Clinical Policy: Critical Issues in the Evaluation of Adult Patients With Suspected Transient Ischemic Attack in the Emergency Department

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ABSTRACT

This clinical policy from the American College of Emergency Physicians addresses key issues for adults presenting to the emergency department with suspected transient ischemic attack. A writing subcommittee conducted a systematic review of the literature to derive evidence-based recommendations to answer the following clinical questions: (1) In adult patients with suspected transient ischemic attack, are there clinical decision rules that can identify patients at very low short-term risk for stroke who can be safely discharged from the emergency department? (2) In adult patients with suspected transient ischemic attack, what imaging can be safely delayed from the initial emergency department workup? (3) In adult patients with suspected transient ischemic attack, is carotid ultrasonography as accurate as neck computed tomography angiography or magnetic resonance angiography in identifying severe carotid stenosis? (4) In adult patients with suspected transient ischemic attack, can a rapid emergency department-based diagnostic protocol safely identify patients at short-term risk for stroke? Evidence was graded and recommendations were made based on the strength of the available data.

INTRODUCTION

Transient ischemic attack (TIA) is part of a spectrum that involves ischemia of the central nervous system. Historically the definition of a TIA has been focal neurologic symptoms that resolve within 24 hours of onset.[1] However, studies have shown that approximately one third of all TIAs have evidence of infarction on neurologic imaging.[2] Thus, the American Heart Association/American Stroke Association (AHA/ASA) in 2009 revised the definition for TIA, using a tissue-based diagnosis: "a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction."[3] If imaging is unavailable and the symptoms last greater than 24 hours, then patients are classified as having had a clinical stroke.[1] Most TIAs, however, are thought to last fewer than 1 or 2 hours.[3]

The incidence of TIA in the United States is approximately 240,000 cases a year. However, the true incidence is likely higher because of patients not reporting their symptoms to their health care provider.[1,4] The risk of an acute ischemic stroke after a TIA ranges from 3.5% to 10% at 2 days, 5% to 10% at 7 days, and 9.2% to 17% at 90 days.[5-13] Because approximately 15% of all ischemic strokes are preceded by a TIA, timely evaluation for modifiable conditions that are high-risk, such as carotid stenosis and atrial fibrillation, is important.[1,4]

Because of the lack of a specific diagnostic test for TIA, the diagnosis of TIA can be difficult to distinguish from stroke mimickers, such as seizures, migraines, syncope, peripheral vestibular disturbance, or psychogenic causes.[14] Studies have demonstrated difficulty among neurologists and non-neurologists in identifying patients with TIA, with one study reporting that 60% of patients admitted with an initial diagnosis of a TIA had a final diagnosis of a nonischemic cause for their symptoms such as seizures, migraines, or neuropathy.[15,16] To help identify TIA, risk-stratification tools that were originally developed to identify TIA patients at high short-term risk for stroke have also been evaluated to predict true TIA.[17,18] Research is also currently under way to evaluate possible biomarkers to help establish the diagnosis of TIA.[19]

Evaluation of TIA patients in the emergency department (ED) has been shown to be variable, depending on resources available. Brain neuroimaging in the ED may include either head computed tomography (CT) or brain magnetic resonance imaging (MRI). Consultation with neurology and admission rates also vary widely.[20]

Currently, there is no specific acute intervention for patients with TIA. The goal of evaluating a patient with TIA is to reduce the potential for future strokes.[1] Whereas antiplatelet agents are used as first-line therapy for secondary prevention, a workup should also include an evaluation that may lead to other secondary prevention treatments. This includes identification of high-risk conditions that have effective therapeutic interventions such as severe carotid stenosis or atrial fibrillation.

This clinical policy will address 4 issues related to emergency physicians based on feedback from the American College of Emergency Physicians (ACEP) membership. The first question will look at clinical decision rules to evaluate whether a patient can be safely discharged home after a suspected TIA. Emergency physicians identified this as a critical issue because hospitals may not have the capacity to admit every TIA patient, and outpatient workups, especially to a specialty TIA clinic, have been shown to be a cost-effective alternative to hospital admission for certain subsets of patients.[21,22]

The second clinical question tackles the issue of emergent imaging in the ED. Although imaging has been recommended for TIA,[1] when TIA symptoms have completely resolved, it is unclear whether imaging can be safely deferred and obtained later on an inpatient basis or during outpatient follow-up.

The third question evaluates the accuracy of carotid ultrasonography compared with CT angiography (CTA)

and magnetic resonance angiography (MRA) in the evaluation of severe carotid stenosis. This is important for emergency physicians because not all imaging modalities may be readily available in their ED.

Finally, challenges exist in obtaining timely evaluation for high-risk causes of TIA. The fourth question evaluates the safety of an expedited ED-based pathway for the evaluation of TIA.

METHODOLOGY

This clinical policy was created after careful review and critical analysis of the medical literature and was based on a systematic review of the literature. Searches of MEDLINE, MEDLINE InProcess, Cochrane, and SCOPUS were performed. All searches were limited to English-language sources, adults, and human studies. Specific key words/phrases, years used in the searches, dates of searches, and study selection are identified under each critical question. In addition, relevant articles from the bibliographies of included studies and more recent articles identified by committee members and reviewers were included.

This policy is a product of the ACEP clinical policy development process, including expert review, and is based on the existing literature; when literature was not available, consensus of emergency physicians was used. Expert review comments were received from emergency physicians, neurologists, members of the AHA/ASA, and ACEP's Medical Legal Committee. Comments were received during a 60-day open comment period, with notices of the comment period sent in an e-mail to ACEP members, published in *EM Today*, and posted on the ACEP Web site. The responses were used to further refine and enhance this policy; however, the responses do not imply endorsement of this clinical policy. Clinical policies are scheduled for revision every 3 years; however, interim reviews are conducted when technology, methodology, or the practice environment changes significantly. ACEP was the funding source for this clinical policy.

Assessment of Classes of Evidence

All articles used in the formulation of this clinical policy were graded by at least 2 methodologists and assigned a Class of Evidence. Each article was assigned a design class with design 1 representing the strongest study design and subsequent design classes (ie, design 2, design 3) representing respectively weaker study designs for therapeutic, diagnostic, or prognostic clinical reports, or meta-analyses (Appendix A). Articles were then graded on dimensions related to the study's methodological features, such as randomization processes, blinding, allocation concealment, methods of data collection, outcome measures and their assessment, selection and misclassification biases, sample size, and generalizability. Using a predetermined process related to the study's design, methodological quality, and applicability to the critical question, articles received a final Class of Evidence grade (ie, Class I, Class II, Class III, or Class X) (Appendix B). Articles identified with fatal flaws or that were ultimately not applicable to the critical question received a Class of Evidence grade "X" and were not used in formulating recommendations for this policy. Grading was done with respect to the specific critical questions; thus, the level of evidence for any one study may vary according to the question for which it is being considered. As such, it was possible for a single article to receive different Classes of Evidence as different critical questions were answered from the same study. Question-specific Classes of Evidence grading may be found in the Evidentiary Table (available online at www.annemergmed.com).

Translation of Classes of Evidence to Recommendation Levels

Strength of recommendations regarding each critical question were made by subcommittee members using results from strength of evidence grading, expert opinion, and consensus among subcommittee members according to the following guidelines:

Level A recommendations. Generally accepted principles for patient care that reflect a high degree of clinical certainty (eg, based on evidence from 1 or more Class of Evidence I or multiple Class of Evidence II studies).

Level B recommendations. Recommendations for patient care that may identify a particular strategy or range of strategies that reflect moderate clinical certainty (eg, based on evidence from 1 or more Class of Evidence II studies or strong consensus of Class of Evidence III studies).

Level C recommendations. Recommendations for patient care that are based on evidence from Class of Evidence III studies or, in the absence of any adequate published literature, based on expert consensus. In instances where consensus recommendations are made, "consensus" is placed in parentheses at the end of the recommendation.

There are certain circumstances in which the recommendations stemming from a body of evidence should not be rated as highly as the individual studies on which they are based. Factors such as heterogeneity of results, uncertainty about effect magnitude and

consequences, and publication bias, among others, might lead to such a downgrading of recommendations.

When possible, clinically oriented statistics (eg, likelihood ratios [LRs], number needed to treat) are presented to help the reader better understand how the results may be applied to the individual patient. For a definition of these statistical concepts, see Appendix C.

This policy is not intended to be a complete manual on the evaluation and management of adults with suspected TIA but rather a focused examination of critical issues that have particular relevance to the current practice of emergency medicine.

It is the goal of the Clinical Policies Committee to provide an evidence-based recommendation when the medical literature provides enough quality information to answer a critical question. When the medical literature does not contain adequate empirical data to answer a critical question, the members of the Clinical Policies Committee believe that it is equally important to alert emergency physicians to this fact.

This clinical policy is not intended to represent a legal standard of care for emergency physicians. Recommendations offered in this policy are not intended to represent the only diagnostic or management options available to the emergency physician. ACEP recognizes the importance of the individual physician's judgment and patient preferences. This guideline defines for the physician those strategies for which medical literature exists to provide support for answers to the critical questions addressed in this policy.

Scope of Application. This guideline is intended for physicians working in EDs.

Inclusion Criteria. This guideline applies to adult patients aged 18 years and older presenting to the ED with a suspected TIA who have had resolution of symptoms.

Exclusion Criteria. This guideline is not intended to be used for pediatric patients.

For potential benefits and harms of implementing the recommendations, see Appendix D.

CRITICAL QUESTIONS

1. In adult patients with suspected TIA, are there clinical decision rules that can identify patients at very low short-term risk for stroke who can be safely discharged from the ED?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. In adult patients with suspected TIA, do not rely on current existing risk stratification instruments (eg, age, blood pressure, clinical features, duration of TIA and presence of diabetes [ABCD2] score) to identify TIA patients who can be safely discharged from the ED.

Level C recommendations. None specified.

Key words/phrases for literature searches: transient ischemic attack, TIA, stroke, critical pathways, practice guidelines, delayed decision, and variations and combinations of the key words/phrases. Searches included January 1, 2000 to search date of March 18, 2015.

Study Selection: Three hundred seventy-eight articles were identified in the search. Seventy-two articles were selected from the search results for further review, with 34 studies included for this critical question.

This critical question focuses on pretest probability assessment for short-term stroke risk after evaluation for suspected TIA. Estimation of pretest probability is imperative for the accurate interpretation of posttest probability for any diagnostic or prognostic test. Pretest probability for short-term stroke risk can be estimated in 3 general ways: objective criteria (eg, risk stratification instruments), clinician gestalt, or extrapolation from studies reporting post-TIA stroke rates in similar populations.

A subset of ED patients with TIA are at increased risk for strokes in the days and weeks after the index ED presentation. Because access to advanced diagnostics such as echocardiography, carotid imaging, and telemetry may be limited, the challenge is timely recognition of TIA patients who are most likely to progress to stroke within a shorter timeframe and who could benefit from interventions such as anticoagulation or carotid endarterectomy to reduce this stroke risk.[23] The 2009 AHA/ASA TIA guidelines recommend hospital admission for (1) individuals with ABCD2 score greater than or equal to 3, (2) those with ABCD2 score 0 to 2 if "uncertain that diagnostic workup can be completed within 2 days as an outpatient," or (3) when "other evidence indicates the patient's event was caused by focal ischemia."[3] Therefore, the most compelling rationale to incorporate TIA risk stratification instruments into clinical practice is evidence that when used alone without additional history, physical examination, imaging, or laboratory testing, they may differentiate low-risk patients with TIA for whom advanced workup and specialty consultations can be deferred from those subsets who are at increased short-term risk (ie, 2 to 7 days) for stroke.

Six TIA risk stratification instruments have been evaluated in studies that met the inclusion criteria: ABCD,[9,11,13,24-30] ABCD2,[6-13,17,26,27,31-47] ABCD3,[12,27,38] the California,[11,13,27,48] the Canadian TIA Score,[42] and the Essen Stroke Risk.[27] None of these instruments have been assessed in a Class I study. All of the studies had a low number of stroke

outcomes, leading to a lack of precision (ie, wide confidence intervals [CIs]) for most point estimates. Most of the prospective studies do not specify whether clinicians were blinded to the risk stratification results or had incorporated these risk estimates into clinical management decisions. In addition, these studies had an unacceptably high rate of lost to follow-up.

The most frequently studied risk stratification instrument is the ABCD2 score (Appendix E).[6-13,17,26,27,31-47] The ABCD2 score was derived and validated using retrospective data from the California and Oxfordshire groups in a Class II[11] study. Using 1,916 patients with suspected TIA in the derivation group and 2,892 in the validation group, they noted a 3.9% and 7.5% frequency for stroke at 2 and 7 days, respectively. Using a threshold of less than 4, the ABCD2 score identified 33.8% of patients as "low risk," with strokes occurring in 1% and 1.2% of these low-risk patients at 2 and 7 days, respectively. Since the derivation of the ABCD2 score, 6 Class II[34,40,42,44,45,47] and 21 Class III[6-10,12,13,17,26,27,31-33,35-39,41,43,46] studies have evaluated this score. These studies varied from multi-institutional prospective studies to single-center retrospective ones. Although the discriminatory accuracy of ABCD2 to distinguish patients with suspected TIA at low or high short-term risk for stroke is less convincing than the original derivation and validation set,[11] many of these subsequent studies did not report LRs or sufficient detail to compute LRs at any timeframe after the TIA.[12,25,27,35,38,41-43] The ABCD2 negative LRs for 2- to 7-day stroke risk among the studies that did report these data vary widely, from 0 to 1.1, with significant imprecision and wide CIs.[7-9,11,13,17,32,34,40,44]

The 7 Class II[11,34,40,42,44,45,47] studies of the ABCD2 score are limited by uncertain blinding of outcome assessors to the ABCD2 score. This could have potentially skewed any observed prognostic accuracy because of aggressive TIA management based on the observed ABCD2 score. These interventions could have prevented short-term strokes that the ABCD2 score would have predicted if preventive interventions guided by the ABCD2 score had not been implemented. Inconsistent reporting of short-term (2- or 7-day) stroke rates and high rates of lost to follow-up were also common limitations. In addition, the feasibility of ED clinicians scoring the ABCD2 in real time was rarely assessed; instead, research teams usually calculated the score either retrospectively or prospectively. In a Class II study, Wasserman et al[47] prospectively evaluated 1,093 consecutive adults with suspected TIA at 2 Canadian tertiary care EDs, including 1.6% admitted from the ED. Strokes were observed in 3.2% of patients at 90 days, which was approximately one-third the rate predicted by the ABCD2 score; stroke outcomes in this study were determined by a neurologist who was not blinded to the ABCD2 score. The ABCD2 negative LR for 90-day stroke was 0.29 (95% CI 0.08 to 0.81).

