

**Supplement to the Guidelines for the Management of Transient Ischemic Attacks: A Statement From the Ad Hoc Committee on Guidelines for the Management of Transient Ischemic Attacks, Stroke Council, American Heart Association**

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## Supplement to the Guidelines for the Management of Transient Ischemic Attacks

### A Statement From the Ad Hoc Committee on Guidelines for the Management of Transient Ischemic Attacks, Stroke Council, American Heart Association

Gregory W. Albers, MD, Chair; Robert G. Hart, MD; Helmi L. Lutsep, MD; David W. Newell, MD; Ralph L. Sacco, MD

In 1994, a panel of the American Heart Association Stroke Council published guidelines for the management of transient ischemic attacks (TIAs).<sup>1</sup> Over the last 5 years, many significant advances in medical and surgical therapy for patients with TIAs have occurred. In addition, new data regarding risk factors for cerebral ischemic events have become available. These scientific advances have prompted this supplement to the 1994 guidelines, which provides updated recommendations for management of patients with TIAs.

Specific stroke-prevention strategies after a TIA are tailored to the most likely cause of the event and the patient's underlying risk factors as determined by a focused, expedient diagnostic evaluation. For more information about epidemiology, etiology, and diagnostic evaluation of TIAs, see the original guidelines.<sup>1</sup> For the current report, panel members followed the rules of evidence used by the 1998 American College of Chest Physicians Conference on Antithrombotic Therapy.<sup>2</sup>

#### Risk Factor Modification

The approach to stroke prevention among patients who have already had their first TIA includes identification and modification of stroke risk factors. Nonmodifiable risk markers for stroke include age, sex, race-ethnicity, and heredity.<sup>3</sup> Although these risk markers cannot be changed, they nonetheless serve as important identifiers of patients at risk of stroke, for whom an aggressive search for other modifiable risk factors might be particularly important. Modifiable stroke risk factors include hypertension, cardiac disease (particularly atrial fibrillation), diabetes, hypercholesterolemia, cigarette smoking, excessive use of alcohol, and physical inactivity. Numerous prospective studies and clinical trials have consistently shown a decreased risk of stroke with control of most

of these conditions, although few of these studies were conducted in TIA cohorts.<sup>1</sup>

Reduction of both systolic and diastolic pressure in hypertensive subjects substantially reduces stroke risk.<sup>4,5</sup> Reduction of isolated systolic hypertension to <140 mm Hg in the elderly, for example, in the recently completed Syst-Eur trial<sup>6</sup> demonstrated that treatment of older patients with isolated systolic hypertension led to a 42% reduction in stroke risk with no significant decline in overall mortality. Current guidelines for the treatment of hypertension have been published by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.<sup>7</sup>

Diabetes mellitus is a well-established stroke risk factor.<sup>8,9</sup> Death due to cerebrovascular disease is substantially increased in patients with 2-hour blood glucose values above the 97.5 percentile compared with those with values below the 80th percentile.<sup>10</sup> Intensive treatment of both type 1 and type 2 diabetes, aimed at obtaining near-normal levels of blood glucose, can substantially reduce the risk of microvascular complications such as retinopathy, nephropathy, and neuropathy but has not been conclusively shown to reduce macrovascular complications, including stroke.<sup>11-14</sup> One recent study<sup>13</sup> demonstrated that aggressive treatment of blood pressure in persons with type 2 diabetes reduced the risk of stroke by 44% ( $P=0.01$ ). Recent guidelines for management of diabetes have been published by the American Diabetes Association.<sup>15</sup>

Lifestyle factors, including cigarette smoking, heavy use of alcohol, and physical inactivity, have all been associated with an increased risk of stroke.<sup>16-19</sup> Modification of these behaviors can lead to a decrease in risk of stroke, which may be mediated by reductions in other stroke risk factors, such as hypertension, diabetes, hypercholesterolemia, and coronary artery disease.

Clinical trials analyzing the relationship of lipid-lowering strategies and stroke have yet to confirm a reduction in risk for patients who have already had a TIA or stroke. Data addressing the impact of treatment with statins on the incidence of stroke are derived exclusively from trials of primary and secondary prevention of coronary disease. In these studies, stroke was either a secondary end point or a nonspecified end point determined on the basis of post hoc analyses. Meta-analyses of the lipid-lowering trials with the

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new statin agents have found significant reductions in stroke risk.<sup>20</sup> A 29% reduced risk of stroke and a 22% reduction in overall mortality were found. Secondary prevention trials showed a 32% reduction in stroke risk, and primary trials demonstrated a 20% reduction. Two large trials<sup>21,22</sup> in which stroke was prespecified as a secondary end point have also shown significant reductions with pravastatin among subjects with coronary artery disease and normal to only modest elevations of cholesterol. Some clinical trials<sup>23,24</sup> have also demonstrated carotid plaque regression with statins. Although statins have not been tested in patients with stroke or TIA, clinical trials in patients with cerebrovascular disease are under way. TIA patients with cardiovascular risk factors and cholesterol levels >200 mg/dL should have a complete lipid analysis (total cholesterol, LDL, HDL, and triglycerides) and most likely will benefit from cholesterol-lowering regimens that include statins.

