Cryptogenic stroke

Contemporary trends, treatments, and outcomes in the United States

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Abstract

Background

Nationwide data on patients with cryptogenic stroke (CS) are lacking. We evaluated patient and hospital characteristics, in-hospital treatments, and discharge outcomes among patients with CS compared with other subtypes in the Get With The Guidelines (GWTG)-Stroke registry.

Methods

We identified patients with ischemic stroke (IS) admitted to GWTG-Stroke participating hospitals between January 1, 2016, and September 30, 2017, with documented National Institutes of Health Stroke Scale (NIHSS) scale and stroke etiology (cardioembolic [CE], large artery atherosclerosis [LAA], small vessel occlusion [SVO], other determined etiology [OTH], or CS). Using multivariable logistic regression, we compared hospital treatments and discharge outcomes by subtype, adjusted for patient and hospital characteristics.

Results

Among 316,623 patients from 1,687 hospitals, there were 63,301 (20.0%) patients with CS. In multivariable analysis, patients with CS received IV thrombolysis more often than other subtypes and had lower mortality than CE, LAA, and OTH but higher mortality than SVO. They were more likely to be discharged home than all other subtypes and be independent at discharge than LAA, OTH, or SVO.

Conclusions

In a large contemporary nationwide registry, CS accounted for 20% of ISs among patients with a documented stroke etiology. Patients with CS had a distinct profile of treatments and outcomes relative to other subtypes. Improved subtype documentation and further research into CS are warranted to improve care and outcomes for patients with stroke.

Ischemic stroke (IS) is a leading cause of disability in the United States.¹ Outcomes and secondary prevention strategies vary by IS subtype or etiology; for example, anticoagulation is reserved primarily for cardioembolic (CE) subtype. In addition, IS subtype has research implications. There are several ongoing and recently completed trials for cryptogenic stroke (CS), as classified by the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria² that encompasses patients with an in-depth evaluation in whom no cause was identified or in

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whom multiple potential causes were identified. For many patients, multiple specific phenotypes exist that may respond to targeted approaches including anticoagulation³ or patent foramen ovale (PFO) closure.^{4–7} Previous population-based and hospital-based cohorts have found that CS^{8–17} accounts for approximately 25%–40% of IS. However, there are relatively few data from the United States, mostly from geographically constrained population studies.^{12,15,17} We therefore sought to evaluate patient and hospital characteristics, in-hospital treatments, and discharge outcomes among patients with CS compared with other subtypes in the Get With The Guidelines (GWTG)-Stroke registry, a large database of acute stroke discharges at over 2,000 hospitals in the United States, accounting for ~60% of incident stroke cases.

Methods

Data source

The GWTG-Stroke registry is a quality improvement program for stroke care in the United States that promotes consistent adherence to the latest scientific management guidelines. Hospitals enter clinical and outcomes data via a web-based Patient Management Tool (PMT; IQVIA, Cambridge, MA).¹⁸

Standard protocol approvals, registrations, and patient consents

Data analysis was performed by the Duke Clinical Research Institute with local institutional review board approval. Under the common rule, sites are granted a waiver of informed consent, as the data are collected from medical records for use locally for quality improvement.

Data collection and study population

Using the GWTG-Stroke registry, we identified patients with final diagnosis of IS at participating hospitals between January 1, 2016, and September 30, 2017, with documented stroke etiology. The documentation of stroke etiology data collection questions and accompanying coding instructions were developed and finalized in 2015 and implemented in January 2016.

