Published in final edited form as:

J Stroke Cerebrovasc Dis. 2006 ; 15(6): 266–272.

Interobserver Agreement in the TOAST Classification of Stroke Based on Retrospective Medical Record Review

James F. Meschia, MD, Kevin M. Barrett, MD, Felix Chukwudelunzu, MD, W. Mark Brown, MA, L. Douglas Case, PhD, Brett M. Kissela, MD, Robert D. Brown Jr, MD, Thomas G. Brott, MD, Tammy S. Olson, Stephen S. Rich, MD, Scott Silliman, MD, and Bradford B. Worrall, MD, MSc For the Siblings with Ischemic Stroke Study (SWISS) Investigators

*From the Department of Neurology (J.F.M., K.M.B., T.G.B.), Mayo Clinic, Jacksonville, Florida; the Department of Neurology (R.D.B.), Mayo Clinic, Rochester, Minnesota; the Department of Neurology (F.C.), Luther-Middelfort Clinic, Eau Claire, Wisconsin; the Department of Biostatistics (W.M.B., L.D.C., S.S.R.), Wake Forest University School of Medicine, Winston-Salem, North Carolina; the Department of Neurology (B.M.K.), University of Cincinnati, Cincinnati, Ohio; the Mayo Alliance for Clinical Trials (T.S.O.), Rochester, Minnesota; the University of Florida (S.S.), Jacksonville, Florida; and the Department of Neurology (B.B.W.), University of Virginia, Charlottesville, Virginia. A list of the SWISS Investigators is available in Meschia JF, et al. *Ann Neurol.* 2005;58:351-61.*

Abstract

Background— The reliability of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification system of stroke in siblings of stroke-affected probands has not been tested. Similarly, the reliability of using clinical medical records to classify ischemic stroke has not been assessed. The purpose of this study was to establish the interrater reliability of sibling stroke subtyping by applying the TOAST criteria to retrospectively obtained medical records.

Methods— Thirty medical records were randomly sampled from among the records of all siblings previously classified as stroke-affected by the Siblings With Ischemic Stroke Study (SWISS) Stroke Verification Committee (SVC). Blinded medical records for these individuals were sent to 6 physician reviewers who independently classified TOAST stroke subtype on the basis of record review.

Results— Using the κ statistic to assess interrater reliability, the overall reliability (standard error) for assigning a TOAST subtype of stroke was 0.54 (0.03). Pair-wise comparisons between the original SWISS SVC diagnoses and the diagnoses made by other reviewers exhibited moderate reliability (κ range, 0.41–0.56). The κ statistics for common stroke subtypes were large vessel, 0.80 (0.06); cardioembolic, 0.80 (0.06); small vessel, 0.53 (0.06); and unknown cause, 0.40 (0.06).

Address reprint requests to James F. Meschia, MD, Department of Neurology, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224.

Authors' Contributions

JFM led the study design, reviewed medical records, and drafted the manuscript. KMB reviewed medical records. FC reviewed medical records. WMB participated in the statistical analysis and helped draft the manuscript. LDC participated in the study design and statistical analysis and helped draft the manuscript. BMK reviewed medical records. RDB reviewed medical records and helped draft the manuscript. TGB participated in study design, reviewed medical records, and helped draft the manuscript. TSO helped coordinate the flow of medical records and case report forms among investigators. SSR participated in the statistical analysis. SS reviewed medical records. BBW reviewed medical records and helped draft the manuscript.

The Siblings with Ischemic Stroke Study (SWISS) is supported by a grant from the National Institute of Neurological Disorders and Stroke (Grant No. R01 NS39987; J.F.M., Principal Investigator).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conclusion— We conclude that TOAST subtyping had moderate interrater reliability. Large-artery and cardioembolic subtype diagnoses seemed most reliable.

