

# National Stroke Association Guidelines for the Management of Transient Ischemic Attacks

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**Objective:** Transient ischemic attacks are common and important harbingers of subsequent stroke. Management varies widely, and most published guidelines have not been updated in several years. We sought to create comprehensive, unbiased, evidence-based guidelines for the management of patients with transient ischemic attacks.

**Methods:** Fifteen expert panelists were selected based on objective criteria, using publication metrics that predicted nomination by practitioners in the field. Prior published guidelines were identified through systematic review, and recommendations derived from them were rated independently for quality by the experts. Highest quality recommendations were selected and subsequently edited by the panelists using a modified Delphi approach with multiple iterations of questionnaires to reach consensus on new changes. Experts were provided systematic reviews of recent clinical studies and were asked to justify wording changes based on new evidence and to rate the final recommendations based on level of evidence and quality. No expert was allowed to contribute to recommendations on a topic for which there could be any perception of a conflict of interest.

**Results:** Of 257 guidelines documents identified by systematic review, 13 documents containing 137 recommendations met all entry criteria. Six iterations of questionnaires were required to reach consensus on wording of 53 final recommendations. Final recommendations covered initial management, evaluation, medical treatment, surgical treatment, and risk factor management.

**Interpretation:** The final recommendations on the care of patients with transient ischemic attacks emphasize the importance of urgent evaluation and treatment. The novel approach used to develop these guidelines is feasible, allows for rapid updating, and may reduce bias.

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A transient ischemic attack (TIA) has been defined classically as “rapidly developed clinical signs of focal or global disturbance of cerebral function lasting fewer than 24 hours, with no apparent non-vascular cause,”<sup>1</sup>

with a more recent proposal to alter the definition to “a brief episode of neurological dysfunction caused by a focal brain or retinal ischemia, with clinical symptoms typically lasting less than an hour, and without

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evidence of acute infarction.”<sup>2</sup> Based on the former definition, an estimated 240,000 TIAs are diagnosed every year in the United States,<sup>3</sup> and the annual number of undiagnosed TIAs likely exceeds this.<sup>4</sup> Recent studies have shown that stroke risk after TIA is high, particularly in the first few days.<sup>3,5–8</sup> Nonetheless, management of TIA has been highly variable with little emphasis on urgency.<sup>9,10</sup>

Consensus guidelines may be useful in improving care, reducing practice variability, and reducing costs and burden of disease, particularly when evidence is evolving rapidly.<sup>11–13</sup> Recently, there has been concern about the quality of methods used to produce guidelines and the potential for bias in the recommendations.<sup>14–16</sup> Several international organizations have sponsored guidelines development for TIA, but most of these were published years ago; some guidelines are meant to apply only to local settings or specific aspects of care, and recommendations have varied among them. Ideal guidelines would be comprehensive, current, practical, evidence-based, widely applicable, and free of perceived bias.

With sponsorship from the National Stroke Association in the United States, we sought to develop guidelines for the management of adults with recent TIA to provide comprehensive recommendations on all aspects of TIA care, broadly applicable in diverse healthcare settings in the developed world, for use by neurologists, emergency physicians, internists, and other primary care physicians. The goal was to create guidelines that would guide management to reduce subsequent risk for stroke, cardiovascular events, and other complications after TIA. We created a novel method of guidelines development to avoid common sources of perceived bias by selecting experts through a data-driven process and by developing consensus through a rigid consensus-building method that prevented overweighting of opinions from dominant personalities.<sup>17</sup> The method was designed to standardize and streamline the process and to make updating more efficient as new evidence becomes available.

## Materials and Methods

We undertook six primary steps to develop TIA guidelines: (1) systematic review of existing guidelines; (2) abstraction of recommendations from included guidelines documents; (3) rating of quality of these recommendations by an expert panel; (4) selection of essential, nonoverlapping recommendations; (5) editing of these recommendations using a modified Delphi approach; and (6) rating of the new recommendations in comparison with prior recommendations.

### Systematic Review of Existing Guidelines

We sought to identify all published guidelines documents in English with specific recommendations on the management of patients with TIA (Fig). The MeSH headings (“cerebro-

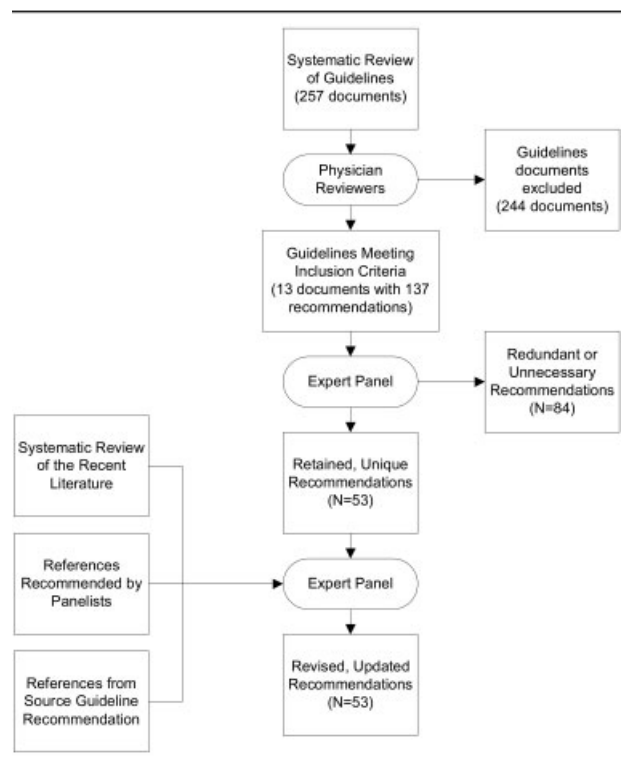


Fig. Diagram showing the steps used to generate new guidelines recommendations. A systematic review located 257 prior guidelines documents with recommendations on transient ischemic attack, of which 13 (containing 137 recommendations) met entry criteria. From these documents, the expert panel identified 53 unique high-quality recommendations in specific topic areas and, aided by a systemic review of recent literature and other sources, updated and revised them using a modified Delphi approach.

vascular accident”; “cerebrovascular disorders”; “ischemic attack, transient”) and keywords (“stroke,” “transient ischemic attack”) were searched in PubMed for January 1, 1995, through June 30, 2005, limited to “Practice Guidelines.” We also searched the National Guidelines Clearinghouse ([www.guidelines.gov](http://www.guidelines.gov)), the National Institute for Clinical Excellence ([www.nice.org.uk](http://www.nice.org.uk)), Organising Medical Networked Information ([omni.ac.uk](http://omni.ac.uk)), and National Electronic Library for Health ([www.nelh.nhs.uk](http://www.nelh.nhs.uk)). Publications that cited existing guidelines, identified through the Institute of Scientific Information (ISI) Web of Science, were also reviewed, and topic experts were asked to identify any additional sources.

Two independent physician reviewers, with a third adjudicating disagreements, reviewed identified guidelines for the following inclusion criteria: (1) is a guidelines document with specific evidence-based, graded recommendation for physicians about treatment; (2) is directly relevant to patients presenting with or having a history of TIA; (3) is sponsored by a governmental or nonprofit organization; (4) has no later guidelines from the same institution that completely encompass the same clinical issues; (5) has guidelines recommendations designed to be relevant to a regional, national, or international audience; (6) is published in print or on the Web since January 1, 1995; and (7) the entire guidelines docu-

Table 1. Levels of Evidence

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<b>Category 1:</b> Based on evidence drawn from randomized, controlled trials (RCTs), or meta-analyses based on RCTs, that have consistent results, narrow confidence intervals, and a low risk for bias.
<b>Category 2:</b> Based on evidence drawn from RCTs with inconsistent results, or meta-analyses of such trials. This category also draws on controlled trials that are not randomized and that have large confidence intervals. Results from RCTs that are based on secondary end points are also included in the category.
<b>Category 3:</b> Based on evidence drawn from observational studies, including cohort studies with concurrent controls and case-control studies. Evidence from studies in which RCT results are generalized beyond the target population is also included.
<b>Category 4:</b> Based on evidence drawn from descriptive studies, including cross-sectional studies, case series and reports, and ecological studies. Cohort studies using historical controls are also included, together with expert medical opinion and general consensus.

