

## Definition and Evaluation of Transient Ischemic Attack A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease

*The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.*

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**Abstract**—This scientific statement is intended for use by physicians and allied health personnel caring for patients with transient ischemic attacks. Formal evidence review included a structured literature search of Medline from 1990 to June 2007 and data synthesis employing evidence tables, meta-analyses, and pooled analysis of individual patient-level data. The review supported endorsement of the following, tissue-based definition of transient ischemic attack (TIA): a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction. Patients with TIAs are at high risk of early stroke, and their risk may be stratified by clinical scale, vessel imaging, and diffusion magnetic resonance imaging. Diagnostic recommendations include: TIA patients should undergo neuroimaging evaluation within 24 hours of symptom onset, preferably with magnetic resonance imaging, including diffusion sequences; noninvasive imaging of the cervical vessels should be performed and noninvasive imaging of intracranial vessels is reasonable; electrocardiography should occur as soon as possible after TIA and prolonged cardiac monitoring and echocardiography are reasonable in patients in whom the vascular etiology is not yet identified; routine blood tests are reasonable; and it is reasonable to hospitalize patients with TIA if they present within 72 hours and have an ABCD<sup>2</sup> score  $\geq 3$ , indicating high risk of early recurrence, or the evaluation cannot be rapidly completed on an outpatient basis. (*Stroke*. 2009;40:2276-2293.)

**Key Words:** AHA Scientific Statements ■ brain ■ brain ischemia ■ cerebral ischemia ■ ischemia ■ stroke ■ transient ischemic attack ■ acute stroke syndromes ■ acute cerebrovascular syndromes

Recent scientific studies have revised our understanding of 3 key aspects of transient ischemic attack (TIA): how it is best defined, what the early risk of stroke and other vascular outcomes is, and how it is best evaluated. This statement reviews and synthesizes recent scientific advances regarding the definition, urgency, and evaluation of TIA and

is designed to aid the clinician in the short- and long-term management of patients with TIA.

### Definition

TIAs are brief episodes of neurological dysfunction resulting from focal cerebral ischemia not associated with

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permanent cerebral infarction. In the past, TIAs were operationally defined as any focal cerebral ischemic event with symptoms lasting <24 hours. Recently, however, studies from many groups worldwide have demonstrated that this arbitrary time threshold was too broad because 30% to 50% of classically defined TIAs show brain injury on diffusion-weighted magnetic resonance (MR) imaging (MRI). Several groups have advanced newer, neuroimaging-informed, operational definitions of TIA such as “a brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction” (p 1715).<sup>1</sup> However, with rare exceptions,<sup>2</sup> the newer definitions have not yet been formally considered for endorsement or rejection by authoritative organizations. This statement reviews the data supporting revision of the definition of TIA. For those aspects found to be strong or conclusive, this statement endorses a specific revised definition, moving the field forward.

### Urgency

Large cohort and population-based studies reported in the last 5 years have demonstrated a higher risk of early stroke after TIA than generally suspected. Ten percent to 15% of patients have a stroke within 3 months, with half occurring within 48 hours. Acute treatments for TIA also have evolved, with new data supporting early rather than delayed carotid endarterectomy for TIA patients with carotid stenosis.

### Methods for Patient Evaluation

Over the last decade, substantial new diagnostic advances have occurred, including the widespread availability of MR angiography (MRA) and computed tomographic (CT) angiography (CTA), the recognition that diffusion MR frequently shows abnormalities in classic TIA patients, and the development and validation of risk stratification algorithms that identify TIA patients at higher and lower risk of early stroke.

Accordingly, clinicians are in need of updated guidance regarding the definition, urgency, and evaluation of patients with TIA. Formal levels of evidence and classes of recommendations are used. Because there are few definitive clinical trials in this area, this document is a scientific statement rather than a guideline. The treatment of TIA was not addressed by this writing panel because it is already covered in the Stroke Council’s guideline statements on treatment of acute cerebral ischemia and secondary prevention after ischemic stroke and TIA.<sup>3</sup>

### Review Methods and Key Words

This scientific statement is intended for use by physicians and allied health personnel caring for patients with transient neurological symptoms resulting from brain, retinal, and spinal cord ischemia. A formal literature search was performed of the following Medline database: using the search strategy *transient ischemic attack* crossed with terms *definition, epidemiology, incidence, prevalence, prognosis, recurrent stroke, diagnosis, imaging, magnetic resonance, diffusion, computed tomography, ultrasound, ECG, Holter, echocardiogram, and laboratory tests*, covering the dates

1990 through June 2007. Writing panel members were each assigned topic areas and filtered the retrieved articles using the criteria identified in the Stroke Council’s *Manual for Guidelines and Scientific Statements* to identify high- or medium-quality studies of diagnostic tests and prognostic instruments. Data were synthesized through the use of evidence tables, meta-analyses, and pooled analysis of individual patient-level data. The American Heart Association (AHA)/American College of Cardiology/Stroke Council Levels of Evidence grading algorithm was used to grade each recommendation (Tables 1 and 2). Prerelease review of the draft guideline was performed anonymously by 3 expert peer reviewers, by the members of the Stroke Council’s Scientific Statements Oversight Committee, and by the members of the Stroke Council Leadership Committee.

### TIA Epidemiology

Precise estimates of the incidence and prevalence of TIAs are difficult to determine mainly because of the varying criteria used in epidemiological studies to identify TIA. Lack of recognition by both the public and healthcare systems of the transitory focal neurological symptoms associated with TIAs also may lead to gross underestimates. Given these limitations, the incidence of TIA in the United States has been estimated to be ≈200 000 to 500 000 per year, with a population prevalence of 2.3% that translates into ≈5 million individuals.<sup>4,5</sup>

TIA incidence rates have been projected from different study cohorts in the United States and abroad, ranging from 0.37 to 1.1 per 1000 per year. An overall TIA incidence rate of 1.1 per 1000 US population has been estimated on the basis of a review of the National Hospital Ambulatory Medical Care Survey among 2 623 000 TIA cases diagnosed in US emergency departments between 1992 and 2000.<sup>6</sup> From the Greater Cincinnati/Northern Kentucky population between 1993 and 1994, the overall race-, age-, and gender-adjusted incidence rate for TIA was found to be 0.83 per 1000.<sup>7</sup> Between the years 2002 and 2004, the Oxford Vascular Study determined that the overall incidence rate of TIA was 0.66 per 1000 per year. Meanwhile, in rural and urban areas of Portugal, the crude overall annual incidence of TIA per 1000 population was found to be 0.67 and slightly higher in the rural region at 0.96 than in the urban area at 0.61.<sup>8</sup> Comparable to stroke incidence, TIA incidence markedly increases with age and varies by race-ethnicity. Increased likelihood of TIA with advancing age was supported in recent UK studies, with 6.41 per 1000 for patients >85 years of age.<sup>9</sup> In the Greater Cincinnati/Northern Kentucky population, the greatest incidence of TIA occurred in black men ≥85 of age at 16 events per 1000. The incidence of TIA increases exponentially with age regardless of race and gender.<sup>7</sup> In addition, TIAs were found to be more common in Mexican Americans compared with non-Hispanic whites at younger ages (45 to 59 years) but not at older ages.<sup>10</sup>

TIA prevalence rates vary, depending on the age distribution of the study population. For instance, the Cardiovascular Health Study estimated a prevalence of TIA in men of 2.7% for 65 to 69 years of age and 3.6% for 75 to 79 years of age. For women, TIA prevalence was 1.6% for 65 to 69 years of

