An Evidence-Based Causative Classification System for Acute Ischemic Stroke

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Regular, evidence-based assignment of patients to etiologic stroke categories is essential to enable valid comparison among studies. We designed an algorithm (SSS-TOAST) that incorporated recent advances in stroke imaging and epidemiology to identify the most probable TOAST category in the presence of evidence for multiple mechanisms. Based on the weight of evidence, each TOAST subtype was subdivided into 3 subcategories as "evident", "probable", or "possible". Classification into the subcategories was determined via predefined specific clinical and imaging criteria. These criteria included published risks of ischemic stroke from various mechanisms and published reports of the strength of associations between clinical and imaging features and particular stroke mechanisms. Two neurologists independently assessed 50 consecutively admitted patients with acute ischemic stroke through reviews of abstracted data from medical records. The number of patients classified as "undetermined-unclassified" per the original TOAST system decreased from 38–40% to 4% using the SSS-TOAST system. The kappa value for interexaminer reliability was 0.78 and 0.90 for the original TOAST and SSS-TOAST respectively. The SSS-TOAST system successfully classifies patients with acute ischemic stroke into determined etiologic categories without sacrificing reliabilty. The SSS-TOAST is a dynamic algorithm that can accommodate modifications as new epidemiological data accumulate and diagnostic techniques advance.

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Accurate classification of ischemic stroke cause is indispensable to stroke research, because stroke outcome,[1–3] recurrent stroke rate,[4–6] and strategies for secondary stroke prevention[7,8] differ by stroke subtype. The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification system is the most widely accepted tool to categorize stroke subtype.[9] It was developed in the early 1990s using the available diagnostic and clinical information of the time. The rules to categorize stroke mechanisms were set to ensure simplicity and facilitate widespread use. However, the scheme has moderate interexaminer reliability.[10–12] The TOAST system as published assigns patients with more than one likely cause, or conflicting clinical and laboratory evidence, into a single category ("stroke of undetermined etiology"). The latter approach enhances the accuracy of assignments to other causative categories, but the interexaminer reliability is retained at the expense of inflating the category of "stroke of undetermined etiology."[9,12,13] This problem is more acute as advances in stroke evaluation now result in more frequent identification of vascular, cardiac, and other systemic abnormalities. At least one potential source of cardiac embolism can now be detected using echocardiography in about 50 to 70% of patients with stroke.[10,14] Likewise, 12% of patients with a cardiac source of embolism and 22% of patients with a lacunar infarction harbor ipsilateral large artery atherosclerosis causing stenosis greater than 50%.[15] Strict application of the classification criteria in the current era could lead to categorization of a significant majority of strokes into the undetermined causative category. Moreover, physicians' "clinical opinion" based on experience may assign a high degree of confidence to one specific stroke cause in a specific patient, but this is difficult to document and injects uncertainty in comparing studies. A classification algorithm that regularizes assignments of the most likely mechanism among coexisting potential stroke causes would therefore be useful.

Recent advances in stroke imaging and epidemiology make it possible to devise criteria to arrive at the most likely mechanism. Recognition of certain topographic patterns of acute infarction suggests particular stroke subtypes.[16] Likewise, determination of the primary stroke risks associated with individual cardiac and vascular pathologies provide a basis for comparing the embolic potential of various stroke mechanisms. In this

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study, we designed and sought to test an algorithm that implemented recent advances in stroke imaging and epidemiology in an attempt to improve the inter-examiner reliability of the TOAST system and minimize the proportion of stroke of undetermined cause.

Patients and Methods

Our motivation was in large part related to a high degree of discordance in stroke subtyping among investigators in a prospective study evaluating the utility of new computed tomography (CT)–based neuroimaging technology to improve prediction of stroke subtype and outcome (Screening Technology and Outcome Project in Stroke [STOPStroke] Study). To regularize the familiar and useful TOAST classification approach, we developed a set of criteria for subtype assignment and termed the modified classification system the Stop Stroke Study TOAST (SSS-TOAST) system. The study was approved by the local institutional review board.

The SSS-TOAST is composed of the same five major stroke subtypes in the TOAST classification system. In the SSS-TOAST system, each causative category is subdivided based on the weight of evidence as "evident," "probable," or "possible"(Table 1). The Figure describes a simple three-step decision algorithm to interpret evidence to identify the level of confidence in assigning a cause. First, a mechanism is deemed to be "evident" only if it is the sole potential mechanism conforming to one of the causative categories listed in Table 1. Second, when there are more than one "evident" stroke mechanisms, the SSS-TOAST system regularizes assignment to a "probable" stroke mechanism based on the presence of specific characteristics of the stroke that make one mechanism more probable than the others. Third, in the absence of any "evident" cause of the stroke, a search is made for "possible" mechanisms that carry a lower or not clearly determined risk for stroke.

