

# Determining the Appropriateness of Selected Surgical and Medical Management Options in Recurrent Stroke Prevention: A Guideline for Primary Care Physicians from the National Stroke Association Work Group on Recurrent Stroke Prevention

Daniel Hanley, MD,\* Philip B. Gorelick, MD, MPH,† William J. Elliott, MD, PhD,‡  
Michael S. Broder, MD, MSHS,¶ Jeffrey L. Saver, MD,# Chelsea S. Kidwell, MD,##  
Susan C. Fagan, PharmD,\*\* Alisa Wilson, PhD,¶¶ Laura Lennihan, MD,††  
William A. Schwer, MD,§ Laurence Z. Rubenstein, MD, MPH,‡‡  
Robert M. Crowell, MD,§§ Stephen J. Haines, MD,||| Carolyn C. Lopez, MD,||,¶¶¶  
Richard Zorowitz, MD,### and Robert W. Dubois, MD, PhD¶¶

---

Despite a decade of successful clinical trials for stroke prevention, substantial gaps exist in the application and implementation of this information in community practice. The frequency of guideline use is low, and there remains controversy regarding the standard of practice. Patients with stroke may have multiple risk factors and concomitant stroke mechanisms, factors that are not addressed in stroke clinical trials and guideline statements. New guidelines are needed to account for these complexities and to provide primary care physicians a practical means to achieve stroke prevention. We sought to develop guidelines that can be implemented by primary care physicians to enhance the use of medical and surgical measures for recurrent stroke prevention. We sought to test the applicability of current evidence-based guidelines to daily practice with routine and complex patient case scenarios to determine whether these could be simplified into a more easily applied form for primary care physicians. We used RAND/UCLA Appro-

---

\*From the Department of Neurology, Johns Hopkins University, Baltimore, Maryland; †Department of Neurologic Sciences, ‡Preventive Medicine, Internal Medicine and Pharmacology, §Department of Family Medicine, and ||Department of Family Practice, RUSH Medical College, Chicago, Illinois; ¶Cerner Health Insights, Beverly Hills, California; #Department of Neurology, University of California-Los Angeles Medical Center; \*\*College of Pharmacy, University of Georgia and Department of Neurology, Medical College of Georgia, Augusta; ††Neurologic Institute, Columbia University, New York, New York; ‡‡Geriatric Research and Clinical Center, Greater Los Angeles Department of Veterans Affairs Healthcare System, Sepulveda, California; §§University of Massachusetts Medical School, Pittsfield; |||Department of Neurological Surgery, Medical University of South Carolina, Charleston; ¶¶American Academy of Family Physicians, Leawood, Kansas; and ###Department of Rehabilitation Medicine, University of Pennsylvania, Philadelphia.

Received May 4, 2004; revised May 11, 2004; accepted May 25, 2004.

Supported by an unrestricted educational grant to the National Stroke Association from Boehringer-Ingelheim Pharmaceuticals and Solvay Pharmaceuticals. Dr Hanley is supported by France Merrick Foundation, The Claude D. Pepper Older American Independent Center (P60AG12583 NIA), Food and Drug Administration (FD-R-001693-01-1), National Institute of Neurological Disorders and Stroke (NINDS) (R01NS24282-08), and the Eleanor Naylor Dana Foundation. Dr Gorelick is supported by National Institutes of Health (R01AG17934) and NINDS (R01NS33430).

Address correspondence to Daniel Hanley, MD, Johns Hopkins University, 600 N Wolfe St, Jefferson 1-109, Baltimore, MD 21287. E-mail: dhanley@jhmi.edu

1052-3057/\$—see front matter

© 2004 by National Stroke Association

doi:10.1016/j.jstrokecerebrovasdis.2004.05.002

priateness Methodology to develop guidelines for the use of interventions supported by randomized controlled trials including carotid revascularization, anticoagulant therapy, antiplatelet therapy, and blood pressure management for the prevention of recurrent stroke. After a systematic literature review of randomized clinical trials we developed a comprehensive list of indications or clinical scenarios to capture decision making. A diverse multidisciplinary panel reviewed and rated each indication according to the RAND Appropriateness Method. First, panelists rated each scenario (1-3 for inappropriate, 4-6 for uncertain, and 7-9 for appropriate) without interaction with other panelists. "Appropriate" was defined as the expected health benefit exceeding its expected negative consequences by a sufficient margin. At a formal interactive session, panelists re-rated all indications. Overall carotid endarterectomy was rated as appropriate when there was 50% to 99% ipsilateral symptomatic carotid artery stenosis, inappropriate with <50% or 100% stenosis (total occlusion), and uncertain when the surgical risk was high. Carotid angioplasty was generally rated as of uncertain value. When there was atrial fibrillation, anticoagulation with warfarin was rated as appropriate when there was a low bleeding risk but of uncertain value when the bleeding risk was high. For patients who were not candidates for warfarin therapy, aspirin, aspirin plus extended-release dipyridamole, or clopidogrel were all rated as appropriate initial therapies. Ticlopidine was considered inappropriate and aspirin plus clopidogrel of uncertain value. With the exception of ticlopidine and aspirin, persons with a prior cerebral ischemic event while on aspirin could receive any of the aforementioned antiplatelet agents or combinations and be considered appropriately treated. The panelists rated a blood pressure of <130/80 mm Hg at 1 year after ischemic stroke as the target level and rated any of the following agents as appropriate initial therapies if there was no diabetes mellitus or proteinuria: diuretics,  $\beta$ -blockers, angiotensin-converting enzyme inhibitors, angiotensin-converting enzyme receptor blockers, or combinations of a diuretic and an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. Patient risk played a significant role in deterring the panel from recommending certain therapies; however, the presence of atrial fibrillation or large or small cerebral vessel syndromes rarely had significant influence on treatment decisions. Appropriateness was less where bleeding or surgical risk was excessive. Using consensus evidence from clinical trials, we have developed recurrent stroke prevention guidelines for routine and more complex patient scenarios according to appropriateness methodology. Broad application of these guidelines in primary practice promises to reduce the burden of recurrent stroke. **Key Words:** Recurrent stroke—prevention—RAND technique—appropriateness.

