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İskemik İnmenin Önlenmesi: Antiplatelet Ajanlar, Karotid Endarterektomi, Anjiyoplasti ve Stent / *Prevention of Ischemic Stroke: Antiplatelet Agents, Carotid Endarterectomy and Angioplasty and Stenting*

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ABSTRACT

Prevention of Ischemic Stroke: Antiplatelet Agents, Carotid Endarterectomy and Angioplasty and Stenting

Stroke is the most common acute neurologic disease and the second most common cause of death among persons living in Turkey. In addition, stroke is a leading cause of disability and human suffering. A preponderance of strokes is secondary to arterial occlusions often due to atherosclerosis. While useful therapies to treat acute stroke are available, prevention remains the most cost-effective strategy for treating patients with ischemic cerebrovascular disease. Components of management to lower the risk of stroke include identification and treatment of risk factors that accelerate atherosclerosis including hypertension, diabetes mellitus, hyperlipidemia, and smoking. In addition, most patients with arterial disease should be treated with an antiplatelet agent such as aspirin, clopidogrel, or aspirin/dipyridamole. New antiplatelet agents are being developed. Carotid endarterectomy is of proven utility in lowering the risk of stroke in carefully selected patients. The role of angioplasty and stenting for treatment of stenotic intracranial or extracranial arterial disease, including the internal carotid artery, is expanding rapidly. With a carefully developed plan addressing management of risk factors, antithrombotic medications and local interventions, the likelihood of ischemic stroke can be reduced.

Keywords: stroke prevention, transient ischemic attack, antiaggregating agents, carotid endarterectomy, angioplasty, stenting

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ÖZET

İnme, Türkiye'de en sık görülen akut nörolojik hastalıktır ve de ölüm nedenleri arasında ikinci sırada bulunmaktadır. Aynı zamanda inme, günlük yaşam aktivitelerinde başkalarına bağımlılığın önde gelen bir nedenidir. İnmelerin büyük bölümü arteryel tıkanmalara, bunların önemli kısmı da ateroskleroza bağlı olarak gelişmektedir. Akut inme için yararlı tedaviler bulunmakla birlikte, koruyucu yöntemler tıkayıcı beyin damar hastalıklarının tedavisinde halen en etkin stratejiyi oluşturmaktadır. İnme riskinin azaltılmasında kullanılan yöntemler hipertansiyon, diabetes

Anahtar kelimeler: inmenin önlenmesi, geçici iskemik atak, antiagregan ajanlar, karotid endarterektomi, anjiyoplasti, stent

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mellitus, hiperlipidemi ve sigara gibi aterosklerozu hızlandıran risk faktörlerinin tanınması ve tedavisini içerir. Buna ek olarak, arteryel hastalığı olan birçok kişinin aspirin, klopidogrel veya aspirin/dipiridamol gibi antiagregan ilaçlarla tedavisi gerekir. Yeni antiagregan ilaçlar geliştirilmektedir. Karotid endarterektomi dikkatle seçilmiş hastalarda inme riskini azalttığı kanıtlanmış bir tedavi yaklaşımıdır. İnternal karotid arter dahil tıkayıcı intrakranyal ve ekstrakranyal arteryel hastalığı olanlarda anjiyoplasti/stentleme girişimlerinin rolü hızla genişlemektedir. Risk faktörlerinin tedavisi, antitrombotik ilaçlar ve lokal girişimleri içeren titizlikle hazırlanmış bir strateji sayesinde iskemik inme riski azaltılabilir.

INTRODUCTION

Worldwide, stroke is a leading public health problem. In Turkey, mortality from cerebrovascular disease accounts for approximately 15% of all deaths; it is second to ischemic heart disease.[1] In addition, stroke is a common cause of human suffering. It is a leading cause of long-term disability or for the need for institutionalized care. Besides motor and sensory impairments, stroke leads to cognitive and behavioral disorders that results in dementia or exacerbates the effects of degenerative diseases such as Alzheimer disease. The economic impact of stroke also is huge, including the financial cost of acute health care and rehabilitation and losses in productivity because the affected patient or family care givers can no longer work. Disabled patients also may need financial help. Prevention is the most cost-effective strategy for management of patients with ischemic cerebrovascular disease. Most strokes in Turkey, as in other countries, are of ischemic origin; this type of stroke is the focus of this discussion.

