Stroke: Vascular and Interventional Neurology

ORIGINAL RESEARCH

Exploring the Unmet Need in Acute Ischemic Stroke Patients Not Treated With Intravenous Alteplase: The Get With The Guidelines-Stroke Registry

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BACKGROUND: Early administration of intravenous tissue plasminogen activator (IV alteplase) improves functional outcomes in patients with acute ischemic stroke, yet many patients are not treated with IV alteplase. There is a need to understand the reasons for nontreatment and the short- and long-term outcomes in this patient population.

METHODS: We analyzed patients ≥65 years old with a primary diagnosis of acute ischemic stroke presenting within 24 hours of time last known well (LKW) but not treated with IV alteplase from 1630 Get With The Guidelines-Stroke hospitals in the United States between January 2016 and December 2016. We report clinical characteristics, reasons for withholding treatment, in-hospital mortality, and 90-day and 1-year outcomes including costs, stratified by time from LKW to presentation (≤4.5, >4.5–6, and >6–24 hours).

RESULTS: Of 39 760 patients (median age 80 [25th–75th quartiles: 73–87], 56.7% female), 19 391 (48.8%) presented within 4.5 hours of LKW. In those with documented reasons for withholding IV alteplase, the most common reasons were rapid improvement of symptoms (3985/14 782, 27.0%) and mild symptoms (3791/14 782, 25.6%). In 1100 out of 1174 (93.7%) patients presenting in the >3.0- to 4.5-hour time window, the most common reason for not treating was a delay in patient arrival. The most common discharge location for those presenting ≤4.5 hours since LKW was home (8660/19 391, 44.7%). The 90-day mortality and readmission rates were 18.9% and 23.0% in those presenting ≤4.5 hours since LKW, 19.0% and 22.2% in those presenting between 4.5 and 6 hours, and 19.1% and 23.2% in those presenting between 6 and 24 hours. Median 90-day total in-hospital costs remained relatively high at $9471 (Q25–Q75: $5622–$21 356) in patients presenting ≤4.5 hours since LKW.

CONCLUSIONS: Patients within the Get With The Guidelines-Stroke registry not treated with IV alteplase have a high risk of readmission and mortality and have high total in-hospital and postdischarge costs. This study may inform future efforts to address the unmet need to improve the scope of IV alteplase delivery along with other aspects of acute ischemic stroke care and, consequently, outcomes in this patient population.

Stroke is the leading cause of long-term disability in the United States with 800 000 Americans suffering a stroke each year at an annual cost of $45 billion.[1] Treatment with intravenous (IV) thrombolysis via alteplase, a recombinant form of tissue plasminogen activator, is associated with improved functional

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outcomes in selected patients with acute ischemic stroke (AIS) treated within 4.5 hours of time last known well (LKW).[2,3] However, only a minority of patients with AIS receive this therapy. Many patients with AIS arrive outside the treatment time window, and among those arriving within the window there are many patients not treated, including some who were eligible for treatment. Thus, despite the widespread availability of IV alteplase there is still an unmet need for additional therapies to modify the course of AIS. Endovascular thrombectomy (EVT) has been proven to improve AIS outcomes up to 24 hours after AIS onset,[4–6] but the eligible patient pool is smaller than for alteplase because it is limited to the subset of AIS with large vessel occlusion.

The magnitude of treatment benefit with IV alteplase is inversely proportional to the interval from LKW to IV alteplase.[7] Thus, under current guidelines[2] the majority of patients presenting greater than 4.5 hours since LKW are ineligible for treatment (with the exception of centers with access to emergent magnetic resonance imaging and the capability to perform patient selection according to the WAKE-UP clinical trial[8]). Patients may not receive IV alteplase if they decline treatment because of its perceived risks or if they have other contraindications to thrombolysis (including recent surgery, prior intracranial hemorrhage, or a systemic bleeding proclivity). Older patients, women, Black and Hispanic Americans, and patients presenting with mild AIS symptoms are less likely to be treated.[9] The use of IV alteplase has increased greatly since the inception of the Get With The Guidelines (GWTG)-Stroke registry[10] and has been boosted at several key milestones. First, Centers for Medicare and Medicaid Services approved a new diagnosis-related group that increased reimbursement for patients with AIS treated with IV alteplase.[11] Second, the European Cooperative Acute Stroke Study III trial[12] demonstrated the efficacy of alteplase in patients treated in the 3- to 4.5-hour time window. This trial prompted a new scientific advisory statement from the American Heart Association/American Stroke Association (AHA/ASA)[13] with recommendations disseminated to all GWTG-Stroke sites resulting in a further increase in IV alteplase use, particularly in the 3- to 4.5-hour window.[14] Still, approximately 25% to 33% of eligible patients do not receive alteplase.[9,10]

Using data from the AHA/ASA GWTG-Stroke registry, we sought to characterize the unmet need for AIS therapies by identifying the frequency with which patients do not receive IV alteplase, reasons for nontreatment (including contraindications to alteplase), outcomes, and costs of care.

Nonstandard Abbreviations and Acronyms

AHA/ASA	American Heart Association/American Stroke Association
AIS	acute ischemic stroke
EVT	endovascular thrombectomy
GWTG	Get With The Guidelines
LKW	last known well
NIHSS	National Institutes of Health Stroke Scale

CLINICAL PERSPECTIVE

What Is New?

There is an unmet need to improve the care of patients with acute ischemic stroke and who are not treated with IV alteplase because this group has a high rate of readmission, mortality, and health care use.

What Are the Clinical Implications?

In addition to interventions that promote reperfusion, this unmet need could also be addressed by strategies to prevent early recurrence, prevent or treat medical complications, and enhance recovery.

METHODS

Because 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. Requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be submitted to www.heart.org/qualityresearch. Additional information regarding the statistical analysis plan and analytic code may also be available from Duke Clinical Research Institute upon request.