© 2004 by National Stroke Association

Stroke is a major public health problem.<sup>1</sup> It is the second leading cause of death worldwide and the third leading cause of death in the United States. Stroke frequently results in hospital admissions, morbidity, and long-term disability. It is estimated that the total annual cost of stroke in the United States is about \$43 billion with an additional cost of up to \$6.1 billion for stroke-related informal care giving.<sup>2</sup> To reduce the burden of stroke, evidence-based guidelines have been developed that define how to modify lifestyle, medical, and other factors to prevent first and recurrent stroke.<sup>3-9</sup> However, outcomes of stroke care are currently suboptimal, as there remain gaps between current and optimal care.<sup>10,11</sup> Quality of care in the community may be variable, as new information from clinical studies is not being incorporated into daily practice. Importantly, current guidelines are restric-

tive, as they do not take into account the complexity of the patient with stroke who may have multiple comorbid conditions, several concomitant pathophysiologic stroke mechanisms,<sup>12</sup> and the need for multiple stroke prevention therapies. Current guidelines do not address, for example, the patient who has symptomatic high-grade extracranial carotid artery stenosis and concurrent atrial fibrillation or the patient with atrial fibrillation who has a high bleeding risk. What are the best stroke preventive regimens for these patients? New guidelines or road maps are needed so that the primary care physician may provide effective stroke prevention for this costly disease.

The current study used the RAND Appropriateness Method to develop guidelines for the prevention of recurrent stroke including both medical and surgical interventions with clear demonstration of efficacy.<sup>13</sup> Because

preventive management reflects the integrated actions of specialists and primary care physicians, we used a representative group of these professionals. The appropriateness methodology used in this study took into account a broad range of everyday patient scenarios encountered by primary care physicians and included both routine situations that might be typical of patients enrolled in standard recurrent stroke prevention clinical trials and more complex situations that may be encountered frequently in practice, but not in clinical trials. These guidelines address the role of carotid revascularization, antiplatelet therapy, anticoagulation, and management of blood pressure to limit the risk of recurrent stroke.

## Methods

The RAND/University of California–Los Angeles Appropriateness Methodology was used to develop guidelines for the use of both medical and surgical interventions for the prevention of recurrent ischemic stroke.<sup>14</sup> To develop these guidelines we: (1) undertook a systematic literature review of randomized clinical trials to determine the effectiveness of medical and surgical interventions in the prevention of secondary stroke; (2) developed a comprehensive list of indications or clinical scenarios designed to reflect the range of patient presentations in primary care practice and to capture decision making—included were all relevant clinical parameters to judge the appropriateness of medical and surgical interventions for postsecondary stroke prevention; and (3) convened a geographically diverse, multidisciplinary consensus panel to review and rate each indication for the use of the alternative management strategies.

### *Literature Review*

In June 2002, we searched the PUBMED computerized bibliographic databases to identify English-language articles of recurrent stroke prevention trials published since 1966. We limited the search to stroke prevention alone rather than all cardiovascular diseases. Search terms and strategies were developed in cooperation with physicians with clinical and research expertise in this field. The search strategy included broad definitions of “stroke,” “secondary,” and “prevention.” For example, the descriptors used for “secondary” included “recurrent,” “recurring,” “recur,” “recurrence,” and “post.” In addition, the search included an extensive list of prevention strategies including, but not limited to, platelet aggregation inhibitors, antithrombins, anticholesterolemic agents, and carotid endarterectomy. After completion of the computerized bibliographic search, the selection of articles for inclusion was limited to randomized clinical trials. Thus, we excluded effectiveness data taken from administrative data sets, such as the CHADS data.<sup>15</sup> Physician reviewers extracted data from clinical trials

regarding general efficacy of therapies and efficacy of specific subgroups relevant to the clinical scenarios.

### *Panel Ratings: Process and Methods*

On the basis of the latest available evidence, we sought to develop a comprehensive list of specific clinical scenarios for recurrent stroke prevention involving treatment with surgical or medical interventions that might be encountered by the primary care physician. Clinical factors included: (1) type of stroke (large vessel vs lacunar syndrome); (2) cardiac rhythm (presence or absence of atrial fibrillation); and (3) extent of ipsilateral carotid artery stenosis (<50%, 50%-69%, 70%-99%, 100%, and type of ulceration [no/small vs large]). Additional factors were specific to the proposed therapy: (1) surgical risk for patients undergoing carotid endarterectomy or angioplasty; and (2) low versus high bleeding risk for patients receiving antiplatelet agents or anticoagulation. For patients with atrial fibrillation who were considered for antiplatelet therapy we examined those currently not on warfarin separately from those receiving this medication. Scenarios for the type of antiplatelet therapy (eg, aspirin vs clopidogrel or combination antiplatelet therapy) included whether the patient had experienced a carotid ischemic event while receiving aspirin and whether they had coexisting coronary artery disease.

We also included clinical scenarios for evaluating the appropriateness of blood pressure control for patients with stroke. These latter scenarios addressed whether or not to lower blood pressure for patients with stroke, the type of medications that should be used in lowering blood pressure, and the target pressure to achieve. Specific clinical factors included: (1) current systolic blood pressure (>180, 160-179, 140-159 mm Hg); (2) presence or absence of cognitive impairment; (3) presence or absence of significant carotid or intracranial stenosis; (4) type of agent (diuretic,  $\beta$ -blocker, calcium channel blocker, angiotensin-converting enzyme [ACE] inhibitor, angiotensin-converting enzyme receptor blocker [ARB], or combinations of diuretics with other agents); and (5) initial therapy versus add-on medication. We did not include data on the presence or absence of comorbidities including extent of coronary artery disease, wall-motion abnormalities, or peripheral vascular disease as the clinical trial data used did not allow for the separation of the effects of these conditions on stroke risk.