In a Class II study, Cancelli et al[34] prospectively evaluated 161 TIA patients in 1 Italian stroke referral center, noting an 11.5% 90-day stroke rate. An ABCD2 score less than 4 was associated with a 0% stroke rate at 2, 7, 30, and 90 days, but only 4 strokes were observed in 2 days, creating an unacceptably wide CI (negative LR 0; 95% CI 0 to 1.9). Stead et al[44] reported 7-day stroke risk in a single-center retrospective study of 637 adult patients with suspected TIA. The 7-day stroke risk was 1%, and strokes occurred in 1.1% of individuals with an ABCD2 score less than 4, representing a negative LR of 1.1 (95% CI 0.2 to 2.6). A Class II study by Ozpolat et al[40] reported on 64 patients with TIA in a Turkish ED using convenience sampling; 12.5% had stroke within 3 days of the TIA, yet none of these patients had an ABCD2 score less than 4, thus representing a negative LR of zero. In a Class II study, Wardlaw et al[45] reported a systematic review of 26 studies including 12,586 patients, assessing 7-day stroke risk with ABCD2 less than 4 (34%) versus greater than or equal to 4 (55%), but they combined heterogeneous prospective and retrospective studies without stratifying analysis by populations, study design, or quality. They also did not report LRs. Finally, a Class II study by Perry et al[42] reported a multicenter prospective study comparing the ABCD2 score with the Canadian TIA Score for predicting the 7-day risk for strokes. Although the Canadian TIA Score was shown to be superior to the ABCD2 score, the Canadian TIA Score has not been validated.

Multiple Class III[8,9,12,13,24,25,27,30,38,48] studies evaluated other risk stratification instruments. Similar to the ABCD2, none of these instruments demonstrated sufficient diagnostic accuracy to identify TIA patients at lower short-term risk for stroke, with negative LRs ranging from 0 to 0.55 and CIs that generally crossed 1. The negative LRs and imprecision of each score are not sufficiently accurate or precise to confidently risk stratify TIA patients for short-term risk of stroke. Several of the modified instruments such as ABCD-I, ABCD2-I, and ABCD3-I incorporate concurrent ED MRI, which is beyond the scope of this question.[8,12,27,29,36]

The ABCD has been evaluated in 3 Class II[11,28,29] studies and 7 Class III[9,13,24-27,30] studies with negative LRs for ABCD less than 4 for 7-day stroke risk, which extended from an LR of 0 (95% CI 0 to 0.55)[28] to 0.12 (95% CI 0.01 to 0.65)[30] to 0.39 (95% CI 0.13 to 0.99).[9] ABCD scores were not more accurate at determining 2-day strokes, with negative LRs of 0.30 (95% CI 0.02 to 1.4).[13] The ABCD3 has been evaluated in 3 Class III[12,27,38] studies, the California score by 1 Class II[11] study and 3 Class

III[13,27,48] studies, and the Essen Stroke Risk by 1 Class III[27] study.

As illustrated in Appendix D, the ABCD2 score, which has both the largest number of studies and the highest Class of Evidence, does not reduce the posttest probability of 2- or 7-day stroke risk sufficiently to identify patients at very low short-term risk for stroke. Multiple other scores including the ABCD, ABCD3, California, Canadian TIA Score, and Essen Stroke Risk, have been evaluated less extensively and also appear to lack sufficient prognostic accuracy to independently identify patients at very low short-term risk for stroke.

To summarize, the literature supports 2 key findings:

1. Extensive research has been performed on the ABCD2 score. However, in contrast to the 2009 AHA/ASA recommendations[3] that were based on limited research, the ABCD2 does not sufficiently identify the short-term risk for stroke to use alone as a risk-stratification instrument.
2. Multiple other risk-stratification instruments have been evaluated less frequently than the ABCD2 score. None have demonstrated the ability to identify individual patients at sufficiently low short-term risk for stroke to use alone as a risk-stratification instrument.

Future Research

- Develop sufficiently accurate post-TIA risk stratification instruments (eg, Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis[49]). Ideally, this would include prospective derivation and validation using readily available clinical personnel rather than research teams and/or retrospective databases.
- Evaluate intrarater and interrater reliability of TIA risk stratification instruments.
- Standardize definition of "short-term" risk for stroke, as well as threshold for discharge from the ED.
- Assess the effect of risk stratification instruments on ED resource use and patient-centered outcomes.[50]
- Evaluate heterogeneous patient populations' ability to comprehend post-TIA stroke risk for use in real-time shared decisionmaking in ED settings, including assessments of health literacy, ethnicity, language, and access to outpatient evaluation.

2. In adult patients with suspected TIA, what imaging can be safely delayed from the initial ED workup?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. (1) The safety of delaying neuroimaging from the initial ED workup is unknown. If noncontrast brain MRI is not readily available, it is reasonable for physicians to obtain a noncontrast head CT as part of the initial TIA workup to identify TIA mimics (eg, intracranial hemorrhage, mass lesion). However, noncontrast head CT should not be used to identify patients at high short-term risk for stroke. (2) When feasible, physicians should obtain MRI with diffusion-weighted imaging (DWI) to identify patients at high short-term risk for stroke. (3) When feasible, physicians should obtain cervical vascular imaging (eg, carotid ultrasonography, CTA, or MRA) to identify patients at high short-term risk for stroke.

Key words/phrases for literature searches: transient ischemic attack, TIA, neuroimaging, CT, MRI, delayed diagnosis, emergency treatment, decisionmaking, risk factors, time factors, risk assessment, and variations and combinations of the key words/phrases. Searches included January 1, 2000 to search date of March 18, 2015.

Study Selection: Four hundred forty-one articles were identified in the search. Eighty-five articles were selected from the search results for further review, with 13 studies included for this critical question.

When an emergency physician provides care to a patient with a suspected TIA, decisions about immediate imaging versus delayed imaging must be made. The primary goal of imaging is to identify serious TIA mimics (eg, intracranial hemorrhage, mass lesion). Another goal is to potentially identify patients at high short-term risk for stroke, commonly defined as occurring within 2 or 7 days after the initial TIA event. However, each imaging modality has different performance characteristics, as well as associated length of stay and cost. The majority of the literature applicable to this clinical question deals with head CT, brain MRI, or cervical vessel imaging. Therefore, the discussion will center on these 3 options.

The majority of studies used in this clinical policy used a time-based definition of TIA (ie, resolution of neurologic deficit within 24 hours). However, immediate imaging may reveal acute ischemic lesions despite resolution of neurologic deficits, changing the diagnosis to stroke. Because both TIA and minor stroke have similar short-term ischemic stroke risk, management considerations may be similar regardless of whether tissue infarction is detected on brain imaging.[1,51]

Based on the study selection criteria, 4 Class II[29,52-54] and 9 Class III[6,8,31,33,39,55-58] studies were identified to answer this critical question. Three Class II[29,52,53] studies and 1 Class III[55] study addressed the benefits of immediate

head CT in patients with suspected TIA. The majority of these studies involving head CT did not specify whether CT imaging was obtained with contrast, but it is presumed that these were noncontrast CT studies. One Class II[54] study and 8 Class III[6,8,31,33,39,56-58] studies addressed the benefits of immediate brain MRI, with some including vascular imaging in patients with suspected TIA.

Head CT

In a multicenter Class II study from Germany,[52] 1,533 patients with suspected TIA underwent head CT as part of the initial diagnostic evaluation. An acute cerebrovascular accident was detected on initial head CT in 47 patients (3.1%) even though every patient received a clinical diagnosis of TIA because of resolution of neurologic deficits within 24 hours. All 1,533 patients were admitted to the hospital, with a mean admission duration of 6 days. While in the hospital, 17 patients (1.1%) experienced an ischemic stroke. No patients with a new infarct on initial head CT experienced another ischemic stroke while in the hospital, and the presence of a new infarct on initial head CT was not associated with a new short-term stroke.

Another multicenter Class II study[29] examined 274 patients presenting to EDs in Italy with suspected TIA. All patients underwent head CT in the ED. The authors attempted to determine the marginal benefit of adding head CT findings to the ABCD score, reformulated as the ABCD-I score, in predicting the short-term risk for stroke. In this cohort, 7 patients (2.6%) experienced an ischemic stroke within 2 days, 10 (3.6%) within 7 days, and 15 (5.5%) within 30 days of initial presentation. The ABCD-I score essentially had the same performance characteristics as the ABCD score in predicting 7-day stroke (odds ratio [OR] for every point was 2.7 versus 2.6). The presence of "leukoaraiosis and/or old/new ischemia lesions" on head CT was not an independent predictor of 7-day stroke.

One Class III study[55] also did not support the ability of head CT to predict the rate of subsequent stroke. There was no difference in the frequency of 90-day stroke between patients who received a head CT and those who did not (10.9% for both groups). However, among patients having an initial head CT, an alternative diagnosis was identified in 4 of 322 (1.2%; 95% CI 0.0% to 3.1%), 1 patient with a chronic subdural and 3 patients with mass lesions.

In contrast to the other studies that did not identify a prognostic value with immediate head CT, a multicenter Class II study that enrolled 2,028 patients from 8 Canadian EDs with TIA or nondisabling stroke supported the ability of early head CT to predict short-term stroke.[53] All patients experienced resolution of neurologic deficit within 24 hours of symptom onset, and each patient received a head CT within 24 hours of presentation. A subsequent stroke within 2 days was identified in 31 subjects (1.5%). Using a logistic regression model, the investigators reported an association with 2-day stroke for acute+chronic ischemia (OR 10.32), acute ischemia+microangiopathy (OR 8.44), and acute+chronic ischemia+microangiopathy (OR 22.69). Although these findings were in contrast to those of the other articles reviewed, this study allowed initial head CT up to 24 hours after presentation and may not reflect the use of immediate CT in the ED.

Brain MRI and/or Cervical Vessel Imaging

One Class II[54] study and 4 Class III[8,33,39,56] studies examined a combination of brain MRI and vascular imaging in the evaluation of suspected TIA. Although some studies incorporated intracranial in addition to cervical vascular imaging, there is insufficient evidence in determining the value of identifying intracranial vascular lesions given the limited number of studies examining this modality, the difficulty in segregating the analysis from the identification of cervical vascular lesions, and the lack of potential beneficial interventions if an intracranial vascular lesion is identified. In a single-center Class II[54] study, 162 patients with TIA underwent multimodal MRI and contrast-enhanced MRA of the head and neck. All 162 patients completed 90 days' follow-up; 23 patients (14.2%) experienced subsequent TIA (n=16) or stroke (n=7). Subsequent ischemic events occurred within 3 days in 13 patients (56.5%) and within 7 days of the initial TIA in 18 patients (78.3%). Although the majority of ischemic events occurred within 7 days of the initial TIA, analysis was directed at the primary endpoint of 90-day events, finding that 23 of 23 patients (100%) with a 90-day ischemic event had an initial imaging abnormality versus 97 of 139 patients (69.8%) without an event. In a multivariable analysis, symptomatic MRA abnormality, defined as intracranial or extracranial stenosis greater than 50% in a territory appropriate to the patient's symptoms, was found to be the only independent predictor of a 90-day ischemic event (OR 12.7).

In a Class III study, Calvet et al[33] examined 343 patients with suspected TIA who received a brain MRI and an intracranial MRA. In addition, all patients underwent carotid Doppler ultrasonography, with 307 of 343 (90%) also receiving cervical contrast-enhanced MRA. Patients without contrast-enhanced MRA had either a normal carotid Doppler result or contraindications to MRA with contrast. Ischemic stroke was observed in 4 of 343 patients (1.2%) within 48 hours and 5 of 343 (1.5%) at 7 days. Positive MRI result with DWI was a univariate predictor of

7-day risk for stroke, and all patients with stroke within 7 days had a positive DWI result and ABCD2 score of 4 or greater (5 of 90; 5.4%). In a multivariable analysis of 90-day stroke risk that included the ABCD2 score, positive DWI result (hazard ratio 8.7) and large artery atherosclerosis (hazard ratio 3.4) were imaging predictors. Unfortunately, a multivariable model for 7-day stroke risk was not reported.

Another Class III[39] study reviewed protocol-guided imaging in 224 patients presenting to a single center with suspected TIA. All patients received a noncontrast head CT in the ED. Those with ABCD2 score of 0 to 3 were eligible to be discharged directly from the ED to a TIA clinic visit in 1 to 2 business days without immediate imaging. An MRI and MRA (cervical and intracranial) were obtained before the clinic visit. Patients with an ABCD2 score of 4 to 5 underwent cervical and intracranial vessel imaging (typically with CTA) in the ED. Those with ABCD2 score greater than 5 were hospitalized. Six of 14 hospitalized patients found to have symptomatic vessel occlusion or high-grade stenosis underwent vascular intervention, although the time to intervention was not well described. One of 157 patients (0.6%) sent to the TIA clinic experienced ischemic stroke. Among all 224 patients, 2 patients (0.9%) experienced a stroke, which was less than the 4% expected stroke rate.