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ment is freely and publicly available. Guidelines characteristics and recommendations relevant to TIA were abstracted similarly. Level of evidence was mapped to a single unified scale (Table 1); each specific prior category of evidence was mapped to a new category after review by two investigators. Four independent reviewers scored each included guidelines document based on the Appraisal of Guidelines Research & Evaluation (AGREE) criteria, with final scores generated based on standard methodology ranging from 100% (perfect adherence with recommended quality parameters) to 0% (no adherence to any parameter).<sup>18</sup> Scoring is based on averages of independent reviewers using specific criteria within five separate domains.

#### Expert Panel Selection

Expert panels are often created either through nominations of participating organizations or through informal processes guided by the chair of the writing committee. To avoid potential biases introduced in these processes, we developed a method of expert selection based on publications, after validating that the approach would be representative of a more democratic nomination process.

A survey was mailed and e-mailed to 13,353 health professionals who had expressed an interest in stroke to the National Stroke Association. These professionals included neurologists, neurosurgeons, vascular surgeons, internists, nurses, emergency medical personnel, and pharmacists. The survey asked for up to three nominations for editors of guidelines on stroke or TIA. From the 149 responses, a total of 170 people were nominated, of whom 20 received at least 3 nominations.

We had anticipated a poor response rate on the questionnaire and also recognized the importance of creating a method of identifying experts that could be implemented more rapidly and efficiently. Thus, we tested whether publication record could be used to predict nominations. We searched for research articles and reviews published in English between 1985 and 2005, with the term *transient ischemic attack*, *TIA*, *cerebrovascular disease*, or *stroke* either as the subject or in the title in the Web of Science or as keywords in PubMed. This procedure yielded 58,191 entries in the Web of Science and 161,049 in PubMed. From this list, for each author, we tallied number of publications, number of publications on human subjects (PubMed restriction), and number of citations of the author's publications. Similar numbers were calculated for publications in which the au-

thor was listed first, second, or last. Criteria for these variables were tested singly and in combination (sum, product, or union of 2 individual variables) to define rules that would identify with the greatest specificity 10 experts who had received at least 3 nominations. The product of total number of publications in the Web of Science and number of PubMed publications restricted to humans ("publication product") yielded the most specific criteria, with 9 of the top 10 experts receiving 3 or more nominations in the survey.

To select panelists with specific expertise in TIA, we performed similar searches with only the term *transient ischemic attack* or *TIA* as a subject, title word, or keyword, which yielded 11,407 publications in PubMed and 3,665 in the Web of Science. Experts were ranked based on the publication product and were invited to participate in the order of their ranking. Those who were retired were excluded.

#### Expert Review and Editing of Recommendations

We assigned the experts to topic-related panels based on their prior publications and declared potential conflicts of interest. Experts with any potential conflict of interest in a specific topic area were excluded from participation in that panel. Each panel was composed of five or six participants.

To avoid biases that may have been introduced by knowledge of the source of recommendations, we presented the abstracted recommendations without attribution to the panels of topic experts. Using a modified Delphi method,<sup>17</sup> which iteratively collects and integrates independent opinions on statement, we asked topic experts who did not have conflicts of interest to complete independently a series of Web-based questionnaires (see Fig). Experts were not brought together by telephone or in person to discuss any of the recommendations, although teleconferences were used to discuss the overall process and expectations.

In the first questionnaire, participants were asked to evaluate each recommendation based on five quality domains, rated on a nine-part Likert Scale ranging from 1 ("strongly disagree") to 9 ("strongly agree"): (1) currency (Is the recommendation based on the most up-to-date evidence available at the start of the guidelines project?); (2) correctness (Is the recommendation appropriate for patients with TIA and valid based on its given category of evidence?); (3) practicality (Is the recommendation able to be implemented and is it useful from a clinician's point of view?); (4) clarity (Is the language of the recommendation direct, unambiguous, and specific?); and (5) freedom from bias (Is the recommendation relatively

unaffected by the commercial biases that commonly affect medical research and opinion?).

In the second survey, recommendations were reordered based on correctness ratings, and experts were asked whether less correct recommendations within a specific topic area could be eliminated or integrated into the highest rated recommendation; specific wording changes for the primary recommendation were solicited. Experts were asked to make changes that improved clarity or that integrated new evidence. In the third and fourth rounds, experts reviewed each other's recommended wording changes, with the majority opinion dictating new changes to a recommendation; again, we asked whether specific recommendations could be eliminated or combined with others.

In the fifth questionnaire, experts were asked to provide additional references that would justify major wording changes for a recommendation. They were provided with a systematic review of the literature within a given topic area, generated by searching PubMed for any clinical studies that had come out after publication of the original recommendation (performed in March 2006, searching keywords "TIA" or "transient ischemic attack" together with terms reflecting the specific subtopic area, limited to human subjects, English, and using the "narrow" clinical study search strategy). Also included were references for the evidence used to justify the original recommendation and any newer references cited as relevant by the reviewing experts (see Fig). Experts were asked to make any additional wording changes based on the evidence and to provide a level of evidence for the recommendations.

Finally, in the sixth questionnaire, all 15 experts were asked to rate each of the 53 new recommendations, as well as the primary source recommendation using the 5 quality domains. Throughout the process, the experts dictated all wording changes in the recommendations; the editorial team developed and administered the surveys but played no role in editing the recommendations. We anticipate updates occurring on a quarterly basis.

### *Statistical Analysis*

Using quality ratings assigned by experts working on a given subtopic, we calculated the median scores for the original pool of recommendations, for the selected highest quality recommendations from existing guidelines documents, and for the final recommendations. Global quality rating scores were created by summing median quality ratings from all five subtopic experts for each of the five quality metrics (eg, correctness, currency). Ratings were compared using the Wilcoxon rank-sum test. SAS (version 8; SAS Institute, Cary, NC) was used to parse data on publications of experts, and subsequent analysis was performed with Stata (version 8; Stata, College Station, TX). Surveys were conducted with Zoomerang (MarketTools, Mill Valley, CA), and results were analyzed with Excel (XP; Microsoft Corporation, Redmond, WA) and Stata.

### *Role of the Sponsor*

This work was sponsored by the National Stroke Association, which approved the original plan and methods, but had no

access to content before publication. Experts were selected without input of the sponsor.

### *Conflict of Interest Declarations*

Experts were asked to list any income, equity, gifts, travel, or grants, personal or to any household member, received from a for-profit or not-for-profit entity in the prior year or anticipated for the following year. No expert participated in the preparation of a subtopic in which a potential conflict of interest existed.

### **Results**

A total of 18 experts were invited to create a panel of 15, with 3 experts declining to participate; we had originally planned to select a panel of 10 members, but conflicts of interest, particularly with manufacturers of antiplatelet agents, forced us to invite additional panelists to have 5 to 6 experts without conflicts covering each topic area.