We convened a panel of 10 physicians representing diversity of specialties (neurology [2], neurosurgery [2], internal medicine [1], geriatrics [1], physical medicine and rehabilitation [2] [one of whom was a board-certified neurologist who practices rehabilitation medicine], and family practice [2]) and from mixed practice settings throughout the continental United States. The panel also included a pharmacist who provided consultation but did not vote. The RAND Appropriateness Method was

**Table 1.** Role of surgical interventions

	Carotid endarterectomy		Carotid angioplasty	
	Risk < 6%	Risk > 6%	Risk < 6%	Risk > 6%
Ipsilateral < 50%	Inappropriate	Inappropriate	Inappropriate	Inappropriate
Ipsilateral: 50%-69%				
No or small ulceration	Appropriate*	Uncertain†	Inappropriate	Inappropriate
Large ulcerative lesion	Appropriate	Uncertain	Inappropriate	Inappropriate
Ipsilateral: 70%-99%				
No or small ulceration	Appropriate	Uncertain	Uncertain	Inappropriate
Large ulcerative lesion	Appropriate	Appropriate‡	Uncertain	Inappropriate
Ipsilateral: 100%	Inappropriate	Inappropriate	Inappropriate	Inappropriate

\*Uncertain if the patient has either atrial fibrillation or presents with a lacunar syndrome.

†Inappropriate if the patient has either atrial fibrillation or presents with a lacunar syndrome.

‡Uncertain if patient has either atrial fibrillation or presents with a lacunar syndrome.

used. In the initial round, panelists received a literature review (evidence table available on request), a list of indications, and a list of operational definitions for terms used in the clinical scenarios (Appendix I and II). Participants rated each scenario without interaction with other panelists. Panelists rated each indication on a 9-point scale (1 = extremely inappropriate, 5 = uncertain, and 9 = extremely appropriate). A scenario was rated as appropriate if the “expected health benefits of the therapy exceeded its expected negative health consequences by a sufficiently wide margin to justify giving the therapy.”

During the panel meeting, the panelists reviewed the summarized first-round ratings, revised the indications structure, modified the definitions of key terms, discussed reasons for the degree of agreement or disagreement in ratings from the first round, and confidentially re-rated all indications. The final ratings were on the basis of the median score of the panelists. We considered the indications appropriate for median ratings between 7 and 9 (without disagreement), inappropriate for median ratings between 1 and 3 (without disagreement), and uncertain for median ratings between 4 and 6 or if panelists disagreed. The consensus method did not force agreement. We defined disagreement when at least two panelists rated an indication as appropriate and at least two rated that same indication as inappropriate, regardless of the median rating.

**Results**

*Overall Findings*

The consensus process produced a simplified approach to the patient with stroke risk factors and was characterized by frequent agreement with respect to optimal risk reduction. Of the 389 indications for stroke prevention, 43% were rated as appropriate, 22% as uncertain, and 35% as inappropriate. According to our definition, the panel disagreed

on about 5% of the indications in the final ratings, decreasing from 25% in the first-round ratings. Disagreement was highest (20% of the 20 indications) for the selection of specific antiplatelet agent or agents. Panelists also disagreed about the appropriateness of continuing aspirin as sole therapy in patients who had a cerebral ischemic event while on aspirin, and the role of aspirin plus clopidogrel in patients who had not experienced a cerebrovascular ischemic event while on aspirin alone. None of the 9 indications pertaining to the choice of initial antihypertensive therapy had disagreement.

**Treatment Modality-specific Findings**

Despite the complexity of the rating structure and the many permutations of multiple clinical factors, the final ratings were readily grouped for simpler presentation by the appropriateness methodology. We collapsed the separate indications in which the categorization of appropriateness did not differ on the basis of clinical factors (eg, all were appropriate, uncertain, or inappropriate).

*Carotid endarterectomy and angioplasty.* The 96 indications pertaining to carotid endarterectomy and carotid angioplasty could be simplified into 10 scenarios (Table 1). For almost all of these scenarios, the factors of clinical presentation (large vessel vs lacunar syndrome) and cardiac rhythm status (presence vs absence of atrial fibrillation) did not influence the final ratings. Patients with <50% or 100% stenosis of the ipsilateral carotid artery were rated as inappropriate surgical candidates. For patients with 70% to 99% stenosis of the ipsilateral carotid artery and either no or small ulceration, or large ulcerative lesion, a carotid endarterectomy was rated as appropriate if the risk associated with the procedure was ≤6%. It was rated as uncertain for patients with no or small ulceration and a surgical risk >6%. As another example, carotid angioplasty was rated as inappropriate for all patients with ipsilateral stenosis of 50% to 69% and those with 70% to 99% stenosis and procedural

**Table 2.** Role of medical therapy

	No atrial fibrillation	Atrial fibrillation	
		Low bleeding risk	High bleeding risk
Antiplatelet therapy	Appropriate	Not on warfarin: Appropriate On warfarin: Uncertain	Not on warfarin: Appropriate On warfarin: Inappropriate
Anticoagulation	Inappropriate	Appropriate	Uncertain

risk >6%. Angioplasty was rated as uncertain for patients with 70% to 99% stenosis and procedural risk ≤6%. Table 1 contains additional clinical scenarios.

*Antithrombotic therapy.* The 120 scenarios for antiplatelet therapy and anticoagulation could be simplified to 7 indications (Table 2). For patients without atrial fibrillation, antiplatelet therapy was rated as appropriate and anticoagulation was rated as inappropriate. For patients with atrial fibrillation, anticoagulation was rated as appropriate for patients with a low bleeding risk and uncertain for patients with a high bleeding risk. For patients with atrial fibrillation, antiplatelet therapy was rated as appropriate when the patient was not also receiving warfarin. If the patient was receiving warfarin, then antiplatelet therapy was rated uncertain for those patients with a low bleeding risk and inappropriate for those with a high bleeding risk. With only one exception, the degree of carotid stenosis and presence or absence of a carotid ulcerative lesion had no impact on the ratings.