Study Design

We performed a retrospective, observational, cohort study using data from the GWTG-Stroke registry (NCT02693223) linked with data from the Centers for

Medicare and Medicaid Services. GWTG-Stroke is a nationwide registry and quality improvement initiative under the auspices of the AHA/ASA that began in April 2003. The full details of registry stewardship, data collection, and data use processes have been published in depth previously.[15] Briefly, participating GWTG-Stroke sites reported deidentified, patient-level data on demographics, medical history, medication exposures, diagnostic testing (including cerebral imaging), acute therapies, in-hospital treatment, complications, and reasons for nontreatment from a specified list of both absolute and relative exclusion criteria within the 0 to 3- and 3- to 4.5-hour time frames, derived from US Food and Drug Administration labeling and professional guidelines. There is a high degree of accuracy and concordance between data entered and medical record review.[16]

Because GWTG-Stroke is an inpatient registry, we further linked patients to Centers for Medicare and Medicaid Services data for long-term outcomes including mortality, readmission, and inpatient costs through a probabilistic linkage using age, sex, admission date, and hospital ID.[17] A previous study showed that the Medicare fee-for-service population within GWTG-Stroke is representative of the general Medicare population.[18] Each participating site receives either (1) human subjects research approval to enroll patients with a waiver of written, informed consent under the Common Rule (45 CFR §46) or (2) a waiver of authorization and exemption from subsequent review by their institutional review board. IQVIA (Parsippany, NJ) serves as the data collection and coordination center, and the Duke Clinical Research Institute (Durham, NC) serves as the data analysis center. This study was approved by the Institutional Review Board of the Duke University School of Medicine.

Participants and Outcomes

We included Medicare fee-for-service patients ≥65 years old with a primary diagnosis of AIS presenting to a GWTG-Stroke hospital within 24 hours of time LKW between January 1, 2016, and December 31, 2016. We excluded patients who received IV alteplase and those with missing data on biological sex, discharge disposition, or IV alteplase treatment status. Additionally, we excluded patients who were transferred from or to another hospital (in essence including only those presenting via emergency medical services or private transport from home/scene) or who left against medical advice. We reported reasons for withholding IV alteplase, in-hospital mortality, discharge destination, ambulatory status at discharge, mortality, and total inpatient costs at 90 days and 1 year. The costs reported in our study refer exclusively to inpatient acute medical care and do not include costs of rehabilitation, skilled nursing, home care, outpatient appointments, outpatient therapies, or pharmacy expenses. For the purposes of our study, health care costs were defined as the inpatient claim payment amount plus the product of claim pass thru per diem amount and claim use day count. Costs are denominated in US dollars. Where cost reflects a negative number, this describes a scenario where Medicare was reimbursed. We also report readmission rates including all-cause readmissions, those related to subsequent AIS or transient ischemic attack (TIA) or those related to a cardiovascular condition. Readmissions for AIS/TIA and any cardiovascular readmission were ascertained using previously described methodology.[19]

Statistical Analysis

We derived descriptive statistics, including medians with interquartile ranges for continuous variables and counts with percentages for categorical variables (which included readmission and survival outcomes). We described the study sample in both narrative and tabular form and compared key clinical characteristics between groups based on LKW to arrival time in hospital. We divided the study sample into 3 groups according to these time frames: ≤4.5, >4.5 to 6, and >6 to 24 hours since LKW. We tested for differences across the groups via the chi-square test for categorical variables and the Kruskal–Wallis test for continuous variables. We tabulated the reasons for no IV alteplase treatment as counts and percentages. We calculated crude rates and medians (with interquartile range) for each outcome (readmission, mortality, discharge venue, and costs) within each group. Cumulative incidence of each of readmission and mortality within 90 days and 1-year postdischarge are described via the Kaplan–Meier statistic. For each outcome, we performed subgroup analyses based on age (divided into those above and below 80), biological sex, and whether or not EVT was performed. One-year mortality was defined as the time from index admission to death or censoring at 1-year postindex admission. Costs were computed from index admission to 90 or 365 days postdischarge. All tests were 2 sided with a threshold of $P<0.05$ defined as statistically significant. Statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC).

The Strengthening the Reporting of Observational Studies in Epidemiology[20] checklist is included in the Supplementary Material to this paper.

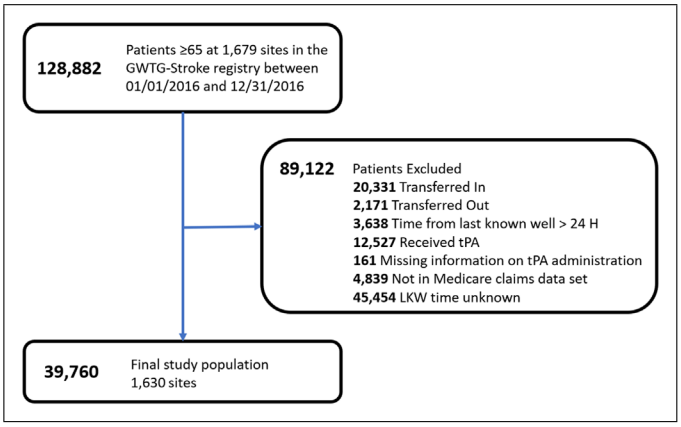

Figure 1. Study population flow chart.
GWTG indicates Get With The Guidelines; LKW, last known well; and tPA, tissue plasminogen activator.

RESULTS

Participants

Within the period of this study, there were 128 882 patients with AIS in the GWTG-Stroke registry. After applying inclusion and exclusion criteria, 39 760 patients were eligible for inclusion in our study. Figure 1 presents the flow chart for the derivation of the study population.