Initial literature searches identified 257 unique guidelines documents with possible relevance to management of patients with TIA (see Fig). Of these documents, 13 were adjudicated to meet all entry criteria.<sup>19–31</sup> Based on standard methods for assessing quality, guidelines documents tended to be rated highly for scope and purpose (mean, 87%; range, 44–100% on the AGREE score domain) and clarity and presentation (mean, 74%; range, 42–96%), but low on editorial independence (mean, 30%; range, 0–92%), applicability (mean, 44%; range, 0–97%), and rigor of development (mean, 48%; range, 17–94%).

A total of 137 recommendations were relevant to care of TIA and were reviewed by the experts. Overall, for 50 of 137 recommendations (36%), experts did not agree that the recommendation was correct, current, practical, clear, and free of bias. Specifically, experts rated 22 recommendations (16%) as incorrect, 21 (15%) as not current, 21 (15%) as impractical, 28 (20%) as unclear, and 17 (12%) as biased. The experts eliminated by consensus 61 redundant recommendations in the second questionnaire and 23 in the third questionnaire, leaving 53 unique recommendations.

Final recommendations were separated into five major categories: initial management (Table 2), evaluation (Table 3), medical treatment (Table 4), surgical treatment (Table 5), and risk factor management (Table 6), separated into subtopics and ordered by level of evidence. These categories were based on guidelines recommendations from a variety of sources, sometimes with substantial wording changes to reflect new evidence or to clarify wording. Additional references justifying new wording changes and not included in the original guidelines document were provided by the experts.

In the final review, experts within subtopics rated final recommendations as correct (median score, 8.3;

Table 2. Recommendations for Initial Management of Transient Ischemic Attack

Recommendation	Source	Additional References
<b>Hospital admission</b>		
<i>Hospitalization</i> should be considered for patients with their first transient ischemic attack (TIA) within the past 24 to 48 hours to facilitate possible early deployment of lytic therapy and other medical management if symptoms recur and to expedite institution of definitive secondary prevention. For others, multiple and increasingly frequent symptoms (“crescendo TIAs”) might also justify hospitalization rather than expedited ambulatory management. Whatever the strategy, speed is key. Patients managed in the outpatient setting should be fully educated about the need to return immediately if symptoms recur (category 4).	Institute for Clinical Systems Improvement, 2005 <sup>19</sup>	None
A <i>timely hospital referral</i> of a recent (within 1 week) TIA is always advisable, and <i>hospital admission</i> is generally recommended in case of crescendo TIAs, or duration of symptoms longer than 1 hour, symptomatic internal carotid stenosis greater than 50%, a known cardiac source of embolus such as atrial fibrillation, a known hypercoagulable state, or an appropriate combination of the California score or ABCD score (category 4).	Italian Guidelines for Stroke Prevention and Management, 2003 <sup>20</sup>	5, 32, 38
A local admissions policy should be developed by hospitals and representative physicians commonly referring patients to the hospital that set out the categories of patients who will usually be referred or admitted to the hospital (category 4).	Scottish Intercollegiate Guidelines Network, 1997 <sup>21</sup>	None
Hospitals and general practitioners should agree on a <i>local admissions policy and a local protocol for referral to specialist assessment clinics</i> for patients with TIA who do not require hospital admission. Local written protocols should be available that set out indications for both initial screening (such as brain imaging, vascular imaging, cardiac assessment, and blood tests) and more specialized investigations (such as angiography, transesophageal echocardiography, or more specialized blood tests) that the clinical situation may merit (category 4).	Singapore Ministry of Health, 2003 <sup>23</sup>	39, 40
<b>Clinic evaluation</b>		
A <i>specialized clinic</i> for the rapid assessment of TIA within 24 to 48 hours of diagnosis should be available (category 4).	Royal College of Physicians Intercollegiate Stroke Working Party, 2004 <sup>22</sup>	5, 6
<b>Timing of initial medical assessment</b>		
Physicians and institutions that provide care for patients with recent TIA should have <i>same-day access to imaging</i> such as computed tomography/computed tomographic angiography (CT/CTA), magnetic resonance/magnetic resonance angiography (MR/MRA), and ultrasound for patients who need it (category 3).	Royal College of Physicians Intercollegiate Stroke Working Party, 2004 <sup>22</sup>	5, 38
Patients with suspected TIA who are not admitted to the hospital should have rapid (within 12 hours) access for urgent assessment and investigation (CT or magnetic resonance imaging [MRI] brain scanning, electrocardiogram [EKG], and carotid Doppler examination). <i>Initial assessment</i> should be performed within 24 to 48 hours if cross-sectional imaging, EKG, or carotid ultrasound is not performed in the emergency department. If they are performed and are negative, a longer period may be appropriate (ie, up to 7 days) (category 4).	Scottish Intercollegiate Guidelines Network, 1997 <sup>21</sup>	41
For patients with a TIA within the past 2 weeks who are not hospitalized, it is recommended that they undergo <i>prompt (within 24-48 hours) investigations</i> (ie, carotid Doppler for TIA consistent with carotid territory, blood work, and cardiac evaluation such as EKG, rhythm strip, and echocardiography) to determine the mechanism of ischemia and subsequent preventive therapy (category 4).	Italian Guidelines for Stroke Prevention and Management, 2003 <sup>20</sup>	5, 32, 38

Table 3. Recommendations for Evaluation of Transient Ischemic Attack

Recommendation	Source	Additional References
<b>General</b>		
A relevant <i>medical assessment</i> should be undertaken and neurological, cardiological, and radiological assessments considered for all patients with transient ischemic attack (TIA) to define the nature of the event, the need for investigations, further management, and rehabilitation. The assessment should include an electrocardiogram (EKG), full blood count, serum electrolytes and creatinine, and fasting blood glucose and lipids (category 4).	Singapore Ministry of Health, 2003 <sup>23</sup>	None
<b>Brain imaging</b>		
The diagnosis of TIA is only clinical. Nevertheless, the use of computed tomography (CT) and computed tomographic angiography (CTA) or magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) may show infarcts and important occlusive cervicocranial vascular disease and is recommended to corroborate differential diagnosis with other pathologies that can mimic TIA (category 4). There is general agreement that patients with manifestations suggestive of hemispheric TIA should receive a <i>CT or MRI scan</i> of the head in the initial diagnostic evaluation to exclude a rare lesion such as a subdural hematoma or brain tumor responsible for symptoms (category 4). CT or MRI may show an area of brain infarction appropriate to TIA symptoms in more than one fourth of patients (category 4).	Italian Guidelines for Stroke Prevention and Management, 2003 <sup>20</sup>	42, 43
<i>Transcranial Doppler</i> is a complementary examination in patients with a recent TIA. It may provide additional information on patency of cerebral vessels, recanalization, and collateral pathways (category 4).	American Heart Association, 1997 <sup>24</sup>	None
	Italian Guidelines for Stroke Prevention and Management, 2003 <sup>20</sup>	None
<b>Carotid imaging</b>		
For TIA patients, <i>Doppler ultrasonography</i> of the neck is a useful investigation for causative workup and for screening patients for possible surgical or endovascular treatment of carotid or vertebral artery disease (category 3).	Italian Guidelines for Stroke Prevention and Management, 2003 <sup>20</sup>	44, 45
Conventional angiography of cerebral vessels was the gold standard examination in trials on carotid endarterectomy; therefore, <i>Doppler ultrasonography</i> of the neck is recommended for preoperative measurement of carotid stenosis only after verifying its accuracy (category 3).	Italian Guidelines for Stroke Prevention and Management, 2003 <sup>20</sup>	None
Supraaortic vessel <i>MRA and/or CTA</i> are recommended if Doppler ultrasonography examination does not yield reliable results in the individual patient and if carotid endarterectomy is considered a serious option (category 4).	Italian Guidelines for Stroke Prevention and Management, 2003 <sup>20</sup>	46
The panel recommends <i>conventional angiography</i> primarily when Doppler ultrasonography and MRA/CTA yield discordant results, or if they are not feasible (category 4).	Italian Guidelines for Stroke Prevention and Management, 2003 <sup>20</sup>	44, 46, 47
<b>Cardiac evaluation</b>		
After a TIA, when a cardioembolic mechanism is suspected, transthoracic echocardiography (TTE) and/or transesophageal echocardiography (TEE) with testing for right-to-left shunting is recommended in patients younger than 45 years when investigations of the neck and brain vessels and hematological screening provide no clue to the cause of the TIA (category 4).	Italian Guidelines for Stroke Prevention and Management, 2003 <sup>20</sup>	48