Chatzikonstantinou et al[8] conducted a Class III study examining 235 patients with suspected TIA who underwent early DWI and carotid Doppler ultrasonography. Seventeen of 235 patients (7.2%) experienced ischemic stroke during hospitalization (mean duration 7.4 days). The ABCD3-I score, a risk tool that incorporates positive DWI findings and relevant carotid stenosis, was found to be a predictor of inhospital stroke.

A Class III[56] study followed 116 patients with suspected TIA to evaluate for subsequent stroke within 30 days. Patients underwent both DWI and cervical vessel imaging. Two strokes (1.8%) occurred during the 30-day follow-up period and both were within the first 48 hours of hospitalization. Subsequent risk for stroke was higher among DWI-positive (6.3%) compared with DWI-negative (1.2%) patients. Twenty of 110 (17.2%) cervical vessel imaging studies were positive and 6 of these patients underwent carotid intervention.

Three Class III studies investigated the use of DWI.[6,31,57] A multicenter study of 944 patients with suspected TIA found that the lack of a lesion on DWI was associated with a low 90-day risk for stroke.[31] The investigators suggested that a combination of ABCD2 score and early DWI may be an effective strategy for predicting the 90-day risk for stroke. Another Class III study[6] reported that early DWI was beneficial in predicting 7-day stroke. Twenty-three of 477 patients (4.8%) experienced subsequent stroke within 7 days of suspected TIA and, based on a logistic regression model, the identification of an acute ischemic lesion on DWI was an independent predictor of 7-day stroke (OR 10.1). A Class III systematic review by Oostema et al[57] included 6 studies examining subsequent stroke within 2 and 7 days after TIA in patients undergoing early DWI. Two-day stroke occurred in 0% to 2.9% of DWI-negative patients and 0% to 14.3% of DWI-positive patients. Seven-day stroke occurred in 0% to 2.9% of DWI-negative patients and 0% to 23.8% of DWI-positive patients.

One Class III study by Daubail et al[58] examined the determination of TIA mechanism as a predictor of early stroke risk. All patients underwent brain imaging and evaluation of the cervical vasculature, with most receiving a head CT and CTA. Ten of 312 patients (3.2%) experienced a recurrent ischemic event, 5 with ischemic strokes and 5 with TIA. Large artery atherosclerosis, defined as stenosis of more than 50% of a cervical or intracranial artery, that could explain the neurologic symptoms of the TIA was identified in 33 of 312 patients (10.6%). Of the 33 patients with a large artery atherosclerosis TIA, 4 (12.1%) experienced a recurrent ischemic event within 48 hours. Large artery atherosclerosis as the etiology of the TIA was a strong independent predictor (OR 12) for a recurrent ischemic event within 2 days.

To summarize, the evidence supports 3 key findings:

1. Although there is limited research quantifying the mimics identified on initial imaging in patients presenting with suspected TIA, it is likely that initial noncontrast brain imaging in the ED will identify some patients with serious alternative diagnoses. However, there is no evidence evaluating the safety of delaying neuroimaging in the ED.
2. Initial noncontrast head CT findings do not reliably predict early stroke in patients presenting with suspected TIA.
3. Both DWI and cervical vascular imaging predict short-term risk for stroke in patients presenting with suspected TIA.

Unfortunately, the literature surrounding this topic focuses on the diagnostic and prognostic values of imaging but does not routinely examine whether early recognition of abnormal findings translates into improved outcomes. It is unclear whether immediate diagnosis of a serious TIA mimic on initial head CT in the ED rather than obtaining urgent outpatient imaging results in improved patient-centered outcomes. Furthermore, although identifying

high-risk patients may allow earlier intervention and more intensive monitoring, meaningful benefits to the TIA population have not been demonstrated. Given the lack of clear evidence that supports improved patient-centered outcomes, consideration of local systems of care and shared decisionmaking that incorporates patient preferences are important in choosing the timing of early imaging for suspected TIA.

Future Research

Much of the literature examining the utility of initial imaging does not examine testing that is practical and available in most EDs and does not use identification of TIA mimics or prediction of early (ie, 2- or 7-day) stroke as the primary outcome. Future research should focus on:

- Quantifying the ability of noncontrast head CT and noncontrast brain MRI to detect clinically important TIA mimics in patients presenting with suspected TIA who have had resolution of symptoms at ED presentation, because the majority of TIA research excludes these patients.
- The safety of delaying neuroimaging from the initial ED workup, including discharge from the ED for an outpatient workup.
- Integration of a risk score and imaging strategy to identify TIA patients at high short-term risk for stroke to improve risk stratification for ED patients with suspected TIA.
- Identifying acute interventions for patients with TIA that improve functional outcomes, quality of life, and other patient-centered outcomes.

3. In adult patients with suspected TIA, is carotid ultrasonography as accurate as neck CTA or MRA in identifying severe carotid stenosis?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. In adult patients with suspected TIA, carotid ultrasonography may be used to exclude severe carotid stenosis because it has accuracy similar to that of MRA or CTA.

Key words/phrases for literature searches: transient ischemic attack, TIA, carotid stenosis, ultrasound, angiogram, CT, MRI, neuroimaging, emergency treatment, decisionmaking, delayed diagnosis, ultrasonography, carotid arteries, angiography, neck, and variations and combinations of the key words/phrases. Searches included January 1, 2000 to search date of March 18, 2015.

Study Selection: Three hundred ninety-eight articles were identified in the search. Thirty-four articles were selected from the search results for further review, with 8 studies included for this critical question.

Carotid endarterectomy has been shown to be beneficial within 2 weeks from a TIA or stroke for severe carotid stenosis, which is defined as stenosis between 70% and 99%, with a number needed to treat of 6 to prevent future stroke or death.[59,60] Historically, catheter-based angiography was the gold criterion for evaluating carotid stenosis. However, noninvasive imaging methods (ie, carotid ultrasonography, CTA, and MRA) have since replaced catheter-based angiography as a first-line test. This question focused on the use of carotid ultrasonography for the detection of severe carotid stenosis because ultrasonography has the benefits of being more available in some ED settings, avoids the need for intravenous contrast, and is typically less expensive than CTA or MRA. Although each institution has its own protocols for carotid ultrasonography, the literature review did not focus on the specifics of these protocols, such as ideal peak velocity, types of Doppler, and the use of contrast, nor did it focus on point-of-care ultrasonography.

A Class III study by D'Onofrio et al[61] prospectively evaluated 32 patients who either had carotid Doppler ultrasonography (DUS) or contrast-enhanced MRA and compared it to either digital subtraction angiography (DSA) or endarterectomy. Both had strong correlation in identifying stenosis, with both identifying 100% of surgical stenosis (defined as carotid stenosis of 60% to 99%). Doppler ultrasonography had a negative LR of 0.07 (95% CI 0.01 to 0.47) and a positive LR of 3.2 (95% CI 1.6 to 6.2), and MRA had a negative LR of 0.07 (95% CI 0.01 to 0.47) and a positive LR of 3.2 (95% CI 1.6 to 6.2). In another Class III[62] study, 313 patients with TIA or minor stroke had DUS. When compared with DSA, using a peak systolic velocity of 230 cm/s, DUS had a sensitivity of 95% (95% CI 92% to 99%), specificity of 51% (95% CI 42% to 61%), negative LR of 0.09 (95% CI 0.04 to 0.20), and positive LR of 2.0 (95% CI 1.6 to 2.4) for carotid stenosis of 70% to 99%.

In a Class III[63] study, 350 patients with TIA or nondisabling stroke were prospectively evaluated for carotid stenosis. DUS demonstrated a sensitivity of 88% (95% CI 82% to 93%), specificity of 76% (95% CI 69% to 82%), negative LR of 0.17 (95% CI 0.11 to 0.26), and positive LR of 3.6 (95% CI 2.7 to 4.7) compared with DSA for severe stenosis (70% to 99%). MRA had a sensitivity of 92.2% (95% CI 86.2% to 96.2%), specificity of 75.7% (95% CI 68.6% to 82.5%), negative LR of 0.10 (95% CI 0.06 to 0.19), and positive LR of 3.8 (95% CI 2.9 to 5.0)

for severe stenosis. In another Class III[64] study, a secondary analysis was performed on 56 patients with suspected carotid stenosis of greater than 50%. Contrast-enhanced MRA, DUS, and DSA were performed within 15 days of enrollment. Contrast-enhanced MRA was read by 3 independent readers, and sensitivity and specificity were scored separately for each reader. Compared with DSA, DUS had a sensitivity of 83% (95% CI 68% to 93%), specificity of 86% (95% CI 76% to 93%), negative LR of 0.19 (95% CI 0.09 to 0.40), and positive LR of 6.0 (95% CI 3.3 to 10.9) for stenosis greater than or equal to 70%, whereas contrast-enhanced MRA had a sensitivity of 95% (95% CI 81% to 99%), specificity ranging from 77% to 85% among the 3 readers, a negative LR of 0.07 (95% CI 0.02 to 0.27), and positive LR of 4.1 (95% CI 2.6 to 6.2). Figure 1 shows the LR from the various studies.

Four Class III meta-analyses were identified.[65-68] All had significant heterogeneity. Blakely et al[65] included 70 articles from 1977 to 1993 assessing direct and indirect comparisons of ultrasonography and MRA with carotid angiography. Carotid DUS, carotid duplex ultrasonography, and MRA had sensitivities between 82% and 86% and specificities of 98% for detecting 100% occlusion. When predicting greater than 70% carotid stenosis, these 3 diagnostic imaging tests and supraorbital Doppler ultrasonography had similar sensitivities ranging from 83% to 86%.

A Class III meta-analysis by Nederkoorn et al[66] included 63 articles from 1994 to 2001 comparing DUS and MRA with DSA. For the diagnosis of 70% to 99% stenosis versus less than 70% stenosis, MRA was found to be more sensitive than DUS, with a sensitivity of 95% (95% CI 92% to 97%) versus 86% (95% CI 84% to 89%), respectively, but similar specificity of 90% (95% CI 86% to 93%) versus 87% (95% CI 84% to 90%), respectively. Another Class III meta-analysis by Jahromi et al[67] included 47 articles from 1996 to 2003 comparing DUS with carotid angiography. Using a threshold peak systolic velocity greater than or equal to 200 cm/s, DUS had a sensitivity of 90% (95% CI 84% to 94%) and a specificity of 94% (95% CI 88% to 97%) for the diagnosis of stenosis of greater than or equal to 70%. However, substantial heterogeneity was identified based on differences in patient populations, study design, equipment, techniques, and training of the sonographer.

Finally, a Class III meta-analysis by Wardlaw et al[68] evaluated 41 studies comparing DUS, CTA, and contrast-enhanced MRA. For carotid stenosis between 70% and 99%, contrast-enhanced MRA had a sensitivity of 94% (95% CI 88% to 97%), specificity of 93% (95% CI 89% to 96%), negative LR of 0.06, and positive LR of 13.4. Doppler ultrasonography had a sensitivity of 89% (95% CI 85% to 92%), specificity of 84% (95% CI 77% to 89%), negative LR of 0.13, and positive LR of 5.6. CTA had a lower sensitivity of 77% (95% CI 68% to 84%), specificity of 95% (95% CI 91% to 97%), negative LR of 0.24, and positive LR of 15.4.

To summarize, the evidence supports 3 key findings:

1) Although ultrasonography appears to be slightly less sensitive than MRA for detecting severe carotid stenosis, the diagnostic test performs well enough clinically to be considered useful in ruling out clinically significant carotid stenosis.
2) The specificity of both MRA and DUS for detecting severe carotid stenosis appears to be similar.
3) There were no studies included directly comparing CTA and DUS.

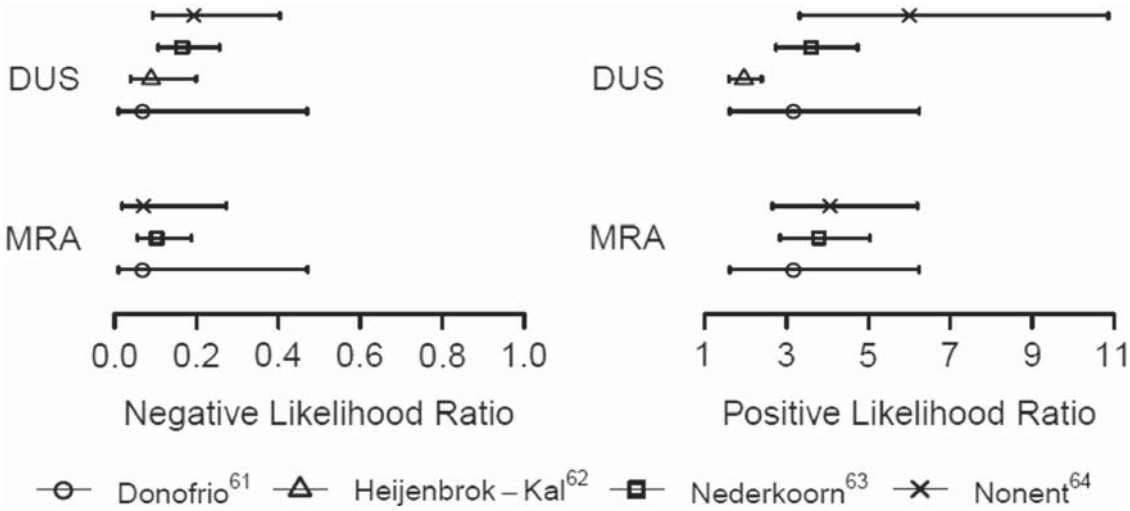

Figure 1. Positive and negative LR for DUS and MRA.* *Calculated based on data from studies.

Future research

The majority of the literature on noninvasive imaging used older technology, often comparing a single modality with a reference standard. The studies evaluating DUS used different protocols in determining severe carotid stenosis. Future research should focus on:

- Comparative effectiveness studies that directly compare noninvasive forms of imaging using standardized protocols that report patient-centered outcomes.
- Determining the accuracy of emergency physician performed point-of-care carotid ultrasonography for the identification of severe carotid stenosis.

