Coexistent Sickle Cell Disease Has No Impact on the Safety or Outcome of Lytic Therapy in Acute Ischemic Stroke

Findings From Get With The Guidelines-Stroke

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Background and Purpose—The recommended treatment for ischemic stroke is tPA (tissue-type plasminogen activator). Although sickle cell disease (SCD) represents no known contraindication to tPA, National Heart Lung and Blood Institute of the National Institutes of Health recommended acute exchange transfusion for stroke in SCD, not tPA. Data on safety and outcomes of tPA in patients are needed to guide tPA use in SCD.

Methods—We matched patients from the American Heart Association and American Stroke Association Get With The Guidelines-Stroke registry with SCD to patients without SCD and compared usage, complications, and discharge outcomes after tPA. Multivariable logistic regression models using generalized estimating equations were used to assess outcomes.

Results—From 2 016 652 stroke patients admitted to Get With The Guidelines-Stroke sites in the United States, 832 SCD and 3328 non-SCD controls with no differences in admission National Institutes of Health Stroke Scale or blood pressure were identified. Neither the fraction receiving thrombolytic therapy (8.2% for SCD versus 9.4% non-SCD) nor symptomatic intracranial hemorrhage (4.9% of SCD versus 3.2% non-SCD; P=0.4502) was different. There was no difference in a prespecified set of outcome measures for those with SCD compared with controls.

Conclusions—Coexistent SCD had no significant impact on the safety or outcome of thrombolytic therapy in acute ischemic stroke. Although the sample size is relatively small, these data suggest that adults with SCD and acute ischemic stroke should be treated with thrombolysis, if they otherwise qualify. Addition studies, however, should track the intracranial hemorrhage rate and provide information on other SCD-related care such as transfusion.

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Key Words: brain infarction ■ quality improvement ■ sickle cell disease ■ stroke ■ thrombolytic therapy

Stroke is an important complication of sickle cell disease (SCD). Both children and adults have elevated risk of brain infarction and intracranial hemorrhage.[1] In some cases with advanced vasculopathy, moyamoya is present.[2] This fact raises concern about intracranial hemorrhage with the use of intravenous tPA (tissue-type plasminogen activator) in patients with SCD and symptoms of acute brain infarction. tPA has been the established class I recommended therapy for acute ischemic stroke (IS) since 1996. SCD was not an exclusion criterion from the pivotal trial,[3] but it is unclear if any such patients were included in the study. Since 1996, guidelines for tPA use have not identified SCD as a contraindication, but the 2016 American Heart Association and American Stroke Association Scientific Statement on tPA use notes that its use in SCD is not well established.[4] In 2014, an expert panel convened by National Heart Lung and Blood Institute to guide clinical treatment in SCD recommended exchange transfusion for acute stroke but did not mention thrombolysis despite the absence of evidence of bleeding risk specific to SCD beyond what is normally expected.[5]

The quality improvement program Get With The Guidelines-Stroke (GWTG-Stroke)[6,7] added a field in 2008 to identify acute stroke patients with SCD. No further qualification was included, and the remainder of the data forms were executed regardless of the answer to this question. This program provides the first systematic evidence of the use of tPA for acute stroke in patients with SCD and provides an opportunity to examine its safety in these patients and other features of its use.

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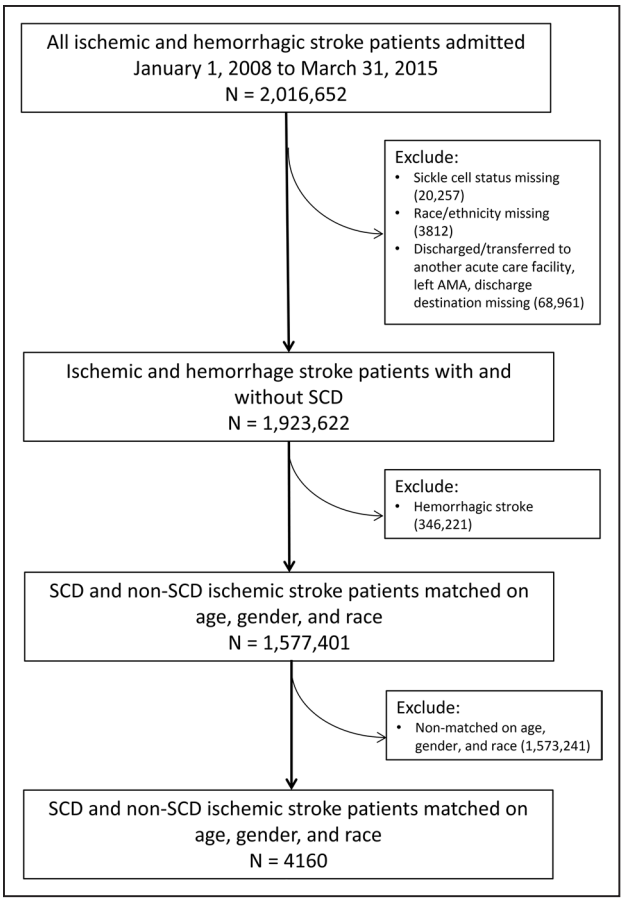