Primary variable of interest

CS subtype was the primary variable of interest and defined as occurring when physician documentation stated that a potential cause of stroke was not identified, or multiple possible causes were identified, following thorough diagnostic evaluation. Coding instructions noted that low- and moderate-risk potential CE sources such as PFO, heart failure with preserved ejection fraction, mitral annulus calcification, or atrial or ventricular arrhythmias other than atrial fibrillation or flutter (AF) were of uncertain significance and not adequate to ascribe stroke mechanism. The GWTG-Stroke coding instructions further subcategorized CS as stroke of (1) undetermined (when a potential etiology was

Patients with cryptogenic stroke were more likely to have better outcomes than all subtypes except those with small vessel disease.

not identified or documented following diagnostic evaluation), (2) unspecified (when there was no documentation of the results of the diagnostic evaluation), or (3) multiple competing etiologies (when a single etiology was uncertain between 2 or more possible causes following diagnostic evaluation). Other stroke subtypes, categorized according to the TOAST criteria,² included CE, large artery atherosclerosis (LAA), small vessel occlusion (SVO), and other determined etiology (OTH).

Patient and hospital characteristics

Demographic data included age, sex, race/ethnicity, health insurance status, and arrival and admission data including on-off hours admission, mode of arrival such as emergency medical services (EMSs), walk-in, or transfer, National Institutes of Health Stroke Scale (NIHSS) score (if documented), and times for arrival and thrombolytic drug administration. Medical history included the presence of AF, coronary artery disease (CAD), previous myocardial infarction (MI), carotid stenosis, diabetes mellitus, heart failure, hypertension, prosthetic heart valve, peripheral vascular disease (PVD), smoking status, previous stroke/TIA, ambulatory status before admission, and previous medications. Hospital characteristics including geographic region, the number of beds, hospital location, teaching and primary stroke center status, and annual volume of stroke by each type were also analyzed. In-hospital treatment included antithrombotic therapy and other risk factor-modifying medications at discharge.

Outcomes

Quality and achievement measures included thrombolytic therapy with IV tissue plasminogen activator (tPA) within 3 hours or 4.5 hours of last known well in eligible patients, administration of tPA within 1 hour of hospital arrival, early antithrombotic therapy, anticoagulation for AF, deep venous thrombosis prophylaxis, lipid lowering, statin initiation, and low-density lipoprotein measurement, smoking cessation, dysphagia screening, stroke education, consideration for rehabilitation, and defect-free care. Ambulatory status, mortality, modified Rankin Scale (mRS) score, discharge destination, and length of stay (LOS) were also analyzed at the time of hospital discharge as outcomes. Because stroke severity is an important predictor of these outcomes, we included only the subset of patients with documented NIHSS score for these analyses (n = 316,263).

Figure Flowchart of cohort assembly for primary and outcome analyses

Statistical Analysis

All statistical analyses were performed using SAS Version 9.3 software (SAS Institute, Cary, NC). Baseline patient and hospital characteristics were described overall and compared across the 5 stroke subtypes. Categorical variables were presented as counts and percentages, and the difference between groups was tested using Pearson χ^2 tests. Continuous variables were presented as mean and SDs or medians with 25th and 75th percentiles, and the difference between groups was tested using the Kruskal-Wallis test.

To further evaluate the association between different documented stroke etiology categories with outcomes, multivariable logistic regression models were performed in those with documented NIHSS scores. Both unadjusted and adjusted odds ratios and 95% confidence intervals are reported. The generalized estimating equation method with exchangeable working correlation matrix was applied to provide valid inference after accounting for the within-site correlation. Covariates in the model included age, sex, race,

relevant vascular risk factor medical history elements (atrial fibrillation, prosthetic heart valve, previous stroke or TIA, CAD or previous MI, carotid stenosis, PVD, hypertension, dyslipidemia, and smoking), arrival during off hours (vs regular hours), EMS arrival, initial NIHSS score, annual IS admission, bed size, region, hospital type (academic vs nonacademic), and urban/rural location. In this cohort, covariates had very low missing rates. Missing sex (0.02%) and hospital characteristics (0.01%–1.03% missing) were excluded, whereas other missing variables were imputed as follows: race (0.02% missing) imputed to “white,” mode of arrival (2.4% missing) imputed to “No EMS,” and medical history panel (missing 0.03%) imputed to “No.” Although insurance status was missing 15.2%, it was not included in multivariable models.