4. In adult patients with suspected TIA, can a rapid ED-based diagnostic protocol safely identify patients at short-term risk for stroke?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. In adult patients with suspected TIA without high-risk conditions,* a rapid ED-based diagnostic protocol may be used to evaluate patients at short-term risk for stroke.

Level C recommendations. None specified.

*High-risk conditions include abnormal initial head CT result (if obtained), suspected embolic source (presence of atrial fibrillation, cardiomyopathy, or valvulopathy), known carotid stenosis, previous large stroke, and crescendo TIA.

Key words/phrases for literature searches: transient ischemic attack, TIA, stroke, risk, diagnosis, emergency, critical pathways, practice guidelines, and variations and combinations of the key words/phrases. Searches included January 1, 2000 to search date of March 18, 2015.

Study Selection: Three hundred forty-nine articles were identified in the search. Sixty articles were selected from the search results for further review, with 8 studies included for this critical question.

Use of a rapid ED-based diagnostic protocol can stratify patients with high short-term risk for stroke. Data from multiple Class II and Class III studies described below demonstrate the safety and feasibility of this approach versus inpatient management in appropriately selected patients. Current evidence also suggests shorter hospital length of stay, decreased hospital cost, and higher compliance with evidence-based guideline recommendations[3] when a properly designed and executed ED-based diagnostic protocol (eg, ED observation unit) is used compared with standard inpatient admission.[56,69] An example of a model for an ED-based diagnostic protocol is shown in Figure 2.

Based on study selection criteria, 5 Class II[21,39,47,69,70] studies and 3 Class III[56,71,72] studies were included to answer this question. Three of these studies looked at ED observation unit protocols,[56,69,70] whereas 5 used a TIA "outpatient" clinic approach in which urgent follow-up was arranged from point of first presentation (ED or primary care).[21,39,47,71,72] The TIA clinic studies used referral to further diagnostic testing (eg, neuroimaging, echocardiogram) that occurred during the interval between point of first presentation and clinic follow-up. These clinic trials were included because the workflow provided could be replicated in an ED-based diagnostic protocol.

A Class II trial by Ross et al[69] prospectively randomized 149 ED TIA patients to an accelerated diagnostic protocol in an ED observation unit versus standard hospital admission. Notable exclusions were an abnormal initial head CT result, known possible embolic source (history of atrial fibrillation, cardiomyopathy, or valvulopathy), known carotid stenosis, previous large stroke, and crescendo TIAs. Their diagnostic protocol consisted of carotid imaging (DUS or MRA), echocardiography, serial clinical evaluation, and cardiac monitoring for at least 12 hours. Patients with recurrent neurologic symptoms, significant carotid stenosis, or evidence of thromboembolic source were admitted. They found that an accelerated diagnostic protocol was associated with a shorter median length of stay (25.6 hours; 95% CI 21.9 to 28.7 versus 61.2 hours; 95% CI 41.6 to 92.2) and lower 90-day costs ($890, 95% CI $768 to $1,510 versus $1,547, 95% CI $1,091 to $2,473), and no increase in adverse outcomes versus mandatory inpatient admission.

A Class II study by Lavallée et al[21] found similar results. They evaluated the value of a 24/7 TIA specialty clinic in which referred patients received comprehensive testing and examination by a vascular neurologist. This study examined 1,085 patients and compared 90-day stroke incidence versus stroke risk predicted by ABCD2 score. The authors reported a 1.2% (95% CI 0.7% to 2.1%) risk for stroke versus an expected 6% risk for stroke based on ABCD2 score. Seventy-four percent of patients were evaluated and discharged on the same day of presentation. The major weakness of this trial was the lack of a true control group.

In a Class II study, Stead et al[70] evaluated the feasibility of TIA evaluation in an ED observation unit. Similar to that used by Ross et al,[69] protocolized care was used to evaluate patients with TIA who were asymptomatic and had a negative head CT result. Of the 418 patients enrolled, only 127 (30.4%) were discharged directly after evaluation from the ED observation unit. A major limitation was the lack of

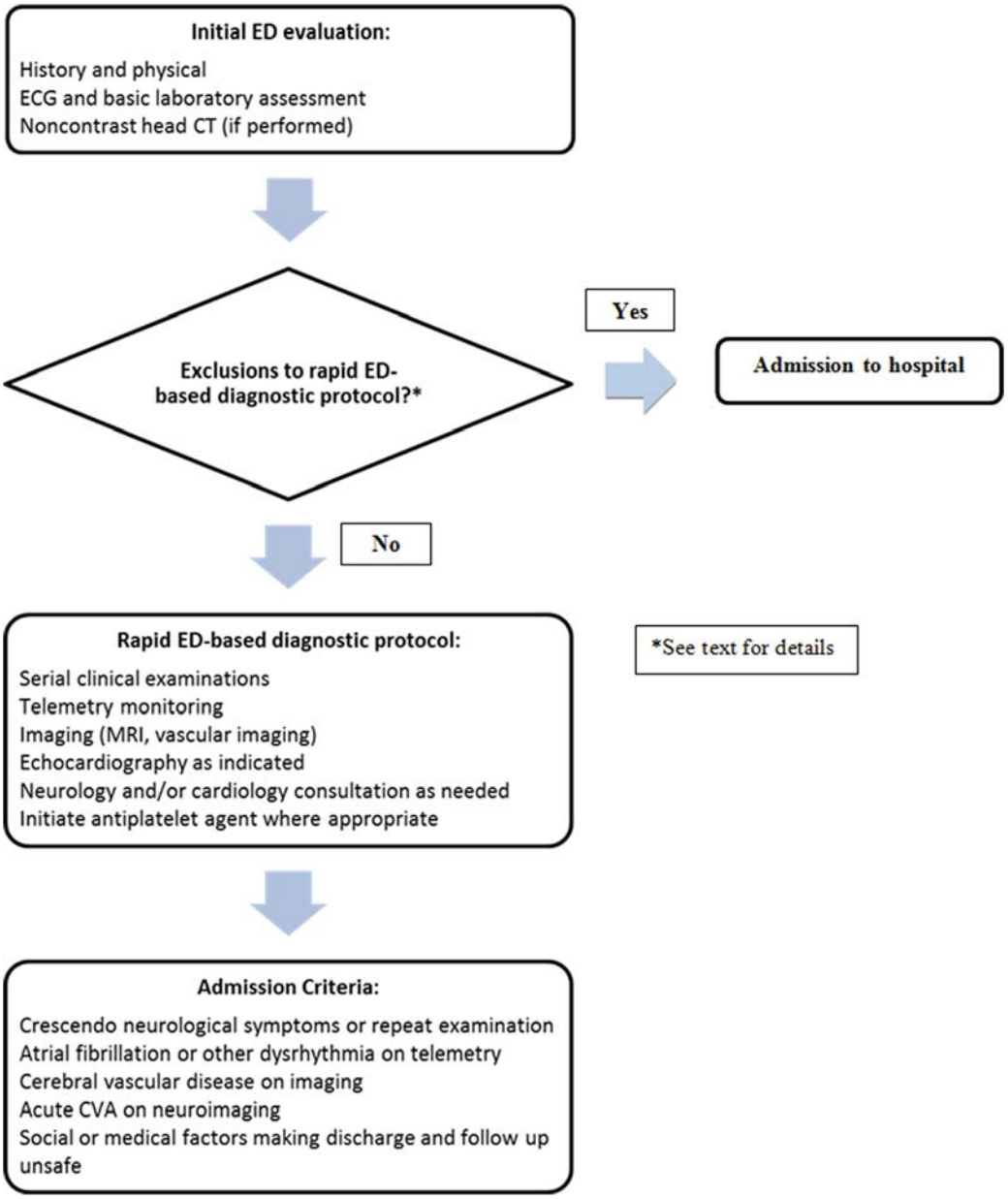

Figure 2. Example of a rapid ED-based diagnostic protocol. This figure is one example of a rapid ED-based diagnostic protocol (eg, ED observation protocol). It is not intended to establish a community standard of care, replace a clinician's medical judgment, or establish a protocol for all patients. Approaches not included in this figure may be appropriate.

a control group; outcomes were compared with the expected rates of stroke at 2 and 7 days. Their conclusion was that their protocol was feasible and safe.

In a Class III study, Oostema et al[56] examined the use of DWI in an accelerated diagnostic protocol conducted in an ED observation unit. Exclusion criteria similar to those used by Ross et al[69] were used. Head CT was not conducted during the initial ED management. All patients in the accelerated diagnostic protocol received neuroimaging, with 94% receiving DWI. A greater percentage of patients in the accelerated diagnostic protocol received cervical vessel imaging compared with those triaged to inpatient management (97% versus 83%). In approximately 13.8% of ED observation unit patients, DWI was positive for acute infarction. This was the only positive finding in 6.9% of patients. The authors estimated a number needed to test of 15 to identify high-risk findings not present on other evaluations. Patients who were DWI positive had a higher 30-day risk for stroke than those without DWI lesions (6.3% versus 1.2%). Oostema et al[56] showed a length of stay similar to that in the study by Ross et al[69] (19 hours), with 59.5% of patients discharged from

the ED observation unit and a nonstatistically significant difference in observed stroke versus predicted stroke by ABCD2 (1.8% versus 4.8%; P=.12).

Multiple studies used an outpatient clinic model for evaluation of suspected TIA.[21,39,47,71,72] These studies differed in their triage criteria, ED evaluation and management, outpatient workup, and time to follow-up. Each study is limited by lack of true control, with some using before-and-after design and others using comparison with predicted stroke risk at outcome.

In a Class II study, Olivot et al[39] stratified patients according to risk factors to different ED workups. Patients at low risk (ABCD2 score of 0 to 3) were eligible for direct discharge from the ED, with referral to an outpatient TIA clinic. Patients at moderate risk (ABCD2 score 4 to 5) had cervical and intracranial vessel imaging while in the ED, and if the results were positive (defined as having >50% narrowing), the patients were admitted. Patients with an ABCD2 score greater than 5 were admitted to the hospital. Patients referred to the TIA clinic were referred for neurovascular imaging and began receiving antiplatelet agents. Of the 224 patients enrolled, 70% were discharged from the ED directly and 61% of patients had vascular imaging performed while in the ED. The median time from ED visit to TIA clinic was 3 days (interquartile range 2 to 5). Of patients discharged from the ED, 9% had acute DWI lesions on outpatient MRI. The observed rate for stroke at 7 and 90 days was lower than expected based on the ABCD2 score.

Two Class III[71,72] studies and 1 Class II[47] study used a model in which ED patients were referred to an outpatient TIA clinic for further workup. Risk stratification and exclusion criteria differed among the studies. Follow-up to the TIA clinic from the ED was also variable, ranging from 2 to greater than 14 days. A lower rate for stroke was found compared with the rate for stroke predicted based on stroke scores. These studies also found a decreased cost associated with referral to the TIA clinic compared with inpatient management; however, they were limited by their lack of prospective control groups and sample size. This also required the development, implementation, and maintenance of an outpatient apparatus that could reliably perform an extensive diagnostic evaluation, as well as follow-up on abnormal test results. Therefore, the results may not be generalizable to centers that do not have similar outpatient resources or where compliance with follow-up is a concern.

To summarize, the evidence supports the 2 following findings:

1) In patients without high-risk conditions, a rapid ED-based diagnostic protocol is equivalent to mandatory admission in terms of patient safety (ie, recurrent cerebrovascular event or stroke).
2) A properly implemented rapid ED-based diagnostic protocol is associated with decreased hospital costs and length of stay compared with inpatient management.

Future Research

Further research to determine which components are essential for the safest and most efficient ED-based rapid diagnostic protocol with an emphasis on patient-centered outcomes is needed.

Relevant industry relationships: There were no relevant industry relationships disclosed by the subcommittee members for this topic.

Relevant industry relationships are those relationships with companies associated with products or services that significantly impact the specific aspect of disease addressed in the critical question.

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Appendix A. Literature classification schema.*

Design/ Class	Therapy†	Diagnosis‡	Prognosis§
1	Randomized, controlled trial or meta-analysis of randomized trials	Prospective cohort using a criterion standard or meta-analysis of prospective studies	Population prospective cohort or meta-analysis of prospective studies
2	Nonrandomized trial	Retrospective observational	Retrospective cohort Case control
3	Case series	Case series	Case series

*Some designs (eg, surveys) will not fit this schema and should be assessed individually.
†Objective is to measure therapeutic efficacy comparing interventions.
‡Objective is to determine the sensitivity and specificity of diagnostic tests.
§Objective is to predict outcome, including mortality and morbidity.

Appendix B. Approach to downgrading strength of evidence.

	Design/Class		
Downgrading	**1**	**2**	**3**
None	I	II	III
1 level	II	III	X
2 levels	III	X	X
Fatally flawed	X	X	X

Appendix C. Likelihood ratios and number needed to treat.*

LR (+)	LR (-)	
1.0	1.0	Does not change pretest probability
1-5	0.5-1	Minimally changes pretest probability
10	0.1	May be diagnostic if the result is concordant with pretest probability
20	0.05	Usually diagnostic
100	0.01	Almost always diagnostic even in the setting of low or high pretest probability

LR, likelihood ratio.
*Number needed to treat (NNT): number of patients who need to be treated to achieve 1 additional good outcome; NNT=1/absolute risk reduction×100, where absolute risk reduction is the risk difference between 2 event rates (ie, experimental and control groups).

Appendix D. Potential benefits and harms of implementing the recommendations.

1. In adult patients with suspected TIA, are there clinical decision rules that can identify patients at very low short-term risk for stroke who can be safely discharged from the ED?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. In adult patients with suspected TIA, do not rely on current existing risk stratification instruments (eg, ABCD2 score) to identify TIA patients who can be safely discharged from the ED.

Level C recommendations. None specified.

Potential Benefit of Implementing the Recommendations: Clinicians recognize the limitations of using existing risk stratification instruments in suspected TIA patients to identify those at very low short-term risk for stroke.