Figure 1. Flow diagram showing selection process for sickle cell disease (SCD) patients and the control group. AMA indicates against medical advice.

Methods

The American Heart Association and American Stroke Association launched the GWTG-Stroke registry quality improvement program in April 2003. The GWTG-Stroke registry aggregates voluntarily submitted, deidentified acute stroke patient data on clinical and demographic characteristics, diagnostic testing, treatments, adherence to quality measures, and in-hospital outcomes via a web-based, real-time decision support patient management tool. Trained hospital personnel ascertain consecutive patients admitted with stroke by prospective clinical identification, retrospective identification using International Classification of Diseases Ninth Revision discharge codes, or a combination. Prospective identification includes regular surveillance of emergency department records (ie, presenting symptoms and chief complaints), ward census logs, or neurological consultations. The eligibility of each stroke patient is confirmed at chart review before abstraction. GWTG-Stroke does not enroll patients <18 years of age. Quintiles, is the data collection coordination center for the American Heart Association/American Stroke Association Get With The Guidelines programs. The Duke Clinical Research Institute (DCRI) serves as the data analysis center and has an agreement to analyze the aggregate de-identified data for research purposes. All analyses performed on these data have been approved by the Duke Medical Center Institutional Review Board.

In 2008, the instructions were modified to include this (Yes or No) field: Documented history of Sickle Cell in the medical record. Include Sickle cell disease or sickle cell trait, or sickle cell anemia. Patient-level data from 1952 fully participating GWTG-Stroke hospitals were analyzed from January 1, 2008 through March 31, 2015. Acute stroke diagnoses were confirmed by chart review, and patient data were then collected and entered by trained hospital personnel. The study population consisted of SCD and non-SCD patients who were discharged with a primary diagnosis of IS or hemorrhagic stroke. Among a total of 3 060 787 patient encounters in 1961 participating hospital sites, patients were excluded if admitted before 2008 before the SCD field was added (N=402 641 patients; 83 sites), SCD status unspecified (N=20 257 patients; 0 sites), race/ethnicity unspecified (N=3812 patients; 1 site), were discharged/transferred to another acute care facility, left against medical advice, or had missing discharge designation information (N=68 961 patients; 7 sites).

The initial breakdown between ischemic and hemorrhagic showed that a greater percentage of SCD patients have hemorrhagic stroke (26%) compared with those without SCD (18%; $P \leq 0.001$). Because only IS patients are eligible for tPA treatment, hemorrhagic stroke patients were excluded from the final study population (N=346 221 patients; 9 sites). Of these patients, 832 had SCD. A cohort of 3328 patients without SCD but otherwise matched for age, race, and sex was selected from the overall data set. The final population consisted of 4160 patients (Figure 1).

Statistical Analysis

Patients with SCD were matched to patients without SCD to prevent or reduce extrapolation of comparisons given the difference in age and race distributions of SCD IS patients compared with the larger IS patient population using 1:4 exact matching on age, race (dichotomized as black and nonblack), and sex.

Patient and hospital characteristics, usage of and complications from thrombolytic therapy, and discharge outcomes were described for IS patients by sickle cell status using proportions for categorical variables and medians with 25th and 75th percentiles for continuous variables. Differences were compared using Pearson χ^2 tests or Fisher exact test, where appropriate, for categorical row variables and Wilcoxon rank-sum tests for continuous row variables.

