Clinical Review

Transient Ischemic Attacks

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Patients with transient cerebral ischemic attacks (TIAs) are generally felt to be at increased risk for stroke. A comprehensive clinical evaluation consisting of a thorough history and physical examination, as well as adjunctive laboratory and radiologic studies, is required to substantiate the diagnosis and to identify the underlying etiology. For patients with TIAs of atherothrombotic origin, the optimal course of management is still controversial. Although surgical therapy, antiplatelet therapy, and anticoagulant therapy have all shown promise in preventing stroke, their precise roles in the management of TIAs still await further elucidation.

Stroke is the third leading cause of death in the United States, ranking behind only coronary heart disease and cancer. There are an estimated 500,000 new cases of stroke each year in the United States, and 27 to 50 percent of these patients die within 30 days of the stroke.[1] Among the stroke survivors, 40 percent require special services, and 10 percent require institutional care.[2] Direct and indirect costs of stroke exceeded $7.3 billion in 1976.[3]

In view of the ineffectiveness of current medical and surgical therapy in limiting or reversing stroke once it has occurred, the focus of stroke therapy has been on prevention. Transient cerebral ischemic attacks (TIAs) have been called the "most important warning symptoms of impending stroke"[4] and represent the one form of cerebrovascular disease that offers the physician the opportunity to prevent stroke. Since TIAs precede atherothrombotic stroke in 50 percent of cases,[5] it is evident that successful management of TIAs can have a significant impact on reducing the death and disability associated with cerebral infarction.

During the past three decades, much attention has been directed at preventing stroke in patients presenting with TIAs. This paper will review the clinical features of TIAs and offer guidelines for their evaluation and management.

Definition and Classification of TIAs

Transient cerebral ischemic attacks are episodes of temporary and focal cerebral dysfunction produced by ischemic vascular mechanisms. They generally are rapid in onset, with the patient going from no symptoms to maximum symptoms in less than five minutes.[4] Although the duration of symptoms can, by definition, be up to 24 hours, most episodes last 2 to 15 minutes, with 90 percent of episodes lasting less than 2 to 6 hours.[6] Resolution of the deficit is complete and usually occurs within a few minutes.

Depending upon the vascular supply felt to be responsible for the neurological deficit, transient ischemic attacks are categorized as either carotid

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or vertebral-basilar. Carotid TIAs include both hemispheric and retinal TIAs and are characterized by unilateral symptoms. Common symptoms of hemispheric TIAs include motor or sensory dysfunction of one or both extremities on the same side, facial paresthesias or paresis, and dysphasia.[7] Retinal TIAs, also identified by the term *amaurosis fugax*, produce a painless loss or impairment of vision in one eye or part of one eye and are caused by ophthalmic artery ischemia.[4] Vertebral-basilar TIAs are manifested by symptoms arising from the brainstem, cerebellum, and the occipital lobes. The sensorimotor symptoms of vertebral-basilar TIAs can be bilateral, can alternate from one side to the other in different attacks, or can cross (involve the ipsilateral face and the contralateral extremity).[8,9] Common symptoms of vertebral-basilar TIAs include motor and sensory deficits involving any combination of the four extremities up to all four, complete or partial loss of vision in both homonymous fields, ataxia, peripheral dysmetria, and unilateral or bilateral hearing loss.[4,10] Vertigo, dysphagia, diplopia, and syncope lack the specificity to be considered to result from a TIA when they occur alone, and thus they should be accompanied by other signs of brainstem ischemia before being considered indicative of vertebral-basilar insufficiency.[11] Dysarthria and homonymous hemianopsia are consistent with both carotid and vertebral-basilar TIAs and therefore do not aid in the differentiation of these two entities.[12]

Prevalence and Incidence

The prevalence of transient ischemic attacks in the elderly population ranges from 13.8 to 63 per 1,000.[13,14] Friedman et al[15] found the incidence of TIAs to be 1.1/1,000/yr in a large retirement community in Seal Beach, California. Among residents of Rochester, Minnesota, the average annual incidence of TIAs was found to be 31/100,000, with rates that increased with age.[16] For patients aged 55 to 64 years, the annual incidence was found to be 0.7/1,000; for patients aged 65 to 74 years, it was found to be 2.2/1,000; and for patients aged over 75 years, it was 2.9/1,000.