Descriptive Data

Key demographic, clinical, and hospital characteristics of the study population, according to arrival window, are presented in Table 1. The median age was 80 (Q25–Q75: 73–87), 22 539/39 760 (56.7%) were female, and 31 817/39 760 (80.0%) were non-Hispanic White. Figure 2A and B report the distribution of arrival times across the study population. A total of 19 391 (48.8%) patients presented within 4.5 hours of time LKW, 3278 (8.2%) presented >4.5 to 6 hours of time LKW, and 17 091 (43.0%) presented >6 and 24 hours since LKW. Patients arriving within 4.5 hours were more likely to have atrial fibrillation/atrial flutter or prior AIS/TIA than those who arrived after 6 hours (33.1% versus 25.3%). Severity (as measured by the National Institutes of Health Stroke Scale [NIHSS] score) did not differ substantially across the subgroups. Median NIHSS was 4 (Q25–Q75: 1–9) in the entire study population, 3 (Q25–Q75: 1–9) in those presenting ≤4.5 hours since LKW, 4 (Q25–Q75: 1–10) in those presenting >4.5 to 6 hours since LKW, and 4 (Q25–Q75: 2–10) in those presenting >6 to 24 hours since LKW. Of 19 391 patients arriving ≤4.5 hours since LKW, 14 189 (73.2%) presented via emergency medical services, of 3278 patients arriving >4.5 to 6 hours of LKW, 2248 (68.6%) presented via emergency medical services, and of 17 091 patients arriving >6 and 24 hours since LKW, 10 932 (64.0%) presented via emergency medical services.

Reasons for Withholding IV Alteplase

Among 19 391 patients presenting ≤4.5 hours from symptom onset and not treated with IV alteplase, 14 782 (76.2%) had a documented reason for no IV alteplase administration. These reasons are presented according to prespecified criteria from the GWTG-Stroke database in Table 2. Over half of patients had a relative exclusion or warning as at least one of the reasons for not receiving IV alteplase. Rapid improvement of symptoms (27.0%, 3985 out of 14 782 patients) and mild symptoms (25.6%, 3 791 out of 14 782 patients) were the most common criteria. Within patients presenting in the 0 to 3-hour window, the most common exclusion criteria were mild (27.4%) and rapidly improving (28.9%) symptoms. In contrast, in those patients presenting in the >3.0 to 4.5-hour time window but not treated, the most common reason for not treating was a delay in patient arrival at 93.7% (1100 out of 1174 patients). Patient/family refusal was the primary reason in only 6.6% (969 out of 14 782 patients). By contrast, “stroke too severe” was almost never listed as a reason for withholding alteplase (0.9%, 135 out of 14 782 patients) by NIHSS criteria and 1% (142 out of 14 782 patients) by radiographic criteria (evidence of established hypodensity encompassing over one third of the cerebral hemisphere). There were 4609 (23.8%) patients arriving within 4.5 hours for whom no reason for withholding IV alteplase was documented.

Outcome and Costs of Care in Patients Not Treated With IV Alteplase

The highest rate of discharge home was among those patients who arrived within 4.5 hours – 44.7% in the

Table 1. Baseline and In-Hospital Characteristics of Patients With AIS Not Treated With IV Alteplase, Stratified by Arrival Time (N [%])*

			Arrival≤4.5 h after LKW				
	Entire study sample (N=39 760)	Arrival≤4.5 h after LKW (n=19 391)	Reasons for lack of IV alteplase treatment not documented (n=4609)	Reasons to not giving IV alteplase documented (n=14 782)	Arrival>4.5–6 h after LKW (n = 3278)	Arrival>6–24 h after LKW (n=17 091)	*P* value
Patient demographics							
Age, median (Q25–Q75) (y)	80.0 (73.0–87.0)	81.0 (73.0—88.0)	81.0 (73.0–87.0)	81.0 (73.0—88.0)	80.0 (72.0–87.0)	79.0 (72.0–86.0)	<0.0001
Female sex	22 539 (56.7%)	10 995 (56.7%)	2617 (56.8%)	8378 (56.7%)	1862 (56.8%)	9682 (56.6%)	0.9855
Race/ethnicity†							
Non-Hispanic							
White	31 817 (80.0%)	15 865 (81.8%)	3767 (81.7%)	12 098 (81.8%)	2582 (78.8%)	13 370 (78.2%)	<0.0001
Black	4182 (10.5%)	1814 (9.4%)	445 (9.7%)	1369 (9.3%)	384 (11.7%)	1984 (11.6%)	
Hispanic	1617 (4.1%)	737 (3.8%)	175 (3.8%)	562 (3.8%)	136 (4.1%)	744 (4.4%)	
Asian	885 (2.2%)	365 (1.9%)	90 (2.0%)	275 (1.9%)	80 (2.4%)	440 (2.6%)	
Other (includes UTD)	1252 (3.1%)	607 (3.1%)	131 (2.8%)	476 (3.2%)	93 (2.8%)	552 (3.2%)	
Medical history‡							
Atrial fib/flutter	11 659 (29.3%)	6422 (33.1%)	1508 (32.7%)	4914 (33.2%)	910 (27.8%)	4327 (25.3%)	<0.0001
Prior stroke/TIA	13 466 (33.9%)	7054 (36.4%)	1689 (36.6%)	5365 (36.3%)	1053 (32.1%)	5359 (31.4%)	<0.0001
Prior CAD/MI	11 418 (28.7%)	5820 (30.0%)	1353 (29.4%)	4467 (30.2%)	929 (28.3%)	4669 (27.3%)	<0.0001
Carotid stenosis	1628 (4.1%)	811 (4.2%)	207 (4.5%)	604 (4.1%)	120 (3.7%)	697 (4.1%)	0.3793
Diabetes	12 965 (32.6%)	6048 (31.2%)	1465 (31.8%)	4583 (31.0%)	1125 (34.3%)	5792 (33.9%)	<0.0001
Peripheral vascular disease	2145 (5.4%)	1052 (5.4%)	249 (5.4%)	803 (5.4%)	179 (5.5%)	914 (5.3%)	0.9278
Hypertension	32 057 (80.6%)	15 625 (80.6%)	3698 (80.2%)	11 927 (80.7%)	2684 (81.9%)	13 748 (80.4%)	0.1138
Dyslipidemia	20 523 (51.6%)	10 076 (52.0%)	2347 (50.9%)	7729 (52.3%)	1669 (50.9%)	8778 (51.4%)	0.3627
Smoker	3500 (8.8%)	1347 (6.9%)	314 (6.8%)	1033 (7.0%)	297 (9.1%)	1856 (10.9%)	<0.0001
Clinical characteristics							
NIHSS score¶	4.0 (1.0–9.0)	3.0 (1.0—9.0)	3.0 (1.0–8.0)	3.0 (1.0—9.0)	4.0 (1.0–10.0)	4.0 (2.0–10.0)	<0.0001
Arrival off hours§	20 673 (52.0%)	10 467 (54.0%)	2485 (53.9%)	7982 (54.0%)	1941 (59.2%)	8265 (48.4%)	<0.0001
Arrival via EMS‖	27 369 (68.8%)	14 189 (73.2%)	3391 (73.6%)	10 798 (73.0%)	2248 (68.6%)	10 932 (64.0%)	<0.0001
LKW to arrival time (min)	282.0 (97.0–655.0)	94.0 (53.0–167.0)	88.0 (51.0—142.0)	96.0 (53.0–180.0)	311.0 (290.0—336.0)	720.0 (526.0–947.0)	<0.0001
Symptom discovery to arrival time (min)#	128.0 (60.0—350.0)	75.0 (45.0–131.0)	70.0 (44.0—120.0)	76.0 (45.0–138.0)	286.0 (124.0—319.0)	444.0 (137.0–762.0)	<0.0001
Medications before admission**							
Diabetic	7744 (19.5%)	3588 (18.5%)	793 (17.2%)	2795 (18.9%)	698 (21.3%)	3458 (20.2%)	<0.0001
Antithrombotic	24 156 (60.8%)	12 287 (63.4%)	2845 (61.7%)	9442 (63.9%)	1928 (58.8%)	9941 (58.2%)	<0.0001
Antiplatelet	19 817 (49.8%)	9721 (50.1%)	2258 (49.0%)	7463 (50.5%)	1630 (49.7%)	8466 (49.5%)	<0.0001
Anticoagulant	6289 (15.8%)	3715 (19.2%)	853 (18.5%)	2862 (19.4%)	439 (13.4%)	2135 (12.5%)	<0.0001
Antihypertensive	24 370 (61.3%)	12 075 (62.3%)	2700 (58.6%)	9375 (63.4%)	2030 (61.9%)	10 265 (60.1%)	<0.0001
Cholesterol reducing	19 686 (49.5%)	9936 (51.2%)	2344 (50.9%)	7592 (51.4%)	1624 (49.5%)	8126 (47.5%)	<0.0001
Antidepressant	5159 (13.0%)	2625 (13.5%)	581 (12.6%)	2044 (13.8%)	435 (13.3%)	2099 (12.3%)	0.0001
None	2773 (7.0%)	1161 (6.0%)	263 (5.7%)	898 (6.1%)	246 (7.5%)	1366 (8.0%)	
Treated with EVT††	824 (2.1%)	490 (2.5%)	92 (2.0%)	398 (2.7%)	72 (2.2%)	262 (1.5%)	<0.0001
Antiplatelet medications at discharge	28 637 (83.9%)	3226 (70.0%)	10 472 (70.8%)	13 698 (82.2%)	2396 (84.7%)	12 543 (85.7%)	<0.0001
Dual antiplatelet medications at discharge	7578 (22.2%)	3587 (21.5%)	844 (21.2%)	2743 (21.6%)	610 (21.6%)	3381 (23.1%)	0.0026
Aspirin/clopidogrel	>6980 (>20.0%)	3279 (19.7%)	755 (19.0%)	2524 (19.9%)	558 (19.7%)	>3140 (>21.0%)	0.0001
Aspirin/dipyridamole	590 (1.7%)	309 (1.9%)	89 (2.2%)	220 (1.7%)	52 (1.8%)	229 (1.6%)	0.1306

