Transient Ischemic Attack: Risk Stratification and Treatment

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A major challenge facing the physician evaluating patients with transient ischemic attack is determining which patients are at highest short-term risk of stroke. A number of stratification schemes have been recently developed incorporating easily obtainable clinical information about the individual patient. Further, emerging data suggest a role for brain and vascular imaging in risk stratification. Many aspects of acute management of transient ischemic attack, such as which patients should be hospitalized and choice of acute antithrombotic therapy, remain controversial because of a lack of evidence from controlled trials. For longer-term prevention, there is much firmer evidence from multiple large randomized trials, and these data are reviewed in this article. [Ann Emerg Med. 2008;52:S27-S39.]

INTRODUCTION

Two major concerns face the clinician caring for a patient with transient ischemic attack. The first is determining the short-term risk of stroke facing the individual patient. The second is deciding how the patient should be treated, including decisions on hospitalization, antithrombotic therapy, and other interventions. These 2 concerns are obviously intertwined, in that patients at low risk for subsequent stroke might be treated more conservatively and patients at high risk for stroke more aggressively. This article reviews current data on risk stratification and treatment of patients with transient ischemic attack. Throughout this article the traditional definition of transient ischemic attack—an episode of focal cerebral ischemia with symptom resolution within 24 hours—is used. This reflects the reality of the clinical definitions used in the multiple studies cited.

MATERIALS AND METHODS

An initial PubMed search was performed using the term "transient ischemic attack" and limited to articles published in English within the past 5 years and relevant to humans. This identified 1,670 articles. The search was narrowed within this cohort by cross-referencing with the following terms: "risk stratification," "management," "treatment," "antiplatelet therapy," and "anticoagulation." Key references cited in relevant articles identified in the search were also evaluated.

RISK STRATIFICATION

At present, 3 broad strategies have been studied as predictors of short-term risk of stroke in patients presenting with transient ischemic attack: (1) clinical risk scores that incorporate characteristics of the patient and neurologic event, (2) diffusion-weighted magnetic resonance imaging (DWI), and (3) vascular imaging to identify large vessel stenosis. From a conceptual standpoint, it may be useful to consider how these strategies parallel the tools used in evaluating patients with suspected acute coronary syndromes. Clinical risk scores are analogous to assessing vascular risk factors and characteristics of chest pain associated with acute coronary syndromes as opposed to mimics. Diffusion-weighted magnetic resonance imaging is analogous to measurement of cardiac enzyme levels. It is a direct measure of neuronal cell death. Use of vascular imaging is analogous to the data obtained from cardiac catheterization, in which the presence of significant vascular disease is considered strongly supportive of an ischemic cause of symptoms even if evidence of tissue infarction is not present. A further strategy involving identification of reversible ischemia using perfusion magnetic resonance imaging (MRI) could be considered analogous to transient electrocardiographic ischemic changes. To date, use of perfusion MRI in risk stratification of patients with transient ischemic attack has not been extensively studied.

Clinical Risk Scores

At present, 3 transient ischemic attack clinical risk stratification scores have been developed and validated: the California score, the ABCD score, and a hybrid of these 2, called the ABCD[2] score.[1-3] In 2000, Johnston et al[1] derived the California score from a cohort analysis of 1,707 patients in a large health maintenance organization who were treated by emergency physicians and given a diagnosis of transient ischemic attack. Patients were treated at 16 hospitals during 1 year. Five variables were found to be independently predictive of stroke: age older than 60 years (odds ratio [OR] 1.8), diabetes (OR 2.0), symptom duration greater than 10 minutes (OR 2.3),

Table 1. Point assignment and ORs (or HR) for stroke after transient ischemic attack in 3 risk scores.[1-3]

Clinical Feature	Points	2 Days	7 Days*	90 Days
California				
Age >60 y	1	—	—	1.8
Diabetes	1	—	—	2.0
Transient ischemic attack duration >10 min	1	—	—	2.3
Weakness with transient ischemic attack	1	—	—	1.9
Speech impairment with transient ischemic attack	1	—	—	1.5
ABCD				
Age >60 y	1	—	2.6*	—
Blood pressure increase (initial systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg)	1	—	9.7*	—
Clinical feature: unilateral weakness	2	—	6.6*	—
Clinical feature: speech disturbance without weakness	1	—	2.6*	—
Duration of symptoms 10–60 min	1	—	3.1*	—
Duration of symptoms >60 min	2	—	6.2*	—
ABCD²				
Age >60 y	1	1.4	1.4	1.5
Blood pressure increase (systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg)	1	2.1	1.9	1.6
Clinical feature: unilateral weakness	2	2.9	3.5	3.2
Clinical feature: speech disturbance without weakness	1	1.4	1.5	1.7
Duration of symptoms 10-60 min	1	2	1.9	1.7
Duration of symptoms >60 min	2	2.3	2.6	2.1
Diabetes	1	1.6	1.4	1.7

*Oxfordshire data reported as HRs; all other data reported as ORs.

and symptoms of weakness (OR 1.9) or speech impairment (either dysarthria or aphasia) (OR 1.5) (Table 1). These risk factors were found to be additive in predicting the risk of stroke. In patients with no risk factors, there were no strokes at 90 days; for patients with all 5 risk factors, 34% experienced a stroke (Table 2). Roughly half of strokes occurred within the first 48 hours after presentation.

In 2005, Rothwell et al[2] proposed the ABCD score to predict 7-day stroke risk in patients with transient ischemic attack. The score was derived from a cohort of 209 patients with transient ischemic attack by using factors previously identified as associated with stroke risk after transient ischemic attack, validated in 190 patients, and then tested for clinical utility in 588 additional patients. The score is composed of the following predictive variables: *A*ge older than 60 years (hazard ratio [HR] 2.6), increased *B*lood pressure defined as presenting systolic blood pressure greater than 140 mm Hg or diastolic blood pressure greater than 90 mm Hg (HR 9.7), *C*linical features of unilateral weakness (HR 6.6) or speech disturbance without weakness (HR 2.6), and *D*uration of symptoms classified as less than 10 minutes (HR 1.0), 10 to 60 minutes (HR 3.1), or greater than 60 minutes (HR 6.2). Point assignments are listed in Table 1. Additional variables were tested but did not reach significance and so were not included in the score. In the validation group, no patients with an ABCD score less than or equal to 3 experienced a stroke within 1 week, whereas scores greater than 3 were associated with a progressively increasing risk of stroke (Table 2).