In an identical manner and to evaluate our findings in patients with CS of undetermined etiology, sensitivity analyses were performed after excluding patients with CS with unspecified or multiple etiologies and patients with CS

Table 1 Baseline and discharge characteristics in the primary analysis cohort with documented IS subtype (n = 348,715)

Variable	Overall (n = 348,715)		CS (n = 69,857)		LAA (n = 81,394)		CE (n = 96,592)		SVO (n = 82,542)		Stroke of other determined etiology (n = 18,330)		p
Demographics													
Age in y													
Mean	70.12		68.35		69.89		73.96		69.29		61.32		<0.0001
SD	14.44		14.85		13.70		13.87		13.55		16.86		
Sex													
Male	176,286	50.55	34,924	49.99	43,339	53.25	46,459	48.10	42,172	51.09	9,392	51.24	<0.0001
Missing	91	0.03	9	0.01	16	0.02	23	0.02	36	0.04	7	0.04	
Race													
White	237,984	68.25	47,691	68.27	55,866	68.64	70,335	72.82	52,367	63.44	11,725	63.97	<0.0001
Black	59,974	17.20	12,884	18.44	13,443	16.52	13,110	13.57	17,072	20.68	3,465	18.90	
Hispanic	24,395	7.00	4,693	6.72	5,834	7.17	6,018	6.23	6,356	7.70	1,494	8.15	
Asian	10,776	3.09	1,752	2.51	2,504	3.08	2,854	2.95	3,033	3.67	633	3.45	
Native American	1,301	0.37	315	0.45	286	0.35	313	0.32	290	0.35	97	0.53	
Native Hawaiian or Pacific Islander	1,102	0.32	159	0.23	245	0.30	318	0.33	294	0.36	86	0.47	
UTD	13,099	3.76	2,355	3.37	3,203	3.94	3,626	3.75	3,095	3.75	820	4.47	
Missing	84	0.02	8	0.01	13	0.02	18	0.02	35	0.04	10	0.05	
Insurance Status													
Private	133,054	38.16	29,696	42.51	29,903	36.74	36,447	37.73	29,203	35.38	7,805	42.58	<0.0001
Medicare	110,996	31.83	20,727	29.67	25,860	31.77	3,4883	36.11	25,535	30.94	3,991	21.77	
Medicaid	36,009	10.33	8,093	11.59	8,651	10.63	8,261	8.55	8,812	10.68	2,192	11.96	
Self-pay or None	13,179	3.78	2,721	3.90	3,332	4.09	2,549	2.64	3,632	4.40	945	5.16	
Not Documented	1,416	0.41	310	0.44	291	0.36	303	0.31	399	0.48	113	0.62	
Missing	54,061	15.50	8,310	11.90	13,357	16.41	14,149	14.65	14,961	18.13	3284	17.92	
Arrival and Admission data													
Stroke onset location													
Not in a health care setting	310,707	89.10	62,858	89.98	72,677	89.29	83,342	86.28	75,768	91.79	16,062	87.63	<0.0001
Chronic health care facility	16,448	4.72	3,122	4.47	3,723	4.57	5,875	6.08	3,101	3.76	627	3.42	
Stroke occurred while the patient was an inpatient in your hospital	9,271	2.66	1,662	2.38	1,957	2.40	3,592	3.72	1,359	1.65	701	3.82	
Outpatient health care setting	4,290	1.23	916	1.31	941	1.16	1,094	1.13	1,057	1.28	282	1.54	
Another acute care facility	5,803	1.66	901	1.29	1,609	1.98	2,014	2.09	855	1.04	424	2.31	
Not documented or cannot be determined	1,904	0.55	374	0.54	401	0.49	583	0.60	329	0.40	217	1.18	
Missing	292	0.08	24	0.03	86	0.11	92	0.10	73	0.09	17	0.09	
Arrival mode													
EMS from home/scene	157,712	45.23	30,616	43.83	37,664	46.27	48,073	49.77	34,465	41.75	6,894	37.61	<0.0001