(*Continued*)

Table 1. (Continued)

			Arrival≤4.5 h after LKW				
	Entire study sample (N=39 760)	**Arrival≤4.5 h after LKW (n=19 391)**	**Reasons for lack of IV alteplase treatment not documented (n=4609)**	**Reasons to not giving IV alteplase documented (n=14 782)**	**Arrival>4.5–6 h after LKW (n = 3278)**	**Arrival>6–24 h after LKW (n=17 091)**	***P* value**
Aspirin/ticlopidine	<11 (0.50%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	<11 (<0.50%)	–
Hospital characteristics							
Region							
Northeast	9245 (23.3%)	4511 (23.3%)	991 (21.5%)	3520 (23.8%)	772 (23.6%)	3962 (23.2%)	0.0145
Midwest	8004 (20.1%)	3795 (19.6%)	944 (20.5%)	2851 (19.3%)	702 (21.4%)	3507 (20.5%)	
South	15 850 (39.9%)	7782 (40.1%)	1908 (41.4%)	5874 (39.7%)	1316 (40.1%)	6752 (39.5%)	
West	6661 (16.8%)	3303 (17.0%)	766 (16.6%)	2537 (17.2%)	488 (14.9%)	2870 (16.8%)	
Academic/teaching hospital‡‡	27 814 (70.0%)	13 515 (69.7%)	3095 (67.2%)	10 420 (70.5%)	2343 (71.5%)	11 956 (70.0%)	0.1076
Rural location¶¶	2215 (5.6%)	1075 (5.5%)	331 (7.2%)	744 (5.0%)	201 (6.1%)	939 (5.5%)	0.3386
No. of beds§§	336.0 (217.0—513.0)	334.0 (214.0–506.0)	319.0 (202.0—489.0)	336.0 (218.0–510.0)	340.0 (218.0—535.5)	339.0 (218.0–519.0)	0.0028
Annual ischemic stroke volume	237.4 (161.6—369.3)	235.8 (161.2–362.6)	225.1 (154.6—346.5)	237.4 (163.0–369.3)	242.8 (164.9—384.0)	240.2 (161.0–375.0)	0.0112
Annual IV-alteplase volume	30.0 (14.0—53.0)	29.0 (14.0–52.0)	26.0 (13.0—49.0)	29.0 (15.0–53.0)	32.0 (15.0—55.0)	30.0 (15.0–53.0)	<0.0001
Stroke center status							
CSC	3117 (7.8%)	1352 (7.0%)	284 (6.2%)	1068 (7.2%)	277 (8.5%)	1488 (8.7%)	<0.0001
PSC	22 532 (56.7%)	11 129 (57.4%)	2518 (54.6%)	8611 (58.3%)	1860 (56.7%)	9543 (55.8%)	
Neither CSC nor PSC	14 111 (35.5%)	6910 (35.6%)	1807 (39.2%)	5103 (34.5%)	1141 (34.8%)	6060 (35.5%)	

AIS indicates acute ischemic stroke; CAD, coronary artery disease; CSC, comprehensive stroke center; EMS, emergency medical services; EVT, endovascular thrombectomy; IV alteplase, intravenous tissue plasminogen activator; LKW, last known well; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; PSC, primary stroke center; Q25, 25th quartile; Q75, 75th quartile; TIA, transient ischemic attack; and UTD, unable to determine.

