

National Stroke Association Guidelines for the Management of TIA

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Abstract

Objective. Transient ischemic attacks (TIAs) 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 TIA.

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 independently rated 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 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 TIA 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.

Introduction

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,”¹ 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 evidence of acute infarction.”² Based on the 24-hour definition, an estimated 240,000 TIAs are diagnosed every year in the U.S.,³ and the annual number of undiagnosed TIAs likely exceeds this.⁴ Recent studies have shown that the stroke risk after TIA is high, particularly in the first few days.^{3, 5-8} Nonetheless, management of TIA has been highly variable with little emphasis on urgency.^{9, 10}

Consensus guidelines may be useful in improving care, reducing practice variability, and reducing costs and burden of disease, particularly when evidence is evolving rapidly.¹¹⁻¹³ Recently, there has been concern about the quality of methods used to produce guidelines and the potential for bias in the recommendations.¹⁴⁻¹⁶ Several international organizations have sponsored guidelines development for TIA, but most of these were published years ago, some 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 U.S., 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 of stroke, cardiovascular events, and other complications after TIA. We created a novel method of guideline 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.¹⁷ The method was designed to standardize and streamline the process and to make updating more efficient as new evidence becomes available.

Methods

We undertook six primary steps in order 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, non-overlapping recommendations; 5) editing of these recommendations using a modified Delphi approach; and 6) rating of the new recommendations with comparison to 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 (Figure). The MeSH headings (cerebrovascular 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), the National Institute for Clinical Excellence (www.nice.org.uk), Organising Medical Networked Information (omni.ac.uk), and National

Electronic Library for Health (www.nelh.nhs.uk). Publications that cited existing guidelines, identified through the 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) Guideline document with specific evidence-based, graded recommendation for physicians about treatment; (2) directly relevant to patients presenting or with a history of TIA; (3) sponsored by a governmental or nonprofit organization; (4) no later guidelines from the same institution that completely encompass the same clinical issues; (5) guidelines recommendations designed to be relevant to a regional, national, or international audience; (6) published in print or on the Web since January 1, 1995; and, (7) the entire guidelines document 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 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).¹⁸ 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 emailed to 13,353 health professionals who had expressed an interest in stroke to the National Stroke Association. This 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 three 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 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 author was listed first, second, or last. Criteria for these variables were tested singly and in combination (sum, product, or union of two individual variables) to define rules that would identify with the greatest specificity 10 experts who had received at least three 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 receiving three or more nominations in the survey.

To select panelists with specific expertise in TIA, similar searches were performed with only the term “transient ischemic attack” or “TIA” as a subject, title word, or key word, which yielded 11,407 publications in PubMed and 3,665 in the Web of Science. Experts were ranked based on the publication product, and 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, the abstracted recommendations were presented without attribution to the panels of topic experts. Using a modified Delphi method,¹⁷ which iteratively collects and integrates independent opinions on statement, topic experts without conflicts of interest were asked to complete independently a series of Web-based questionnaires (Figure). 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, they were asked to evaluate each recommendation based on five quality domains, rated on a 9-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 implementable and 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” along with terms reflecting the specific subtopic area, limited to human subjects, English, and employing 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 (Figure). 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 five 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 up median quality ratings from all five subtopic experts for each of the five quality metrics (e.g., 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, College Station, TX). Surveys were conducted with Zoomerang (MarketTools, Mill Valley, CA) and results were analyzed with Excel (XP, Microsoft, 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 prior to publication. Experts were selected without input of the sponsor.

Results

A total of 18 experts were invited to create a panel of 15, with three 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 in order 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 (Figure). Of these, 13 were adjudicated to meet all entry criteria.¹⁹⁻³¹ 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%, 42-96%), but low on editorial independence (mean 30%, 0-92%), applicability (mean 44%, 0-97%), and rigor of development (mean 48%, 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 were based on guideline 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, range 7.0-9.0), current (median 8.0, range 7.0-9.0), practical (8.8, 7.0-9.0), clear (8.5, 6.0-9.0), and unbiased (9.0, 8.0-9.0). Final edited recommendations were rated as superior to the highest rated recommendation in the prior literature (median global quality score 42.8, range 38-45, for final recommendations vs. 42.0 for highest rated existing recommendations, range 37-45; $p=0.03$), 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 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.