Table 3 summarizes the selection of specific agents for patients rated as appropriate for antiplatelet therapy. The presence or absence of coexisting stable coronary artery disease did not influence the choice of therapy. Ticlopidine was rated inappropriate. Clopidogrel and the combination of aspirin plus extended-release dipyridamole were both rated as appropriate, although the former had a lower median score (9 vs 7, respectively). Aspirin alone was rated as appropriate if there had been no prior event while on aspirin, and uncertain if a prior event had occurred while on aspirin. The combination of aspirin plus clopidogrel was rated as appropriate if the patient had a cerebrovascular event while on aspirin alone, and uncertain if no prior event occurred while on aspirin.

*Antihypertensive therapy.* Table 4 summarizes the treatment target for antihypertensive therapy. For patients

presenting with a systolic blood pressure ≥160 mm Hg, the panel rated it appropriate to achieve a blood pressure <140/85 mm Hg (either at 3 or 12 months), uncertain for a target <130/80 mm Hg at 3 months, but appropriate to achieve that target after 1 year. For patients presenting with a blood pressure of 140 to 159 mm Hg, the panel rated the target of <130/80 mm Hg as appropriate either after 3 or 12 months. The panel rated inappropriate a target blood pressure of <120/75 mm Hg.

Table 5 summarizes the initial choice of antihypertensive therapy. Diuretics, β-blockers, ACE inhibitors/ARBs, or the combinations of diuretic/ACE and diuretic/ARB were rated as appropriate first-line regimens. Although both rated as appropriate, the combination regimen of diuretic/ACE has a higher median score than the combination regimen of diuretic/ARB (9 vs 7). Initial regimens containing calcium channel blockers or the combination of a diuretic and a β-blocker were rated as uncertain.

Table 6 presents the choice of add-on therapy for those patients who did not initially achieve target blood pressure levels. For patients who were already receiving a diuretic, the addition of an ACE inhibitor, ARB, or β-blocker was rated as appropriate, whereas the addition of calcium channel blocker was rated uncertain. For patients on a β-blocker, the addition of a diuretic, ACE inhibitor, or ARB were all rated as appropriate, although with slightly different median scores (9, 8, and 7, respectively). Other therapeutic options are listed in Table 6.

**Discussion**

We studied the appropriateness of 5 major interventions for recurrent stroke prevention that were supported

**Table 3.** Antiplatelet therapy

Cerebrovascular event	Ticlopidine	Clopidogrel	Aspirin	Extended-release dipyridamole + Aspirin	Clopidogrel + Aspirin
Prior event did not occur on aspirin	Inappropriate	Appropriate	Appropriate	Appropriate	Uncertain*
Prior event occurred on aspirin	Inappropriate	Appropriate	Uncertain	Appropriate	Appropriate*

\*Match trials results pending.

**Table 4.** Blood pressure target

Current systolic blood pressure	Target blood pressure (mm Hg)			
	<140/85	<130/80		<120/75
		3 mo or 1 y	After 3 mo	
≥180	Appropriate	Uncertain	Appropriate	Inappropriate
160-179	Appropriate	Uncertain	Appropriate	Inappropriate
140-159	Appropriate	Appropriate	Appropriate	Inappropriate

by prior clinical trial evidence of efficacy and safety. The interventions included carotid endarterectomy; carotid angioplasty; and antiplatelet, anticoagulation, and anti-hypertensive therapies. Our approach is unique as we incorporated more complex clinical scenarios encountered by primary care physicians that have not been addressed previously in clinical trials or other evidence-based reviews. Therefore, our guidelines may have greater applicability for primary care physicians as they represent both routine and complex practice scenarios. Primary care physicians see a variety of patients with stroke who may have multiple risk factors and more than one possible cause for stroke. Our guidelines have captured these more common complex contingencies and have provided a road map for recurrent stroke prevention in these and more routine cases.

For carotid endarterectomy, the panel indicated that appropriate candidates included patients with 50% to 69% symptomatic stenosis and 70% to 99% symptomatic stenosis whether there was no or small ulceration, or large ulceration. Our panel broadly supported the use of carotid endarterectomy when there was 50% to 99% symptomatic carotid stenosis and a surgical risk ≤ 6%. The panel supported endarterectomy when the risk of operation was ≥6% in the group with larger ulceration and 70% to 99% stenosis in selected stroke subtypes (Table 1). The panel rated the use of this procedure inappropriate for patients with <50% or 100% ipsilateral symptomatic carotid stenosis. Uncertainty was noted, however, in those at higher risk of complications after endarterectomy (>6%) in all categories of symptomatic stenosis in the 50% to 99% range with the exception of those who had a large ulceration of the carotid artery. Overall, the presence of atrial fibrillation or lacunar stroke syndrome had little influence on our panel’s decision to recommend carotid endarterectomy.

Carotid endarterectomy has been the subject of a prior appropriateness assessment. In 1988, Winslow et al<sup>16</sup> reported that carotid endarterectomy was substantially overused and estimated that it was used inappropriately 32% of the time. This study was published before the availability of the results of pivotal trials that compared carotid endarterectomy plus medical management with medical management alone.<sup>17-20</sup> Overall, these latter

studies have shown that operation is of some benefit for patients with 50% to 69% symptomatic carotid stenosis, highly beneficial for those with 70% symptomatic carotid stenosis or greater but without near occlusion, and not beneficial for most patients with <50% symptomatic carotid stenosis.<sup>21</sup> In North America the benefit of endarterectomy for symptomatic carotid disease is thought to outweigh the risk if perioperative complications occur in ≤6% to 7% of patients.

Our guidelines support the results of prior studies of endarterectomy<sup>17-21</sup> but, in addition, provide new information. Patients who are at high risk for endarterectomy and have high-grade symptomatic carotid stenosis (70%-99%) and a large ulceration should be considered for operation, as should those with atrial fibrillation. Thus, we have provided a clear threshold for endarterectomy in those at high risk of operation and in those with atrial fibrillation.