*Please note that some cells have been edited to adhere to the CMS cell suppression policy.

†Race/ethnicity was missing for <200 patients (<0.5%).

‡The medical history panel was missing for 77 patients (<0.2%).

¶Initial NIHSS was missing for 2758 patients (6.9%).

§Refers to arrival at the hospital on weekdays between 6:00 pm and 7:00 am, weekends, or holidays.

‖Arrival information was missing for 22 patients (0.1%).

#Symptom discovery to arrival time was missing for 5399 patients (13.6%).

**Medication status was missing across categories as follows: diabetic medications (9723 patients [24.5%]), antithrombotic medication (1386 patients [3.5%]), antiplatelet medications (5492 patients [13.8%]), anticoagulant medications (18 331 patients [46.1%]), antihypertensive medications (7927 patients [19.9%]), lipid-lowering agents (362 patients [0.9%]), and antidepressant medications (10 608 patients [26.7%]).

††EVT treatment status was missing for 9864 patients (24.8%).

‡‡Academic/teaching hospital status was missing for 466 patients (1.2%).

¶¶Rural/urban location status was missing for <200 patients (<0.5%).

§§Number of beds was missing for 662 patients (1.7%).

group presenting ≤4.5 hours from LKW, 35.4% in the group presenting >4.5 to 6 hours from LKW, and 35.8% in the group presenting >6 to 24 hours since LKW. Patients presenting within 4.5 hours of LKW also had the highest rate of ambulation at discharge – 47.4% compared with 40.8% in the >4.5- to 6-hour group and 42.0% in the >6- to 24-hour group. The readmission rate at 90 days was 23.0% (4257 out of 18 536 patients) in those presenting ≤4.5 hours since LKW, 22.2% (697 out of 3 137 patients) in those presenting between >4.5 and 6 hours since LKW, and 23.2% (3785 out of 16 319 patients) in those presenting between >6 and 24 hours since LKW. Rates of cardiovascular readmission were similar across time windows. Eleven percent of patients presenting within 4.5 hours of LKW had a cardiovascular readmission within 90 days as did 10.6% of those presenting in the >4.5- to 6-hour window and 10.8% of those in the >6- to 24-hour window. Within 90 days of the index event, 4.3% of patients presenting within 4.5 hours of LKW, 4.2% of patients presenting between >4.5 and 6 hours of LKW, and 4.6% of patients presenting between >6 and 24 hours of LKW were readmitted for IS/TIA.

The unadjusted 90-day mortality rate was 18.9% (3669 out of 19 391 patients) in those presenting ≤4.5 hours since LKW, 19.0% (623 out of 3278 patients) in those presenting >4.5 to 6 hours since LKW, and 19.1% (3266 out of 17 091 patients) in those