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

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^{18, 33} for producing guidelines and used a systematic review of recent literature to assure that those recommendations were evidence-based and appropriately graded. 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 in order 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 guideline 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 of 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 are not broadly representative of the many fields involved in TIA care. We believe this rigid approach was justified by the reduced risk of bias rather than one that could lead to selection of experts with particular view points. However, our data-driven approach was generated using nominations from a questionnaire to which the response rate was only 1% and a higher response 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 supporting literature through February 2006. However, several of the source guidelines were updated during the process, including the 2006 AHA Guidelines for prevention of stroke in patients with ischemic stroke or TIA, and these new documents were not reviewed by the experts.³⁴⁻³⁷ 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 frequently updating.

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Appendix: 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.

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Figure Legend

Diagram showing the steps used to generate new guidelines recommendations. A systematic review located 257 prior guidelines documents with recommendations on TIA, of which 13 (containing 137 recommendations) met entry criteria. From these, 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.

Table 1. Levels of Evidence

Category 1: 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 of bias.

Category 2: 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, that have large confidence intervals. Results from RCTs that are based on secondary endpoints are also included in the category.

Category 3: 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.

Category 4: 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, along with expert medical opinion and general consensus.

Table 2. Recommendations for Initial Management of TIA

Recommendation	Source	Additional References
Hospital Admission		
<p><u>Hospitalization</u> should be considered for patients with their first TIA within the past 24 - 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).</p>	<p>Institute for Clinical Systems Improvement, 2005¹⁹</p>	<p>none</p>
<p>A <u>timely hospital referral</u> of a recent (within 1 week) TIA is always advisable and <u>hospital admission</u> is generally recommended in case of crescendo TIAs, or duration of symptoms >1 hour, symptomatic internal carotid stenosis >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).</p>	<p>Italian Guidelines for Stroke Prevention and Management, 2003²⁰</p>	<p>5, 32, 38</p>
<p>A <u>local admissions policy</u> should be developed by hospitals and representative physicians commonly referring patients to the hospital, setting out the categories of patients who will usually be referred or admitted to the hospital (Category 4).</p>	<p>Scottish Intercollegiate Guidelines Network, 1997²¹</p>	<p>none</p>
<p>Hospitals and general practitioners should agree on a <u>local admissions policy</u> and a <u>local protocol for referral to specialist assessment clinics</u> for patients with TIA who do not require hospital admission. Local written protocols should be available, setting 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) which the clinical situation may merit (Category 4).</p>	<p>Singapore Ministry of Health, 2003²³</p>	<p>39, 40</p>
Clinic Evaluation		
<p>A <u>specialized clinic</u> for the rapid assessment of TIA within 24 – 48 hours of diagnosis should be available (Category 4).</p>	<p>Royal College of Physicians Intercollegiate Stroke Working Party, 2004²²</p>	<p>5, 6</p>
Timing of Initial Medical Assessment		
<p>Physicians and institutions that provide care for patients with recent TIA should have <u>same-day access to imaging</u> such as CT/CTA, MR/MRA and ultrasound for patients who need it (Category 3).</p>	<p>Royal College of Physicians Intercollegiate Stroke Working Party, 2004²²</p>	<p>5, 38</p>
<p>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 MRI brain scanning, EKG, and carotid Doppler examination). <u>Initial assessment</u> should be performed within 24 – 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 of time may be appropriate (i.e. up to 7 days) (Category 4).</p>	<p>Scottish Intercollegiate Guidelines Network, 1997²¹</p>	<p>41</p>

For patients with a TIA within the last 2 weeks who are not hospitalized, it is recommended that they undergo prompt (within 24 – 48 hours) investigations (i.e. 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,
2003²⁰

