American Journal of Emergency Medicine (2012) **30**, 794–799

The American Journal of Emergency Medicine

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Review

Transient ischemic attack (TIA): the initial diagnostic and therapeutic dilemma☆,☆☆

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Received 25 January 2011; accepted 1 March 2011

Abstract Many patients with transient ischemic attacks (TIA) are at high risk of stroke within the first few days of onset of symptoms. Emergency physicians and primary care physicians need to assess these patients quickly and initiate appropriate secondary stroke prevention strategies. Recent refinements in diagnostic imaging have produced valuable insight into risk stratification of patients with TIA. Clinical data regarding urgent initiation of antiplatelet therapy specifically in this patient population with non-cardioembolic TIA are limited but promising. This review outlines the diagnostic tools available for rapid assessment of patients presenting with symptoms of TIA and discusses clinical trials that apply to these vulnerable patients.

1. Introduction

Frequently a harbinger of stroke, transient ischemic attacks (TIAs) affect an estimated 5 million Americans, or 2.3% of the US population [1,2]. These statistics translate to a rate of 200 000 to 500 000 persons with TIA per year in the United States. Despite the prognostic significance of TIA, as many as half of all patients who have TIA are unaware of its symptoms and fail to report them to their primary care physician [1]. Thus, the actual prevalence of this condition may be considerably larger.

In general, the high risk of stroke after TIA has been underappreciated. It has been reported that up to 17% of patients who have had a TIA will experience a stroke during the first 90 days [3-5]. Short-term risk of stroke is higher following TIA than following ischemic stroke [2,6] and is two times greater than the risk of myocardial infarction in patients with acute coronary syndrome [2].

A TIA is difficult to diagnose based solely on clinical findings, in part because symptoms resolve over time. A recent study found high inter-rater variability even among trained stroke neurologists [7]. Given the diagnostic challenges, it is not surprising that greater than 50% of individuals admitted with transient neurological attacks are misdiagnosed during the critical early hours in the ED [8]. This article will review practical approaches to rapid risk assessment and referral.

2. Differential diagnosis of TIA and stroke

Accurate diagnosis of transient neurological attacks is important to ensure timely treatment of the underlying

☆ Disclosure: This work was supported by Boehringer Ingelheim Pharmaceuticals, Inc (BIPI). Writing and editorial assistance was provided by Ann Sherwood, PhD, of Publication CONNEXION (Newtown, PA), which was contracted by BIPI for these services. The author meets criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE), was fully responsible for all content and editorial decisions, and was involved at all stages of manuscript development. The author received no compensation related to the development of the manuscript.

☆☆ Author Funding: 1. NIH/NINDS Research Grant Support, 2. Genentech Speaker's Bureau.

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doi:10.1016/j.ajem.2011.03.004

problem, initiation of secondary stroke prevention, and avoidance of subjecting patients to inappropriate thrombolytic treatment. A retrospective analysis of 254 patients who received tissue plasminogen activator (tPA) showed that 9 (3.5%) had a stroke mimic [9]. Another 23 (9%) did not develop ischemic injury and were diagnosed as having TIA, and 222 (87%) had ischemic stroke. Those who were misdiagnosed were younger and more likely to have been treated at a community hospital than at a stroke center. Compared with those with stroke, individuals with TIA had lower baseline levels of serum glucose, lower prevalence of coronary artery disease, and less severe stroke symptoms [9].

Recent analysis of patients admitted to a US ED with transient focal neurological episodes that were initially diagnosed as TIA found that as many as 60% had other conditions [8]. The most common misdiagnoses of TIA were toxic-metabolic derangements, atypical seizures, suspected acephalic migraine or migraine accompaniments, peripheral nerve or spine processes, psychiatric conditions, and unclassifiable or cryptogenic spells. These results are similar to findings at a German stroke clinic where overdiagnosis of stroke occurred in 47% of patients over a 3-year period [10]. Thus, physicians should be aware of factors that may suggest that the focal symptoms are caused by stroke mimic: age less than 50 years [11], convulsions, confusion, headache, loss of consciousness, nausea, vomiting, and dizziness [12,13].