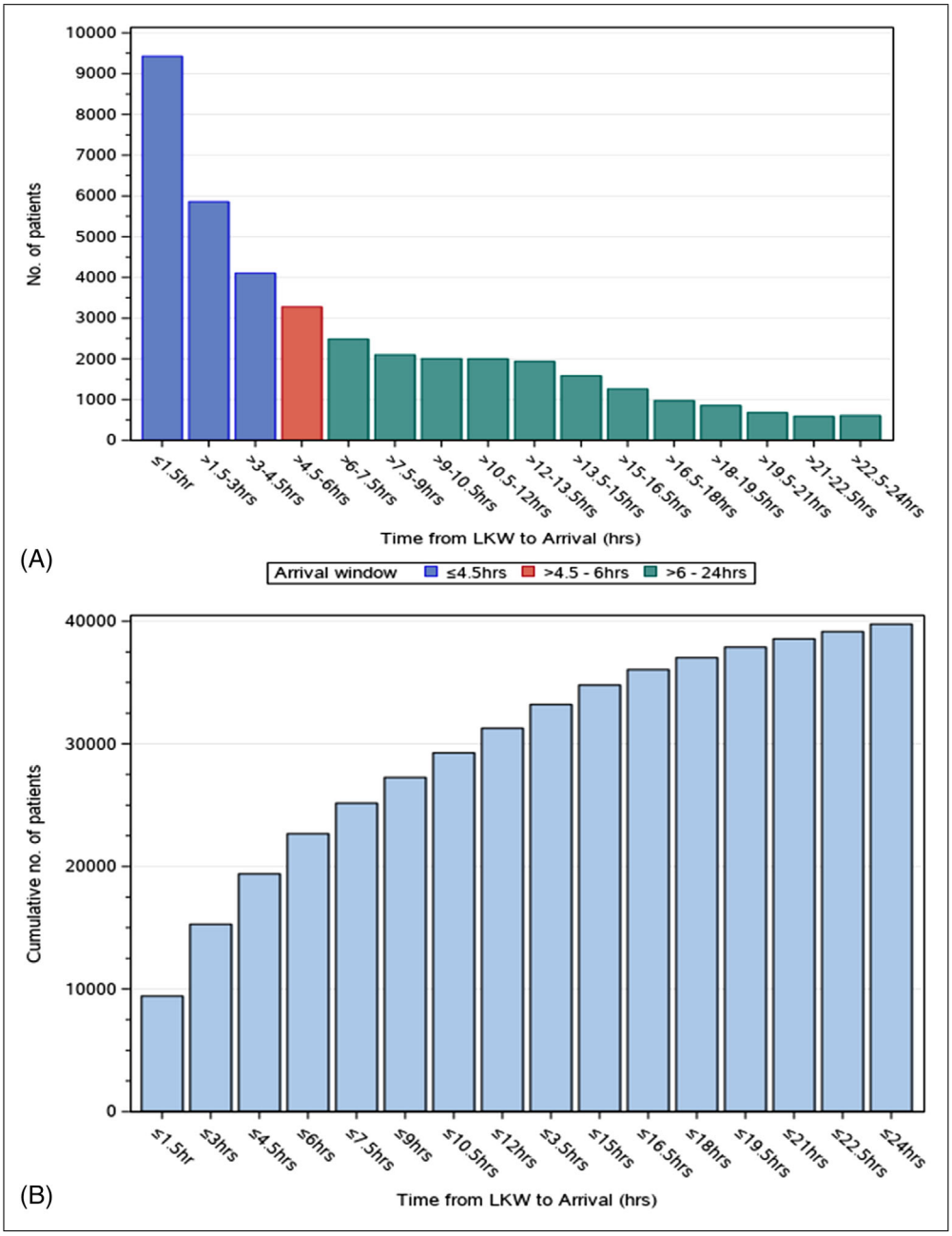

Figure 2. Arrival times of patients according to arrival window. (**A**) Number of patients presenting within the key time windows examined in this study. (**B**) Cumulative number of patients presenting according to 1.5-hour epochs. LKW indicates last known well.

presenting >6 and 24 hours since LKW. The median length of stay did not differ across subgroups – 3 (Q25–Q75: 2–5) in the ≤4.5 and >6- to 24-hour groups and 4 (Q25–Q75: 2–5) in the >4.5- to 6-hour group. The median 90-day costs (including index event and any readmission) were $9471 (Q25–Q75: $5622–$21 356) in patients presenting within 4.5 hours, $10 884 (Q25–Q75: $6036–$25 992) in patients presenting in the >4.5- to 6-hour time window and $11 162 (Q25–Q75: $6073–$26 372) in patients presenting in the >6- to 24-hour time window. The median 1-year costs (including index admission and any readmission) were $10 452 (Q25–Q75: $5887–$24 419) in patients presenting within 4.5 hours, $12 183 (Q25–Q75: $6341–$28 874) in patients presenting in the >4.5- to 6-hour time window and $12 343 (Q25–Q75: $6370–$28 781) in patients presenting in the >6- to 24-hour time window. Among those patients with postdischarge readmission costs, the 1-year total was $19 310, $21 486, and $21 168 among patients presenting in the <4.5, >4.5- to 6, and >6- to 24-hour time windows, respectively.

Table 2. Reasons for No IV Alteplase among Patients Arriving Within 4.5 Hours of AIS Onset With Documented Reasons for No IV Alteplase*,†

	Overall(n=14 782)	0–3 h arrival window(n=13 608)	>3–4.5 h arrival window(n=1174)
Exclusion criteria (contraindications), 0–3 h window	2784 (18.8%)		36 (3.1%)
Elevated blood pressure (SBP>185 mmHg or DBP>110 mmHg) despite treatment	255 (1.7%)	>235 (>1.5%)	<11 (<1.0%)
Recent intracranial/spinal surgery/significant head trauma or prior stroke in previous 3 mo	424 (2.9%)	>400 (>3.0%)	<11 (<1.0%)
History of previous intracranial hemorrhage, intracranial neoplasm, arteriovenous malformation	475 (3.2%)	>455 (>3.0%)	<11 (<1.0%)
Active internal bleeding	120 (0.8%)	120 (0.9%)	0 (0.0%)
Acute bleeding diathesis (low platelets, increased PTT, INR>=1.7, or NOAC use)	1447 (9.8%)	1427 (10.5%)	20 (1.7%)
Symptoms suggest subarachnoid hemorrhage	37 (0.3%)	37 (0.3%)	0 (0.0%)
CT demonstrates multilobar infarction (hypodensity>one third cerebral hemisphere)	142 (1.0%)	>120 (>0.5%)	<11 (<1.0%)
Arterial puncture at noncompressible site in previous 7 d	<11 (<0.5%)	<11 (<0.5%)	0 (0.0%)
Blood glucose concentration <50 mg/dL (2.7 mmol/L)	<11 (<0.5%)	<11 (<0.5%)	0 (0.0%)
Exclusion criteria (contraindications), 3–4.5 h window	2391 (16.2%)	2339 (17.2%)	52 (4.4%)
Elevated blood pressure (SBP>185 mmHg or DBP>110 mmHg) despite treatment	197 (1.3%)	>175 (>1.0%)	<11 (<1.0%)
Recent intracranial/spinal surgery/significant head trauma or prior stroke in previous 3 mo	378 (2.6%)	>355 (>2.5%)	<11 (<1.0%)
History of previous intracranial hemorrhage, intracranial neoplasm, arteriovenous malformation	407 (2.8%)	>380 (>2.5%)	<11 (<1.0%)
Active internal bleeding	100 (0.7%)	>80 (>0.5%)	<11 (<1.0%)
Acute bleeding diathesis (low platelets, increased PTT, INR unicode22641.7, or NOAC use)	1247 (8.4%)	1221 (9.0%)	26 (2.2%)
Symptoms suggest subarachnoid hemorrhage	24 (0.2%)	>10 (>0.1%)	<11 (<1.0%)
CT demonstrates multilobar infarction (hypodensity>one third cerebral hemisphere)	133 (0.9%)	>110 (>0.5%)	<11 (<1.0%)
Arterial puncture at noncompressible site in previous 7 d	<11 (<0.5%)	<11 (<0.5%)	0 (0.0%)
Blood glucose concentration <50 mg/dL (2.7 mmol/L)	<11 (<0.5%)	<11 (<0.5%)	0 (0.0%)
Relative exclusion criteria (warnings), 0–3 h window	8574 (58.0%)	8406 (61.8%)	168 (14.3%)
Care-team unable to determine eligibility	958 (6.5%)	886 (6.5%)	72 (6.1%)
IV or IA thrombolysis/thrombectomy at an outside hospital before arrival	21 (0.1%)	>10 (<0.5%)	<11 (<1.0%)
Life expectancy <1 y or severe comorbid illness or CMO on admission	291 (2.0%)	>270 (>1.9%)	<11 (<1.0%)
Pregnancy	0 (0.0%)	0 (0.0%)	0 (0.0%)
Patient/family refusal	1044 (7.1%)	>1000 (>7.3%)	<11 (<1.0%)
Rapid improvement	3985 (27.0%)	3936 (28.9%)	49 (4.2%)
Stroke severity too mild	3791 (25.6%)	3734 (27.4%)	57 (4.9%)
Recent acute myocardial infarction (within previous 3 mo)	42 (0.3%)	>20 (>0.1%)	<11 (<1.0%)
Seizure at onset with postictal residual neurological impairments	181 (1.2%)	>160 (>1.0%)	<11 (<1.0%)
Major surgery or serious trauma within previous 14 d	183 (1.2%)	>160 (>1.0%)	<11 (<1.0%)
Recent gastrointestinal or urinary tract hemorrhage (within previous 21 d)	140 (0.9%)	>120 (>0.5%)	<11 (<1.0%)
Relative exclusion criteria (warnings), 3–4.5 h window	8098 (54.8%)	7870 (57.8%)	228 (19.4%)
Care-team unable to determine eligibility	929 (6.3%)	851 (6.3%)	78 (6.6%)
IV or IA thrombolysis/thrombectomy at an outside hospital prior to arrival	18 (0.1%)	>10 (<0.5%)	<11 (<1.0%)
Life expectancy <1 y or severe comorbid illness or CMO on admission	256 (1.7%)	>230 (>1.5%)	<11 (<1.0%)