The authors of the California score and ABCD score subsequently combined data from their respective studies, standardized patient selection methods and definitions, and reanalyzed the combined data to derive a unified optimal risk score.[3] C-statistics (a measure of the discriminatory ability of a risk score, with 1.0 indicating perfect discrimination and 0.5 being no better than chance) were used to quantify the prognostic value of the score. The derivation cohort included 1,916 patients from the original ABCD and California score cohorts, and subsequent validation was undertaken in 4 independent transient ischemic attack populations encompassing 2,893 patients. This led to the ABCD² score, which added an item for scoring history of diabetes. ORs of individual items are presented in Table 1. Improved prognostic value based on C-statistics was seen with the ABCD² score compared with the previous scores. In the validation cohort, the ABCD² score performed well (C-statistics 0.62 to 0.83 across cohorts and risk periods of 2, 7, or 90 days). Overall, 21% (n=1,012) of patients were classified as high risk (score 6 to 7), with an 8.1% 2-day stroke risk; 45% (n=2,169) as moderate risk (score 4 to 5), with a 4.1% 2-day risk; and 34% (n=1,628) as low risk (score 0 to 3), with a 1.0% 2-day risk. Rates of stroke at days 7 and 90 are presented in Table 2.

Subsequent studies have been performed to independently validate the risk scores. Tsivgoulis et al[4] performed a retrospective record review assessing the ABCD score in 226 patients with transient ischemic attack in Greece, using an outcome of 7- and 30-day stroke risk, and found the score highly predictive of stroke. There were no strokes in patients whose score was less than 3. When adjusting for stroke risk factors, previous transient ischemic attack, medications before transient ischemic attack, and stroke prevention strategies, a

Table 2. Frequency (%) of stroke after transient ischemic attack with 3 risk scores.[1-3]

Risk Score	Points	2 Days	7 Days	90 Days
California				
	0	—	—	0
	1	—	—	3
	2	—	—	7
	3	—	—	11
	4	—	—	15
	5	—	—	34
ABCD				
	0	—	0.0	—
	1	—	0.0	—
	2	—	0.0	—
	3	—	0.0	—
	4	—	2.2	—
	5	—	16.3	—
	6	—	35.5	—
ABCD²				
Low	0–3	1.0	1.2	3.1
Moderate	4–5	4.1	5.9	9.8
High	6–7	8.1	11.7	17.8

—, Data not reported.

score greater than or equal to 5 was associated with an 8-fold greater risk of stroke. The same group also subsequently tested the ABCD² score in the same population and found it performed slightly better than the ABCD score, with a C-statistic of 0.80 compared with 0.77 for 7-day stroke risk.[5] In a retrospective review, an Australian group found that of 98 consecutive patients with transient ischemic attack presenting to the emergency department (ED), 4 of 4 strokes at 7 days and 6 of 7 strokes at 90 days occurred in patients with ABCD scores greater than 4.[6] On the other hand, a prospective study in Spain found little predictive value of the ABCD score. In 345 consecutive patients with transient ischemic attack, there were 17 strokes at 7 days (4.9%), and the stroke rate was evenly distributed across ABCD scores, with 7 of 17 strokes occurring in patients with scores less than 4.[7]

It is somewhat self-evident that the primary goal of any scheme to risk-stratify patients with transient ischemic attack in the emergency setting should be to predict the short-term risk of stroke. However, development and validation of clinical risk stratification scores have occurred in the context of routine clinical care, with patients receiving medical interventions considered appropriate by treating physicians. These are not, therefore, natural history studies, and the event rates observed are necessarily biased by early treatment. The ability of clinical risk scores to identify treatment-urgent patients, such as those with carotid stenosis requiring revascularization or cardioembolism warranting anticoagulation, has not been established. In one study of 117 patients with acute transient ischemic attack at a single center, the ABCD score performed poorly in identifying "high-risk" patients, defined as those with large vessel stenosis, cardioembolism, or subsequent stroke or death.[8] These findings emphasize that risk scores may

supplement but not replace clinical judgment in the assessment of individual patients. Additional data obtained during the evaluation of patients with transient ischemic attack, such as clinically silent infarcts on brain imaging, atrial fibrillation on electrocardiography, or the presence of large vessel stenosis, may indicate a significant short-term risk of stroke regardless of risk score (see below). Further, clinical features—such as time from transient ischemic attack to presentation, history of stroke, or features suggesting an unusual cause of transient ischemic attack, such as neck pain indicating arterial dissection or fever suggesting infectious endocarditis—must be incorporated into the assessment of risk in the individual patient.

Diffusion-Weighted Imaging

Studies of diffusion-weighted magnetic resonance imaging in patients with transient ischemic attack have reported diffusion-weighted magnetic resonance imaging lesions in 16% to 67% of patients.[9] When present, a diffusion-weighted magnetic resonance imaging lesion establishes conclusively that cerebrovascular ischemia has occurred. Not surprisingly, patients with a diffusion-weighted magnetic resonance imaging lesion represent a high-risk group. In a small study of 83 patients with transient ischemic attack, the presence of a diffusion-weighted magnetic resonance imaging lesion doubled the risk of a subsequent vascular event. In patients with a diffusion-weighted magnetic resonance imaging lesion and symptoms longer than 1 hour, the risk was increased 4-fold.[10] Another study of 120 patients with transient ischemic attack or minor stroke evaluated within 12 hours of symptom onset showed a 90-day stroke rate of 4.2% in diffusion-weighted magnetic resonance imaging-negative patients and 14.7% in diffusion-weighted magnetic resonance imaging-positive patients (P=.10).[11] Conversely, this same group found that, compared with patients with a diffusion-weighted magnetic resonance imaging lesion, those with negative diffusion-weighted magnetic resonance imaging result were 4.6 times more likely to present with a recurrent transient ischemic attack and 4.3 times less likely to present with a stroke.[12]