Etiology

Transient ischemic attacks occur when a focal area of the brain becomes dysfunctional as the result of a temporary reduction of blood flow.

Table 1. Causes of Transient Ischemic Attacks

Atherosclerotic disease of the cerebral vessels
Cardiogenic emboli
Transient episodes of hypotension
Orthostatic hypotension, cardiac dysrhythmias
Nonarteriosclerotic vasculopathies
Systemic lupus erythematosus, polyarteritis nodosa, syphilitic vasculitis, temporal arteritis, Behcet's syndrome, Wegener's granulomatosis, fibromuscular hyperplasia
Extracranial mechanical interference with cerebral vessels
Cervical spondylosis, atlantoaxial subluxation
Conditions associated with hypercoagulability or hyperviscosity
Thrombocytosis, polycythemia, oral contraceptives, estrogens, malignancy, sickle cell disease, Waldenström's macroglobulinemia, multiple myeloma
Subclavian steal syndrome

Although a heterogeneous group of causes are responsible for TIAs (Table 1), most of them produce TIAs either via a hemodynamic mechanism operating in a specific vascular territory or by transient embolic occlusion of a cerebral vessel.[17]

Atherosclerotic disease of the cerebral vessels is the most common cause of TIAs and is responsible for up to 90 percent of episodes in patients over the age of 50 years.[8] Atherosclerotic plaques can reduce local blood flow by either of two possible mechanisms. The "artery-to-artery emboli" theory proposes that TIAs are due to platelet-fibrin aggregates or atherosclerotic debris dislodging from an ulcerated atheromatous plaque and embolizing distally.[7] The alternate theory of pathogenesis suggests that transient thrombosis of a critically stenotic cerebral artery can produce a TIA by reducing local blood flow in a distal area of the brain already compromised by a marginal collateral circulation.[9,18]

Cerebral embolism of cardiac origin is the second most frequent cause of transient episodes of cerebral dysfunction.[7] Cardiac causes associated with TIAs include mitral stenosis, atrial fibrillation, mural thrombus following myocardial infarc-

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tion, ventricular aneurysm, mitral valve prolapse, prosthetic heart valve, bacterial endocarditis, atrial myxoma, and congestive cardiomyopathy.[19]

Rare causes of TIAs include transient episodes of hypotension,[7,20] nonarteriosclerotic vasculopathies,[7,12,21] subclavian steal syndrome,[7] and conditions associated with hypercoagulability or hyperviscosity.[7,9,12]

Natural History

Various studies support the widely accepted concept that transient ischemic attacks are associated with an increased risk for stroke, with an incidence of cerebral infarction approaching 25 to 40 percent within five years[4,22-24] and an annual incidence of stroke of 5 to 8 percent.[4,21,25]

This increased risk for stroke following TIAs is generally felt to be highest in the first few months and the first year following the initial episode. Whisnant et al[16] reported that 21 percent of their patients with TIAs who had a stroke did so within one month of their first TIA; furthermore, 28 percent of the strokes in their series occurred within three months and 50 percent occurred within the first year following the initial ischemic event.

The mortality rate has also been found to be significantly increased in patients with TIAs.[16,22] Coronary artery disease and cerebral infarction are primarily responsible for this increased mortality.

Clinical Evaluation

The clinical evaluation of patients with suspected TIAs begins with a thorough history and physical examination. A detailed description of the episodes should be obtained. The amount of time elapsed since the initial episode should be determined in view of its possible prognostic significance. In addition, the clinician should pay particular attention to factors of pathophysiologic importance. The patient's cardiovascular risk profile (eg, hypertension, diabetes mellitus, cigarette smoking, hyperlipidemia) should be routinely determined and an inquiry made regarding a prior history of angina pectoris and intermittent claudication. Risk factors for cardiogenic emboli should also be identified; such factors would include a history of rheumatic heart disease, recent myocardial infarction, atrial fibrillation, and the presence of a prosthetic heart valve. Numerous conditions can be mistaken for a TIA, and the clinician should be cognizant of them when interviewing the patient. For example, brain tumors can produce episodes of transient neurologic deficits, and in one series they were actually associated with such episodes in 10 percent of cases.[26]

A careful physical examination should be performed, focusing on the cardiovascular and neurological systems. The blood pressure (both supine and upright) should be measured in both arms, and all peripheral pulses assessed. Carotid artery abnormalities (eg, decreased pulsation, presence of bruit) and retinal emboli seen on fundoscopic examination are particularly important findings, since their presence is indicative of extracranial carotid artery disease.[27] The heart should be examined carefully for the presence of dyskinetic pulsations, pathologic murmurs, and rhythm disturbances. A comprehensive neurologic examination is important to detect any neurological deficit that would not only suggest the possibility of a prior cerebral infarction but also raise the possibility of a cerebral mass lesion.