The panel also evaluated the role of carotid angioplasty because this procedure is being performed relatively frequently in practice, and we thought that it was important to make a guideline statement about its use even though there were only preliminary or smaller scale clinical trial data available for review. The panel rated the role of carotid angioplasty as inappropriate in most cases or of uncertain benefit. Clinical trials are underway to further evaluate the safety and efficacy of carotid angioplasty

**Table 5.** Initial choice of antihypertensive therapy

Therapy	
Diuretic	Appropriate
β-Blocker	Appropriate
ACE inhibitor	Appropriate
ARB	Appropriate
Diuretic + ACE	Appropriate
Diuretic + ARB	Appropriate
Calcium channel blocker	Uncertain
Diuretic + calcium channel blocker	Uncertain
Diuretic + β-blocker	Uncertain

Abbreviations: ACE, Angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

**Table 6.** Choice of antihypertensive add-on therapy

	Diuretic	ACE	ARB	Beta blocker	Calcium channel blocker
Diuretic		Appropriate			Uncertain
Beta blocker	Appropriate				
Calcium channel blocker				Uncertain	
ACE inhibitor	Appropriate		Appropriate	Uncertain	
ARB	Appropriate				
Diuretic + ACE	Appropriate				
Diuretic + ARB				Appropriate	Uncertain
Diuretic + beta blocker	Appropriate				
Diuretic + calcium channel blocker			Appropriate	Uncertain	

Abbreviations: ACE, Angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

versus carotid endarterectomy. Until results of the pending trials are available, the panel thought that the benefit to patients from this intervention was uncertain. The results of a recent trial suggest a potential role for this developing therapy may evolve in the foreseeable future.<sup>22</sup>

Long-term administration of oral anticoagulation therapy has been considered a standard for recurrent stroke prevention in persons with atrial fibrillation who are at high risk of stroke recurrence.<sup>5,23-25</sup> Our expert panel ranked the use of anticoagulation appropriate when the bleeding risk was low and uncertain when the bleeding risk was high. In the absence of atrial fibrillation, the panel rated the use of anticoagulation inappropriate. Overall, the degree of carotid stenosis and the presence or absence of an ulcerative lesion had little impact on the panel's final rating. Prior guidelines for recurrent stroke prevention in atrial fibrillation have not addressed the concomitant occurrence of various degrees of carotid stenosis or the presence or absence of an ulcerative carotid lesion. Our guideline gives a clear indication for the use of anticoagulation in these patients. Anticoagulation therapy is being underused for stroke prevention in atrial fibrillation.<sup>10,11</sup> The degree of carotid stenosis or the presence or absence of a carotid ulcerative lesion should not deter the primary care physician from administering this type of therapy when there are no contraindications.

Antiplatelet agent administration was judged to be appropriate for those patients with atrial fibrillation who were not on warfarin therapy. For those patients with atrial fibrillation on warfarin, the panel rated the use of antiplatelet agents of uncertain value if there was a low

bleeding risk and inappropriate in the presence of a high bleeding risk. These ratings are consistent with prior clinical trial evidence of recurrent stroke prevention,<sup>5,26</sup> but add new information in that we do not believe that antiplatelet agents are necessary in patients with atrial fibrillation who are already taking warfarin.

Evidence-based guidelines recommend the use of either aspirin (50-325 mg/day), aspirin (25 mg) plus extended-release dipyridamole (200 mg twice daily), or clopidogrel (75 mg/day) for recurrent stroke prevention.<sup>5</sup> Our expert panel rated any of these 3 therapies as being appropriate for persons with an ischemic cerebral event that did not occur while taking aspirin, but rated ticlopidine as being inappropriate and the combination of aspirin plus clopidogrel as being of uncertain value. For those with a prior cerebral ischemic event while taking aspirin, aspirin plus extended-release dipyridamole, clopidogrel, and aspirin plus clopidogrel were considered appropriate therapies. However, aspirin alone was of uncertain value, and ticlopidine was rated as inappropriate.

Administration of combination antiplatelet therapy has become popular in recurrent stroke prevention practice. Aspirin plus extended-release dipyridamole<sup>27</sup> has been approved for use by the Food and Drug Administration for recurrent stroke prevention in persons with transient ischemic attack or prior ischemic stroke. Our guideline provides new information by clarifying the role of combination therapy with aspirin and clopidogrel while we await the results of ongoing clinical trials that are testing this therapy.

Our panel rated the target blood pressure goal of <130/80 mm Hg as appropriate after 1 year's time, but

<120/75 mm Hg as inappropriate at this same time point. At 3 months after stroke, blood pressure lowering to <140/85 mm Hg was rated as appropriate whether the current systolic blood pressure was  $\geq$ 180 mm Hg or as low as 140 to 159 mm Hg, but uncertain for a blood pressure target of <130/80 mm Hg if the current systolic blood pressure was  $\geq$ 160 mm Hg. These guidelines reflect recent clinical trial evidence that lowering blood pressures reduces the risk of stroke recurrence.<sup>28</sup> The Perindopril Protection Against Recurrent Stroke Study showed that a 9/4-mm Hg drop in blood pressure in persons with a priori ischemic or hemorrhagic stroke or transient ischemic attack who were treated with the ACE inhibitor perindopril (with or without the diuretic indapamide) was associated with a relative risk reduction of stroke of 28% (95% confidence interval 17-38;  $P < .0001$ ).<sup>29</sup> Combination therapy with perindopril plus indapamide was associated with a blood pressure drop of 12/5 mm Hg and a reduction of stroke risk by 43%, whereas single therapy with perindopril reduced blood pressure by only 5/3 mm Hg and produced no significant reduction in the risk of stroke. However, no trials have specifically addressed the optimal blood pressure target for recurrent stroke prevention,<sup>30</sup> and these guidelines provide assistance to clinicians who face this decision on a daily basis.