Patients with diffusion-weighted magnetic resonance imaging lesions also appear to be at greater risk for harboring a treatment-urgent cause of their transient ischemic attack, such as high-grade large vessel stenosis or a cardioembolic source. In a small study of 61 patients with transient ischemic attack, less than 10% of diffusion-weighted magnetic resonance imaging-negative patients had a high-risk mechanism identified compared with 60% of diffusion-weighted magnetic resonance imaging-positive patients (P<.001).[8] A meta-analysis of 19 studies that examined diffusion-weighted magnetic resonance imaging in patients with transient ischemic attack found that a diffusion-weighted magnetic resonance imaging lesion was associated with the presence of atrial fibrillation (OR 2.75; 95% confidence interval [CI] 1.78 to 4.25; P<.001) and ipsilateral carotid stenosis (OR 1.93; 95% CI 1.34 to 2.76; P=.001).[13]

This same meta-analysis also found that several features of the clinical risk stratification scores described above were

associated with the presence of diffusion-weighted magnetic resonance imaging lesions.[13] These features include symptom duration longer than 1 hour, speech abnormalities (aphasia or dysarthria), and motor weakness. Age and history of hypertension or diabetes were not associated with diffusion-weighted magnetic resonance imaging lesions, however. The relationship between the composite ABCD score and presence of diffusion-weighted magnetic resonance imaging lesions remains uncertain, with conflicting results from individual studies.[8,13] These findings raise the question of whether diffusion-weighted magnetic resonance imaging provides supplemental predictive value beyond that from clinical risk stratification scores. At least 1 study, which examined 203 patients with acute transient ischemic attack, has found that the presence of a diffusion-weighted magnetic resonance imaging lesion independently predicts the risk of subsequent stroke, even after adjusting for ABCD score.[14] On multivariate analysis, an ABCD score greater than or equal to 5 was associated with an HR of 5.0 (95% CI 1.0 to 25.8; P=.06), and the presence of a diffusion-weighted magnetic resonance imaging lesion was associated with an HR of 10.3 (95% CI 1.2 to 86.7; P=.03) for subsequent stroke. Larger studies examining the independent predictive value of diffusion-weighted magnetic resonance imaging are clearly warranted.

Vascular Imaging

The presence of symptomatic large vessel disease appears to be associated with a high short-term risk of stroke. A retrospective analysis of the subgroup of 603 patients with carotid disease of any severity and a hemispheric transient ischemic attack enrolled in the medical arm of the North American Symptomatic Carotid Endarterectomy Trial [NASCET] demonstrated a 90-day stroke risk of 20.1%, with most of this risk accruing within the first 20 days after the index transient ischemic attack.[15] Interestingly, in this cohort early stroke risk did not significantly increase with higher degrees of stenosis. Although this analysis did not include a matched comparator group without carotid disease, the observed stroke rate is considerably higher than that reported in other studies of unselected patients with transient ischemic attack.

Two other reports have also provided evidence that the presence of large vessel disease increases short-term risk of stroke in patients with transient ischemic attack. Purroy et al[7] studied 345 patients with transient ischemic attack within 24 hours of symptom onset. Carotid and transcranial ultrasonography was used to identify patients with large vessel disease. On multivariate analysis, including adjustment for ABCD score, the only independent predictor of early stroke risk (within 7 days) was the presence of large vessel occlusive disease (HR 5.9; 95% CI 2.2 to 15.9). Coutts et al[11] reported a series of 120 patients with transient ischemic attack or minor stroke who underwent magnetic resonance angiography of the brain within 12 hours of symptom onset. Of this cohort, 12.5% had an intracranial vessel occlusion, all of whom also had a diffusion-weighted magnetic resonance imaging abnormality. The 90-day stroke rate in this

group was 32.6% compared with 10.8% for those with a diffusion-weighted magnetic resonance imaging lesion but no vessel occlusion and 4.3% with no diffusion-weighted magnetic resonance imaging lesion and no vessel occlusion. One limitation of this latter study is that imaging was performed on only the intracranial vessels; the effect of extracranial large vessel disease was not examined.

The identification of large vessel disease, in particular disease affecting the extracranial internal carotid artery, has particular relevance as a risk stratification tool because of strong evidence showing a benefit of early revascularization in these patients. The role of carotid revascularization is discussed in more detail below.

DISPOSITION (HOSPITALIZATION, OBSERVATION UNITS, OUTPATIENT EVALUATION)

One of the more difficult challenges facing the emergency physician is to determine which patients with transient ischemic attack should be hospitalized. On the one hand, hospitalization may expedite diagnostic evaluation, hastening identification and intervention for specific high-risk causes of transient ischemic attack (eg, carotid stenosis). Early supportive care may also minimize the effect of ongoing or recurrent cerebral ischemia, relevant given the potentially high short-term risk of stroke. Further, hospitalized patients who have a stroke after transient ischemic attack may receive expedited thrombolysis. In a cost-utility analysis, Nguyen-Huynh and Johnston[16] reported that hospitalization for 24 hours had a cost-effectiveness ratio of $55,044 per quality-adjusted life-year purely by allowing the rapid administration of thrombolytic therapy. On the other hand, most patients with transient ischemic attack will not experience a stroke in the short term, the benefit of hospitalization is uncertain, and there is considerable expense and resource consumption associated with admission.

At present, there are limited clinical data on the benefit of hospitalization. Poisson et al[17] recently reported findings from a prospective, population-based stroke surveillance study in Texas. During a 5-year period, 552 transient ischemic attacks were identified, and 69% of these patients were hospitalized. The risk of stroke at 30 days was 2% in those hospitalized compared with 7% in those discharged (P=.002). Indirect evidence for a possible benefit of hospitalization comes from 2 single-center studies (n=117 and n=203) following patients with transient ischemic attack admitted to stroke units, which found 90-day stroke rates of 1.7% and 3.5%, respectively.[8,14] These event rates are substantially below those identified in most observational studies, despite enrollment of significantly high-risk transient ischemic attack populations (according to ABCD scores) in both studies. Whether this represents the therapeutic effect of aggressive inpatient evaluation and management or differences in specific patient characteristics between studies remains an open question.