3. Differentiating TIA from stroke

Historically, TIA has been defined as an episode of focal neurological dysfunction with abrupt onset and rapid resolution lasting less than 24 hours that is due to altered circulation to a limited region of the brain. However, evidence has been available for more than 20 years indicating that, in many cases, TIA symptoms resolve much sooner than 24 hours, and that duration of symptoms is not a reliable differentiator between TIA and stroke. Symptoms of TIA are resolved within less than 1 hour in 60% of cases and within less than 2 hours in 71% of cases. In fact, symptoms take 24 hours to resolve in fewer than 1 in 6 patients [14]. Furthermore, waiting to determine whether symptoms resolve in less than 24 hours to rule out stroke can delay stroke prevention. With recent refinements in diagnostic imaging, the absence of infarction has come to replace the duration of symptoms as the hallmark of TIA. Thus, the current definition of TIA endorsed by the American Heart Association is “a brief episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction” [2]. This change is important because it recognizes TIA as a clinically important entity, similar to the recognition of angina as a distinct clinical entity.

Early diagnostic imaging is used in patients with suspected ischemic stroke to rule out hemorrhage and to confirm diagnosis by identifying ischemic lesions prior to initiation of thrombolytic therapy. Until recently, computed tomographic (CT) scans were considered the gold standard in this clinical setting [15,16]. Accumulating evidence has shown considerable superiority using diffusion-weighted magnetic resonance imaging (DWI) compared with CT scanning. The diagnostic accuracy of early CT scans and DWI were compared in a meta-analysis of studies involving a total of 221 patients [15]. DWI performed within 12 hours of symptom onset allowed significantly greater diagnostic accuracy (odds ratio [OR] 25, 95% confidence interval [CI] 8 to 79; P <.0001) [15]. A similar trend was observed with scans performed within 3 hours of symptom onset [15]. Although DWI is not always readily available and feasible, evidence-based guidelines have begun to recommend DWI over noncontrast CT for the diagnosis of acute ischemic stroke within 12 hours of symptom onset [15,16].

Characterization of DWI to facilitate assessment in individuals with symptoms of TIA also has shown promise. Easton et al report that pooled data from19 studies involving 1117 patients demonstrated ischemic lesions in approximately 39% of patients with TIA, and they also report that, depending on the affected arterial bed, 76% to 100% of these patients show infarction on follow-up scans [2]. Moreover, ischemic lesions observed soon after onset of TIA are generally smaller than in patients with stroke, although there is no size cutoff that can distinguish one event from another [17]. However, evidence suggests that ischemic lesions in patients with TIA are an important predictor of stroke risk. Ay et al reported that not only were individuals with TIA and DWI-positive lesions at higher short-term risk for stroke than those without ischemic lesions, they were 15 times more likely to experience a stroke during hospitalization than those who had stroke initially [17].

4. Assessing stroke risk in patients with transient neurological attacks

Rapid assessment of patients with suspected TIA is needed to differentiate patients with stroke who are candidates for thrombolytic therapy from those at high risk for stroke who should remain hospitalized for observation, as well as from those who may be safely discharged. The risk factors for severe disabling stroke at 6 months post-TIA are shown in Fig. 1 [18].

Factors associated with higher risk are age (>60 years), modified Rankin score greater than 2, cardiogenic source of emboli, and infarct on CT or magnetic resonance imaging (MRI). Hypertension and diabetes showed a trend toward higher risk that did not reach the level of statistical significance in this analysis. Treatment at a dedicated stroke center was the only indicator of positive outcome.

