Agreement between TOAST and CCS ischemic stroke classification

The NINDS SiGN Study

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ABSTRACT

Objective: The objective of this study was to assess the level of agreement between stroke subtype classifications made using the Trial of Org 10172 Acute Stroke Treatment (TOAST) and Causative Classification of Stroke (CCS) systems.

Methods: Study subjects included 13,596 adult men and women accrued from 20 US and European genetic research centers participating in the National Institute of Neurological Disorders and Stroke (NINDS) Stroke Genetics Network (SiGN). All cases had independently classified TOAST and CCS stroke subtypes. Kappa statistics were calculated for the 5 major ischemic stroke subtypes common to both systems.

Results: The overall agreement between TOAST and CCS was moderate (agreement rate, 70%; $\kappa = 0.59$, 95% confidence interval [CI] 0.58–0.60). Agreement varied widely across study sites, ranging from 28% to 90%. Agreement on specific subtypes was highest for large-artery atherosclerosis ($\kappa = 0.71$, 95% CI 0.69–0.73) and lowest for small-artery occlusion ($\kappa = 0.56$, 95% CI 0.54–0.58).

Conclusion: Agreement between TOAST and CCS diagnoses was moderate. Caution is warranted when comparing or combining results based on the 2 systems. Replication of study results, for example, genome-wide association studies, should utilize phenotypes determined by the same classification system, ideally applied in the same manner. *Neurology*® 2014;83:1653–1660

GLOSSARY

CI = confidence interval; **CCS** = Causative Classification of Stroke; **NINDS** = National Institute of Neurological Disorders and Stroke; **SiGN** = Stroke Genetics Network; **TOAST** = Trial of Org 10172 Acute Stroke Treatment.

Trial of Org 10172 in Acute Stroke Treatment (TOAST)[1] and the Causative Classification of Stroke (CCS)[2–4] are 2 well-established systems for classifying ischemic stroke. They use broadly similar categories of stroke diagnoses, e.g., large-vessel, small-vessel, and cardioembolic stroke, but may not necessarily be interchangeable. TOAST and CCS require different data and use different classification criteria and decision-making rules. It is therefore critical to understand the agreement rate between these 2 systems in diverse clinical and research settings. Delineation of the level of agreement between TOAST and CCS would be important to assess the validity of combining ischemic stroke subtyping using these 2 systems.

This report investigates the agreement between TOAST and CCS within the Stroke Genetics Network (SiGN), a collaborative study involving a network of international genetic research centers. This analysis is a retrospective pooled analysis of several independent research efforts, each of which enrolled patients under different research protocols.[5] TOAST and CCS were compared by assessing identical subtype assignment and accounting for agreement by chance by using a κ statistic. Because there is no gold standard in etiologic stroke classification, we make no qualitative judgments regarding which system is "better" at subtype assignment, rather report agreement to help inform whether the 2 systems make similar assignments.

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NINDS SiGN Study coinvestigators are listed on the *Neurology*® Web site at www.neurology.org.

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METHODS The Stroke Genetics Network (SiGN) is a multinational collaboration with the goal of finding genetic determinants of stroke.[5] The SiGN Study standardized the phenotyping of the cases across all genetic research centers. The CCS system was chosen to facilitate study administration because of the Web-based, semiautomated, and evidence- and rule-based nature of the system (https://ccs.mgh.harvard.edu).[2] In addition to classifying stroke cases by subtype, the CCS system also has the practical benefit for large consortia of standardizing and centralizing all individual data points that underlie subtype classification.[2] A centralized committee of 4 expert neurologists met weekly to monitor subtype data quality and site performance. This panel aimed to ensure consistency of CCS assignments across all SiGN centers but did not contribute to subtype classifications directly.

CCS subtyping of stroke cases for this report was performed based on reviews of data available in study-specific case report forms and medical records by 41 adjudicators from 10 European and 10 US sites. Adjudicators included neurology residents (n = 10), neurologists (n = 17), stroke fellows (n = 12), one nurse, and one student. Adjudicators completed an interactive online training module and a certification module available at the CCS Web site (https://ccs.mgh.harvard.edu). Data adjudication began in June 2011 and was still ongoing at the time of data analysis for this report. This study included 13,596 cases adjudicated as of July 7, 2013. A centralized committee of 4 expert neurologists met weekly to monitor data quality and site performance. Feedback was provided during subtyping to ensure quality of data.