Current guidelines on the need for hospitalization vary widely. In this respect, the recent National Stroke Association

transient ischemic attack guidelines, published in 2006, are instructive.[18] Generation of these guidelines involved a novel method of systematic review of transient ischemic attack guidelines previously published by multiple organizations throughout the world, followed by a modified Delphi approach of iterative questionnaires given to a panel of experts to reach consensus recommendations. At the end of this process, it was recommended that hospitalization be "considered" for patients presenting with a first transient ischemic attack within the past 24 to 48 hours and it was "generally recommended" for patients with crescendo transient ischemic attacks, duration of symptoms greater than 1 hour, symptomatic carotid stenosis greater than 50%, a known cardiac source of embolus, a known hypercoagulable state, or an appropriate combination of the California score or ABCD score. It was also recommended that the option of outpatient evaluation within 24 to 48 hours in a specialized transient ischemic attack clinic be available.

Recently, 2 studies have been published supporting use of urgent-access specialized transient ischemic attack clinics. In the Early Use of Existing Strategies for Stroke (EXPRESS) study, Rothwell et al[19] studied the effect of implementation of a rapid-access transient ischemic attack clinic that included immediate diagnostic testing and treatment initiation. This study was nested within an ongoing population-based incidence study of transient ischemic attack and stroke, the Oxford Vascular Study, ensuring complete case ascertainment and follow-up. In the initial phase of the study, before implementation of the transient ischemic attack clinic, the rate of stroke at 90 days was 10.3% (32/210 patients). After implementation, the stroke rate decreased to 2.1% (6/281 patients, P=.0001).[19] Lavallée et al[20] established a hospital-based clinic with urgent around-the-clock access for patients with transient ischemic attack. During a 2-year period, 1,085 patients with suspected transient ischemic attack were evaluated. The 90-day stroke rate was 1.24%, compared with a predicted stroke rate based on patient ABCD^2 scores of almost 6%.

At least in the United States, urgent neurologic evaluation and diagnostic testing can be challenging to arrange on an outpatient basis because of multiple logistical barriers, such as scheduling limitations and insurance approval requirements. Indeed, current limited data on the outpatient evaluation of transient ischemic attack suggest that distinctly suboptimal results are achieved in clinical practice. Goldstein et al[21] examined a group of 95 patients in the United States who presented to their primary care physician with a first transient ischemic attack. Only 23% underwent a brain imaging study, 40% underwent carotid imaging, 18% underwent electrocardiography, and 19% underwent echocardiography. Overall, 31% had no evaluations within the first month of the index visit beyond an examination in the office. Less than half of patients with transient ischemic attack with a history of atrial fibrillation began receiving anticoagulants. Clearly, the availability of urgent evaluation and diagnostic resources will

vary according to region, insurance coverage, and other issues of health care access.

Another disposition option is the use of an observation unit, often in the ED, to carry out an accelerated diagnostic protocol. This approach has been developed for ED patients with chest pain and at low to intermediate risk of acute cardiac ischemia. In a 2003 survey, such units were present in almost 20% of hospitals.[22] Relative to traditional inpatient care, ED accelerated diagnostic protocols for chest pain have been shown to decrease length of stay and cost, as well as improve patient satisfaction and quality of life, with comparable diagnostic outcomes.[23,24]

In 2007, Ross et al[25] reported a prospective randomized study of 149 patients with transient ischemic attack who were randomized to either inpatient admission (control group) or ED observation unit admission for management using a transient ischemic attack accelerated diagnostic protocol. All patients with transient ischemic attack had normal findings on computed tomography (CT) of the head, electrocardiography, and laboratory studies and no known embolic source. Both groups had orders for serial clinical examinations, a neurology consultation, carotid Doppler ultrasonography, echocardiography, and cardiac monitoring. Accelerated diagnostic protocol patients with positive testing results were admitted. Compared with the inpatient control group, patients in the accelerated diagnostic protocol group had total lengths of stay that were half as long (26 versus 61 hours), lower 90-day total direct costs ($890 versus $1,547), and comparable 90-day clinical outcomes. All positive accelerated diagnostic protocol patient outcomes were identified in the ED, with 15% of patients subsequently admitted, all because of clinical outcomes. In this protocol-driven model, more accelerated diagnostic protocol patients underwent carotid imaging (97% versus 90%) and in less time (median 13 versus 25 hours) and more accelerated diagnostic protocol patients underwent echocardiography (97% versus 73%) in less time (median, 19 versus 43 hours). Both groups had comparable rates of related return visits (12% each), subsequent strokes (3 versus 2), and major clinical events (4 each). This approach offers a promising alternative to inpatient admission for patients with transient ischemic attack but requires a commitment of resources. Further refinements with alternative imaging and risk stratification tools may increase the utility of this strategy.

TREATMENT

Conceptually, it is useful to divide transient ischemic attack treatment into that given in the hyperacute period to prevent early recurrent stroke, before extensive diagnostic testing has been completed, and that made with a goal of longer-term prevention of stroke. This distinction reflects the reality of clinical trial data, some of which involve strategies initiated within hours of the index event and some of which involve prevention strategies initiated many days or weeks after the index event. In actual clinical practice, however, this distinction is increasingly blurred as rapid diagnostic testing (such as CT angiography) occurs in the ED and as ED observation units

enter the clinical paradigm, resulting in decisions about longer-term prevention strategies being increasingly made in the ED.

Acute Treatment of Transient Ischemic Attack

Initial treatment of patients with transient ischemic attack should begin with basic supportive care measures to optimize potentially compromised cerebral blood flow. This includes positioning the patient with the head of the bed flat, permissive hypertension, and administration of intravenous fluids. In a study of 69 patients with acute transient ischemic attack, using MRI perfusion imaging, one-third of patients had evidence of a perfusion abnormality.[26] Changing head position is a simple, often overlooked measure to increase cerebral perfusion. Studies using transcranial Doppler monitoring have shown that mean flow velocity in the middle cerebral artery can increase 20% when head position is lowered from 30 degrees to 0 degrees.[27] Some patients will have demonstrable recovery of neurologic deficits when positioned flat, particularly in cases of large vessel occlusion or high-grade stenosis.

