risk.[9-11] Oral anticoagulants are prescribed to lower the risk of cardioembolic events among patients who are at high risk for cardiac disorders, including patients with atrial fibrillation. These medications are also prescribed to many patients with prothrombotic disorders. The efficacy of oral anticoagulant therapy in preventing recurrent ischemic events in patients with stroke secondary to arterial disease has been tested in 4 clinical trials.[54-57] Results of these trials demonstrate that oral anticoagulants are not superior to antiplatelet agents in preventing ischemic events, including recurrent stroke, among patients with arterial disease. Therefore, there is currently no indication for use of long-term oral anticoagulant therapy in patients with stroke secondary to atherosclerotic disease.[10]

Antiplatelet agents are the antithrombotic medication of choice for preventing ischemic events among persons who have symptomatic atherosclerotic disease in any vascular site. These agents can be effective regardless of patient age, sex, or concomitant diabetes mellitus or hypertension.[58] In a meta-analysis of randomized clinical trials that included participants with stroke or TIA, antiplatelet therapy (vs control) was associated with significant absolute reduction in nonfatal recurrent stroke (8.3% vs 10.8%; $P<.001$), nonfatal myocardial infarction (1.7% vs 2.3%; $P<.001$), and vascular death (8.0% vs 8.7%; $P=.04$).[58] Because of their proven efficacy, antiplatelet agents remain the standard against which other medications or surgical interventions for reducing risk of ischemic events are compared.

Aspirin, the combination of aspirin with extended-release dipyridamole, ticlopidine, and clopidogrel have been shown to provide effective secondary prevention for patients after ischemic stroke. Aspirin, in dosages from 30 mg/d to 1300 mg/d, has been found to protect patients from secondary ischemic events.[58-61] Aspirin is generally tolerated well by patients; however, gastritis, peptic ulcer disease, and gastrointestinal bleeding are known complications of long-term use. These adverse effects of aspirin may be reduced by using lower doses or enteric-coated preparations.

The combination of aspirin and dipyridamole has been compared with aspirin alone in several clinical trials, most notably the European Stroke Prevention Study 2 (ESPS-2)[62] and the European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT).[63] Compared with the use of either aspirin or dipyridamole alone, the combination of these agents significantly reduced the relative risk of recurrent stroke among patients enrolled in ESPS-2.[62] In ESPRIT, the combination of aspirin and dipyridamole was significantly more effective than aspirin alone in prevent-

TABLE 4. **American College of Chest Physicians Guidelines for Antithrombotic Therapy in Patients With Ischemic Stroke of Noncardioembolic Origin (Secondary Prevention)**

Guideline	Recommendation, level of evidence[a]
Antiplatelet therapy recommended over anticoagulation[b]	1, A
Patients undergoing carotid endarterectomy should take aspirin (81-325 mg/d) before and after surgery	1, A
Patients with well-documented prothrombotic disorders should use oral anticoagulants over antiplatelet agents	2, C
Patients receiving aspirin who are at moderate to high risk of bleeding should use low doses of aspirin	1, C+
Combination of aspirin (25 mg) and extended-release dipyridamole (200 mg) twice daily recommended over aspirin	2, A
Clopidogrel recommended over aspirin	2, B
Patients hypersensitive to aspirin should take clopidogrel	1, C+

[a] Recommendation: 1 = certain benefits from intervention; 2 = less certain benefits from intervention. Level of evidence: A = consistent data from randomized clinical trials; B = inconsistent data from randomized clinical trials; C+ = overwhelming data from observational studies; C = data from observational studies.
[b] Acceptable antiplatelet medications for initial therapy are aspirin (50-325 mg/d), combination of aspirin (25 mg) and extended-release dipyridamole (200 mg) twice daily, or clopidogrel (75 mg/d).
Data from *Chest*.[11]

ing the primary composite outcome (ie, vascular death, nonfatal myocardial infarction, nonfatal stroke, or major bleeding complication).[63]

In both ESPS-2 and ESPRIT, the risk of bleeding was the same with aspirin monotherapy as it was with aspirin plus dipyridamole.[62,63] The primary adverse effect associated with use of dipyridamole is headache, which, in some cases, may be sufficiently severe to necessitate treatment cessation.[62,63]

In 3 clinical trials,[64-66] the use of ticlopidine was compared with aspirin and with placebo in patients who had ischemic stroke or TIA. Ticlopidine has been found to be superior to placebo in reducing the number of ischemic events (Canadian American Ticlopidine Study [CATS][64]) and superior to aspirin in reducing recurrent ischemic events (Ticlopidine Aspirin Stroke Study [TASS][65]). However, in the African American Antiplatelet Stroke Prevention Study,[66] no significant difference in outcome rates was observed between patients treated with aspirin and those treated with ticlopidine.

Potential complications of ticlopidine use include diarrhea, abdominal distress, skin eruptions, neutropenia, and thrombotic thrombocytopenic purpura.[64-66] Although these potentially severe adverse effects, which largely occur within the first 3 months of treatment, are relatively rare, they occur frequently enough that most physicians in the United States no longer prescribe ticlopidine.