Management to lessen the risk of ischemic stroke may be divided into measures for primary or secondary prevention. Primary prevention involves prescription of therapies to asymptomatic persons who have a moderate risk for ischemic vascular events, including those with people with atrial fibrillation or risk factors for advanced atherosclerosis. Secondary prevention includes the use of interventions given to persons who have had symptoms including ischemia in other circulations (coronary or peripheral artery disease), or amaurosis fugax, transient ischemic attack (TIA), or previous ischemic stroke. Patients with prior neurologic symptoms have a much higher risk of a major or disabling stroke than those who are asymptomatic. Because the risk of stroke is higher among symptomatic persons, these individuals have the potential for greater benefit from the administration of interventions, including antithrombotic agents, and surgical therapies that may have some inherent risk of complications. Recently, several groups identified features that identify those patients with TIA who are at especially high risk for stroke.[2-4] The features, which include age > 60 years, a blood pressure greater than 140/90 mm Hg, aphasia or hemiparesis, duration of symptoms > 1 hour, or diabetes, in effect, clarify the diagnosis of TIA as the cause of a transient episode of neurologic dysfunction. These findings also forecast a high risk of a vascular event in the first few days and should be a stimulus for emergency admission, rapid evaluation, and early administration of medical or surgical interventions.

Interventions to prevent ischemic stroke are divided into three large categories (Table 1). Patients should be evaluated to identify those risk factors that predispose to advanced atherosclerosis, heart disease and stroke. Treatment includes lifestyle changes and medications. Antithrombotic medications include oral anticoagulants and antiplatelet agents. Surgical interventions include carotid endarterectomy, angioplasty and stenting, and other reconstructive operations. The medical

Table 1. Components of management to prevent ischemic stroke

Control of risk factors
- Arterial hypertension
- Diabetes mellitus
- Hyperlipidemia
- Smoking

Changes in lifestyle and medications

Antithrombotic therapy
- Oral anticoagulants
- Antiplatelet agents
  - Aspirin
  - Aspirin/dipyridamole
  - Clopidogrel
  - Ticlopidine

Combinations of medications

Surgical interventions
- Carotid endarterectomy
- Bypass operations
- Endovascular operations

and surgical therapies are selected on a case-by-case basis and are based on factors including whether the patient has or has not had symptoms. The presumed etiology of the patient's symptoms and the presumed vascular territory also are important considerations. In addition, the patient's prior experience with or specific contraindications for medications may affect treatment decisions. For example, if the patient has had recurrent ischemic symptoms despite treatment with aspirin, another antithrombotic agent may be given. Similarly, a history of aspirin allergy would mean that a non-aspirin containing antiplatelet agent would be prescribed. Fortunately, guidelines provide information and recommendations that physicians may use to help define their patients' treatment.[5-9]