For example, a 61-year-old right-handed woman is evaluated in the ED 2 hours after a now-resolved 20-minute episode of right arm weakness without associated speech difficulty. Initial workup result is unremarkable in the ED, and the provider contemplates sending the patient home for outpatient follow-up. According to a large cohort study, TIA patients have an estimated 5% risk of having a stroke within 2 days.[11] Given that her ABCD2 score is less than or equal to 4 (negative LR 0.81),[7] her posttest probability is 4%. In this case, the risk is not sufficiently low enough to discharge the patient home (see Figure 3 for calculation).

Potential Harm of Implementing the Recommendations: The harm associated with the implementation of this recommendation is largely unknown, but given the lack of evidence-based guidance, practice variability in the ED management of TIA patients with respect to subsequent test ordering, consultations, and disposition decisions will likely persist.

2. In adult patients with suspected TIA, what imaging can be safely delayed from the initial ED workup?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. (1)The safety of delaying neuroimaging from the initial ED workup is unknown. If noncontrast brain MRI is not readily available, it is reasonable for physicians to obtain a noncontrast head CT as part of the initial TIA workup to identify TIA mimics (eg, intracranial hemorrhage, mass lesion). However, noncontrast head CT should not be used to identify patients at high short-term risk for stroke. (2) When feasible, physicians should obtain MRI with DWI to identify patients at high short-term risk for stroke. (3) When feasible, physicians should obtain cervical vascular imaging (eg, carotid ultrasonography, CTA, or MRA) to identify patients at high short-term risk for stroke.

Potential Benefit of Implementing the Recommendations: Immediate noncontrast head CT or noncontrast brain MRI may identify life-threatening TIA mimics in the ED. Immediate MRI with DWI and/or

Bayesian reasoning uses LRs and pretest odds to estimate posttest odds, using this equation.

Pretest odds×LR=posttest odds

Odds=Probability/(1-probability)
Probability=Odds/(odds+1)

So using the case above, pretest probability=5% so pretest odds=0.05/(1 to 0.05)=0.053
Pretest odds×LR (-)=posttest odds=0.053×0.81=0.043
Posttest probability=0.043/(0.043+1)=0.04, or 4%

Figure 3. Example: Calculation of posttest probability.

cervical vascular imaging may identify patients at high short-term risk for stroke, leading to admission for close clinical monitoring, treatment of high-risk conditions, and possible inhospital interventions for new symptoms.

Potential Harm of Implementing the Recommendations: Additional ED imaging may add to ED cost and length of stay. Contrast-enhanced studies are associated with allergic reaction or anaphylaxis, nephrogenic systemic fibrosis (MRI contrast), and a possible increased risk for renal injury.

The identification of patients at high short-term risk for stroke on immediate imaging has not been demonstrated to lead to interventions that clearly improve patient-centered outcomes (eg, mortality, disability, functional outcomes). Consequently, hospitalization may result in unnecessary increased costs, increased hospital length of stay, and potential nosocomial complications.

3. In adult patients with suspected TIA, is carotid ultrasonography as accurate as neck CTA or MRA in identifying severe carotid stenosis?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. In adult patients with suspected TIA, carotid ultrasonography may be used to exclude severe carotid stenosis because it has accuracy similar to that of MRA or CTA.

Potential Benefit of Implementing the Recommendations: Screening for severe carotid stenosis by ultrasonography has the potential to reduce cost and exposure to radiation and contrast compared with CTA or MRA.

Potential Harm of Implementing the Recommendations: The use of carotid ultrasonography may miss a small percentage of patients with severe carotid stenosis.

4. In adult patients with suspected TIA, can a rapid ED-based diagnostic protocol safely identify patients at short-term risk for stroke?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. In adult patients with suspected TIA without high-risk conditions,* a rapid ED-based diagnostic protocol may be used to evaluate patients at short-term risk for stroke.

Level C recommendations. None specified.

*High-risk conditions include abnormal initial head CT result (if obtained), suspected embolic source (presence of atrial fibrillation, cardiomyopathy, or valvulopathy), known carotid stenosis, previous large stroke, and crescendo TIA.

Potential Benefit of Implementing the Recommendations: Clinicians can minimize risk of premature discharge from the ED for patients with TIA while potentially decreasing the length of stay and cost versus a protocol that mandates routine hospital admission of TIA patients.

Potential Harm of Implementing the Recommendations: Implementing this recommendation could increase ED length of stay, which may have a negative effect on flow and the care of other ED patients. It may also lead to further testing or interventions that do not ultimately improve patient-centered outcomes.

Appendix E. ABCD2 score.[11]

Risk Factor	Points
Age ≥60 y	1
Blood pressure ≥140/90 mm Hg	1
Clinical Features	
Unilateral weakness	2
Language disturbance without weakness	1
Diabetes	1
Duration ≥60 min	2
Duration 10 to 59 min	1
Duration <10 min	0

(Reprinted from *Lancet*. 2007;369:283-292, with permission from Elsevier.)

Evidentiary Table.

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Ay et al[6] (2009)	III for Q1 III for Q2	Single academic center; retrospective cohort study	Adult patients admitted to the hospital with TIA; exclusions included isolated monocular blindness and those who did not have MRI performed in the first 24 h; outcome: stroke at 7 days; assessed impact of DWI in addition to ABCD2 score to predict early risk of stroke after TIA	Q1: N=479; 23 (5%) with ischemic stroke at 7 days; of the 23 with stroke at 7 days, 2 (9%) (95% CI 1% to 28%) had a low-risk (0 to 3) ABCD2 score; of the 121 patients with low-risk ABCD2 and negative DWI result, 0 (0%) (95% CI 0% to 3%) had 7-day stroke Q2: N=477; 23 (4.8%) patients with subsequent stroke within 7 days of index TIA; the 7-day risk for stroke (95% CI): ABCD2 <4, DWI 0.0% (not applicable); ABCD2 ≥4, DWI 2.0% (0.06 to 3.94); ABCD2 <4, DWI+4.9% (1.71 to 11.51); ABCD2 ≥4, DWI+14.9% (8.36 to 21.44); acute ischemic lesion on DWI was an independent predictor of 7-day stroke (OR 10.10) in a logistic regression model including ABCD2 score	Q1: Retrospective chart review; large numbers of patients excluded from original cohort of 904 patients; including 7% for not being within 24 h of onset, 26% for missing MRI, and 14% for missing follow-up information; small number of outcomes Q2: Excluded patients with isolated transient monocular blindness and patients who did not have DWI performed within the first 24 h of symptom onset; only 72% capture after excluding those without DWI, 57% with missing follow-up data (some corrected with multiple imputation; unclear whether data were missing at random); limited number of patients had stroke within 7 days of index TIA

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Chandratheva et al[7] (2010)	III	Single community, population-based; prospective cohort study	Adult TIA patients; risk factor: ABCD2 score; outcome: recurrent TIA or stroke within 7 days	N=500; incidence of stroke was 10%; *c*-statistic to predict 7-day stroke was 0.71 (95% CI 0.63 to 0.79); ABCD2 <4 negative LR* 0.81 (95% CI 0.6 to 1.0)	Secondary analysis of the Oxford Vascular Study; study population included in other publications; risk factor and outcome assessment performed by study neurologists in unblinded fashion; results may not generalize to ED setting
Chatzikonstantinou et al[8] (2013)	III for Q1 III for Q2	Single academic medical center in Germany; prospective cohort study	Consecutive TIA patients admitted to a stroke unit (per the article all TIA patients are admitted); DWI conducted immediately or within 24 h; risk-stratified: ABCD2 (low, moderate, high), ABCD3-I (low, moderate, high) and fluctuation of symptoms; outcome: stroke (mean 7-day follow-up)	Q1: N=253 patients with TIA admitted to the stroke unit; 17 (7.2%) with early stroke; ABCD2 score was not correlated with early stroke (*P*=.54); negative LR* 0.68 (95% CI 0.26 to 1.34); combination of symptom fluctuation and positive DWI result was associated with stroke (*P*=.003) Q2: N=235; overall incidence of stroke was 7.2%; on univariate analysis, ABCD3-I (*P*=.02) and fluctuation of symptoms (77% vs 25%; *P*<.001) were associated with stroke, whereas ABCD2 was not (*P*=.54)	Q1: Unclear whether those who were diagnosing stroke were blinded to the ABCD2 score, DWI, or symptom fluctuation; low risk or early stroke were not clearly defined; unclear whether there was a difference in the care provided based on initial ABCD2 score Q2: MRI interpretation not blinded to clinical symptoms and interrater reliability not assessed; outcome assessment not described

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Fothergill et al[9] (2009)	III	Rochester, MN, epidemiology project; secondary analysis of registry data	All residents of Rochester, MN, who experienced TIA; exclusions included those not included in the registry and those with amaurosis fugax; chart review; outcome: stroke at 7, 30, and 365 days	N=284 patients;12.7% with 7-day stroke and 14.5% with 30-day stroke; 5.4% with low (0 to 3) ABCD2 score had 7- and 30-day stroke, and 16.2% at 365 days; for stroke at 7-days: ABCD <4 negative LR* 0.39 (95% CI 0.13 to 0.99) and ABCD2 <4 negative LR* 0.43 (95% CI 0.14 to 1.1)	Limited methodologic detail
Giles et al[10] (2011)	III	12 independent stroke research centers; retrospective multicenter analysis of patient-level data from previously published studies	Patients with TIA; aggregation of patient-level data; outcome: stroke at 7 or 90 days	N=4,574 patients, among whom 3,206 were imaged with DWI and 1,368 were imaged with CT; 884 (27.6%) had a stroke in the MRI cohort; 327 (23.9%) had a stroke in the CT cohort; 7-day stroke occurred in 72 (2.2%) and 73 (5.3%) of MRI and CT cohorts, respectively; among MRI patients, positive DWI was associated with 7-day stroke (7.1% vs 0.4%; *P*<.0001); higher ABCD2 score was associated with a greater likelihood for stroke (*P*<.0001); however, 2.3% of patients with stroke at 7 days had an ABCD2 score less than 4 if there was evidence of infarction on CT or MRI	A very large study across multiple sites with an aggregation of patient-level data; no consistency in study design between the various sites

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Johnston et al[11] (2007)	II	Multicenter validation study between California and Oxfordshire, UK; data were collected retrospectively in the California group and prospectively in the Oxfordshire group	Patients with TIA; outcomes: 2-, 7-, and 90-day stroke	N=4,809 in both derivation and validation groups, with n=1,916 and n=2,892, respectively; 442 patients (9.2%) had strokes in 90 days, 360 (7.5%) at 7 days, and 189 (3.9%) at 2 days; 1,628 were classified as low-risk (ABCD2 score <4); 2-day stroke risk 1%, 7-day risk 1.2%, and 90-day stroke risk 3.1%; 2,169 were classified as moderate risk (ABCD2 score 4 to 5); 2-day stroke risk 4.1%, 7-day risk 5.9%, and 90-day stroke risk 9.8%; ABCD2 score and negative LR*, respectively: 0 (0 [95% CI 0.02 to 4]); ≤1 (0 [95% CI 0 to 0.8]); ≤2 (0.22 [95% CI 0.1 to 0.5]); ≤3 (0.26 [95% CI 0.2 to 0.4]); 1,012 were classified as high-risk (ABCD2 score >5); 2-day stroke risk 8.1%, 7-day risk 11.7%, and 90-day stroke risk 17.8%	ABCD2 score outperformed the California score in derivation and validation group; data acquisition was different between the UK cohort and the US cohort
Kiyohara et al[12] (2014)	III	Multiple stroke centers; retrospective cohort study	Adult TIA patients; risk factor: ABCD2, ABCD3, ABCD3-I scores; outcome: 7-day, 90-day, and 3-y stroke	N=693; incidence of 7-day stroke was 6.9%; *c*-statistic to predict 7-day stroke: ABCD2: 0.54 (95% CI 0.46 to 0.62); ABCD3: 0.61 (95% CI 0.54 to 0.68); ABCD3-I: 0.66 (95% CI 0.57 to 0.74)	Only patients with hospital discharge diagnosis of TIA were included, causing possible spectrum bias
Nguyen et al[13] (2010)	III	Single, academic setting; retrospective cohort study	Adult patients with TIA, identified from ED discharge diagnosis database; outcome: stroke at 2, 7, and 30 days	N=363; 3.1% with outcome at 2 days, 4.3% at 7 days, and 5.2% at 30 days; ABCD2 score with sensitivities of 80% (95% CI 44% to 97%), 93% (95% CI 64% to 100%), and 94% (95% CI 69% to 100%) at 2, 7, and 30 days, respectively	Retrospective chart review with limited methodologic detail; >10% excluded because of miscoding of data; small numbers of outcomes

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Josephson et al[17] (2008)	III	16 community hospitals in Northern California belonging to a single health maintenance organization; retrospective cohort	Subjects identified from medical records having primary diagnosis of TIA; compared results from subjects with working diagnosis of TIA from EM and primary care physicians to confirmed WHO diagnosis; risk model: ABCD2 score (age≥60 y, BP≥140/90 mm Hg, clinical features, duration, diabetes); outcome: recurrent stroke 90 days after incident TIA	N=713 patients with questionable TIA from original study; 642 (90%) deemed true TIA by expert review; 90-day risk of adverse events (95% CI): presumed TIA 21% (18 to 24); true TIA 24% (20 to 27); not TIA 1.4% (0 to 7.6); ABCD2 score and 90-day stroke risk, respectively: 0 (0%); 1 (5%); 2 (6%); 3 (7%); 4 (19%); 5 (24%); 6 (36%); 7 (43%)	Secondary/subset analysis of data from Johnston et al[48]; subsample has double the stroke risk of the original study; possible selection bias; 90-day outcome is questionable as short-term for daily EM practice; no a-priori power calculation
Lavallée et al[21] (2007)	II	University hospital 24-h TIA clinic, Paris, France; prospective cohort	Community awareness of SOS-TIA clinic undertaken with TIA awareness leaflet sent to potential referring physicians (15,000); TIA WHO definition; outcomes: process measures and stroke rates at 90 days compared with rates predicted by the ABCD2 score	N=1,085 patients; 108 (17%) of the 643 patients with confirmed TIA had brain tissue damage; 43 (5%) of patients with confirmed or possible TIA had urgent carotid revascularization; 808 (74%) of all patients seen were sent home on the same day; 90-day stroke rate 1.24% (95% CI 0.72 to 2.12) predicted rate from ABCD2 score (5.96%)	Study included minor strokes; study was a hospital-based 24-h stroke clinic, similar to an ED observation unit; it was not an ED-based protocol, but it could conceivably be conducted in an ED setting; major weakness is lack of true control group; compared actual stroke incidence vs expected stroke incidence predicted by ABCD2 score