TOAST subtypes were determined locally by site investigators following individual study protocols without benefit of central oversight. Of note, TOAST subtypes were determined using the same data sources that were available for the CCS classifications. TOAST and CCS classifications were done by different physicians and at different time points in the majority of study sites but using the same study or site-specific case report forms. CCS adjudicators were required to confirm that they were fully blind to TOAST results before they began to enter patient data into CCS.

Two deviations from the above-mentioned protocol warrant acknowledgment. One center (STGEORGE) had completed case phenotyping using the CCS system before the initiation of the SiGN Study. Therefore, this center did not conduct CCS subtyping under the oversight of the expert panel. One other study (BASICMAR) utilized a computer algorithm rather than a certified adjudicator to extract data from a study data source to populate the required fields in CCS for 389 cases of their total of 1,088 cases.

For the purposes of this report, a complete investigation was defined as having head imaging (CT, MRI, or both), vascular imaging of both the intracranial and extracranial vasculature, and a cardiac evaluation consisting of echocardiography (either transthoracic or transesophageal) unless cardiac source of embolism was identified by medical history, physical examination, or ECG. Cranial imaging (either CT or MRI) was required for inclusion in the SiGN case set.

Statistical analysis was performed using SAS 9.2 (SAS Institute, Cary, NC). Percent of absolute agreement in subtype assignments is reported. Agreement was also estimated by κ statistics, and 95% confidence intervals (CIs) are provided for interpretation. Nonweighted κ values were calculated for 5 major stroke subtypes common to both systems: large-artery atherosclerosis, cardioaortic embolism, small-artery occlusion, other causes, and undetermined causes (i.e., cryptogenic causes, unclassifiable cases because of multiple competing etiologies, and incomplete evaluation).

RESULTS In total, 16,267 cases were enrolled in SiGN via the Web-based CCS system as of July 7, 2013. Of those, 13,596 stroke cases had subtypes classified using the TOAST system by the individual studies. Sample characteristics varied considerably by study design among the participating sites (table 1). For example, GEOS (Genetics of Early Onset Stroke)[6] targeted recruitment among young stroke patients. WHI, the Women's Health Initiative, recruited women only and reported low levels of current smoking. The diversity of study designs and populations allows for evaluation of the agreement between TOAST and CCS across a variety of clinical and research settings.

The overall agreement between CCS and TOAST was moderate (table 2) (κ = 0.59, 95% CI 0.58–0.60), although the agreement varied across study sites (χ^2 [df = 19] = 782; $p < 0.0001$) (table 2). Agreement on specific subtypes was highest for large-artery atherosclerosis (κ = 0.71) and lowest for small-artery occlusions (κ = 0.56). Table 3 provides the cross-tabulation for subtype agreement. The 2 systems identified approximately equal number of cases as undetermined (CCS 4,673 cases and TOAST 4,664 cases), but did not show much agreement on which those undetermined cases were (table 3). The agreement of TOAST and CCS for undetermined cases was only κ = 0.44 (95% CI 0.43–0.46). Agreement between TOAST and CCS regarding undetermined cases was primarily based on cases CCS determined to be "incomplete evaluations" (κ = 0.30). Cases classified by CCS as either "cryptogenic embolism" or "unclassified" had no agreement with the TOAST category of "undetermined" ($\kappa < 0.05$).

Stroke subtype agreement varied substantially across genetic research centers (see table 2). Part of this variability across study sites could be attributable to the variable process used to implement TOAST subtyping across sites. Additional variability could be attributable to the presence or absence of certain diagnostic evaluations available to each center (table 4). Agreement was slightly higher in the presence of vessel imaging, but slightly lower when a cardiac evaluation was performed. Agreement between TOAST and CCS was slightly lower when a complete evaluation was conducted (defined as the presence of brain imaging, cardiac evaluation, vascular imaging of the intra- and extracranial circulations). Regardless, the slight variation in agreement in the presence or absence of certain diagnostic evaluations (table 4) is not sufficient to account for the large variation seen across genetic research centers (table 2). The overall agreement reported here (κ = 0.59) belies the fact that in any particular center agreement ranged from excellent (STGEORGE κ = 0.85) to poor (BRAINS κ = 0.12).