TREATMENT of RISK FACTORS for ACCELERATED ATHEROSCLEROSIS

Atherosclerotic disease is endemic in most countries in the world including Turkey. This arteriopathy evolves over a person's lifetime with the first pathological changes appearing in young adulthood. Later in life, the arterial disease leads to occlusion or thromboembolism. Several factors are associated with an accelerated course of atherosclerosis; the most important are arterial hypertension, diabetes mellitus, hyperlipidemia, and smoking.[10] These conditions are found in a sizable percentage of Turkish patients with stroke.[11] In addition, approximately 30% - 40% of Turkish patients with an ischemic stroke also will have clinical evidence of ischemic heart disease. Management of risk factors is a fundamental step in efforts to lower the risk of stroke among asymptomatic patients (primary prevention) and recurrent stroke (secondary prevention).[9] All patients with symptomatic ischemic cerebrovascular disease should be evaluated for these risk factors and appropriate lifestyle changes or medications should be prescribed.[6-8] Some medications that treat risk factors also may have additional protective effects on the vasculature and that could lower the risk of stroke independent of the actions on the risk factors, in particular the statins, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers may have vasoprotective properties.[12-18] For example, a recent trial demonstrated that rosuvastatin was effective in preventing stroke among persons with an elevated high-sensitivity C-reactive protein.[19] Also another recent trial testing the efficacy of combinations of antihypertensive agents showed that the combination of amlodipine and benazepril was more effective that the combination of a diuretic and benazepril in preventing ischemic events, including stroke.[20] The general recommendations of the American Heart Association for interventions to lower the risk of stroke are included in Table 2.[6,8] These recommendations likely will evolve as new information about the effectiveness of new interventions is reported. While guidelines provide a broad roadmap for the management of risk factors, the advice for specific lifestyle changes and the selection of specific medications continues to be made on a case-by-case basis.

Table 2. Measures to control risk factors

	For Accelerated Atherosclerosis
Lifestyle changes	weight loss, increase exercise changes in diet – saturated fats, salt, sugar limit alcohol consumption, stop smoking
Medications	• Control blood pressure – goal of < 120/80 mm Hg Diuretics, β-blockers, ACE-I, ARB, Ca++ channel blockers • Lower lipid levels – goal of LDL cholesterol < 100 mg/dL Diabetics – goal of LDL cholesterol < 70 mg/dL Statins, other lipid lowering medications • Control glucose levels – goal of HgA1C of < 7% Insulin, oral agents • Stop smoking – may use medications

Adapted from the American Heart Association recommendations[6,8]
LDL – low density lipoprotein, ACE-I – angiotensin converting enzyme inhibitor, ARB – angiotensin receptor blocker, HgA1C – hemoglobin A1C, Ca++ – calcium

ANTITHROMBOTIC MEDICATIONS

Both oral anticoagulants and antiplatelet agents are administered to patients at high risk for ischemic stroke. Oral anticoagulants are of accepted utility in lowering the risk of thromboembolic events among patients with high-risk cardiac lesions including those with atrial fibrillation.[5-8] These medications also are prescribed to some patients with ischemia secondary to hypercoagulable disorders. However, the role of oral anticoagulants in prevention of stroke caused by

arterial disease is limited.[21-24] In the Warfarin-Aspirin Recurrent Stroke Study, more deaths or strokes were reported among patients taking warfarin than those prescribed aspirin.[23] The Warfarin-Aspirin Symptomatic Intracranial Disease study looked at the safety and utility of aspirin or warfarin among patients with symptomatic intracranial arterial stenoses and found no benefit from treatment with the anticoagulant.[24] While oral anticoagulants often are prescribed to persons who have "failed" treatment with antiplatelet agents or for other potential indications such as a recent dissection of an extracranial artery, there is no established role for these medications in stroke prevention among persons with arterial disease.

Antiplatelet agents have been extensively tested for their ability to prevent stroke, myocardial infarction, vascular death or other ischemic events.[25] These medications are effective among men and women of all age groups. The presence or absence of diabetes or hypertension does not influence their efficacy. Antiplatelet agents are the standard against which other therapies, including surgical procedures, are compared. They are the foundation of management to lower the risk of stroke.

Aspirin is a mainstay of antithrombotic therapy and it often is the first medication prescribed to patients with new ischemic symptoms.[5-7] Aspirin has many advantages; it is inexpensive and the side effect profile of the medication is well known (Table 3).[24-26]

Table 3. Antiplatelet agents for prevention of ischemic stroke

Medication	Daily dose	Side effects
Aspirin	75 – 1300 mg	Bleeding
		Allergic reactions
		Gastritis*
Dipyridamole	500 mg (ER)	Headache
		Bleeding
Clopidogrel	75 mg	Bleeding
		Skin eruptions
		TTP*
		Gastrointestinal distress
Ticlopidine	500 mg	Bleeding
		Skin eruptions
		TTP
		Neutropenia
		Gastrointestinal distress

*Gastritis also includes peptic ulcer disease and upper gastrointestinal hemorrhage, TTP – thrombotic thrombocytopenia purpura

Clinical trials demonstrate that lower daily doses (75 mg-300 mg) are equal or superior to larger doses.[27-29] As a result, current guidelines recommend low daily doses.[5-7] The efficacy of the lower doses of aspirin is important because the gastrointestinal side effects of the medication, including gastritis, peptic ulcer disease, and gastrointestinal bleeding, are linked to large doses. In addition, aspirin often is administered in conjunction with other antiplatelet agents or anticoagulants.