Keywords

affected sibling pair study; cerebral infarction; classification; ischemic stroke; medical record review; reliability

Background

Stroke is a heterogeneous neurologic disorder. To facilitate robust clinical studies in patients with stroke, accurate classification of different stroke syndromes into homogenous subgroups is important (1). Earlier classifications of stroke subtypes predated widespread use of medical technologies such as magnetic resonance imaging (MRI) and transesophageal echocardiography, placing greater reliance on clinical examination findings and pathologic reports. Older systems of classification were often incomplete and difficult to apply in routine clinical settings (2).

The Trial of Org 10172 in Acute Stroke Treatment (TOAST) investigators devised a system of categorization of subtypes of ischemic stroke based on inferred cause (3). Using clinical features and the results of all available ancillary diagnostic studies, the TOAST criteria classify ischemic stroke into 5 subtypes based on cause: cardioembolic stroke, large-artery atherosclerosis, small-artery occlusion (lacunes), stroke of other determined cause, and stroke of undetermined cause. The TOAST classification system has gained wide acceptance for both clinical and research purposes. Epidemiologic studies (4), stroke risk assessment studies (5, 6), and stroke intervention studies (7,8) have all benefited from the TOAST classification system.

Characterization of ischemic stroke subtypes has been variable in genetics research (9). However, the TOAST classification system is gaining greater acceptance in stroke family history studies (10) and molecular genetics research (11,12). There are no data on the reliability of TOAST classification of stroke in siblings of stroke-affected probands. Similarly, there are no data on the reliability of using clinical medical records to classify retrospectively ischemic stroke, despite several studies using this strategy.

The purpose of this study was to determine the interrater reliability of diagnosing the TOAST subtype for the index ischemic stroke in siblings recruited to the Siblings With Ischemic Stroke Study (SWISS) (13). SWISS is an ongoing North American multicenter study of affected sibling pairs. Its primary aim is to discover risk factor loci for ischemic stroke through a genome-wide scan. The reliability of classifying ischemic stroke in siblings was tested because siblings in SWISS undergo diagnostic evaluations for their index symptomatic ischemic stroke in diverse clinical settings.

Methods

In SWISS, siblings were screened for stroke using the Questionnaire for Verifying Stroke-Free Status (QVSS) (14–16). Medical records were searched for siblings who responded positively to at least 1 item. Once medical records were obtained, staff at the Mayo Alliance for Clinical Trials (Rochester, Minnesota) compiled sibling medical records for SWISS in standard fashion. Records were subdivided into the following sections: clinical notes, head imaging reports, cerebrovascular imaging reports, cardiac data, and other reports. The records were assigned a SWISS identification number, and personal identifiers (name, address, telephone numbers, medical record number, birth date, and names of family members and caregivers) were deleted.

The SWISS Stroke Verification Committee (SVC) reviewed all available sibling medical records. The SVC adjudicated whether the sibling had had a stroke. For siblings found to have had a stroke, the SVC adjudicated whether the stroke was a first-ever or recurrent stroke, date of index stroke, and TOAST subtype of index stroke.

Before reviewing the records, SVC stroke subtype adjudicators received a copy of the publication that originally described the TOAST classification system (3). The adjudicators were instructed to read the publication before reviewing any records and to refer to the publication as needed throughout the record review process. Before reviewing the records, all adjudicators had to demonstrate an understanding of the TOAST classification system by classifying stroke subtype using a standardized series of clinical vignettes (Appendix). All adjudicators were physicians with experience in evaluating and treating patients with ischemic stroke.