We used the best available published evidence to determine the level of confidence in assigning a mechanism. We separated an "evident" mechanism from a "possible" mechanism using an arbitrary 2% annual or one-time primary stroke risk threshold. The 2% threshold was chosen because it is the approximate, annual, primary, ipsilateral stroke risk associated with asymptomatic carotid stenosis greater than 50%.[17–20] The primary risk is defined as the risk for first-ever stroke associated with a particular mechanism in the absence of an effective treatment. Thus, for instance, a cardiac source of embolism cannot compete with more than 50% stenosis due to large artery atherosclerosis as another "evident" stroke mechanism unless the annual or one-time primary stroke risk associated with its presence exceeds 2%.Table 2 lists our estimates based on current literature review of the high- and low-risk cardiac sources of embolism with respect to the 2% threshold.

When there was more than one "evident" stroke mechanism, we assign a "probable" mechanism if specific clinical and imaging criteria are met. This assignment was standardized using several rules. First, the presence of a temporal relation with the onset of stroke qualified the mechanism as probable (cardiac or vascular surgery, acute myocardial infarction [AMI], arterial dissection, drug-induced stroke). Second, a nonchronic occlusion or near-occlusive stenosis (characterized either by hairlike lumen or string sign on angiography where the blood flow has been severely impeded or a severe stenosis where the diameter of the residual lumen is much smaller than that of the embolus) in arteries supplying the vascular territory related to the infarction was assigned probable when there were coexisting proximal sources of embolism. Third, the positive likelihood ratio (PLR) was used to describe the strength of associations among clinical and imaging features and particular stroke mechanisms. Features with a PLR greater than an arbitrarily defined cutoff of 2 qualify a stroke mechanism as probable. The PLR is defined as the probability that a person with a given stroke subtype will have a particular clinical or imaging feature divided by the probability that a person with no such mechanism will have the same clinical or imaging features.[21] A total of 25 features were examined, and 6 features were identified to have a PLR of 2 or greater (Table 3). For large artery atherosclerosis, the features with a PLR of 2 or greater included: (1) prior history of one or more transient monocular blindness, transient ischemic attack, or stroke in the territory of index atherosclerotic artery within the last month[22–24]; (2) the presence of internal watershed infarction; or (3) multiple, ipsilateral, punctate, acute or temporally separate infarctions including the internal watershed regions.[25,26] For cardioaortic embolism, the features with a PLR of 2 or greater included: (1) a history of systemic embolism,[27] or (2) the presence of multiple acute infarctions in both anterior circulations or in both anterior and posterior circulation for cardioaortic embolism.[16,28] For small artery disease, the sixth feature with a PLR of 2 or greater was the presence of stereotypic lacunar transient ischemic attacks within the last week.[29–32]

The primary annual or one-time risks used to calculate PLR for each clinical and imaging stroke feature were determined through a comprehensive review of published studies in the English-language literature. A Medline search was done by investigators (H.A., K.L.F., W.J.K.) using relevant keywords. To keep consistency across studies, we included only articles that used the TOAST classification system or studies that documented a detailed description of the criteria for stroke subtyping. The quality of evidence was defined as follows: (1) *class A*: evidence provided by a prospective, population-based, longitudinal study or metaanalyses of prospective studies, or by a longitudinal cohort study of individuals with the suspected condition, using a gold standard for case definition; (2) *class B*: evidence supplied by retrospective review of follow-up data collected from individuals with an established condition. Data provided from case–control studies or anecdotal case series were not used. Consensus among examiners was sought for the quality of evidence. Table 2 lists the quality of evidence for each cardiac pathology. In conditions for which there is conflicting evidence (primary risk falling into different sides of the threshold), the item was listed as a source with uncertain stroke risk.