Clopidogrel has pharmacologic effects similar to ticlopidine but with an improved safety profile. Although cases of thrombotic thrombocytopenic purpura have been reported with the use of clopidogrel, the frequency of these cases is much less than with the use of ticlopidine.[67,68] In the Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial,[69] clopidogrel significantly reduced the relative risk of major vascular events in patients with atherosclerotic vascular disease (ie, CAD, ischemic stroke, or symptomatic PAD) by 8.7% compared with aspirin (P=.043) without increasing the risk of bleeding. In the subgroup of patients who had previous stroke, the risk reduction with clopidogrel use compared with placebo was 7.3%, but this difference was not statistically significant (P=.26).[69]

Recently, results were reported for the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial,[70] a randomized comparison of the effects of aspirin plus extended-release dipyridamole vs clopidogrel alone for secondary prevention in 20,332 patients with noncardioembolic ischemic stroke. During a mean follow-up period of 2.5 years, no significant differences were observed between the aspirin plus extended-release dipyridamole regimen and the clopidogrel regimen for rates of recurrent stroke (9.0% vs 8.8%, respectively; P=.78) or composite rates of stroke, myocardial infarction, or vascular death (13.1% vs 13.1%, respectively; P=.83).[70] Although major hemorrhagic events and intracranial bleeding tended to occur more frequently among patients taking aspirin and dipyridamole than among those taking clopidogrel (4.1% vs 3.6%, respectively; P=.06), no significant difference was observed in the combined rates of recurrent stroke and major hemorrhage.[71] More patients taking the combination of aspirin and dipyridamole than those taking clopidogrel had to permanently discontinue treatment, largely because of headaches (5.9% vs 0.9%, respectively).[70]

Overall, the results of PRoFESS[70] show that monotherapy with clopidogrel and the combination of aspirin with extended-release dipyridamole are equally effective in preventing recurrent ischemic events after a stroke.

The combination of aspirin and clopidogrel has been shown to be effective for secondary prevention of recurrent ischemic events in patients with acute myocardial ischemia.[71,72] This combination has also been tested in a broader range of at-risk patients, including those with ischemic stroke or TIA. In the Management of Atherothrombosis With Clopidogrel in High-Risk Patients With Recent TIA or Ischaemic Stroke (MATCH) trial,[73] the combination of aspirin and clopidogrel was compared with clopidogrel alone in patients with a history of stroke or TIA. Results suggested that the combination of aspirin and clopidogrel is not more efficacious than clopidogrel monotherapy in lowering the risk of recurrent ischemic events. Furthermore, the trial found that combination therapy resulted in excess bleeding in patients with cerebrovascular disease.[73]

The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial[74] compared the combination of aspirin and clopidogrel with aspirin alone in patients who had documented ischemic cerebrovascular disease, CAD or PAD, or 3 or more atherothrombotic risk factors with no documented disease. The combination increased the risk of severe bleeding in patients and did not have a significant effect on reducing the risk of myocardial infarction, stroke, or vascular death.[74] However, subgroup analysis of the enrolled population with history of myocardial infarction, stroke, or symptomatic PAD revealed that the aspirin-clopidogrel combination significantly reduced the risk of recurrent ischemic events without increasing the rate of severe bleeding.[75]

In the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial,[76] the combination of clopidogrel and aspirin was found to be superior to aspirin monotherapy in preventing microembolic signals in patients with recently diagnosed symptomatic carotid stenosis. However, the clinical meaning of this finding has

yet to be determined because a clinical correlation with a reduction in ischemic events has not been shown.

A brief course of dual antiplatelet therapy with aspirin and clopidogrel, presumably after a loading dose of clopidogrel, might be a strategy for treatment of high-risk patients with recent TIA. The rationale behind such an approach is to aggressively inhibit platelet function during the period of greatest risk for stroke. Results from the Fast Assessment of Stroke and Transient Ischaemic Attack to Prevent Early Recurrence (FASTER) pilot study[77] suggest that dual aspirin and clopidogrel therapy may reduce the risk of stroke within 90 days of TIA. However, further research is needed to determine the clinical usefulness of this strategy for patients with recent TIA or ischemic stroke.

Current evidence-based treatment guidelines for secondary prevention of ischemic events recommend that patients with noncardioembolic stroke or TIA be treated with antiplatelet agents.[9-11] Aspirin monotherapy, aspirin plus extended-release dipyridamole, and clopidogrel monotherapy are all acceptable options for initial therapy. Although clopidogrel alone and aspirin plus extended-release dipyridamole have been shown to be more effective than aspirin alone, many physicians continue to prescribe aspirin because of its established efficacy, well-known adverse-effect profile, over-the-counter availability, and low cost. Current guidelines do not recommend the use of clopidogrel over aspirin plus extended-release dipyridamole (or vice versa) for patients with noncardioembolic stroke or TIA.[9,10] Guidelines further suggest that individual patient characteristics should be considered when selecting a specific medication.[9,10]

It should be kept in mind that the results of PRoFESS[70] may have an effect on future recommendations.