Six reviewers participated in this interrater reliability study. Four of the 6 reviewers were not members of the SVC. The remaining 2 reviewers (J.F.M., T.G.B.) performed all the reviews for the SVC. For efficiency, a reviewer did not review medical records again for this reliability study if he had already done so as part of his duties on the SVC. For the purposes of this study, the SVC diagnoses were tested as if generated by a single reviewer (reviewer 5 of 6), although for any given set of sibling records a TOAST diagnosis was made by either J.F.M. or T.G.B. Diagnoses made by the SVC member who did not make the original SVC diagnosis (eg, T.G.B. if J.F.M. made the original SVC diagnosis) were treated as if generated by a single reviewer (reviewer 6 of 6). All reviewers were neurologists who had undergone the same TOAST subtype training and certification process used in SWISS. Reviewers assessed the medical records of 30 siblings whom an SVC adjudicator had previously deemed to be stroke-affected. The siblings whose records were reviewed were selected at random by the SWISS Statistical Center (Winston-Salem, North Carolina) from among all stroke-affected siblings, excluding the siblings of probands enrolled at a French-Canadian center and oversampling siblings with cardioembolic strokes to ensure that at least 5 with that diagnosis were included in the sample of 30. All 6 reviewers assessed the medical records independently. Each reviewer was blinded to the diagnoses made by all other reviewers.

The extent of the medical evaluations was assessed by determining the rate at which common diagnostic tests were performed to characterize the cerebral infarct and to identify pertinent comorbid conditions such as atrial fibrillation and carotid atherosclerosis.

Statistical Methods

χ^2 tests were used to assess differences in the distributions of categorical phenotypes between the random sample of sibling used in this study and the cohort of concordant siblings from which the random sample was taken. A 2-sample *t* test for independent samples was used to compare age between the 2 groups.

Interrater reliability was assessed using the kappa (κ) statistic. We used the guidelines proposed by Landis and Koch to interpret the level of agreement: $\kappa > 0.80$, excellent agreement; $\kappa = 0.60$ to 0.80 , substantial agreement; $\kappa = 0.40$ to 0.60 , moderate agreement; and $\kappa < 0.40$, poor to fair agreement (17). The following stroke subtypes were used: 1) large vessel, 2) cardioembolism, 3) small vessel, 4) other determined cause, and 5) undetermined cause. A sixth category—no stroke/missing—was included to account for instances in which reviewers did not provide a diagnosis. Reasons for missing data were not systematically collected. Separate estimates for κ were obtained by treating the no stroke/missing category as missing data using the algorithm written by Chen et al (18). These analyses were repeated on the subset of the participants who self-reported having a stroke.

The Mayo Foundation Institutional Review Board approved this study.

Results

The randomly sampled siblings in this study were screened for participation in SWISS between March 31, 2000, and November 6, 2003. The 30 siblings included were from 30 separate pedigrees. The probands of the siblings were enrolled at centers in 8 different states in the United States. Among the 30 siblings evaluated in this study, head computed tomography (CT) was performed on 80% (24/30) and MRI was performed on 60% (18/30). A cervical arterial imaging study (carotid ultrasonography, magnetic resonance angiography, or digital subtraction angiography) was performed on 97% (29/30). Intracranial arterial study (magnetic resonance angiography, digital subtraction angiography, CT angiography, or transcranial Doppler ultrasonography) was performed on 100% (30/30). Electrocardiography was performed on 73% (22/30). Cardiac ultrasonography (transthoracic or transesophageal) was performed on 67% (20/30).

Subject characteristics for the siblings included in this study are summarized in Table 1. The majority of subjects were male (67%) and white (83%). Ages ranged from 46 to 88 years, with a median of 70 years. Seventy-three percent smoked, 70% had hypertension, 27% had diabetes mellitus, 33% had chronic fibrillation, and 23% had had a myocardial infarction. The distributions of these characteristics did not differ significantly between the 30 siblings who were included in this study and the 101 concordant siblings who were not. The distribution of TOAST subtypes (based on the original SVC determination) for the siblings included in this study was 23% large vessel, 17% cardioembolic, 37% small vessel, 7% other cause, and 17% unknown cause. This distribution differed significantly from that of the unselected siblings because we purposely oversampled the cardioembolic cases. Responses on the QVSS were similar for the 2 groups (Table 2).

The distribution of TOAST subtypes (Table 3) was similar for the large-vessel, cardioembolic, and other cause categories among the 6 reviewers. The distribution for the small-vessel, unknown cause, and no stroke/missing categories varied considerably. One reviewer had 2 missing values, another reviewer had 4 missing values, and a third reviewer had 10 missing values. The remaining reviewers had complete sets of readings.