Multivariable logistic regression using generalized estimating equations was used to assess the effect of SCD on outcomes. Models adjusted for clinically relevant factors were medical history of atrial fibrillation/flutter, previous stroke/transient ischemic attack, coronary artery disease/previous myocardial infarct, carotid stenosis, diabetes mellitus, peripheral vascular disease, hypertension, dyslipidemia, smoking, arrival by emergency medical service (EMS), arrival during

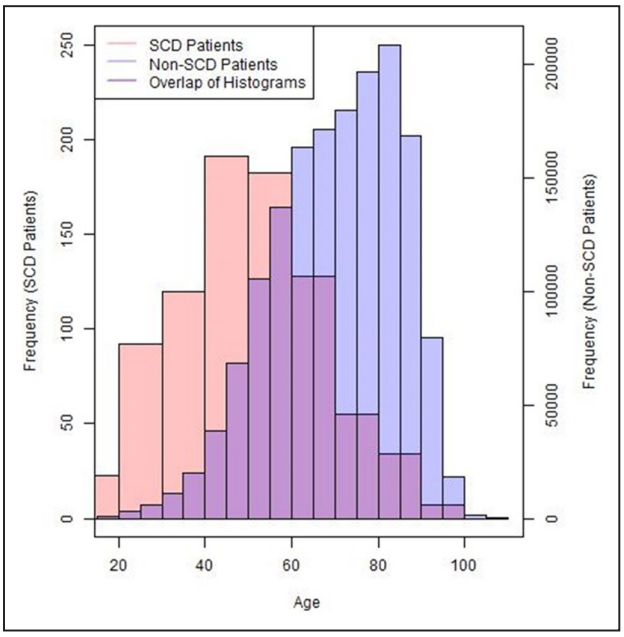

Figure 2. Age distribution of sickle cell disease (SCD) ischemic stroke patients in relation to those without SCD in the Get With The Guidelines-Stroke program.

nonregular hours, geographic region, hospital type (teaching/nonteaching), number of beds, annual IS volume, rural location, and The Joint Commission primary stroke center status.

Multiple imputation was used to handle missing data in the models. Missing rates for most variables were 0%, except for arrival by EMS (7.3% overall), hospital type (0.5% overall), and number of beds (0.5% overall). Hospital characteristics were not imputed. Arrival by EMS was imputed using the fully conditional specification method; 25 imputed data sets were created.

All tests were 2-tailed with a level of statistical significance of $P<0.05$. Statistical analyses were performed using SAS version 9.4 software (SAS Institute Inc, Cary, NC).

Results

Between January 2008 and April 2015, a total of 1 577 401 IS patients meeting study criteria were directly admitted to 1952 fully participating GWTG-Stroke hospitals in the United States. Before matching, SCD patients with IS tended to be younger than those without SCD (Figure 2). The median age of SCD was 50 years (25th–75th percentile: 39–62 years); the median age of non-SCD patients was 72 years (25th–75th percentile: 61–82 years). In addition, SCD patients were more often female (58.3% versus 51.6%; $P<0.0001$) and black (85.2%

Table 1. Selected Patient and Hospital Characteristics of the SCD and Non-SCD Groups, After Matching on Age, Sex, and Black Versus Nonblack Race

