

Classification of Subtype of Acute Ischemic Stroke

Definitions for Use in a Multicenter Clinical Trial

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Background and Purpose: The etiology of ischemic stroke affects prognosis, outcome, and management. Trials of therapies for patients with acute stroke should include measurements of responses as influenced by subtype of ischemic stroke. A system for categorization of subtypes of ischemic stroke mainly based on etiology has been developed for the Trial of Org 10172 in Acute Stroke Treatment (TOAST).

Methods: A classification of subtypes was prepared using clinical features and the results of ancillary diagnostic studies. "Possible" and "probable" diagnoses can be made based on the physician's certainty of diagnosis. The usefulness and interrater agreement of the classification were tested by two neurologists who had not participated in the writing of the criteria. The neurologists independently used the TOAST classification system in their bedside evaluation of 20 patients, first based only on clinical features and then after reviewing the results of diagnostic tests.

Results: The TOAST classification denotes five subtypes of ischemic stroke: 1) large-artery atherosclerosis, 2) cardioembolism, 3) small-vessel occlusion, 4) stroke of other determined etiology, and 5) stroke of undetermined etiology. Using this rating system, interphysician agreement was very high. The two physicians disagreed in only one patient. They were both able to reach a specific etiologic diagnosis in 11 patients, whereas the cause of stroke was not determined in nine.

Conclusions: The TOAST stroke subtype classification system is easy to use and has good interobserver agreement. This system should allow investigators to report responses to treatment among important subgroups of patients with ischemic stroke. Clinical trials testing treatments for acute ischemic stroke should include similar methods to diagnose subtypes of stroke. (*Stroke* 1993;24:35-41)

KEY WORDS • cerebral ischemia • clinical trials • classification

Categorization of subtypes of ischemic stroke has had considerable study, but definitions are hard to formulate and their application for diagnosis in an individual patient is often problematic. In the past, classifications have been based primarily on risk factor profiles, clinical features of the stroke, and the findings on brain imaging studies (computed tomography [CT] or magnetic resonance imaging [MRI]).¹ Yet, clinical and brain imaging features overlap and are not specific for any particular subtype of ischemic stroke.

Bamford et al² recently reported that outcomes and likelihood of recurrent stroke differed markedly by

stroke subtype; large hemispheric infarcts, usually resulting from occlusion of the internal carotid artery or proximal middle cerebral artery, had the worst prognosis. These investigators classified the strokes based on clinical features that forecasted the size and site of the ischemic lesion, but they did not consider the potential etiology of the stroke. Other investigators have noted that the etiology of stroke does influence prognosis. Sacco et al³ noted that mortality was higher among patients with large-artery atherosclerotic lesions than among patients with lacunes. Recurrent strokes are more likely among patients with cardioembolic stroke than among patients with stroke of other causes.^{4,5} The 1-month mortality after cardioembolic stroke is also higher than that with strokes of other etiologies.^{6,7}

Determining the cause of stroke does influence choices for management. Carotid endarterectomy is of proven usefulness in preventing recurrent stroke in patients with large-artery stenosis, as are aspirin and ticlopidine in patients with small-artery occlusive disease or lesser degrees of large-artery stenosis.⁸⁻¹⁰ Clinical trials of these modalities have specifically excluded patients with cardioembolic stroke, but no separate analyses were performed on patients with large-vessel or small-vessel disease. Anticoagulants¹¹ or even cardiac surgery may be prescribed to prevent recurrent cardio-

The centers and investigators in TOAST are listed in the appendix.

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TABLE 1. TOAST Classification of Subtypes of Acute Ischemic Stroke

Large-artery atherosclerosis (embolus/thrombosis)*
Cardioembolism (high-risk/medium-risk)*
Small-vessel occlusion (lacune)*
Stroke of other determined etiology*
Stroke of undetermined etiology
a. Two or more causes identified
b. Negative evaluation
c. Incomplete evaluation

TOAST, Trial of Org 10172 in Acute Stroke Treatment.

*Possible or probable depending on results of ancillary studies.

embolic stroke. Therefore, investigators in clinical trials testing responses to acute treatment for ischemic stroke should distinguish and analyze responses by stroke subtype. Because most clinical trials involve the collaboration of several institutions, investigators should strive for uniformity in diagnosis. A stroke subtype classification that is unambiguous, practical, and easy to apply to every patient is important.