(*Continued*)

Table 2. (Continued)

	Overall(n=14 782)	0–3 h arrival window(n=13 608)	>3–4.5 h arrival window(n=1174)
Pregnancy	0 (0.0%)	0 (0.0%)	0 (0.0%)
Patient/family refusal	969 (6.6%)	955 (7.0%)	14 (1.2%)
Rapid improvement	3708 (25.1%)	3636 (26.7%)	72 (6.1%)
Stroke severity too mild	3608 (24.4%)	3520 (25.9%)	88 (7.5%)
Recent acute myocardial infarction (within previous 3 mo)	41 (0.3%)	>20 (>0.1%)	<11 (<1.0%)
Seizure at onset with postictal residual neurological impairments	158 (1.1%)	>135 (>1.0%)	<11 (<1.0%)
Major surgery or serious trauma within previous 14 d	167 (1.1%)	>140 (>1.0%)	<11 (<1.0%)
Recent gastrointestinal or urinary tract hemorrhage (within previous 21 d)	128 (0.9%)	>100 (>0.5%)	<11 (<1.0%)
Additional relative exclusion criteria, 3–4.5 h window	1883 (12.7%)	1804 (13.3%)	79 (6.7%)
Age>80	1233 (8.3%)	1173 (8.6%)	60 (5.1%)
History of both diabetes and prior ischemic stroke	149 (1.0%)	138 (1.0%)	11 (0.9%)
Taking an oral anticoagulant regardless of INR	683 (4.6%)	657 (4.8%)	26 (2.2%)
Severe stroke (NIHSS>25)	135 (0.9%)	115 (>0.5%)	<11 (<1.0%)
Other (hospital-related) reasons, 0–3 h window	4961 (33.6%)	3857 (28.3%)	1104 (94.0%)
Delay in patient arrival	4312 (29.2%)	3212 (23.6%)	1100 (93.7%)
In-hospital time delay	25 (0.2%)	25 (0.2%)	0 (0.0%)
Delay in stroke diagnosis	215 (1.5%)	>190 (>1.0%)	<11 (<1.0%)
No IV access	<11 (<0.5%)	<11 (<0.5%)	0 (0.0%)
Advanced age	466 (3.2%)	455 (3.3%)	11 (0.9%)
Stroke too severe	119 (0.8%)	119 (0.9%)	0 (0.0%)
Other	1019 (6.9%)	983 (7.2%)	36 (3.1%)
Other (hospital-related) reasons, 3–4.5 h window	2815 (19.0%)	2398 (17.6%)	417 (35.5%)
Delay in patient arrival	1443 (9.8%)	1055 (7.8%)	388 (33.0%)
In-hospital time delay	20 (0.1%)	20 (0.1%)	0 (0.0%)
Delay in stroke diagnosis	198 (1.3%)	175 (>1.0%)	<11 (<1.0%)
No IV access	<11 (<0.5%)	<11 (<0.5%)	0 (0.0%)
Advanced age	478 (3.2%)	458 (3.4%)	20 (1.7%)
Stroke too severe	110 (0.7%)	>90 (>0.5%)	<11 (<1.0%)
Other	960 (6.5%)	922 (6.8%)	38 (3.2%)

CMO indicates comfort measures only; CMS, Medicare and Medicaid Services; CT, computed tomography; DBP, diastolic blood pressure; IA, intraarterial; INR, international normalized ratio; IV alteplase, intravenous tissue plasminogen activator; NIHSS, National Institutes of Health Stroke Scale; NOAC, novel oral anticoagulant; PTT, partial thromboplastin time; and SBP, systolic blood pressure.

*Please note that some cells have been edited to adhere to the CMS cell suppression policy.

†Counts and frequencies are not exclusive; certain patients have more than one reason and they are counted toward each of the reasons.

Full details on discharge destination, length of stay, readmissions, mortality, and costs are presented in Table 3 and organized by arrival window.

Other Analyses

Supplementary Table S1 reports event outcomes and costs based on whether or not EVT was performed. Patients in whom EVT was not performed were more likely to be discharged home and ambulate independently than those who were treated with thrombectomy. Supplementary Table S2 reports event outcomes and costs by age (stratified into those patients above and below 80 years old) and Supplementary Table S3 reports event outcomes and costs stratified by biological sex. The rates of discharge to inpatient rehabilitation are comparable for all subgroups to the overall rates. By contrast, 1-year mortality rates are higher in patients >80 years old compared to those ≤80 (41% versus 18%) and in female versus male patients (32% versus 26%).