There are no data available from randomized clinical trials to address the risks or benefits of postmenopausal hormone replacement therapy after a TIA. Ongoing trials, such as the Women's Estrogen Stroke Trial and the Postmenopausal Estrogen and Progestin Intervention trial, may help provide more evidence-based recommendations regarding the use of postmenopausal hormone replacement therapy. Data from observational studies suggest that hormone replacement therapy may be associated with a reduction in myocardial infarction and death. Data suggesting an increased risk of stroke from oral contraceptive use cannot be extrapolated to postmenopausal hormone replacement therapy (for which the goal is to obtain physiological levels of estrogen).

Studies<sup>25,26</sup> are continuing regarding the importance of other risk factors, including elevation of homocysteine, lipoprotein fractions [including lipoprotein (a)], and hypercoagulable states from antiphospholipid antibodies, factor V, protein C, and protein S deficiencies.

Despite the wealth of data on the importance of stroke risk factors, control of these conditions is still inadequate because of poor patient compliance and adherence to behavior modifications as well as decreased detection and treatment by healthcare providers.<sup>27,28</sup> Further reductions in the risk of stroke among patients with TIA will require enhancements in our ability to detect, modify, and treat cerebrovascular risk factors.

## Medical Therapy for TIAs

### Antiplatelet Agents

Antiplatelet agents are typically the treatment of choice for prevention of future stroke in patients who have experienced a TIA of presumed atherothrombotic origin. Four different antiplatelet agents have shown efficacy for preventing stroke and/or other vascular events in patients with cerebrovascular disease. The selection of a specific agent is typically based on interpretation of the results of randomized clinical trials that have tested these agents in populations of patients who have had a recent TIA or stroke. Aspirin continues to be the most economical and frequently chosen antiplatelet agent for treatment of patients after a TIA. The greatest controversy regarding the use of aspirin for stroke prevention involves

dose selection. Recent clinical trials have addressed this issue.

### Optimal Dose of Aspirin to Prevent Stroke After TIA

Aspirin doses ranging from 25 mg 2 times per day<sup>29</sup> to 325 mg 4 times per day<sup>30</sup> have been shown to be efficacious for prevention of stroke after TIA. Controversy continues to surround the question of whether aspirin doses in the higher end of this range (ie,  $\geq 650$  mg/d) offer more protection against stroke than lower doses.<sup>31-34</sup> Two well-executed randomized trials directly compared different aspirin doses in patients with TIAs and minor ischemic stroke (1200 versus 300 mg/d<sup>35</sup> and 283 versus 30 mg/d<sup>36</sup>) and found no statistically significant differences. Some have criticized these results because patients recruited into these trials were younger and had a relatively lower risk of stroke than most TIA patients, and because modest differences favoring high-dose aspirin were not excluded with statistical confidence.<sup>31,34</sup> Nevertheless, available data from these direct comparisons in TIA patients suggest that the efficacy of aspirin for prevention of stroke is similar for all doses in the ranges tested. Indirect comparisons and results of *in vitro* studies have been marshaled to support the possible additional efficacy of high-dose aspirin,<sup>31,34</sup> but their clinical relevance remains unclear.

A recently completed randomized trial, the Aspirin Carotid Endarterectomy (ACE) study, also directly compared different doses of aspirin in 2849 patients after carotid endarterectomy. The rate of the event constellation of stroke, myocardial infarction, or death within 3 months of surgery was modestly (6.2% versus 8.4%) but significantly lower in those assigned lower doses of aspirin (81 or 325 mg/d) versus higher doses (650 or 1300 mg/d) ( $P < 0.03$ ).<sup>37</sup> The effect on stroke as a separate end point was similar: 64 versus 85 ( $P = \text{NS}$ ) among those receiving lower versus higher doses, respectively. These findings contrast with the nonrandomized post hoc analysis of long-term follow-up data from the North American Symptomatic Carotid Endarterectomy Trial (NASCET),<sup>38</sup> which suggested that high doses of aspirin might be more effective than low doses. Although the relevance of these findings to patients with TIA who have not had surgery is open to question, the results of the ACE study lend support to the use of lower doses of aspirin in patients with cerebrovascular atherosclerosis.

The gastrointestinal toxicity of aspirin is dose related, but even low-dose aspirin (ie, 50 to 75 mg/d) slightly increases the risk of major bleeding, particularly gastrointestinal hemorrhage.<sup>39</sup> Enteric coating reduces gastrointestinal toxicity and appears to inhibit thromboxane synthetase similarly to equal doses of uncoated preparations despite altered pharmacokinetics and dynamics, although this has not been thoroughly studied in elderly stroke-prone patients.

Recently, the US Food and Drug Administration advocated the use of aspirin in doses of 50 to 325 mg/d for prevention of stroke. There appears to be an emerging consensus in North America, irrespective of specialty, favoring the use of aspirin 325 mg/d for prevention of stroke.<sup>40</sup> For those unable to tolerate aspirin 325 mg/d because of minor dyspepsia, the

options include taking aspirin with meals, using an enteric-coated formulation, or taking a lower dose. It is the view of this writing group that reasonable management of patients with TIA includes aspirin in doses of 50 to 1300 mg/d. With respect to the lack of established benefit of higher doses coupled with modest dose-related toxicity, the writing group recommends a dosage range of 50 to 325 mg of aspirin per day for most TIA patients.