We advocate, along with others, that imaging proof of acute infarction or ischemia is required as a starting point to the accurate classification of ischemic stroke.[33] An otherwise evident or probable mechanism is toned down to "possible" if there is no imaging proof of infarction or ischemia in a location consistent with symptoms. The SSS-TOAST system, like other causative classification systems, assumes that all patients with stroke are evaluated by a basic level of di-

Table 1. Stop Stroke Study Trial of Org 10172 in Acute Stroke Treatment (SSS-TOAST) Classification Criteria to Determine Causative Subtypes of Acute Ischemic Stroke

Stroke Mechanism	Level of Confidence	Criteria
Large artery atherosclerosis	Evident	1. Either occlusive or stenotic (≥50% diameter reduction) vascular disease judged to be due to atherosclerosis in the clinically relevant extracranial or intracranial arteries,[18,19,77] *and* 2. The absence of acute infarction in vascular territories other than the stenotic or occluded artery
	Probable	1. Prior history of one or more transient monocular blindness (TMB), transient ischemic attacks (TIAs), or stroke from the territory of index artery affected by atherosclerosis within the last month,[22–24] *or* 2. Evidence of near-occlusive stenosis or nonchronic complete occlusion judged to be due to atherosclerosis in the clinically relevant extracranial or intracranial arteries (except for the vertebral arteries), *or* 3. The presence of ipsilateral and unilateral internal watershed infarctions or multiple, temporally separate, infarctions exclusively within the territory of the affected artery[25,26]
	Possible	1. The presence of an atherosclerotic plaque protruding into the lumen and causing mild stenosis (<50%) in a clinically relevant extracranial or intracranial artery[35–37] and prior history of two or more TMBs, TIAs, or strokes from the territory of index artery affected by atherosclerosis, at least one event within the last month, *or* 2. Evidence for evident large artery atherosclerosis in the absence of complete diagnostic investigation for other mechanisms
Cardioaortic embolism	Evident	The presence of a high-risk cardiac source of cerebral embolism (see Table 2)
	Probable	1. Evidence of systemic embolism,[27] *or* 2. Presence of multiple acute infarctions that have occurred closely related in time within both right and left anterior or both anterior and posterior circulations in the absence of occlusion or near-occlusive stenosis of all relevant vessels; other diseases that can cause multifocal ischemic brain injury such as vasculitides, vasculopathies, and hemostatic or hemodynamic disturbances must not be present[16,28]
	Possible	1. The presence of a cardiac condition with low or uncertain primary risk of cerebral embolism (see Table 2), *or* 2. Evidence for evident cardioaortic embolism in the absence of complete diagnostic investigation for other mechanisms
Small-artery occlusion	Evident	Imaging evidence of a single clinically relevant acute infarction less than 20mm in greatest diameter within the territory of basal or brainstem penetrating arteries in the absence of any other pathology in the parent artery at the site of the origin of the penetrating artery (focal atheroma, parent vessel dissection, vasculitis, vasospasm, and so on)
	Probable	The presence of stereotypic lacunar TIAs within the past week[29–32]
	Possible	1. Presenting with a classical lacunar syndrome in the absence of imaging that is sensitive enough to detect small infarctions,[53,54] *or* 2. Evidence for evident small artery occlusion in the absence of complete diagnostic investigation for other mechanisms
Other causes	Evident	Presence of a specific disease process that involves clinically appropriate brain arteries
	Probable	A specific disease process that has occurred in clear and close temporal relation to the onset of brain infarction such as arterial dissection, cardiac or arterial surgery, and cardiovascular interventions
	Possible	Evidence for an evident other cause in the absence of complete diagnostic investigation for mechanisms listed above
Undetermined causes	Unknown (no "evident" or "possible" criteria for the causes (above)	Cryptogenic embolism: 1. Angiographic evidence of abrupt cutoff consistent with a blood clot within otherwise angiographically normal looking intracranial arteries, *or* 2. Imaging evidence of complete recanalization of previously occluded artery, *or* 3. Presence of multiple acute infarctions that have occurred closely related in time without detectable abnormality in the relevant vessels[16,28] Other cryptogenic: those not fulfilling the criteria for cryptogenic embolism Incomplete evaluation: absence of diagnostic tests that, up to the examiner's judgment, would have been essential to uncover the underlying cause
	Unclassified	The presence of more than one evident mechanism where there is either probable evidence for each or no probable evidence to be able to establish a single cause

agnostic tests. The comprehensiveness of testing is, however, difficult to proscribe because classification systems rely on data from many different sources. For studies that rely on accurate classification, the comprehensiveness of testing should be stated explicitly because it will influence the final classification. Optimal use of the SSS TOAST relies on imaging of the brain (CT, magnetic resonance imaging [MRI]) and intracranial and extracranial vessels (ultrasonography,

CT angiography, MR angiography); monitoring the cardiac rhythm, function, and structure (electrocardiogram, transthoracic echocardiography); and obtaining relevant blood tests. When basic cardiac investigations do not indicate a cardiac source and further cardiac testing is considered "relevant," then transesophageal echocardiography and Holter monitoring may be required to appropriately classify patients. Blood tests for hypercoagulable states and immunological disorders and other diagnostic tests depend on the level of suspect from a particular cause.