Three scoring systems reflecting these risk factors—the ABCD score (age [A], blood pressure [B], clinical features [weakness/speech disturbance] [C], transient ischemic attack duration [D], and diabetes history [D]), the California score,

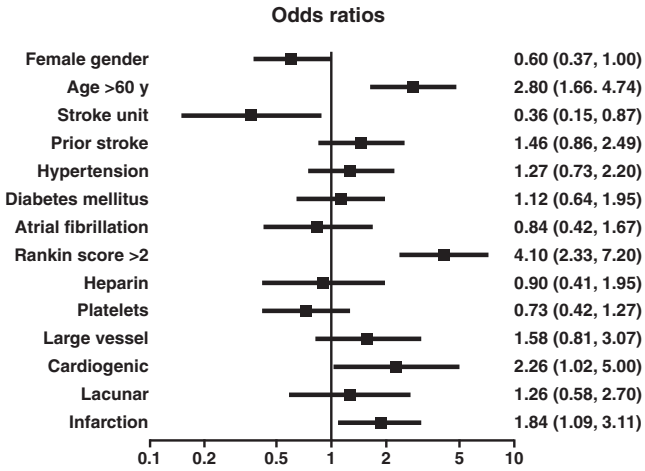

Fig. 1 Multivariate analysis of death and dependence 6 months after TIA. (Reprinted with permission from Daffertshofer M, Mielke O, Pullwitt A, Felsenstein M, Hennerici M. Transient ischemic attacks are more than "ministrokes." Stroke. 2004; 35:2453-8.)

and a combination of the two (ABCD2)—are currently used for triage purposes (Table 1) [19]. A recent retrospective analysis comparing the 3 scoring systems found no difference among them in predictive accuracy for stroke risk at 2, 7, and 30 days [19]. Chandratheva et al showed that an ABCD2 score was strongly predictive of stroke risk at 24 hours (P = .0003) [20]. The ABCD2 score was highly sensitive (86% for moderate-to-high-risk TIA) at the expense of specificity (35%), with a negative predictive value of 92% at 7 days after index event [21].

Combining imaging data may provide greater selectivity in predicting outcomes. Although large-scale studies are needed, a systematic review and meta-analysis showed a positive correlation between lesions on DWI and clinical predictors of stroke (duration, motor weakness, dysphasia, dysarthria) and underlying etiology (atrial fibrillation and carotid stenosis) [22].

Combining ABCD2 and DWI status significantly increases the predictive value of both approaches [23]. As shown in Table 2, adding DWI positivity to the prediction model has a significant effect in demonstrating the 7-day stroke risk post-TIA. Both an ABCD2 score of 4 or greater and acute infarction on DWI were independent predictors of 7-day stroke risk [23]. Adding DWI status to the dichotomized ABCD2 score increased the area under the receiver operating characteristic curve to 0.81 (95% CI 0.74 to 0.88; P = .003) from 0.66 (95% CI 0.57 to 0.76) using the ABCD2 score alone [23]. Thus the corresponding specificity was 73% for the CIP model and 47% for the ABCD2 score at a sensitivity of 80% on the receiver operating characteristic curve [23].

Table 1 ABCD2 scoring

Factor	Point Scored
Age ≥ 60	1
Blood pressure ≥ 140/90 mmHg	1
Clinical features	
Speech disturbance without weakness	1
Unilateral weakness	2
Duration	
10-59 min	1
≥ 1 h	2
Diabetes	1

Data from Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, Sidney S. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet. 2007;369:283-92.

5. Early secondary stroke prevention in patient with TIA or minor stroke

Early diagnosis of TIA, often in the emergency department (ED), is critical to reducing the short-term risk of stroke and to reducing morbidity and mortality if stroke ensues. In the Early use of eXisting PREventive Strategies for Stroke (EXPRESS) study, urgent initiation of secondary stroke prevention with drugs, such as aspirin, clopidogrel, statins, or antihypertensive agents, in patients with TIA or minor stroke reduced the risk of any stroke within the first 90 days by 80% (10.3% vs 2.1%, P <.0001), independent of age and gender [24]. Moreover, the ischemic risk reduction was not associated with increased risk of intracerebral hemorrhage or other bleeding [24]. In the same study, early recognition of stroke symptoms provided a greater opportunity for timely thrombolytic therapy, which contributed to a significantly reduced risk of fatal or disabling stroke (1/281 patients vs 16/310 patients; P = .0005) [25]. In the EXPRESS study, urgent intervention compared with less urgent (not immediate) hospital admission significantly reduced hospital admissions for recurrent stroke (5 vs 25, P = .001), the overall number of hospital bed days (672 vs 1957, P = .017), and the hospital bed days for vascular causes (427 vs 1365, P = .016) [25].