Excluding the original diagnoses made by the SVC, all 5 reviewers agreed on the diagnosis of stroke subtype in 37% (11/30) of siblings; 4 reviewers agreed on stroke subtype in 30% (9/30) of siblings; 3 or fewer reviewers agreed on the subtype diagnosis in 33% (10/30) of siblings. Reliability of the TOAST subtyping, as quantified by the κ statistic, is summarized in Table 4. The overall κ (standard error) of 0.54 (0.03) represents moderate agreement among the 5 non-SVC reviewers. The overall κ of 0.52 (0.02) for all 6 reviewers was slightly lower. Pair-wise κ statistics were calculated for all reviewers and ranged between 0.44 (0.10) and 0.70 (0.09). These pair-wise results represent moderate to substantial agreement. Agreement was best for the large-vessel and cardioembolic categories (0.80 [0.06] for each). The κ statistics for the small-vessel and unknown cause classifications were 0.53 (0.06) and 0.40 (0.06), respectively. The κ statistic for stroke of other cause did not differ significantly from zero.

Twenty-nine of the 30 siblings self-reported stroke, and results in this subgroup were almost identical to those for the overall group. When the no stroke/missing category was treated as missing data, the overall κ statistic for subtype diagnosis increased marginally to 0.60 (0.03). When the category of other determined cause (used only once by 1 new reviewer) was additionally considered missing, the overall κ increased slightly to 0.61 (0.03).

Discussion

Several approaches can be taken to classify ischemic stroke. Some epidemiologic studies have classified stroke purely on the basis of findings from the physical examination (19). Other epidemiologic studies have used mechanistic or etiologic classification systems that consider results of testing but that have not been validated for retrospective medical record review (20,21). Some clinical trials have used classification systems, including TOAST, that combine clinical features with the results of neuroimaging and ancillary tests to categorize stroke subtype (3). Although the TOAST classification has demonstrated reliability in the acute setting for differentiating small-vessel disease from other causes of stroke (22), accurate subtype classification is best determined after review of cerebrovascular studies performed as part of a thorough stroke evaluation (23).

In our study, the interrater reliability in a randomly selected sample of siblings of SWISS subjects was moderate. The overall agreement achieved in our study ($\kappa=0.54$) was identical to the interphysician agreement reported in a prior reliability study of TOAST classification (24). Use of a computerized algorithm has been reported to improve the reliability of TOAST subtype classification (25), but this finding has not been reproduced on a large scale. Our results on TOAST reliability were comparable to those seen with prospective medical record review of first-ever stroke in a Bavarian community-based register (4). The agreement for the cardioembolic and large-artery subtypes was very good to excellent in our study, with a κ of 0.80 for each category. Other reliability studies of the TOAST classification system have demonstrated similarly high degrees of interphysician agreement for these subtypes (24).

Observed differences in stroke subtype classification were likely influenced by several factors. Variability between centers in the use of CT or MRI modalities may have contributed to uncertainty in diagnosing stroke. Suboptimal or incomplete documentation of neurologic deficits may have reduced the likelihood of diagnosing small-vessel occlusion, which relies on the presence of a lacunar syndrome such as pure motor hemiparesis or pure sensory stroke. Also, the variable use of less common ancillary testing such as screening for an inherited or acquired hypercoagulable state may have influenced the likelihood of diagnosing stroke of other determined cause.

Our data show that the TOAST system can be used with modest reliability even when applied retrospectively to medical records from study participants who received their care for stroke in diverse clinical settings. Subtyping stroke is one way of reducing the heterogeneity of the ischemic stroke phenotype. It is important to be able to reliably diagnose endophenotypes because some genes may impart differential risk across these endophenotypes.

Our study has implications regarding classification of ischemic stroke that go beyond the use of the TOAST system in multicenter pedigree-based research. The TOAST system has been applied retrospectively in several studies of highly diverse patient populations, including cardiac transplant patients (26), pediatric patients (27), and cancer patients (28). Clinical practice variability in evaluating ischemic stroke leads inevitably to variability in the clinical data available for classifying stroke retrospectively in the research setting (29). Our study shows the limitations of classifying ischemic stroke using review of medical records generated in diverse clinical settings across North America.