5, 32, 38

Table 3. Recommendations for Evaluation of TIA

Recommendation	Source	Additional References
General		
A relevant <u>medical assessment</u> should be undertaken and neurological, cardiological, and radiological assessments considered for all patients with TIA to define the nature of the event, the need for investigations, further management and rehabilitation. The assessment should include an EKG, full blood count, serum electrolytes and creatinine, and fasting blood glucose and lipids (Category 4).	Singapore Ministry of Health, 2003 ²³	none
Brain Imaging		
The diagnosis of TIA is only clinical. Nevertheless the use of <u>computed tomography (CT) and computed tomography angiography (CTA) or magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA)</u> may show infarcts and important occlusive cervico-cranial vascular disease, and is recommended to corroborate differential diagnosis with other pathologies that can mimic TIA (Category 4).	Italian Guidelines for Stroke Prevention and Management, 2003 ²⁰	42, 43
There is general agreement that patients with manifestations suggestive of hemispheric TIA should receive a <u>CT or MRI scan</u> 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 reveal an area of brain infarction appropriate to TIA symptoms in over one fourth of patients. (Category 4).	American Heart Association, 1997 ²⁴	none
<u>Transcranial Doppler</u> 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).	Italian Guidelines for Stroke Prevention and Management, 2003 ²⁰	none
Carotid Imaging		
For TIA patients, <u>Doppler ultrasonography</u> of the neck is a useful investigation for etiological work up 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 ²⁰	44, 45
Conventional angiography of cerebral vessels was the gold standard examination in trials on carotid endarterectomy, therefore <u>Doppler ultrasonography</u> 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 ²⁰	none
Supra-aortic vessel <u>MRA and/or CTA</u> 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 ²⁰	46
The panel recommends <u>conventional angiography</u> primarily when Doppler ultrasonography and MR/CT angiography yield discordant results or if they are not feasible (Category 4).	Italian Guidelines for Stroke Prevention and Management, 2003 ²⁰	44, 46, 47
Cardiac Evaluation		
After a TIA, when a cardioembolic mechanism is suspected, transthoracic <u>echocardiography</u> (TTE) and/or transesophageal echocardiography (TEE) with testing for right to left shunting is recommended in patients under 45 years of age 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 ²⁰	48

Table 4. Recommendations for Medical Treatment of TIA

Recommendation	Source	Additional References
Noncardioembolic TIA		
Daily long-term <u>antiplatelet therapy</u> 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 ²¹	49
Where available, the combination of <u>aspirin (50 mg) and sustained-release dipyridamole (200 mg twice daily)</u> is a reasonable option for patients with TIA as first choice to reduce the risk of stroke (Category 1).	European Stroke Initiative, 2004 ²⁷	none
<u>Clopidogrel</u> may be slightly more effective than aspirin in the prevention of further vascular events (Category 1).	European Stroke Initiative, 2004 ²⁷	none
After a <u>noncardioembolic TIA</u> , <u>oral anticoagulation</u> is not recommended because there is no documented evidence of a higher benefit compared with antiplatelet therapy at an INR range of 2.0 - 3.0, while the risk of cerebral hemorrhagic complications is higher at an INR range above 3.0 (Category 1).	Italian Guidelines for Stroke Prevention and Management, 2003 ²⁰	50-55
Combination treatment with <u>sustained-release dipyridamole and aspirin</u> is a reasonable option for prevention of non-fatal stroke for people at high risk of cerebral ischemic events (Category 3).	New Zealand Guidelines Group, 2003 ²⁵	none
For patients who have had an <u>atherothrombotic TIA while taking aspirin</u> , clopidogrel (75 mg daily) or aspirin (25 mg) plus sustained-release dipyridamole (200 mg) twice daily are generally recommended (Category 3).	American Heart Association, 1999 ²⁶	none
Patients with TIA who are starting treatment with thienopyridine derivatives should receive <u>clopidogrel instead of ticlopidine</u> because clopidogrel has fewer side-effects and requires less monitoring (Category 4).	European Stroke Initiative, 2004 ²⁷	none
For patients with noncardioembolic TIA, <u>clopidogrel</u> may be prescribed as first choice or when aspirin alone, or aspirin in combination with dipyridamole are not tolerated (Category 4).	American College of Chest Physicians, 2004 and European Stroke Initiative, 2004 ^{27, 28}	none
Cardioembolic TIA		
For patients with persistent or paroxysmal <u>atrial fibrillation</u> (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 ²⁶	52, 54, 56-59
Aspirin (325 mg per day), or if aspirin intolerant, clopidogrel (75 mg), is recommended after a cardioembolic TIA associated with <u>nonvalvular atrial fibrillation</u> , but only if oral anticoagulation cannot be administered (Category 1).	Italian Guidelines for Stroke Prevention and Management, 2003 ²⁰	54, 60-64
Anticoagulants should not be used for patients with TIA who are in sinus rhythm (Category 1) unless there is a <u>high risk of cardiac embolism</u> due to paroxysmal atrial fibrillation or flutter, recent myocardial infarction, mechanical heart valve prosthesis, mitral stenosis, intracardiac clot, or severe dilated cardiomyopathy [EF <20%] (Category 4).	Royal College of Physicians Intercollegiate Stroke Working Party, 2004 ²²	52, 54, 56-59, 61, 65-76
In patients with <u>mitral valve prolapse or strands</u> , who have a history of TIA, we recommend antiplatelet therapy (Category 3).	American College of Chest Physicians, 2004 ²⁸	none