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Bray et al[24] (2007)	III	426-bed tertiary care university hospital in Australia; retrospective cohort	Consecutive patients with TIA and symptoms <24 h between July and December 2004; standardized medical record review; outcome: stroke within 90 days	N=98 of 102 TIA patients; 7 patients with stroke in 90 days (4 within 7 days); negative LR* 0 (95% CI 0 to 1.2) using ABCD score 0 to 4 as "low risk"; 6 of 7 strokes at 90 days were classified as high-risk by ABCD score; negative LR* 0.29 (95% CI 0.01 to 1.2); sensitivity 86% (95% CI 42% to 99%) and specificity 54% (95% CI 43% to 64%)	Retrospective; unclear blinding of abstractor; unclear whether those diagnosing stroke were blinded to ABCD score; small number of outcomes
Cucchiara et al[25] (2006)	III	Single urban, academic medical center; prospective cohort study	Adults with suspected TIA presenting within 48 h of symptom onset; risk factor: low-risk (ABCD score <4) or high-risk (ABCD score ≥4); outcome: 90-day stroke	N=117; incidence of stroke was 2%; specificity 43 of 113=0.38 (95% CI 0.29 to 0.48)	Inadequate sample size to estimate sensitivity; low incidence of stroke may be related to aggressive management of TIA; specificity* not reported in article
Giles and Rothwell[26] (2010)	III	Meta-analysis of prospective and retrospective cohort studies	Adult TIA patients; risk factor: ABCD and ABCD2 scores; outcome: 2-, 7-, and 90-day stroke	18 studies of ABCD score and 18 studies of ABCD2 score; pooled estimates for *c*-statistic to predict 7-day stroke: 0.72 (95% CI 0.67 to 0.77) for ABCD and 0.72 (95% CI 0.63 to 0.80) for ABCD2 score; significant heterogeneity among included studies (P<.001) for both scores	Quality of individual studies not described; assessment of heterogeneity unclear/inadequate; sensitivity analysis excluding lower-quality studies not performed

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Purroy et al[27] (2012)	III	Multicenter study from 2008 to 2009 in Spain; prospective cohort study	Comparison of ABCD score, ABCD2 score, ABCD-I score, ABCD3 score, California score, Essen Stroke Risk Score; outcome: 7- and 90-day stroke	N=1,137 patients; ABCD3 score was statistically associated (*P*=.004) with 7-day stroke and with 90-day stroke (*P*=.015); ABCD3V score was associated with 7-day risk (*P*<.001) and with 90-day stroke outcome (*P*=.003)	It is possible that the clinician integrated the scoring systems into their management decisions, which may have attenuated the effects of the scoring systems themselves
Rothwell et al[28] (2005)	II	Multisite, population-based cohort of TIA patients; prospective cohort study	Adult patients with TIA, followed longitudinally; outcome: stroke at 7 days	Multiple cohorts; N=587; derivation and N=400 validation; among 190 patients with "probable or definite TIA," 62 patients had ABCD scores ≤3 and 0 (0%; 95% CI 0 to 6) had 7-day stroke; negative LR* 0 (95% CI 0 to 0.55)	Original derivation study of ABCD score; validation performed on external sample
Sciolla et al[29] (2008)	II for Q1 II for Q2	Multicenter; prospective cohort study	Adult patients with TIA; consecutive sample; exclusions included symptoms >24 h or those not evaluated by attending neurologist; calculated ABCD-I; outcome: stroke at 7 and 30 days	Q1: N=287 patients; of the 76 patients with ABCD scores ≤3, 0 (0%; 95% CI 0 to 5) had 7- or 30-day stroke, negative LR* 0 (95% CI 0 to 1.2); of the 58 patients with ABCD-I scores ≤3, 0 (0%; 95% CI 0 to 6) had 7- or 30-day stroke, negative LR* 0 (95% CI 0 to 1.6) Q2: N=274; ABCD 4 to 5 increases 30-day stroke risk; HR=4.1, 1.3 to 12.6; ischemic stroke occurred in 15 (5.5%) patients <30 days, 10 (3.6%) strokes occurring within 7 days, and 7 (2.6%) strokes occurring in 2 days; the ABCD-I score demonstrated minimally improved performance characteristics compared with the ABCD score in predicting 7-day stroke (OR for every point 2.68 vs 2.55)	Q1: Potential for selection bias, given enrollment requirement of attending neurologist; unclear whether neurologists knew of or used the ABCD score during study, which could have led to treatment bias Q2: Excluded patients who did not have a CT in the ED and those who were lost to follow-up; all patients were evaluated by neurologists; relatively small sample size; unclear about the timing of the CT

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Tsivgoulis et al[30] (2006)	III	Single institution; retrospective cohort study	Adult patients with TIA, as determined by attending neurologist; outcome: stroke at 30 days	N=226 patients; 10% with stroke at 30 days; of 39 patients with ABCD scores ≤3, 2 (5%) (95% CI 1 to 17) had stroke at 30 days	ABCD scores calculated and chart abstractors blinded to outcomes; unclear whether ABCD score entered into decisionmaking at the time of patient care, leading to a form of treatment bias
Asimos et al[31] (2009)	III for Q1 III for Q2	Multicenter; prospective cohort study	Adult ED patients admitted for presumptive TIA; exclusions included previous stroke, unknown symptom onset, an ABCD2 score that could not be calculated, and those who did not have DWI within 24 h of admission; outcome: ischemic stroke, disabling at 90 days	Q1: N=944 patients; 41 (4%) with 90-day disabling stroke; low-risk by ABCD2 (defined as ≤3) had a negative LR 0.21 (95% CI 0.06 to 0.82); combination of low-risk ABCD2 score and a negative early DWI had 100% sensitivity (95% CI 34% to 100%) Q2: N=944; 41 (4%) had disabling stroke; if ABCD2 low-risk and negative DWI result, then sensitivity for predicting 90-day stroke=100% (95% CI 34.2 to 100); if ABCD2 moderate-to-high and negative DWI result, the sensitivity for predicting 90-day stroke=92.3% (95% CI 79.7 to 97.4); negative LR=0.11 (95% CI 0.04 to 0.32)	Q1: Convenience sampling; excluded 40% to 45% of the sample because of missing data; very small number of outcomes, especially among patients determined to be low risk by ABCD2 score; very limited methodologic detail Q2: No description of chart review methods by the site investigators; from an initial sample of 167, 343 (21%) had to be excluded because of missing data; furthermore, 375 of 1,324 (28.3%) did not have a DWI within 24 h of admission; generalizability limited because subjects had to have MRI within 24 h of symptom onset; MRI was not conducted in 28.3% of patients (375), and there is likely to be selection bias as a result

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Asimos et al[32] (2010)	III for Q1	Multicenter; prospective cohort study	Adult ED patients admitted for presumptive TIA; exclusions included previous stroke, unknown symptom onset; outcome: ischemic stroke at 7 days	N=1,667 patients; 373 (23%) with 7-day ischemic stroke and 69 (4%) were disabling; 13% of patients with outcome had low-risk (0 to 3) ABCD2 score; negative LR 0.54 (95% CI 0.39 to 0.74); 4% of patients without disabling outcome had low-risk ABCD2 score; negative LR 0.16 (95% CI 0.04 to 0.64)	Convenience sampling; 37% of sample with missing ABCD2 data, although imputation used to account for missing data; small number of outcomes (at 7 days in low-risk subset of 38 ischemic strokes and 2 disabling strokes)
Calvet et al[33] (2009)	III for Q1 III for Q2	Single academic institution; prospective cohort study	Consecutive patients admitted to stroke unit with probable or possible TIA and within 48 h of symptom onset; patients received standardized evaluation, including ABCD2 score, DWI; outcome: stroke within 3 mo	Q1: N=343; 136 (40%) with positive DWI result; ABCD2 score and positive DWI findings were associated with 7-day and 3-mo risk for stroke (HR 10; 95% CI 1.1 to 93.4); positive DWI result was independently associated with stroke (HR 8.7; 95% CI 1.1 to 71) Q2: N=343 patients among whom 339 were able to receive DWI; DWI result was positive in 40% of patients; 10 patients had stroke at follow-up and 14 had recurrent TIA; of the 10 stroke patients, 5 strokes occurred within 7 days, with 4 happening within 48 h; positive DWI was associated with 90-day stroke, HR=8.7 (95% CI 1.1 to 71.0); LAA was associated with 90-day risk for stroke, HR=3.4 (95% CI 1.0 to 11.8)	Q1: Limited methodologic detail; 7% lost to follow-up, although indirect follow-up made with patients' general practitioner Q2: Single tertiary referral center with a very high rate of positive DWI results

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Cancelli et al[34] (2011)	II	Prospective cohort study; regional academic stroke referral center, Udine, Italy	Community-based registry of cerebrovascular events; subjects identified from hospital admissions or referrals to a 24-h open-access outpatient clinic for neurologic emergencies; risk model: ABCD2 score (age ≥60 y, BP ≥140/90 mm Hg, clinical features, duration, diabetes); outcome: recurrent stroke 2, 7, 30, and 90 days after incident TIA	N=161; 18 (11.2%) with recurrent stroke within 90 days; overall risk; ABCD2 score <4, 0% risk for recurrent CVA at 2, 7, 30, and 90 days; ABCD2 score <4 negative LR 0 (95% CI 0 to 1.9) at 2 days*; ABCD2 score 4 to 5 (95% CI): 2 days 1.4% (0.2 to 9.6); 7 days 8.4% (3.9 to 17.8); 30 days 9.9% (4.8 to 19.5); 90 days 12.7% (6.8 to 23.0); ABCD2 score 6 to 7 (95% CI): 2 days 8.8% (2.9 to 24.9); 7 days 8.8% (2.9 to 24.9); 30 days 8.8% (2.9 to 24.9); 90 days 23.9% (12.7 to 42.2)	Few patients had recurrent stroke, leading to wide CIs and imprecision; single province (Udine) in Italy; substudy of TIA cases from a larger population-based study of all CVA cases; no adjustment for multiple comparisons; only incident cases (first in lifetime) were used for the calculation of ABCD2 score; unclear whether medical record abstraction was blinded to outcomes; low number of outcomes (only 4 strokes at 2 days)
Cucchiara et al[35] (2009)	III	Single academic center; prospective cohort study	Adult patients with TIA; exclusions included terminal illness or warfarin use; outcome: composite of stroke or death within 90 days, ≥50% arterial stenosis, or cardioembolic source requiring anticoagulation	N=167 patients; 41 (25%) with composite outcome; increasing ABCD2 score associated with outcomes (OR 1.9; 95% CI 1.1 to 1.3); after adjusting for ABCD2 score, positive DWI result was associated with outcomes (OR 16.1; 95% CI 4.8 to 53)	Only 3% lost to follow-up at 90 days; ABCD2 score calculated retrospectively, and thus not used for decisionmaking; investigators blinded to ABCD2 score; use of composite outcome without reporting individual outcomes

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Giles et al[36] (2010)	III	Multicenter; secondary analysis of cohort data; systematic review	Individual-level data from systematic reviews and previously unpublished research; outcome: stroke at 7 and 90 days	12 studies; 4,574 patients; >20% with stroke; ABCD2-I score (incorporation of "infarct" by CT or DWI) improved the ABCD2 score from AUC 0.66 (95% CI 0.53 to 0.78) to 0.78 (95% CI 0.72 to 0.85)	Large, heterogeneous sample; secondary analysis with limited methodologic detail; use of random effects to account for heterogeneity among studies; principal reporting of AUC for prognostic accuracy assessments, limiting ability to understand sensitivity/specificity of various cut points
Griffiths et al[37] (2014)	III	Two Australian EDs; prospective cohort study in 2008 to 2010	Adults with low-risk TIA were referred for outpatient if ABCD2 score <4, CT result of head negative, and no high-risk features (carotid disease, atrial fibrillation, crescendo TIA); if ABCD2 score $\geq$4 then neurology consultation; outcome: stroke	N=200; 3 (1.5%) with stroke 127 of 200 (64%) had carotid imaging; 143 followed up with neurologist; 7 returned for inpatient assessment; 171 of 200 (85.5%) had post discharge medical follow-up; 191 of 200 (95.5%) discharged from ED on antiplatelet therapy	Consecutive sample of a convenience sample; only 3 patients (1.5%) had stroke outcome; loss to follow-up=29; not all patients received the criterion standard (stroke diagnosed by neurologist); 143 met with neurologist