Table 1. Applying Classification of Recommendations and Level of Evidence

		SIZE OF TREATMENT EFFECT <span style="float: right;">→</span>			
		CLASS I <i>Benefit &gt;&gt;&gt; Risk</i> Procedure/Treatment <b>SHOULD</b> be performed/administered	CLASS IIa <i>Benefit &gt;&gt; Risk</i> <i>Additional studies with focused objectives needed</i> <b>IT IS REASONABLE</b> to perform procedure/administer treatment	CLASS IIb <i>Benefit ≥ Risk</i> <i>Additional studies with broad objectives needed; additional registry data would be helpful</i> Procedure/Treatment <b>MAY BE CONSIDERED</b>	CLASS III <i>Risk ≥ Benefit</i> Procedure/Treatment should <b>NOT</b> be performed/administered <b>SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL</b>
ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	<ul style="list-style-type: none"> <li>■ Recommendation that procedure or treatment is useful/effective</li> <li>■ Sufficient evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>■ Recommendation in favor of treatment or procedure being useful/effective</li> <li>■ Some conflicting evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>■ Recommendation's usefulness/efficacy less well established</li> <li>■ Greater conflicting evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>■ Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>■ Sufficient evidence from multiple randomized trials or meta-analyses</li> </ul>
	LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	<ul style="list-style-type: none"> <li>■ Recommendation that procedure or treatment is useful/effective</li> <li>■ Evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>■ Recommendation in favor of treatment or procedure being useful/effective</li> <li>■ Some conflicting evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>■ Recommendation's usefulness/efficacy less well established</li> <li>■ Greater conflicting evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>■ Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>■ Evidence from single randomized trial or nonrandomized studies</li> </ul>
	LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	<ul style="list-style-type: none"> <li>■ Recommendation that procedure or treatment is useful/effective</li> <li>■ Only expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>■ Recommendation in favor of treatment or procedure being useful/effective</li> <li>■ Only diverging expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>■ Recommendation's usefulness/efficacy less well established</li> <li>■ Only diverging expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>■ Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>■ Only expert opinion, case studies, or standard of care</li> </ul>
Suggested phrases for writing recommendations†		should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	is not recommended is not indicated should not is not useful/effective/beneficial may be harmful

\*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as gender, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use. A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Even though randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

†In 2003, the ACC/AHA Task Force on Practice Guidelines developed a list of suggested phrases to use when writing recommendations. All guideline recommendations have been written in full sentences that express a complete thought, such that a recommendation, even if separated and presented apart from the rest of the document (including headings above sets of recommendations), would still convey the full intent of the recommendation. It is hoped that this will increase readers' comprehension of the guidelines and will allow queries at the individual recommendation level.

age and 4.1% for 75 to 79 years of age.<sup>11</sup> In the younger Atherosclerosis Risk in Communities cohort, the overall prevalence of TIAs was found to be 0.4% among adults 45 to 64 years of age.<sup>12</sup>

Among patients who present with stroke, the prevalence of prior TIA has been reported to range from 7% to 40%. The percentage varies, depending on such factors as how TIA is defined, which stroke subtypes are evaluated, and whether the study is a population-based series or a hospital-based series.<sup>13,14</sup> In the population-based Northern Manhattan Stroke Study, the prevalence of TIAs among those who presented with first ischemic stroke was 8.7%.<sup>15</sup> The majority of TIAs occurred within 30 days of the patient's first ischemic stroke, with 41% of the TIAs lasting <1 hour. Studies that have included patients with prior stroke such as the Harvard Stroke Registry and National Institute of Neurological Disorders and Stroke data bank have reported higher rates of

TIAs as great as 50% among those with atherothrombotic stroke.<sup>16,17</sup> In 2 population-based studies (Oxford Vascular Study and Oxfordshire Community Stroke Project) and 2 other randomized trials (UK TIA Aspirin Trial and the European Carotid Surgery Trial), the timing of a TIA before stroke was highly consistent, with 17% occurring on the day of the stroke, 9% on the previous day, and another 43% at some point during the 7 days before the stroke.<sup>18–20</sup> In another population-based study that was biethnic with Mexican Americans and non-Hispanic whites, approximately half of the 90-day stroke risk for TIA occurred within the first 2 days, suggesting that in general TIA patients are at very high risk for a recurrent cerebrovascular event<sup>21</sup> (see TIA: Short-Term Stroke Risk below).

Variability in the use of brain imaging and the type of diagnostic imaging used can also markedly affect estimates of the incidence and prevalence of TIAs. One study has esti-

**Table 2. Definition of Classes and Levels of Evidence Used in AHA Recommendations**

Class I	Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment
Class IIa	The weight of evidence or opinion is in favor of the procedure or treatment
Class IIb	Usefulness/efficacy is less well established by evidence or opinion
Class III	Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful
Level of Evidence A	Data derived from multiple randomized clinical trials
Level of Evidence B	Data derived from a single randomized trial or nonrandomized studies
Level of Evidence C	Consensus opinion of experts
Diagnostic recommendation	
Level of Evidence A	Data derived from multiple prospective cohort studies using a reference standard applied by a masked evaluator
Level of Evidence B	Data derived from a single grade A study or $\geq 1$ case-control studies or studies using a reference standard applied by an unmasked evaluator
Level of Evidence C	Consensus opinion of experts

mated that a revision of TIA definitions to include the absence of changes on an MRI could lead to a reduction in the incidence of TIAs by  $\approx 30\%$  and a resultant 7% increase in the number of cases labeled as stroke.<sup>22</sup> Thus, a blend of factors related to the diagnostic process influences the ultimate diagnosis of a TIA.

### Definition

Often, health professionals and the public consider TIAs benign but regard strokes as serious. These views are incorrect. Stroke and TIA are on a spectrum of serious conditions involving brain ischemia. Both are markers of reduced cerebral blood flow and an increased risk of disability and death. However, TIAs offer an opportunity to initiate treatment that can forestall the onset of permanently disabling injury.<sup>23,24</sup>

The traditional definition of a TIA was a sudden, focal neurological deficit of presumed vascular origin lasting <24 hours. The arbitrary 24-hour threshold used to distinguish TIA from stroke arose in the mid-1960s.<sup>1</sup> At that time, it was assumed that transient symptoms disappeared completely because no permanent brain injury had occurred. The term *TIA* was applied to events lasting up to 24 hours, and the term *reversible ischemic neurological deficit* was applied to events lasting 24 hours to 7 days.

Only symptoms enduring >7 days were thought to reliably indicate infarction and received the designation *stroke*. During the 1970s, it became clear that the great preponderance of events lasting 24 hours to 7 days were associated with infarction, rendering the term reversible ischemic neurological deficit obsolete, and it disappeared from standard nomenclature. More recently, high-resolution CT and especially diffusion-weighted MRI studies have demonstrated that many ischemic episodes with symptoms lasting <24 hours also are associated with new infarction. One third of individuals with traditionally defined TIAs exhibit the signature of new infarction on diffusion-weighted MRI. These findings highlight an inconsistency between the concept of TIA (ischemia causing symptoms but no infarction) and the traditional definition of TIA. With these observations in mind, a group of cerebrovascular physicians proposed a tissue-based, rather than time-based, definition in 2002<sup>1</sup>: “transient ischemic attack (TIA): a brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction” (p 1715).

This proposed new definition has been well received. Many cerebrovascular experts endorsed the new definition,<sup>2,25</sup> and it has been widely incorporated into the study design of major clinical trials (Warfarin-Aspirin Recurrent Stroke Study [WARSS],<sup>26</sup> Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment [RESPECT],<sup>27</sup> Prevention Regimen for Effectively Avoiding Second Strokes [PROFESS],<sup>28</sup> Evaluation of the STARflex Septal Closure System in Patients With a Stroke or Transient Ischemic Attack Due to Presumed Paradoxical Embolism Through a PFO [CLOSURE 1]). However, some have raised concerns. To shed additional light on key issues, individual committee members organized a pooled, patient-level data analysis integrating data from published studies of TIA and MRI.