In clinical practice, we foresee two circumstances in which the basic diagnostic tests are not fully performed. The first occurs if "relevant" causative investigations are stopped when a positive test result is obtained. In this circumstance, an otherwise "evident" mechanism can be denigrated to "possible." The second, called "incomplete evaluation," designates failure to investigate for the "relevant" stroke mechanism in the absence of positive evidence. The adjudication of "relevant" is acknowledged to be difficult but could be stated explicitly for a given study using the SSS-TOAST classification system.

Definitions for Stop Stroke Study Trial of Org 10172 in Acute Stroke Treatment Subtypes

LARGE ARTERY ATHEROSCLEROSIS. An evident mechanism requires the presence of either occlusive or stenotic (≥50% diameter reduction) vascular disease due to atherosclerosis. Characteristic angiographic or sonographic features, as well as exclusion of other causes of vascular stenosis, can make the diagnosis of atherosclerosis. The rules apply to both extracranial and intracranial stenoses. The degree of stenosis is calculated per North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria.[34] The SSS-TOAST system considers protruding atheroma causing less than 50% stenosis as possible cause of stroke provided that it is associated with recurrent recent clinical events and there is no evidence for any other evident mechanism[35–37] (see Table 1).

CARDIOAORTIC EMBOLISM. Cardiac emboli sources with high and low or uncertain risk for stroke per 2% primary annual or one-time risk for ischemic stroke are listed in Table 2. There are major differences with respect to the original TOAST categorization of cardiac emboli sources. First, the following items were added to the TOAST list as new cardioaortic sources of embolism: chronic myocardial infarction with low ejection fraction (<28%),[38] congestive heart failure with low ejection fraction (<30%),[39] papillary fibroelastoma,[40] and complex atheroma in the ascending aorta or proximal arch.[41] Second, based on recent evidence, mitral valve prolapse no longer confers an independent risk for ischemic stroke.[42,43] This item was removed from the original TOAST list. Wall motion abnormalities were also deleted from the list because of the lack of reliable data showing that they confer a primary risk for stroke. Wall motion abnormalities often occur in the setting of prior myocardial infarction, left ventricular aneurysm, or dilated cardiomyopathy, all of which were already taken into account in the SSS-TOAST system. Third, atrial flutter,[44] bioprosthetic cardiac valve,[45–48] and nonbacterial thrombotic endocarditis[49,50] listed as medium-risk sources in the TOAST system appeared to convey a stroke risk that is comparable with high-risk sources, and therefore were classified as high-risk sources in the SSS-TOAST system.

All high-risk cardiac emboli sources listed in Table 2 pose greater than 2% annual or one-time primary risk for ischemic stroke except for AMI. In the era of contemporary treatment of AMI with thrombolytics, antithrombotics, and antiplatelets, the incidence of ischemic stroke (in-hospital or 1 month) after AMI has declined to about 1%.[51,52] Nonetheless, AMI was listed among other high-risk cardiac sources because of its temporal relation to stroke.

The low-risk group includes cardiac sources with less than 2% primary risk for stroke, yet some cardiac abnormalities associated with increased risk for recurrent stroke but undetermined risk for first-ever stroke were also included in this category. These included atrial septal aneurysm (with or without patent foramen ovale) and left ventricular aneurysm without thrombus. Complex aortic atheroma (protruding atheroma >4mm in thickness, mobile debris, or plaque ulceration)[41] represents the pathological characteristics of atherosclerosis, yet it is listed under cardioaortic sources of embolism in the SSS-TOAST system. This decision was made because embolic vascular events associated with aortic atheroma show similar clinical and imaging features with cardiac sources of embolism, such as concurrent systemic embolism and multiple bilateral acute infarctions. Such features are used to differentiate aortic embolism as the most likely mechanism in the concurrent presence of a more distal cause such as atherosclerosis of the cervical arteries. Table 2 lists complex aortic atheroma as a separate item from other cardiac sources so that patients with this specific condition can be selected for data analysis with patients having other atherosclerotic causes as well.

