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Trends in Reperfusion Therapy for In-Hospital Ischemic Stroke in the Endovascular Therapy Era

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IMPORTANCE A significant proportion of acute ischemic strokes occur while patients are hospitalized. Limited contemporary data exist on the utilization rates of intravenous thrombolysis or endovascular therapy for in-hospital stroke.

OBJECTIVE To use a national registry to examine temporal trends in the use of intravenous and endovascular reperfusion therapies for treatment of in-hospital stroke.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study analyzed data from 267 956 patients who underwent reperfusion therapy for stroke with in-hospital or out-of-hospital onset reported in the Get With the Guidelines-Stroke national registry from January 2008 to September 2018.

EXPOSURES In-hospital onset vs out-of-hospital onset of stroke symptoms.

MAIN OUTCOMES AND MEASURES Temporal trends in the use of reperfusion therapy, process measures of quality, and the association between functional outcomes and key patient characteristics, comorbidities, and treatments.

RESULTS Of 67 493 patients with in-hospital stroke onset, this study observed increased rates of vascular risk factors (standardized mean difference >10%) but no significant differences in age or sex in patients undergoing intravenous thrombolysis only (mean [interquartile range {IQR}] age, 72 [80-62] y; 53.2% female) or those undergoing endovascular therapy (mean [IQR] age, 69 [59-79] y; 49.8% female). Of these patients, 10 481 (15.5%) received intravenous thrombolysis and 2494 (3.7%) underwent endovascular therapy. Compared with 2008, in 2018 the proportion of in-hospital stroke among all stroke hospital discharges was higher (3.5% vs 2.7%; $P < .001$), as was use of intravenous thrombolysis (19.1% vs 9.1%; $P < .001$) and endovascular therapy (6.4% vs 2.5%; $P < .001$) in patients with in-hospital stroke, with a significant increase in endovascular therapy in mid-2015 ($P < .001$). Compared with patients who received intravenous thrombolysis for out-of-hospital stroke onset, those with in-hospital onset were associated with longer median (IQR) times from stroke recognition to cranial imaging (33 [18-60] vs 16 [9-26] minutes; $P < .001$) and to thrombolysis bolus (81 [52-125] vs 60 [45-84] minutes; $P < .001$). In adjusted analyses, patients with in-hospital stroke onset who were treated with intravenous thrombolysis were less likely to ambulate independently at discharge (adjusted odds ratio, 0.78; 95% CI, 0.74-0.82; $P < .001$) and were more likely to die or to be discharged to hospice (adjusted odds ratio, 1.39; 95% CI, 1.29-1.50; $P < .001$) than patients with out-of-hospital onset who also received intravenous thrombolysis treatment. Comparisons among patients treated with endovascular therapy yielded similar findings.

CONCLUSIONS AND RELEVANCE In this cohort study, in-hospital stroke onset was increasingly reported and treated with reperfusion therapy. Compared with out-of-hospital stroke onset, in-hospital onset was associated with longer delays to reperfusion and worse functional outcomes, highlighting opportunities to further care for patients with in-hospital stroke onset.

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I n-hospital onsets of acute ischemic stroke (AIS) account for 2.2% to 10.8% of all AIS.[1-4] These in-hospital AISs are often associated with more severe clinical syndromes, increased medical comorbidities, and higher rates of poor functional outcome and in-hospital mortality.[3,5,6] The limited national data that exist on the use of intravenous thrombolysis (IVT) for treatment of in-hospital stroke have shown that patients with in-hospital strokes have longer delays from recognition to imaging and to thrombolysis and are overall less likely to be treated with IVT even in the absence of contraindications than patients with out-of-hospital stroke onset.[1,4,7-9]

No large national data have yet been reported on the use of endovascular therapy (EVT) in patients with AIS onset in the hospital.[4] Given the changing landscape of reperfusion therapy with the advent of EVT, we sought to characterize the temporal trends of reperfusion therapy for in-hospital stroke, comparing patient characteristics, process measures of quality, and outcomes for in-hospital vs out-of-hospital stroke onset in a national registry.[10]

Methods

We performed a retrospective cohort analysis of the American Heart Association Get With the Guidelines–Stroke registry, a voluntary, national stroke registry and performance improvement program with more than 6 million stroke admissions reported. The details and validity of the program have been previously described.[11,12] IQVIA is the data coordination center. The Duke Clinical Research Institute is the statistical coordinating center and analyzes deidentified data under an institutional review board–approved protocol. The requirement for obtaining informed consent was waived by local institutional review boards. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Study Population

We retrospectively reviewed patients 18 years or older admitted to Get With the Guidelines–Stroke hospitals between January 1, 2008, and September 30, 2018. Patients were included if they were admitted via the emergency department with AIS or experienced AIS while hospitalized, for a total of 2 869 919 patients from 2338 sites (eFigure 1 in the Supplement). Because imaging and treatment times from initial presentation are significantly confounded by interhospital transfers, patients were excluded if they were admitted via hospital to hospital transfer (408 806 patients and 2 sites were excluded). Patients were also excluded if they left against medical advice or had unknown discharge disposition (27 529 patients and 3 sites were excluded) or if reperfusion data were missing (5356 patients excluded). Sites with less than 30 thrombolysis or thrombectomy attempts (190 435 patients, 978 sites) during the 10-year study period were excluded. These sites were thought to be nonrepresentative, low-volume centers without a robust system of stroke care to deliver reperfusion therapy.

Key Points

Question How has reperfusion therapy for in-hospital onset of ischemic stroke changed in the endovascular era?

Findings This cohort study of 2 237 793 patients found that in-hospital stroke onset was increasingly reported. Endovascular therapy use steadily increased after 2015, whereas the rate of intravenous thrombolysis use doubled since 2008; however, patients with in-hospital stroke onset underwent intravenous thrombolysis and endovascular therapies at significantly slower rates with worse functional outcomes than those with out-of-hospital onset.

Meaning Although patients with in-hospital stroke onset were increasingly reported and treated with reperfusion therapy, disparities in care persisted, highlighting opportunities to further care for these patients, including the use of dedicated inpatient stroke protocols to bridge this disparity in stroke care.

The study population of interest comprised patients with in-hospital or out-of-hospital stroke onset who were treated with either IVT or EVT (267 956 patients from 1355 sites). Data from patients were not analyzed if they did not undergo reperfusion therapy. The exposure of interest was patient location at time of stroke symptom recognition by the health system, dichotomized by onset in the hospital vs out of the hospital.