Diagnostic Studies

Although diagnostic tests have little or no importance in establishing the diagnosis of a TIA, they are felt to be of value in elucidating pathogenic mechanisms, detecting risk factors for atherosclerosis, excluding conditions that may mimic TIAs, and assessing the patient's ability to tolerate possible modalities of therapy.[28] Diagnostic studies traditionally obtained in patients with TIAs include the complete blood count, the erythrocyte sedimentation rate, platelet count, plasma glucose, blood urea nitrogen, serum lipid levels, serologic test for syphilis, urinalysis, a coagulation panel, chest x-ray examination, and an electrocardiogram.[10,28]

Neurological studies play an important role in the diagnostic evaluation of selected patients with suspected TIAs. An electroencephalogram can provide important information in patients suspected of having a seizure disorder masquerading as a TIA. Although some authorities have recommended that cerebral computerized axial tomography (CAT scan) be obtained routinely in all patients with transient cerebral ischemia to exclude stroke or tumor,[18,29] others feel it should be reserved for those patients with an atypical presentation or with persistent focal neurological deficits

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on examination.[30] A lumbar puncture is not felt to be useful in the diagnostic evaluation of TIAs and is usually performed only when anticoagulation therapy is contemplated to help exclude intracranial bleeding.

For patients with transient neurological symptoms felt to be related to cardiac phenomenon, special cardiac studies may be indicated. A 24-hour Holter monitor should be obtained if cardiac dysrhythmia is a diagnostic consideration. Recent studies have demonstrated that two-dimensional echocardiography should not be obtained routinely in patients with TIAs and that it should be reserved for patients with known cardiac disease (eg, atrial fibrillation, previous transmural anterior myocardial infarction, mitral stenosis, and severe congestive cardiomyopathy).[31]

Noninvasive Carotid Evaluation

A variety of noninvasive cerebrovascular studies are available. Although most of them are very sensitive for detecting significant stenosis in the internal carotid artery, they are generally incapable of detecting nonstenotic ulcerated plaques, defining the actual degree of stenosis, and differentiating between severe stenosis and complete occlusion.[1] Thiele et al[32] felt that noninvasive studies were inadequate in the evaluation of TIAs, since they would have failed to detect nearly 50 percent of the clinically significant carotid lesions in his study of 109 patients with symptomatic cerebral ischemia.

Although Machleder[30,33] has suggested that noninvasive studies be used to select patients most likely to benefit from angiography and surgery, other authorities have recommended that surgical candidates with classical carotid TIAs should "bypass the noninvasive laboratory" and proceed directly to angiography.[34] Ackerman[34] has suggested that noninvasive studies be used in patients with probable TIAs who have relative contraindications to angiography as well as in those patients who have an equivocal history for TIA. Another proposed role for noninvasive testing is as a means for monitoring the progression of atherosclerotic lesions in patients managed medically and for detecting the recurrence of lesions in those patients managed surgically.[33,34]

Digital Subtraction Angiography

Intravenous angiography using a digital subtraction system is a relatively new radiologic technique for evaluating the extracranial carotid vascular system. It is superior to noninvasive testing, since it is capable of detecting ulceration and mild stenosis and can differentiate between total and subtotal internal carotid artery occlusion.[35] Adequate visualization of the carotid bifurcation can be achieved in 71 to 96 percent of arteries evaluated, and a high correlation with conventional angiography has been reported in arteries adequately visualized (97 percent accuracy).[35,36] With further perfection of technique, digital subtraction angiography possesses the potential not only to refine the indications for conventional angiography but actually to replace it in many cases.