For patients who experience an initial or recurrent TIA while taking aspirin ("aspirin failures"), there is no good evidence that altering the dose of aspirin instead of continuing the original dose will reduce the risk of subsequent stroke.<sup>41</sup> Those who experience TIA or minor ischemic stroke while taking aspirin appear to have a particularly high risk for subsequent stroke. Most clinicians empirically replace aspirin with another antiplatelet agent in this circumstance. Although such an approach seems sensible, it is not evidence based.<sup>41-43</sup>

### Alternative Antiplatelet Agents

#### *Ticlopidine*

Ticlopidine hydrochloride prevents platelet aggregation induced by adenosine diphosphate (ADP). It is approved in the United States for prevention of stroke in patients with TIA or minor stroke. Two large, multicenter, randomized trials have evaluated the efficacy of ticlopidine in patients with cerebrovascular disease.

The Canadian American Ticlopidine Study (CATS)<sup>44</sup> assessed the efficacy of ticlopidine in patients who had a recent moderate to severe atherothrombotic (74%) or lacunar (26%) stroke for reducing the incidence of important vascular events: stroke, myocardial infarction, or vascular death. Patients with strokes occurring from 1 week to 4 months earlier were randomized to 250 mg of ticlopidine 2 times per day or placebo. A total of 1053 patients at 25 centers in Canada and the United States were enrolled in the study. According to an intention-to-treat analysis, the relative risk reduction for the cluster of important vascular events was 23.3%.

In the Ticlopidine Aspirin Stroke Study (TASS),<sup>45</sup> the efficacy of ticlopidine was compared with aspirin in reducing the incidence of stroke and death from all causes in 3069 patients with a recent TIA (50%), reversible ischemic neurological deficit (12%), minor stroke (23%), or >1 of these events (15%). Patients with ischemic symptoms that occurred within 3 months of randomization were assigned to receive either 250 mg of ticlopidine twice a day or 650 mg of aspirin twice a day. According to an intention-to-treat analysis, the overall risk reduction of fatal and nonfatal stroke by ticlopidine at 3 years was 21%. Ticlopidine also reduced the risk of stroke and all causes of death by 12% compared with aspirin. In a subgroup analysis of the TASS study, ticlopidine was noted to be particularly effective in patients who had been taking aspirin or anticoagulant therapy at the time of their qualifying cerebral ischemic event.<sup>42</sup>

Diarrhea was the most frequent side effect of ticlopidine, occurring in 12.5% of patients. Neutropenia was more common in the ticlopidine groups in the TASS and CATS studies than in the comparison groups and occurred in 2.4% of all

ticlopidine patients; it was severe in 0.8% of patients (none of the patients in the aspirin group of TASS had severe neutropenia) but was reversible in all. Because severe neutropenia occurred within 90 days of initiation of therapy, a recommendation was made to screen for this potential side effect by obtaining a complete blood count with differential every 2 weeks. Since the release of this drug, reports have described another hematologic problem, thrombotic thrombocytopenic purpura.<sup>46</sup>

Although ticlopidine is efficacious in stroke prevention, its usefulness is limited by its side effects. Ticlopidine is typically used in patients who are intolerant to aspirin or who have had an ischemic event despite taking aspirin. Because the majority of side effects occur within the first 3 months, patients who have tolerated these early months of therapy can generally continue taking the drug.

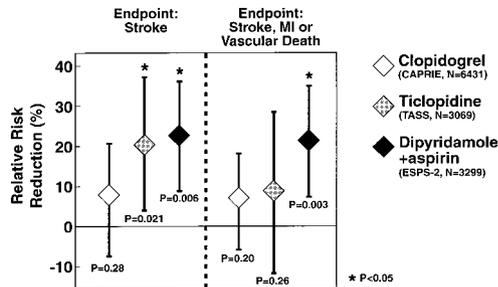
#### *Clopidogrel*

Clopidogrel is chemically related to ticlopidine and also works by inhibiting platelet aggregation induced by ADP. A potentially better side-effect profile than that of ticlopidine generated interest in this antiplatelet agent.

The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial<sup>47</sup> assessed the relative efficacy of clopidogrel and aspirin in reducing the risk of a composite outcome cluster of ischemic stroke, myocardial infarction, or vascular death. Stroke by itself was not a prespecified end point in this trial. A 75 mg/d dose of clopidogrel was compared with a 325 mg/d dose of aspirin in patients with recent ischemic stroke or myocardial infarction or patients who had symptomatic atherosclerotic peripheral arterial disease. Patients in the stroke subgroup had had a stroke within 6 months of randomization and exhibited persistent neurological signs for  $\geq 1$  week. TIA patients were not eligible for this study. In the entire group of 19 185 patients enrolled in the study, intention-to-treat analysis showed a statistically significant but quite small relative risk reduction of 8.7% for the event cluster in favor of clopidogrel. For the 6431 patients in the stroke subgroup, the relative risk reduction was a nonsignificant 7.3% in favor of clopidogrel ( $P=0.26$ ). The majority of these stroke subgroup patients developed a stroke as their first outcome event.

The safety profile of the drug appeared to be at least as good as that of aspirin. Although diarrhea and rash occurred more commonly in the clopidogrel group than in the aspirin group, gastrointestinal distress and hemorrhage were reported more often in the aspirin cohort. Because the clopidogrel-treated patients showed no excess myelotoxicity, routine blood count monitoring is not recommended as it is for ticlopidine.