<p>Antiplatelet therapy is recommended after a TIA associated with <u>patent foramen ovale</u> if anticoagulation is not deemed indicated (Category 3).</p>	<p>Italian Guidelines for Stroke Prevention and Management, 2003²⁰</p>	<p>77</p>
<p>After a TIA in patients with <u>prosthetic heart valve</u> who are already on adequate oral anticoagulation, the combination of oral anticoagulants plus aspirin (81 mg per day) or dipyridamole is recommended (Category 3).</p>	<p>Italian Guidelines for Stroke Prevention and Management, 2003²⁰</p>	<p>none</p>
<p>Other Situations</p>		
<p>Patients with recent TIA and <u>unstable angina or non-Q wave MI</u> should be treated with a combination of clopidogrel 75 mg and aspirin 75 – 100 mg (Category 1).</p>	<p>European Stroke Initiative, 2004²⁷</p>	<p>78</p>
<p>Patients who have a history of TIA and who are undergoing <u>endarterectomy</u> should receive aspirin therapy (50 – 325 mg) beginning before surgery unless there are contraindications (Category 2).</p>	<p>American Heart Association, 1998²⁹</p>	<p>79</p>
<p>Clinicians should inquire about the use of <u>alternative complementary medicines</u> when assessing cardiovascular risk or prescribing medicine. Some herbal medicines have potential for toxic effects (Category 1) and some interact with medication (e.g., 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).</p>	<p>New Zealand Guidelines Group, 2003²⁵</p>	<p>none</p>

Table 5. Surgical Treatment

Recommendation	Source	Additional References
<p>Carotid endarterectomy Carotid endarterectomy is of overall benefit for symptomatic patients with recent (within 2 to 4 weeks) hemispheric nondisabling carotid artery ischemic events and ipsilateral <u>70% to 99% carotid artery stenosis</u>, and may also be beneficial for symptomatic patients with retinal transient ischemia (Category 1).</p>	American Heart Association, 1998 ²⁹	41, 80
<p>Carotid surgery may be indicated for certain patients with a history of carotid territory TIA and ipsilateral <u>stenosis of 50% to 69%</u> 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 males with recent (within 2 to 4 weeks) hemispheric symptoms and an irregular/ulcerated plaque (Category 4).</p>	European Stroke Initiative, 2004 ²⁷	41, 80, 81
<p>Carotid endarterectomy is not recommended for patients with carotid territory TIA with ipsilateral <u>stenosis less than 50%</u> (NAS CET criteria) (Category 1).</p>	Italian Guidelines for Stroke Prevention and Management, 2003 ²⁰	80
<p>Patients with moderate or severe internal carotid artery stenosis ipsilateral to a carotid TIA should be considered for carotid endarterectomy by an <u>experienced surgeon</u> (Category 1).</p>	Singapore Ministry of Health, 2003 ²³	none
<p>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, <u>preferably within 2 weeks of TIA</u> (cerebral or retinal) (Category 2).</p>	Royal College of Physicians Intercollegiate Stroke Working Party, 2004 ²²	41, 80-82
<p>Extracranial-intracranial bypass <u>Extracranial-intracranial bypass</u> is generally not recommended for patients with TIAs (Category 1). However, research is ongoing to determine whether there may be a subgroup of patients who might benefit from this treatment.</p>	American Heart Association, 1999 ²⁶	none