Similar results were reported after the establishment of a clinic providing 24-h access for patients with symptoms of TIA [26]. Of the 1085 patients admitted over a 2-year period, 643 had confirmed TIA. Patients with stroke attributed to atherothrombosis or cerebral arteriolopathy or of unknown etiology received immediate antiplatelet therapy. Patients with atrial fibrillation who were not using anticoagulation therapy prior to symptom onset were given subcutaneous low-molecular-weight heparin plus an oral anticoagulant Urgent carotid revascularization was performed for individuals with symptomatic high-grade stenosis. Patients' primary care physicians received a discharge notice with general recommendations for secondary prevention care [26]. The 90-day stroke rate for all patients was 1.24% (95% CI 0.72 to 2.12), substantially lower than the 5.96% rate predicted by patients' ABCD2 scores [26].

Table 2 7-day stroke risk after TIA using the Clinical- and Imaging-based Prediction (CIP) model

ABCD2 ≥ 4	Acute infarct on DWI	No. of patients	Subsequent Stroke	Stroke risk	Risk stratification
-	-	121	0	0.0%	Low risk (1.2%, 95% CI
+	-	201	4	2.0%	0.0% to 2.5%)
-	+	41	2	4.9%	High risk (12.3%; 95% CI
+	+	114	17	14.9%	7.1% to 17.4%)

Republished with permission from Ay H, Arsava EM, Johnston SC, Vangel M, Schwamm LH, Furie KL, Koroshetz WJ, Sorensen AG. Clinical- and imaging-based prediction of stroke risk after transient ischemic attack: the CIP model. Stroke 2009 Jan;40:181-6.

The purpose of urgent antithrombotic treatment in patients with TIA or minor stroke is to reduce the extent of ischemic injury and to lower the risk of secondary stroke. The highest risk for stroke following TIA occurs within the first 48 hours after symptom onset. The Fast Assessment of Stroke and Transient ischaemic attack to prevent Early Recurrence (FASTER) study [27] evaluated early antiplatelet therapy in this population. However, the study was stopped early owing to enrollment difficulties, which may have affected the statistical significance of the results. Patients with TIA or minor stroke enrolled in this pilot study were randomized to treatment with clopidogrel (300 mg loading dose followed by 75 mg daily; 198 patients) or placebo (194 patients) within 24 hours of symptom onset. Although there was a reduction in the absolute risk of stroke within 90 days (−3.8% [95% CI −9.4 to 1.9]; $P = .19$) it was not statistically significant. The benefit was accompanied by a small increase in risk of hemorrhagic stroke [27].

In another study, the EARLY trial, 548 patients with ischemic stroke accompanied by measureable neurological deficit were randomly assigned to receive treatment with dual therapy (aspirin plus dipyridamole) either within 24 hours of stroke onset (early initiation) or beginning 7 days after stroke onset and following 7 days of aspirin monotherapy (late initiation) [28]. The late initiation group received aspirin 100 mg once daily for the first 7 days followed by dual therapy with aspirin 25 mg and Extended Release-dipyridamole (ER-DP) 200 mg twice daily from day 8 through day 90. In the early initiation group, dual therapy with aspirin 25 mg and (ER-DP) 200 mg twice daily was initiated within 24 hours of stroke onset and continued for 90 days. As shown in Fig. 2, Kaplan-Meier analysis showed fewer events in the composite end point (nonfatal stroke, TIA, nonfatal myocardial infarction, and major bleeding complications) starting at 7 days. Because this was a pilot study, it was not powered to detect a statistically significant difference in this composite efficacy and safety end point [28]. Early initiation of dual therapy was associated with a higher incidence of adverse events during the first 7 days and overall higher rates of discontinuation (20%) compared with late initiation of dual therapy (15%) [28].