Population Characteristics

Patient characteristics included age, sex, race/ethnicity, insurance status, medical comorbidities, preadmission medications, vital signs on presentation, National Institutes of Health Stroke Scale (NIHSS) score on arrival, and mode of arrival. Hospital characteristics included the volume of patients with ischemic stroke, stroke certification by the Joint Commission, academic status, rural location, geographic region, and number of beds.

Outcome Measures

Primary outcomes were time intervals to cranial imaging, to IVT, and to EVT. For out-of-hospital stroke onset, the index time was the time of presentation to the emergency department. For in-hospital stroke onset, the index time was symptom recognition because it was the first opportunity by health care staff to mobilize stroke systems of care. This permitted direct comparisons of systems of stroke care once the stroke response team had been activated. Latency from symptom onset to imaging was not analyzed owing to intrinsic differences between time intervals for in vs out of the hospital that would not reflect comparable systems of care. Symptom recognition was therefore used as the index time to directly compare the efficiency of systems of stroke care for in-hospital vs out-of-hospital stroke onset once the system had been activated and had the opportunity to respond. Secondary outcomes included rates of thrombolysis within 60 minutes, endovascular therapy within 120 minutes, in-hospital mortality, and symptomatic intracranial hemorrhage as well as the distribution at discharge of potential postacute destinations, ambulatory status, and modified Rankin Scale scores.

Statistical Analysis

We described the annual reperfusion rates of IVT only, or of EVT with or without IVT, among patients with in-hospital onset of ischemic stroke from 2008 to 2018. The Cochran-Armitage test for trend was used to assess the trend for each reperfusion treatment. Quarterly reperfusion rates were also calculated and are presented in plots. A linear model was fitted on quarterly IVT rates, and a piecewise linear model was fitted on quarterly EVT rates with 2 cutoffs, at 2013 and 2015, to assess the temporal trends. Cutoffs were chosen based on the triad of negative trials in 2013 and the subsequent positive trials in 2015.[13-20]

We then compared patient demographic characteristics, clinical data, and hospital characteristics between patients with in-hospital vs out-of-hospital onset in each treatment cohort. Categorical variables are presented as counts and proportions, and differences were tested using the Pearson χ^2 test. Continuous variables are presented as the median (interquartile range [IQR]), and differences between groups were tested using the Wilcoxon rank sum test. Given the large sample size, percent standardized mean differences (SMDs) were also provided for all variables between the groups of patients with in-hospital vs out-of-hospital stroke onset to help distinguish meaningful differences between groups. Standardized mean differences greater than 10% are considered a meaningful difference, rather than using P values alone for consideration of statistical significance.

Unadjusted and adjusted associations between short-term outcomes and symptom location were analyzed in each treatment cohort by using logistic regression models. Covariates in the multivariable models included patient characteristics: age, sex, race/ethnicity (White, Black, Hispanic, Asian, and other), medical history (atrial fibrillation or flutter, previous stroke or transient ischemic attack, coronary artery disease or prior myocardial infarction, diabetes, heart failure, carotid stenosis, peripheral vascular disease, hypertension, dyslipidemia, and smoking), arrival during routine working hours, NIHSS score, admission year, and hospital characteristics (geographic region, teaching status, rural location, number of beds, annual admissions for ischemic stroke, and stroke center certification). Generalized estimating equations were used to account for the correlation of cases from the same site. Missing covariates were handled by imputation based on patient or hospital characteristics and the extent of missingness, as detailed in eTable 1 in the Supplement.

Analyses were performed using SAS, version 9.4 (SAS Institute Inc). All P values are from 2-sided tests and are considered statistically significant at less than .05.

Results

After exclusions, we identified 2 237 793 patients discharged with acute ischemic stroke at 1355 sites (eFigure 1 in the Supplement). Of these patients, 67 493 (3.0%) (mean [IQR] age, 72 [60-82] years; 53.2% female) at 1340 sites had in-hospital stroke onset. There was a significant increase in the proportion of in-hospital strokes among all AIS discharges reported in Get With

the Guidelines from 2008 to 2018 (2.7% vs 3.5%; $P < .001$), and a significant increase in the percentage of sites entering any stroke with in-hospital onset into the Get With the Guidelines registry (61.9% to 73.6%; $P < .001$) (**Figure**, A). Of 67 493 patients with in-hospital stroke onset, 10 481 (15.5%) were treated with IVT and 2494 (3.7%) underwent EVT. Of the 2 170 250 patients with out-of-hospital stroke, 214 345 (9.9%) were treated with IVT and 40 636 (1.9%) underwent EVT. During the study period, IVT utilization rates for in-hospital stroke onset steadily increased (9.1% vs 19.1%; $P < .001$) (Figure, B and C). Inclusion of sites with low numbers of reperfusions did not modify this trend (eTable 2 in the Supplement). During this same period, the rate of EVT for in-hospital stroke onset was stable at 2.5% from 2008 through the first quarter (Q1) of 2015, with nonsignificant changes in utilization rates both before 2013 and between Q1 2013 and the Q1 2015. After the positive endovascular trials were published in Q1 2015, there was a 0.23% per quarter increase in EVT rates every quarter thereafter ($P < .001$; Figure, D). As of the third quarter of 2018, 6.9% of strokes with in-hospital onset were treated with EVT. Given the increasing reports of both in-hospital stroke and reperfusion therapy, we assessed the demographic, clinical, and outcome differences between groups of patients with stroke onset in vs out of the hospital who had received reperfusion therapies.

Intravenous Thrombolysis Only

First, we compared patients receiving IVT only, dichotomized by location of stroke onset. Patients did not differ significantly by race/ethnicity, age, or sex between stroke onset in the hospital vs out of the hospital or by treatment with reperfusion therapy. There were important differences in medical comorbidities, with higher rates of vascular risk factors, heart failure, and kidney insufficiency and lower functional ambulatory status among patients with AIS having in-hospital onset, and higher rates of premorbid medications for these risk factors among patients with AIS having in-hospital onset who underwent EVT (**Table 1**). The patients in these cohorts were otherwise similar, except for a small but significant difference in the NIHSS score distribution among IVT-treated patients. Given that the criteria to offer reperfusion therapy may have changed after the publication of the 2015 randomized EVT trials, we repeated this analysis restricted to patients treated during or after 2015 and found similar between-group differences in demographic and baseline characteristics (eTable 3 in the Supplement). A full list of all baseline characteristics assessed is reported in eTable 4 in the Supplement.