Cerebral Angiography

Cerebral angiography remains the most definitive diagnostic procedure currently available to determine the extent and site of atherosclerotic lesions and the feasibility of surgical treatment. Cerebral angiography, however, is associated with significant risk to the patient, with a morbidity rate that ranges from 5 to 13 percent and a mortality rate of 0.2 to 0.7 percent.[37-39] In addition, the risk of stroke resulting from angiography has been estimated at 0.3 to 1.2 percent.[38,40]

Cerebral angiography should be reserved for patients with carotid TIAs for whom surgery would be recommended if an appropriate surgical lesion was found and for patients with TIAs in whom diagnostic doubt exists despite a comprehensive evaluation.[7,9,27] Since vertebral-basilar TIAs are generally not amenable to surgical therapy, angiography is not recommended for such patients except in "unusual circumstances" or when definite TIAs persist despite appropriate medical management.[29]

Management

The patient presenting with a history of TIAs is felt to be at increased risk for stroke, and such a case thus demands prompt evaluation and management. Since patients with recent onset of their symptoms (within 3 to 8 weeks of their initial episode) or a crescendo pattern (attacks increasing in frequency or severity) are felt to be at particularly high risk for imminent stroke, it is generally rec-

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ommended that such patients be hospitalized for diagnostic workup, and neurological consultation be obtained. Although proof of its efficacy is lacking, many authorities also favor rapid anticoagulation with heparin as interim therapy in such a situation, provided no contraindications to it are present.[8,18,29,41,42] Heparin should be initiated only after intracranial hemorrhage is excluded; it is best administered in a continuous infusion adjusted to keep the partial thromboplastin time 2 to 2.5 times control.

Since TIAs have a diverse number of causes, specific therapy will naturally depend on the specific pathologic process responsible. For patients with TIAs that are due to atherothrombotic phenomenon, the optimal course of management is still controversial. Although it is generally accepted that atherosclerotic risk factors (especially hypertension) should be identified and treated in such patients, the precise role of surgical therapy, anticoagulant therapy, and antiplatelet therapy has not been clearly defined.

Anticoagulant Therapy

Although anticoagulant therapy has been used for nearly three decades in the treatment of transient ischemic attacks, its value in such patients remains controversial. No prospective, randomized study has ever shown it to be of benefit,[12,20,21,24] and thus support for its efficacy can be found only in uncontrolled or nonrandomized studies. Siekert et al[22] followed 335 patients with TIAs, 175 of whom were treated with oral anticoagulants. During the three- to eight-year follow-up period, four strokes (2.3 percent) occurred among the treated patients, whereas 33 strokes (20.6 percent) occurred among the controls. Whisnant et al[43] retrospectively studied the results of anticoagulant therapy in patients with TIAs by means of the actuarial method of analysis. In his series of 198 patients, no difference in mortality was found, but a significantly decreased risk of cerebral infarction was noted in the patients on long-term anticoagulants. Of particular interest was their finding that the greatest benefit of therapy occurred in the first two months of treatment following the initial TIA episode.

Based on the available data, most authorities have concluded that anticoagulant therapy can be effective in preventing stroke and should be used in selected patients.[4,20,24,44] The most widely advocated role for anticoagulants is in the therapy for the patient with recent onset or frequent, recurrent episodes of TIAs in whom the possibility of surgery has been excluded.[8,21,29,41-43] Anticoagulant therapy has been favored over antiplatelet therapy in women with TIAs[23,37] and in those patients known to have severe, atherostenotic extracranial disease.[17]

Long-term anticoagulation is generally achieved with a coumarin derivative, eg, warfarin. The dose of the oral anticoagulant should be adjusted to maintain the prothrombin time 1.5 to 2 times control. The optimal duration of therapy is unknown, although most authorities favor a two- to six-month course.[4,18,36,41,44]

Anticoagulation therapy should not be started without a careful consideration of its potential dangers. Bleeding is the major complication of therapy, and it has been estimated that a minimum of 5 percent of patients on oral anticoagulants will have a major bleeding episode (eg, gastrointestinal bleeding, intracranial hemorrhage, retroperitoneal bleeding).[45] In a study by Whisnant et al,[11] the risk of intracranial hemorrhage was found to be nearly fourfold higher in patients on anticoagulants, with almost all of the hemorrhages occurring in patients over 65 years old and after a year or more of treatment. To minimize the risks associated with anticoagulant therapy, Millikan and associates[4,41] have recommended that the following guidelines be met before initiating therapy: (1) indications for anticoagulant therapy must be precisely defined after workup of the patient, (2) the physician must be knowledgeable of the proper use of anticoagulants, (3) accurate tests of prothrombin time or partial thromboplastin time are available, (4) absolute cooperation of the patient in following instructions must be enlisted, and (5) no contraindications to treatment exists, such as active bleeding tendencies, poorly controlled hypertension, severe renal or hepatic disease, and so on.