Continued

Table 1 Baseline and discharge characteristics in the primary analysis cohort with documented IS subtype (n = 348,715)
(continued)

Variable	Overall (n = 348,715)		CS (n = 69,857)		LAA (n = 81,394)		CE (n = 96,592)		SVO (n = 82,542)		Stroke of other determined etiology (n = 18,330)		p
Private transport/taxi/other from home/scene	114,166	32.74	24,536	35.12	23,497	28.87	23,680	24.52	36,093	43.73	6,360	34.70	
Transfer from other hospital	64,916	18.62	12,528	17.93	17,614	21.64	20,642	21.37	9,911	12.01	4,221	23.03	
ND or unknown	2,213	0.63	438	0.63	537	0.66	490	0.51	609	0.74	139	0.76	
Missing	9,708	2.78	1,739	2.49	2,082	2.56	3,707	3.84	1,464	1.77	716	3.91	
Arrival during off hours	164,302	47.12	32,622	46.70	38,803	47.67	46,786	48.44	37,299	45.19	8,792	47.97	<0.0001
NIH Stroke Scale (median)	316,263	4.00	63,301	3.00	74,578	5.00	88,179	5.00	73,875	3.00	16,330	3.00	<0.0001
25th		1.00		1.00		2.00		2.00		1.00		1.00	
75th		9.00		8.00		12.00		13.00		5.00		8.00	
Missing (%)		9.31		9.38		8.37		8.71		10.50		10.91	
Medical history													
Hypertension	265,847	76.29	52,424	75.08	62,366	76.71	74,579	77.26	64,635	78.36	11,843	64.63	<0.0001
Diabetes mellitus	122,096	35.04	24,485	35.07	28,815	35.44	30,164	31.25	33,262	40.33	5,370	29.31	<0.0001
Dyslipidemia	164,451	47.19	33,611	48.14	38,232	47.02	46,787	48.47	38,802	47.04	7,019	38.31	<0.0001
Previous stroke/TIA	106,524	30.57	22,028	31.55	24,900	30.63	29,428	30.49	24,957	30.26	5,211	28.44	<0.0001
Atrial fibrillation/flutter	71,687	20.57	8,125	11.64	11,207	13.78	43,363	44.92	7,596	9.21	1,396	7.62	<0.0001
CAD/previous MI	81,911	23.51	15,579	22.31	19,726	24.26	26,955	27.93	16,692	20.24	2,959	16.15	<0.0001
PVD	15,919	4.57	3,164	4.53	4,230	5.20	4,642	4.81	3,173	3.85	710	3.87	<0.0001
CHF	34,645	9.94	5,894	8.44	6,809	8.37	15,079	15.62	5,709	6.92	1,154	6.30	<0.0001
Prosthetic heart valve	4,805	1.38	762	1.09	699	0.86	2,585	2.68	622	0.75	137	0.75	<0.0001
Carotid stenosis	13,234	3.80	2,434	3.49	5,395	6.64	2,989	3.10	1,965	2.38	451	2.46	<0.0001
Current smoker	65,934	18.92	14,181	20.31	18,124	22.29	12,843	13.31	16,782	20.35	4,004	21.85	<0.0001
Medical history panel missing	253	0.07	32	0.05	88	0.11	67	0.07	59	0.07	7	0.04	<0.0001
Discharge antithrombotic therapy													
Antiplatelet													
Yes	266,288	76.36	57,993	83.02	63,280	77.75	8,627	60.70	73,171	88.65	13,217	72.11	<0.0001
No	38,179	10.95	4,600	6.58	5,076	6.24	22,060	22.84	3,987	4.83	2,456	13.40	
Missing	44,248	12.69	7,264	10.40	13,038	16.02	15,905	16.47	5,384	6.52	2,657	14.50	
Anticoagulant													
Yes	84,848	24.33	10,986	15.73	13,547	16.64	44,950	46.54	10,866	13.16	4,499	24.54	<0.0001
No	219,619	62.98	51,607	73.88	54,809	67.34	35,737	37.00	66,292	80.31	11,174	60.96	
Missing	44,248	12.69	7,264	10.40	13,038	16.02	15,905	16.47	5,384	6.52	2,657	14.50	
Hospital characteristics													
Annual ischemic stroke admissions													
N, median	348,695	248.50	69,850	244.25	81,387	243.92	96,587	270.92	82,541	230.11	18,330	263.54	<0.0001