SMALL ARTERY DISEASE. An evident mechanism requires the imaging proof of infarction within a territory supplied by a single penetrating artery originating from the proximal branches of the circle of Willis, basilar artery, or distal vertebral arteries. The five classical clinical syndromes are not considered supportive of evident or probable mechanisms because these syndromes are solely a function of infarction location, which is already a criterion for diagnosis.[53,54] Diffusion-weighted imaging (DWI) is the preferred method of imaging because of its advantages in the imaging of acute small lesions and defining the temporal relevance.[55,56] Instead of 15mm, the SSS-TOAST system sets the largest diameter in an axial slice for penetrating artery infarctions at 20mm. This was based on our observations, along with others,[16,54] that acute infarctions up to 20mm in largest diameter on DWI within the territory of penetrating arteries occur in the absence of any mechanism other than small artery disease. Moreover, serial imaging studies suggest that about 50% volume shrinkage occurs from acute to chronic time points in lacunar infarctions. Assuming that these infarctions are spherical in shape, the autopsy-based (chronic) 15mm limit corresponds to 20mm on acute neuroimaging.[57–60]

OTHER CAUSES. The other causes category includes patients with a diverse array of stroke mechanisms. Disorders included

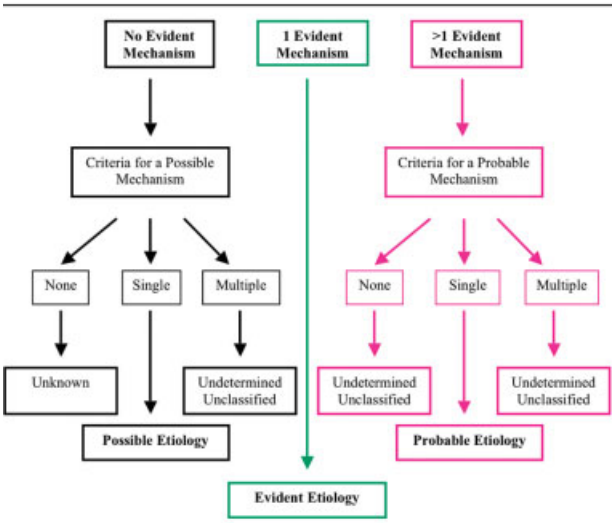

Fig. The decision algorithm to assign a mechanism. The algorithm works as follows: When there is only one evident mechanism (see mechanisms listed as evident in Table 1 and high-risk sources in Table 2), the cause is assigned as "evident" (green path). If there are multiple evident mechanisms, some criteria are applied to identify a probable mechanism (red path). If these criteria confirm one particular mechanism, the cause is called "probable." If there is no probable criterion, the cause is undetermined-unclassified because there are multiple causes. If there are probable criteria for more than one subtype, the cause is again undetermined-unclassified. If there is no evident mechanism (black path), the probable criteria are skipped and possible evidence is sought (see mechanisms listed as possible in Table 1 and low or uncertain risk sources in Table 2). If there is possible evidence for one mechanism, the cause is called "possible." If there is no possible evidence, the cause is undetermined-unknown. If there is possible evidence for more than one subtype, the cause is undetermined-unclassified.

in this category are difficult to further categorize into more homogenous groups. The associations between these disorders and stroke are often hard to establish and require expertise, as well as strict adherence to the published guidelines for each. This category includes the following major groups of disorders: arterial dissections; infectious or inflammatory diseases of extracranial and intracranial arteries; intrinsic diseases of arterial wall other than infection or inflammation (fibromuscular dysplasia, Sneddon's syndrome); disorders of platelets and hemostatic system; stroke associated with migraine and drugs; cerebral venous thrombosis; hereditary syndromes (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy [CADASIL], congenital cutaneovascular syndromes); hypoperfusion syndromes due to pump failure, hyperviscosity, or altered vascular tone (sepsis, medications); and iatrogenic causes such as endovascular interventions and cardiac or arterial surgery.

The diagnostic criteria for disorders in this category are often quite straightforward, yet there are some such as migraine- and drug-related stroke that deserve further consideration. The following criteria adopted by The International Headache Society were used for migraine-related stroke[61]: (1) neurological symptoms should start as a typical aura symptom of a typical migraine attack, (2) one or more typical aura symptoms should persist for longer than 60 minutes, and (3) all other causes must have been excluded. For drug-related stroke, we used a similar definition that looked for a temporal relation (stroke onset within 48 hours of a drug use that is known to be associated with increased risk for stroke, or positive urine or blood test) in the absence of another attributable cause.