Dipyridamole, which is available in shorter acting and sustained released formulations, blocks the uptake of adenosine in the platelet and is a reversible inhibitor of platelet aggregation. Besides prolonging platelet survival, dipyridamole also is a vasodilator. The usefulness of dipyridamole in preventing strokes has been tested in a series of clinical trials (Table 4). The most common side effect is headache, which is related to the vasodilator effects of dipyridamole. Headaches are most likely to occur among persons with a past history of migraine but starting the medication with a lower dose of dipyridamole may lessen the likelihood of the side effect. The combination of dipyridamole and aspirin recently was shown to have an associated increased risk of bleeding.[30] While the second European Stroke Prevention Study showed evidence of efficacy for treatment with dipyridamole monotherapy, the

Table 4. Trials of dipyridamole in prevention of stroke

ESPS – 2		
	ASPIRIN & DIPYRIDAMOLE N = 1650	**ASPIRIN N = 1649**
Stroke	137 8.3%	206 12.5%
Stroke/death	286 17.3%	330 28%
ESPRIT		
	ASPIRIN & DIPYRIDAMOLE N = 1363	**ASPIRIN N = 1376**
Stroke	96 7%	116 8.4%
Stroke/death	173 12.7%	216 15.7%
PRoFESS		
	ASPIRIN & DIPYRIDAMOLE N = 10181	**CLOPIDOGREL N = 10151**
Stroke	916 9%	898 8.8%
Stroke/MI/death	1333 13.1%	1333 13.1%
Bleeding	419 4.1%	365 3.6%

Adapted from ESPS – 2,[31] the ESPRIT study[32] and the PRoFESS study[30]

combination of aspirin and dipyridamole was found to be more effective.[31] The superiority of the combination was confirmed by another international trial.[32] More recently, the efficacy and safety of the combination of aspirin and dipyridamole was compared to clopidogrel.[30] Overall, the two medications were found to be similarly effective (Table 4).

Clopidogrel and ticlopidine also are widely used. Metabolites of these medications block the ADP receptor of the platelet and secondarily inactivate the glycoprotein IIb/IIIa receptor. Ticlopidine was tested in two large trials; in both the medication was found to be effective and the risk of bleeding was relatively low.[33,34] Subsequently, Gorelick et al.[35] tested the ability of ticlopidine to lower the risk of stroke among African-American patients; it was not more effective than aspirin. The use of ticlopidine has declined considerably because of potential serious side effects, particularly thrombotic thrombocytopenia purpura and neutropenia. Clopidogrel was tested, in comparison to aspirin, in a large clinical trial that enrolled patients with symptomatic ischemic heart disease, cerebrovascular disease, or peripheral vascular disease.[36] While a benefit from treatment with clopidogrel was shown, it primarily was found among patients with symptomatic peripheral artery disease; there was modest efficacy among patients with stroke. Still, clopidogrel is a widely used antiplatelet agent. Clopidogrel is safer than ticlopidine; in particular, the risk of serious hematologic reactions is lower.[37] The usual daily dosage is 75 mg but initiation of therapy with this dose does not lead to inhibition of platelet function for approximately 1 week. Thus, a loading dose of 300-600 mg of clopidogrel is prescribed for immediate antiplatelet effects.[38,39]