A broad range of classes of antihypertensive medication was rated as appropriate for initial therapy as was combination therapy with a diuretic and ACE inhibitor or ARB (Table 5). However, calcium channel blockers alone or in combination with a diuretic, and a diuretic  $\beta$ -blocker combination were rated as uncertain. Uncertainty about the use of calcium channel blockers and  $\beta$ -blockers in general practice may have been influenced by the results of two recently published clinical trials.<sup>31,32</sup> Standard guidelines, however, recommend diuretics as an initial therapy for uncomplicated hypertension, whereas in more complicated cases (eg, diabetics, those with heart failure or substantial proteinuria) the use of an ACE inhibitor or ARB is indicated. Most recently stroke has been recognized as a specialized condition benefiting from the use of an ACE and diuretic.<sup>30</sup>

Finally, our panel rated a host of classes of antihypertensive medication as appropriate add-on therapy for patients who did not achieve the initially determined target blood pressure goal. These results are summarized in Table 6. Overall, the panel rated the addition of ACE inhibitors, ARBs, or  $\beta$ -blockers to first-line diuretic therapy as appropriate and the addition of calcium channel blockers and  $\beta$ -blockers, in some circumstances, as of uncertain value. Clinical trial evidence for administration of appropriate add-on therapy for blood pressure control in recurrent stroke prevention is lacking.<sup>30</sup> Our guideline helps to narrow this gap for primary care physicians.

## Conclusion

In primary care practice, adherence to stroke and cardiovascular disease interventions may be relatively low.<sup>33-36</sup> Patients, for example, may be overwhelmed by financial cost and multiplicities of therapies, concerned about side effects of medications or experiencing them, confused about the pathophysiologic process and rationale for interventions, and lacking motivation to be partners in the prevention process. They may also develop complications of stroke such as depression or cognitive impairment that may interfere with successful intervention efforts. Similarly, primary care physicians, confronted by a complex recurrent stroke prevention case, may not be familiar with stroke pathophysiology and rationale for recurrent prevention, may find themselves in a situation that requires a very labor-intensive approach to management, and may not be well-trained to communicate with patients to affect substantial stroke prevention. Use of multiple interventions poses a further challenge for the patient and treating physician.

Mechanisms that simplify therapy to its essentials and allow for a sustained therapeutic approach may increase compliance and effectiveness of stroke prevention therapy.<sup>37</sup> Organized stroke care is one of the mechanisms to help achieve this goal.<sup>10,38</sup> Strategies to improve adherence such as providing patient reminders to attend office visits, clinic orientations, education about medications, developing patient agreements for return visits, self-monitoring, interventions that promote patient participation, multilevel interventions, and those that incorporate comprehensive interventions may lead to improved outcomes.<sup>39-45</sup> Our guideline assists in this process by allowing primary care physicians to focus on the complexity of high-risk medical conditions and concomitant stroke mechanisms that are specifically germane to recurrent stroke risk reduction, and provides a road map to therapy for stroke prevention in these patients. Embedded within the complexity of recurrent stroke prevention is the recognition of the need for multimodality therapy.<sup>46</sup>

A summary of our ratings or road map for the 5 recurrent stroke preventions is listed in Table 7. Primary care physicians may use this guideline to assist them in routine and more complex decision making for recurrent stroke prevention. A next step would be to implement the guideline in primary care practice to determine how this consensus-based road map performs and to assess patient outcomes.

## Study Limitations

A limitation of any consensus process is the extrapolation beyond known evidence. Although clinical trials have examined the risks and benefits of carotid endarterectomy in subgroups on the basis of angiographic findings, little evidence exists for the efficacy of the procedure



**Table 7.** Summary of appropriate ratings for carotid revascularization, antiplatelet therapy, anticoagulation therapy, and management of blood pressure for recurrent stroke prevention

Intervention	Indication	Appropriateness	Evidence basis
Carotid endarterectomy for ipsilateral stenosis	50%-99% and surgical risk $\leq$ 6%	Appropriate	I
	<50% or 100%	Inappropriate	I
	70%-99% with large ulcer and surgical risk > 6%*	Appropriate	II
	50%-69% and no ulcer or ulcer any size,† or 70%-99% and no or small ulcer and surgical risk > 6%	Uncertain	II
Carotid angioplasty for ipsilateral stenosis	<50, 100%, 50%-69%, or 70%-99% and surgical risk > 6%	Inappropriate	II
	70%-99% and surgical risk $\leq$ 6%	Uncertain	II
Warfarin	Atrial fibrillation and low bleeding risk	Appropriate	I
	Atrial fibrillation and high bleeding risk	Uncertain	III
<b>Antiplatelet therapy: Not previously on antiplatelet agent</b>			
Aspirin		Appropriate	I
Aspirin plus extended-release dipyridamole		Appropriate	I
Clopidogrel		Appropriate	I
Aspirin plus clopidogrel		Uncertain	II‡
Ticlopidine		Inappropriate	III
<b>Antiplatelet therapy: Prior cerebral ischemic event while on aspirin</b>			
Aspirin		Uncertain	III
Aspirin plus extended-release dipyridamole		Appropriate	III
Clopidogrel		Appropriate	III
Aspirin plus clopidogrel		Appropriate	III
Ticlopidine		Inappropriate	III
<b>Initial choice of antihypertensive therapy</b>			
Diuretics		Appropriate	I
$\beta$ -Blocker		Appropriate	I
ACE		Appropriate	I
ARB		Appropriate	I
Diurectic plus ACE or ARB		Appropriate	I
Calcium channel blocker alone or with diurectic		Uncertain	I
Diurectic plus $\beta$ -blocker		Uncertain	III

Abbreviations: ACE, Angiotensin-converting enzyme; ARB, angiotensin receptor blocker; I, well-designed randomized controlled trial; II, randomized clinical trials with design deficiencies for stroke-prevention outcomes; III, epidemiologic analysis, case series, and other clinical reports.

\*Uncertain if atrial fibrillation or lacunar syndrome.

†Inappropriate if atrial fibrillation or lacunar syndrome.

‡MATCH trial results pending.

for patients with atrial fibrillation, and no trial had adequate power to examine the combination of factors and stenosis determined by conventional cerebral angiogra-

phy in conjunction with atrial fibrillation or lacunar syndrome. Similarly, there is a paucity of data to guide the use of various types of medical therapy (e.g., antithrom-

botic agents, blood pressure-lowering agents) on the basis of the extent of carotid stenosis. The expert panel had evidence for the individual clinical factors and used its judgment to assess the appropriateness when patients presented with combinations of those factors. Any guideline that uses a consensus process can be subject to reviewer bias. This can exist because of the lack of prospective data, lack of depth of reviewer experience, or an unrepresentative sampling of experts to staff a panel. By starting with an evidence-based review, and selecting a geographically and clinically diverse group of stroke experts, we have made every effort to avoid bias. We acknowledge that neither broad clinical experience nor the extrapolation of randomized controlled clinical trial information from a narrowly defined group of patients to a more liberally defined group provides a guarantee about the correctness of any opinion.