Clear and close temporal relation to the onset of brain infarction was sought for some of the disorders in this category to identify a probable cause in the presence of multiple mechanisms. The temporal window for AMI and ar-

Table 2. Cardioaortic Sources of Cerebral Embolism

Sources with high primary risk for ischemic stroke
Sources of embolism of thrombotic origin
[a]Left atrial thrombus[78,79]
[a]Left ventricular thrombus[80]
[a]Atrial fibrillation[81,82]
[a]Paroxysmal atrial fibrillation[82,83]
[a]Sick sinus syndrome[84,85]
[a]Sustained atrial flutter[44]
[a]Recent myocardial infarction[51,52] (within 1 month)
[a]Rheumatoid mitral or aortic valve disease[86]
[a]Bioprosthetic and mechanical heart valves[45–48]
[a]Chronic myocardial infarction together with low ejection fraction less than 28%[38]
[a]Symptomatic congestive heart failure with ejection fraction less than 30%[39]
[b]Dilated cardiomyopathy[87,88]
[b]Nonbacterial thrombotic endocarditis[49,50]
Sources with embolism not predominantly of thrombotic origin
[a]Infective endocarditis[89,90]
[a]Papillary fibroelastoma[40]
[b]Left atrial myxoma[91]
Sources with low or uncertain primary risk for ischemic stroke
Cardiac sources of embolism
[a]Mitral annular calcification[92]
[b]Patent foramen ovale[93]
Atrial septal aneurysm
Atrial septal aneurysm and patent foramen ovale
Left ventricular aneurysm without thrombus
Isolated left atrial smoke (no mitral stenosis or atrial fibrillation)
Aortic sources of embolism
[a]Complex atheroma in the ascending aorta or proximal arch[41]

The high- and low-risk cardioaortic sources were separated using an arbitrary 2% annual or one-time primary stroke risk threshold. Either class A evidence (provided by a prospective longitudinal study) or class B evidence (supplied by retrospective review of follow-up data) was used in the determination of primary stroke risks. The Stop Stroke Study Trial of Org 10172 in Acute Stroke Treatment (SSS-TOAST) system was designed for first-ever strokes. All low-risk cardiac and aortic pathologies listed become a high-risk source when the algorithm is used to classify a recurrent stroke associated with that particular cause.

[a]Class A evidence.
[b]Class B evidence.

Table 3. Clinical and Imaging Features Used in the Positive Likelihood Ratio Analyses

Lacunar transient ischemic attacks (TIAs) within the last week[a]
Prior transient monocular blindness, TIA, or stroke within the last month[a]
Internal watershed infarctions[a]
Multiple small lesions in one anterior circulation[a]
Multiple bilateral or anterior-posterior infarctions[a]
Systemic embolism[a]
Abrupt onset[b]
Rapid improvement[b]
Seizure at onset[b]
Decreased level of consciousness at onset[c]
Deficit on awakening[b]
Fractional arm weakness[b]
Hemineglect[b]
Isolated visual field defect[b]
Isolated Wernicke's aphasia[c]
Isolated hemianopia[c]
Hemorrhagic conversion[c]
Superficial and deep infarction[b]
Isolated cortical infarction[b]
Superficial posterior cerebral artery infarction[b]
Global posterior cerebral artery infarction[b]
Posterior division middle cerebral artery infarction[c]
Anterior division middle cerebral artery infarction[b]
Multiple lesions in the posterior circulation[b]
Corticosubcortical single lesion[c]

[a]Clinical and imaging features with positive likelihood ratio (PLR) greater than 2.
[b]Features were disqualified because of a PLR smaller than 2.
[c]Features were disqualified because data were from studies that did not use the TOAST classification system or did not document a detailed description of the criteria for stroke subtyping.

terial dissection was set to 30 days because the process of healing takes about 4 weeks.[62] In addition, most strokes occur within this period after both AMI and arterial dissection.[63,64] The published evidence regarding the timing of stroke after cardiac surgery, carotid endarterectomy, and angioplasty/stenting show that the majority of strokes occur within the first 24 hours, after which the risk for stroke rapidly decreases to a constant rate in about 9 to 12 days.[65–68] The SSS-TOAST system arbitrarily sets the temporal window for cardiac or vascular procedures to 14 days.

UNDETERMINED CAUSES. Major subtypes for undetermined causes are listed in Table 1. The SSS-TOAST system introduces cryptogenic embolism as a new category in the "undetermined class." Catheter, CT, or MR angiographic evidence of abrupt vessel cutoff in an otherwise normal-appearing artery suggests the embolic diagnosis. If available, complete recanalization of a prior occlusion by angiographic methods or ultrasound supports an embolic cause. It is important to identify other causes of focal arterial thrombosis to avoid misclassification, such as hypercoagulability states and inflammatory, infectious, or other disorders of the vessel wall. The presence of multiple simultaneous bihemispheric or anterior and posterior circulation infarctions supports an embolic cause provided that there is no other cause for multiple infarctions.[16,28,69]