Patients with in-hospital stroke onset who received IVT only had longer median (IQR) times from presentation to cranial imaging (33 [18-60] vs 16 [9-26] minutes; $P < .001$) or to IVT bolus (81 [52-125] vs 60 [45-84] minutes; $P < .001$) and from cranial imaging to IVT bolus (61 [36-101] vs 42 [28-62] minutes; $P < .001$) (**Table 2**). These results were similar when restricting analyses to patients presenting from 2015 (eTable 5 in the Supplement). Latencies to cranial imaging and IVT improved each year during the 10-year study period, although the differences between the in-hospital and out-of-hospital groups persisted ($P < .01$) (eFigure 2 in the Supplement). The median

Figure. Proportions and Trends of Reperfusion Therapy for Patients With In-Hospital Stroke Onset From 2008 to 2018 in the Get With The Guidelines-Stroke National Database
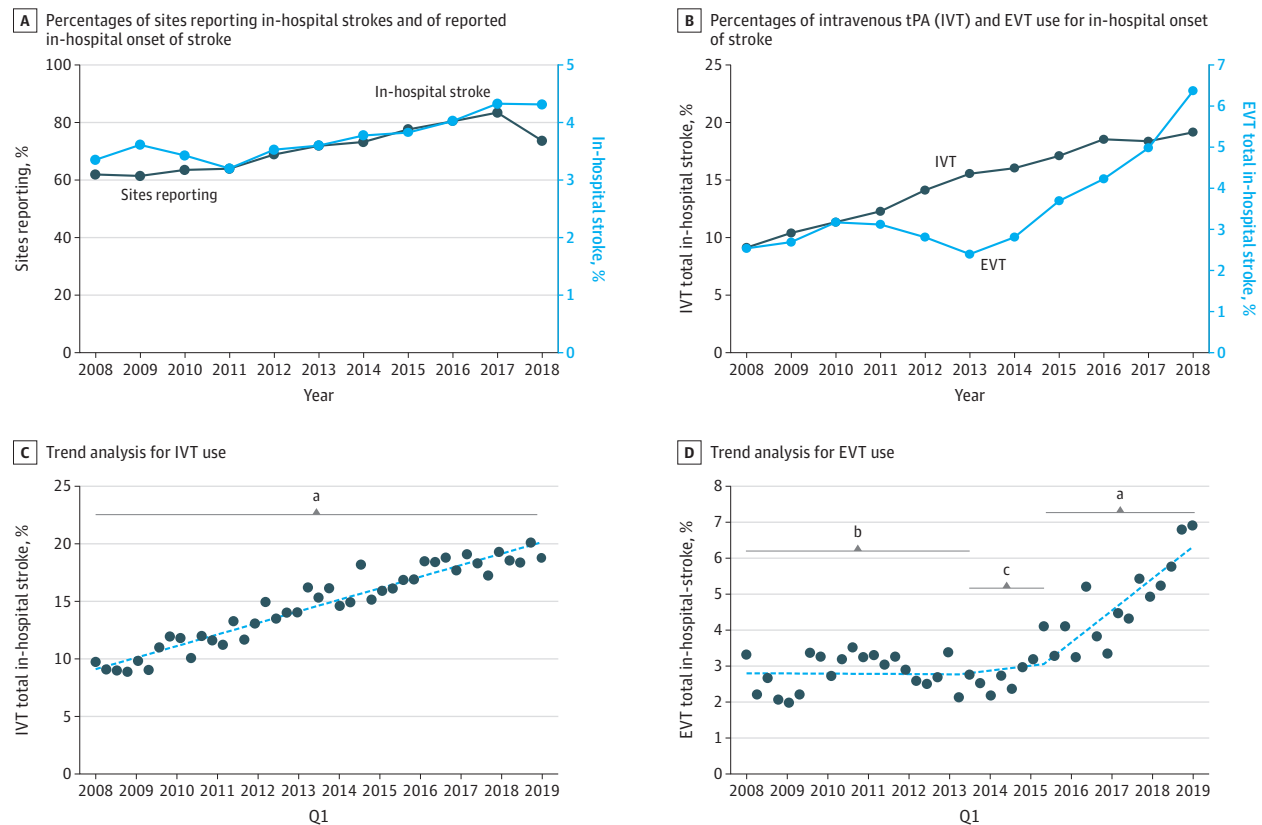
A and B, Trend analysis performed with the Cochran-Armitage test; P < .001 for both metrics presented in each plot. C, Linear model fitted on quarterly intravenous thrombolysis (IVT) rates indicates a slope of 0.26 (P < .001) and an estimated annual utilization rate increase of 1.05%. D, Piecewise linear models with cutoffs at 2013 and 2015 were used to account for the publishing of the negative (2013) and subsequent positive (2015) endovascular therapy (EVT) trials. No significant increase in EVT use before 2015; estimated annual increase in EVT use after 2015 is 0.93%, with a slope of 0.23 (P < .001). Q1 indicates first quarter; and tPA, tissue plasminogen activator.

[a] P < .001.
[b] P = .94.
[c] P = .40.

(IQR) modified Rankin Scale score at hospital discharge was clinically similar but statistically different in both groups (3 [1-4] vs 3 [1-4]; P < .001) but was missing in a large number of participants (49.7% of patients with in-hospital onset and 55.7% of patients with out-of-hospital onset) and was not further analyzed.

After adjusting for available patient and hospital characteristics, patients with in-hospital stroke onset were less likely than those with out-of-hospital onset to be treated with IVT within 60 minutes of onset (adjusted odds ratio [aOR], 0.45; 95% CI, 0.42-0.48; P < .001) (Table 3). Patients with in-hospital onset had worse functional outcomes at hospital discharge, with decreased likelihood of independent ambulation (aOR, 0.78; 95% CI, 0.74-0.82; P < .001) or of being discharged to home (aOR, 0.69; 95% CI, 0.66-0.73; P < .001), and increased likelihood of in-hospital mortality or discharge to hospice (aOR, 1.39; 95% CI, 1.29-1.50; P < .001). The rates of symptomatic intracranial hemorrhage were not different between the 2 groups (aOR, 0.93; 95% CI, 0.83-1.05; P = .26).