Table 1 Descriptive characteristics of the cases in the SiGN Study with both CCS and TOAST classifications, by genetic research center

Study	No.	Age, y (SD)	% Female	% Vascular imaging	% Cardiac evaluation	% Head CT	% Brain MRI	% Complete investigation[a]
SiGN	13,596	66.6 (15.2)	48.1	65.1	79.2	92.5	57.0	54.8
BASICMAR	1,088	74.8 (11.7)	47.2	96.3	67.6	99.5	41.8	64.2
BRAINS	346	70.3 (13.8)	46.5	23.4	42.5	93.4	35.8	12.7
EDIN	620	71.0 (11.8)	45.5	1.3	46.3	79.0	25.5	0.7
GASROS	613	64.7 (14.9)	36.4	98.7	92.7	86.3	83.2	91.8
GCNKSS	642	67.3 (14.3)	50.2	54.8	84.6	93.3	58.3	47.8
GEOS	891	41.3 (6.9)	41.3	81.8	91.5	90.6	85.3	76.1
GRAZ	512	67.9 (14.3)	39.3	93.0	77.0	97.5	58.6	70.7
ISGS	675	63.6 (14.9)	43.1	91.4	80.4	91.0	84.3	73.9
KRAKOW	1,486	68.7 (14.0)	48.2	20.7	85.5	99.0	19.7	19.1
LEUVEN	524	67.6 (14.6)	41.8	91.0	96.9	92.4	84.9	88.4
MCISS	876	69.6 (14.7)	49.4	90.3	94.4	92.9	82.0	86.2
MIAMISR	314	62.6 (14.4)	35.0	97.8	99.4	99.0	85.7	97.1
MUNICH	524	66.7 (14.4)	40.8	99.8	92.4	86.8	82.3	92.4
NOMAS	438	69.3 (12.7)	54.3	77.9	95.9	98.2	48.2	77.4
OXVASC 2002-2008	554	74.2 (12.6)	50.9	23.6	56.7	93.5	24.4	15.0
REGARDS	489	71.7 (8.5)	46.8	52.4	74.8	90.6	65.4	43.6
SAHLSIS	1,083	55.6 (11.0)	35.5	50.5	79.0	98.7	58.1	41.1
STGEORGE	678	75.2 (12.9)	47.2	98.5	71.1	—	—	70.4
SWISS	407	62.9 (12.8)	46.7	67.1	70.0	64.6	47.7	51.4
WHI	836	74.0 (6.7)	100.0	36.8	73.2	89.2	55.5	28.6

Abbreviations: BASICMAR = BASe de datos de ICtus del hospital del MAR (Spain); BRAINS = Bio-Repository of DNA in Stroke (England); CCS = Causative Classification of Stroke; EDIN = Edinburgh stroke study (Scotland); GASROS = Genes Affecting Stroke Risk and Outcome Study (Boston); GCNKSS = Greater Cincinnati Northern Kentucky Stroke Study (Cincinnati); GEOS = Genetics of Early-Onset Stroke (Baltimore); GRAZ = Graz Stroke Study (Austria); ISGS = Ischemic Stroke Genetics Study (Jacksonville); KRAKOW = Krakow stroke study (Poland); LEUVEN = Leuven stroke study (Belgium); MCISS = Middlesex County Ischemic Stroke Study (New Jersey); MIAMISR = Miami Stroke Registry (Miami); MUNICH = Munich stroke study (Germany); NOMAS = Northern Manhattan Aging Study (New York); OXVASC = Oxford Vascular Study (England); REGARDS = Reasons for Geographic And Racial Differences in Stroke (Birmingham); SAHLSIS = Sahlgrenska Academy Study on Ischemic Stroke (Sweden); SiGN = Stroke Genetics Network; STGEORGE = St. George's Stroke Study (England); SWISS = Siblings With Ischemic Stroke Study (Jacksonville); TOAST = Trial of Org 10172 Acute Stroke Treatment; WHI = Women's Health Initiative (Boston).

[a] Complete investigation = head imaging (either CT or MRI or both), vascular imaging (requires both intracranial and extracranial arterial imaging), and cardiac evaluation (echocardiography performed unless cardiac source of embolism identified on physical examination and ECG).

A sensitivity analysis was performed removing the 2 centers that deviated from the network protocol. Removing the STGEORGE and relevant BASICMAR cases resulted in lower overall agreement ($\kappa = 0.57$).