INTEREXAMINER RELIABILITY AND COMPARISON WITH ORIGINAL TRIAL OF ORG 10172 IN ACUTE STROKE TREATMENT. To determine reproducibility of diagnoses per SSS-TOAST system, we calculated the interexaminer reliability rate. Two stroke neurologists independently assessed 50 consecutively admitted patients with acute ischemic stroke. Evaluations were made through reviews of abstracted data from medical records. When additional information was needed, examiners were able to access all clinical and imaging data through the electronic data retrieval system. The examiners first assessed patients according to the original TOAST, then to the SSS-TOAST criteria. All rules specified in both classification systems were strictly applied. The interexaminer reliability was evaluated using the κ statistic.[70] Confidence intervals for κ were calculated using the large-sample normal approximation to the standard errors of the estimates. A κ of 1 indicates perfect agreement, whereas zero shows only chance agreement; in general, excellent agreement refers to values greater than 0.80, whereas 0.61 to 0.80 indicates substantial agreement, and 0.41 to 0.60 indicates moderate agreement. Interexaminer agreement rates for different classifications were compared using a z test.

Results

The study population was composed of 34 male and 16 female patients with a mean age of 64 years (range, 21–89 years). Of the 50 patients, 49 (98%) had CT and CT angiography; 46 (92%) had MRI with or without MR angiography; 43 (86%) had transthoracic or transesophageal echocardiography, or both; and 23 (46%) had vascular Doppler studies. The κ value for interexaminer reliability was 0.78 (95% confidence interval, 0.64–0.92) for the original TOAST using the seven categories listed in Table 4. For the SSS-TOAST, the κ values calculated with or without taking the level of confidence (evident, probable, and possible categories) into account were 0.86 (95% confidence interval, 0.76–0.96) and 0.90 (95% confidence interval, 0.80–1.00), respectively (see Table 4). The interexaminer reliability per the SSS-TOAST was not statistically different from the original TOAST ($p = 0.16$). Disagreement in SSS-TOAST classification occurred in six patients. In two patients, there was disagreement on whether small subtle DWI hyperintensities were true infarcts. In another two patients, disagreement occurred over use of the SSS-TOAST rules by the examiners. Disagreement for the remaining two patients was due to missed laboratory information during the review of the abstracted data.

Discussion

Studies of acute treatment and secondary prevention of stroke consistently indicate break down of data into causative stroke subtypes.[71,72] Causative classification systems regularize decisions on stroke cause using cer-

Table 4. Examiners' Assignments Using the Original Trial of Org 10172 in Acute Stroke Treatment (TOAST) and Stop Stroke Study TOAST (SSS-TOAST) Systems

	Original TOAST		SSS-TOAST	
Patient No.	Examiner I	Examiner II	Examiner I	Examiner II
1	2	2	2 (c)	2 (c)
2	6	6	1 (b)	1 (a)
3	5	5	5	5
4	2	2	2 (c)	2 (c)
5	6	6	4 (a)	4 (a)
6	1	4	1 (a)	4 (a)
7	6	6	7	7
8	2	6	2 (c)	3 (a)
9	5	5	1 (c)	1 (c)
10	5	5	5	5
11	2	2	5	2 (c)
12	5	5	2 (c)	2 (c)
13	5	5	5	5
14	6	6	2 (b)	2 (b)
15	3	3	3 (a)	3 (a)
16	5	4	4 (a)	4 (a)
17	2	2	2 (c)	2 (c)
18	6	6	1 (b)	1 (b)
19	5	5	5	5
20	5	5	5	5
21	5	5	5	5
22	6	6	2 (a)	2 (a)
23	1	1	1 (a)	1 (c)
24	6	6	1 (a)	1 (a)
25	1	6	1 (a)	1 (a)
26	6	2	2 (c)	2 (c)
27	1	1	1 (a)	1 (a)
28	2	2	2 (c)	2 (c)
29	5	6	5	3 (a)
30	6	6	3 (a)	3 (a)
31	2	2	2 (c)	2 (c)
32	2	2	2 (c)	2 (c)
33	6	6	1 (b)	1 (b)
34	3	1	3 (a)	3 (a)
35	2	2	2 (a)	2 (a)
36	5	5	5	5
37	6	2	2 (c)	2 (c)
38	5	5	5	5
39	6	6	6	6
40	3	3	3 (a)	3 (a)
41	6	6	1 (a)	1 (a)
42	6	6	1 (a)	1 (a)
43	1	1	1 (a)	1 (a)
44	6	6	4 (a)	4 (a)
45	2	2	2 (a)	2 (a)
46	6	6	6	6
47	6	6	1 (b)	1 (b)
48	6	6	3 (a)	3 (a)
49	6	6	1 (a)	1 (a)
50	2	2	2 (a)	2 (a)