Endovascular Therapy

We next compared patients who received EVT, dichotomized by location of stroke onset. Compared with patients with out-of-hospital stroke onset who received EVT, those with in-hospital onset were more likely to have vascular risk factors, including coronary artery disease, peripheral vascular disease, chronic heart failure, and chronic kidney failure, and were more likely to be taking antiplatelet, anticoagulant, antihypertensive, cholesterol-reducing, or diabetic drugs (Table 1). Restricting the patients included to only those treated after the publication of the 2015 EVT trials did not modify the observed between-group differences in demographic and baseline characteristics (eTable 3 in the Supplement). A full list of baseline characteristics is reported in eTable 6 in the Supplement.

Despite similar NIHSS scores, patients with in-hospital stroke onset who received EVT had longer median (IQR) times from presentation to cranial imaging (38 [22-69] vs 15 [9-26] minutes; P < .001; SMD 102.9%) and to arterial puncture

Table 1. Demographic and Baseline Characteristics of Patients Receiving IVT Only or EVT After Experiencing In-Hospital vs Out-of-Hospital Stroke Onset

Variable	IVT only, No. (%)				EVT, No. (%)			
	Overall (n = 224 826)	In-hospital stroke (n = 10 481)	Out-of-hospital stroke (n = 214 345)	SMD, %[a]	Overall (n = 43 130)	In-hospital stroke (n = 2494)	Out-of-hospital stroke (n = 40 636)	SMD, %[a]
Demographic characteristic								
Age, mean (IQR), y[b]	71 (59-82)	72 (60-82)	71 (59-82)	3.7	71 (59-81)	69 (59-79)	71 (59-81)	6.7
Female	112 720 (50.1)	5579 (53.2)	107 141 (50.0)	6.5	21 651 (50.2)	1243 (49.8)	20 408 (50.2)	0.8
Race/ethnicity								
White	156 608 (69.7)	7238 (69.2)	149 370 (69.8)		29 661 (68.8)	1754 (70.4)	27 907 (68.7)	
Black	34 818 (15.5)	1752 (16.7)	33 066 (15.4)		6745 (15.6)	371 (14.9)	6374 (15.7)	
Hispanic (any race)	17 243 (7.7)	736 (7.0)	16 507 (7.7)	4.3	3207 (7.4)	187 (7.5)	3020 (7.4)	5.5
Asian	6664 (3.0)	295 (2.8)	6369 (3.0)		1487 (3.4)	67 (2.7)	1420 (3.5)	
Other, not reported	9283 (4.1)	445 (4.3)	8838 (4.1)		2009 (4.7)	113 (4.5)	1896 (4.7)	
Medical history[c]								
Coronary artery disease	53 571 (23.9)	3073 (29.4)	50 498 (23.7)	13.0	10 127 (23.5)	813 (32.6)	9314 (23.0)	21.7
Diabetes	63 803 (28.5)	3449 (33.0)	60 354 (28.3)	10.2	10 754 (25.0)	725 (29.1)	10 029 (24.7)	9.8
Peripheral vascular disease	7920 (3.5)	545 (5.2)	7375 (3.5)	8.6	1663 (3.9)	171 (6.9)	1492 (3.7)	14.3
Heart failure	20 792 (9.3)	1512 (14.5)	19 280 (9.0)	16.9	5005 (11.6)	415 (16.7)	4590 (11.3)	15.4
Chronic kidney insufficiency	11 203 (5.0)	788 (7.5)	10 415 (4.9)	11.0	2244 (5.2)	206 (8.3)	2038 (5.0)	13.0
Premorbid ambulation								
Independent	154 624 (88.3)	7366 (86.4)	147 258 (88.4)		31 803 (87.6)	1818 (82.2)	29 985 (88.0)	
With assistance	6459 (3.7)	414 (4.9)	6045 (3.6)	7.9	1084 (3.0)	118 (5.3)	966 (2.8)	17.3
Unable to ambulate	4083 (2.3)	177 (2.1)	3906 (2.3)		666 (1.8)	60 (2.7)	606 (1.8)	
Arrival information								
Off-hour presentation[d]	121 506 (54.0)	5724 (54.6)	115 782 (54.0)	1.2	22 295 (51.7)	1426 (57.2)	20 869 (51.4)	11.7
Initial NIHSS score, median (IQR)	8 (4-15)	8 (4-14)	8 (4-15)	12.3	16 (10-21)	16 (9-21)	16 (10-21)	1.9
Premorbid medication								
Antiplatelet	94 950 (47.1)	4797 (50.0)	90 153 (47.0)	6	15 877 (42.7)	1075 (50.3)	14 802 (42.2)	16.4
Anticoagulant	11 805 (8.5)	720 (11.0)	11 085 (8.3)	9.1	6968 (22.9)	559 (31.7)	6409 (22.3)	21.3
Antihypertensive	124 113 (65.9)	6465 (69.6)	117 648 (65.7)	8.4	25 133 (64.5)	1695 (72.1)	23 438 (64.0)	17.3
Cholesterol reducer	95 571 (42.6)	4796 (45.9)	90 775 (42.5)	6.9	17 508 (40.7)	1142 (45.9)	16 366 (40.4)	11.2
Diabetic	39 327 (21.6)	2323 (25.8)	37 004 (21.4)	10.4	6715 (18.0)	505 (22.2)	6210 (17.7)	11.3

Abbreviations: EVT, endovascular therapy; IQR, interquartile range; IVT, intravenous thrombolysis; NIHSS, National Institutes of Health Stroke Scale; SMD, standardized mean difference.

[a] SMD higher than 10.0% is considered meaningful.

[b] Continuous variable.

[c] Additional variables tested but not reported owing to the lack of significant differences between arrival mode for either IVT or EVT include atrial fibrillation/flutter, prosthetic heart valve, previous stroke/ transient ischemic attack, carotid stenosis, hypertension, smoking, and dyslipidemia.

[d] Defined as any stroke presentation and recognition outside of regular hours (7 AM to 6 PM weekdays, excluding holidays).

(165 [113-245] vs 138 [96-202] minutes; P < .001; SMD, 29.8%) (Table 2); however, the delay from computed tomography to arterial puncture was not significantly different as measured by SMD (126 [79-211] vs 120 [81-178] minutes; P < .001; SMD 7.8%). These results were similar when restricting the analysis to patients presenting from 2015 (eTable 5 in the Supplement). Latencies to cranial imaging and EVT improved each year during the 10-year study period, although the differences between the in-hospital and out-of-hospital groups persisted (P < .01) (eFigure 2 in the Supplement). Fewer patients with in-hospital stroke had IVT before EVT (25.8% vs 45.6%; P < .001). The median (IQR) modified Rankin Scale score at hospital discharge was higher for patients with in-hospital stroke onset (4 [3-6] vs 4 [3-5]; P < .001), but this variable was missing in 40.9% of patients in the EVT group with in-hospital

onset and 40.2% in the EVT group with out-of-hospital onset and was not further analyzed.