Acknowledgements

Editing, proofreading, and reference verification were provided by the Section of Scientific Publications, Mayo Clinic.

The authors declare that they have no competing interests.

References

1. Funalot B, Varenne O, Mas JL. A call for accurate phenotype definition in the study of complex disorders [letter]. *Nat Genet* 2004;36:3. [PubMed: 14702027]
2. Brown RD, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Stroke incidence, prevalence, and survival: secular trends in Rochester, Minnesota, through 1989. *Stroke* 1996;27:373–80. [PubMed: 8610298]
3. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke: definitions for use in a multicenter clinical trial: TOAST: Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993;24:35–41. [PubMed: 7678184]
4. Kolominsky-Rabas PL, Weber M, Gefeller O, Neundoerfer B, Heuschmann PU. Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. *Stroke* 2001;32:2735–40. [PubMed: 11739965]
5. Heuschmann PU, Neureiter D, Gesslein M, Craiovan B, Maass M, Faller G, et al. Association between infection with *Helicobacter pylori* and *Chlamydia pneumoniae* and risk of ischemic stroke subtypes: results from a population-based case-control study. *Stroke* 2001;32:2253–8. [PubMed: 11588309]
6. Parnetti L, Caso V, Santucci A, Corea F, Lanari A, Floridi A, et al. Mild hyperhomocysteinemia is a risk-factor in all etiological subtypes of stroke. *Neurol Sci* 2004;25:13–7. [PubMed: 15060810]
7. Marti-Fabregas J, Gomis M, Arboix A, Aleu A, Pagonabarraga J, Belvis R, et al. Favorable outcome of ischemic stroke in patients pretreated with statins. *Stroke* 2004 May;35:1117–21. [PubMed: 15073403]Epub 2004 Apr 8.
8. Urbach H, Hartmann A, Pohl C, Omran H, Wilhelm K, Flacke S, et al. Local intra-arterial thrombolysis in the carotid territory: does recanalization depend on the thromboembolus type? *Neuroradiology* 2002 Aug;44:695–9. [PubMed: 12185548]Epub 2002 Jun 29.
9. Meschia JF. Addressing the heterogeneity of the ischemic stroke phenotype in human genetics research. *Stroke* 2002;33:2770–4. [PubMed: 12468768]
10. Schulz UG, Flossmann E, Rothwell PM. Heritability of ischemic stroke in relation to age, vascular risk factors, and subtypes of incident stroke in population-based studies. *Stroke* 2004 Apr;35:819–24. [PubMed: 15001788]Epub 2004 Mar 4.
11. Gretarsdottir S, Thorleifsson G, Reynisdottir ST, Manolescu A, Jonsdottir S, Jonsdottir T, et al. The gene encoding phosphodiesterase 4D confers risk of ischemic stroke. *Nat Genet* 2003 Oct;35:131–8. [PubMed: 14517540]Epub 2003 Sep 21. Erratum in: *Nat Genet*. 2005 May;37:555.
12. Meschia JF, Brott TG, Brown RD Jr, Crook R, Worrall BB, Kissela B, et al. SWISS Study Group; ISGS Study Group; MSGD Study Group. Phosphodiesterase 4D and 5-lipoxygenase activating protein in ischemic stroke. *Ann Neurol* 2005;58:351–61. [PubMed: 16130105]
13. Meschia JF, Brown RD Jr, Brott TG, Chukwudelunzu FE, Hardy J, Rich SS. The Siblings With Ischemic Stroke Study (SWISS) protocol. *BMC Med Genet* 2002;3:1. [PubMed: 11882254]Epub 2002 Feb 12.
14. Meschia JF, Lojacono MA, Miller MJ, Brott TG, Atkinson EJ, O'Brien PC. Reliability of the questionnaire for verifying stroke-free status. *Cerebrovasc Dis* 2004;17:218–23. [PubMed: 14707425]Epub 2003 Dec 29.
15. Meschia JF, Brott TG, Chukwudelunzu FE, Hardy J, Brown RD Jr, Meissner I, et al. Verifying the stroke-free phenotype by structured telephone interview. *Stroke* 2000;31:1076–80. [PubMed: 10797168]
16. Jones WJ, Williams LS, Meschia JF. Validating the Questionnaire for Verifying Stroke-Free Status (QVSFS) by neurological history and examination. *Stroke* 2001;32:2232–6. [PubMed: 11588306]
17. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33:159–74. [PubMed: 843571]
18. Chen, B.; Zaebs, D.; Seel, L. SUGI 30 Proceedings. Philadelphia, PA: 2005 Apr 10–13. A macro to calculate kappa statistics for categorizations by multiple raters. [cited 2005 Nov 29]. Available from: <http://www2.sas.com/proceedings/sugi30/155–30.pdf>
19. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet* 1991;337:1521–6. [PubMed: 1675378]