The current approach to stroke care is to institute treatment as rapidly as possible. As a result, in many instances the decision to begin treatment is made before an extensive, time-consuming evaluation for a likely etiology can be completed. Thus, a diagnosis of presumed subtype of ischemic stroke that is initially based on clinical features is needed. However, diagnosing stroke subtype based only on clinical findings is quite difficult. A determination can be confirmed later when the results of a laboratory evaluation are available. Therefore, a diagnostic system that can be used both at the time of initial assessment and initiation of treatment and then again after studies have been completed would be an attribute for a stroke treatment trial. This procedure has not been extensively used in the existing classifications of stroke subtypes.^{2,7,12-17}

For the Trial of Org 10172 in Acute Stroke Treatment (TOAST), a placebo-controlled, randomized, blinded study of the low-molecular-weight heparinoid given to patients within 24 hours after stroke, we developed a system for diagnosis of subtype of ischemic stroke that uses components of existing diagnostic schemes. We then tested the ease of use of this algorithm and attached definitions. Two neurologists who had not participated in the preparation of the TOAST diagnostic system independently used it in diagnosing subtype of ischemic stroke. Interrater agreement was then measured. This report describes the methodology for diagnosing stroke subtype using the TOAST system and presents the results of bedside testing.

TOAST Subtype Classification System

The TOAST classification system includes five categories: 1) large-artery atherosclerosis, 2) cardioembolism, 3) small-artery occlusion (lacune), 4) stroke of other determined etiology, and 5) stroke of undetermined etiology (Table 1). Diagnoses are based on clinical features and on data collected by tests such as brain imaging (CT/MRI), cardiac imaging (echocardiography, etc.), duplex imaging of extracranial arteries, arteriography, and laboratory assessments for a prothrombotic state.

The physician can apply the clinical and imaging findings when first assessing the patient and then consider the results of other diagnostic tests later. An important part of the classification is the ability of the physician to categorize a specific subtype diagnosis as probable or possible based on the degree of certainty. A "probable" diagnosis is made if the clinical findings, neuroimaging data, and results of diagnostic studies are consistent with one subtype and other etiologies have been excluded. A "possible" diagnosis is made when the clinical findings and neuroimaging data suggest a specific subtype but other studies are not done. Because many patients will have a limited number of diagnostic tests, the probable and possible subcategorizations allow the physician to make as precise a subgroup diagnosis as can be achieved.

Large-artery atherosclerosis. These patients will have clinical and brain imaging findings of either significant (>50%) stenosis or occlusion of a major brain artery or branch cortical artery, presumably due to atherosclerosis (Table 2). Clinical findings include those of cerebral cortical impairment (aphasia, neglect, restricted motor involvement, etc.) or brain stem or cerebellar dysfunction. A history of intermittent claudication, transient ischemic attacks (TIAs) in the same vascular territory, a carotid bruit, or diminished pulses helps support the clinical diagnosis. Cortical or cerebellar lesions and brain stem or subcortical hemispheric infarcts greater than 1.5 cm in diameter on CT or MRI are considered to be of potential large-artery atherosclerotic origin. Supportive evidence by duplex imaging or arteriography of a stenosis of greater than 50% of an appropriate intracranial or extracranial artery is needed. Diagnostic studies should exclude potential sources of cardiogenic embolism. The diagnosis of stroke secondary to large-artery atherosclerosis cannot be made if duplex or arteriographic studies are normal or show only minimal changes.

Cardioembolism. This category includes patients with arterial occlusions presumably due to an embolus arising in the heart (Table 2). Cardiac sources are divided into high-risk and medium-risk groups based on the evidence of their relative propensities for embolism¹⁶ (Table 3). At least one cardiac source for an embolus must be identified for a possible or probable diagnosis of cardioembolic stroke. Clinical and brain imaging findings are similar to those described for large-artery atherosclerosis. Evidence of a previous TIA or stroke in more than one vascular territory or systemic embolism supports a clinical diagnosis of cardiogenic stroke. Potential large-artery atherosclerotic sources of thrombosis or embolism should be eliminated. A stroke in a patient with a medium-risk cardiac source of embolism and no other cause of stroke is classified as a possible cardioembolic stroke.

Small-artery occlusion (lacune). This category includes patients whose strokes are often labeled as lacunar infarcts in other classifications¹⁸ (Table 2). The patient should have one of the traditional clinical lacunar syndromes and should not have evidence of cerebral cortical dysfunction. A history of diabetes mellitus or hypertension supports the clinical diagnosis. The patient should also have a normal CT/MRI examination or a relevant brain stem or subcortical hemispheric lesion with a diameter of less than 1.5 cm demonstrated.