1 = large artery atherosclerosis; 2 = cardioaortic embolism; 3 = small artery occlusion; 4 = other causes; 5 = undetermined-unknown; 6 = undetermined-unclassified; 7 = undetermined-incomplete evaluation; (a) = evident; (b) = probable; (c) = possible.

tain rules to ensure unity among physicians and comparability among studies. Because of the diversity in stroke causes, it is difficult to formulate a causative stroke classification system that is both simple and free of meticulous regulations. The extent of rules, however, needs to be properly weighted against the algorithm's ease of use and reliability. Each new rule impairs the examiners' compliance to the algorithm. This study describes an evidence-based, causative classification algorithm for acute ischemic stroke. The SSS-TOAST system incorporates new clinical and imaging criteria into the original TOAST system. It uses fairly simple rules (see Table 1) to manage the wealth of published information on stroke mechanism. Our results show that the SSS-TOAST algorithm is straightforward and can be applied with high reliability.

The SSS-TOAST system uses comprehensive brain imaging to a considerable extent. CT and MR angiographic techniques allow evaluation of the major cerebral vessels. DWI offers both temporal and spatial information about infarction.[73] DWI also identifies punctate infarctions that are beyond the sensitivity of CT and conventional MRI techniques.[55] This advantage translates into recognition of certain infarction patterns associated with specific stroke mechanisms.[16,26,28] These patterns are summarized among the probable criteria in Table 1.

One inherent weakness of any classification system is the lack of a gold standard, such as pathological confirmation, to define the exact mechanism of stroke.[9,74,75] Pathological verification of suspected mechanism often is not feasible in stroke because most victims survive their attack. The footprints of a causative factor often disappear or metamorphose until the patient dies. Therefore, causative classification systems rely on associations and rarely provide definite causes. The SSS-TOAST system is based on two arbitrary thresholds to define such associations, "the positive likelihood ratio" (PLR) and "the primary stroke risk ratio." The published data available to define each stroke feature with respect to these thresholds, however, are extremely heterogenous. Although we acknowledge this problem, it is not entirely possible to homogenize the published data. We argue that the use of the published data with respect to defined risk thresholds makes a classification system more flexible. Modifications can be incorporated as new epidemiological data accumulate and diagnostic techniques advance. In this way, the SSS-TOAST is a dynamic algorithm and the method of classification is transparent to the reader, in contrast with the case in which assignment to the most likely category is made based on an individual physician's "best guess."

In the SSS-TOAST system, no primary risk threshold was used to stratify diverse disorders in the category of "other causes" into evident and possible mechanisms. This was largely because the data in the literature regarding the primary stroke risks associated with these disorders were scarce and inconsistent. We believe, as the causative data accumulate, it will be possible to generate a table for "other causes" that is similar to Table 2, in which each disorder is stratified with respect to its primary stroke risk. Such studies may also help to define disease-specific clinical and imaging features with a PLR greater than 2. Nonetheless, the category of other causes accounts for only about 1 to 2% of all strokes,[76] and their coexistence with other potential stroke mechanisms is rare.

The current algorithm identifies one causal mechanism per stroke event and ignores the interaction that might occur between two or more evident mechanisms. Ischemic stroke is often a collective product of multiple abnormalities. Unfortunately, it is currently not possible to regularize interactions among multiple abnormalities. The SSS-TOAST system should be regarded as an algorithm to identify the most likely mechanism with greater contribution to the occurrence of stroke. Clinicians, however, should be alert that treatment decisions in some patients with stroke probably require a more comprehensive approach that is not only specific to the cause, but also takes into account the interaction effects.

In the current era of advanced diagnostic evaluation, it is likely that multiple causes will be identified in patients with ischemic stroke. The SSS-TOAST system classifies such patients into determined causative categories without sacrificing reliability. High reliability, together with greater ability to identify stroke causes, assures utility in future clinical studies. Nonetheless, these results are based on the clinical practice in two academic centers; the algorithm's performance needs to be confirmed in other settings by examiners who did not take part in the development of the SSS-TOAST system for the generalizability of the results. Computerized algorithms, such as the one developed by Goldstein and coworkers,[10] that use clinical and laboratory data as input parameters and determine the causative subtypes using available criteria may also be used to enhance the algorithm's reliability in such settings. As it currently stands, the SSS-TOAST allows investigators to openly define their stroke subtyping method. International consensus on classification criteria is commonly used to improve research in many other neurological and nonneurological illnesses. The SSS-TOAST could provide a framework by which such a consensus effort might eventuate in improved subtyping in stroke research.

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