DISCUSSION To accelerate advances in stroke treatment, prevention, and discovery of genetic and other novel risk factors, the heterogeneity of ischemic stroke must be addressed. Identifying the genetic determinants of many complex diseases has proven challenging[7]; stroke is no exception. Success is more likely to occur in large studies and active consortia of individual studies.[8] Standardization and harmonization of phenotypes will reduce misclassification error when combining analysis efforts in consortia. In the study of stroke, this often means the standardization of subtyping among cases.

Previously reported levels of agreement between the TOAST and CCS classification systems were high.[9,10] In a prospective cohort study of North Dublin, a single physician performed data abstraction and classification in both TOAST and CCS in 381 patients with first-ever ischemic stroke. An overall agreement was not reported, but agreement between the 2 systems on specific subtypes ranged from excellent ($\kappa = 0.95$ for cardioembolism) to moderate ($\kappa = 0.69$ for other and undetermined causes). Another study of 690 ischemic stroke patients from a single center (also included in this report, STGEORGE) reported excellent overall agreement ($\kappa = 0.85$). We report a lower overall agreement between the 2 systems, with some centers witnessing much less agreement between TOAST and CCS. This could be attributable to differences among the studies in their ability to take into account the whole spectrum

Table 2 Agreement statistics, κ (95% confidence interval), between CCS and TOAST for the SiGN Study

Study	No.	% Agreed	Overall κ	CE κ	LAA κ	SAO κ	Other κ	Undetermined κ
SiGN	13,596	0.70	0.59 (0.58-0.60)	0.68 (0.67-0.70)	0.71 (0.69-0.73)	0.56 (0.54-0.58)	0.64 (0.61-0.67)	0.44 (0.43-0.46)
BASICMAR	1,088	0.87	0.81 (0.78-0.84)	0.85 (0.82-0.88)	0.82 (0.78-0.87)	0.89 (0.86-0.92)	—	—
BRAINS	346	0.28	0.12 (0.07-0.17)	0.30 (0.19-0.42)	0.14 (0.05-0.24)	0.09 (0.02-0.17)	—	0.03 (−0.06 to 0.11)
EDIN	620	0.69	0.47 (0.41-0.53)	0.64 (0.55-0.72)	0.76 (0.67-0.84)	0.31 (0.21-0.40)	—	0.36 (0.29-0.43)
GASROS	613	0.69	0.59 (0.54-0.64)	0.62 (0.55-0.68)	0.69 (0.62-0.76)	0.57 (0.46-0.67)	0.67 (0.58-0.77)	0.42 (0.33-0.51)
GCNKSS	642	0.78	0.69 (0.65-0.74)	0.78 (0.72-0.84)	0.81 (0.74-0.87)	0.65 (0.58-0.73)	0.70 (0.45-0.95)	0.59 (0.52-0.65)
GEOS	891	0.66	0.53 (0.49-0.58)	0.61 (0.55-0.68)	0.70 (0.62-0.78)	0.69 (0.63-0.76)	0.42 (0.34-0.51)	0.39 (0.33-0.44)
GRAZ	512	0.78	0.70 (0.66-0.75)	0.74 (0.68-0.80)	0.87 (0.81-0.92)	0.64 (0.54-0.74)	0.84 (0.72-0.96)	0.54 (0.45-0.62)
ISGS	675	0.63	0.51 (0.46-0.56)	0.55 (0.48-0.62)	0.64 (0.57-0.71)	0.40 (0.31-0.50)	0.78 (0.67-0.90)	0.36 (0.29-0.43)
KRAKOW	1,486	0.75	0.62 (0.59-0.65)	0.67 (0.63-0.71)	0.83 (0.79-0.87)	0.22 (0.12-0.32)	0.83 (0.73-0.92)	0.52 (0.47-0.56)
LEUVEN	524	0.67	0.54 (0.49-0.60)	0.62 (0.55-0.68)	0.67 (0.58-0.75)	0.49 (0.36-0.62)	0.79 (0.67-0.91)	0.33 (0.25-0.42)
MCISS	876	0.61	0.50 (0.46-0.54)	0.56 (0.50-0.62)	0.57 (0.51-0.63)	0.74 (0.67-0.81)	0.60 (0.49-0.71)	0.22 (0.16-0.28)
MIAMISR	314	0.68	0.58 (0.52-0.65)	0.66 (0.57-0.74)	0.63 (0.53-0.73)	0.68 (0.58-0.79)	0.48 (0.31-0.65)	0.34 (0.20-0.48)
MUNICH	524	0.63	0.51 (0.45-0.56)	0.65 (0.58-0.72)	0.53 (0.45-0.62)	0.42 (0.27-0.57)	0.67 (0.55-0.79)	0.30 (0.22-0.39)
NOMAS	438	0.65	0.54 (0.48-0.60)	0.55 (0.47-0.64)	0.76 (0.67-0.84)	0.65 (0.56-0.73)	0.36 (0.00-0.72)	0.31 (0.22-0.40)
OXVASC 2002-2008	554	0.76	0.66 (0.61-0.71)	0.83 (0.78-0.88)	0.88 (0.81-0.95)	0.39 (0.30-0.49)	1.00 (1.00-1.00)	0.57 (0.50-0.63)
REGARDS	489	0.62	0.47 (0.41-0.53)	0.47 (0.37-0.56)	0.65 (0.56-0.75)	0.45 (0.34-0.56)	0.56 (0.41-0.72)	0.37 (0.28-0.45)
SAHLSIS	1,083	0.68	0.56 (0.52-0.60)	0.70 (0.65-0.76)	0.73 (0.66-0.79)	0.31 (0.23-0.38)	0.84 (0.79-0.89)	0.41 (0.35-0.46)
STGEORGE	678	0.90	0.85 (0.82-0.89)	0.91 (0.87-0.94)	0.89 (0.85-0.94)	0.85 (0.79-0.90)	—	0.78 (0.72-0.83)
SWISS	407	0.54	0.38 (0.32-0.44)	0.45 (0.33-0.56)	0.65 (0.56-0.74)	0.13 (0.06-0.20)	0.53 (0.34-0.72)	0.27 (0.18-0.36)
WHI	836	0.64	0.50 (0.45-0.54)	0.66 (0.59-0.72)	0.61 (0.52-0.70)	0.46 (0.39-0.53)	0.45 (0.30-0.60)	0.38 (0.32-0.45)