Permissive hypertension denotes the avoidance of blood pressure–lowering agents. In the setting of acute cerebrovascular ischemia, cerebral autoregulation may be impaired, and cerebral perfusion, particularly in regions dependent on collateral blood flow, may be directly dependent on systemic blood pressure. A controlled trial of nimodipine as a putative neuroprotectant in acute ischemic stroke found that poor outcomes in nimodipine-treated patients were associated with blood pressure lowering.[28] Additional studies have also identified early blood pressure lowering as a predictor of poor outcome after stroke.[29] Isotonic intravenous fluids should be given to ensure euvolemia and maintain intravascular volume. Fluid administration should be tailored to the patient's cardiac status, with a 500-mL bolus of normal saline solution followed by infusion of 100 to 150 mL/hour, reasonable for patients without known or suspected heart failure. Close neurologic observation to identify recurrent symptomatic cerebral ischemia is essential.

Once neuroimaging, typically CT, has excluded the possibility of hemorrhage, antithrombotic therapy should be started. To date, there have been limited data from randomized trials specifically involving treatment of transient ischemic attack in the first 24 to 48 hours after symptom onset. A larger amount of data exists for ischemic stroke, and because the 2 conditions are pathophysiologically comparable, it is logical to extrapolate these data to transient ischemic attack. However, there are 2 major caveats to this extrapolation. First, because larger cerebral infarctions are associated with an increasing risk of intracerebral bleeding, it is probable that patients with transient ischemic attack have a lower risk of bleeding complications compared with patients with stroke.[30] Second, somewhat counterintuitively, the risk of early recurrent stroke appears to be substantially higher in patients with transient ischemic attack than completed ischemic stroke, such that interventions might have a more robust treatment effect.[15,31,32]

Antiplatelet Therapy

Two large studies, the International Stroke Trial (IST) and the Chinese Acute Stroke Trial (CAST), have tested early aspirin therapy in acute ischemic stroke. IST randomized 19,435 patients to aspirin 300 mg daily or no aspirin with treatment started within 48 hours of symptom onset.[33] This trial also randomized patients to one of 2 doses of subcutaneous heparin or no heparin in a factorial design (described below). Treatment with aspirin reduced recurrent ischemic stroke from 3.9% to 2.8% (*P*<.05) and nonsignificantly reduced mortality (9.0% versus 9.4%) at 2 weeks or hospital discharge. There was no significant excess of intracranial bleeding with aspirin therapy. CAST randomized 21,106 patients to aspirin 160 mg daily or placebo within 48 hours of symptom onset.[34] At 4 weeks or hospital discharge, recurrent ischemic stroke was reduced from 2.1% to 1.6% (*P*=.01) and mortality from 3.9% to 3.3% (*P*=.04) with aspirin therapy. There was a nonsignificant excess of intracranial bleeding with aspirin (1.1% versus 0.9%). A much smaller trial, the Multicentre Acute Stroke Trial-Italy, also suggested a benefit of early aspirin therapy.[35]

A prospectively planned pooled analysis of IST and CAST was performed, assessing events during the trial treatment period (4 weeks in CAST, 2 weeks in IST).[36] This showed that aspirin treatment reduced recurrent ischemic stroke by 7 per 1,000 treated (*P*<.0001) and reduced mortality by a further 4 per 1,000 treated (*P*=.05). Aspirin resulted in an increase in intracranial bleeding of 2 per 1,000 treated (*P*=.07). Overall, then, the net benefit of early aspirin therapy in patients with acute ischemic stroke was 9 per 1,000.

For perspective, it is useful to compare this clinical benefit with that observed with early aspirin therapy given to patients with acute myocardial infarction. For instance, in the large International Study of Infarct Survival 2, aspirin therapy in patients with acute myocardial infarction decreased recurrent myocardial infarction, stroke, or death by 35 to 40 per 1,000 at 5 weeks.[37]

A pilot trial of combination aspirin and clopidogrel in patients with high-risk transient ischemic attack or minor stroke, the Fast Assessment of Stroke and Transient Ischemic Attack to Prevent Early Recurrence (FASTER) study, has been recently completed.[38] This study randomized 392 patients within 24 hours of symptom onset to aspirin alone versus aspirin and clopidogrel and also to simvastatin versus placebo in a 2×2 factorial design. Compared with aspirin alone, combination aspirin and clopidogrel failed to demonstrate superiority but was associated with a nonsignificant trend toward reduction in the primary endpoint of stroke within 90 days (7.1% versus 10.8%; *P*=.19). Most events occurred early in the trial, with a median time to stroke endpoint of 1 day. A significant excess of symptomatic bleeding events was seen with combination therapy (3.0% versus 0%; *P*=.03). Further studies of combination aspirin and clopidogrel in the short-term treatment of transient ischemic attack appear warranted to

better define the potential benefit in early stroke reduction compared with the risk of bleeding complications.

Anticoagulation

Only very limited data are available about acute anticoagulation specifically in patients with transient ischemic attack. Three small studies examining intravenous heparin have been published, but limitations of study design and the small numbers of patients studied preclude any meaningful conclusions being drawn from these data.[39-41]

A much larger body of clinical trial data exists for acute anticoagulation in patients with ischemic stroke. A meta-analysis of multiple trials of heparin or low-molecular-weight heparin showed no evidence of a net benefit of acute anticoagulation in ischemic stroke.[42] However, extrapolation of these data to transient ischemic attack should be tempered by several observations. First, in the largest study of heparin in acute ischemic stroke, the IST, a reduction in recurrent ischemic stroke at 2 weeks was demonstrated (2.9% versus 3.8%), but this was offset by an equivalent increased risk of cerebral hemorrhage (1.2% versus 0.4%).[33] Second, it is known that the risk of cerebral hemorrhage increases with the size of cerebral infarction.[30] Patients with transient ischemic attack, therefore, may have a lower risk of hemorrhage from acute anticoagulation than patients with acute ischemic stroke. Third, the benefit of anticoagulation may be magnified as the risk of recurrent events increases. Finally, given the heterogeneous pathophysiology of stroke, it is plausible that anticoagulation may be useful in certain stroke mechanisms but not others. Indeed, some studies have suggested a benefit of anticoagulation specifically in stroke caused by large vessel stenosis but not in stroke caused by other mechanisms.[43,44]

In summary, the use of acute anticoagulation in transient ischemic attack remains an area of great uncertainty. At present, there is no clear evidence establishing a benefit of this therapy; however, its use in select cases, particularly those at high short-term risk of stroke, may be reasonable.