### Arguments in Favor of the New Definition

**The classic 24-hour definition is misleading in that many patients with transient <24-hour events actually have associated cerebral infarction.**

#### Evidence

Sixteen studies were identified reporting diffusion MRI findings in traditional 24-hour TIA patients.<sup>29–44</sup> All studies demonstrated a high frequency of restricted diffusion lesions in clinically appropriate locations. The committee’s pooled analysis of 808 patients from 10 centers demonstrated that restricted diffusion lesions were present in 33% (Table 3).<sup>45</sup> Serial MRI studies have demonstrated that these diffusion-weighted imaging (DWI) lesions frequently evolve into chronic ischemic lesions on follow-up T2 or fluid-attenuated inversion recovery images. The 24-hour symptom duration rule thus misclassifies up to one third of patients who have actually experienced underlying tissue infarction as not having suffered tissue injury.

#### Conclusion

A 24-hour duration of symptoms does not accurately demarcate patients with and without tissue infarction (**Class III, Level of Evidence A**).

**Table 3. Frequency of DWI Abnormality in Patients With Transient Neurological Episodes of Different Durations: Pooled Data From 10 MRI Studies Enrolling 818 Patients<sup>45</sup>**

Duration of Symptoms, h	DWI Hyperintensity
0–1	33.6
1–2	29.5
2–3	39.5
3–6	30.0
6–12	51.1
12–18	50.0
18–24	49.5

**The traditional definition can impede the administration of acute stroke therapies.**

#### *Evidence*

Acute stroke interventions such as intravenous tissue plasminogen activator must be administered much sooner than 24 hours after symptom onset. In addition, the sooner tissue plasminogen activator is administered, the greater its efficacy is.<sup>46</sup> Some physicians are reluctant to initiate acute stroke interventions because of concern that symptoms may resolve spontaneously. A 24-hour definition for TIA encourages the wait and see approach rather than immediate initiation of urgent interventions. However, patients with deficits lasting  $\geq 1$  hour are highly likely to develop permanent deficits unless an effective therapy is initiated. Fewer than 1 in 6 patients who have symptoms that have lasted for 1 hour will have their symptoms fully resolve by 24 hours.<sup>47</sup> Among patients with potentially disabling deficits who are eligible for thrombolytic therapy within 3 hours of onset, only 2% of placebo-treated individuals fully recover within 24 hours of symptom onset.<sup>48</sup>

#### *Conclusion*

Defining TIA with a 24-hour maximum duration has the potential to delay the initiation of effective stroke therapies (**Class I, Level of Evidence C**).

**A 24-hour limit for transiently symptomatic cerebral ischemic is arbitrary and not reflective of the typical duration of these events.**

#### *Evidence*

Most studies have found that most classically defined TIAs are brief,  $< 1$  hour in duration.<sup>47,49–51</sup> In the pooled analysis of MR-studied patients, 60% of events were  $< 1$  hour, 71% were  $< 2$  hours, and only 14% were  $> 6$  hours.<sup>45</sup> Consideration of symptom durations alone, regardless of association with underlying tissue injury, provides no indication that the 24-hour time point is of any special significance.

#### *Conclusion*

The frequency distribution of durations of transiently symptomatic cerebral ischemic events shows no special relationship to the 24-hour time point (**Class III, Level of Evidence A**).

**Disease definitions in clinical medicine, including those for ischemic injuries, are most useful when tissue based.**

#### *Evidence*

Seeking the pathological basis of disease and directing treatment at underlying biological processes are central tenets of modern medicine. Tissue-based definitions are the rule for ischemic injuries affecting other end organs. For example, angina is distinguished from myocardial infarction not by symptom duration but by evidence of myocardial tissue injury. Time-based definitions unproductively focus diagnostic attention on the temporal course rather than underlying pathophysiology.<sup>52</sup> The key diagnostic issue in patients with cerebral ischemic events is not how long the event lasted but rather the cause of the ischemia and whether cerebral injury occurred. A tissue-based definition of TIA encourages use of neurodiagnostic tests to identify brain injury and its vascular genesis.

#### *Conclusion*

A tissue-based definition of TIA will harmonize cerebrovascular nosology with other ischemic conditions and appropriately direct diagnostic attention to identifying the cause of ischemia and whether brain injury occurred (**Class IIa, Level of Evidence C**).

### **Arguments Against the New Definition**

**The new definition requires brain imaging that will vary depending on the availability of imaging resources. Stroke and TIA incidence rates will differ depending on whether and when detailed imaging studies are performed.**

#### *Evidence*

The new definition of TIA is not different from other medical diagnoses in that it is based on all available information from the history, examination, and diagnostic studies. Just as diagnostic tests such CT or MRI are required to differentiate an ischemic from a hemorrhagic stroke,<sup>53</sup> diagnostic tests play a key role in the new definition of TIA to identify whether there is evidence of brain infarction. In some situations, the diagnosis of stroke can be inferred from clinical data in the absence of positive imaging evidence (see below).

#### *Conclusion*

Imaging studies currently play a central role in both determining the origin of and classifying acute cerebrovascular syndromes (**Class I, Level of Evidence A**).

**Stroke and TIA rates will not be directly comparable to previously defined rates if the new definition is adopted.**

#### *Evidence*

Stroke and TIA rates will likely be altered on the basis of the new definition, and rates based on the new definition will not be directly comparable with prior studies.<sup>7,22</sup> Advances in diagnostic methods typically change the precision with which diagnoses are rendered. In the analogous setting of acute coronary ischemia, the recent introduction of serum troponin measurements that more sensitively identify myocyte injury has increased the incidence of myocardial infarction, in lieu of angina, by one-third.<sup>54,55</sup> When comparison with prior TIA data is required, investigators can collect data regarding symptom

duration. Events classified with the new definition can then be classified on the basis of the traditional definition for comparison with historical data.

### Conclusions

The new definition will modestly alter stroke and TIA prevalence and incidence rates, but these changes are to be encouraged, not discouraged, because they reflect increasing accuracy of diagnosis (**Class IIa, Level of Evidence C**). To facilitate comparison with prior studies, symptom duration is an important data element to collect in epidemiological studies (**Class IIa, Level of Evidence C**).

**Primary care physicians may be confused as to whether to designate a presumed transient event of brain ischemia a stroke or TIA if they do not have immediate access to neuroimaging or other diagnostic resources.**

### Evidence

Just as it is difficult to determine whether a severe episode of chest pain represents an angina attack or a myocardial infarction without diagnostic testing,<sup>56</sup> it is difficult to determine whether transient ischemic neurological symptoms have resulted in brain infarction without a diagnostic evaluation.

### Conclusion

It would be reasonable to adopt a term such as *acute neurovascular syndrome* (see below) that can be used until the diagnostic evaluation is completed or if a diagnostic evaluation is not performed (**Class IIa, Level of Evidence C**). A specific proposal for such terminology is beyond the scope of this TIA statement.

**Terms such as cerebral infarction with transient symptoms or transient symptoms with infarction have been suggested to describe events that last <24 hours but are associated with cerebral infarction while retaining the 24-hour time threshold in syndrome definition.**

### Evidence

Cerebral infarctions can occur in association with highly transient symptoms as a result of infarction in less eloquent brain regions, redundancy in neural networks, neuroplasticity, and additional mechanisms.<sup>37,45,57</sup> However, there is no evidence to support incorporation of any particular time criterion for cerebral infarction with transient symptoms or transient symptoms with infarction. A cerebral infarction with symptoms lasting 23 hours does not appear to differ in any fundamental way from a cerebral infarction with symptoms lasting 25 hours. There is no biological justification to continue to treat the 24-hour time point as particularly important to recognize.

### Conclusions

It is reasonable to use terms like cerebral infarction with transient signs without a fixed time criterion (**Class IIa, Level of Evidence A**). We do not support linking any of these terms to a 24-hour time criterion because all cerebral infarction definitions with specific time limitations are capricious (**Class III, Level of Evidence A**). We prefer to emphasize that all episodes of acute brain ischemia should be urgently assessed, including events not associated with underlying

tissue infarction, events associated with minor degrees of infarction, and events associated with major infarction.