Variable	SCD (n=832)	Non-SCD (n=3328)	*P* Value
Matching characteristics			
Age, median (25th–75th percentile)	50 (39–62)	50 (39–62)	…
Female sex, n (%)	485 (58.3)	1940 (58.3)	…
Black race, n (%)	709 (85.2)	2836 (85.2)	…
Patient characteristics			
Arrival by EMS, n (%)	301 (40.1)	1406 (45.3)	0.0109
Arrival during off h, n (%)	388 (46.6)	1542 (46.3)	0.8765
Onset to arrival time in min, median (25th–75th percentile)	267 (82–780)	216 (66–600)	0.0398
NIHSS score, median (25th–75th percentile)	4 (2–9)	4 (1–10)	0.0760
Medical history, %			
Atrial fibrillation or flutter	44 (5.3)	178 (5.4)	0.9450
CAD/MI	131 (15.8)	460 (13.8)	0.1553
Diabetes mellitus	202 (24.3)	1134 (34.1)	<0.0001
Dyslipidemia	212 (25.5)	909 (27.3)	0.2866
Hypertension	484 (58.2)	2323 (69.8)	<0.0001
Previous stroke/TIA	320 (38.5)	1003 (30.1)	<0.0001
Prosthetic heart valve	17 (2.0)	30 (0.9)	0.0053
Smoker	195 (23.4)	978 (29.4)	0.0006
Systolic blood pressure in mm Hg, median (25th–75th percentile)	143 (125–165)	151 (133–174)	<0.0001
Diastolic blood pressure in mm Hg, median (25th–75th percentile)	81 (71–92)	87 (74–100)	<0.0001
Hospital characteristics			
Teaching hospital, n (%)	608 (74.4)	2344 (70.6)	0.0298
TJC primary stroke center, n (%)	419 (50.4)	1682 (50.4)	0.9259
Rural location, n (%)	11 (1.3)	63 (1.9)	0.2668
Hospital region, n (%)			
Northeast	180 (21.6)	656 (19.7)	0.4221
Midwest	167 (20.1)	665 (20.0)	
South	417 (50.1)	1686 (50.7)	
West	68 (8.2)	321 (9.7)	
Hospital size (no. of beds), median (25th–75th percentile)	459 (306–706)	428 (306–653)	0.0624
Annual volume of ischemic stroke admissions, median (25th–75th percentile)	229.2 (163.2–350.9)	238.2 (163.2–361.6)	0.4323
Annual volume of tPA administration, median (25th–75th percentile)	18.4 (10.7–29.1)	17.6 (10.1–27.8)	0.1728

CAD indicates coronary artery disease; EMS, emergency medical service; MI, myocardial infarct; NIHSS, National Institutes of Health Stroke Scale; SCD, sickle cell disease; TIA, transient ischemic attack; TJC, The Joint Commission; and tPA, tissue-type plasminogen activator.

versus 16.4%, $P<0.001$) compared with non-SCD patients. In addition to the 85% SCD patients noted to be black, 9% were designated as white, 3% Hispanic, and 3% other.

After matching on age, sex, and race, there were no differences between SCD patients and non-SCD patients in these factors ($P=1.00$ for all; Table 1). There were no differences in admission systolic (143 versus 144 mm Hg) or diastolic blood pressure (81 versus 82 mm Hg) in the SCD cohort versus the non-SCD cohort. There were no differences in the National Institutes of Health Stroke Scale scores as shown in Table 1 (SCD patients: 4, 25th–75th percentile: 2–9; non-SCD patients: 4, 25th–75th percentile: 1–10; $P=0.0760$). SCD patients were less likely to have arrived to the hospital via EMS (40.1% versus 51.6%; $P<0.0001$) and had a longer onset to arrival time ($P=0.0398$). SCD patients tended to have had a previous stroke or TIA before the current event (38.5% versus 30.1%; $P<0.0001$). SCD patients were more likely to be admitted to teaching hospitals, but no other characteristics differed in where SCD and non-SCD patients were admitted. Patients with SCD who did not get intravenous tPA were less likely to have arrived via EMS (39.2% versus 55.6%, $P=0.0302$), less likely to be inpatients when the stroke occurred (4.8% versus 15.1%, $P=0.0011$), less likely to have certain laboratories and stroke severity recorded (glucose: 68.6% versus 90.6%, 0.0007; creatinine: 71.2% versus 84.9%, $P=0.0312$; National Institutes of Health Stroke Scale score=66.7% versus 96.2%, $P<0.0001$), and have less severe strokes (median National Institutes of Health Stroke Scale score=4, 25th–75th percentile: 2–8 versus 8 [5–13]; $P<0.0001$). All other baseline characteristics were similar.

There were no differences in the percentage of SCD patients (8.2%) who received thrombolytic therapy, either as intravenous tPA, intra-arterial tPA, or both compared with the patients without SCD (10.1%, $P=0.9818$). SCD and non-SCD patients did not differ in the type of tPA received (SCD group: 82.1% received intravenous tPA, 14.3% received intra-arterial tPA, 3.6% received both; non-SCD: 80.5% received intravenous tPA, 14.4% received intra-arterial tPA, 5.2% received both; $P=0.9818$ for all comparisons). Median onset to treatment times of 148 minutes (25th–75th percentile: 100–179) for patients with SCD versus 145 minutes (25th–75th percentile: 115–171) for the non-SCD cohort was not statistically significant. Median door-to-needle times were slightly shorter in the SCD group, 73 minutes (25th–75th percentile: 52–99) versus 79 minutes (25th–75th percentile: 58–101) in the non-SCD cohort but not different statistically ($P=0.3891$).