The combination of clopidogrel and aspirin often is prescribed to patients with acutely symptomatic coronary artery disease and those having endovascular procedures.[40] The long-term administration of the combination of clopidogrel and aspirin also has been tested among high-risk symptomatic or asymptomatic patients, including those with a previous TIA or ischemic stroke (Table 5).[41-43] In the MATCH trial, the combination was compared to monotherapy with clopidogrel; no reduction in the aggregate end point of stroke, myocardial infarction or vascular death was found but there was doubling of the risk of serious bleeding.[41] In the CHARISMA trial, the combination of aspirin and clopidogrel was not superior to aspirin monotherapy in preventing stroke, myocardial infarction or vascular death.[42] A modest increase in bleeding risk was found. In a subgroup analysis of outcomes among only the subjects with established cardiovascular disease, Bhatt et al.[43] reported fewer ischemic events with the combination of medications and that the risk of serious bleeding was not increased. Recently, a pilot study looked at the potential utility of a short course of treatment with clopidogrel and aspirin among patients with recent TIA or stroke.[44] The rationale was to give a combination of medications during the period of highest risk for stroke. A loading dose of clopidogrel was given and the patients were treated for 90 days. While the results are not definitive, recurrent stroke (hemorrhagic or ischemic) occurred in 21 of the 194 subjects treated with aspirin alone and in 14 of 199 subjects treated with both aspirin and clopidogrel.

Table 5. Trials testing the combination of aspirin and clopidogrel in patients with ischemic cerebrovascular disease

MATCH				
	ASPIRIN & CLOPIDOGREL N = 3797		**CLOPIDOGREL N = 3802**	
Stroke, myocardial infarct or death	596	15.7%	636	16.7%
Serious bleeding	96	2.6%	49	1.3%
CHARISMA				
	ASPIRIN & CLOPIDOGREL N = 7802		**ASPIRIN N = 7721**	
Stroke, myocardial infarct, vasc death	534	6.4%	573	7.3%
Severe bleeding	130	1.7%	104	1.3%
SYMPTOMATIC PATIENTS IN CHARISMA				
	N = 4735		**N = 4743**	
Stroke, myocardial infarct, vasc death	347	7.3%	416	8.8%
Severe bleeding	71	1.5%	79	1.7%

Adapted from MATCH study[41] and CHARISMA study[42,43] vasc = vascular

This study's results are sufficiently interesting that additional research is needed. It is possible that a short course of treatment with aspirin and clopidogrel may be useful in lowering the risk of stroke in the first days and weeks after a TIA.

Other antiplatelet agents are being tested. Prasugrel is a third generation thienopyridine that has actions that are similar to clopidogrel. This potent antiplatelet agent has faster inhibition of platelet function than clopidogrel and less variation in responses among patients.[45] While the agent has not been tested among patients with recent TIA or stroke, it is being evaluated in the setting of acute coronary artery disease. A trial that enrolled 13,608 subjects with moderate-to-high risk coronary artery disease with planned stenting compared the combination of aspirin and prasugrel to treatment with clopidogrel and aspirin.[46] In comparison to aspirin and clopidogrel, the combination of aspirin and prasugrel significantly reduced the number of ischemic events (vascular death, myocardial infarction or stroke) (12.1% vs. 9.9% p<0.01). However, the frequency of severe bleeding complications was higher with prasugrel/aspirin (2.4%) than with clopidogrel/aspirin (1.8%). Additional research testing the utility of prasugrel is underway. It is unclear if the agent will be used on a long-term basis or for prevention of stroke among persons with recent ischemic neurological symptoms. A new antiplatelet agent (SCH530348) is a direct platelet thrombin receptor antagonist that could be used to treat patients with acute coronary artery thrombosis and on a long-term basis.[47-49] A multinational clinical trial currently is enrolling patients with cardiac ischemia, stroke or peripheral vascular disease to a double blind trial in which either placebo of the new agent is added to conventional antiplatelet therapy.