range, 7.0–9.0), current (median score, 8.0; range, 7.0–9.0), practical (median score, 8.8; range, 7.0–9.0), clear (median score, 8.5; range, 6.0–9.0), and unbiased (median score, 9.0; range, 8.0–9.0). Final edited recommendations were rated as superior to the highest rated recommendation in the prior literature (median global quality score of 42.8 [range, 38–45] for final recommendations vs 42.0 [range, 37–45] for highest rated existing recommendations;  $p = 0.03$ ), and also to the entire list of prior recommendations in guidelines meeting inclusion criteria (median global quality score, 36; range, 16–45;  $p < 0.0001$ ).

### Discussion

These guidelines on management of patients with TIA provide a much needed update. Numerous guidelines have been published previously, but the experts rated 36% of prior recommendations as incorrect, out of date, unclear, impractical, or biased. These updated guidelines synthesize components from the best prior documents and modify them to incorporate new evidence, to clarify wording, and to represent the balanced opinion of experts without conflicts of interest. Overall, these new recommendations reflect a greater sense of urgency in the care of patients with TIA, with

Table 4.  
Recommendations for Medical Treatment of Transient Ischemic Attack

Recommendation	Source	Additional References
<b>Noncardioembolic transient ischemic attack (TIA)</b>		
Daily long-term <i>antiplatelet therapy</i> should be prescribed immediately for the secondary prevention of stroke and other vascular events in patients who have sustained a noncardioembolic TIA (category 1).	Scottish Intercollegiate Guidelines Network, 1997 <sup>21</sup>	49
Where available, the combination of <i>aspirin (50mg) and sustained-release dipyridamole (200mg twice daily)</i> is a reasonable option for patients with TIA as first choice to reduce the risk for stroke (category 1).	European Stroke Initiative, 2004 <sup>27</sup>	None
<i>Clopidogrel</i> may be slightly more effective than aspirin in the prevention of further vascular events (category 1).	European Stroke Initiative, 2004 <sup>27</sup>	None
After a <i>noncardioembolic TIA</i> , <i>oral anticoagulation</i> is not recommended because there is no documented evidence of a higher benefit compared with antiplatelet therapy at an international normalized ratio (INR) range of 2.0 to 3.0, whereas the risk for cerebral hemorrhagic complications is higher at an INR range greater than 3.0 (category 1).	Italian Guidelines for Stroke Prevention and Management, 2003 <sup>20</sup>	50-55
Combination treatment with <i>sustained-release dipyridamole and aspirin</i> is a reasonable option for prevention of nonfatal stroke for people at high risk for cerebral ischemic events (category 3).	New Zealand Guidelines Group, 2003 <sup>25</sup>	None
For patients who have had an <i>atherothrombotic TIA while taking aspirin</i> , clopidogrel (75mg daily) or aspirin (25mg) plus sustained-release dipyridamole (200mg) twice daily are generally recommended (category 3).	American Heart Association, 1999 <sup>26</sup>	None
Patients with TIA who are starting treatment with thienopyridine derivatives should receive <i>clopidogrel instead of ticlopidine</i> because clopidogrel has fewer side effects and requires less monitoring (category 4).	European Stroke Initiative, 2004 <sup>27</sup>	None
For patients with noncardioembolic TIA, <i>clopidogrel</i> may be prescribed as first choice or when aspirin alone or aspirin in combination with dipyridamole is not tolerated (category 4).	American College of Chest Physicians, 2004 <sup>28</sup> ; European Stroke Initiative, 2004 <sup>27</sup>	None
<b>Cardioembolic TIA</b>		
For patients with persistent or paroxysmal <i>atrial fibrillation</i> (valvular or nonvalvular) who have had a cardioembolic TIA, long-term oral anticoagulation is recommended (category 1). For these patients, target INR of 2.5 (range, 2.0-3.0) is recommended. Aspirin is recommended for patients with contraindications to oral anticoagulation.	American Heart Association, 1999 <sup>26</sup>	52, 54, 56-59
Aspirin (325mg/day), or clopidogrel (75mg) if aspirin is intolerant, is recommended after a cardioembolic TIA associated with <i>nonvalvular atrial fibrillation</i> , but only if oral anticoagulation cannot be administered (category 1).	Italian Guidelines for Stroke Prevention and Management, 2003 <sup>20</sup>	54, 60-64
Anticoagulants should not be used for patients with TIA who are in sinus rhythm (category 1) unless there is a high risk for cardiac embolism due to paroxysmal atrial fibrillation or flutter, recent myocardial infarction, mechanical heart valve prosthesis, mitral stenosis, intracardiac clot, or severe dilated cardiomyopathy (ejection fraction < 20%) (category 4).	Royal College of Physicians Intercollegiate Stroke Working Party, 2004 <sup>22</sup>	52, 54, 56-59, 61, 65-76
In patients with <i>mitral valve prolapse or strands</i> , who have a history of TIA, we recommend antiplatelet therapy (category 3).	American College of Chest Physicians, 2004 <sup>28</sup>	None
Antiplatelet therapy is recommended after a TIA associated with <i>patent foramen ovale</i> if anticoagulation is not deemed indicated (category 3).	Italian Guidelines for Stroke Prevention and Management, 2003 <sup>20</sup>	77
After a TIA in patients with <i>prosthetic heart valve</i> who are already on adequate oral anticoagulation, the combination of oral anticoagulants plus aspirin (81mg/day) or dipyridamole is recommended (category 3).	Italian Guidelines for Stroke Prevention and Management, 2003 <sup>20</sup>	None
<b>Other situations</b>		
Patients with recent TIA and <i>unstable angina or non-Q-wave myocardial infarction (MI)</i> should be treated with a combination of clopidogrel 75mg and aspirin 75 to 100mg (category 1).	European Stroke Initiative, 2004 <sup>27</sup>	78
Patients who have a history of TIA and who are undergoing <i>endarterectomy</i> should receive aspirin therapy (50-325mg) beginning before surgery unless there are contraindications (category 2).	American Heart Association, 1998 <sup>29</sup>	79
Clinicians should inquire about the use of <i>alternative complementary medicines</i> when assessing cardiovascular risk or prescribing medicine. Some herbal medicines have potential for toxic effects (category 1), and some interact with medication (eg, warfarin) (category 4). Feverfew, garlic, ginkgo biloba, ginger, and ginseng may alter bleeding time and should not be used concomitantly with warfarin (category 4). St John's Wort reduces serum digoxin levels and can enhance the metabolism of warfarin (category 4).	New Zealand Guidelines Group, 2003 <sup>25</sup>	None

clear recommendations for emergent evaluation and treatment. Most recommendations can be implemented directly by practitioners. However, additional resources, and even significant institutional changes, may be required to comply with some of the recommendations. The necessity and length of hospitalization and alternative settings for evaluation are covered

incompletely in the current recommendations and are the subject of active research.