LONG-TERM STROKE PREVENTION AFTER TRANSIENT ISCHEMIC ATTACK

As with ischemic stroke, the optimal long-term prevention strategy in patients with transient ischemic attack depends on determining the underlying mechanism causing the cerebrovascular event. Although many times this determination will take place outside of the ED or will depend on neurologic consultation, there are several mechanisms of transient ischemic attack that have particular relevance to the emergency physician because they have specific, distinct therapeutic implications. Representative mechanism-specific therapies are outlined below.

Carotid Endarterectomy for Cervical Carotid Stenosis

In patients with transient ischemic attack referable to carotid stenosis of 70% or greater, revascularization with carotid endarterectomy is an extremely robust intervention to reduce the risk of recurrent stroke. In the 2 large randomized trials of carotid endarterectomy, the European Carotid Surgery Trial and the North American Symptomatic Carotid Endarterectomy Trial, a 10% to 15% absolute reduction in subsequent stroke was demonstrated.[45] A lesser benefit was observed in patients with 50% to 69% stenosis. A pooled analysis of the European Carotid Surgery Trial and the North American Symptomatic Carotid Endarterectomy Trial showed a dramatically greater benefit with intervention within 2 weeks of the symptomatic event as opposed to at later points.[45] These data emphasize the need for prompt surgical consultation and intervention.

Older age should not be considered a contraindication to carotid endarterectomy; in fact, in the carotid surgery trials, patients 75 years or older derived a much greater benefit than younger patients.[46]

Anticoagulation for Carotid or Vertebral Artery Dissection

The mural hematoma present in arterial dissection can undergo progressive thrombosis culminating in vessel occlusion or can serve as a proximal embolic source, in either instance leading to recurrent cerebrovascular ischemia. There have been no randomized trials to assess optimal antithrombotic therapy in arterial dissection. A Cochrane Database systematic review of carotid dissection, which included only reported case series because of the lack of controlled trials, found no statistically significant difference between antiplatelet and anticoagulant therapy (23.7% antiplatelet versus 14.3% anticoagulant dead or disabled; OR 1.94; 95% CI 0.76 to 4.91).[47] Recurrent stroke was observed in 1.7% with anticoagulation versus 3.8% with antiplatelet therapy and 3.3% with no therapy. These data are severely limited, given their nonrandomized nature. Nevertheless, many experts advocate anticoagulation for patients with arterial dissection, particularly in the setting of transient ischemic attack, given the relatively lower risk of bleeding.

Atrial Fibrillation

Warfarin is substantially more effective than aspirin at preventing recurrent stroke in patients who have experienced transient ischemic attack or stroke because of atrial fibrillation. In a meta-analysis of 12 trials involving almost 13,000 patients, warfarin was associated with a 39% relative risk reduction (95% CI 22% to 52%) compared with antiplatelet therapy, with only a modest absolute increased risk of bleeding complications.[48] Recently, additional clinical trial data have provided clear evidence of benefit even in elderly patients.[49]

Combination antiplatelet therapy with aspirin and clopidogrel is not a substitute for warfarin. The Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W) randomized 6,706 patients to adjusted-dose warfarin or combination therapy with aspirin and clopidogrel.[50] The annual risk of vascular events was 3.9% with warfarin and 5.6% with aspirin and clopidogrel (P=.0003). Major bleeding was not significantly different between the 2 groups, and total bleeding was in fact more frequent in the aspirin and clopidogrel group.

Although long-term anticoagulation is clearly indicated, it remains uncertain whether patients with transient ischemic attack and atrial fibrillation should be treated with parenteral anticoagulant therapy in the immediate period after presentation. Two studies have addressed the issue in patients with ischemic stroke, and both showed no net benefit of early parenteral anticoagulation compared with aspirin.[33,51] However, as mentioned previously, differences in risk of hemorrhage and early recurrence between patients with transient ischemic attack and patients with stroke limit extrapolation of these data. This remains an area of considerable uncertainty, and practice patterns vary widely.

Infectious Endocarditis

Embolic transient ischemic attack caused by bacterial endocarditis mandates immediate anti-infective therapy and cardiology consultation. Intravenous anticoagulation should be avoided in these patients, particularly in the acute period, given a high risk of intracranial bleeding.

Antiplatelet Therapy

Aspirin. In patients with stroke or transient ischemic attack, long-term aspirin therapy reduces the risk of recurrent stroke, myocardial infarction, or vascular death by about 20%, such that 36 events will be prevented per 1,000 patients treated for about 2.5 years.[52] Higher-dose aspirin (300 to 1,500 mg) is no more effective than low-dose aspirin (50 to 75 mg) but is associated with a greater incidence of adverse effects.[52,53] Platelet inhibition with low-dose aspirin (<100 mg) may require up to 7 days to reach maximal levels. Therefore, when an immediate antiplatelet effect is desired, a loading dose of at least 160 mg should be given.[54]

Thienopyridines (clopidogrel, ticlopidine). Clopidogrel was shown to be slightly more effective than aspirin in a single large trial (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events [CAPRIE]), which enrolled 19,185 patients with vascular disease, about one third of whom were enrolled with a recent stroke.[55] The relative risk reduction compared with aspirin was 8.7% for the primary endpoint of stroke, myocardial infarction, or vascular death, such that about 10 events will be prevented per 1,000 patients treated for 2 years with clopidogrel compared with aspirin. The adverse effect profile of clopidogrel was comparable to that of aspirin, though clopidogrel is associated with a slightly lower risk of gastrointestinal bleeding (2.0% clopidogrel versus 2.7% aspirin).

Ticlopidine, another thienopyridine agent, has shown conflicting results in clinical trials.[56-58] The adverse effect of severe neutropenia severely limits its utility in current practice.

Combination antiplatelet therapies. Two large studies have shown that the combination of aspirin and extended-release dipyridamole is considerably more effective than aspirin alone in preventing recurrent stroke in patients with cerebrovascular disease.