**The phrase “typically <1 hour” in the new definition is not helpful because the 1-hour time point, like the 24-hour time point, does not accurately distinguish between patients with or without acute cerebral infarction.**

### Evidence

Among episodes lasting <24 hours, the majority of events are indeed  $\leq 1$  hour in duration. In the Levy<sup>47</sup> series, 60% of the <24-hour episodes were <1 hour in duration. In the pooled analysis of MR-studied patients, 60% of events were <1 hour, 11% were 1 to 2 hours, and only 14% were >6 hours.<sup>45</sup> However, the 1-hour time point did not reliably differentiate patients likely to exhibit infarction from those who were unlikely to exhibit infarction, nor did other <24-hour time points that have been proposed for a revised TIA definition, including  $\leq 2$  hours.<sup>58–60</sup> As shown in Table 3, although the likelihood of cerebral infarction increases with longer symptom duration, the time course of the clinical manifestations is only a modest determinant of brain infarction. Approximately 30% of TIAs lasting <1 hour demonstrate evidence of brain injury based on DWI MRI. Furthermore, no single time threshold corresponds to a high likelihood of cerebral infarction.<sup>45</sup> Once an episode lasts >6 hours, underlying tissue infarction is more likely than not to be present. However, <60% of events that last between 6 and 24 hours demonstrate evidence of brain infarction on DWI (Table 3).

### Conclusion

It is impossible to define a specific time cutoff that can distinguish whether a symptomatic ischemic event will result in brain injury with high sensitivity and specificity (**Class III, Level of Evidence A**).

## AHA-Endorsed Revised Definition of TIA

On the basis of the above considerations, the writing committee found that the key elements of the 2002 Working Group’s proposed definition are well supported by the data in the literature. However, the writing committee also determined that the reference to a 1-hour time point in the new definition was not helpful because the 1-hour time point does not demarcate events with and without tissue infarction. Accordingly, the writing committee endorses the following revised definition:

**Transient ischemic attack (TIA): a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.**

By using a tissue rather than time criterion, this revised definition recognizes TIA as a pathophysiological entity. Similar to an attack of angina, the typical duration of a TIA is <1 or 2 hours, but occasionally, prolonged episodes occur. Diagnostic certainty will depend on the extent of evaluation the individual patient receives. This concept is not unique to brain ischemia; it is typical of most medical diagnoses. Brain imaging currently and serum diagnostic studies likely in the future increase diagnostic certainty regarding whether a particular episode of focal ischemic deficits was a TIA or a cerebral infarction.

Based on the new definitions of TIA, an ischemic stroke is defined as an **infarction of central nervous system tissue**. Similar to TIAs, this definition of ischemic stroke does not have an arbitrary requirement for duration. Unlike TIAs, ischemic strokes may be either symptomatic or silent. Symptomatic ischemic strokes are manifest by clinical signs of focal or global cerebral, spinal, or retinal dysfunction caused by central nervous system infarction. A silent stroke is a documented central nervous system infarction that was asymptomatic.

Some infarcts cannot be visualized, even with state-of-the-art imaging techniques (eg, isolated small lateral medullary infarcts). Therefore, in some situations, the diagnosis of an ischemic stroke will be rendered on the basis of clinical features despite the lack of imaging confirmation such as prolonged deficits lasting several days and clinical syndrome consistent with a small deep infarct. In other situations, the imaging study is performed too soon to identify tissue injury. For example, a patient may present with a clinical syndrome typical of a stroke and have a CT scan performed, especially within the first few hours, that does not reveal acute ischemic abnormalities. If the symptoms persist, the patient is left with a permanent neurological disability, and no follow-up imaging studies are performed, a diagnosis of ischemic stroke is certainly appropriate.

The definition of TIA proposed above is not constrained by limitations of DWI or any other imaging modality. The definition is tissue based, similar to the diagnoses of cancer and myocardial infarction. However, unlike the situation with cancer but similar to that with myocardial infarction, the histological diagnosis of brain infarction typically must be inferred from clinical, laboratory, and imaging data. The most appropriate clinical, laboratory, and imaging modalities to support the diagnosis of TIA versus stroke will evolve over time as diagnostic techniques advance. Specific criteria for the diagnosis of brain infarction also will evolve, just as the laboratory criteria for the diagnosis of myocardial infarction evolved as new serum markers were identified. However, the definition of the entity will not vary; ischemic stroke requires infarction, whereas TIA is defined by symptomatic ischemia with no evidence of infarction. The sensitivity and specificity of currently available neuroimaging studies are discussed below.

For patients with relatively brief symptom duration (eg, symptoms that persist several hours but less than a day) who do not receive a detailed diagnostic evaluation, it may be difficult to determine whether stroke or TIA is the most appropriate diagnosis. For these patients, it would be reasonable that a term such as *acute neurovascular syndrome* should be chosen, analogous to the terminology used in cardiology (**Class IIa, Level of Evidence C**).<sup>61–63</sup> These terms also are appropriate for patients who have just developed acute cerebrovascular symptoms in whom it is not yet known whether deficits will rapidly resolve or persist and in whom neurodiagnostic testing has not yet been undertaken. Again, a specific proposal for such terminology is beyond the scope of this TIA statement.

### TIA: Short-Term Stroke Risk

It has long been recognized that TIA can portend stroke,<sup>64,65</sup> with several studies demonstrating elevated long-term stroke

risk.<sup>66–74</sup> Numerous studies also have shown that the short-term risk of stroke is particularly high, with most studies finding risks exceeding 10% in 90 days.<sup>7,13,21,75–84</sup> Risk is particularly high in the first few days after TIA, with most studies finding that one quarter to one half of the strokes that occur within 3 months occur within the first 2 days.<sup>7,21,75,79,82,84,85</sup> For example, studies in northern California and Oxfordshire found the risk of stroke in the first 24 hours after TIA to be  $\approx 4\%$ ,<sup>75,86</sup> which is about twice the risk of myocardial infarction or death in patients presenting with acute coronary syndromes ( $\approx 2\%$  at 24 hours).<sup>87</sup> These findings underscore the need for prompt evaluation and treatment of patients with symptoms of ischemia.

Ischemic stroke appears to carry a lower short-term risk of subsequent ischemic stroke than TIA, with reported 3-month risks generally ranging from 4% to 8%.<sup>79–81,83,88–101</sup> The degree of early recovery may be predictive of greater risk, possibly by indicating that tissue is still at risk.<sup>102–106</sup>

Risk of cardiac events also is elevated after TIA. In 1 large study, 2.6% of TIA patients were hospitalized for major cardiovascular events (myocardial infarction, unstable angina, or ventricular arrhythmia) within 90 days.<sup>107</sup> Over the course of  $\geq 5$  years, a nearly equal number of patients with TIA will have myocardial infarction or sudden cardiac death as will have a cerebral infarction.<sup>108</sup> A prior AHA scientific statement provides detailed guidance on the coronary risk evaluation in patients with TIA.<sup>109</sup>

### Risk Stratification

Several studies have identified risk factors for stroke after TIA, which may be useful in making initial management decisions. Three very similar formal prediction rules have been developed and cross-validated in northern California and Oxfordshire.<sup>75,85</sup> The California score and the ABCD score both predict short-term risk of stroke well in independent populations of patients presenting acutely after a TIA.<sup>110</sup> The newer ABCD<sup>2</sup> score was derived to provide a more robust prediction standard and incorporates elements from both prior scores.<sup>110</sup> Patients with TIA score points (indicated in parentheses) for each of the following factors: age  $\geq 60$  years (1); blood pressure  $\geq 140/90$  mm Hg on first evaluation (1); clinical symptoms of focal weakness with the spell (2) or speech impairment without weakness (1); duration  $\geq 60$  minutes (2) or 10 to 59 minutes (1); and diabetes (1). In combined validation cohorts, the 2-day risk of stroke was 0% for scores of 0 or 1, 1.3% for 2 or 3, 4.1% for 4 or 5, and 8.1% for 6 or 7.