Although clopidogrel had a slightly greater efficacy than aspirin in reducing the combined end point of myocardial infarction, stroke, and vascular death in patients with atherosclerotic vascular diseases, the absolute benefit was small (0.5% absolute annual risk reduction), and there was no significant benefit in patients with a recent stroke. Compared with aspirin, clopidogrel had a smaller relative risk reduction for stroke than ticlopidine. No direct comparisons between clopidogrel and ticlopidine are available (see Figure 1).



**Figure 1.** Comparison of the efficacy of alternative antiplatelet agents with aspirin in patients with cerebrovascular disease: major outcome events (relative risk reductions and 95% confidence intervals) in 3 large trials that compared an alternative antiplatelet agent with aspirin therapy alone. These data suggest that each of the 3 alternative agents is more effective than aspirin alone for prevention of major vascular events. Data from ESPS-2 for the combined vascular end point reflect stroke and/or MI and/or sudden death. Data taken from: Albers GW, Easton JD, Sacco RL, Teal P. Antithrombotic and thrombolytic therapy for ischemic stroke. *Chest*. 1998;114:683S–698S.

However, clopidogrel clearly has an advantage over ticlopidine in its side-effect profile. Clopidogrel offers another alternative to aspirin that is particularly useful for patients with intolerance to aspirin. It is also likely to be useful for patients who have an ischemic event despite aspirin therapy.

#### Dipyridamole and Aspirin

The combination of aspirin, a cyclo-oxygenase inhibitor, and dipyridamole, a cyclic nucleotide phosphodiesterase inhibitor, theoretically offers a pharmacological advantage over each of these agents alone. This combination was evaluated in 5 trials of cerebral ischemia, 4 of which included a comparison with aspirin. The first 3 trials were relatively small. The French Toulouse Study enrolled 440 patients with TIAs.<sup>48</sup> There was no statistically significant difference in outcome measures among groups receiving aspirin 900 mg/d, aspirin plus dihydroergotamine, aspirin plus dipyridamole and dihydroergotamine, or dihydroergotamine alone. A study by Bousser et al,<sup>49</sup> the Accidents Ischemiques Cerebraux Lies a l'Atherosclerose (AICLA) study, included 604 patients with TIAs (16%) or small strokes (84%). Patients were randomly assigned to receive aspirin 1000 mg/d, aspirin combined with dipyridamole 225 mg/d, or placebo. There was a 42% reduction in risk of stroke with aspirin compared with placebo. No added benefit was derived with dipyridamole. In the American-Canadian Cooperative Study,<sup>50</sup> 890 patients with carotid-distribution TIAs were evaluated. Brain or retinal infarction occurred in 60 (14%) of 442 patients taking aspirin and in 53 (12%) of 448 patients taking aspirin plus dipyridamole, which was not a significant difference.

The European Stroke Prevention Study (ESPS)<sup>51</sup> compared placebo with aspirin 975 mg/d plus dipyridamole 225 mg/d in 2500 patients with TIAs (33%), reversible ischemic neurological deficits (7%), or stroke (60%). Because no patients were given aspirin alone, this study did not permit comparison of the combination with aspirin therapy. However, there was an overall reduction of 33% in the risk of stroke and death and a reduction of 38% in the risk of stroke alone for those assigned to the combination treatment compared with placebo.

A second European Stroke Prevention Study (ESPS-2)<sup>29</sup> was designed to ascertain the efficacy of aspirin and an extended-release formulation of dipyridamole for prevention of stroke or death and to determine whether the combination of the 2 agents was superior to each agent given alone. ESPS-2 was larger than previous trials investigating the dipyridamole and aspirin combination; it included 6602 patients with stroke (76.3%) or TIA (23.7%) within 3 months of enrollment. The study had a 2×2 factorial design, which allowed comparisons between 4 treatment groups: aspirin 25 mg BID; extended-release dipyridamole 200 mg BID; the combination of aspirin 25 mg BID and extended-release dipyridamole 200 mg BID; and matched placebo. Compared with placebo, stroke risk was significantly reduced by 18% with aspirin alone, 16% with dipyridamole alone, and 37% with combination therapy. The risk of the combination of stroke or death was also reduced by each active treatment, although no effect was seen on death alone. When combination therapy with aspirin and dipyridamole was compared with aspirin alone, there was a statistically significant 23.1% reduction in stroke risk, whereas combination therapy compared with dipyridamole alone reduced stroke risk by 24.7%. Nearly twice as many events were avoided with combination therapy as with aspirin or dipyridamole alone. The narrow confidence interval of the ESPS-2 trial overlapped the wide confidence intervals of the earlier, smaller trials, which was compatible with a consistent beneficial treatment effect of the dipyridamole and aspirin combination.

The most common side effects of extended-release dipyridamole-containing preparations were headache and gastrointestinal events. The aspirin-containing regimens produced more frequent and severe bleeding episodes.

In comparison with aspirin, reductions in stroke risk with the combination therapy of extended-release dipyridamole and aspirin were greater than those reported for clopidogrel (see Figure 1); however, these agents have not been compared directly. The aspirin and extended-release dipyridamole combination was well tolerated and provides another useful alternative to aspirin for prevention of stroke. Combinations of aspirin and ticlopidine or clopidogrel have not been tested in TIA or stroke patients. Therefore, the efficacy and safety of these combinations in patients at risk of stroke are unknown.