Our intent was to provide recommendations relevant to the care of patients with recent TIA. However, at the conclusion of the processes, the experts generally agreed that all final recommendations could be applied to minor ischemic stroke, as well as to TIA. The sim-

Table 5. Surgical Treatment

Recommendation	Source	Additional References
<b>Carotid endarterectomy</b>		
Carotid endarterectomy is of overall benefit for symptomatic patients with recent (within 2-4 weeks) hemispheric, nondisabling, carotid artery ischemic events and ipsilateral 70 to 99% carotid artery stenosis, and it may also be beneficial for symptomatic patients with retinal transient ischemia (category 1).	American Heart Association, 1998 <sup>29</sup>	41, 80
Carotid surgery may be indicated for certain patients with a history of carotid territory transient ischemic attack (TIA) and ipsilateral stenosis of 50 to 69% without a severe neurological deficit (category 1). This is valid only for centers with a perioperative complication rate (all strokes and death) of less than 6%. The subgroup of patients most likely to benefit from surgery is older men with recent (within 2-4 weeks) hemispheric symptoms and an irregular/ulcerated plaque (category 4).	European Stroke Initiative, 2004 <sup>27</sup>	41, 80, 81
Carotid endarterectomy is not recommended for patients with carotid territory TIA with ipsilateral stenosis less than 50% (North American Symptomatic Carotid Endarterectomy Trial [NASCET] criteria) (category 1).	Italian Guidelines for Stroke Prevention and Management, 2003 <sup>20</sup>	80
Patients with moderate or severe internal carotid artery stenosis ipsilateral to a carotid TIA should be considered for carotid endarterectomy by an <i>experienced surgeon</i> (category 1).	Singapore Ministry of Health, 2003 <sup>23</sup>	None
In patients with symptomatic internal carotid artery stenosis for whom carotid endarterectomy is a reasonable option, surgery should be performed as soon as the patient is fit for the procedure, preferably within 2 weeks of TIA (cerebral or retinal) (category 2).	Royal College of Physicians Intercollegiate Stroke Working Party, 2004 <sup>22</sup>	41, 80-82
<b>Extracranial-intracranial bypass</b>		
<i>Extracranial-intracranial bypass</i> generally is not recommended for patients with TIAs (category 1). However, research is ongoing to determine whether there may be a subgroup of patients who may benefit from this treatment.	American Heart Association, 1999 <sup>26</sup>	None

ilarities between TIA and minor ischemic stroke in causative factors, prognosis, evaluation, and treatment have been widely acknowledged; thus, applicability of recommendations to both TIA and minor stroke is not surprising.<sup>32</sup> Both these “warning” events provide an opportunity for timely and effective stroke prevention. However, it should be recognized that the experts were not asked during the review and editing process to consider these recommendations as covering minor stroke.

There are numerous existing guidelines documents covering aspects of TIA care, but quality varies and most have not been updated in several years. The new methods we used to develop the current guidelines were designed to reduce bias, to assure comprehensive coverage of important aspects of care, and to streamline the development process to reduce barriers to updating. We also generally adhered to published, high-quality recommendations<sup>18,33</sup> for producing guidelines and used a systematic review of recent literature to assure that those recommendations were evidence-based and graded appropriately. Our processes ensured that no expert participated in preparation or rating of a recommendation where a potential conflict of interest might exist.

There are several limitations to the methods we used.

First, the constraints we placed on experts and the editorial team to reduce bias made the editing of recommendations somewhat cumbersome, sometimes with several wording changes being suggested and evaluated at once. Second, we produced a series of recommendations with reference to the source guidelines document from which the original recommendation was published; however, we did not attempt to include the supportive text and discussion that frequently accompanies recommendations and places them in the context of care decisions or the literature. Our goal was to provide high-quality recommendations, but the source guidelines documents may be more readable and educational. Third, we chose experts in a fully data-driven way after validation that our method reproduced nomination from practitioners in the field. Consequently, our experts were not broadly representative of the many fields involved in TIA care. We believe this rigid approach was justified by the reduced risk for bias, rather than one that could lead to selection of experts with particular viewpoints. However, our data-driven approach was generated using nominations from a questionnaire to which the response rate was only 1%, and a higher response

Table 6. Recommendations for Risk Factor Management in Patients with Transient Ischemic Attack

Recommendation	Source	Additional References
<b>Cardiovascular risk</b>		
Everyone with a history of transient ischemic attack (TIA) should be considered for treatment to reduce their cardiovascular risk. Risk factors for recurrent cerebrovascular ischemic events should be treated appropriately. This includes <i>lowering blood pressure and blood cholesterol</i> (with lifestyle modifications and/or drug therapy) in all patients with atherothrombotic TIA, regardless of the baseline blood pressure and cholesterol measurements (category 1).	Royal College of Physicians Intercollegiate Stroke Working Party, 2004 <sup>22</sup>	None
Because patients with TIA have a substantial frequency of coexistent heart disease that may shorten life expectancy and cause marked morbidity, the potential presence of <i>coronary artery disease, cardiac arrhythmias, congestive heart failure, and valvular heart disease</i> should be considered and treated appropriately (category 3).	American Heart Association, 1999 <sup>26</sup>	83-95
<b>Cholesterol</b>		
Treatment with a <i>statin</i> is recommended for most people after atherothromboembolic TIA (category 3).	New Zealand Guidelines Group, 2003 <sup>25</sup>	96-98
Treatment of <i>hyperlipidemia</i> is recommended. The American Heart Association (AHA) Step II diet ( $\leq 30\%$ of calories derived from fat, $< 7\%$ from saturated fat, and $< 200\text{mg/day}$ cholesterol consumed) is recommended together with maintenance of ideal body weight and engagement in regular physical activity. If fasting lipid levels remain increased (low-density lipoprotein [LDL] $> 130\text{mg/dl}$ ) for 3 months or longer, use of a lipid-lowering agent such as a statin is recommended. The goal of therapy should be an LDL level less than $100\text{mg/dl}$ (category 3).	American Heart Association, 1999 <sup>26</sup>	None
<b>Diabetes</b>		
<i>Fasting blood glucose</i> levels less than $126\text{mg/dl}$ ( $7\text{mmol/L}$ ) are recommended. Diet, regular exercise (at least three times a week), and oral hypoglycemics or insulin should be prescribed as needed to control diabetes for long-term secondary prevention of stroke (category 3).	American Heart Association, 1999 <sup>26</sup>	99-104
<b>Hypertension</b>		
People presenting after a TIA should start <i>blood pressure-lowering medication</i> unless the person has symptomatic hypotension. This medication should be given in addition to other appropriate medications such as an <i>antithrombotic agent</i> (aspirin, another antiplatelet agent, or warfarin), a <i>statin or other lipid-lowering agent</i> , and <i>diabetes management</i> . Treatment should start concurrently with intensive <i>lifestyle advice</i> . It is usually advisable to wait 7 to 14 days before starting blood pressure-lowering medication (category 1).	New Zealand Guidelines Group, 2003 <sup>25</sup>	99, 100
After TIA that is not due to dissection or cardiac embolism, the patient's <i>blood pressure</i> should be reduced to less than 140/90 or less than 130/80mm Hg for diabetics, regardless of its initial level (unless the patient has symptomatic hypotension), with an angiotensin-converting enzyme (ACE) inhibitor alone or in combination with a diuretic, or with an angiotensin receptor blocker (category 1). For normotensive patients, consideration should be given to lowering blood pressure by approximately $9/4\text{mm Hg}$ provided there is no high-grade carotid stenosis (category 3).	European Stroke Initiative, 2004 <sup>27</sup> ; American Heart Association, 1999 <sup>26</sup>	105-115
<b>Lifestyle</b>		
All <i>smokers</i> should be encouraged to stop smoking. Smoking cessation has major and immediate health benefits for smokers of all ages. The recording of current and past smoking habits is recommended as part of a comprehensive cardiovascular risk assessment. Counseling, nicotine replacement therapies, bupropion, and formal smoking cessation programs may all be helpful (category 3).	New Zealand Guidelines Group, 2003 <sup>25</sup>	116
Encourage patients with TIA and a body mass index (BMI) greater than 25 (especially anyone who has a BMI $> 30$ ) to commence graduated lifestyle change aimed at weight reduction (category 3).	New Zealand Guidelines Group, 2003 <sup>25</sup>	None
Physical activity (at least 10 minutes of exercise such as walking, bicycling, running, or swimming $\geq 3$ to 4 times/week) is generally recommended for patients with TIA (category 3).	American Heart Association, 1999 <sup>26</sup>	117, 118
The use of antioxidant supplements (vitamins E and C and $\beta$ -carotene) is not recommended for the prevention or treatment of cardiovascular disease (category 3).	New Zealand Guidelines Group, 2003 <sup>25</sup>	None
Generally, patients with TIA should be given appropriate advice on reducing the intake of <i>salt</i> (category 3).	American Heart Association, 1999 <sup>26</sup>	None
<b>Hormone replacement therapy</b>		
It may be harmful to use <i>hormone replacement therapy</i> for secondary stroke prevention in postmenopausal women (category 2).	European Stroke Initiative, 2004 <sup>27</sup>	None