These prediction rules do not incorporate imaging findings, which have been shown to have prognostic value. The presence of a new infarct on brain imaging, which was consistent with the classic definition of TIA but would now lead to a diagnosis of stroke, is associated with an  $\approx 2$ - to 15-fold increase in subsequent short-term risk of stroke.<sup>35,37,79,83,111,112</sup> Evidence of vessel occlusion on acute brain MRA also has been associated with a 4-fold increased short-term risk of stroke.<sup>112</sup> MRI changes have been associated with the clinical factors identified in prior prediction rules,<sup>42</sup> so it is unclear how much they will add to validated prediction rules such as ABCD.<sup>2</sup>

## Hospitalization

Hospitalization rates after TIA vary widely among practitioners, hospitals, and regions. A study from the National Hospital Ambulatory Medical Care Survey found that 54% of patients with TIA were admitted to the hospital, with rates varying from 68% in the northwest United States to 41% in the west.<sup>6</sup>

Close observation during hospitalization has the potential to allow more rapid and frequent administration of tissue plasminogen activator should a stroke occur. A cost-utility analysis demonstrated that hospitalization was cost-effective for patients with 24-hour risk of stroke >4% solely on this basis.<sup>113</sup> Prospective studies are required on the efficacy and safety of the use of tissue plasminogen activator in patients with recent prior clinical symptoms lasting <24 hours associated with small DWI lesions. In the past, these patients were diagnosed as having TIA, which did not contraindicate lytic therapy. Now, these patients will be classified as minor cerebral infarction patients. However, it is likely that the risk of bleeding with lytic therapy is much lower in these patients than in patients with large recent prior cerebral infarcts. Hospitalization may have other benefits as well. It permits cardiac monitoring and facilitates rapid diagnostic evaluation. Rates of adherence to secondary prevention interventions may also be greater after hospitalization.<sup>114</sup> No randomized trial has evaluated the benefit of hospitalization or the utility of the ABCD<sup>2</sup> score in assisting with triage decisions.

## Diagnostic Evaluation

### TIA: Diagnostic Evaluation

Rapid advances in imaging technology in the past 25 years have contributed significantly to our understanding of the pathophysiology of TIAs. The goals of the modern neuroimaging evaluation of TIA are (1) to obtain evidence of a vascular origin for the symptoms either directly (evidence of hypoperfusion and/or acute infarction) or indirectly (identification of a presumptive source such as a large-vessel stenosis)<sup>98</sup>; (2) to exclude an alternative nonischemic origin; (3) to ascertain the underlying vascular mechanism of the event (eg, large-vessel atherothrombotic, cardioembolic, small-vessel lacunar), which, in turn, allows selection of the optimal therapy; and (4) to identify prognostic outcome categories.

MRI is not as widely available as CT and is generally more expensive. In a study of TIAs evaluated in emergency departments in Ontario, Canada, from May to December 2000, only 3% received MRI within 30 days.<sup>84</sup> A study of TIAs seen in regions throughout the United States from 1992 to 2001 revealed that MRI was performed in <5% of cases.<sup>6</sup> However, the rates of neuroimaging with CT or MRI increased significantly over the 10 years of the study, rising to >70% by 2001. The percentage of those with MRI studies in the later years of the study was not specified.

### Computed Tomography

The use of head CT scans in patients with TIAs has been the subject of numerous reports over the past few decades. CT studies performed in the 1980s first suggested that TIAs may,

in fact, be associated with neuroimaging evidence of infarction.

Among patients who present to the emergency department with a TIA, studies show that ≈50% to 70% have a CT performed. In a 10-year analysis of TIA patients obtained from the National Hospital Ambulatory Medical Care Survey, CT scans were performed in 56% of patients.<sup>6</sup> In 16 Northern California emergency departments, Douglas et al<sup>111</sup> found that CTs were obtained in 67% of patients. A nonvascular pathology (tumors, abscesses, or subdural hematomas) is identified on CT in only 1% to 5% in various series.<sup>115,116</sup>

With respect to the frequency of identifying brain infarcts in patients with TIAs, one needs to analyze whether the infarcts reported are new or old, whether they are in a clinically relevant vascular territory or not, and whether the infarcts are cortical or in a perforator territory. The Dutch TIA Trial studied 606 patients and found a relevant infarct in 13% of patients and an anatomically irrelevant infarct in 6%, for a total frequency of 19%.<sup>117</sup> In the cohort of patients with anterior circulation TIAs, 58% of infarcts were in perforator distributions and 42% were cortical in nature. In the northern California study, a new infarct was identified in 4% of patients.<sup>111</sup> Numerous CT studies have reported an increased frequency of lesions with longer duration of the TIA.

Prognostic information with regard to CT findings has been reported in global TIA populations and those with specific underlying conditions such as internal carotid artery stenosis. In the northern California study, the authors reported that a new infarct on CT was associated with an increased risk of stroke during the 90-day follow-up period after adjustment for confounding variables.<sup>111</sup> The North American Symptomatic Carotid Endarterectomy Trial investigators did not find an increased risk of stroke in patients with CT evidence of a relevant infarct in the 70% to 99% stenosis group. However, this investigative group did report that CT-identified leukoaraiosis was associated with an increased risk of stroke in a mixed group of TIA and stroke patients with 50% to 99% internal carotid artery stenosis, especially for those patients with widespread leukoaraiosis.<sup>118</sup>

The utility of other CT modalities (CTA, CT perfusion) has not been studied extensively in patients with TIAs. There have been studies reporting that a CT battery including noncontrast head CT, CTA, and CT perfusion can be accomplished fairly quickly in patients with acute stroke and can provide comprehensive information.<sup>119</sup> However, systematic reports of a multimodal CT approach for evaluation of patients with TIA alone are lacking. Limitations of CT include radiation and iodine contrast exposure.<sup>120</sup>

### Magnetic Resonance Imaging

Conventional MRI is more sensitive than standard CT in identifying both new and preexisting ischemic lesions in TIA patients. Across various studies, MRI has shown at least 1 infarct somewhere in the cerebrum in 46% to 81% of TIA patients.<sup>121,122</sup> In the past decade, new MRI techniques of diffusion and perfusion imaging have afforded new insights into the pathophysiology of cerebral ischemia. The spectrum of ischemic tissue alterations underlying transient clinical symptoms is now understood to variably include synaptic



transmission failure, cytotoxic edema, and permanent tissue injury, and these processes are easily delineated in individual patients on MRI.<sup>61</sup> Moreover, clinical studies have demonstrated that MRI is of substantial clinical utility in patients with TIAs.

Pooled data from reports in the literature to date (19 studies) have now confirmed that DWI provides a more precise evaluation of ischemic insult in TIA patients compared with standard CT and MRI studies.<sup>29–32,34–38,40–44,123–127</sup> These series show convergent results regarding the frequency of DWI positivity among TIA patients; among the 19 studies including 1117 patients, the aggregate rate of DWI positivity is 39%, with frequency by site ranging from 25% to 67%. Few studies have systematically assessed the follow-up imaging characteristics of DWI-positive lesions in the setting of TIA. In 2 series, the proportion of patients demonstrating corresponding T2-weighted signal evidence of permanent injury on follow-up imaging ranged from 76% to 100%.<sup>36,127</sup> Animal studies have demonstrated that even when early diffusion lesions reverse, the underlying tissue typically demonstrates neuronal dropout.<sup>128,129</sup> Accordingly, the small group of patients with transient symptoms who evidence acute diffusion abnormalities but not late T2 changes still fall within the broad tissue definition of stroke.

Only 2 small studies have systematically assessed perfusion-weighted MRI in the evaluation of TIA patients. In both of these series, perfusion abnormalities were found in approximately one third of patients.<sup>30,38</sup> In these 2 series, the frequency of isolated PWI abnormalities (without DWI lesions) ranged from 3% to 13%.

Several studies have analyzed the imaging characteristics of DWI-positive lesions.<sup>29,37,125</sup> Compared with patients with clinical stroke, DWI-positive lesions tend to be smaller in TIA patients. In their series of 36 patients with DWI-positive lesions, Ay and colleagues<sup>37</sup> reported multiple lesions in 17 patients. There does not appear to be a predilection for cortical or subcortical regions or particular vascular territories.