The RAND Method has been shown to have both reliability and validity, and guidelines using the approach have strongly reflected the underlying evidence when it was available.<sup>16,47-49</sup> Finally, we were not able to directly assess patient preferences. However, during the course of discussion at the panel's face-to-face meeting, patient preference was mentioned as an important factor when making appropriateness decisions for all interventions.

## Appendix I

### *Definitions of Key Terms*

**Mild stroke:** No symptoms or symptoms that might include slight disability. Patient is still able to perform daily activities without assistance or able to look after own affairs without assistance (on the basis of Rankin score of 0, 1, or 2). See Appendix II for reference and Rankin score description.

**Lacunar syndrome in the carotid or anterior circulation:** Evidence of a typical lacunar syndrome (no cortical involvement). See Appendix II for detailed TOAST criteria.

**Large vessel syndrome in the carotid or anterior circulation:** Evidence of a typical cortical syndrome. See Appendix II for detailed TOAST criteria.

**Risk  $\leq$  6%:** A perioperative risk of stroke or death less than or equal to 6% during the 30-day postoperative period. Perioperative risk includes a combination of patient, physician, and hospital risk factors.

**Risk  $>$  6%:** A perioperative risk of stroke or death greater than 6% based during the 30-day postoperative period. Perioperative risk includes a combination of patient, physician, and hospital risk factors.

**High bleeding risk:** Recent gastrointestinal bleeding or patient at high risk for falls (e.g., prior frequent falls or difficulty with balance or gait).

**Low bleeding risk:** No recent gastrointestinal bleeding. Patient is not at high risk for falls.

Degree of stenosis:

- Ipsi  $<$  50%: Carotid artery stenosis as determined by angiography.
- Ipsi 50% to 69%: Carotid artery stenosis as determined by angiography.
- Ipsi 70% to 99%: Carotid artery stenosis as determined by angiography.
- Ipsi 100%: Carotid artery stenosis as determined by angiography.

**No or small ulceration:** Lesions less than 10 mm<sup>2</sup> measured by angiography, where the measure is the product of the depth and length of the ulcer. Assume that the measurement is on the basis of the angiographic view of the ulceration at its largest point.

**Large ulcerative lesion:** Lesions 10 mm<sup>2</sup> or larger measured by angiography, where the measure is the product of the depth and length of the ulcer. Assume that the measurement is on the basis of the angiographic view of the ulceration at its largest point.

**Cognitive impairment:** impairment in memory, language, executive function, or visuospatial function causing difficulties with shopping, writing checks, balancing a checkbook, or other similar activity.

## Appendix II

### *Rankin Score Description*

- 0 = No symptoms at all
- 1 = No significant disability despite symptoms; able to carry out all usual duties and activities
- 2 = Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
- 3 = Moderate disability; requiring some help, but able to walk without assistance
- 4 = Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
- 5 = Severe disability; bedridden, incontinent, and requiring constant nursing care and attention
- 6 = Dead

Reference: Rankin J. Cerebral vascular accidents in patients over the age of 60. *Scott Med J* 1957;2:200-215.

### *TOAST Criteria for Lacunar Syndrome*

Lacunar or Deep Hemispheric Syndrome (no cortical involvement):

- Pure motor hemiparesis
- Pure sensory stroke
- Ataxic hemiparesis
- Dysarthria-clumsy hand
- Hemichorea/ballism

*TOAST Criteria for Large Vessel Syndrome*

## Major or Minor Hemispherical Syndrome

Aphasia with hemiparesis, hemisensory loss, and/or homonymous hemianopia

Nondominant hemispherical syndrome with hemiparesis, hemisensory loss, and/or homonymous hemianopia

Anterior cerebral artery syndrome (cortical)

Broca aphasia without hemiparesis

Conduction aphasia without hemiparesis

Wernicke aphasia without other signs

Aphasia with vanishing hemiparesis/mild motor signs

Isolated homonymous hemianopia

Homonymous hemianopia with associated behavior signs

Pure nondominant behavior signs

Reference: NIH-sponsored Trial of Organon 10172 in Acute Stroke Treatment (TOAST) study.