Continued

Table 1 Baseline and discharge characteristics in the primary analysis cohort with documented IS subtype (n = 348,715)
(continued)

Variable	Overall (n = 348,715)		CS (n = 69,857)		LAA (n = 81,394)		CE (n = 96,592)		SVO (n = 82,542)		Stroke of other determined etiology (n = 18,330)		p
25th	165.68		166.52		163.74		178.85		156.15		169.57		
75th	391.08		397.85		373.71		414.49		353.63		418.06		
Missing (%)	0.01		0.01		0.01		0.01		0.00		0.00		
Number of beds													
N, median	344,724	393	69,185	396	80,382	391	95,452	417	81,566	357	181,39	440	<0.0001
25th	253		259		251		267		230		258		
75th	625		650		599		657		546		672		
Missing (%)	1.14		0.96		1.24		1.18		1.18		1.04		
Region													
West	66,748	19.14	12,067	17.27	15,236	18.72	19,155	19.83	16,271	19.71	4,019	21.93	<0.0001
South	140,617	40.32	28,194	40.36	33,520	41.18	37,336	38.65	34,477	41.77	7,090	38.68	
Midwest	69,700	19.99	14,750	21.11	16,861	20.72	18,545	19.20	15,898	19.26	3,646	19.89	
Northeast	71,650	20.55	14,846	21.25	15,777	19.38	21,556	22.32	15,896	19.26	3,575	19.50	
Teaching hospital													
Yes	272,887	78.26	54,602	78.16	63,398	77.89	77,556	80.29	62,522	75.75	14,809	80.79	<0.0001
No	71,112	20.39	14,558	20.84	17,120	21.03	17,840	18.47	18,420	22.32	3,174	17.32	
Missing	4,716	1.35	697	1.00	876	1.08	1,196	1.24	1,600	1.94	347	1.89	
Rural location													
Yes	11,764	3.37	2,500	3.58	3,228	3.97	2,696	2.79	2,891	3.50	449	2.45	<0.0001
No	336,786	96.58	6,7294	96.33	78,116	95.97	93,874	97.19	79,628	96.47	17,874	97.51	
Missing	165	0.05	63	0.09	50	0.06	22	0.02	23	0.03	7	0.04	

Abbreviations: CE = cardioembolic; CS = cryptogenic stroke; IS = ischemic stroke; LAA = large artery atherosclerosis; MI = myocardial infarction; ND = not documented; OTH = other determined etiology; PVD = peripheral vascular disease; SVO = small vessel occlusion; UTD = undetermined.

with a history of AF. A *p* value <0.05 was significant in final models.

Data availability

Data were collected by the American Heart Association (the steward of the data according to contracts between the American Heart Association and participating hospitals) and are stored securely at the Duke Clinical Research Institute (DCRI). Given that data were collected for clinical care and quality improvement, rather than primarily for research, data sharing agreements require an application process for other researchers to access the data. Interested researchers can submit proposals to utilize GWTC for research purposes, including for validation purposes. Proposals can be submitted at www.heart.org/qualityresearch. Additional information regarding the statistical analysis plan and analytic code may also be available from DCRI upon request.

Results

Among 827,949 patients from 1,936 sites, 348,175 (42.1%) had IS with documented subtype (see the figure for flowchart). Those included, compared with excluded, were more likely to be interfacility transfers and treated at higher volume and academic centers and more likely to have complete medical history data and higher rates on defect-free care (achievement and qualities measures); however, they also had higher LOS and reduced rates of discharge home and independence at discharge (table e-1, links.lww.com/CPJ/A135).