Surgical Therapy

Carotid endarterectomy is the most commonly performed surgical procedure for atherosclerotic cerebrovascular disease.[20] It is potentially the most definitive form of therapy for TIAs, since it not only removes the potential source of emboli but also attempts to restore normal blood flow to the affected area. Although absolute proof of its efficacy is still lacking,[4,7,8,20,29,37] several studies

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are available that support its value in the prevention of stroke. The Joint Study of Extracranial Arterial Occlusion, still the only randomized, prospective study to compare surgery with medical therapy in the treatment of occlusive cerebrovascular disease,[20] generally supported a role for carotid endarterectomy in the treatment of TIAs. Based on the cumulative survival rates of the 1,225 patients entered into this study, Bauer et al[46] concluded that "surgical therapy appeared more beneficial for unilateral carotid stenosis in patients with transient attacks. . . ." Furthermore, when only patients with TIAs and no neurological deficits were considered, an incidence of stroke of 4 percent (average follow-up, 42 months) was found for the surgically treated group vs 15 percent in the medically treated group when perioperative complications were excluded from the analysis.[47] When Frank[44] reanalyzed the data to include the patients who died or had a stroke in the immediate postoperative period, however, no statistical significance between surgical and nonsurgical management was found. Numerous uncontrolled, therapeutic surgical trials have been reported that demonstrate a benefit from endarterectomy when their results are compared with the 5 to 8 percent annual stroke incidence in patients with TIAs derived from natural history studies. Thompson et al[48] reviewed the long-term results of 292 patients with TIAs followed up to 13 years after carotid endarterectomy and reported that only 8 percent of them had developed stroke or a "worsening" of their neurological status. Allen and Preziosi[49] reported a stroke incidence of only 3.4 percent in their series of 120 patients treated with carotid endarterectomy and followed a median of 20 months.

It is generally agreed that the most suitable candidate for carotid endarterectomy is the patient with carotid TIAs who is found to have either an ulcerated plaque (especially if deep or complex) or a stenosis of greater than 50 percent of the vessel diameter (lumenal diameter less than 2 mm) at the appropriate carotid bifurcation.[8,9,29] Endarterectomy is generally not advised in patients with severe intracranial disease or with complete occlusion of the internal carotid artery.[8,48-50] Surgery has not been shown to be effective in patients with vertebral-basilar TIAs, and these patients are generally managed medically.[9,21,29,37]

In selecting those patients with carotid TIAs who might potentially benefit from surgery, the clinician must carefully weigh the perceived benefits against the risks associated with performing the operation. A review of recent published series of carotid endarterectomy for TIAs revealed a postoperative stroke rate that ranged from 0.8 percent to 27.0 percent and a mortality rate that ranged from 0.0 percent to 11.2 percent.[51] What constitutes an acceptable operative risk was addressed by Jonas and Haas,[52] who analyzed the data from the Joint Study of Extracranial Arterial Occlusion and concluded that an operative stroke rate that exceeded 2.9 percent negated any benefit of surgical therapy over medical therapy. In view of this and similar data, many investigators recommend surgery only if it can be accomplished with a combined morbidity (stroke) and mortality rate of less than 3 percent.[17,21,23,41]

Perioperative morbidity and mortality is determined primarily by two factors—the skill and experience of the surgical team, and the condition of the patient at the time of surgery. Improvements in surgical and anesthetic techniques as well as better patient selection have resulted in operative complication rates as low as 1 to 2 percent in selected medical centers.[29,49,51] Sundt et al[50] found that patients at increased risk for serious morbidity (defined as stroke or myocardial infarction) and mortality in the perioperative period could be identified by consideration of certain predetermined risk factors. Neurologically stable patients with significant medical risk factors (eg, myocardial infarction occurring in the past six months, congestive heart failure, severe hypertension, chronic obstructive pulmonary disease, angina pectoris, severe obesity, and age over 70 years) were reported to have a postoperative complication rate of 7 percent. Neurologically unstable patients, defined as those having a progressive neurological deficit, a deficit of less than 24 hours' duration, frequent, daily TIAs, or neurological deficits due to multiple prior cerebral infarctions, were found to have a 10 percent risk for perioperative stroke. Javid et al[53] deemed carotid endarterectomy inadvisable in patients aged over 65 years with hypertension and a prior myocardial infarction because of the excessively high early and late mortality found in their series of 56 patients treated with endarterectomy.