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Merwick et al[38] (2010)	III	Derivation and validation of a refined prediction score using pooled multicenter analysis of patients with TIA; data were abstracted from existing stroke registries	Patients with TIA; outcomes: 2-, 7-, 28-, and 90-day stroke	N=3,886 in both derivation and validation groups, with N=2,654 and N=1,232, respectively; 73 patients (3.9%) had strokes in 90 days, 56 (3.0%) at 28 days, 49 (1.9%) at 7 days, and 27 (1.0%) at 2 days; 7-day risk for stroke increased with ABCD2 score; 0.6% with score <4, 2.5% for 4 to 5, and 4.3% with a score of >5; 7-day risk for stroke increased with ABCD3 score; 0% with score <4 and 3.9% with a score of >5	Physicians making treatment and diagnosis decisions were not blinded to the results of the ABCD2 score or neuroimaging, which could have influenced the results
Olivot et al[39] (2011)	III for Q1 III for Q2 II for Q4	Single tertiary care academic medical center; prospective cohort study	Patients with TIA triaged using ABCD2 score and vascular imaging; ABCD2 score: 0 to 3, discharged from ED to TIA clinic; ABCD2 score: 4 to 5, CTA obtained in ED, if >50% then admitted; ABCD2 score: >5, admitted to hospital; outcomes: stroke, death, and vascular death at 7, 30, and 90 days	Q1, Q2: N=224 consecutive patients; 157 patients (70%) discharged to TIA clinic and 67 (30%) were hospitalized; rates of vascular event in those who were sent to the clinic were lower than predicted at 0.9% (95% CI 0.3% to 3.2%) vs 4% Q4: N=224; 157 patients (70%) discharged for outpatient workup; 67 (30%) hospitalized and 116 had minor stroke or TIA; stroke rate at 7, 30, and 90 days was 0.6% (95% 0.1% to 3.5%) for patients referred to stroke clinic and 1.5% (95% CI 0.3% to 8.0%) for hospitalized patients; overall stroke rate for both: 0.9% (95% CI 0.3% to 3.2%), which is significantly lower than ABCD2 score expected rate	Q1, Q2: Generalizability is limited as a result of being conducted at a tertiary care facility and a single center; the study may have been underpowered for the outcome, given the wide CIs around the point estimate Q4: Included TIA (n=86), possible TIA (n=23), and minor stroke (n=7) patients; lower stroke rate may reflect high socioeconomic status Stanford population; unclear which patients received antiplatelet intervention; high follow-up rate; may not reflect practice in other environments

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Ozpolat et al[40] (2013)	II	Single ED in Istanbul; prospective cohort study in 2010	Convenience sample of adults with TIA for whom ABCD2 score was applied by emergency physicians; low risk (0 to 3), vs medium (4 to 5) and high (6 to 7) risk; sensitivity and specificity for stroke on day 3 calculated with ROC; outcome: stroke within 3 days of TIA presentation	N=64; primary outcome: 8 (12.5%) had stroke, 0 of 13 with low risk (ABCD2 score <4) had stroke, 4 of 33 (12.1%) with medium risk had stroke, and 4 of 18 (22.2%) with high-risk; AUC=0.76 with highest sensitivity and specificity ABCD2 score ≥4	Unclear whether person who determined whether there was a stroke was blinded to the ABCD2 score; sample size was small, and no comments about MRI or CT findings
Paul et al[41] (2012)	III	Regional academic stroke referral center Oxford, UK; prospective cohort	Community-based registry of cerebrovascular events; subjects identified from hospital admissions or referrals to an open-access outpatient clinic for neurologic emergencies with weekend services; TIA confirmed by study team; risk model: ABCD2 score (age ≥60 y, BP ≥140/90 mm Hg, clinical features, duration, diabetes); outcome: 7-day stroke risk after single and recurrent TIA stratified by ABCD2 score of the first TIA	N=1,000 patients with TIA; risk 95% CI; 7-day recurrent TIA: 17.0% (14.6 to 19.4); 7-day stroke: 9.2% (7.2 to 11.2); 7-day stroke risk ABCD2 score <4, 1 TIA 6.3% (3.6 to 9.0); ABCD2 score <4 recurred 6.3% (1.4 to 11.2); ABCD2 score ≥4, 1 TIA 10.9% (8.2 to 13.6); ABCD2 score ≥4 recurred 16.0% (7.8 to 24.2)	Registry data with prospective collection and chart review verification; no mention of outcome abstraction or data collection blinded to ABCD2 scores or presence of recurrent TIA; study likely underpowered; only 18 stroke outcomes in the recurrent TIA group

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Perry et al[42] (2014)	II	Multiple-center, academic; prospective cohort study	Adult TIA patients; risk factor: Canadian TIA Score, ABCD2 score; outcome: 7-day stroke	N=3,906; incidence of 7-day stroke was 2%; *c*-statistic for Canadian TIA rule 0.78 (95% CI 0.73 to 0.84); *c*-statistic for ABCD2 0.64 (95% CI 0.59 to 0.70)	Derivation study for Canadian TIA Score; results not validated in independent population; low incidence for stroke limits power
Sheehan et al[43] (2010)	III	Population-based study from North Dublin, Ireland; secondary analysis of a prospective cohort	Patients with TIA were risk stratified based on ABCD2 score, carotid stenosis, or atrial fibrillation; outcome: 90-day stroke	N=443 TIA cases; stroke occurred in 3.4% at 7 days, 5.4% at 28 days, and 7.5% at 90 days; no association between ABCD2 score and subsequent stroke; no association between atrial fibrillation and subsequent stroke; carotid stenosis had an HR of 2.56 (95% CI 1.27 to 5.15) risk for stroke	Population-based study; it is possible that the predictive utility of the ABCD2 score was reduced by the incorporation into the treatment decision of the clinicians
Stead et al[44] (2011)	II	Single academic medical center; retrospective cohort study	Adult TIA patients; risk factor: low (0 to 3), intermediate (4 to 5) high (6 to 7) risk by ABCD2 score; outcome: 7-day stroke	N=637; overall incidence of 7-day stroke was 1%; incidences of 7-day stroke were 1.1% (95% CI 0.3 to 3.8), 0.3% (95% CI 0.05 to 1.7), and 2.7% (95% CI 0.9 to 7.6) in the low-, intermediate- and high-risk ABCD2 score categories, respectively; negative LR* 1.1	Aggressive management of TIA (including carotid ultrasonography for all patients with expedited endarterectomy, if indicated) may have resulted in low incidence for stroke and could have attenuated predictive ability of ABCD2 score

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Wardlaw et al[45] (2014)	II	Systematic review of 26 studies (13 were retrospective)	Two investigators performed search, used PRISMA guidelines, described heterogeneity; random effects meta-analysis I^2 for heterogeneity; outcome: performance of ABCD2 (score ≥4 vs <4) to predict stroke risk at 7 and 90 days	N=12,586 in the 26 studies; primary outcome: 7-day stroke risk if ABCD2 score ≥4, 4,590 of 6,920 (66%) vs <4, 2,330 of 6,920 (34%); 90-day stroke risk if ABCD2 score ≥4, 6,294 of 9,849 (64%) vs <4, 3,555 of 9,849 (36%); if ABCD2 score>4: pooled stroke risk at 7 days=4.7 (95% CI 2.4 to 8.7); at 90 days=8.2 (95% CI 4.7 to 14); pooled sensitivity at 7 days=85.8% (95% CI 80.4 to 90.0); specificity at 7 days=36.1% (95% CI 30.6 to 42.1); pooled sensitivity at 90 days=84.6% (95% CI 80.2 to 88.2); specificity at 90 days=37.0% (95% CI 30 to 43.4)	Combination of prospective and retrospective studies with large amount of heterogeneity

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Wardlaw et al[46] (2015)	III	Meta-analysis of prospective and retrospective cohort studies	Identified all published studies in which the ABCD2 score was used to predict risk for stroke among patients with suspected TIA or minor stroke; evaluated proportion of recurrent stroke patients at 7 and 90 days with ABCD2 score <4 or ≥4 by bivariate ROC curve random-effects meta-analyses	N=4,443 patients; 29 studies included; 15 prospective, 14 retrospective cohort studies; to reduce the potential impact of study methods on heterogeneity, the authors analyzed the 10 studies that provided data on stroke recurrence at both 7 and 90 days, 5 were retrospective cohort studies; recurrent stroke % (95% CI) 7 days: ABCD2 score ≥4: 5.2% (2.8 to 9.4); ABCD2 score <4: 1.4% (0.7 to 3.1); 90 days: ABCD2 score ≥4: 8.9% (5.3 to 14.5); ABCD2 score <4: 2.4% (1.3 to 4.4); performance ABCD2 score ≥4 7 days: sensitivity 86.7 (95% CI 81.4 to 90.7); specificity 35.4 (95% CI 33.3 to 38.3); negative LR 0.38*; 90 days: sensitivity 85.4 (95% CI 81.1 to 88.9); specificity 36.2 (95% CI 34.0 to 37.6); negative LR* 0.40	Studies included were of varying quality (2 Class II, most Class III), with some included articles being fatally flawed, with ADCD2 scores influencing workup and follow-up decisions; no attempted sensitivity analyses or regression model to account for study differences; no sensitivity analysis based on the higher-quality studies was reported

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Wasserman et al[47] (2010)	II for Q1 II for Q4	Two urban academic EDs; prospective cohort study	Consecutive adults with rapid-access stroke clinic follow-up; ABCD2 score calculated by emergency physician; patients classified as high-risk (ABCD2 score >6), moderate-risk (ABCD2 score 4 to 5), or low-risk (ABCD2 score <4) were scheduled to consult a stroke neurologist within 7 days, 7 to 14 days, or more than 14 days of the index TIA, respectively; outcome: 90-day stroke risk	Q1: N=1,093; 1.6% admitted from the ED; 90-day stroke risk was 3.2% (1/3 of what was predicted by ABCD2 score) and 1/3 occurred within 2 days; low-risk 32%, moderate-risk 49%, and high-risk 19%; median ABCD2 score if referred from clinic was 4 vs 5 if patients were not referred or if patient was seen by a neurologist in the ED; ABCD2 score <4, negative LR* 0.29 (95% CI 0.08 to 0.81) for 90-day stroke Q2: N=982 patients who followed up at the stroke clinic, 31 with stroke within 90 days of index TIA; 90-day risk for stroke in all patients was 3.2% (95% CI 2.07 to 4.25) (ABCD2 score predicted 9.2%); 1.6% of patients with TIA/minor stroke were admitted from the ED; risk of subsequent TIA, myocardial infarction, or death by 90 days was 5.5%, 0.1%, and 1.7%, respectively	Q1: Neurologist making the outcome determination for stroke may not have been blinded to the ABCD2 score; 22 lost to follow-up Q2: Included only patients with final diagnosis of TIA; few adverse events

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Johnston et al[48] 2000	III	Sixteen community hospitals in Northern California, belonging to a single health maintenance organization; retrospective cohort	Subjects identified from medical records as having primary diagnosis of TIA; primary analysis with working diagnosis of TIA from EM and primary care physicians; definite TIA based on WHO criteria; primary outcome: stroke occurring within 90 days of TIA presentation and distinguishable from the initial event leading to TIA diagnosis; secondary outcomes: recurrent TIA and adverse cardiovascular events	N=1,707; 180 (10.5 %) patients with stroke within 90 days; 91 (5.3%) within 2 days; risk factors for stroke within 90 days: age >60 y: OR 1.8 (95% CI 1.1 to 2.7), diabetes OR 2.0 (95% CI 1.4 to 2.9), episode >10 min OR 2.3 (95% CI 1.3 to 4.2), weakness OR 1.9 (95% CI 1.4 to 2.6), speech impaired OR 1.5 (95% CI 1.1 to 2.1); number of risk factors and 90-day stroke risk, respectively: 0, 1 (3%), 2 (7%), 3 (11%), 4 (15%), and 5 (34%); adverse cardiovascular events (2.6%); deaths (2.6%); recurrent TIA (12.7%); stroke with any above (25.1%)	Presumptive diagnosis was primary outcome; 90-day outcome is questionable as short term for daily emergency medicine practice; half of adverse outcomes were within 2 days; it is questionable whether the strokes were evolving or discrete events; no a-priori power calculation reported; assumption is that all TIAs are captured with the primary diagnosis report from the charts; cases are from 1 health maintenance organization having unique insurance coverage and demographics
Al-Khaled et al[52] (2012)	II	Multicenter, academic medical centers; prospective cohort study	Consecutive adult patients with TIA, admitted to hospital and who underwent cranial CT for diagnostic evaluation; exclusions included possible seizure, history of migraine; outcome: new ischemic stroke	N=1,533; 3.1% with new infarct; 17 patients (1.1%) experienced a subsequent ischemic stroke during the 6-day follow-up period; presence of new infarct on initial CT was not associated with short-term stroke	Appropriate blinding of data collection and CT evaluation

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Wasserman et al[53] (2015)	II	Multiple centers, academic; prospective cohort study	Adult TIA patients; risk factor: acute ischemia, chronic ischemia, or microangiopathy on CT; outcome: 2-, or 90-day stroke	N=2,028; incidence for stroke was 1.5% at 2 days; adjusted OR for 2-day stroke: acute ischemia alone 2.7 (95% CI 0.9 to 8.1); acute ischemia+chronic ischemia 10.4 (95% CI 2.8 to 38); acute ischemia+microangiopathy 8.4 (95% CI 1.8 to 39); acute ischemia+chronic ischemia+microangiopathy 24 (95% CI 4 to 123)	CT interpretation not blinded to clinical symptoms and interrater reliability not assessed; forward selection of variables in multivariable logistic regression model; results require validation in independent population