Overall, 69,857 (20.0%) of the 348,175 included patients with documented etiology were classified as CS, 81,394 (23.3%) as LAA, 96,592 (27.7%) as CE, 82,542 (23.7%) as SVD, and 18,330 (5.3%) as OTH. Among patients with CS, 51.0% were undetermined, 19.9% were unspecified, and 28.7% were

multiple etiologies. On univariate analysis comparing across groups (table 1), patients with CS were slightly younger, less often white, more often privately insured, less often arrived by EMS, and had lower NIHSS scores than patients with CE. Patients with CS were also more likely to be admitted to smaller bed size and volume hospitals than patients with CE. In-hospital care and treatments differed by stroke subtype such that patients with CS achieve similar rates on quality and achievement measures as other subtypes except that tPA treatment was lower in those with OTH subtype. In-hospital mortality and LOS were lower in patients with CS compared with patients with CE or LAA but higher than those with SVO. Patients with CS were more likely to be ambulating at discharge and be discharged home than patients with CE or LAA (table e-2, links.lww.com/CPJ/A135).

In multivariable analysis for the outcomes of interest (table 2 and table e-3, links.lww.com/CPJ/A135), patients with CS were more likely to receive tPA within 4.5 hours of last known well than all other groups but less likely to receive early antithrombotic therapy than other subtypes except OTH. Patients with CS had lower mortality and LOS than CE, LAA, and OTH subtypes but higher than SVO. Discharge home was more likely in patients with CS than all other subtypes, and patients with CS were more likely to be independent (mRS < 3) than patients with LAA, OTH, or SVO subtypes. In sensitivity analysis excluding patients with CS with either unspecified or multiple etiologies or those with a previous history of AF but for whom the current index stroke was felt to be cryptogenic, the results were similar (tables e-4 to e-6).

Discussion

In this nationwide analysis of current clinical practice, we observed that stroke subtype is documented in approximately 50% of records, raising an important opportunity for quality improvement, and among ISs with documented subtype in

GWTG-Stroke, CS accounts for one-fifth of discharges. Furthermore, we noted that patients with CS were more likely to receive thrombolysis within 4.5 hours and have lower mortality and discharge outcomes than other subtypes except for patients with small vessel disease independent of initial stroke severity.

Our results have several implications for clinical practice. First, our finding that patients with CS have different risk factors and prognosis justifies identifying these patients in routine clinical practice. However, stroke subtype classification should require standardized diagnostic evaluation and review by qualified clinicians to apply TOAST or other criteria. Second, we found that a substantial number of patients are classified as CS, and within this category, the identification of radiographic picture of suspected embolic stroke of undetermined source (ESUS) should probably trigger further advanced diagnostic evaluation for specific treatable causes such as occult paroxysmal atrial fibrillation^{19,20} and PFO.^{5–7} Furthermore, new strategies to prevent recurrent stroke in patients with ESUS without AF are of major clinical interest and the subject of several recent and ongoing clinical trials.^{21,22} A more complete understanding of CS through comprehensive registry-based collection could provide valuable new insights into which subjects may be at a greater risk of recurrent stroke.

These implications suggest an opportunity for ongoing quality improvement in stroke subtype documentation. Future initiatives could measure, track, and intervene to improve rates of subtype classification and assess whether documentation is linked to increased use of established therapies such as anticoagulation for atrial fibrillation–related stroke and interventions including carotid revascularization for symptomatic stenosis and PFO closure for younger patients. Improved subtyping would also lead to better provision of proven secondary prevention strategies in patients with known etiologies, advanced diagnostic evaluation such as long-term atrial fibrillation monitoring in patients with ESUS, and identification of patients for clinical trials.