On meta-analysis of pooled data from this trial and from the FASTER trial, the benefit of early initiation of dual antiplatelet therapy in patients with TIA or stroke did rise to the level of statistical significance (risk ratio 0.68 [95% CI, 0.49 to 0.93] $P = .014$) [28]. To account for the difference in study populations between the two trials, patients from the EARLY trial were stratified by severity of stroke symptoms. Stroke severity did not appear to influence the outcomes of the meta-analysis [28].

5.1. Treatment guidelines

5.1.1. Antiplatelet therapy

Extrapolating from results in patients with ischemic stroke, it appears that early initiation of antiplatelet therapy provides a small net benefit over later initiation of treatment. Pooled results from 2 large studies evaluating administration of aspirin monotherapy within 48 hours of stroke onset showed small but significant benefit compared with placebo [29]. Based on these findings, current treatment guidelines recommend initiating aspirin 325 mg within 24 to 48 hours after onset of acute ischemic stroke in patients who have not undergone thrombolysis [29]. Although they do not address the timing of therapy initiation, the 2010 update of AHA/ASA guidelines for secondary prevention of stroke in individuals with stroke or TIA recommends antiplatelet agents for patients with noncardioembolic stroke or TIA to reduce long-term risk of vascular events including stroke [30]. Specifically, aspirin (50 to 325 mg/d) monotherapy, the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily , and clopidogrel 75 mg monotherapy are all acceptable options for initial therapy [30].

Because of limited clinical data, intravenous therapy with glycoprotein IIb/IIIa receptor inhibitors is not recommended in the acute ischemic stroke setting [29].

5.1.2. Anticoagulation

In general, initiation of anticoagulation is seldom recommended for patients with minor stroke who are not candidates for thrombolytic treatment with tPA. A systematic review by the Cochrane collaboration demonstrated that anticoagulation did not reduce the odds of death or dependency from stroke. Although anticoagulants prevented pulmonary embolism, they also increased the risk of hemorrhage, leading to the conclusion that they cannot be recommended for treatment of acute ischemic stroke [31]. However, in patients with ischemic stroke or TIA with atrial fibrillation, therapy with a vitamin K antagonist (target international normalized ratio [INR] 2.5; range, 2.0 to 3.0) is recommended [30].