Various studies have suggested that DWI positivity is associated with several clinical characteristics, including longer symptom duration, motor deficits, aphasia, and large-vessel occlusion present on MRA.<sup>29,35,42</sup> In a multicenter, patient-level analysis of 808 patients in which DWI lesions were present in 33% of TIA patients, presence of motor symptoms, longer duration of TIA, and MRI within 24 hours of resolution of symptoms were univariate predictors of DWI positivity.<sup>45</sup> In patients with available data, motor symptoms were present in 67% (144 of 215) of DWI-positive versus 52% (236 of 451) of DWI-negative patients (odds ratio, 1.85; 95% CI, 1.32 to 2.59). Median duration of symptoms was longer among patients with a DWI abnormality (60 minutes [interquartile range, 15 to 240 minutes] versus 30 minutes [IQR, 10 to 180 minutes];  $P=0.01$ ). Time epoch analysis indicated that patients first became more likely than not to have a DWI abnormality when their symptoms lasted >6 hours. DWI positivity was more frequent in patients who underwent MRI within 24 hours of symptom resolution than those imaged after 24 hours (37.1% versus 29.8%; odds ratio, 1.39; 95% CI, 1.00 to 1.93). DWI-positive and DWI-negative patient groups showed no differences in age, sex, or presence

of language symptoms (25% in both groups; odds ratio, 1.01; 95% CI, 0.70 to 1.44).

Recently, several studies have demonstrated that DWI positivity has important prognostic implications. Studies show that classically defined TIA patients who have abnormalities on DWI scans have a higher risk of recurrent ischemic events than those without such abnormalities. Redgrave and colleagues<sup>130</sup> found that, among 200 classically defined TIA patients, DWI positivity correlated with the ABCD and California clinical scores for predicting risk of stroke after TIA. Purroy and colleagues<sup>35</sup> performed MRI within 7 days of symptom onset in 83 classic TIA patients. Symptoms lasted <1 hour in 55.4% of the patients, and there was no DWI lesion in 67.5% of patients. After a mean follow-up of 389 days, new vascular events were seen in 19.3% of cases. Predictors of new vascular events included symptom duration of >1 hour and a DWI abnormality. Vascular events occurred in 40% of patients with both of these features. Another predictor of new vascular events was the presence of large-vessel occlusive disease.

Coutts et al<sup>112</sup> performed a similar study, obtaining MRI within 24 hours of symptom onset in 120 patients with minor stroke (National Institutes of Health Stroke Scale [NIHSS] score of 1 to 3) or TIA with hemiparesis or aphasia lasting >5 minutes. TIAs made up 57.5% of the cohort. Stroke recurrence was assessed at 90 days and was adjusted for NIHSS score and baseline glucose. In patients with both DWI lesions and vessel occlusion, stroke recurrence was 32.6%, whereas it was 10.8% if only a DWI lesion was present (about half of this group had TIAs clinically) and only 4.3% if neither feature was present. Patients with a DWI lesion and vessel occlusion at baseline had poorer functional outcomes.

Similarly, Ay and colleagues<sup>37</sup> reported that the in-hospital recurrent ischemic stroke and TIA rate was 19.4% in DWI-positive TIA patients compared with 1.3% of patients with ischemic stroke. This finding suggests that DWI-positive patients are at higher risk than both DWI-negative TIA patients and patients with ischemic stroke.

Another study evaluated the ABCD score for stratifying risk in classic TIA patients and assessed DWI findings in 61 of the 117 patients in whom the test was obtained.<sup>126</sup> The predictive value of a DWI lesion was higher than the other predictors examined (even after adjustment for the ABCD score) for a variety of subsequent risks, including stroke or death within 90 days,  $\geq 50\%$  stenosis in a relevant artery, or a cardioembolic source warranting anticoagulation.

In the studies just described, recurrent vascular events were captured clinically, and nonsystematic follow-up imaging was done. To assess predictors of new silent ischemia, another report by Coutts et al<sup>131</sup> evaluated 143 patients with classic TIAs or minor strokes (NIHSS <6) with 3-T MRI within 15.8 hours of symptom onset and again at 30 days. No DWI lesion was present at baseline in 32.1%. New lesions were seen on MRI at 30 days in 9.8% of cases, 43% (6 of 14) of which were clinically asymptomatic. Twenty-nine percent of new lesions occurred in TIA patients. In a multivariate model, predictors of new lesions included increasing lesion number at baseline, age, and baseline glucose. Grouped

together, those with large-artery or cardioembolic causes were more likely to have recurrent events.

In summary, patients with TIA or minor stroke who have DWI lesions, especially when multiple, are at higher risk of recurrent ischemic events. The presence of large-vessel occlusion is also a predictor of new events. MRI can help to triage patients with TIA or minor stroke. In addition, it can help to determine which TIA patients to admit to hospital, and it may help in identifying patients to treat with more aggressive therapies. As shown previously, DWI also can assist with stroke localization and understanding the mechanism of the stroke.

## Vessel Imaging

### Extracranial Disease

The yield of vascular imaging in patients with TIA alone is infrequently studied because most of the collected data originate in populations with stroke alone or stroke and TIA. The tests that are considered in this setting include carotid ultrasound/transcranial Doppler (CUS/TCD), MRA, and CTA. Requirements for rigorous studies of diagnostic tests often remain unmet, namely well-defined consecutive unselected patients, standardized test performance and interpretation, blinded interpretation, comparison to a reference standard, and adequate sample size.

Ideally, patients with TIA should be evaluated expeditiously (see section above) with tests assessing the extracranial and intracranial circulation. The choice of tests reflects local strengths in that expertise in vascular imaging is often not outstanding for all tests at all institutions. Other medical conditions such as the presence of a pacemaker or renal failure also will influence the choice of testing. Despite the widespread availability of noninvasive vascular imaging, patients often remain underinvestigated. A study of 265 Canadian patients with TIA found that over the next 30 days, fewer than half had undergone CUS, a finding similar to that of a prior report.<sup>84,132</sup>

Lesions amenable to endarterectomy or stenting are common in patients with TIA. CUS detects >50% stenosis of the extracranial internal carotid artery in 8% to 31% of patients with TIA and very minor stroke.<sup>133,134</sup> CUS provides reliable assessment of the carotid bifurcation. A sensitivity of 88% and specificity of 76% have been reported.<sup>135</sup> Investigators also have reported optimal cut points or ultrasound definitions of significant disease in TIA and stroke patients,<sup>136</sup> but they are not likely to be applicable to all centers. CUS findings carry prognostic significance. When 311 consecutive TIA patients underwent CUS/TCD within 24 hours of symptoms, patients with moderate to severe intracranial stenosis or extracranial stenosis had 3 times the risk for stroke within 90 days of follow-up.<sup>137</sup>

Supra-aortic MRA and CTA also provide reliable assessment of the carotid bifurcation and of the intracranial circulation. MRA has the advantage of being performed in conjunction with brain MRI, but it cannot be performed in patients with pacemakers and can be done only with difficulty in severely claustrophobic patients. MRA sensitivity of 92% and specificity of 76% for extracranial carotid disease have

been reported.<sup>135</sup> Contrast-enhanced MRA is reported to be more accurate than nonenhanced time-of-flight techniques and in some centers has supplanted the use of catheter angiography, but rigorous data regarding its accuracy were not provided.<sup>138</sup> Contrast enhancement is restricted in patients with severe renal disease.