Table 2 Absolute rates and adjusted odds ratios and 95% CIs for discharge outcomes by stroke subtype^a

	In-hospital mortality		Independent ambulation at discharge		Discharge home		mRS score 0–2 at discharge	
	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)
LAA	5.91	1.46 (1.36–1.57)	45.21	0.88 (0.83–0.94)	45.17	0.78 (0.76–0.81)	36.03	0.88 (0.81–0.95)
CE	5.68	1.14 (1.07–1.21)	43.85	1.01 (0.96–1.07)	44.00	0.93 (0.90–0.96)	35.08	1.05 (0.99–1.12)
SVO	1.18	0.62 (0.56–0.69)	56.25	0.91 (0.86–0.97)	56.41	0.88 (0.85–0.91)	48.07	0.94 (0.88–1.01)
OTH	4.12	1.47 (1.33–1.63)	54.64	0.86 (0.77–0.96)	54.76	0.75 (0.71–0.79)	44.92	0.80 (0.73–0.87)
CS (ref)	2.86	—	53.89	—	55.32	—	44.98	—

Abbreviations: CE = cardioembolic; CI = confidence interval; CS = cryptogenic stroke; LAA = large artery atherosclerosis; mRS = modified Rankin Scale; SVO = small vessel occlusion; OR = odds ratio; OTH = other determined cause.

^a Models were adjusted for age, sex, race, atrial fibrillation, prosthetic heart valve, previous stroke or transient ischemic attack, coronary artery disease or previous myocardial infarction, carotid stenosis, peripheral vascular disease, hypertension, dyslipidemia, smoking, arrival during off hours (vs. regular hours), emergency medical services arrival, annual ischemic stroke admission, bed size, region, hospital type (academic vs not), urban/rural location, and NIHSS scores.

Compared with other population-based and hospital-based registries of IS in the United States,^{12,14,15,17,23} the rate of CS in our study is lower (20% vs 36–41%). Many of the previous studies were published before modern imaging including routine use of brain MRI and vascular imaging such as CT and magnetic resonance angiography. It is also possible that when multiple etiologies were identified, clinicians chose to select the most likely subtype, a practice that would not have been allowed in research studies where strict adherence to the TOAST subtype classification schema would have been followed. Unlike other studies, we did not find that patients with CS were younger than patients without CS, disproportionately affected minorities, or had differences in medical risk factors with the exception of less cardiac disease history.^{15,16,24}

We observed that patients with CS had milder initial stroke severity than CE stroke and LAA subtypes. Despite this, patients with CS were more likely to receive thrombolytic therapy within 4.5 hours of last known well than all other subtypes independent of initial stroke severity. Patients with CS were more likely to have better outcomes than all subtypes except those with small vessel disease. Unmeasured confounding factors including infarct volume and some poststroke complications, not available or analyzed in this study, may explain these findings.

Although simple, the TOAST classification system has only modest interrater reliability.^{25,26} Compared with the TOAST system, the Causative Classification of Stroke System (CCS, available at ccs.mgh.harvard.edu)²⁷ and Atherosclerosis, Small-vessel disease, Cardioembolism and Other causes methods²⁸ have higher interrater reliability, but are more complex, require richly detailed clinical, laboratory and imaging data, and are, therefore, less commonly used in practice or in research.^{29,30} A previous study also noted that the TOAST classification system and the CCS, which uses a web-based semiautomated approach, have excellent agreement and that only 5.8% of patients with CS by TOAST would have been reclassified to a definite subtype by CCS.³¹

Our study has other limitations. First, selection bias may have affected our results because stroke subtype documentation was more common at larger, teaching hospitals and associated with better quality and achievement measure performance, suggesting that our results may disproportionately reflect practices from high-performance, large, academic centers and thereby limit the generalizability of our findings. Second, as noted above, there is a potential for misclassification error, given the modest interrater reliability of the TOAST classification system and its use outside the research setting. Because the expertise and training of clinicians involved in the determination of stroke subtype is not known, we cannot verify that a standard approach to diagnostic testing and subtype adjudication was used between hospitals or even within hospitals. Third, we are unable to