CAROTID ENDARTERECTOMY

Carotid endarterectomy is of established utility for lessening the risk of ischemic stroke among symptomatic patients with moderate-to-severe (50% - 99%) stenosis of the origin of the internal carotid artery. In general, the efficacy of surgery is greatest among persons with more severe stenosis of 70% - 99%. Current guidelines recommend the operation for patients with recent (< 6 months) symptoms, who have an acceptable surgical risk, and for whom a skilled surgeon is available.[6,7] Both European and American guidelines emphasize the importance of doing surgery as soon as possible after the most recent neurologic symptoms; in general, the benefits of the operation are the greatest when it is performed within the first two weeks. Despite the success of clinical trials that demonstrated efficacy of the operation, controversy persists about the role of carotid endarterectomy for treatment of asymptomatic persons with stenosis of the internal carotid artery.[50,51] The guidelines do include recommendations for surgery in carefully selected patients with severe, asymptomatic stenoses of the internal carotid artery.[9]

While a large international trial found that extracranial-to-intracranial bypass operations were not superior to medical management in some patients with intracranial atherosclerotic disease or occlusion of the internal carotid artery, the operation has been performed for treatment of the occasional patient with moyamoya.[52,53] More recently, investigators evaluated a subset of particularly high-risk patients with occlusion of the internal carotid artery.[54-56] Patients who have compromised collateral flow might benefit from the operation and a clinical trial now is enrolling patients to test whether the extracranial-to-intracranial bypass is safe and effective in this group. With the advances in endovascular therapy, it is unlikely that bypass operations will have a major role in the treatment of patients with stenotic lesions of the intracranial vasculature.

ANGIOPLASTY and STENTING

The role of endovascular procedures for treatment of symptomatic or asymptomatic stenotic lesions of the extracranial or intracranial vascular circulation is

growing. Potential advantages of angioplasty and stenting include treatment of vascular lesions that cannot be easily approached by conventional surgical procedures including the extracranial portions of vertebral artery, distal extracranial segment of the internal carotid artery, and most intracranial locations. Trials have evaluated the safety and potential efficacy of endovascular procedures in treating patients with atherosclerotic disease of the origin of the internal carotid artery.[57-60] Results are mixed. The EVA-3S trial randomly assigned patients with symptomatic narrowing greater than 60% to either carotid endarterectomy or angioplasty/ stenting (Table 6).[61] It was halted prematurely because of an unacceptably high rate of stroke within 30 days of the procedure among the subjects having the endovascular intervention. Longer term follow-up demonstrated that the differences favoring surgery between the two treatment groups persisted.[60] A German trial randomized patients with symptoms in the previous 120 days and who had narrowing greater than 70% to either endovascular treatment or carotid endarterectomy.[62] While no differences in 30 day mortality were noted between the two treatment groups, a slightly higher rate of stroke was seen with angioplasty/stenting. A trend favoring surgery was seen on longer term follow-up at two years.[57] On the other hand, SAPPHIRE compared subjects judged as being at high risk for complications with carotid endarterectomy to treatment with the operation or carotid angioplasty/stenting.[58] Symptomatic patients with stenoses > 50% or asymptomatic patients with stenoses > 80% were enrolled. The 30-day mortality and 1-year mortality and rates of ipsilateral strokes were higher among the subjects having carotid endarterectomy. In a report of 3-year follow-ups of the subjects, there was little difference between the two treatment groups.[59] Because these data do not provide conclusive evidence about the relative indications of the two interventions, additional clinical trials are underway. Among them is the Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST) that is enrolling symptomatic subjects (within 6 months and stenosis of greater than 50%) or asymptomatic subjects (stenosis greater than 60%). Early outcomes of efficacy are the rates of stroke, myocardial infarction or death while longer-term outcomes are the rates of ipsilateral ischemic stroke.