CTA requires exposure to contrast dye, limiting its use in patients with dye allergies and renal dysfunction, but yields results comparable to MRA and carotid Doppler. CTA has been reported to have an excellent (100%) negative predictive value for excluding >70% stenosis compared with catheter angiography, thereby functioning well as a screening test.<sup>139</sup>

Ultrasound, CTA, or MRA should be performed as the initial screen of the carotid bifurcation. In patients with abnormal tests, a common strategy includes a second confirmatory noninvasive test to evaluate the carotid bifurcation before endarterectomy if there is no plan to perform catheter angiography. If 2 noninvasive tests are discordant, catheter angiography should be considered before endarterectomy. Despite a great deal of research on the subject, there are no data that allow a clear recommendation for 1 testing algorithm over another. Error rates of 15% to 30% have been reported with these tests during attempts to identify endarterectomy candidates, even when combinations of tests are used.<sup>140,141</sup>

Cost-effectiveness analyses found CUS as a stand-alone examination to be the preferred strategy for selecting patients for endarterectomy,<sup>135</sup> but that finding has been refuted at other institutions.<sup>142</sup> Another study found contrast-enhanced MRA to be most accurate for 70% to 99% stenosis (sensitivity, 94%; specificity, 93%) compared with US, MRA, and CTA (sensitivity, 89%; specificity, 84%). Despite that finding, CUS was suggested as the initial test, but accuracy had to be carefully audited to optimize outcomes. Speed of testing was crucial to rapidly identify patients with severe disease who would benefit from early endarterectomy. Testing strategies that used contrast-enhanced MRA rather than catheter angiography as a confirmatory test have been found to be effective.<sup>143</sup>

Structural characteristics of carotid plaques can be identified and have been found to differ among patients with TIA and stroke.<sup>144</sup> Echolucent plaque detected by high-resolution B-mode ultrasound correlates with clustering of conventional vascular risk factors and large-artery strokes compared with other stroke subtypes and compared with TIA.<sup>145</sup> Echolucency<sup>144</sup> and surface irregularity detected by MRI<sup>146</sup> can be correlated with symptomatic versus asymptomatic status. Recent reports with positron emission tomography and MRI correlate plaque inflammation with plaque stability.<sup>147</sup> At present, there is no defined clinical role for these findings.

### Intracranial Disease

TCD provides information regarding intracranial stenoses. Recent data identify the following predictive values for TCD identification of intracranial stenosis: positive predictive value of 36% and negative predictive value of 86%.<sup>148</sup> The high negative predictive value and the lower positive predictive value reflect the low prevalence of intracranial stenosis. MRA and CTA had comparable

performance for identifying intracranial stenosis.<sup>148</sup> The prevalence of intracranial disease is much higher in non-white populations. Reports found that 51% to 77% of Asian patients with TIA had intracranial stenosis or occlusion.<sup>149,150</sup>

TCD can detect microembolic signals (MESs) seen with extracranial or cardiac sources of embolism. High numbers of MESs are a marker of risk in patients with TIA of carotid origin, spurring research into optimal strategies for medical therapy and the timing of endarterectomy in those with an extracranial carotid source.<sup>151</sup> In a cohort of patients unselected for stroke mechanism, MESs were more common in patients with large-artery occlusive disease and were more prevalent in patients treated with anticoagulation rather than antiplatelet agents. The authors did not recommend routine screening because only 6% of patients had MESs within 14 days of symptoms.<sup>152</sup> The prospective Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) study enrolled 107 patients with recently symptomatic carotid disease and MESs and found fewer patients with MESs, fewer MESs per hour, and fewer strokes in patients treated with clopidogrel and aspirin than in patients treated with aspirin alone in the first week after presentation.<sup>153</sup> Stroke patients with MCA stenosis and MESs are at higher risk of future ischemic symptoms.<sup>154</sup> At present, there is no defined clinical role for these findings.

Conventional cerebral angiography is an important diagnostic tool in the evaluation of patients with cerebrovascular disease, including stroke and TIA. Despite recent advances in noninvasive diagnostic neuroimaging, cervicocerebral angiography remains the gold standard for the diagnostic evaluation of patients with a wide range of cervical and intracranial vascular diseases.<sup>155</sup> Moreover, recent advances in high-resolution rapid-sequence fluoroscopic imaging, digital image reconstruction with 3-dimensional techniques, catheter technology, and non-ionic contrast media have made cervicocerebral angiography easier and safer over the past 2 decades.<sup>156</sup> However, if noninvasive imaging provides firm diagnostic findings, cerebral angiography may not be required.

### Cardiac and Other Testing

Sparse data exist in the available literature to guide the recommended cardiac evaluation of TIA patients. There are few studies regarding the cardiac evaluation of patients with TIA alone because most of the collected data originate in populations with stroke alone or stroke and TIA. The tests that are considered in this setting include ECG, transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), and Holter monitoring. Requirements for rigorous studies of diagnostic tests remain unmet: well-defined consecutive unselected patients, standardized test performance and interpretation, blinded interpretation, comparison to a reference standard, and adequate sample size.

Cardiac evaluation in patients with no cardiac history or absent signs of cardiac disease on examination or ECG yields important abnormalities in a minority of patients. Fewer than 3% of TTEs in stroke or TIA patients will reveal an

abnormality suggesting a cardioembolic source in the absence of clinical evidence of heart disease. In 205 unselected patients with TIA, a full cardiac and angiographic investigation found a cardioembolic source in 6%. Most of the patients with a cardioembolic source had some evidence of heart disease.<sup>157</sup> In 1 study of 441 unselected patients, TTE or TEE found a major source of embolism in 10% and a minor source in 46%,<sup>158</sup> and 8% of those evaluated had no cardiac history but required anticoagulation for a documented source of embolism confirmed by TEE.<sup>158</sup>

The yield of cardiac evaluation increases if other potential sources of cerebral symptoms have been ruled out. A study of 237 patients with cryptogenic stroke or TIA found potentially treatable sources of embolism by TEE in 61% of patients. Patient age and topography of the ischemic event did not correlate with the type of cardioembolic source (ie, patent foramen ovale [PFO], left atrial clot, or aortic arch atheroma).<sup>159</sup>

TIAs require urgent evaluation, but there is little evidence that early echocardiographic evaluation has a higher yield. Immediate echocardiography yields a low incidence of findings: In 65 patients with cryptogenic stroke, TIA, or lacunar stroke, TEE performed within 3 days of presentation yielded an atrial thrombus in 1 patient, and 5 had spontaneous echo contrast.<sup>160</sup>

The echocardiographic method used is important. TEE is more sensitive than TTE for atheroma of the aortic arch and abnormalities of the interatrial septum (eg, atrial septal aneurysm, PFO, atrial septal defect), atrial thrombi, and valvular disease. The use of contrast increases the detection of right-to-left shunts.<sup>161</sup> In 231 consecutive patients with cryptogenic stroke or TIA, both TTE and TEE were performed; 127 had an embolic source, and 90 of these were found only on TEE. Major embolic sources were found in 46 patients (20%), and only TEE detected 38 of these. Left atrial thrombus was the most common source. TEE results were independent of the age of the patient.<sup>161</sup> Another group found major sources of embolism in 22% of similar patients evaluated by TEE.<sup>162</sup> One study of TIA patients alone noted that TEE changed treatment in 22% of patients and led to anticoagulation in 12%.<sup>163</sup> Another study of TEE in 491 patients >65 years of age found a preponderance of aortic arch atheroma and atrial septal aneurysms, in contrast to PFO and left atrial clot, leading the authors to conclude that TEE in the elderly would not commonly change management because there are no clear treatments for the detected abnormalities.<sup>164</sup>

Stroke subtype may play a role in the decision to perform cardiac evaluation. A study of 175 patients with stroke or TIA found that PFO was twice as common in patients than control subjects and that PFO was found more often with nonlacunar stroke than lacunar. The nonlacunar stroke patients also had a greater degree of shunting. No complicated aortic arch atheromas were detected. Atrial septal aneurysm was more frequent, especially with nonlacunar stroke.<sup>165</sup> Patient age and topography of the ischemic event did not correlate with the type of cardioembolic source (ie, PFO, left atrial clot, or aortic arch atheroma).<sup>159</sup>

It is common for significant cardiac and carotid lesions to coexist. In a Finnish study, 20% of stroke or TIA patients who were candidates for endarterectomy or anticoagulation had severe carotid stenosis and/or a high-risk cardiac source of embolic lesions detected by either CUS or TEE, 56% had moderate carotid disease and/or a medium-risk cardioembolic source, and 11% had both a moderate or severe carotid stenosis and a potential cardioembolic source.<sup>166</sup> Another study found that 19% had a cardioembolic source associated with carotid disease appropriate for the symptoms.<sup>157</sup>