Symptomatic intracerebral hemorrhage was reported in 4.9% of SCD patients compared with 3.2% in the non-SCD cohort, but these differences were not statistically significant ($P=0.4502$; Table 2). There was also no difference in the percentage of any serious tPA complications reported, defined as symptomatic intracerebral hemorrhage, life-threatening systemic hemorrhage, or other serious complication to tPA (6.6% in the SCD group, 6.0% in the non-SCD group; $P=0.7732$).

Discharge destinations and outcomes are shown in Table 3. In-hospital death was reported in 3.5% of SCD patients, which was not different than the percentage in the non-SCD group (5.0%, $P=0.5654$). Patients with SCD and low-density lipoprotein levels ≥100 or not documented were slightly more likely to be prescribed statins at discharge ($P=0.0322$). Before discharge, patients with SCD were more likely than patients without SCD to receive stroke education in several domains, including personal, modifiable risk factors, the importance of EMS activation, stroke warning signs, and the use of prescribed medications. No other significant differences were noted.

After adjusting for potential confounders, there was no negative impact of SCD on key indicators of outcome (Table 3).

Table 2. Lytic Therapy and Safety Among SCD and Non-SCD Cohorts, After Matching on Age, Sex, and Black Versus Nonblack Race

Variable	SCD (n =832)	Non-SCD (n =3328)	*P* Value
Thrombolytic therapy			
Any thrombolytic therapy, n (%)	61 (8.2)	290 (9.4)	0.3024
Thrombolytic therapy types among patients receiving thrombolytic therapy, n (%)			0.9818
Intravenous tPA only	46 (82.1)	223 (81.1)	
IA tPA only	8 (14.3)	42 (15.3)	
Both intravenous tPA and IA tPA	2 (3.6)	10 (3.6)	
Onset to treatment time in min, median (25th–75th percentile)	148 (100–179)	145 (115–171)	0.6602
Door-to-needle time in min, median (25th–75th percentile)	73 (52–99)	79 (58–101)	0.3891
Arrive by 2 h, treat with intravenous tPA by 3 h	32 (78.1)	189 (79.1)	0.8814
Complications of thrombolytic therapy*			
Symptomatic ICH	3 (4.9)	9 (3.2)	0.4502
Life-threatening systemic hemorrhage	0 (0.0)	2 (0.7)	1.0000
Other serious complication	1 (1.6)	7 (2.5)	1.0000
Any serious complication	4 (6.6)	17 (6.0)	0.7732

IA indicates intra-arterial; ICH, intracerebral hemorrhage; SCD, sickle cell disease; and tPA, tissue-type plasminogen activator.

*Out of patients who received thrombolytic therapy.

Discussion

This study provides the first systematic evidence for the use of tPA in SCD patients with acute IS and also represents the largest report on acute stroke in SCD to date. These data indicate that SCD patients with stroke are younger and include a greater fraction of hemorrhages when compared with all strokes. On the basis of GWTG data, SCD patients are being treated with thrombolytics at the expected rate and have complication rates that are not significantly higher than

Table 3. Association of SCD on Selected Outcomes

Outcomes	Unadjusted Model		Adjusted Model	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
In-hospital mortality	1.14 (0.73–1.76)	0.5676	1.21 (0.77–1.91)	0.4150
Discharged to home	0.96 (0.82–1.13)	0.6089	0.90 (0.76–1.08)	0.2686
Independent ambulation at discharge	0.98 (0.82–1.17)	0.7879	0.94 (0.78–1.14)	0.5290
Length of stay >4 d	1.14 (0.97–1.35)	0.1220	1.15 (0.97–1.38)	0.1151
Composite achievement measure	1.04 (0.80–1.37)	0.7530	1.04 (0.78–1.38)	0.8129