Given the implications of CS on diagnostic evaluation and management, optimizing documentation of ischemic stroke subtype at all levels of hospitals should be a major public health priority.

evaluate the details of the diagnostic tests completed and whether results conformed with TOAST categories (e.g., LAA requires >50% ipsilateral stenosis). We are also unable to verify whether infarct patterns met established criteria for either small vessel disease (infarct size <1.5 cm in maximum diameter), or ESUS, or CE stroke (cortical or multi-infarct pattern). Thus, we cannot independently validate the TOAST subtype assignment at GWTG-Stroke sites. Fourth, it is possible that some stroke mimics were disproportionately misclassified as CS. Finally, residual or unmeasured confounding may explain some of our findings.

In a large contemporary nationwide analysis, we observed that CS accounts for approximately one-fifth of IS subtypes. Furthermore, we confirm that outcomes in this group are generally intermediate between those of CE and large artery atherosclerotic stroke and small vessel disease. Given the implications of CS on diagnostic evaluation and management, optimizing documentation of IS subtype at all levels of hospitals should be a major public health priority.

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Disclosure

S. Prabhakaran. reports that he is a member of the AHA/ASA Cryptogenic Stroke Oversight Committee. S.R. Messe and D. Kleindorfer report no disclosures. E.E. Smith discloses that he is a member of the GWTG steering committee. G.C. Fonarow reports serving on the GWTG steering committee; receiving grant funding from the Patient-Centered Outcome Research Institute; and being an employee of the University of California, which has a patent on an endovascular therapy. H. Xu, X. Zhao, B. Lytle, and J. Cigarroa report no disclosures. L.H. Schwamm reports serving as chair of the American Heart Association/American Stroke Association GWTG stroke clinical work group and hospital accreditation science committee;

TAKE-HOME POINTS

- Among records with documented subtype in a nationwide registry, CS accounts for 20% of IS.
- Such patients experience an intermediate discharge outcome better than CE and LAA subtypes but worse than SVO.
- Improved subtype documentation and further research into CS are warranted to improve care and outcomes for patients with stroke.

serving as a stroke systems consultant to the Massachusetts Department of Public Health; and serving as a scientific consultant regarding trial design and conduct to Penumbra (data and safety monitoring committee, Separator 3D and MIND trial) and Medtronic (Victory AF and Stroke AF trials). Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

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Appendix Authors

Name	Location	Contribution
Shyam Prabhakaran, MD, MS	University of Chicago, Illinois	Drafting/revising the manuscript; study concept or design; and analysis or interpretation of the data
Steven R. Messé, MD	University of Pennsylvania, Philadelphia, PA	Drafting/revising the manuscript
Dawn Kleindorfer, MD	University of Cincinnati, Cincinnati, OH	Drafting/revising the manuscript; study concept or design; and analysis or interpretation of the data
Eric E. Smith, MD, MPH	University of Calgary, Calgary, AB	Study concept or design; and analysis or interpretation of the data
Gregg C. Fonarow, MD	UCLA, Los Angeles, CA	Drafting/revising the manuscript; data acquisition; and analysis or interpretation of the data
Haolin Xu, MS	Duke Clinical Research Institute, Durham, NC	Study concept or design; analysis or interpretation of the data; and statistical analysis
Xin Zhao, PhD	Duke Clinical Research Institute, Durham, NC	Analysis or interpretation of the data; and statistical analysis

Appendix (continued)

Name	Location	Contribution
Barbara Lytle, PhD	Duke Clinical Research Institute, Durham, NC	Analysis or interpretation of the data; and study supervision
Joaquin Cigarroa, MD	Oregon Health and Sciences University, Portland, OR	Drafting/revising the manuscript; and analysis or interpretation of data
Lee H. Schwamm, MD	Massachusetts General Hospital, Boston, MA	Drafting/revising the manuscript; and study concept or design

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