TABLE 2. Features of TOAST Classification of Subtypes of Ischemic Stroke

Features	Subtype			
	Large-artery atherosclerosis	Cardioembolism	Small-artery occlusion (lacune)	Other cause
Clinical				
Cortical or cerebellar dysfunction	+	+	-	+/-
Lacunar syndrome	-	-	+	+/-
Imaging				
Cortical, cerebellar, brain stem, or subcortical infarct >1.5 cm	+	+	-	+/-
Subcortical or brain stem infarct <1.5 cm	-	-	+/-	+/-
Tests				
Stenosis of extracranial internal carotid artery	+	-	-	-
Cardiac source of emboli	-	+	-	-
Other abnormality on tests	-	-	-	+

TOAST, Trial of Org 10172 in Acute Stroke Treatment.

Potential cardiac sources for embolism should be absent, and evaluation of the large extracranial arteries should not demonstrate a stenosis of greater than 50% in an ipsilateral artery.

Acute stroke of other determined etiology. This category includes patients with rare causes of stroke, such as nonatherosclerotic vasculopathies, hypercoagulable states, or hematologic disorders. Patients in this group

should have clinical and CT or MRI findings of an acute ischemic stroke, regardless of the size or location. Diagnostic studies such as blood tests or arteriography should reveal one of these unusual causes of stroke. Cardiac sources of embolism and large-artery atherosclerosis should be excluded by other studies.

Stroke of undetermined etiology. In several instances, the cause of a stroke cannot be determined with any degree of confidence. Some patients will have no likely etiology determined despite an extensive evaluation. In others, no cause is found but the evaluation was cursory. This category also includes patients with two or more potential causes of stroke so that the physician is unable to make a final diagnosis. For example, a patient with a medium-risk cardiac source of embolism who also has another possible cause of stroke identified would be classified as having a stroke of undetermined etiology. Other examples would be a patient who has atrial fibrillation and an ipsilateral stenosis of 50%, or the patient with a traditional lacunar syndrome and an ipsilateral carotid stenosis of 50%.

Testing the TOAST Classification

Twenty patients with acute ischemic stroke who were admitted to the University of Iowa Hospitals and Clinics were independently assessed by two physicians who had not participated in the authorship of the system of subtype diagnosis. Before examination of the patients, the physicians agreed to apply the rules of the classification system strictly without any exceptions.

The two physicians agreed in their final diagnosis of subtype of ischemic stroke in 19 of 20 patients (Table 4). In the only patient assessed differently, one physician diagnosed sick sinus syndrome as a cardioembolic cause of the stroke while the other diagnosed the stroke as being of undetermined etiology.

A diagnosis of stroke of undetermined etiology was made in one young woman who had a stroke within 1 week after childbirth because a prothrombotic state was suspected but could not be confirmed by laboratory studies. Two potential causes of stroke were found in a man with a pure motor hemiparesis secondary to a small

TABLE 3. TOAST Classification of High- and Medium-Risk Sources of Cardioembolism

High-risk sources	
Mechanical prosthetic valve	
Mitral stenosis with atrial fibrillation	
Atrial fibrillation (other than lone atrial fibrillation)	
Left atrial/atrial appendage thrombus	
Sick sinus syndrome	
Recent myocardial infarction (<4 weeks)	
Left ventricular thrombus	
Dilated cardiomyopathy	
Akinetic left ventricular segment	
Atrial myxoma	
Infective endocarditis	
Medium-risk sources	
Mitral valve prolapse	
Mitral annulus calcification	
Mitral stenosis without atrial fibrillation	
Left atrial turbulence (smoke)	
Atrial septal aneurysm	
Patent foramen ovale	
Atrial flutter	
Lone atrial fibrillation	
Bioprosthetic cardiac valve	
Nonbacterial thrombotic endocarditis	
Congestive heart failure	
Hypokinetic left ventricular segment	
Myocardial infarction (>4 weeks, <6 months)	

TOAST, Trial of Org 10172 in Acute Stroke Treatment.