## Anticoagulants

### Cardioembolic Stroke

Adjusted-dose oral anticoagulation with warfarin continues to be the therapy of choice for stroke prevention in patients with atrial fibrillation who have had a TIA. The superior efficacy of anticoagulation over aspirin for prevention of stroke in patients with atrial fibrillation and a recent TIA or minor stroke was shown in the European Atrial Fibrillation Trial.<sup>52</sup> In addition, considerable data from multiple randomized trials have shown that oral anticoagulation is the treatment of choice for primary stroke prevention in high-risk atrial fibrillation patients. Patients with atrial fibrillation who are at high risk of stroke include persons with a history of hypertension, poor left ventricular function, rheumatic mitral valve disease, prosthetic heart valves, a prior stroke, TIA, systemic embolism, or age >75 years.<sup>53</sup>

The efficacy of aspirin for prevention of cardioembolic stroke is considerably less than warfarin. Aspirin is recommended for patients at high risk of cardioembolism who have contraindications to oral anticoagulation. Anticoagulant therapy is appropriate for patients with several other high-risk sources of cardiogenic emboli who have a TIA; however, randomized clinical trials have not been performed in these specific patient populations. These high-risk sources for recurrent cardiac embolization include mechanical prosthetic heart valves, recent myocardial infarction, left ventricular thrombus, dilated cardiomyopathies, and marantic endocarditis. The role of anticoagulation for patients with TIA who have a patent foramen ovale or an atrial septal aneurysm is not clear. An ongoing study is comparing the efficacy of aspirin with oral anticoagulation in patients with patent foramen ovale who suffered a recent cryptogenic stroke. Mitral valve prolapse, a common valvular abnormality, was formerly thought to cause stroke, but more recent population-based and case-control studies have not demonstrated an increased risk.<sup>54,55</sup>

#### **Optimal Intensity of Anticoagulation**

Recent studies have addressed the optimal intensity of oral anticoagulation for prevention of stroke in patients with atrial fibrillation. Results from a large case-control study<sup>56</sup> and 2 randomized clinical trials<sup>52,57</sup> suggest that the efficacy of oral anticoagulation declines significantly below an International Normalized Ratio (INR) of 2.0. Recent surveys indicate that a high percentage of atrial fibrillation patients who are taking warfarin have subtherapeutic levels of anticoagulation.<sup>58</sup> Current recommendations suggest a target INR of 2.5 (range 2.0 to 3.0) for most indications for oral anticoagulation.<sup>59</sup>

#### **Anticoagulation for Atherothrombotic Stroke**

The relative efficacy of oral anticoagulation compared with antiplatelet therapy has not been adequately studied in patients with atherothrombotic stroke or TIA. At present, the only large randomized trial available compared very-high-intensity oral anticoagulation (INR 3.0 to 4.5) with aspirin (30 mg/d) in patients with a recent TIA or minor stroke.<sup>60</sup> This study was terminated prematurely because of a high rate of major hemorrhage in the anticoagulation group. These results demonstrate that an INR range of 3.0 to 4.5 is not safe for patients with a recent TIA or atherothrombotic stroke. The Warfarin Aspirin Recurrent Stroke Study is a large ongoing trial comparing a lower target INR (1.4 to 2.8) with aspirin (325 mg/d) in patients with a recent atherothrombotic stroke. A European study (European and Australian Stroke Prevention in Reversible Ischemia Trial) is also comparing the efficacy of oral anticoagulation with antiplatelet therapy for secondary stroke prevention. The results of these trials are expected to significantly clarify the role of oral anticoagulation after a noncardioembolic cerebral ischemic event.

It is possible that specific atherothrombotic stroke subtypes may respond favorably to oral anticoagulation. For example, a nonrandomized retrospective study<sup>61</sup> found that patients with symptomatic intracranial stenosis had a lower stroke rate when they took warfarin rather than aspirin. A randomized trial based on these preliminary results is currently under way (the Warfarin-Aspirin Symptomatic Intracranial Disease

study). Some experts also recommend anticoagulation therapy for patients who experienced a TIA while taking an antiplatelet agent or for persons with crescendo TIAs. Some clinicians use short-term anticoagulation after a TIA while an urgent evaluation is being performed. No adequate data are available to support or refute this practice. TIA patients with extracranial cervical artery dissections, severe carotid stenosis before endarterectomy, antiphospholipid antibody syndrome, or cerebral venous sinus thrombosis may respond favorably to anticoagulation therapy; however, randomized clinical trial data are not available for these specific disorders.