After adjusting for patient and hospital characteristics, patients with in-hospital stroke onset were less likely to be treated within 120 minutes of symptom recognition or emergency department arrival (aOR, 0.65; 95% CI, 0.57-0.75; P < .001) (Table 4). Despite a decreased risk of symptomatic intracranial hemorrhage among EVT-treated patients with in-hospital stroke onset compared with out-of-hospital onset (aOR, 0.75; 95% CI, 0.61-0.92; P = .005), functional outcomes at hospital discharge were still worse for those with in-hospital onset, with decreased likelihood of ambulating independently (aOR, 0.77; 95% CI, 0.68-0.86; P < .001) or being discharged to home (aOR, 0.68; 95% CI, 0.61-0.77; P < .001). Patients who received EVT for stroke with in-hospital onset

Table 2. Quality Metrics and Short-term Treatment Outcome for Patients Receiving IVT Only or EVT After Experiencing In-Hospital vs Out-of-Hospital Stroke Onset

	IVT only, No. (%)				EVT, No. (%)			
Variable	Overall (n = 224 826)	In-hospital stroke (n = 10 481)	Out-of-hospital stroke (n = 214 345)	SMD, %[a]	Overall (n = 43 130)	In-hospital stroke (n = 2494)	Out-of-hospital stroke (n = 40 636)	SMD, %[a]
Quality metrics[b]								
Presentation to CT, min[c]								
Median (IQR)	16 (9-26)	33 (18-60)	16 (9-26)	80.5	16 (9-28)	38 (22-69)	15 (9-26)	102.9
Missing	7287 (3.3)	2274 (22.4)	5013 (2.4)		1113 (2.7)	368 (15.6)	745 (1.9)	
CT to treatment, min[c]								
Median (IQR)	43 (28-63)	61 (36-101)	42 (28-62)	50.2	120 (81-180)	126 (79-211)	120 (81-178)	7.8
Missing	10 281 (4.6)	606 (6.0)	9675 (4.5)		5847 (13.9)	374 (15.9)	5473 (13.8)	
Presentation to treatment, min[c]								
Median (IQR)	60 (45-85)	81 (52-125)	60 (45-84)	44.4	139 (97-204)	165 (113-245)	138 (96-202)	29.8
Missing	2202 (1.0)	438 (4.2)	1764 (0.8)		5383 (12.5)	442 (17.7)	4941 (12.2)	
Received EVT and IVT								
Yes	NA	NA	NA	NA	19 172 (44.5)	642 (25.8)	18 530 (45.6)	42.3
Missing					35 (0.1)	5 (0.2)	30 (0.1)	
Short-term outcome								
Discharge disposition								
Home	105 143 (46.8)	4217 (40.2)	100 926 (47.1)		11 497 (26.7)	526 (21.1)	10 971 (27.0)	
Hospice	10 976 (4.9)	497 (4.7)	10 479 (4.9)		2954 (6.8)	190 (7.6)	2764 (6.8)	
SNF	32 267 (14.4)	1696 (16.2)	30 571 (14.3)		6912 (16.0)	422 (16.9)	6490 (16.0)	
IRF	51 773 (23.0)	2398 (22.9)	49 375 (23.0)	19.7	13 251 (30.7)	722 (28.9)	12 529 (30.8)	22.2
Acute care facility	7415 (3.3)	644 (6.1)	6771 (3.2)		1023 (2.4)	35 (1.4)	988 (2.4)	
Other health care facility	3781 (1.7)	206 (2.0)	3575 (1.7)		1354 (3.1)	89 (3.6)	1265 (3.1)	
In-hospital death	13 471 (6.0)	823 (7.9)	12 648 (5.9)		6139 (14.2)	510 (20.4)	5629 (13.9)	
Discharge ambulatory status								
Independent	95 144 (48.6)	4212 (45.1)	90 932 (48.8)		12 302 (30.9)	631 (26.9)	11 671 (31.1)	
With assistance	55 512 (28.3)	2654 (28.4)	52 858 (28.3)		11 812 (29.7)	623 (26.5)	11 189 (29.9)	
Unable to ambulate	31 735 (16.2)	1650 (17.7)	30 085 (16.1)	9.8	9566 (24.0)	585 (24.9)	8981 (24.0)	18.8
In-hospital death	13 471 (6.9)	823 (8.8)	12 648 (6.8)		6139 (15.4)	510 (21.7)	5629 (15.0)	
Missing	28 964 (12.9)	1142 (10.9)	27 822 (13.0)		3311 (7.7)	145 (5.8)	3166 (7.8)	
sICH								
Yes	8373 (3.8)	357 (3.5)	8016 (3.9)	2.0	2587 (6.1)	129 (5.2)	2458 (6.1)	3.8
Missing	6977 (3.1)	222 (2.1)	6755 (3.2)		492 (1.1)	36 (1.4)	456 (1.1)	

Abbreviations: CT, computed tomography; EVT, endovascular therapy; IRF, inpatient rehabilitation facility; IQR, interquartile range; IVT, intravenous thrombolysis; NA, not applicable; sICH, symptomatic intracranial hemorrhage within 36 hours of treatment; SMD, standardized mean difference; SNF, skilled nursing facility.

[a] SMD higher than 10% is considered meaningful.

[b] Index times for quality intervals are the time of presentation to the emergency department for out-of-hospital stroke and time to symptom recognition for in-hospital stroke onset.

[c] Continuous variable.

were more likely to die or be discharged to hospice (aOR, 1.58; 95% CI, 1.43-1.75; *P* < .001).

Discussion

Using a representative, nationwide registry of patients with acute ischemic stroke from 2008 to 2018, we found that in-hospital stroke onset was increasingly reported and treated with reperfusion therapy, but was nevertheless associated with longer de-

lays in imaging and treatment initiation and worse functional outcomes than patients with out-of-hospital stroke onset.