**References**

- Bonita R, ed. Stroke prevention: A global perspective. New York: Oxford University Press, 2001.
- Hickenbottom S, Fendrick A, Kutcher J, et al. A national study of the quantity and cost of informal caregiving for the elderly with stroke. *Neurology* 2002;58:1112-1120.
- Gorelick P, Sacco R, Smith D, et al. Prevention of a first stroke: A review of guidelines and a multidisciplinary consensus statement from the National Stroke Association. *JAMA* 1999;281:1112-1120.
- Goldstein L, Adams R, Becker K, et al. Primary prevention of ischemic stroke: A statement for healthcare professionals from the Stroke Council of the American Heart Association. *Circulation* 2001;103:163-182.
- Albers G, Amarenco P, Easton J, et al. Antithrombotic and thrombolytic therapy for ischemic stroke. *Chest* 2001;119:300S-320S (suppl).
- European Committee SIE. European Stroke Initiative recommendations for stroke management. *Cerebrovasc Dis* 2000;10:335-351.
- Strauss S, Majumdar S, McAlister F. New evidence for stroke prevention: Scientific review. *JAMA* 2002;288:1388-1395.
- Pearson T, Blair S, Daniels S, et al. AHA guidelines for primary prevention of cardiovascular disease and stroke, 2002 update: Consensus panel guide to comprehensive risk reduction for adult patients without coronary or other atherosclerotic vascular disease. American Heart Association Science Advisory and Coordinating Committee. *Circulation* 2002;106:388-391.
- Antithrombotic Collaboration. Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71-86.
- Holloway R, Benesch C, Rush S. Stroke prevention: Narrowing the evidence-practice gap. *Neurology* 2000;54:1899-1906.
- Hart R, Bailey R. An assessment of guidelines for prevention of ischemic stroke. *Neurology* 2002;59:977-982.
- Helgason C, Watkins F, Jobe T. Measurable differences between sequential and parallel diagnostic decision processes for determining stroke subtype: A representation of interacting pathologies. *Thromb Haemost* 2002;88:210-212.
- Park R, Fink A, Brook R, et al. Physician ratings of appropriate indications for three procedures: Theoretical indications vs indications used in practice. *Am J Public Health* 1989;79:445-447.
- Fitch K, Bernstein S, Aguilar M, et al. The RAND/UCLA appropriateness method user's manual. Santa Barbara: The RAND Corporation, 2001.
- Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: Results from the National Registry of Atrial Fibrillation. *JAMA* 2001;285:2864-2870.
- Winslow C, Solomon D, Chassin M, et al. The appropriateness of carotid endarterectomy. *N Engl J Med* 1988;318:721-727.
- European Group CSTC. MRC European Carotid Surgery Trial: Interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. *Lancet* 1991;337:1235-1243.
- North Collaborators ASCET. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991;325:445-453.
- European Group CSTsC. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: Final results of the MRC European Carotid Surgery Trial (ECST). *Lancet* 1998;351:1379-1387.
- Barnett H, Taylor D, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. *N Engl J Med* 1998;339:1415-1425.
- Rothwell P, Eliasziw M, Gutnikov S, et al. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet* 2003;361:107-116.
- Gray WA. A cardiologist in the carotids. *J Am Coll Cardiol* 2004;43:1602-1605.
- European Group AFTES. Secondary prevention in non-rheumatic atrial fibrillation after transient ischemic attack or minor stroke. *Lancet* 1993;342:1255-1262.
- Hart R, Halperin J. Atrial fibrillation and thromboembolism: A decade of progress in stroke prevention. *Ann Intern Med* 1999;131:688-695.
- Stroke Study PiAFI. Patients with nonvalvular atrial fibrillation at low risk of stroke during treatment with aspirin. *JAMA* 1998;279:1273-1277.
- Mohr J, Thompson J, Lazar R, et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. *N Engl J Med* 2001;345:1444-1451.
- Diener H, Cunha L, Forbes C, et al. European Stroke Prevention Study 2: Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* 1996;143:1-13.
- Gorelick P. New horizons for stroke prevention: PROGRESS and HOPE. *Lancet Neurol* 2002;1:149-156.
- PROGRESS Group C. Randomized trial of a perindopril-based blood-pressure lowering regimen among 6105 individuals with previous stroke or transient ischemic attack. *Lancet* 2001;358:1033-1041.
- Chobanian A, Bakris G, Black H, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report. *JAMA* 2003;289:2560-2671.

31. The Group ALLHAT. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288:2981-2997.
32. Dahlof B, Devereux R, Kjeldsen S, et al. Cardiovascular morbidity and mortality in the Losartan Intervention for Endpoint reduction in hypertension study (LIFE): A randomised trial against atenolol. *Lancet* 2002;359:995-1003.
33. Ruland S, Raman R, Chaturvedi S, et al. for the AAASPS Investigators. Awareness, treatment, and control of vascular risk factors in African Americans with stroke. *Neurology* 2003;60:54-68.
34. Kernan W, Viscoli C, Brass L, et al. Blood pressure exceeding national guidelines among women after stroke. *Stroke* 2003;31:415-419.
35. Qureshi A, Suri M, Guterman L, et al. Ineffective secondary prevention in survivors of cardiovascular events in the US population: Report from the Third National Health and Nutrition Examination Survey. *Arch Intern Med* 2001;161:415-419.
36. Nieto F, Alonso J, Chambless L, et al. Population awareness and control of hypertension and hypercholesterolemia: The Atherosclerosis Risk in Communities Study. *Arch Intern Med* 1995;155:677-684.
37. Tipton M, Fleming M, eds. Stroke prevention in managed care: A five dimensional health improvement model. New York: Parthenon Publishing, 2002.
38. Gorelick P, ed. An integrated approach to stroke prevention. 3rd ed. London: Science Press, 2002.
39. Miller N, Hill M, Kottke T, et al. The multilevel compliance challenge: Recommendations for a call to action, a statement for healthcare professionals. *Circulation* 1997;95:1085-1090.
40. Macharia W, Leon G, Rowe B, et al. An overview of intervention to improve compliance with appointment keeping for medical services. *JAMA* 1992;267:1813-1817.
41. Devine E, Reifschneider E. A meta-analysis of the effects of psychosocial care in adults. *Nurs Res* 1995;44:237-245.
42. Mullen P, Somons-Morton D, Ramirez G, et al. A meta-analysis of trials evaluating patient education and counseling for three groups of preventive health behaviors. *Patient Educ Couns* 1997;32:157-173.
43. The Center for Health Studies of Group Health Cooperative of Puget Sound. An indexed bibliography of self-management for people with chronic disease (ed 1). Washington, DC, Center for the Advancement of Health, 1996.
44. Haynes R, McKibbon K, Kanani E. Systematic review of randomized trials of interventions to assist patients to follow prescriptions for medications. *Lancet* 1996;348:383-386.
45. Roth H, Caron H, Hsi B. Estimating a patient's cooperation with his regimen. *Am J Med Sci* 1971;262:269-273.
46. Gorelick P. Stroke prevention therapy beyond anti-thrombotics: Unifying mechanisms in ischemic stroke pathogenesis and implications for therapy. An invited review. *Stroke* 2002;33:862-875.
47. Merrick N, Fink A, Park R, et al. Derivation of clinical indications for carotid endarterectomy by and expert panel. *Am J Public Health* 1987;77:187-190.
48. Kravitz R, Laouri M, Kahan J, et al. Validity of criteria used for detecting underuse of coronary revascularization. *JAMA* 1995;274:632-638.
49. Shekelle P, Kahan J, Bernstein S, et al. The reproducibility of a method to identify the overuse of medical procedures. *N Engl J Med* 1998;338:1888-1895.