## **Surgical Management**

### **Carotid Artery Disease**

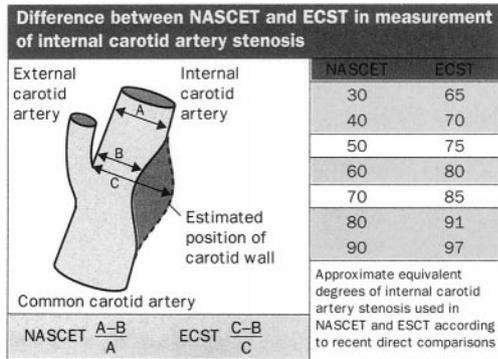
Atherosclerotic narrowing of the internal carotid artery at the carotid bifurcation in the neck is a common cause of TIA and stroke. During the late 1980s and 1990s, the value of carotid endarterectomy for stroke prevention was assessed by prospective randomized trials. Three major prospective randomized trials—NASCET, the European Carotid Surgery Trial (ECST), and the Veterans Affairs Cooperative Study Program 309 (VACSP 309)—evaluated the efficacy of carotid endarterectomy in symptomatic patients (patients with TIAs or small strokes) with high-grade carotid stenosis. The results of these trials were reported in 1991 and showed a clear benefit of carotid endarterectomy.<sup>62–64</sup> Endarterectomy was not beneficial for patients with mild stenosis (<30%) in the ECST.<sup>63</sup>

### **Recent Results for Moderate Carotid Stenosis**

The results of NASCET and ECST, which compared surgical and medical therapy in patients with recently symptomatic moderate carotid stenosis, were reported in 1998.<sup>39,65</sup> The long-term (up to 8 years) outcome in patients with high-grade stenosis who were entered in the trials was also reported.

NASCET reported the results for symptomatic patients with moderate carotid stenosis who were randomly assigned to receive medical care (1108 patients) or surgery (1118 patients). Entry criteria included moderate carotid stenosis and a nondisabling stroke or TIA referable to the stenosis within 180 days. Patients were stratified into 2 groups (either a 50% to 69% or 30% to 49% stenosis of the internal carotid artery measured angiographically). Average follow-up was 5 years, and primary outcome measures were fatal or nonfatal stroke ipsilateral to carotid stenosis. For patients with 50% to 69% stenosis, the rate of ipsilateral stroke over the 5-year period was 22.2% in the medically treated group and 15.7% in the surgically treated group (6.5% absolute risk reduction over 5 years,  $P=0.045$ ).<sup>39</sup> In patients with <50% stenosis, the ipsilateral stroke rate was slightly lower (14.9%) in those treated with endarterectomy than in those who were medically treated (18.7%), but this was not significantly different ( $P=0.16$ ). The benefit achieved by surgery was greatest among men, in patients with recent stroke (rather than TIA) as the qualifying event, and in patients with hemispheric rather than visual symptoms.

The final results of ECST were also reported in 1998.<sup>65</sup> This report contained long-term follow-up data on patients with a moderate degree of stenosis randomly assigned to surgery or medical treatment as well as additional follow-up



**Figure 2.** Differences in measurement techniques used by NASCET and ECST. Comparisons of differences in stenosis severity by the 2 methods are also illustrated. Reprinted with permission from: Donnan GA, Davis SM, Chambers BR, Gates PC. Commentary: surgery for prevention of stroke. *Lancet*. 1998;351:1372–1373.

in patients with severe carotid stenosis and mild carotid stenosis. This multicenter, prospective, randomized, controlled trial enrolled a total of 3024 patients. Entry criteria included  $\geq 1$  transient or mild symptomatic ischemic vascular event in the distribution of a carotid artery with some degree of carotid stenosis.

Like the results of NASCET, the results of ECST revealed that surgery was most effective in patients with more severe degrees of carotid stenosis. In the entire group (all degrees of stenosis), 669 (37%) of the patients in the surgery group and 440 (36.5%) of the patients in the control group sustained a major stroke or death (not significantly different). There was a 7% chance of major stroke or death complicating surgery. The risk of major ischemic strokes was much higher ipsilateral to an unoperated symptomatic carotid artery with a stenosis  $>80\%$  for 2 to 3 years after randomization. The long-term risk of major stroke or death in medically treated patients with carotid stenosis  $>80\%$  of the original lumen diameter at 3 years was 26.5% versus 14.9% in the surgically treated group for an absolute benefit of 11.6% over 3 years ( $P=0.001$ ). As in the NASCET findings, women benefited less than men from surgery.

It is important to consider that the degree of carotid stenosis in ECST was measured differently than that in NASCET.<sup>66,67</sup> The degree of carotid stenosis is significantly higher if calculated by the NASCET rather than the ECST method<sup>66</sup> (see Figure 2). Stroke rates in medically treated patients with carotid stenosis increase dramatically with stenosis  $>80\%$  as measured by the ECST method. This corresponds roughly to a 60% stenosis measured by the NASCET method.

In summary, it appears that patients with a recent TIA or nondisabling stroke with ipsilateral carotid stenosis benefit from surgery if the stenosis is  $>50\%$  as measured by the NASCET method; however, this benefit appears to be less pronounced in women. Sex and age differences, as well as comorbidity, must be considered when treatment options are evaluated in patients with stenosis of 50% to 69%, because the absolute benefit of surgery is relatively small for these patients. Women or patients with retinal TIAs with carotid stenosis  $<70\%$  may not benefit from surgery. Recently

symptomatic patients with  $>70\%$  stenosis as measured by the NASCET method can expect a far greater benefit from carotid endarterectomy. Surgical benefits appear to be particularly robust for men, patients with hemispheric symptoms and without diabetes, and for persons with significant ulcers as demonstrated by angiography. The benefit of carotid endarterectomy is highly dependent on surgical risk. NASCET had strict criteria for qualifying surgeons and used ongoing quality assessments to ensure acceptable levels of perioperative complications.