The European Stroke Prevention Study-2 randomized 6,602 patients with recent stroke or transient ischemic attack to one of 4 groups: placebo, aspirin alone, extended-release dipyridamole alone, or the combination of aspirin and extended-release dipyridamole.[59] Compared with placebo, both aspirin and extended-release dipyridamole reduced the risk of the primary endpoint (fatal and nonfatal stroke) by an approximately similar degree (relative risk reduction 18% and 16%, respectively). Combination aspirin and extended-release dipyridamole was significantly more effective than either agent alone, with a relative risk reduction of 23% compared with aspirin and no significant increase in major bleeding. Thus, about 30 strokes will be prevented for every 1,000 patients treated for 2 years with combination aspirin and extended-release dipyridamole compared with aspirin alone.

The European/Australasian Stroke Prevention in Reversible Ischemia Trial randomized 2,763 patients with recent stroke or transient ischemic attack to aspirin or aspirin in combination with dipyridamole.[60] The primary endpoint was a composite of stroke, myocardial infarction, vascular death, or major bleeding, and a significant benefit in favor of combination therapy was demonstrated (HR 0.80; 95% CI 0.66 to 0.98), such that about 30 events will be prevented for every 1,000 patients treated for 3.5 years. The major adverse effect of combination therapy with aspirin and dipyridamole is headache related to the dipyridamole component. This is generally self-limited and improves after several days of medication use.

Two large trials have studied combination therapy with clopidogrel and aspirin. In the Management of Atherothrombosis with Clopidogrel in High-risk Patients trial, the combination of clopidogrel and aspirin was compared with clopidogrel alone in 7,599 patients with stroke or transient ischemic attack and an additional high-risk feature.[61] Combination therapy was no more effective than clopidogrel monotherapy at preventing recurrent vascular events but was associated with a substantial excess of life-threatening and major hemorrhage (4.5% versus 1.9%; $P<.001$).

Clopidogrel and aspirin combination therapy has also been compared with aspirin alone. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance study, which enrolled 15,603 subjects with clinically evident vascular disease or multiple risk factors, showed no overall benefit to combination therapy.[62] This study included 4,300 patients with cerebrovascular disease, including transient ischemic attack. Subgroup analysis in this group did not demonstrate a significant advantage to combination clopidogrel and aspirin compared with aspirin alone. The combination of clopidogrel and aspirin should therefore be avoided in most patients with cerebrovascular disease.

Ongoing clinical trials. The largest antiplatelet trial for stroke prevention yet conducted, the Prevention Regimen for Effectively Avoiding Second Strokes study, is in process, with results expected in mid-2008.[63] More than 20,000 patients have been enrolled in this trial, which will compare the combination
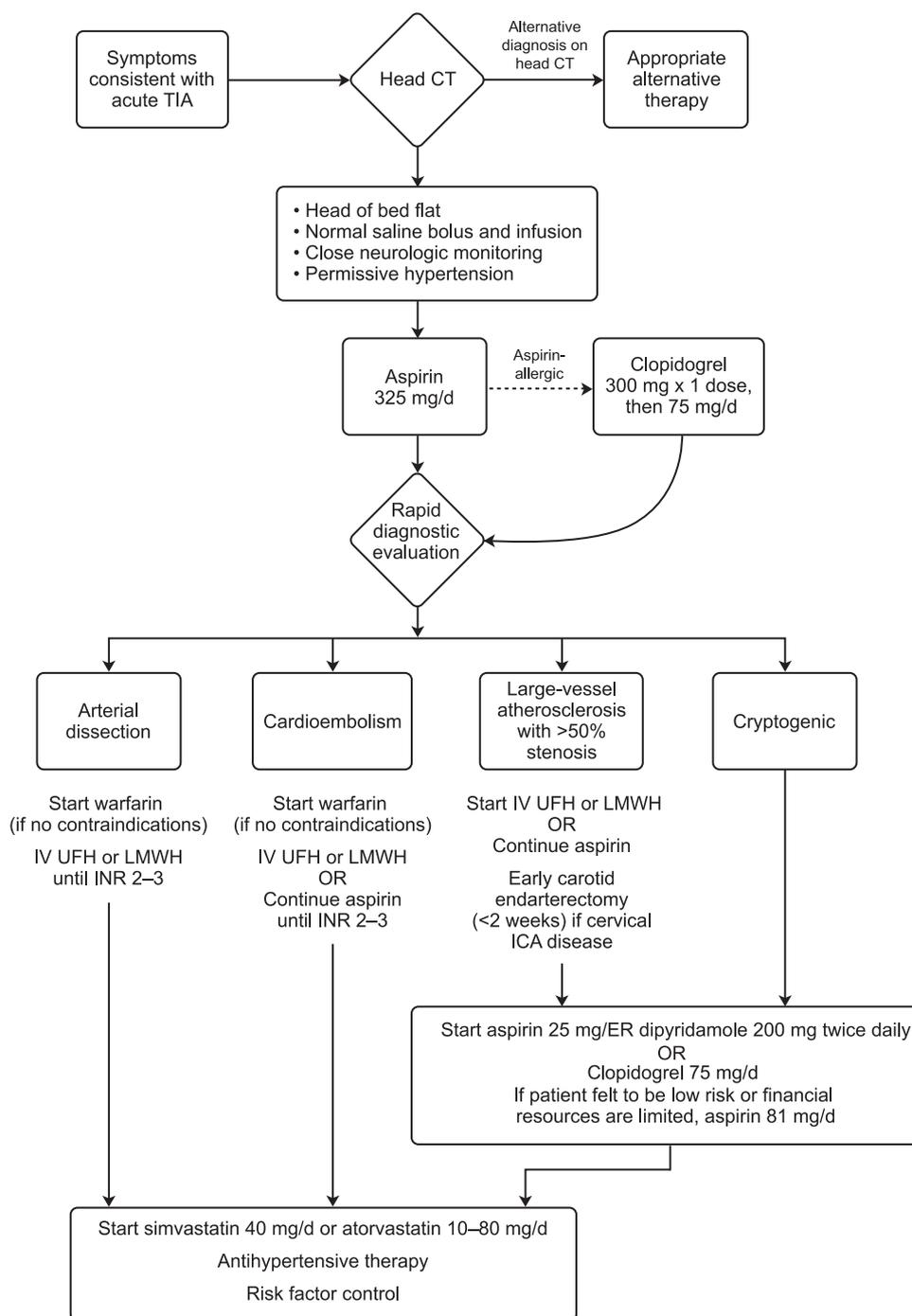
Figure. One approach to management of patients with transient ischemic attack. *ER,* Extended-release; *ICA,* internal carotid artery; *INR,* international normalized ratio; *IV,* intravenous; *LMWH,* low-molecular-weight heparin; *UFH,* unfractionated heparin.

of aspirin and extended-release dipyridamole with clopidogrel monotherapy in patients with a history of stroke or a transient ischemic attack with imaging evidence of tissue infarction.