20. Petty GW, Brown RD Jr, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes: a population-based study of incidence and risk factors. *Stroke* 1999;30:2513–6. [PubMed: 10582970]
21. Woo D, Gebel J, Miller R, Kothari R, Brott T, Khoury J, et al. Incidence rates of first-ever ischemic stroke subtypes among blacks: a population-based study. *Stroke* 1999;30:2517–22. [PubMed: 10582971]
22. Fure B, Wyller TB, Thommessen B. TOAST criteria applied in acute ischemic stroke. *Acta Neurol Scand* 2005;112:254–8. [PubMed: 16146496]
23. Madden KP, Karanjia PN, Adams HP Jr, Clarke WR. Accuracy of initial stroke subtypes diagnosis in the TOAST study: Trial of ORG 10172 in Acute Stroke Treatment. *Neurology* 1995;45:1975–9. [PubMed: 7501144]
24. Gordon DL, Bendixen BH, Adams HP Jr, Clarke W, Kappelle LJ, Woolson RF, the TOAST Investigators. Interphysician agreement in the diagnosis of subtypes of acute ischemic stroke: implications for clinical trials. *Neurology* 1993;43:1021–7. [PubMed: 8492920]
25. Goldstein LB, Jones MR, Matchar DB, Edwards LJ, Hoff J, Chilukuri V, et al. Improving the reliability of stroke subgroup classification using the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria. *Stroke* 2001;32:1091–8. [PubMed: 11340215]
26. Belvis R, Marti-Fabregas J, Cocho D, Garcia-Bargo MD, Franquet E, Agudo R, et al. Cerebrovascular disease as a complication of cardiac transplantation. *Cerebrovasc Dis* 2005;19:267–71. [PubMed: 15731558]Epub 2005 Feb 22.
27. Wraige E, Hajat C, Jan W, Phol KR, Wolfe CD, Ganesan V. Ischaemic stroke subtypes in children and adults. *Dev Med Child Neurol* 2003;45:229–32. [PubMed: 12647923]
28. Cestari DM, Weine DM, Panageas KS, Segal AZ, DeAngelis LM. Stroke in patients with cancer: incidence and etiology. *Neurology* 2004;62:2025–30. [PubMed: 15184609]
29. Paradowski B, Maciejak A. TOAST classification of subtypes of ischaemic stroke: diagnostic and therapeutic procedures in stroke: a four-year observation. *Cerebrovasc Dis* 2005;20:319–24. [PubMed: 16131800]Epub 2005 Aug 30.

Abbreviations

CT	computed tomographic, computed tomography
MRI	magnetic resonance imaging
QVSS	questionnaire for verifying stroke-free status
SVC	Stroke Verification Committee
SWISS	Siblings With Ischemic Stroke Study
TOAST	Trial of Org 10172 in Acute Stroke Treatment

Appendix. TOAST Certification

Case 1

A 71-year-old man presented to the hospital with a 15-hour history of sudden loss of feeling over the right side of his face and his right arm and right leg. He did not have any warning symptoms. He had a 10-year history of hypertension and a 5-year history of diabetes mellitus.