Abbreviations: BASICMAR = BASe de datos de ICtus del hospital del MAR (Spain); BRAINS = Bio-Repository of DNA in Stroke (England); CCS = Causative Classification of Stroke; CE = cardiac embolism; EDIN = Edinburgh stroke study (Scotland); GASROS = Genes Affecting Stroke Risk and Outcome Study (Boston); GCNKSS = Greater Cincinnati Northern Kentucky Stroke Study (Cincinnati); GEOS = Genetics of Early-Onset Stroke (Baltimore); GRAZ = Graz Stroke Study (Austria); ISGS = Ischemic Stroke Genetics Study (Jacksonville); KRAKOW = Krakow stroke study (Poland); LAA = large-artery atherosclerosis; LEUVEN = Leuven stroke study (Belgium); MCISS = Middlesex County Ischemic Stroke Study (New Jersey); MIAMISR = Miami Stroke Registry (Miami); MUNICH = Munich stroke study (Germany); NOMAS = Northern Manhattan Aging Study (New York); OXVASC = Oxford Vascular Study (England); REGARDS = Reasons for Geographic And Racial Differences in Stroke (Birmingham); SAHLSIS = Sahlgrenska Academy Study on Ischemic Stroke (Sweden); SAO = small-artery occlusion; SiGN = Stroke Genetics Network; STGEORGE = St. George's Stroke Study (England); SWISS = Siblings With Ischemic Stroke Study (Jacksonville); TOAST = Trial of Org 10172 Acute Stroke Treatment; WHI = Women's Health Initiative (Boston).
Subtype-specific kappas are missing for some studies because of either one classification system, or both, not classifying any cases as the relevant subtype.

Table 3 Cross-classification of 13,596 cases by TOAST and CCS

	TOAST					
	LAA	CE	SAO	Other	Undetermined	Total
CCS						
LAA	1,691	113	83	18	453	2,358
CE	103	3,063	155	27	761	4,109
SAO	27	68	1,297	12	296	1,700
Other	42	59	22	439	203	765
Undetermined	246	485	902	71	2,960	4,664
Total	2,109	3,788	2,459	567	4,673	13,596

Abbreviations: CCS = Causative Classification of Stroke; CE = cardiac embolism; LAA = large-artery atherosclerosis; SAO = small-artery occlusion; TOAST = Trial of Org 10172 Acute Stroke Treatment.

of variance in determining etiologic stroke subtypes. The present study, in our opinion, offers less bias because of its larger sample size, higher number of raters, multicenter design, and methodology that required a blinded assessment of CCS and TOAST subtypes. The current report provides agreement statistics stratified by study center and demonstrates variability in agreement rates with many genetic research centers having poor agreement (14 of 20 have $\kappa < 0.60$). One could interpret our results to indicate that in many research settings, the agreement between the 2 systems is quite low and data from standardized chart abstractions studies may not reflect the complexities of many practical implementations.