rate should be sought if more reliable prediction of expert nomination is desired.

These current guidelines incorporate guidelines published between January 1995 and June 2005 and also supporting literature through February 2006. However, several of the source guidelines were updated during the process, including the 2006 American Heart Association (AHA) Guidelines for prevention of stroke in patients with ischemic stroke or TIA, and these new documents were not reviewed by the experts.<sup>34–37</sup> We anticipate comparing expert quality ratings of recommendations from updated guidelines with the existing recommendations produced in this document and replacing those for which a newer recommendation is preferred. In addition, publication of major new findings, such as results of clinical trials, can be reviewed by the expert panels and recommendations amended as appropriate, allowing for constant updating as new evidence becomes available. We anticipate that these guidelines will receive broad distribution to physicians caring for patients with TIA through brochures, pocket cards, and most importantly, a Web site that will allow frequent updating.

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### References

1. WHO MONICA Project Principal Investigators. The World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. *J Clin Epidemiol* 1988;41:105–114.
2. Albers GW, Caplan LR, Easton JD, et al. Transient ischemic attack: proposal for a new definition. *N Engl J Med* 2002; 347:1713–1716.
3. Kleindorfer D, Panagos P, Pancioli A, et al. Incidence and short-term prognosis of transient ischemic attack in a population-based study. *Stroke* 2005;36:720–723.
4. Johnston SC, Fayad PB, Gorelick PB, et al. Prevalence and knowledge of transient ischemic attacks among US adults. *Neurology* 2003;60:1424–1428.
5. Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency-department diagnosis of transient ischemic attack. *JAMA* 2000;284:2901–2906.
6. Coull AJ, Lovett JK, Rothwell PM. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. *BMJ* 2004;328:326–328.
7. Daffertshofer M, Mielke O, Pullwitt A, et al. Transient ischemic attacks are more than “ministrokes.” *Stroke* 2004;35: 2453–2458.
8. Hill MD, Yiannakoulis N, Jeerakathil T, et al. The high risk of stroke immediately after transient ischemic attack: a population-based study. *Neurology* 2004;62:2015–2020.
9. Goldstein LB, Bian J, Samsa GP, et al. New transient ischemic attack and stroke: outpatient management by primary care physicians. *Arch Intern Med* 2000;160:2941–2946.
10. Johnston SC, Smith WS. Practice variability in management of transient ischemic attacks. *Eur Neurol* 1999;42:105–108.
11. Deutsch SC, Denton M, Borenstein J. Clinical practice guidelines: a tool to help provide quality care. *Geriatrics* 1998; 53:54–73.
12. Ray-Coquard I, Philip T, Lehmann M, et al. Impact of a clinical guidelines program for breast and colon cancer in a French cancer center. *JAMA* 1997;278:1591–1595.

13. Eagle KA, Montoyo CK, Riba AL, et al. Guideline-based standardized care is associated with substantially lower mortality in Medicare patients with acute myocardial infarction: the American College of Cardiology's Guidelines Applied in Practice (GAP) Projects in Michigan. *J Am Coll Cardiol* 2005;46:1242–1248.
14. Hart RG, Bailey RD. An assessment of guidelines for prevention of ischemic stroke. *Neurology* 2002;59:977–982.
15. Shaneyfelt TM, Mayo-Smith MF, Rothwangl J. Are guidelines following guidelines? The methodological quality of clinical practice guidelines in the peer-reviewed medical literature. *JAMA* 1999;281:1900–1905.
16. McAlister FA, Campbell NR, Zarnke K, et al. The management of hypertension in Canada: a review of current guidelines, their shortcomings and implications for the future. *CMAJ* 2001;164:517–522.
17. Normand SL, McNeil BJ, Peterson LE, Palmer RH. Eliciting expert opinion using the Delphi technique: identifying performance indicators for cardiovascular disease. *Int J Qual Health Care* 1998;10:247–260.
18. The AGREE Collaboration. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines. *Qual Saf Health Care* 2003;12:18–23.
19. Institute for Clinical Systems Improvement. Diagnosis and initial treatment of ischemic stroke. Bloomington, MN: Institute for Clinical Systems Improvement, 2005:63.
20. Stroke Prevention and Educational Awareness Diffusion. Italian guidelines for stroke prevention and management: syntheses and recommendations. Milan, Italy: Stroke Prevention and Educational Awareness Diffusion, 2003:38.
21. Scottish Intercollegiate Guidelines Network. Management of patients with stroke. I: Assessment, investigation, immediate management and secondary prevention. National clinical guideline. Edinburgh, United Kingdom: Scottish Intercollegiate Guidelines Network, 1997:32.
22. Royal College of Physicians Intercollegiate Stroke Working Party. National clinical guidelines for stroke. 2nd ed. London: Royal College of Physicians, 2004:134.
23. Singapore Ministry of Health. Stroke and transient ischaemic attacks: assessment, investigation, immediate management and secondary prevention. Clinical practice guidelines. Singapore: Singapore Ministry of Health, 2003:38.
24. Culebras A, Kase CS, Masdeu JC, et al. Practice guidelines for the use of imaging in transient ischemic attacks and acute stroke. A report of the Stroke Council, American Heart Association. *Stroke* 1997;28:1480–1497.
25. New Zealand Guidelines Group. Evidence-based best practice guideline: the assessment and management of cardiovascular risk. Wellington, New Zealand: New Zealand Guidelines Group, 2003:190.
26. Albers GW, Hart RG, Lutsep HL, et al. AHA Scientific Statement. 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. *Stroke* 1999;30:2502–2511.
27. Leys D, Kwicinski H, Bogousslavsky J, et al. Prevention. European Stroke Initiative. *Cerebrovasc Dis* 2004;17(suppl 2):15–29.
28. Albers GW, Amarenco P, Easton JD, et al. Antithrombotic and thrombolytic therapy for ischemic stroke: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126:483S–512S.
29. Biller J, Feinberg WM, Castaldo JE, et al. Guidelines for carotid endarterectomy: a statement for healthcare professionals from a Special Writing Group of the Stroke Council, American Heart Association. *Circulation* 1998;97:501–509.
30. Sowerby Centre for Health Informatics at Newcastle. PRODIGY guidance: atrial fibrillation. Vol. 2005. Newcastle, United Kingdom: Sowerby Centre for Health Informatics at Newcastle, 2004.
31. Eccles M, Freemantle N, Mason J. North of England evidence based guideline development project: guideline on the use of aspirin as secondary prophylaxis for vascular disease in primary care. North of England Aspirin Guideline Development Group. *BMJ* 1998;316:1303–1309.
32. Rothwell PM, Buchan A, Johnston SC. Recent advances in management of transient ischaemic attacks and minor ischaemic strokes. *Lancet Neurol* 2006;5:323–331.
33. Shiffman RN, Shekelle P, Overhage JM, et al. Standardized reporting of clinical practice guidelines: a proposal from the Conference on Guideline Standardization. *Ann Intern Med* 2003;139:493–498.
34. Sacco RL, Adams R, Albers G, et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. *Stroke* 2006;37:577–617.
35. Sowerby Centre for Health Informatics at Newcastle. PRODIGY guidance: atrial fibrillation. Vol. 2006. Newcastle, United Kingdom: Sowerby Centre for Health Informatics at Newcastle, 2005.
36. Institute for Clinical Systems Improvement. Diagnosis and initial treatment of ischemic stroke. Bloomington, MN: Institute for Clinical Systems Improvement, 2006:63.
37. Stroke Prevention and Educational Awareness Diffusion. Italian guidelines for stroke prevention and management: syntheses and recommendations. Milan, Italy: Stroke Prevention and Educational Awareness Diffusion, 2005:38.
38. Rothwell PM, Giles MF, Flossmann E, et al. A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. *Lancet* 2005;366:29–36.
39. Blight A, Pereira AC, Brown MM. A single consultation cerebrovascular disease clinic is cost effective in the management of transient ischaemic attack and minor stroke. *J R Coll Physicians Lond* 2000;34:452–455.
40. Alberts MJ, Hademenos G, Latchaw RE, et al. Recommendations for the establishment of primary stroke centers. Brain Attack Coalition. *JAMA* 2000;283:3102–3109.
41. Rothwell PM, Eliasziw M, Gutnikov SA, et al. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet* 2004;363:915–924.
42. Robless P, Baxter A, Byrd S, et al. The prevalence of cerebral infarcts in the Asymptomatic Carotid Surgery Trial (ACST) in relation to prior contralateral symptoms. *Int Angiol* 1998;17:187–193.
43. Patel SG, Collie DA, Wardlaw JM, et al. Outcome, observer reliability, and patient preferences if CTA, MRA, or Doppler ultrasound were used, individually or together, instead of digital subtraction angiography before carotid endarterectomy. *J Neurol Neurosurg Psychiatry* 2002;73:21–28.
44. Deriu GP, Milite D, Damiani N, et al. Carotid endarterectomy without angiography: a prospective randomised pilot study. *Eur J Vasc Endovasc Surg* 2000;20:250–253.
45. Lewis RF, Abrahamowicz M, Cote R, Battista RN. Predictive power of duplex ultrasonography in asymptomatic carotid disease. *Ann Intern Med* 1997;127:13–20.