Local Management of Large-Artery Atherosclerosis

Surgical and endovascular interventions are options for the treatment of patients with symptomatic atherosclerotic narrowing of large intracranial or extracranial arteries. Carotid endarterectomy (CEA) is an effective treatment for reducing the risk of stroke in patients with symptomatic moderate to severe stenosis (ie, > 50% narrowing) of the internal carotid artery.[78,79] In general, the benefit from surgery is greatest among patients with stenosis in the range of 70% to 99%. Currently, the use of CEA, in conjunction with antiplatelet agents and with medications targeting atherosclerotic risk factors, is recommended for carefully selected patients who have stenosis of the internal carotid artery.[10]

In an international trial, extracranial-intracranial bypass surgery was not found to be superior to treatment with medication.[80] However, some patients with symptomatic occlusion of the internal carotid artery are at high risk of recurrent stroke after surgery. Extracranial-intracranial bypass surgery is currently being assessed in the Carotid Occlusion Surgery Study (COSS) for use in patients with occlusion of the internal carotid artery who cannot be treated with CEA or endovascular interventions.[81]

Angioplasty, usually combined with stenting, is often used to treat patients with symptomatic arterial stenosis in either intracranial or extracranial locations of the carotid or vertebrobasilar circulations. Considerable interest has been shown in using endovascular treatments for these patients, and the number of patients who are being treated for stroke by angioplasty is increasing rapidly. Unfortunately, the clinical role of endovascular treatment needs to be better defined because much of the available information on this treatment is derived from uncontrolled series.

Published results of clinical trials comparing CEA with carotid artery angioplasty and stenting are mixed.[82-84] Ongoing clinical trials, such as the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST), should help clarify the roles of CEA and carotid artery angioplasty/stenting in the treatment of patients with severe stenoses at the origin of the internal carotid artery.

The clinical usefulness of endovascular interventions for treatment of patients with stenotic lesions of the extracranial vertebral arteries or intracranial vessels is also not established. Available data on such interventions are derived from small case series.[85-88] Ongoing clinical trials are addressing the role of endovascular treatment for these indications.

Carotid endarterectomy remains the preferred surgical intervention for treating symptomatic patients with severe stenosis of the origin of the internal carotid artery.[10] The decision for surgery is affected by such factors as the patient's neurologic status, concomitant diseases, severity of the arterial condition, and presence of ulceration or of an intraluminal thrombus as well as by the skill of the surgeon. Carotid artery angioplasty and stenting are typically reserved for patients who have a contraindication for CEA, including recurrent stenosis after carotid surgery, previous radiation therapy, contralateral occlusion of the internal carotid artery, or for those who are poor surgical risks. Endovascular interventions may be considered as treatment for patients who have symptomatic extracranial vertebral artery stenosis or intracranial arterial lesions that have not responded to medication-based treatment.

DISCUSSION

With the aging of the US population and improved management of patients with heart disease, the number of people who are diagnosed as having atherosclerotic disease and who are at high risk of stroke is increasing. The number

of patients who are at risk of both primary and recurrent ischemic stroke is also on the rise, and, as such, preventive measures are crucial for these patients.

Current guidelines delineate the importance of 3 components of care in treating patients with symptomatic atherosclerotic cerebrovascular disease: risk-factor management, antiplatelet therapy, and surgical procedures. These components are equally important in the primary prevention of stroke. Control of risk factors, particularly hypertension, hyperlipidemia, diabetes mellitus, and smoking, is fundamental to stroke prevention. Control of these risk factors can be accomplished by lifestyle modifications and pharmaceutical interventions and must be maintained throughout the continuum of care.

The goal of hypertension management should be a normal blood pressure for the patient. No specific antihypertensive regimen is ideal for all patients. Therefore, pending the results of ongoing and future studies, physicians should consider a patient's history when prescribing a blood pressure–lowering treatment plan. Although some evidence suggests that aggressive reduction of cholesterol levels may be associated with a modest increase in the risk of hemorrhagic stroke, the benefits of statins in reducing the risk of recurrent ischemic stroke and other ischemic vascular events outweigh the risk of bleeding. Aggressive management of blood pressure and lipid levels complements the control of blood glucose levels in patients with diabetes mellitus.

Virtually all patients who have had ischemic stroke should be treated with antiplatelet agents, such as aspirin, aspirin plus extended-release dipyridamole, or clopidogrel. In selecting medications, physicians should consider the patient's previous treatment and history of ischemic events, as well as potential contraindications, such as allergies. In appropriate cases, CEA should be considered as complementary to use of medications, including antiplatelet agents. Pending the results of ongoing clinical trials, extracranial-intracranial bypass surgery and carotid artery stenting may be options for certain patients with atherosclerotic cerebrovascular disease.

CONCLUSION

Use of an integrated treatment approach (involving risk-factor management, antiplatelet therapy, and surgical procedures, when indicated) presents the opportunity to lower the risk of recurrent stroke and other ischemic events in patients with recent ischemic stroke or TIA. Future research may provide support for using new medications, clarify the role of currently available medications, and better define the appropriate role of surgery, particularly endovascular treatments.

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