TABLE 4. Interphysician Agreement in Stroke Subtype Using TOAST Classification

Case	Diagnosis based on clinical/neuroimaging features		Diagnosis also using results of ancillary studies	
	Observer		Observer	
	1	2	1	2
1	C	C	C	C
2	C	C	C	C
3	C	C	C	C
4	C	C	C	C
5	S	U	S	S
6	S	S	S	S
7	S	S	S	S
8	L	L	L	L
9	L	L	L	L
10	S	S	L	L
11	L	L	U	U
12	O	O	U	U
13	C	C	U	U
14	U	U	U	U
15	U	U	U	U
16	C	C	C	U
17	U	U	U	U
18	L	L	U	U
19	C	C	U	U
20	U	U	L	L

TOAST, Trial of Org 10172 in Acute Stroke Treatment; C, cardioembolism; S, small-artery occlusion; L, large-artery atherosclerosis; O, stroke of other determined etiology; U, stroke of undetermined etiology.

infarct in the internal capsule and a left ventricular thrombus detected on echocardiography. This patient was classified as having a stroke of undetermined etiology because the findings were compatible with two different conditions. Seven other patients were classified as having strokes of undetermined etiology because ancillary tests did not demonstrate a likely etiology. In two of these patients a cardiogenic cause was suspected, and in two large-vessel atherosclerosis was suspected based on clinical and imaging features.

Both physicians changed their initial diagnosis, which was based on clinical examination and neuroimaging, in seven patients when the results of ancillary studies were taken into account.

Discussion

Physicians usually intuitively determine the subtypes of ischemic stroke based on clinical features and the results of diagnostic studies. While this nonstandardized approach may be acceptable for clinical practice, a clinical trial should strive for uniform diagnoses to obtain greater interphysician consistency. The features must be applied studywide for results to gain acceptance, but they must also be easy to use and sufficiently pragmatic that physicians in other situations can also use them. The TOAST classification system is straightforward and follows a logical progression. It is clinically relevant and can supplement other independent assessments, including the severity of neurological deficits.

Our data also demonstrate a high degree of interrater agreement in stroke subtype diagnosis when physicians apply the TOAST diagnostic system to individual cases.

While the TOAST classification notes the presence or absence of risk factors, the onset and course of the stroke, and the nature of the neurological findings, diagnoses are strongly influenced by the results of diagnostic tests. The results of ancillary studies are stressed because many clinical phenomena are nonspecific for stroke subtype. In the Stroke Data Bank, this approach has proved useful.^{13,14} The two investigators in this study had to change their initial diagnosis in about one third of the patients when the results of ancillary studies became available. Because most etiologic diagnoses in stroke are not based on pathological confirmation and are thus presumptive, investigators are allowed to express their certainty by classifying the likelihood of diagnosis as probable or possible. This is an important attribute of the TOAST classification system because it permits more careful scrutiny of those cases in whom the diagnosis is uncertain and may help any adjudication process. Any categorization of subtypes of ischemic stroke contains some mixture of patients with similar but not identical brain injuries or vascular pathologies. It also includes some degree of inflexibility, a feature that is in common with any system of grouping patients; for example, a physician cannot diagnose cardioembolism in a patient who has a suggestive history when the diagnostic studies do not substantiate the presence of heart disease.

Based on the experiences of several large single-center or multicenter demographic studies, the most common causes of stroke are large-artery atherosclerosis, cardioembolism, and small-artery occlusion.^{7,12,19} Because these are the three largest groupings of ischemic stroke and because the prognoses of patients in these divisions differ, examining responses to acute treatment in these groups is clinically important. Researchers of the Harvard Cooperative Stroke Registry merged patients with artery-to-artery embolism (atheroembolic stroke) and those with embolism secondary to heart disease into a single category.¹² This combination was based on a clinical course that was presumably suggestive of embolism, regardless of etiology. We elected to distinguish patients with embolism secondary to heart disease from those who have symptomatic large-artery atherosclerosis. Instead, we are uniting patients with cerebral embolism secondary to extracranial or intracranial atherosclerosis with those who have local thrombosis superimposed on atherosclerosis. This decision is supported by the shared risk factor and clinical profiles and the compatible results of diagnostic studies. The short-term and long-term prognoses and treatment of patients with embolism or thrombosis secondary to atherosclerotic cerebrovascular disease are also akin.¹⁹ Finally, it is almost impossible to determine with any degree of certainty if a stroke in a patient with severe large-artery atherosclerosis is solely due to thrombosis or if there is also an element of embolism.