Table 6. Trials of carotid endarterectomy or carotid angioplasty / stenting

	CAROTID ENDARTERECTOMY		**CAROTID ANGIOPLASTY/STENTING**	
SPACE	**N = 607**		**N = 589**	
30 Days				
Ipsilateral stroke	31	5.1%	39	6.6%
Mortality	5	1%	6	1%
2 Years				
Ipsilateral stroke	43	7%	49	8.3%
Mortality	32	5.2%	28	4.7%
EVA 3-S	**N = 262**		**N = 265**	
30 Days				
Stroke	9	3.4%	24	9.1%
Mortality	1	0.5%	1	0.5%
4 Years				
Ipsilateral stroke	15	5.7%	30	11.3%
Other stroke	4	1.5%	4	1.5%
Mortality	34	13%	36	13.6%
SAPPHIRE	**N = 167**		**N = 167**	
1 Year				
Ipsilateral stroke	8	4.8%	7	4.2%
Mortality	21	12.6%	12	7.2%
3 Years	**N = 117**		**N = 143**	
Ipsilateral stroke	9	10.5%	11	7.6%
Other stroke	9	10.5%	5	3.5%
Mortality	35	29.9%	31	21.7%

Adapted from[57,59,60]

Current guidelines include recommendations for carotid angioplasty and stenting in prevention of stroke. Indications include symptomatic severe narrowing of the carotid artery at locations that are not accessible to carotid endarterectomy, recurrent stenosis of the carotid artery after carotid endarterectomy, prior radiation therapy in the area of the operative field, or concomitant high-risk medical conditions that may make conventional surgery dangerous.[6,7] At present, there are no firm recommendations about the role of angioplasty/stenting in the treatment of patients with severe but asymptomatic stenosis of the internal carotid artery. With technical advances of the endovascular procedures, which hopefully will increase their safety and efficacy, one can anticipate that role of carotid artery angioplasty/stenting will grow in the years ahead.

Even less information is available about the utility of endovascular procedures for treatment of patients with either posterior circulation stenotic disease or severe narrowing of the intracranial arteries. Most reports are from small anecdotal series.[63] Current guidelines mention that these procedures could be considered for symptomatic patients that fail to respond to medical therapies.[6,7] Still, much more research is needed. A new trial testing the utility of intracranial endovascular procedures in comparison to best medical therapy (Stenting vs. Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis/SAMMPRIS) will enroll patients with recent TIA or stroke (within 30 days) and that have a stenosis of 70-90%. All patients will receive aggressive medical management of risk factors and antithrombotic medications while one-half will have the endovascular intervention. This trial has just started recruitment.

CONCLUSIONS

Management of patients with ischemic cerebrovascular disease is multifaceted and all components of treatment are equally important. Changes in lifestyle and medications aimed at treating risk factors for accelerated atherosclerosis among both asymptomatic and symptomatic patients are fundamental. For patients with TIA or stroke not secondary to cardioembolism, antiplatelet agents are preferred. These medications are relatively safe and they are effective in lowering the risk of myocardial infarction, ischemic stroke, or vascular death. These medications may be given as a monotherapy, in combination with oral anticoagulants or other antiplatelet agents, or in conjunction with surgery or endovascular procedures. Current guidelines recommend aspirin (daily dose 75-325 mg/day), clopidogrel (75 mg/day) or the combination of aspirin and dipyridamole. The choice of antiplatelet agent still is made on a case-by-case basis.

Carotid endarterectomy remains the preferred surgical intervention for patients with severe stenosis (symptomatic or asymptomatic) of the proximal segment of the internal carotid artery. However, the indications for endovascular procedures are expanding. Endovascular interventions have potential advantages including treatment of lesions that cannot be addressed by carotid endarterectomy. Additional clinical research on the utility of endovascular interventions is underway. Both carotid endarterectomy and endovascular procedures should be considered as complementary to medical management including the use of antiplatelet agents.

These are exciting times for physicians who treat patients with ischemic cerebrovascular disease. Based on advances in research, options for treatment of patients at high risk for ischemic stroke likely will expand in the future. New antithrombotic medications are being developed and tested. Aggressive medical treatment to protect the vascular endothelium and to slow the course of atherosclerosis likely will evolve. Reconstructive vascular operations are being re-evaluated. Endovascular procedures likely will be offered to patients that currently cannot be treated with a local arterial intervention. Future management to prevent stroke among high-risk patients likely will differ considerably from current treatment. New effective therapies likely will lower the risk of the important public health problem of stroke.

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