46. Nederkoorn PJ, Mali WP, Eikelboom BC, et al. Preoperative diagnosis of carotid artery stenosis: accuracy of noninvasive testing. *Stroke* 2002;33:2003–2008.
47. Henderson RD, Eliasziw M, Fox AJ, et al. Angiographically defined collateral circulation and risk of stroke in patients with severe carotid artery stenosis. North American Symptomatic Carotid Endarterectomy Trial (NASCET) Group. *Stroke* 2000;31:128–132.
48. Kapral MK, Silver FL. Preventive health care, 1999 update: 2. Echocardiography for the detection of a cardiac source of embolus in patients with stroke. Canadian Task Force on Preventive Health Care. *CMAJ* 1999;161:989–996.
49. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71–86.
50. The Stroke Prevention in Reversible Ischemia Trial (SPIRIT) Study Group. A randomized trial of anticoagulants versus aspirin after cerebral ischemia of presumed arterial origin. *Ann Neurol* 1997;42:857–865.
51. Sandercock P, Mielke O, Liu M, Counsell C. Anticoagulants for preventing recurrence following presumed non-cardioembolic ischaemic stroke or transient ischaemic attack. *Cochrane Database Syst Rev* 2003;CD000248.
52. The European Atrial Fibrillation Trial Study Group. Optimal oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and recent cerebral ischemia. *N Engl J Med* 1995;333:5–10.
53. Chimowitz MI, Lynn MJ, Howlett-Smith H, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med* 2005;352:1305–1316.
54. Hart RG, Pearce LA, Koudstaal PJ. Transient ischemic attacks in patients with atrial fibrillation: implications for secondary prevention: the European Atrial Fibrillation Trial and Stroke Prevention in Atrial Fibrillation III trial. *Stroke* 2004;35:948–951.
55. Yamaguchi T. Optimal intensity of warfarin therapy for secondary prevention of stroke in patients with nonvalvular atrial fibrillation: a multicenter, prospective, randomized trial. Japanese Nonvalvular Atrial Fibrillation-Embolism Secondary Prevention Cooperative Study Group. *Stroke* 2000;31:817–821.
56. Saxena R, Koudstaal PJ. Anticoagulants versus antiplatelet therapy for preventing stroke in patients with nonrheumatic atrial fibrillation and a history of stroke or transient ischemic attack. *Cochrane Database Syst Rev* 2004;CD000187.
57. Gage BF, van Walraven C, Pearce L, et al. Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. *Circulation* 2004;110:2287–2292.
58. Algra A, De Schryver EL, van Gijn J, et al. Oral anticoagulants versus antiplatelet therapy for preventing further vascular events after transient ischemic attack or minor stroke of presumed arterial origin. *Stroke* 2003;34:234–235.
59. van Walraven C, Hart RG, Singer DE, et al. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. *JAMA* 2002;288:2441–2448.
60. Cohen A, Tzourio C, Chauvel C, et al. Mitral valve strands and the risk of ischemic stroke in elderly patients. The French Study of Aortic Plaques in Stroke (FAPS) Investigators. *Stroke* 1997;28:1574–1578.
61. Gilon D, Buonanno FS, Joffe MM, et al. Lack of evidence of an association between mitral-valve prolapse and stroke in young patients. *N Engl J Med* 1999;341:8–13.
62. Orenca AJ, Petty GW, Khandheria BK, et al. Mitral valve prolapse and the risk of stroke after initial cerebral ischemia. *Neurology* 1995;45:1083–1086.
63. Freed LA, Levy D, Levine RA, et al. Prevalence and clinical outcome of mitral-valve prolapse. *N Engl J Med* 1999;341:1–7.
64. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. *Lancet* 1994;343:687–691.
65. Gorter JW, Algra A, van Gijn J, et al. SPIRIT: predictors of anticoagulant-related bleeding complications in patients after cerebral ischemia. *Cerebrovasc Dis* 1997;7:3 (Abstract).
66. Gorter JW. Major bleeding during anticoagulation after cerebral ischemia: patterns and risk factors. Stroke Prevention In Reversible Ischemia Trial (SPIRIT). European Atrial Fibrillation Trial (EAFT) study groups. *Neurology* 1999;53:1319–1327.
67. The European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) Study Group. Oral anticoagulation in patients after cerebral ischemia of arterial origin and risk of intracranial hemorrhage. *Stroke* 2003;34:e45–e46.
68. Mohr JP, Thompson JL, Lazar RM, et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. *N Engl J Med* 2001;345:1444–1451.
69. EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet* 1993;342:1255–1262.
70. Laupacis A, Albers G, Dalen J, et al. Antithrombotic therapy in atrial fibrillation. *Chest* 1998;114:579S–589S.
71. Petty GW, Orenca AJ, Khandheria BK, Whisnant JP. A population-based study of stroke in the setting of mitral valve prolapse: risk factors and infarct subtype classification. *Mayo Clin Proc* 1994;69:632–634.
72. Hylek EM, Skates SJ, Sheehan MA, Singer DE. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. *N Engl J Med* 1996;335:540–546.
73. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial. *Lancet* 1996;348:633–638.
74. Albers GW, Yim JM, Belew KM, et al. Status of antithrombotic therapy for patients with atrial fibrillation in university hospitals. *Arch Intern Med* 1996;156:2311–2316.
75. Hirsh J, Dalen JE, Anderson DR, et al. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest* 1998;114:445S–469S.
76. Edvardsson N, Juul-Moller S, Omblus R, Pehrsson K. Effects of low-dose warfarin and aspirin versus no treatment on stroke in a medium-risk patient population with atrial fibrillation. *J Intern Med* 2003;254:95–101.
77. Mas JL, Arquizan C, Lamy C, et al. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. *N Engl J Med* 2001;345:1740–1746.
78. Peters RJ, Mehta SR, Fox KA, et al. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. *Circulation* 2003;108:1682–1687.
79. Taylor DW, Barnett HJ, Haynes RB, et al. Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy: a randomised controlled trial. ASA and Carotid Endarterectomy (ACE) Trial Collaborators. *Lancet* 1999;353:2179–2184.
80. Rothwell PM, Eliasziw M, Gutnikov SA, et al. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet* 2003;361:107–116.
81. Rothwell PM, Mehta Z, Howard SC, et al. Treating individuals 3: from subgroups to individuals: general principles and the example of carotid endarterectomy. *Lancet* 2005;365:256–265.