### Angioplasty and Stent Placement

Transluminal angioplasty with intravascular placement of stents for treatment of carotid stenosis is currently being evaluated as an alternative to carotid endarterectomy. Some initial case series have reported relatively low complication rates, and some investigators advocate this method of treatment for patients who are at high risk for surgery because of heart disease or other comorbid factors. However, other recent reports have suggested that the complication rate from this procedure may be higher than initially reported.<sup>68</sup> Early results have demonstrated high rates of restoration of the luminal diameter in the internal carotid artery.<sup>69</sup> Case series have included patients with asymptomatic as well as symptomatic carotid stenosis and mixtures of patients with various degrees of comorbidity. The long-term effects of stenting and rate of restenosis are unknown. Prospective randomized trials comparing angioplasty and stenting with carotid endarterectomy are ongoing.<sup>70,71</sup> Until the results of these studies are available, this procedure should be considered investigational. Recent case series have also provided preliminary data regarding the safety and efficacy of angioplasty for treatment of symptomatic intracranial stenosis.<sup>72,73</sup> A high degree of technical success and low complication rates have been reported.

### Extracranial-Intracranial Bypass

Extracranial-intracranial bypass is a procedure designed to improve blood flow to the brain by direct vascular conduits from the external carotid circulation to the intracranial circulation.<sup>74</sup> The effects of superficial temporal to middle cerebral artery bypass were evaluated for patients with TIAs or mild strokes in a large, prospective, randomized trial funded by the National Institutes of Health and conducted in 71 North American, European, and Asian centers.<sup>75</sup> Entry criteria included recent cerebral ischemic symptoms combined with carotid occlusion, carotid artery narrowing distal to the carotid bifurcation, or intracranial stenosis. Although a high patency rate of the bypass was demonstrated, the study found that superficial temporal artery–middle cerebral artery bypass had no advantage over medical therapy.

Because this trial included patients without hemodynamic insufficiency, it is possible that patients selected on a hemodynamic basis may benefit from the procedure.<sup>76–79</sup> New imaging techniques such as positron emission tomography, xenon computed tomography, and transcranial Doppler with vasoreactivity testing have been shown to identify patients with extracranial occlusive disease who are at high risk for subsequent stroke.<sup>80–82</sup> Randomized clinical trials will be

**Use of Antithrombotic Agents in Patients With TIAs**

Event	Recommended Therapy	Therapeutic Options
TIA (atherothrombotic)	ASA 50–325 mg/d	ER-DP 200 mg+ASA 25 mg BID Clopidogrel 75 mg/d Ticlopidine 250 mg BID ASA 50–1300 mg/d
TIA (atherothrombotic) and aspirin-intolerant* or if TIA occurs during ASA therapy†	ER-DP 200 mg+ASA 25 mg BID Clopidogrel 75 mg/d	Ticlopidine 250 mg BID Warfarin (INR 2–3) ASA 50–1300 mg/d
TIA (cardioembolic)	Warfarin target INR 2.5 (range 2–3)	ASA 50–325 mg/d (if contraindications to warfarin)

ASA indicates acetylsalicylic acid (aspirin); ER-DP, extended-release dipyridamole.

\*Neither ER-DP+ASA or ASA alone is recommended for patients who are allergic to aspirin or unable to take low-dose aspirin.

†The recommended antithrombotic agents have not been specifically tested in patients who have experienced a TIA during ASA therapy.

required to establish whether extracranial-intracranial bypass surgery can benefit a specific subgroup of patients. Patients with moyamoya disease who have had TIAs or recent strokes may benefit from extracranial-intracranial bypass or encephalodural synangiosis procedures; however, results of well-controlled trials are not available.<sup>83–86</sup>

**Surgery for Vertebrobasilar Disease**

TIAs referable to the posterior circulation can result from occlusive disease of the vertebrobasilar system. The 2 most common sites for vertebral artery atheroma are the origin of the vertebral artery and slightly distal to the transition from the extracranial to the intracranial portion.<sup>87–89</sup> Surgical and endovascular treatments have been performed for patients with TIAs or small strokes referable to atheromatous disease of the vertebrobasilar system.<sup>90–92</sup> Small case series have reported favorable results. Vertebral artery transposition to the common carotid artery is increasingly used for vertebral origin stenosis.<sup>87,92–95</sup> Angioplasty can also be performed at this site. Either direct endarterectomy or angioplasty with or without stenting has also been performed for patients with symptomatic intracranial vertebral artery stenosis.<sup>88,90,96</sup> For mid-vertebral lesions with fixed stenosis or positional obstruction with ischemic symptoms, surgical reconstruction or decompression can be effective in relieving symptoms.<sup>92,97</sup> Bypass procedures have also been used in patients with vertebrobasilar ischemia.<sup>91</sup> Comparisons of surgery and endovascular therapy are lacking, and there are no randomized controlled trials comparing these procedures with medical therapies.

**Recommendations****Risk Factor Management**

Risk factor guidelines are grade C because randomized trials have not been completed in TIA patients.

1. After thorough evaluation to determine the cause of the TIA, hypertension should be treated to maintain systolic blood pressure below 140 mm Hg and diastolic blood pressure below 90 mm Hg. For persons with diabetes, blood pressure levels <130/85 mm Hg are recommended.