The most recent surgical innovation in the management of TIAs is the extracranial-intracranial

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bypass procedure. Using microsurgical techniques, surgeons have successfully performed superficial temporal-to-middle cerebral artery anastomosis as well as occipital-to-posterior inferior cerebellar artery anastomosis. The efficacy of the former procedure is currently being investigated by an ongoing international cooperative study, where it is being performed in patients with TIAs found to have internal carotid artery occlusion, inaccessible carotid stenosis, or middle cerebral artery stenosis or occlusion.[54]

Antiplatelet Therapy

Antiplatelet therapy represents the most recent therapeutic approach to patients with TIAs. Its usage is based on the rationale that abnormal platelet adherence and platelet-fibrin emboli are responsible for a significant number of ischemic cerebral events. Numerous antiplatelet drugs have been studied, but only aspirin has been shown to be an effective drug in the treatment of TIAs. In the Canadian Cooperative Study,[25] 585 patients with TIAs were followed an average of 26 months to determine whether aspirin (325 mg four times a day) or sulfinpyrazone (200 mg four times a day) singly or in combination influenced the subsequent occurrence of TIA, stroke, or death. Aspirin was found to reduce the risk of continuing TIAs, stroke, or death by 19 percent and the risk of stroke or death by 31 percent. On subset analysis, a significant benefit could be found only for men, in whom a 48 percent reduction in stroke or death was found. In addition, no benefit for sulfinpyrazone was found either alone or in combination with aspirin.

The Anturane-TIA Italian study[55] confirmed the Canadian study finding that aspirin was beneficial for preventing stroke in men and also reported a "favorable trend" for women treated with sulfinpyrazone (400 mg twice a day). Fields et al,[56] in a double-blind American cooperative study, followed 178 patients with carotid TIAs, 88 of whom were treated with aspirin 650 mg twice a day. After six months of follow-up, there was evidence that aspirin was effective in reducing the frequency of TIAs but not in reducing the risk of stroke or death. In the subset of patients with TIAs who had a stenotic or ulcerated carotid lesion anatomically appropriate to their symptoms, however, a significant reduction in stroke or death was found in the aspirin-treated group. From a therapeutic standpoint, it is important to note that none of the aspirin studies are truly applicable to the patient with TIAs of recent onset, a patient felt to be at particularly high risk for stroke. The mean duration of time between the initial TIA and entry into the Canadian study was 12.4 months, whereas approximately 20 percent of patients in the American cooperative study were more than two years from the time of their initial TIA.

Theoretically, the patient most likely to benefit from antiplatelet therapy is the one with TIAs secondary to platelet-fibrin emboli arising from an ulcerated, atheromatous plaque.[17,33] Although the precise role of antiplatelet therapy in the treatment of TIAs is still evolving, its usage has been suggested in the following situations: (1) as first-line therapy in all patients with classic TIAs,[57] (2) as first-line therapy in male patients in whom surgery is not advised,[57] (3) for patients with TIAs in whom surgery and anticoagulants are contraindicated,[17,29,42] (4) as adjunctive therapy following anticoagulant therapy,[18,42] (5) as adjunctive therapy following carotid endarterectomy,[58] and (6) for patients with TIAs who continue to have symptoms despite adequate anticoagulation.[37]

The optimal antiplatelet drug regimen is still controversial and is the focus of ongoing studies. Although the Food and Drug Administration has recommended that aspirin be administered in a daily dose of 1,300 mg (325 mg four times a day or 650 mg twice a day), it has been argued that a lower dose might be more efficacious. A British clinical trial is currently under way comparing aspirin in doses of 600 mg twice a day vs 300 mg per day.[59] Synergism between aspirin and other antiplatelet drugs (eg, dipyridamole, sulfinpyrazone) has also been theorized and is under current clinical investigation.[7]

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