The lack of good agreement between TOAST and CCS is not surprising because these 2 systems use different classification criteria, definitions for subtypes, and diagnostic investigation requirements (table 5). Furthermore, their internal reliability also differs; existing studies by independent investigators demonstrate a moderate interrater reliability for the TOAST classification system with κ values ranging between 0.42 and 0.54.[11–15] In contrast, interrater reliability of the CCS ranges between 0.8 and 0.9.[2–4] These studies tended to be small and with varying methodologies. Well-powered reliability studies of both systems are still needed. While TOAST and CCS differ from each other in several ways, they both are subject to variability because of differences in adjudicators' ability to

Table 4 Agreement statistics, κ (95% confidence interval), between CCS and TOAST for the SiGN Study by the presence of diagnostic evaluations

	No.	Overall κ	CE κ	LAA κ	SAO κ	Other κ	Undetermined κ
Vascular imaging							
Present	8,846	0.61 (0.60-0.62)	0.67 (0.65-0.68)	0.70 (0.68-0.72)	0.67 (0.65-0.69)	0.67 (0.64-0.70)	0.40 (0.37-0.42)
Absent	4,750	0.54 (0.52-0.56)	0.72 (0.70-0.74)	0.69 (0.65-0.73)	0.34 (0.30-0.37)	0.51 (0.43-0.59)	0.45 (0.43-0.48)
Cardiac evaluation							
Present	10,768	0.57 (0.56-0.58)	0.66 (0.64-0.67)	0.68 (0.66-0.70)	0.56 (0.54-0.59)	0.61 (0.58-0.65)	0.40 (0.38-0.42)
Absent	2,828	0.61 (0.59-0.64)	0.35 (0.23-0.46)	0.80 (0.77-0.83)	0.53 (0.50-0.57)	0.74 (0.69-0.80)	0.54 (0.51-0.57)
Head CT							
Present	11,948	0.58 (0.57-0.59)	0.67 (0.66-0.69)	0.70 (0.68-0.72)	0.55 (0.53-0.57)	0.65 (0.62-0.68)	0.43 (0.41-0.45)
Absent	970	0.51 (0.47-0.55)	0.59 (0.53-0.65)	0.68 (0.61-0.74)	0.47 (0.40-0.54)	0.58 (0.47-0.69)	0.37 (0.31-0.43)
Brain MRI							
Present	7,358	0.57 (0.56-0.59)	0.62 (0.60-0.65)	0.69 (0.66-0.71)	0.61 (0.59-0.63)	0.66 (0.63-0.70)	0.40 (0.37-0.42)
Absent	5,560	0.58 (0.56-0.60)	0.71 (0.69-0.73)	0.72 (0.69-0.75)	0.43 (0.39-0.46)	0.55 (0.49-0.62)	0.46 (0.44-0.49)
Complete evaluation							
Present	7,451	0.58 (0.56-0.59)	0.65 (0.63-0.66)	0.67 (0.65-0.69)	0.64 (0.61-0.67)	0.63 (0.59-0.67)	0.37 (0.34-0.39)
Absent	6,145	0.60 (0.58-0.61)	0.73 (0.71-0.75)	0.77 (0.75-0.80)	0.48 (0.45-0.51)	0.66 (0.61-0.71)	0.49 (0.47-0.51)

Abbreviations: CCS = Causative Classification of Stroke; CE = cardiac embolism; LAA = large-artery atherosclerosis; SAO = small-artery occlusion; SiGN = Stroke Genetics Network; TOAST = Trial of Org 10172 Acute Stroke Treatment.