82. Gasecki AP, Eliasziw M, Ferguson GG, et al. Long-term prognosis and effect of endarterectomy in patients with symptomatic severe carotid stenosis and contralateral carotid stenosis or occlusion: results from NASCET. North American Symptomatic Carotid Endarterectomy Trial (NASCET) Group. *J Neurosurg* 1995;83:778–782.
83. Ness J, Aronow WS. Prevalence of coexistence of coronary artery disease, ischemic stroke, and peripheral arterial disease in older persons, mean age 80 years, in an academic hospital-based geriatrics practice. *J Am Geriatr Soc* 1999;47:1255–1256.
84. Kirshner HS, Biller J, Callahan AS 3rd. Long-term therapy to prevent stroke. *J Am Board Fam Pract* 2005;18:528–540.
85. Love BB, Grover-McKay M, Biller J, et al. Coronary artery disease and cardiac events with asymptomatic and symptomatic cerebrovascular disease. *Stroke* 1992;23:939–945.
86. Eliasziw M, Kennedy J, Hill MD, et al. Early risk of stroke after a transient ischemic attack in patients with internal carotid artery disease. *CMAJ* 2004;170:1105–1109.
87. Di Pasquale G, Andreoli A, Pinelli G, et al. Cerebral ischemia and asymptomatic coronary artery disease: a prospective study of 83 patients. *Stroke* 1986;17:1098–1101.
88. Di Pasquale G, Pinelli G, Grazi P, et al. Incidence of silent myocardial ischaemia in patients with cerebral ischaemia. *Eur Heart J* 1988;9(suppl N):104–107.
89. Gates P, Peppard R, Kempster P, et al. Clinically unsuspected cardiac disease in patients with cerebral ischaemia. *Clin Exp Neurol* 1987;23:75–80.
90. Gates PC, Eliasziw M, Algra A, et al. Identifying patients with symptomatic carotid artery disease at high and low risk of severe myocardial infarction and cardiac death. *Stroke* 2002;33:2413–2416.
91. Vickrey BG, Rector TS, Wickstrom SL, et al. Occurrence of secondary ischemic events among persons with atherosclerotic vascular disease. *Stroke* 2002;33:901–906.
92. Dexter DD Jr, Whisnant JP, Connolly DC, O'Fallon WM. The association of stroke and coronary heart disease: a population study. *Mayo Clin Proc* 1987;62:1077–1083.
93. Sacco RL, Wolf PA, Kannel WB, McNamara PM. Survival and recurrence following stroke. The Framingham study. *Stroke* 1982;13:290–295.
94. Heyman A, Wilkinson WE, Hurwitz BJ, et al. Risk of ischemic heart disease in patients with TIA. *Neurology* 1984;34:626–630.
95. Rokey R, Rolak LA, Harati Y, et al. Coronary artery disease in patients with cerebrovascular disease: a prospective study. *Ann Neurol* 1984;16:50–53.
96. Corvol JC, Bouzamondo A, Sirol M, et al. Differential effects of lipid-lowering therapies on stroke prevention: a meta-analysis of randomized trials. *Arch Intern Med* 2003;163:669–676.
97. Collins R, Armitage J, Parish S, et al. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. *Lancet* 2004;363:757–767.
98. The Stroke Council. Statins after ischemic stroke and transient ischemic attack. *Stroke* 2004;35:1023.
99. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993;16:434–444.
100. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837–853.
101. Church TS, LaMonte MJ, Barlow CE, Blair SN. Cardiorespiratory fitness and body mass index as predictors of cardiovascular disease mortality among men with diabetes. *Arch Intern Med* 2005;165:2114–2120.
102. Bassuk SS, Manson JE. Epidemiological evidence for the role of physical activity in reducing risk of type 2 diabetes and cardiovascular disease. *J Appl Physiol* 2005;99:1193–1204.
103. Berthet K, Neal BC, Chalmers JP, et al. Reductions in the risks of recurrent stroke in patients with and without diabetes: the PROGRESS Trial. *Blood Press* 2004;13:7–13.
104. Nathan DM, Cleary PA, Backlund JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005;353:2643–2653.
105. Dahlof B, Devereux RB, Kjeldsen SE, 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.
106. HOPE Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE sub-study. *Lancet* 2000;355:253–259.
107. 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.
108. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). ALLHAT Collaborative Research Group. *JAMA* 2000;283:1967–1975.
109. Schrader J, Luders S, Kulschewski A, et al. Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention: principal results of a prospective randomized controlled study (MOSES). *Stroke* 2005;36:1218–1226.
110. Schrader J, Luders S, Kulschewski A, et al. The ACCESS Study: evaluation of Acute Candesartan Cilexetil Therapy in Stroke Survivors. *Stroke* 2003;34:1699–1703.
111. Arima H, Hart RG, Colman S, et al. Perindopril-based blood pressure-lowering reduces major vascular events in patients with atrial fibrillation and prior stroke or transient ischemic attack. *Stroke* 2005;36:2164–2169.
112. Hilleman DE, Lucas BD Jr. Angiotensin-converting enzyme inhibitors and stroke risk: benefit beyond blood pressure reduction? *Pharmacotherapy* 2004;24:1064–1076.
113. Fukui T, Rahman M, Hayashi K, et al. Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial of cardiovascular events in high-risk hypertensive patients: rationale, design, and methods. *Hypertens Res* 2003;26:979–990.
114. Progress Management Committee. PROGRESS—Perindopril Protection Against Recurrent Stroke Study: characteristics of the study population at baseline. *J Hypertens* 1999;17:1647–1655.
115. Chobanian AV, Bakris GL, Black HR, 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;289:2560–2572.
116. Lancaster T, Stead LF. Individual behavioural counselling for smoking cessation. *Cochrane Database Syst Rev* 2005; CD001292.
117. Kernan WN, Viscoli CM, Brass LM, et al. Decline in physical performance among women with a recent transient ischemic attack or ischemic stroke: opportunities for functional preservation a report of the Women's Estrogen Stroke Trial. *Stroke* 2005;36:630–634.
118. Lee IM, Hennekens CH, Berger K, et al. Exercise and risk of stroke in male physicians. *Stroke* 1999;30:1–6.