Table 6. Recommendations for Risk Factor Management in Patients with TIA

Recommendation	Source	Additional References
Cardiovascular Risk		
<p>Everyone with a history of TIA should be considered for treatment to reduce their cardiovascular risk. Risk factors for recurrent cerebrovascular ischemic events should be treated appropriately. This includes <u>lowering blood pressure and blood cholesterol</u> (with lifestyle modifications and/or drug therapy) in all patients with atherothrombotic TIA, irrespective of the baseline blood pressure and cholesterol measurements (Category 1).</p>	<p>Royal College of Physicians Intercollegiate Stroke Working Party, 2004²²</p>	<p>none</p>
<p>Because patients with TIA have a substantial frequency of coexistent heart disease which may shorten life-expectancy and cause marked morbidity, the potential presence of <u>coronary artery disease, cardiac arrhythmias, congestive heart failure, and valvular heart disease</u> should be considered and treated appropriately (Category 3).</p>	<p>American Heart Association, 1999²⁶</p>	<p>83-95</p>
Cholesterol		
<p>Treatment with a <u>statin</u> is recommended for most people following atherothromboembolic TIA (Category 3).</p>	<p>New Zealand Guidelines Group, 2003²⁵</p>	<p>96-98</p>
<p>Treatment of <u>hyperlipidemia</u> is recommended. The AHA Step II diet (≤30% of calories derived from fat, <7% from saturated fat, and <200 mg per day cholesterol consumed) is recommended along with maintenance of ideal body weight and engagement in regular physical activity. If fasting lipid levels remain elevated (LDL >130 mg/dL) for ≥3 months, use of a lipid-lowering agent such as a statin is recommended. The goal of therapy should be an LDL level <100 mg/dL (Category 3).</p>	<p>American Heart Association, 1999²⁶</p>	<p>none</p>
Diabetes		
<p><u>Fasting blood glucose</u> levels <126 mg/dL (7 mmol/L) are recommended. Diet, regular exercise (at least 3 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).</p>	<p>American Heart Association, 1999²⁶</p>	<p>99-104</p>
Hypertension		
<p>People presenting after a TIA should start <u>blood pressure lowering medication</u> unless the person has symptomatic hypotension. This medication should be given in addition to other appropriate medications such as an <u>antithrombotic agent</u> (aspirin, another antiplatelet agent, or warfarin), a <u>statin or other lipid-lowering agent</u>, and <u>diabetes management</u>. Treatment should start concurrently with intensive <u>lifestyle advice</u>. It is usually advisable to wait 7 to 14 days before starting blood pressure lowering medication (Category 1).</p>	<p>New Zealand Guidelines Group, 2003²⁵</p>	<p>99, 100</p>
<p>After TIA that is not due to dissection or cardiac embolism, the patient's <u>blood pressure</u> should be lowered to <140/90 or <130/80 for diabetics, irrespective of its initial level (unless he or she has symptomatic hypotension), with an 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 mm Hg provided there is no high-grade carotid stenosis (Category 3).</p>	<p>European Stroke Initiative, 2004; American Heart Association, 1999^{26, 27}</p>	<p>105-115</p>