His examination was notable for loss of response to pinprick, light touch, and temperature sensation in the right half of his face and in his right arm and right leg. Auscultation of the heart was normal, and radial pulses were regular. Electrocardiography showed normal sinus rhythm. Head computed tomography showed a possible hypointensity in the left thalamus.

Case 2

A 34-year-old woman was at work when she suddenly lost vision in her left eye. The vision recovered within 15 minutes. Before her vision recovered completely, she began speaking “gibberish” to coworkers and was dropping things with her right hand. She was immediately taken to a local emergency department. She smoked cigarettes and used oral contraceptives. She had no history of hypertension, diabetes, deep vein thrombosis, or spontaneous miscarriages. Her symptoms partially resolved by the time she was examined, but she had right hand clumsiness and a right pronator drift. Computed tomography done within 3 hours of onset of symptoms, chest radiography, electrocardiography, and routine laboratory studies all yielded normal findings. The following day, the patient complained of left lateral neck and left retro-orbital pain. Conventional cerebral angiography showed a long tapering stenosis just distal to the carotid bulb, extending to the skull base. There was a pseudoaneurysm of the left internal carotid artery.

Case 3

A 65-year-old man presented with a history of sudden, painless loss of half of his vision. Examination revealed a left homonymous hemianopsia. Head magnetic resonance imaging showed a right posterior cerebral artery territory ischemic stroke measuring 3.5 cm in greatest diameter. Electrocardiography revealed new-onset atrial fibrillation.

Case 4

A 58-year-old woman with a history of lupus and recurrent deep vein thrombosis presented with right-sided weakness. Examination showed moderate weakness involving her right arm and right leg, and the paretic limbs were numb. Mild deficits in constructional praxis and delayed recall were also observed. Magnetic resonance imaging revealed nonenhancing white matter signal abnormalities in the hemispheres bilaterally. One lesion involved the posterior limb of the internal capsule and thalamus on the left. Transesophageal echocardiography was unremarkable. Complete blood cell count showed mild microcytic anemia. A lupus anticoagulant was detected.

Case 5

A 69-year-old man presented with ataxic gait, posterior headache, and nausea. Examination showed dysmetria in his right leg and right arm. Head computed tomography showed a distal posterior inferior cerebellar artery infarct involving the cerebellum but sparing the brain stem. He had had an anterior wall myocardial infarction 2 months earlier. Transthoracic echocardiography demonstrated a left ventricular thrombus.

Case 6

A 73-year-old woman with a history of hypertension and coronary artery disease developed sudden loss of vision in the left eye which lasted 4 minutes. She did not seek medical attention at the time. Two weeks later, she was doing a crossword puzzle when suddenly she was not able to read the clues. She tried to call a friend for help, but her speech is garbled. The friend came over to check on her, and her speech is back to normal. The patient was taken to the

emergency department, and in transit, her right arm went limp and she again lost the ability to express herself verbally. In the emergency department, she was found to have a right facial droop and a limp right arm, and she was nearly mute. Head computed tomography showed early ischemic changes in the middle cerebral artery distribution. Carotid Doppler study showed 80% to 95% stenosis of the left internal carotid artery.

Table 1

Demographic and Stroke Statistics for the Random Sample of Concordant Siblings Used in This Reliability Study and the Cohort of Unselected Concordant Siblings From Which This Sample Was Taken*