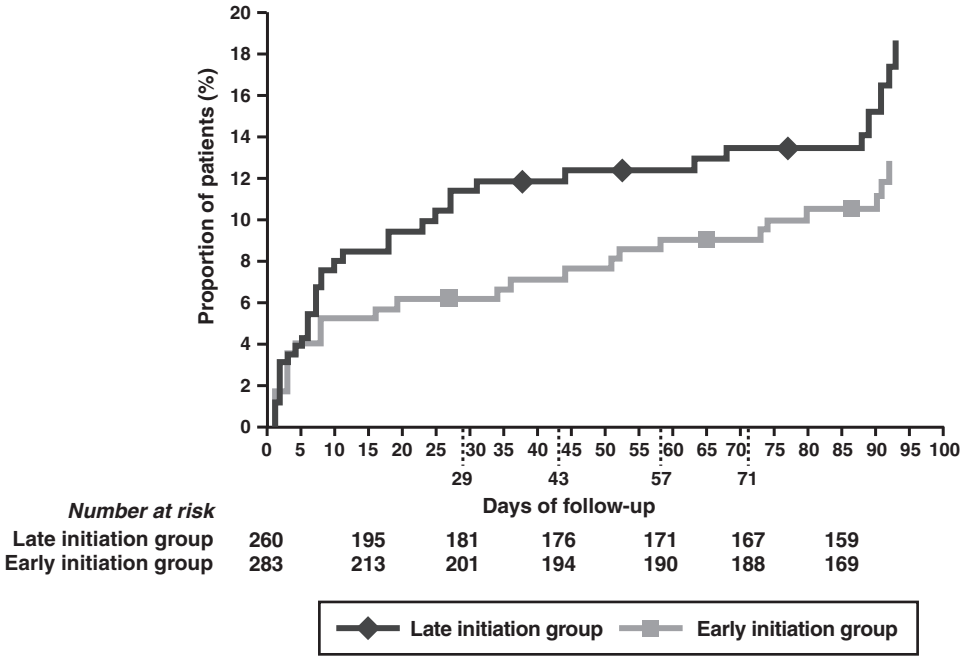

Fig. 2 Time to first event included in composite end point (nonfatal stroke, TIA, nonfatal myocardial infarction, and major bleeding complications) in patients with ischemic stroke treated with aspirin 25 mg plus dipyridamole 200 mg twice daily (early initiation group) or aspirin 100 mg (late initiation group) within 24 h of symptom onset for the first 7 days followed by aspirin 25 mg plus dipyridamole 200 mg twice daily for up to 90 days. (Hazard ratio [HR, 0.73, 95% confidence interval [CI] 0.44 to 1.19; $P = .20$). (Republished with permission from Dengler R, Diener HC, Schwartz A, Grond M, Schumacher H, Machnig T, Eschenfelder CC, Leonard J, Weissenborn K, Kastrup A, Haberl R; EARLY Investigators. Early treatment with aspirin plus extended-release dipyridamole for transient ischaemic attack or ischaemic stroke within 24 h of symptom onset (EARLY trial): a randomised, open-label, blinded-endpoint trial. Lancet Neurol. 2010;9(2):159-66.)

5.1.3. Treatment of other modifiable risk factors

Acute administration (<24 h) of antihypertensives and anticoagulants is not recommended. However, antihypertensives can be started after 24 h in patients who are neurologically stable [29].

No recommendation is given regarding when statin therapy should be started. Statin therapy with intense lipid-lowering effects is recommended to reduce the risk of stroke and cardiovascular events among patients with ischemic stroke or TIA with evidence of arthrerosclerosis, an LDL-C level ≥100 mg/dL, and who are without known coronary artery disease [30]. Of note, in the FASTER trial, an increase in stroke risk was observed with early administration of simvastatin [27], although large-scale studies are needed to confirm this result.

Sustained hyperglycemia (plasma glucose >140 mg/dL) during the first 24 h after stroke is associated with poor outcomes. Insulin therapy should be considered for individuals with plasma glucose >140 to 180 mg dL [29].

6. Emergency Department disposition of the TIA patient

With the current close attention give to healthcare cost containment, unnecessary hospitalization for observation is to be avoided. At the same time, discharge of patients at high risk for stroke during the first 48 hours of symptom onset can be more costly in the long run as well as potentially fatal. Use of emergency department observation units (EDOUs) can bridge the need for testing and observation in a less costly setting. Moreover, EDOUs can be used to improve patient education on stroke prevention. In a recent study of 418 patients admitted to an EDOU, 30% were discharged directly from the EDOU, whereas the remainder were admitted to the hospital. Although no direct comparison was made in this study, the 90-day risk of stroke was 2.4% [32], considerably lower than the 10% risk generally attributed to this population.

7. Discussion

Stroke mortality has declined in recent years, but stroke remains the primary cause of disability in the United States, and its resulting economic and societal burden is enormous [1]. Urgent treatment of TIA has been shown to reduce the short-term risk of stroke in this highly vulnerable population [24,25]. Major advances in clinical diagnostic tools and especially in imaging techniques have facilitated the ability to diagnose TIA and to initiate necessary secondary stroke prevention therapy. Moreover, diagnostic imaging may improve identification of those patients with TIA who are at high risk and thus may benefit from hospitalization. With the advent of these advanced diagnostics tools, such as DWI MRI, the reported incidence of stroke has increased by 7 % while that of TIA has

decreased by 33%, as a result of the reclassification of TIA diagnoses made with the aid of these imaging methods [2]. Although the available clinical data presents a tantalizing picture of further stroke risk reduction by initiating antiplatelet therapy early, further large scale studies are needed to clarify what is the optimum time after onset of TIA symptoms that therapy for stroke risk reduction can be safely initiated.

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