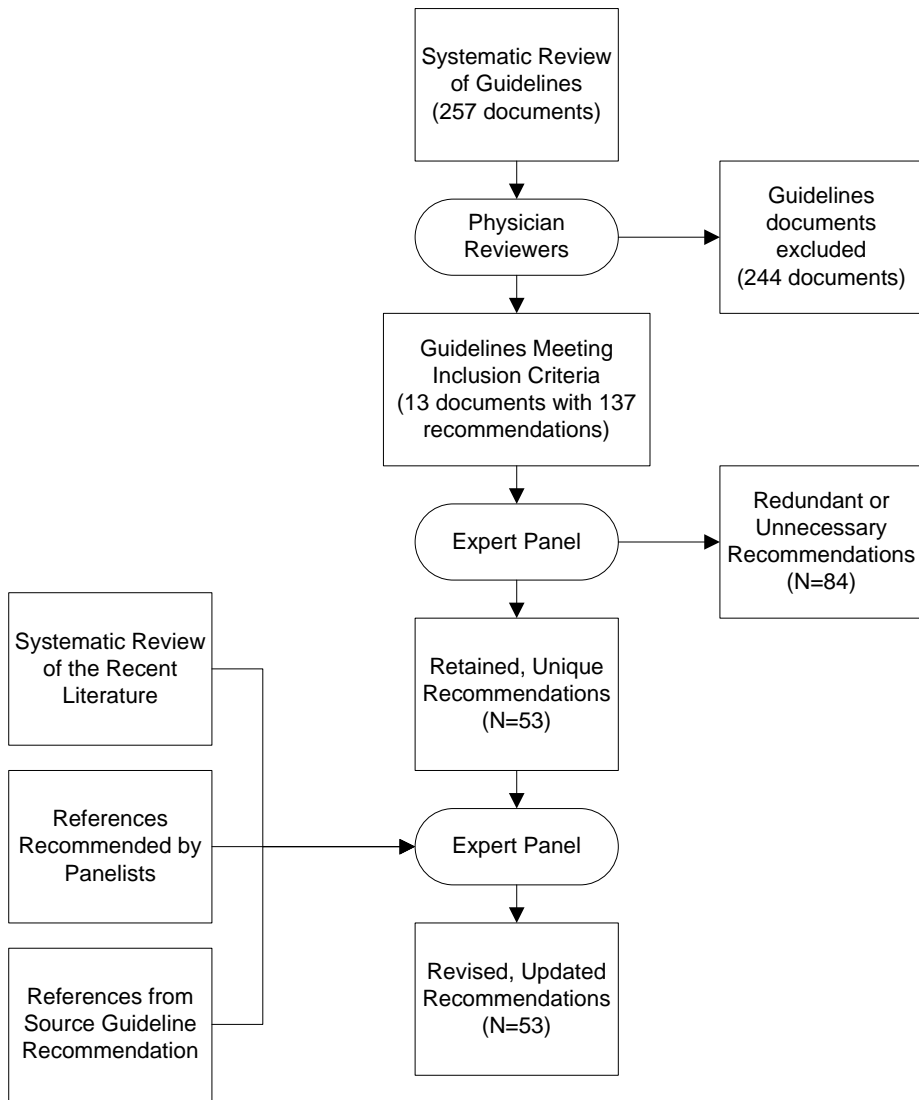
Lifestyle

All <u>smokers</u> 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 ²⁵	116
Encourage patients with TIA and a BMI greater than 25 (especially anyone who has a BMI >30), to commence graduated lifestyle change aimed at <u>weight reduction</u> (Category 3).	New Zealand Guidelines Group, 2003 ²⁵	none
<u>Physical activity</u> (at least 10 minutes of exercise such as walking, bicycling, running or swimming ≥ 3 to 4 times per week) is generally recommended for patients with TIA (Category 3).	American Heart Association, 1999 ²⁶	117, 118
The use of <u>antioxidant supplements</u> (vitamins E and C and betacarotene) is not recommended for the prevention or treatment of cardiovascular disease (Category 3).	New Zealand Guidelines Group, 2003 ²⁵	none
Generally, patients with TIA should be given appropriate advice on reducing the intake of <u>salt</u> (Category 3).	American Heart Association, 1999 ²⁶	none

Hormone Replacement Therapy

It may be harmful to use <u>hormone replacement therapy</u> for secondary stroke prevention in postmenopausal women (Category 2).	European Stroke Initiative, 2004 ²⁷	none
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Figure



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