In-hospital stroke onset was increasingly reported in this national registry, both in terms of percentages of overall cases and of sites reporting in-hospital stroke onset (Figure). We hypothesized that in the endovascular era, EVT would be increasingly used while IVT rates would remain relatively stable. As hypothesized, EVT utilization rates for in-hospital strokes significantly increased after the publication of the pivotal 2015 trials, with quarterly increases of 0.2% after publication in the

Table 3. Association Between In-Hospital Stroke Onset and IVT Treatment Only Outcome in an Adjusted Model

Short-term outcome	Unadjusted analysis		Adjusted for patient characteristics[a]		Adjusted for patient and hospital characteristics[a,b]	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Symptom recognition to IVT ≤60 min	0.50 (0.47-0.53)	<.001	0.45 (0.42-0.48)	<.001	0.45 (0.42-0.48)	<.001
In-hospital mortality or discharge to hospice[c]	1.21 (1.14-1.29)	<.001	1.38 (1.28-1.49)	<.001	1.39 (1.29-1.50)	<.001
Discharge to home[c]	0.75 (0.72-0.79)	<.001	0.69 (0.65-0.72)	<.001	0.69 (0.66-0.73)	<.001
Symptomatic intracranial hemorrhage	0.90 (0.80-1.01)	.07	0.94 (0.84-1.06)	.30	0.93 (0.83-1.05)	.26
Independent ambulation at discharge[c]	0.83 (0.79-0.87)	<.001	0.78 (0.74-0.82)	<.001	0.78 (0.74-0.82)	<.001

Abbreviations: IVT, intravenous thrombolysis; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.

[a] The following patient variables were included in the adjusted models: age, sex, race, medical history (atrial fibrillation, prior stroke or transient ischemic attack, coronary artery disease, diabetes, heart failure, carotid stenosis, peripheral vascular disease, hypertension, dyslipidemia, and smoking), arrival via ambulance, arrival during on or off hours, NIHSS score, and admission year.

[b] The following hospital characteristics were included: geographic region, teaching status, rural location, number of beds, annual admissions for ischemic stroke, and stroke center certification status.

[c] In-hospital deaths were not excluded from the denominator population for these outcomes.

Table 4. Association Between In-Hospital Stroke Onset and EVT Outcome in an Adjusted Model

Short-term outcome	Unadjusted analysis		Adjusted for patient characteristics[a]		Adjusted for patient and hospital characteristics[a,b]	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Symptom recognition to EVT ≤120 min	0.65 (0.58-0.73)	<.001	0.65 (0.57-0.75)	<.001	0.65 (0.57-0.75)	<.001
In-hospital mortality or discharge to hospice[c]	1.48 (1.36-1.61)	<.001	1.57 (1.42-1.73)	<.001	1.58 (1.43-1.75)	<.001
Discharge to home[c]	0.76 (0.69-0.84)	<.001	0.68 (0.61-0.76)	<.001	0.68 (0.61-0.77)	<.001
Symptomatic intracranial hemorrhage	0.84 (0.70-1.02)	.08	0.75 (0.61-0.92)	.005	0.75 (0.61-0.92)	.005
Independent ambulation at discharge[c]	0.83 (0.75-0.92)	.001	0.77 (0.69-0.86)	<.001	0.77 (0.68-0.86)	<.001

Abbreviations: EVT, endovascular therapy; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.

[a] The following patient variables were included in the adjusted models: age, sex, race, medical history (atrial fibrillation, prior stroke or transient ischemic attack, coronary artery disease, diabetes, heart failure, carotid stenosis, peripheral vascular disease, hypertension, dyslipidemia, smoking), arrival via ambulance, arrival during on or off hours, NIHSS score, and admission year.

[b] The following hospital characteristics were included: geographic region, teaching status, rural location, number of beds, annual admissions for ischemic stroke, and stroke center certification status.

[c] In-hospital deaths were not excluded from the denominator population for these outcomes.

first quarter of 2015 through the end of this study period. In contrast to our hypothesis, the reported IVT utilization rate also significantly increased throughout this period, doubling during this 10-year span (9.1% vs 19.1%). Some of this increase may be due to increased ascertainment and reporting of in-hospital strokes, with a greater tendency to include cases if they received IVT or EVT.

Despite the observed increase in utilization rates, the present study found that disparities in both care and outcomes persisted for in-hospital stroke onset. Compared with patients with out-of-hospital stroke onset, those with in-hospital onset had longer times from symptom recognition to imaging and reperfusion therapy initiation, and these patients had worse functional outcomes even when controlling for known patient- and hospital-specific factors in adjusted analyses. It is possible that unmeasured confounding accounted for some of the difference in outcomes, but it is possible that the time delays were also important associated factors. In both the EVT- and IVT-treated cohorts, in-hospital stroke onset was associated with decreased odds of discharging to home or ambulating independently at hospital discharge, and increased likelihood of in-hospital mortality or hospice placement. This study also found that EVT for in-hospital onset was associated with decreased symptomatic

intracranial hemorrhage, although this is likely due in part to these patients being less likely to have received IVT prior to EVT (25.8% vs 45.6%). The lower utilization rates of IVT have been previously attributed to medical contraindications or delayed recognition from time last known to be well, and despite the decreased rates of symptomatic intracranial hemorrhage observed for the in-hospital patients who received EVT, these patients still had worse outcomes.[4] These data suggest that there may be unmeasured confounding factors beyond time delays that are associated with worse outcomes among patients who receive EVT.

Our data notably conflict with recent reports of comparable or even faster treatment times and equivalent outcomes for patients with in-hospital stroke onset who received EVT, although these reports were indexed to symptom onset and not to our use of stroke presentation.[21,22] Those studies were limited by being reported from single, high-volume centers, uncertainty about any bias regarding when in-hospital EVT was offered, and the low frequency of EVT for in-hospital stroke at any given institution. Conversely, our report leverages a national database to analyze time intervals in 2494 patients who experienced strokes at a hospital and were treated with EVT to show that similar to patients treated with IVT, patients receiving EVT had longer delays to treatment and

worse functional outcomes despite already being in the hospital at stroke onset.