The contingent of patients with cardioembolic stroke is separated from other groups because their short-term and long-term prognoses differ. In addition, their responses to treatment with an antithrombotic drug may be distinct and of clinical interest. While the likelihood of embolism is high among patients with infective

endocarditis and recent myocardial infarction, heart diseases such as lone atrial fibrillation, mitral valve prolapse, or a bioprosthetic valve are accompanied by a much lower risk. Cardiac lesions such as an atrial septal aneurysm, a dilated left atrial appendage, or a patent foramen ovale are often detected by transesophageal or contrast echocardiography, but the cause-and-effect relation of these abnormalities with stroke is not established. For these reasons, we divided the cardiac lesions into high-risk and medium-risk groups and require that those patients with medium-risk cardiac conditions have studies to exclude other causes of stroke before the diagnosis of cardioembolism is made. This strict approach should increase the precision of the diagnosis of cardioembolic stroke.

Small lacunar infarcts in the deep regions of the brain are usually the result of occlusion of small penetrating arteries and usually cause rather specific clinical syndromes.²⁰ Because the short-term prognosis of these patients is very good, investigators may be tempted to exclude these patients from a clinical trial. However, the risk factor profile and some of the clinical symptoms of the lacunar syndromes overlap with those of large-artery atherosclerosis, and barring patients with lacunar stroke will be problematic. Small lacunar infarcts have to be distinguished from subcortical infarcts as the result of embolism to or occlusion of large intracerebral arteries, which are mostly at least 1.5 cm in diameter. We are restricting the diagnosis of small-vessel occlusion to those patients with one of the traditional lacunar syndromes who have a lesion smaller than 1.5 cm in diameter.

A clinical trial such as TOAST will recruit a small number of patients with stroke of other etiologies. With the exception of patients with familial hypercoagulable disorders or known multisystem diseases such as vasculitis, the presentation of these uncommon causes of stroke is often nonspecific and admission of these patients into a clinical trial is likely. Management of these patients often differs from that of patients with the more common causes of stroke, and thus their responses should be reported separately. Conversely, the number of patients with any one of these less common causes of stroke will be insufficient to reach any specific noteworthy conclusions, and thus, they cannot be analyzed separately.

Other investigators have noted problems in achieving agreement among physicians.^{21–24} Even after the results of diagnostic tests were considered, the neurologists in this study were unable to discern the cause of ischemic stroke in nine of 20 patients. Many of these patients presumably had atherosclerotic disease but did not have confirmatory laboratory evidence, which is supported by the finding that the prognosis of patients with stroke of an unknown etiology is similar to that of patients with stroke secondary to large-artery atherosclerosis.²⁵ We are including the category of stroke of undetermined etiology so that we can analyze responses to treatment in this very important group.

In this system, a specific subtype diagnosis cannot be made for patients with suggestive historical or physical evidence who do not have confirmatory findings on diagnostic testing. While such a requirement may lessen sensitivity and increase the number of cases of stroke of undetermined etiology, it will increase specificity and

lessen the likelihood of misclassification of patients in the other categories. Allowance of exceptions in a classification such as ours, which is used by several different investigators at different institutions, would result in less reliable overall assessment. We prefer uniformity with obvious reasons for each rating and accept misclassification in a minority of cases, rather than allow each physician the opportunity to make individual diagnoses. In addition, the diagnosis of stroke of undetermined etiology may prompt more careful review and possible adjudication for a cause of stroke based on historical or clinical features.

A large number of diagnostic studies are needed to use the TOAST classification system effectively; this is a potential problem. We are aware of the costs of this action, but the great increase in interobserver agreement when diagnostic tests are involved justifies this approach in a clinical trial. Conversely, we cannot require that all patients have all diagnostic tests; there may be contraindications for specific studies or the treating physician may opt not to perform the test. To compensate for this situation, the TOAST system allows for a “possible” stroke subtype diagnosis. In patients who do not participate in a clinical trial, diagnostic studies should be performed on an individual basis.²⁶ The success of any categorization depends on the compliance of the reporting physicians. Investigators must adhere to the definitions for diagnosis and avoid subjective judgments for the data to be meaningful. We obtained very good interobserver agreement. The two physicians followed the rules of the classification very strictly and, as a result, agreement was much higher than that reported in other studies using different systems of stroke subtype diagnosis.^{21–24} However, inconsistencies in diagnosis among collaborating physicians will still need to be monitored, and an adjudication process should be used to finalize any uncertain or contested stroke subtype diagnoses. We propose that a system for subtype diagnosis, such as the one we are using, be applied in future clinical trials that recruit patients with acute ischemic stroke.

Appendix

TOAST Research Group

TOAST Participating Clinical Centers

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