Characteristics	Random sample	Unselected siblings	P value
Total	30 (100)	101 (100)	
Age, y			.84
Mean±SD	69.5±11.5	68.9±10.9	
Median (range)	70 (46–88)	71 (44–93)	
Sex			.20
Male	20 (67)	54 (54)	
Female	10 (33)	47 (47)	
Ethnicity			.06
White	25 (83)	95 (94)	
Other	5 (17)	6 (6)	
Stroke risks [†]			
Diabetes mellitus	8 (27)	32/99 (32)	.56
Hypertension	21 (70)	72/100 (72)	.83
Atrial fibrillation			
Chronic	10 (33)	19/99 (19)	.10
Intermittent	0 (0)	6/99 (6)	.33 [‡]
Myocardial infarction	7 (23)	25/100 (25)	.85
Smoker	22 (73)	65/98 (66)	.47
Stroke subtype			.02 [‡]
Large vessel	7 (23)	24 (24)	.96
Cardioembolic	5 (17)	3 (3)	.02 [‡]
Small vessel	11 (37)	40 (39)	.77
Other cause	2 (7)	1 (1)	.13 [‡]
Unknown cause	5 (17)	34 (33)	.09

* Values are number (percentage) unless indicated otherwise.

[†] Missing data for some risk factors.

[‡] Fisher exact calculations were used because of low cell counts.

Responses to the Questionnaire Verifying Stroke-Free Status Stratified by Questionnaire Item for a 30-Patient Random Sample and Concordant Siblings*

Table 2

Question	Random sample	Unselected siblings	P value
1. Were you ever told by a physician that you had a stroke?	28/29 (97)	89/97 (92)	.68 [†]
2. Were you ever told by a physician that you had a ministroke or transient ischemic attack (TIA)?	12/29 (41)	49/95 (52)	.34
3. Have you ever had sudden painless weakness on 1 side of your body?	16/29 (55)	62/95 (65)	.32
4. Have you ever suddenly had numbness or a dead feeling on 1 side of your body?	15/29 (52)	60/95 (63)	.27
5. Have you ever had sudden painless loss of vision in 1 or both eyes?	10/29 (34)	28/95 (30)	.61
6. Have you ever suddenly lost half of your vision?	2/29 (7)	14/95 (15)	.36 [†]
7. Have you ever suddenly lost the ability to understand what people are saying?	8/29 (28)	34/95 (36)	.41
8. Have you ever suddenly lost the ability to express yourself verbally or in writing?	14/29 (48)	55/95 (58)	.36

* Values are number of affirmative responses/number of completed questionnaires (percentage). The random sample included 30 subjects and the number of unselected siblings was 101.

[†] Fisher exact calculations were used because of low cell counts.

Table 3

Distribution of TOAST Subtypes Among the 6 Reviewers*

Reviewer	TOAST Subtype				
	Large vessel	Cardioembolic	Small vessel	Other cause	Unknown cause
A	5 (17)	4 (13)	8 (27)	0 (0)	9 (30)
B	7 (23)	5 (17)	5 (17)	0 (0)	13 (43)
C	6 (20)	6 (20)	3 (10)	1 (3)	12 (40)
D	5 (17)	7 (23)	10 (33)	0 (0)	8 (27)
E	4 (13)	5 (17)	5 (17)	0 (0)	6 (20)
SVC	7 (23)	5 (17)	11 (37)	2 (7)	5 (17)
					4 (13)
					0 (0)
					2 (7)
					0 (0)
					10 (33)
					0 (0)

SVC, Stroke Verification Committee; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

* Values are number (percentage), calculated for 30 study subjects.

Table 4
Pair-Wise and Category κ Statistics (Standard Error) for SWISS TOAST Data

Reviewer	Pair-wise comparison between reviewers and SVC adjudicator					
	A	B	C	D	E	SVC
A		0.52 (0.11)	0.49 (0.11)	0.70 (0.09)	0.50 (0.11)	0.49 (0.10)
B			0.59 (0.11)	0.65 (0.11)	0.44 (0.10)	0.49 (0.11)
C				0.57 (0.10)	0.51 (0.10)	0.47 (0.10)
D					0.48 (0.10)	0.56 (0.11)
E						0.41 (0.10)

SE, standard error; SVC, Stroke Verification Committee; SWISS, Siblings With Ischemic Stroke Study; TOAST, Trial of Org 10172 in Acute Stroke Treatment.