Adjusted models also included the following covariates: medical history of atrial fibrillation/flutter, previous stroke/transient ischemic attack, coronary artery disease/previous myocardial infarct, carotid stenosis, diabetes mellitus, peripheral vascular disease, hypertension, dyslipidemia, smoking, arrival by emergency medical service, arrival during nonregular h, geographic region, hospital type (teaching/nonteaching), number of beds, annual ischemic stroke volume, rural location, and The Joint Commission primary stroke center status. CI indicates confidence interval; OR, odds ratio; and SCD, sickle cell disease.

other patients with stroke, although the intracranial hemorrhage rate was nominally higher in SCD. These data provide no evidence of an adverse impact of having SCD in the setting of acute IS in terms of mortality, discharge home, ambulatory status at discharge, or overall tPA complications. These patients, however, do arrive less often by EMS and later. Arriving later may be a function of not using EMS or may indicate that closer hospitals are bypassed in favor of teaching hospitals where the patients likely receive most of their critical medical care.

There are several limitations to be considered: (1) the query on SCD contains no information on specific genotype; however, it is likely based on the relative probabilities and the fact that SC trait is often undiagnosed that the great majority of these cases are the SS genotype and (2) SCD patients are often cared for by hematologists; it is possible that these patients were cared for in atypical pathways, such as admission to a medical service with a neurology consult instead of the opposite situation. The GWTG ascertainment algorithms anticipate that not all stroke patients will be cared for in a stroke unit and therefore have systems in place to identify and enroll patients no matter where in the hospital they are cared for. A potential ascertainment bias exists in the distribution of GWTG sites in general with these being larger hospitals with resources to conduct GWTG. This fact is unlikely to affect these results because most patients with SCD are cared for in larger specialized tertiary centers likely to be GWTG-participating sites.

Conclusions

Coexistent SCD had no associated impact on the safety or outcome of thrombolytic therapy in acute IS, although sICH within 36 hours was numerically more frequent in SCD patients. The fact that SCD patients use EMS relatively less and arrive later may indicate that more education on early presentation may be needed. SCD-specific guidelines should be revised to emphasize acute treatment with tPA along with other care. Stroke guidelines should be revisited to strengthen the recommendation for tPA use in SCD based on these data. Adults with SCD and acute IS should be treated with thrombolysis if they otherwise qualify based on current guidelines. Additional studies should track the intracranial hemorrhage rate and capture SCD-specific care such as transfusion.

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References

1. Ohene-Frempong K, Weiner SJ, Sleeper LA, Miller ST, Embury S, Moohr JW, et al. Cerebrovascular accidents in sickle cell disease: rates and risk factors. *Blood*. 1998;91:288–294.
2. Dobson SR, Holden KR, Nietert PJ, Cure JK, Laver JH, Disco D, et al. Moyamoya syndrome in childhood sickle cell disease: a predictive factor for recurrent cerebrovascular events. *Blood*. 2002;99:3144–3150.
3. Tissue plasminogen activator for acute ischemic stroke. *N Eng J Med*. 1995;333:1581–1588. doi: 10.1056/NEJM199512143332401.
4. Demaerschalk BM, Kleindorfer DO, Adeoye OM, Demchuk AM, Fugate JE, Grotta JC, et al; American Heart Association Stroke Council and Council on Epidemiology and Prevention. Scientific rationale for the inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke: a statement for healthcare professionals from the American

Heart Association/American Stroke Association. *Stroke*. 2016;47:581–641. doi: 10.1161/STR.0000000000000086.
5. Evidence-Based Management of Sickle Cell Disease: Expert Panel Report, 2014. NHLBI, NIH website. http://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines. Accessed April 12, 2016.
6. Schwamm LH, Fonarow GC, Reeves MJ, Pan W, Frankel MR, Smith EE, et al. Get With The Guidelines-Stroke is associated with sustained improvement in care for patients hospitalized with acute stroke or transient ischemic attack. *Circulation*. 2009;119:107–115. doi: 10.1161/CIRCULATIONAHA.108.783688.
7. LaBresh KA, Reeves MJ, Frankel MR, Albright D, Schwamm LH. Hospital treatment of patients with ischemic stroke or transient ischemic attack using the "Get With The Guidelines" program. *Arch Intern Med*. 2008;168:411–417. doi: 10.1001/archinternmed.2007.101.

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