These delays highlight challenges in standardizing acute care protocols for relatively low-frequency events throughout a hospital. We initially hypothesized that the greatest delay would be mobilizing the patient to the initial computed tomography scan, but that after cranial imaging was conducted, times from imaging to reperfusion therapy would be comparable. Activating acute stroke responders, identifying the appropriate radiology suite, and mobilizing an interdisciplinary team to transport the patient are likely slower in the inpatient setting as opposed to the emergency department, where higher volumes and numbers of dedicated personnel can facilitate the acute stroke treatment pathway. Even after the initial computed tomography scan, the present study found that there were still longer delays to both IVT bolus and arterial access for EVT. These delays likely reflect the lack of rigorous protocol use and adherence, similar to the early experience reported in the interventional cardiology literature, or the inability to rapidly access a legally authorized representative to provide consent.[23] Once the patient reaches the scanner, mobilizing reperfusion therapy resources should be similar, irrespective of location of stroke onset. In fact, several institutions have shown that with dedicated inpatient stroke protocols, treatment times and likelihood of offering reperfusion therapy can be significantly improved.[24-28] Those protocols vary, but they all share the following characteristics: defining a dedicated inpatient stroke response team, widespread educational programs for all hospital staff to recognize both the symptoms and acuity of a stroke, and expanding the pool of staff who can trigger an acute stroke response. Ensuring that the acute stroke alert activates a multidisciplinary set of responders (including stroke nursing, intravenous access nurse, neurologist, pharmacist, and radiologist) further accelerates and streamlines the initial stroke response. The paucity of in-hospital strokes in nonneurologic units complicates efforts to consistently execute those protocols, but there may be added yield in practicing the protocols in higher-frequency units, such as postsurgical units and cardiac units.[1] Finally, patients who require specialized nonneurologic care and experience an in-hospital stroke may be less likely to be transferred to a stroke unit. Given the improved outcomes associated with stroke units, this lack of transfer may further contribute to our observed differences associated with functional outcomes.[29]

Limitations

Our report has a number of limitations. First, by analyzing national registry data, we only evaluated hospitals that voluntarily chose to participate in this registry. This voluntary participation likely overrepresents facilities that were more invested in stroke quality improvement and may not have fully captured the state of in-hospital stroke nationally. Second, there may be reporting bias. Patients with in-hospital stroke onset who underwent reperfusion therapy may be more likely to be reported in the database than patients who did not receive reperfusion therapy, whereas those who were examined in consultation without IVT or EVT, or who were never examined by a neurologist, may be more likely to go unreported in the da-

tabase, especially if they were not discharged with a primary diagnosis of ischemic stroke. In addition, the incidence of in-hospital strokes is significantly lower in registry data sets than in single-center data sets, likely reflecting the decreased likelihood to report in-hospital strokes.[1,4,30-32] Furthermore, severe strokes may be more likely to be reported than minor strokes, confounding the reported proportions and severity of in-hospital stroke. Our analyses likely underestimated the denominator of both the proportion and rate of reperfusion for in-hospital stroke. Reporting bias is nevertheless unlikely to entirely explain the annual increase in reporting and reperfusion therapy for in-hospital stroke. Prior US and Canadian registry data reported 11% and 12% IVT use, respectively, for in-hospital stroke through 2012, consistent with our observations in the early part of our study period (eTable 1 in the Supplement).[1,4] As disparities in care for in-hospital stroke onset have been increasingly recognized, inpatient protocols have been developed to increase both the rates and speed of IVT administration.[24-28] Although the true denominator remains unknown, our data likely reflected this increased effort to both recognize and treat in-hospital stroke, with a consistent year-by-year increase in both reporting and reperfusion for in-hospital stroke onset. Third, prearrival notification systems, where present and used, alert emergency departments and stroke teams before the arrival of individuals with stroke onset outside the hospital, thereby potentially further accelerating the emergency department times to care. There is no corollary for this for in-hospital stroke onset. Finally, the indication for hospital admission is not reported in the national registry for in-hospital stroke onset, thereby limiting the ability to further comment on comorbidities or procedural complications that may be enriched in the inpatient cohort, such as cardiac interventions. It is likely that the comorbidities listed do not fully capture the general illness severity of already hospitalized patients and that these comorbid illnesses likely contribute to the worse functional outcome. Nevertheless, although comorbidities likely contribute to the observed worse outcomes, they do not negate the observed treatment delays in these patients. The inferior outcomes are likely associated with both treatment delays and comorbid illnesses.

Conclusions

In-hospital stroke onset was increasingly reported and treated with both intravenous and endovascular reperfusion therapies. Indeed, we found that a higher percentage of reported patients with in-hospital stroke than with out-of-hospital stroke received EVT. Nevertheless, disparities in systems of stroke care persist. This study found that patients with in-hospital stroke onset underwent intravenous and endovascular therapies at significantly slower rates with attendant worse functional outcomes than did patients with out-of-hospital stroke. These data highlight increased reporting of in-hospital stroke and use of reperfusion therapy while emphasizing opportunities to further improve inpatient systems of stroke care. Dedicated inpatient stroke protocols are advised to bridge this disparity in stroke care.

REFERENCES

1. Saltman AP, Silver FL, Fang J, Stamplecoski M, Kapral MK. Care and outcomes of patients with in-hospital stroke. *JAMA Neurol*. 2015;72(7):749-755. doi:10.1001/jamaneurol.2015.0284

2. Emmett ES, Douiri A, Marshall IJ, Wolfe CDA, Rudd AG, Bhalla A. A comparison of trends in stroke care and outcomes between in-hospital and community-onset stroke—the South London Stroke Register. *PLoS One*. 2019;14(2):e0212396. doi:10.1371/journal.pone.0212396

3. Bekelis K, Missios S, Coy S, MacKenzie TA. Comparison of outcomes of patients with inpatient or outpatient onset ischemic stroke. *J Neurointerv Surg*. 2016;8(12):1221-1225. doi:10.1136/neurintsurg-2015-012145

4. Cumbler E, Wald H, Bhatt DL, et al. Quality of care and outcomes for in-hospital ischemic stroke: findings from the national Get With The Guidelines-Stroke. *Stroke*. 2014;45(1):231-238. doi:10.1161/STROKEAHA.113.003617

5. Moradiya Y, Levine SR. Comparison of short-term outcomes of thrombolysis for in-hospital stroke and out-of-hospital stroke in United States. *Stroke*. 2013;44(7):1903-1908. doi:10.1161/STROKEAHA.113.000945

6. Walker AE, Robins M, Weinfeld FD. The National Survey of Stroke: clinical findings. *Stroke*. 1981;12(2, pt 2)(suppl 1):I13-I44.

7. Zhang C, Lou M, Chen Z, et al. Analysis of intravenous thrombolysis time and prognosis in patients with in-hospital stroke. Article in Chinese.

Zhejiang Da Xue Xue Bao Yi Xue Ban. 2019;48(3):
260-266.