Guidelines for Antiplatelet Therapy for Stroke Prevention

The American Heart Association/American Stroke Association (AHA/ASA) and American College of Chest Physicians (ACCP) have each published independent guidelines on use of antiplatelet therapy for prevention of recurrent stroke after a stroke or transient ischemic attack.[64,65] In general, these guidelines are in accordance with each other. Both recommend use of antiplatelet therapy for patients with noncardioembolic transient ischemic attack (AHA/ASA: class I, level of evidence A; ACCP: grade I). Aspirin 50 to 325 mg/day, the combination

of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily, and clopidogrel 75 mg/day are all considered acceptable options for initial therapy. Initial therapy with aspirin and extended-release dipyridamole is suggested instead of aspirin alone (AHA/ASA: class IIa, level of evidence A; ACCP: grade 2A), and clopidogrel may be considered instead of aspirin alone (AHA/ASA: class IIb, level of evidence B; ACCP grade 2B). The combination of aspirin and clopidogrel is not routinely recommended (AHA/ASA: class III, level of evidence A). For patients allergic to aspirin, clopidogrel is recommended (AHA/ASA: class IIa, level of evidence B; ACCP: grade 1C+). The AHA/ASA guidelines also emphasize that selection of antiplatelet agents should be individualized according to patient characteristics such as risk profile and tolerance to adverse effects.

Other Prevention Strategies

Large randomized controlled trials have demonstrated a significant reduction in the risk of recurrent vascular events in patients with cerebrovascular disease treated with statin medications.[66,67] In these trials, there was little divergence in the event rates between statin-treated patients and patients receiving placebo within the first year. In the pilot FASTER trial, described above, there was no benefit to early initiation of simvastatin in patients with transient ischemic attack or minor stroke.[38] This lack of an early statin effect has also been shown in patients with acute coronary syndromes.[68] On the other hand, 2 observations suggest a possible role for early initiation of statin therapy. First, initiation of statin therapy during hospitalization may increase long-term compliance.[69] Second, animal models of ischemic stroke and some clinical trial data have suggested a potential neuroprotectant effect of statin class medications.[70,71]

Although most experts in cerebrovascular disease agree that blood pressure should not be lowered in the acute setting after transient ischemic attack, it is also clear from controlled trials that long-term blood pressure control is an essential aspect of reducing risk of subsequent stroke.[72] Current AHA/ASA guidelines for acute ischemic stroke suggest that antihypertensive treatment in the acute setting be withheld unless the systolic blood pressure exceeds 220 mm Hg or diastolic blood pressure exceeds 120 mm Hg, or unless there is another indication for blood pressure lowering (eg, cardiac ischemia or aortic dissection).[73] These same guidelines also suggest restarting antihypertensive medications for patients with preexisting hypertension who are neurologically stable after 24 hours. At least 1 international guideline suggests waiting 7 to 14 days after transient ischemic attack before starting antihypertensive therapy.[18] Patients with large vessel stenosis or occlusion probably face the greatest risk from early blood pressure lowering. In these patients, hypertension may reflect a physiological compensatory mechanism to maintain cerebral flow. Conversely, if vascular imaging has excluded large vessel stenosis, then relatively earlier initiation of antihypertensive therapy may be sensible. Patient compliance with

antihypertensive therapy may be greater when started at hospital or ED discharge. Given the clear-cut long-term benefit of antihypertensive therapy, this advantage must be taken into consideration, depending on individual patient characteristics.

General measures to improve vascular health include smoking cessation, control of blood glucose level in diabetic patients, regular exercise, and healthy eating habits. The patient who has just experienced transient ischemic attack, and family members who may have witnessed the event, may have considerable fear of subsequent stroke. This may be a powerful motivating factor, allowing counseling on these important issues to be particularly effective in the acute period. The Figure summarizes one approach to treatment of patients with transient ischemic attack.

TREATMENT OF STROKE IN THE IMMEDIATE POST-TRANSIENT ISCHEMIC ATTACK PERIOD

Patients who develop stroke after transient ischemic attack are eligible for thrombolytic therapy.[74] Pooled data from randomized controlled trials have demonstrated that thrombolytic therapy for acute ischemic stroke is critically time dependent, with earlier treatment associated with better outcomes.[75] Close neurologic observation in the ED or hospital setting may therefore allow expedited thrombolysis should a stroke occur after transient ischemic attack.

CONCLUSION

The past decade has brought a new recognition of the high short-term risk of stroke facing patients with transient ischemic attack. Coincident with this has been an increasing appreciation that transient ischemic attack should be evaluated and treated with the same urgency and rigor applied to patients with suspected unstable angina. Further research is needed to optimize our ability to risk-stratify patients and to provide evidence-based guidance on best treatment strategies, particularly in the emergency setting.

KEY CONCEPTS
- Clinical features that predict increased short-term risk of stroke after transient ischemic attack include older age, hypertension, diabetes, symptoms of weakness or speech impairment, and symptom duration greater than 10 minutes.
- Magnetic resonance imaging with diffusion-weighted imaging and vascular imaging may play an important role in risk-stratifying patients with transient ischemic attack.
- Flat head positioning, isotonic fluid administration, and permissive hypertension are basic measures to improve cerebral blood flow and mitigate cerebral ischemia.
- For most patients with transient ischemic attack, aspirin should be started as soon as neuroimaging has ruled out the possibility of hemorrhage.
- The specific cause of the transient ischemic attack in individual patients must be determined to select the most appropriate long-term preventive therapy.

- Patients who experience stroke after transient ischemic attack should be considered for thrombolysis.

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