Table 5 Characteristics of the TOAST and CCS classification systems

	TOAST	CCS
Year of publication	1993	2005
Diagnosis of LAA	Requires imaging of a limited portion of the extracranial circulation	Result influenced by intracranial imaging (if performed)
Diagnosis of SAO	Does not require imaging confirmation	Does require imaging confirmation
Size limit for lacunar infarct	15 mm	20 mm
Imaging of the parent artery in lacunar infarcts required	No	Yes
Threshold to separate high- and low-risk cardiac sources	No	2% absolute primary risk threshold
Criteria to identify the most likely etiology in the presence of multiple etiologies	No	Yes
Criteria to identify a known subtype in patients with missing tests	No	Yes

Abbreviations: CCS = Causative Classification of Stroke; LAA = large-artery atherosclerosis; SAO = small-artery occlusion; TOAST = Trial of Org 10172 Acute Stroke Treatment.

interpret diagnostic test findings as well as variability in the completeness and quality of available diagnostic investigations. Regarding the latter point, we found that agreement for a subtype was generally higher when diagnostic investigations were complete for that particular subtype. For instance, in patients with complete cardiac evaluation, the agreement for cardiac embolism was almost twice as high compared to those with incomplete cardiac investigation ($\kappa = 0.66$ vs 0.35; table 4). Likewise, agreement for small-artery occlusion was higher in the presence of brain MRI ($\kappa = 0.61$ vs 0.43). In contrast to cardiac embolism and small-artery occlusion, there was no difference in agreement for large-artery atherosclerosis between cases with and without complete vascular evaluation. This may be attributable to diagnosis of large-artery atherosclerosis being contingent on extracranial carotid artery stenosis—the most common site for large-artery atherosclerosis—which does not require a complete assessment of both extracranial and intracranial vessels.

These findings suggest that availability of objective diagnostic information reduces the subjective component in decision-making for stroke subtypes regardless of the classification system used. Nevertheless, too much diagnostic information provides the opportunity for differential investigator interpretation in the absence of rule-based criteria and this may in turn reduce agreement between CCS and TOAST. In line with this, we found that overall agreement rate was lower, albeit slightly, when all investigations (brain imaging, brain vascular imaging, and cardiac evaluation) were complete than when they were incomplete ($\kappa = 0.58$ vs 0.60). We also found that the agreement rate for the undetermined group was lower than rates in other etiologic categories. The undetermined group is a heterogeneous category consisting of cryptogenic stroke (undetermined-unknown), multiple competing etiologies (undetermined-unclassified), and missing diagnostic tests (incomplete evaluation). Lower agreement rate in the undetermined category reflects differences between TOAST and CCS in dealing with multiple potential causes and missing diagnostic tests. CCS takes into account the completeness of diagnostic investigations and strength of evidence favoring one mechanism over others in the presence of multiple mechanisms in identifying stroke subtypes. In contrast, TOAST provides limited guidance on these issues leading to room for opinion in many practical implementations and hence variance in subtype assignments.

The present study required a uniform Web-based training and certification of investigators to be able to perform CCS. The same standardization was not applied to the TOAST classification. The TOAST classification was done locally, using local interpretations of the TOAST classification system, and before the formation of the SiGN collaboration. This differential application of TOAST is likely responsible for the variability in agreement seen between the centers. Thus, the overall agreement captures both differences in the subtyping systems and differences in their applications. The optimal test to compare the 2 classifications would have included prospective data-quality assessment and centrally trained certified investigators for performing also the TOAST classification at the same time as the CCS. However, we address this limitation by assessing agreement separately within each genetic research center, and the agreement between the 2 systems was modest at best for a majority of them. In only 2 of the 20 studies can agreement between TOAST and CCS be classified as excellent ($\kappa > 0.80$). Of note, both of those studies used protocols for CCS assignment that deviated from the

recommended consortium design. In addition, a computerized tool for TOAST classification has also been made available[12] and an additional question of interest may be how well the computerized TOAST agrees with CCS.

The agreement between CCS and TOAST reported here is lower than previously reported. The low agreement between the 2 systems described here simply means that the 2 systems classify stroke cases in different categories, although perhaps unfortunately, the names of the categories are similar. The practical implication of this finding is that combining or comparing classifications across systems should proceed with caution, and where possible, rephenotyping should be encouraged before combining data. For example, replication of results from genetic association studies should be made using phenotypes from the same classification system. A large benefit of the CCS system is the standardization of input and output data across cases from different sites. This feature allows for flexible analysis and further stratification of stroke phenotypes and hence promises utility in genetic studies such as SiGN.

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