2. Cigarette smoking should be discontinued. Counseling, nicotine replacement therapies, bupropion, and formal smoking cessation programs may all be helpful.
3. Coronary artery disease, cardiac arrhythmias, congestive heart failure, and valvular heart disease should be treated appropriately.
4. Excessive use of alcohol should be eliminated. Formal alcohol cessation programs are recommended. Mild to moderate use of alcohol (1 to 2 drinks per day) has been associated with a reduction in stroke rates.
5. Treatment of hyperlipidemia is recommended. The AHA Step II diet ( $\leq 30\%$  of calories derived from fat,  $< 7\%$  from saturated fat, and  $< 200$  mg/d cholesterol consumed) is recommended along with maintenance of ideal body weight and engagement in regular physical activity. If lipid levels remain elevated (LDL  $> 130$  mg/dL), use of a lipid-lowering agent, preferably a statin, is recommended. The goal of therapy should be an LDL level  $< 100$  mg/dL.
6. Fasting blood glucose levels  $< 126$  mg/dL are recommended. Diet and oral hypoglycemics or insulin should be prescribed as needed to control diabetes.
7. Physical activity (30 to 60 minutes of exercise  $\geq 3$  to 4 times per week) is recommended.
8. Discontinuation of postmenopausal estrogen replacement therapy is not recommended.

**Medical Therapy (Table)****Atherothrombotic TIAs**

Patients who have had an atherothrombotic TIA should receive daily therapy with an antiplatelet agent to reduce the risk of recurrent stroke (grade A-1). Aspirin, clopidogrel, ticlopidine, and the combination of aspirin and extended-release dipyridamole are all acceptable options for initial therapy (grade A-2).

In general, aspirin at a dosage range of 50 to 325 mg/d is recommended as initial therapy for patients who are not allergic or intolerant to aspirin. For patients who have an atherothrombotic TIA while taking aspirin, there is no compelling evidence that increasing the dose of aspirin provides additional benefit. Alternative antiplatelet agents are typically considered for these patients, although they have not been specifically evaluated in patients who have “failed aspirin.” Although ticlopidine may be

more effective for preventing stroke (on the basis of indirect comparisons), clopidogrel (75 mg/d) is generally recommended in favor of ticlopidine (250 mg BID) (grade C-2) because of its superior safety profile. The combination of extended-release dipyridamole and aspirin may also be more effective than clopidogrel (on the basis of indirect comparisons; grade C-2), and both have a favorable safety profile.

Anticoagulant therapy is not routinely recommended for patients with atherothrombotic TIAs, as either short- or long-term therapy (grade B-2). Anticoagulant therapy is an option for patients with a TIA who continue to have symptoms despite antiplatelet therapy (grade C-2). At anticoagulation intensities of INR 3.0 to 4.5, the risk of brain hemorrhage outweighs the potential benefits (grade A-1). Therefore, if oral anticoagulants are used for atherothrombotic TIA patients, a target INR <3.0 should be chosen.

### Cardioembolic TIAs

Long-term oral anticoagulation is recommended for patients with atrial fibrillation who have a TIA (grade A-1). For these patients, a target INR of 2.5 (range 2.0 to 3.0) is recommended. Oral anticoagulation is also beneficial for prevention of stroke in patients with other high-risk cardiac sources of embolism (see section on Anticoagulants, Cardioembolic Stroke). Aspirin is recommended for patients with contraindications to oral anticoagulation.

## Surgical Management

### Extracranial Carotid Artery Disease

#### Stenosis of 70% to 99%\*

Carotid endarterectomy is indicated for patients who are good surgical candidates and who have experienced  $\geq 1$  TIA or minor stroke within the last 2 years, regardless of the response to antiplatelet drugs (grade A-1).

#### Stenosis of 50% to 69%\*

Patients with a recent TIA or minor stroke have a reduced stroke rate with endarterectomy versus medical treatment and should be considered for endarterectomy (grade A-1). The absolute benefit of surgery is less than that for patients with higher degrees of stenosis and among women and patients with retinal TIAs. Consideration should be given to clinical features that influence stroke risk and surgical morbidity.

#### Stenosis <50%\*

Patients with <50% stenosis with recent symptoms of cerebral ischemia do not benefit from carotid endarterectomy (grade A-1). Antiplatelet therapy is recommended for these patients (see section on Medical Therapy).

### Endovascular Treatment

Prospective trials evaluating the results of angioplasty and stent placement in comparison with carotid endarterectomy are now in progress. The use of endovascular treatment is not routinely recommended for treatment of carotid bifurcation stenosis.

### Bypass Surgery

Extracranial-intracranial bypass is not recommended for patients with TIAs (grade A-1). A subgroup of patients with anterior circulation ischemia unresponsive to medical therapy with hemodynamic disturbances may benefit from bypass surgery. Additional studies are required to determine the role of surgery in these patients. Patients with moyamoya disease may benefit from extracranial-intracranial bypass (grade C-2).

### Therapy for Vertebrobasilar Ischemia

Surgical or endovascular therapy may be appropriate for patients with significant vertebrobasilar stenosis who have continued symptoms referable to the posterior circulation despite medical therapy. For significant stenosis at the origin of the vertebral artery, vertebral artery transposition to the common carotid artery or angioplasty and stenting are treatment options (grade C-2). For significant stenosis at the distal vertebral artery, endarterectomy, bypass, or endovascular procedures are treatment options. For midvertebral lesions with fixed stenosis or positional obstruction with ischemic symptoms, surgical reconstruction or decompression can be effective in relieving symptoms (grade C-2).

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