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Nah et al[54] (2014)	II	Urban medical center, Seoul, Korea; prospective cohort study	Assessed the usefulness of multimodal MRI in assessing TIA patients and predicting the risk of recurrent TIAs or strokes; multimodal MRI included DWI, PWI, FLAIR imaging, time-of-flight MRA of the circle of Willis, and contrast-enhanced MRA from the aortic arch to the head; WHO stroke definition; outcome: presence of any cerebrovascular events (clinical TIA or stroke) at 7 and 90 days	N=162; 120 patients (74%) had at least 1 abnormality in DWI or PWI or MRA; all 162 patients completed the 3-mo follow-up; 23 patients (14.2%) experienced subsequent TIA (n=16) or stroke (n=7); subsequent ischemic events occurred within 7 days of the initial TIA in 18 patients (78.3%); area under ROC curve (95% CI) ABCD2 score: 0.50 (0.37 to 0.62) ABCD3-I score: 0.58 (0.44 to 0.72) DWI: 0.53 (0.40 to 0.66) PWI: 0.63 (0.50 to 0.75) MRA with symptoms: 0.73 (0.64 to 0.83); in a multivariable analysis, symptomatic MRA abnormality was found to be the only independent predictor of 90-day ischemic event (OR 12.7)	Changed MRI protocol from 3 mo FLAIR imaging in all DWI negative patients to 3-day follow up DWI; limited number of patients had stroke within 7 days and 90 days of index TIA
Douglas et al[55] (2003)	III	Multicenter study in Northern California between 1997 and 1998; retrospective cohort study	Study of the association of CT findings with 90-day stroke risk; outcome: 90-day stroke risk	N=478 patients; 322 patients underwent a head CT within 48 h of presentation; no difference in 90-day strokes in those who received a head CT and those who did not (10.9% vs 10.9%); alternative diagnosis made in 4 of 322 patients (1.2% [95% CI* 0.0 to 3.1])	

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Oostema et al[56] (2014)	III for Q2 III for Q4	Two, large, urban community hospitals; prospective cohort study	Adult patients evaluated in a TIA pathway implemented in an ED observation unit; exclusions included definitive non-TIA diagnosis or not consenting; used TIA WHO definition; outcomes: combined rate of incident ischemic stroke or recurrent TIA within 7 and 30 days of initial evaluation	Q2: N=166; 15% (95% CI 9 to 22) had acute infarction by DWI or CT; 2 strokes (1.8%) occurred during the 30-day follow-up period and both were within the first 48 h while patients were hospitalized; risk of subsequent stroke was higher among DWI-positive (6.3%) compared to DWI-negative (1.2%) patients; 20 of 110 (17.2%) of cervical vessel imaging studies were positive and 6 of these patients underwent carotid intervention Q4: N=116 patients, 92 (80%) placed into ED observation unit; 69 (59.6%) were discharged from the ED; 71 patients (61.2%) (95% CI 52.1% to 69.6%) had a negative evaluation on all of their diagnostic tests; 5 (4.3%) (95% CI 1.6% to 10.0%) experienced the primary clinical end-point for stroke (n=2) or recurrent TIA (n=3) within 30 days	Q2: Some medical record review, specifically for radiographic studies; 73% telephone follow-up for outcomes; small sample, although <5% withdrew Q4: Only 73.3% reached for telephone follow-up for 7 days and 30-day outcomes; few adverse events reported for recurrent stroke
Oostema et al[57] (2013)	III	Systematic review of prospective and retrospective cohort studies	Adult TIA patients; risk factor: DWI lesion; outcome: 2- and 7-day stroke	N=6 studies; incidence of 2-day stroke ranged from 0% to 2.9% in DWI-negative patients and 0% to 14% among DWI-positive patients; incidence of 7-day stroke occurred in 0% to 2.9% of DWI-negative patients and 0% to 23.8% of DWI-positive patients	Formal meta-analysis not performed; only 2 of 6 studies enrolled ED patients

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Daubail et al[58] (2014)	III	Single, academic medical center; retrospective chart review	Adults with TIA admitted to the hospital; outcome: TIA or stroke within 48 h after admission	N=312 patients; 10 of 312 patients (3.2%) experienced a recurrent ischemic event, 5 with ischemic strokes and 5 with TIA; TIA mechanism of LAA was a strong independent predictor (OR 12.03) of 2-day recurrent ischemia; of 111 patients with DWI, 28 (25%) had ischemic lesions	All included patients were managed by a stroke-trained neurologist; limited methodologic detail

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
D'Onofrio et al[61] (2006)	III	Prospective comparison of Doppler ultrasonography and contrast-enhanced MRA with DSA and endarterectomy	Consecutive patients with "symptoms of carotid disease and ultrasonography with stenosis >50% of ICA who underwent endarterectomy"; outcome of interest: identify 60% to 99% stenosis; criterion standard: DSA and endarterectomy findings categorized as <39%, 40% to 59%, 60% to 79%, and 80% to 99%	N=32; Spearman rank correlation for degree of stenosis with Doppler vs DSA (0.86) and MRA vs DSA (0.81); when compared to DSA, ultrasonography had sensitivity of 95% and specificity of 70%, negative LR=0.07 (95% CI 0.01 to 0.47),* and positive LR=3.2 (95% CI 1.6 to 6.2)*; when compared to DSA, MRA had sensitivity of 95%, specificity of 70%, negative LR=0.07 (95% CI 0.01 to 0.47),* and positive LR=3.2 (95% CI 1.6 to 6.2)*	Included patients with minor stroke, and all patients had to have >50% ICA stenosis; does not compare ultrasonography to CTA or MRA (only to DSA and pathology); sample size is very small
Heijenbrok-Kal et al[62] (2006)	III	Single academic medical center; prospective cohort study	Adult TIA or minor stroke patients; test: duplex ultrasonography; standard: DSA	N=313; among 131 patients with high-grade stenosis by DSA, peak systolic velocity with threshold of 230 cm/s had sensitivity 95% (95% CI 92% to 99%), specificity 51% (95% CI 42% to 61%), negative LR=0.09 (95% CI 0.04 to 0.20),* and positive LR=2.0 (95% CI 1.6 to 2.4)*	Included minor stroke patients; angiography performed up to 4 wk after ultrasonography; study performed from 1997 to 2000, so results may be less applicable now, given improvements in ultrasonographic technology; ultrasonography not compared directly with CTA or MRA

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Nederkoorn et al[63] (2002)	III	Single, academic medical center; prospective, cross-sectional study	Consecutive, symptomatic adult patients with suspected carotid stenosis; all patients underwent Doppler ultrasonography and MRA; criterion standard: DSA	N=350; Doppler ultrasonography demonstrated sensitivity of 88% (95% CI 82% to 93%), specificity of 76% (95% CI 69% to 82%), negative LR=0.17 (95% CI 0.11 to 0.26),* and positive LR=3.6 (95% CI 2.7 to 4.7)*; MRA demonstrated sensitivity of 92% (95% CI 86% to 96%), specificity of 76% (95% CI 69% to 83%), negative LR=0.10 (95% CI 0.06 to 0.19),* and positive LR=3.8 (95% CI 2.9 to 5.0)*	Limited methodologic detail; possible selection bias; timing, sequence, and blinding of diagnostic studies unclear

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Nonent et al[64] (2011)	III	Prospective enrollment; secondary cross-sectional analysis; multiple academic medical centers	Secondary analysis of data from the CARMEDAS multicenter study; patients received DUS within 15 days of study enrollment; outcome defined by DSA as criterion standard, assessed by blinded radiologists	N=56; for stenosis ≥70%, DUS yielded sensitivity of 83% (95% CI 68% to 93%), specificity of 86% (95% CI 76% to 93%), negative LR=0.19 (95% CI 0.09 to 0.40),* and positive LR=6.0 (95% CI 3.3 to 10.9)*; contrast-enhanced MRA yielded sensitivity of 94.6% (95% CI 81.4% to 99.4%), specificity 77% to 85% (between the 3 readers, negative); using specificity of 77%, negative LR=0.07 (95% CI 0.02 to 0.27)* and positive LR=4.1 (95% CI 2.6 to 6.2)*	Secondary analysis of existing dataset; small study sample; potential for spectrum bias given that patients had to have suspected carotid artery stenosis of 50% or greater; potential for selection and workup biases because the 56 patients represented <50% of patients enrolled in the full study because of actual diagnostic testing performed
Blakeley et al[65] (1995)	III	Systematic review/meta-analysis	Structured literature searches from 1977 through 1993	70 articles; 6,406 patients; given carotid artery as unit of analysis, 12,265 arteries studied; pooled sensitivities were similar between ultrasonography and MRA, with sensitivities of 82% to 86%, with overlapping CI for detecting 100% occlusion; pooled sensitivities were similar between ultrasonography and MRA, with sensitivities of 83% to 86%, with overlapping CI for detecting stenosis between 70% and 99%	Inclusion of both prospective and retrospective studies; may not be contemporaneous or inclusive of more contemporaneous research

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Nederkoorn et al[66] (2003)	III	Systematic review of English-language studies	Comparison of the diagnostic utility of DUS, MRA, and conventional DSA; DSA was used as the reference standard	63 published studies were included; for diagnosis of 70% to 99% stenosis vs <70% stenosis, MRA had a sensitivity of 95% (95% CI 92% to 97%) and a specificity of 90% (95% CI 86% to 93%); for diagnosis of 70% to 99% stenosis vs <70% stenosis, DUS had a sensitivity of 86% (95% CI 84% to 89%) and a specificity of 87% (95% CI 84% to 90%)	Type of MRI scanner predicted performance of MRA, whereas verification bias predicted performance of DUS
Jahromi et al[67] (2005)	III	Meta-analysis of prospective and retrospective cohort studies	Systematic review of studies that compared DUS with the criterion standard of angiography; outcomes: sensitivity and specificity combined across studies using weights that were the inverse of the combined within-study and between-study variance (a random-effects model)	N=47 studies of varying quality; 30 (68%) retrospective; 35 (75%) described blinding; 15 (32%) described handling un-interpretable results; for the diagnosis of angiographic stenosis of ≥70%, a peak systolic velocity ≥200 cm/s had a sensitivity of 90% (95% CI 84% to 94%) and a specificity of 94% (95% CI 88% to 97%)	No sensitivity analysis or regression model to account for study differences; no sensitivity analysis based on the higher-quality studies

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Wardlaw et al[68] (2006)	III	Systematic review and meta-analysis of both prospective and retrospective diagnostic studies	Literature identified by structured searches from 1980 to 2004	N=41 studies; N=2,541 patients; N=4,876 arteries; for stenosis 70% to 99%: contrast-enhanced MRA sensitivity 94% (95% CI 88% to 97%), specificity 93% (95% CI 89% to 96%), negative LR=0.06,* and positive LR=13.4*; Doppler ultrasonography: sensitivity 89% (95% CI 85% to 92%), specificity 84% (95% CI 77% to 89%), negative LR=0.13,* positive LR=5.6*; CTA: sensitivity 77% (95% CI 68% to 84%), specificity 95% (95% CI 91% to 97%), negative LR=0.24,* positive LR=15.4*	Heterogeneity among studies; evidence of publication bias
Ross et al[69] (2007)	II	University-affiliated suburban teaching hospital; randomized controlled trial	Adult patients with TIA; patients randomized to accelerated diagnostic protocol vs inpatient care; primary outcome: index visit length of stay; secondary outcome: 90-day total direct costs and clinical outcomes, including stroke, major clinical event, recidivism, timeliness of diagnostic testing, percentage of test completion, and test results	N=151; baseline characteristics similar between groups; length of stay was less in those randomized to accelerated protocol (25 vs 61 h); 90-day costs were also less ($890 vs $1,547); both groups had comparable recidivism, subsequent strokes, and major clinical events	Small sample; unblinded

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Stead et al[70] (2009)	II	Prospective study from 2004 to 2006	Patients evaluated for the feasibility of a protocol for evaluation of TIA in ED observation unit; outcome: stroke risk at 48 h, 1 wk, 1 mo, and 3 mo by telephone interview or chart review; criterion standard: attending stroke neurologist	N=418; stroke risk at 2 days: 0.96%, 1.2% at 7 days, 1.9% at 30 days, and 2.4% at 90 days; 127 patients (30.4%) were discharged after ED observation unit evaluation; 69.6% admitted because of high-risk factors	5% loss to follow-up; no description of who was evaluating whether patient had a stroke, and there was no interrater reliability; relatively small sample size
Martinez-Martinez et al[71] (2013)	III	Single medical center/clinic; prospective quasi-experimental (before-after) study	Adult patients with TIA with low-to-moderate risk; comparisons between use of TIA clinic (after phase) and no TIA clinic (before phase); outcome: 90-day stroke	N=211; stroke occurred in comparable numbers of patients between study groups (2.4% vs 1.2%, *P*=.70)	Limited methodologic detail; looked at TIA outpatient clinic for low-to-moderate-risk patients; low short-term risk for stroke; timing for stroke not presented

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Sanders et al[72] (2012)	III	Single tertiary academic medical center in Victoria, Australia; retrospective before- and-after cohort study	Comparison of the admission-based model in the before period, with a new nonadmission-based protocol called the M3T pathway; outcome: comparison of 90-day strokes in the 2 models	N=488 treated with the M3T model and 169 treated with the admission-based model; of the 468 of 488 patients with follow-up in the M3T model, 1.5% had stroke at 90 days (95% CI 0.73% to 3.05%); of the 150 of 169 patients with follow-up treated with the admission-based model, 4.67% had stroke (95% CI 2.28% to 9.32%)	Major limitations include a single-center study; there was no controlling for trends over time in treatment for strokes

AUC, area under the curve; *BP*, blood pressure; *c*, concordance; *CARMEDAS*, carotide-angiographie par résonance magnétique-échographie-doppler-angioscanner; *CI*, confidence interval; *CT*, computed tomography; *CTA*, computed tomography angiography; *CVA*, cerebrovascular accident; *DSA*, digital subtraction angiography; *DUS*, duplex ultrasonography; *DWI*,diffusion-weighted imaging; *ED*, emergency department; *EM*, emergency medicine; *FLAIR*, fluid attenuation inversion recovery; *h*, hour; *HR*, hazard ratio; *ICA*, internal carotid artery; *LAA*, large artery atherosclerosis; *LR*, likelihood ratio; *M3T*, Monash TIA Triaging Treatment; *mo*, month; *MRA*, magnetic resonance angiography; *MRI*, magnetic resonance imaging; *PRISMA*, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; *PWI*, perfusion-weighted imaging; *Q*, question; *ROC*, receiver operating characteristic; *TIA*, transient ischemic attack; *UK*, United Kingdom; *vs*, versus; *WHO*, World Health Organization; *wk*, week; *y*, year.

*Calculated from data in the study.