8. Cumbler E, Murphy P, Jones WJ, Wald HL,
Kutner JS, Smith DB. Quality of care for in-hospital
stroke: analysis of a statewide registry. *Stroke*. 2011;
42(1):207-210. doi:10.1161/STROKEAHA.110.590265

9. Farooq MU, Reeves MJ, Gargano J, Wehner S,
Hickenbottom S, Majid A; Paul Coverdell National
Acute Stroke Registry Michigan Prototype
Investigators. In-hospital stroke in a statewide
stroke registry. *Cerebrovasc Dis*. 2008;25(1-2):12-20.
doi:10.1159/000111494

10. Smith EE, Saver JL, Cox M, et al. Increase
in endovascular therapy in Get With the
Guidelines-Stroke after the publication of pivotal
trials. *Circulation*. 2017;136(24):2303-2310. doi:10.
1161/CIRCULATIONAHA.117.031097

11. 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(4):411-417. doi:10.1001/
archinternmed.2007.101

12. Xian Y, Fonarow GC, Reeves MJ, et al. Data
quality in the American Heart Association Get With
The Guidelines (GWTG-Stroke): results from
a national data validation audit. *Am Heart J*. 2012;
163(3):392-398.e1. doi:10.1016/j.ahj.2011.12.012

13. Jovin TG, Chamorro A, Cobo E, et al; REVASCAT
Trial Investigators. Thrombectomy within 8 hours
after symptom onset in ischemic stroke. *N Engl J Med*.
2015;372(24):2296-2306. doi:10.1056/
NEJMoa1503780

14. Saver JL, Goyal M, Bonafe A, et al; SWIFT
PRIME Investigators. Stent-retriever thrombectomy
after intravenous t-PA vs. t-PA alone in stroke.
N Engl J Med. 2015;372(24):2285-2295. doi:10.
1056/NEJMoa1415061

15. Campbell BC, Mitchell PJ, Kleinig TJ, et al;
EXTEND-IA Investigators. Endovascular therapy for
ischemic stroke with perfusion-imaging selection.
N Engl J Med. 2015;372(11):1009-1018. doi:10.1056/
NEJMoa1414792

16. Goyal M, Demchuk AM, Menon BK, et al;
ESCAPE Trial Investigators. Randomized
assessment of rapid endovascular treatment of
ischemic stroke. *N Engl J Med*. 2015;372(11):1019-
1030. doi:10.1056/NEJMoa1414905

17. Berkhemer OA, Fransen PS, Beumer D, et al;
MR CLEAN Investigators. A randomized trial of
intraarterial treatment for acute ischemic stroke.
N Engl J Med. 2015;372(1):11-20. doi:10.1056/
NEJMoa1411587

18. Ciccone A, Valvassori L, Nichelatti M, et al;
SYNTHESIS Expansion Investigators. Endovascular
treatment for acute ischemic stroke. *N Engl J Med*.
2013;368(10):904-913. doi:10.1056/NEJMoa1213701

19. Broderick JP, Palesch YY, Demchuk AM, et al;
Interventional Management of Stroke (IMS) III
Investigators. Endovascular therapy after
intravenous t-PA versus t-PA alone for stroke.
N Engl J Med. 2013;368(10):893-903. doi:10.1056/
NEJMoa1214300

20. Kidwell CS, Jahan R, Gornbein J, et al;
MR RESCUE Investigators. A trial of imaging
selection and endovascular treatment for ischemic
stroke. *N Engl J Med*. 2013;368(10):914-923. doi:10.
1056/NEJMoa1212793

21. Caparros F, Ferrigno M, Decourcelle A, et al.
In-hospital ischaemic stroke treated with
intravenous thrombolysis or mechanical
thrombectomy. *J Neurol*. 2017;264(8):1804-1810.
doi:10.1007/s00415-017-8570-4

22. Lu MY, Chen CH, Yeh SJ, et al. Comparison
between in-hospital stroke and community-onset
stroke treated with endovascular thrombectomy.
PLoS One. 2019;14(4):e0214883. doi:10.1371/
journal.pone.0214883

23. Sun CH, Bhatt DL, Nogueira RG, Gupta R.
Endovascular therapy for stroke: getting to the
"heart" of the matter. *Circulation*. 2014;129(10):
1152-1160. doi:10.1161/CIRCULATIONAHA.113.003703

24. Koge J, Matsumoto S, Nakahara I, et al.
Improving treatment times for patients with

in-hospital stroke using a standardized protocol.
J Neurol Sci. 2017;381:68-73. doi:10.1016/j.jns.2017.
08.023

25. Kassardjian CD, Willems JD, Skrabka K, et al.
In-patient code stroke: a quality improvement
strategy to overcome knowledge-to-action gaps
in response time. *Stroke*. 2017;48(8):2176-2183.
doi:10.1161/STROKEAHA.117.017622

26. Yoo J, Song D, Baek JH, et al. Comprehensive
code stroke program to reduce reperfusion delay
for in-hospital stroke patients. *Int J Stroke*. 2016;11
(6):656-662. doi:10.1177/1747493016641724

27. Cumbler E, Anderson T, Neumann R, Jones WJ,
Brega K. Stroke alert program improves recognition
and evaluation time of in-hospital ischemic stroke.
J Stroke Cerebrovasc Dis. 2010;19(6):494-496.
doi:10.1016/j.jstrokecerebrovasdis.2009.09.007

28. Nolan S, Naylor G, Burns M. Code gray—an
organized approach to inpatient stroke. *Crit Care
Nurs Q*. 2003;26(4):296-302. doi:10.1097/
00002727-200310000-00005

29. Cadilhac DA, Kilkenny MF, Lannin NA, et al;
Australian Stroke Clinical Registry Consortium.
Outcomes for Patients with in-hospital stroke:
a multicenter study from the Australian Stroke
Clinical Registry (AuSCR). *J Stroke Cerebrovasc Dis*.
2019;28(5):1302-1310. doi:10.1016/j.
jstrokecerebrovasdis.2019.01.026

30. Aly N, McDonald K, Leathley M, Sharma A,
Watkins C. Retrospective case note review of acute
and inpatient stroke outcomes. *BMJ*. 2000;320
(7248):1511-1512. doi:10.1136/bmj.320.7248.1511

31. Azzimondi G, Nonino F, Fiorani L, et al.
Incidence of stroke among inpatients in a large
Italian hospital. *Stroke*. 1994;25(9):1752-1754.
doi:10.1161/01.STR.25.9.1752

32. Dulli D, Samaniego EA. Inpatient and
community ischemic strokes in a university
hospital. *Neuroepidemiology*. 2007;28(2):86-92.
doi:10.1159/000098551