Holter monitoring is abnormal in a minority of unselected patients with TIA. However, prolonged cardiac monitoring (inpatient telemetry or Holter monitor) is useful in patients with an unclear origin after initial evaluation.<sup>167–169</sup> Patients with a history of palpitations or evidence of structural heart disease by ECG or echocardiogram might reflect a higher-yield population. In addition, longer monitoring may be expected to yield greater results. In 1 consecutive series of 28 patients with no identified cause of stroke or TIA, including testing with Holter monitoring for 24 hours, 14% had paroxysmal atrial fibrillation on a 4-day automatic cardiac event recorder.<sup>170</sup>

### Routine Blood Tests

No systematic studies have been performed to assess the value of blood tests in patients with TIA. It is reasonable to perform the same routine blood tests in patients presenting with TIAs as in patients presenting with ischemic stroke. These include a complete blood count, chemistry panel, and basic coagulation studies (prothrombin time, partial thromboplastin time) (**Class IIa, Level of Evidence B**).<sup>3</sup> These tests are useful to exclude TIA mimics (eg, hypoglycemia) and can help identify less common causes of thrombotic events (eg, polycythemia vera). A fasting lipid profile also is appropriate.

Specialized coagulation tests can be considered in younger patients with TIAs (Table 4), particularly when no vascular risk factors exist and no underlying cause is identified. A few blood test abnormalities have been identified in TIA populations in isolated studies (eg, serum viscosity,<sup>171</sup> prothrombin fragment 1.2<sup>172</sup>), but they require further study to determine whether they affect prognosis. Similarly, inflammatory parameters such as C-reactive protein have an unclear impact on TIA prognosis because of conflicting studies,<sup>173,174</sup> and these tests are not routinely recommended. Impaired glucose tolerance is common in older patients with TIA or minor stroke,<sup>175</sup> and studies are in progress to determine whether pharmacological agents that address impaired glucose tolerance reduce stroke risk in this population.

### Summary

Neuroimaging studies, particularly diffusion-perfusion-weighted MRI, have fundamentally altered our understanding of the pathophysiology of TIA. In routine clinical practice, MRI permits confirmation of focal ischemia rather than another process as the cause of a patient's deficit, improves accuracy of diagnosis of the vascular localization and cause of TIA, and assesses the extent of preexisting cerebrovascular injury. Accordingly, MRI, including diffusion sequences,

**Table 4. Optional Coagulation Screening Tests (Consider in Younger Patients With TIAs, Particularly When No Vascular Risk Factors Exist and No Underlying Cause Is Identified)**

Protein C, protein S, antithrombin III activities
Activated protein C resistance/factor V Leiden
Fibrinogen
D-Dimer
Anticardiolipin antibody
Lupus anticoagulant
Homocysteine
Prothrombin gene G20210A mutation
Factor VIII
Von Willebrand factor
Plasminogen activator inhibitor-1
Endogenous tissue plasminogen activator activity

should now be considered a preferred diagnostic test in the investigation of the patient with potential TIAs. Additional diagnostic workup, including vessel imaging, cardiac evaluation, and laboratory testing, should be completed according to the AHA acute stroke guidelines.<sup>176</sup>

### Class I Recommendations

1. Patients with TIA should preferably undergo neuroimaging evaluation within 24 hours of symptom onset. MRI, including DWI, is the preferred brain diagnostic imaging modality. If MRI is not available, head CT should be performed (**Class I, Level of Evidence B**).
2. Noninvasive imaging of the cervicocephalic vessels should be performed routinely as part of the evaluation of patients with suspected TIAs (**Class I, Level of Evidence A**).
3. Noninvasive testing of the intracranial vasculature reliably excludes the presence of intracranial stenosis (**Class I, Level of Evidence A**) and is reasonable to obtain when knowledge of intracranial steno-occlusive disease will alter management. Reliable diagnosis of the presence and degree of intracranial stenosis requires the performance of catheter angiography to confirm abnormalities detected with noninvasive testing.
4. Patients with suspected TIA should be evaluated as soon as possible after an event (**Class I, Level of Evidence B**).

### Class II Recommendations

1. Initial assessment of the extracranial vasculature may involve any of the following: CUS/TCD, MRA, or CTA, depending on local availability and expertise, and characteristics of the patient (**Class IIa, Level of Evidence B**).
2. If only noninvasive testing is performed before endarterectomy, it is reasonable to pursue 2 concordant noninvasive findings; otherwise, catheter angiography should be considered (**Class IIa, Level of Evidence B**).
3. The role of plaque characteristics and detection of MESS is not yet defined (**Class IIb, Level of Evidence B**).
4. ECG should occur as soon as possible after TIA (**Class I, Level of Evidence B**). Prolonged cardiac monitoring

- (inpatient telemetry or Holter monitor) is useful in patients with an unclear origin after initial brain imaging and electrocardiography (**Class IIa, Level of Evidence B**).
5. Echocardiography (at least TTE) is reasonable in the evaluation of patients with suspected TIAs, especially in patients in whom no cause has been identified by other elements of the workup (**Class IIa, Level of Evidence B**). TEE is useful in identifying PFO, aortic arch atherosclerosis, and valvular disease and is reasonable when identification of these conditions will alter management (**Class IIa, Level of Evidence B**).
  6. Routine blood tests (complete blood count, chemistry panel, prothrombin time and partial thromboplastin time, and fasting lipid panel) are reasonable in the evaluation of patients with suspected TIAs (**Class IIa, Level of Evidence B**).
  7. It is reasonable to hospitalize patients with TIA if they present within 72 hours of the event and any of the following criteria are present:
    - a. ABCD<sup>2</sup> score of  $\geq 3$  (**Class IIa, Level of Evidence C**).
    - b. ABCD<sup>2</sup> score of 0 to 2 and uncertainty that diagnostic workup can be completed within 2 days as an outpatient (**Class IIa, Level of Evidence C**).
    - c. ABCD<sup>2</sup> score of 0 to 2 and other evidence that indicates the patient's event was caused by focal ischemia (**Class IIa, Level of Evidence C**).

## Disclosures

### Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Ownership Interest	Consultant/Advisory Board	Other
J. Donald Easton	Brown University	None	None	None	None	Boehringer Ingelheim*; Sanofi-Aventis*	None
Jeffrey L. Saver	UCLA Medical Center	None	None	None	None	AGA Medical*; Co-Axia*; Ferrar*; Pfizer*; ImaRx, Fibrogen*	None
Gregory W. Albers	Stanford University	Aventis*; Boehringer Ingelheim*; NMT*; Novartis*	None	Genentech*; BI Pharma*	None	Lundbeck*; Boehringer Ingelheim*	None
Mark J. Alberts	Northwestern University Medical School	AGA Medical*; BMS†; Boehringer Ingelheim*; Sanofi-Synthelabo†; Schering-Plough*	None	Accumetrics*; AstraZeneca*; BMS†; Boehringer Ingelheim*; diaDexus*; Pfizer*; Sanofi-Synthelabo†	None	Accumetrics*; AstraZeneca*; Bayer*; Boehringer Ingelheim*; BMS†; diaDexus*; Pfizer*; Sanofi-Synthelabo†; Schering-Plough*	Athena*; Mitsubishi*; TAP Pharmaceuticals*
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Edward Feldmann	Brown University	None	None	Occasional lectures on TIA/stroke treatment*	None	None	Medicolegal consultation regarding cause and treatment of stroke*
Thomas S. Hatsukami	University of Washington, Seattle	Hoffmann-LaRoche, Ltd*	None	None	None	None	Cambridge University Press*
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Elaine Miller	University of Cincinnati	None	None	None	None	None	None
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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

\*Modest.

†Significant.

Reviewer Disclosures

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This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

\*Significant.

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