DISCUSSION

Key Results

This analysis identified a large unmet need for new AIS therapies. Among patients with AIS arriving less than 24 hours after LKW time, 51.2% arrived after the alteplase window and 48.8% arrived within the alteplase window but were not treated. Of the latter group, 76.2% had at least 1 documented reason

Table 3. Unadjusted Rates and Costs Among Patients With AIS Not Treated With IV Alteplase, Stratified by Arrival Window

Outcome	Arrival ≤4.5 h after onset (n=19 391)	Arrival>4.5–6 h after onset (n=3278)	Arrival>6–24 h after onset (n=17 091)
Discharge destination			
Home	8660/19 391 (44.7 %)	1160/3278 (35.4%)	6122/17 091 (35.8%)
Hospice	1382/19 391 (7.1%)	234/3278 (7.1%)	1264/17 091 (7.4%)
Skilled nursing facility	4232/19 391 (21.8%)	771/3278 (23.5%)	3688/17 091 (21.6%)
Inpatient rehab facility	3971/19 391 (20.5%)	924/3278 (28.2%)	5017/17 091 (29.4%)
In-hospital death	847/19 391 (4.4%)	139/3278 (4.2%)	762/17 091 (4.5%)
Ambulatory status at discharge			
Ambulate independently	8314/17 549 (47.4%)	1205/2950 (40.8%)	6468/15 416 (42.0%)
Ambulate with assistance/unable	8546/17 549 (48.7%)	1617/2950 (54.8%)	8417/15 416 (54.6%)
Other	689/17 549 (3.9%)	128/2950 (4.3%)	531/15 416 (3.4%)
90-d all-cause readmissions			
Rate	4257/18 536 (23.0%)	697/3137 (22.2%)	3785/16 319 (23.2%)
Cumulative incidence rate (95% CI)	23.1 (22.5,23.7)	22.3 (20.9,23.8)	23.3 (22.7,24.0)
1-y all-cause readmissions			
Rate	7898/18 536 (42.6%)	1317/3137 (42.0%)	6760/16 319 (41.4%)
Cumulative incidence rate (95% CI)	43.3 (42.6,44.0)	42.7 (41.0,44.5)	42.3 (41.5,43.0)
90-d cardiovascular readmissions			
Rate	2038/18 536 (11.0%)	331/3137 (10.6%)	1756/16 319 (10.8%)
Cumulative incidence rate (95% CI)	11.0 (10.6,11.5)	10.6 (9.6,11.7)	10.8 (10.4,11.3)
1-y cardiovascular readmissions			
Rate	3872/18 536 (20.9%)	627/3137 (20.0%)	3252/16 319 (19.9%)
Cumulative incidence rate (95% CI)	21.2 (20.7,21.8)	20.4 (19.0,21.8)	20.3 (19.7,21.0)
90-d IS/TIA readmissions			
Rate	797/18 536 (4.3%)	131/3137 (4.2%)	746/16 319 (4.6%)
Cumulative incidence rate (95% CI)	4.3 (4.0,4.6)	4.2 (3.5,5.0)	4.6 (4.3,4.9)
1-y IS/TIA readmissions			
Rate	1529/18 536 (8.2%)	239/3137 (7.6%)	1369/16 319 (8.4%)
Cumulative incidence rate (95% CI)	8.4 (8.0,8.8)	7.8 (6.9,8.8)	8.6 (8.1,9.0)
90-d mortality			
90-d mortality	3669/19 391 (18.9%)	623/3278 (19.0%)	3266/17 091 (19.1%)
Kaplan–Meier rate (95% CI)	18.9 (18.4,19.5)	19.0 (17.7,20.4)	19.1 (18.5,19.7)
1-y mortality			
1-y mortality	5810/19 391 (30.0%)	978/3278 (29.8%)	4969/17 091 (29.1%)
Kaplan–Meier rate (95% CI)	30.0 (29.3,30.6)	29.8 (28.3,31.4)	29.1 (28.4,29.8)
LOS, d, median (Q25–Q75)*	3.0 (2.0–5.0)	4.0 (2.0–5.0)	3.0 (2.0–5.0)
90-d costs†			
Index admission to discharge+90-d costs	$9471 (5622–21 356)	$10 884 (6036–25 992)	$11 162 (6073–26 372)
90-d postdischarge readmission costs	$0 (0–11 689)	$0 (0–16 422)	$0 (0–17 385)
90-d postdischarge readmission costs in those with at least 1 readmission	$18 846 (11 204–30 203)	$20 816 (12 802–31 854)	$20 748 (12 918–31 691)
1-y costs†			
Index admission to discharge+1-y costs	$10 452 (5887–24 419)	$12 183 (6341–28 874)	$12 343 (6370–28 781)
1-y postdischarge readmission costs	$0 (0–14 865)	$0 (0–19 517)	$0 (0–19 838)
1-y postdischarge readmission costs in those with at least 1 readmission	$19 310 (10 921–32 308)	$21 486 (12 548–33 536)	$21 168 (12 582–33\)

AIS indicates acute ischemic stroke; IV alteplase, intravenous tissue plasminogen activator; LOS, length of stay; LTCH, long-term care hospital; Q25, 25th quartile; Q75, 75th quartile; and TIA, transient ischemic attack.

*LOS refers to the index hospitalization only and not the cumulative LOS of successive hospitalizations.

†These costs refer exclusively to inpatient acute medical care and do not include costs of rehabilitation, skilled nursing, home care, outpatient appointments, outpatient therapies, or pharmacy expenses.

for nontreatment and 23.8% had no documented reason. Although the median NIHSS was low in all of the nontreated patient groups and did not differ by timing of arrival, there were nonetheless many patients with poor outcomes. Of the nontreated patients, 19.0% died within 90 days and 59.9% could not be discharged home, either dying in hospital or requiring some form of inpatient rehabilitation or inpatient care. Costs were high: median costs were $10 238 at 90 days and $11 281 at 1 year. Taken together, these data show that even among these "mild" AIS there is still an unmet need to favorably modify the course of AIS within the first 24 hours.

Reasons for Nontreatment With IV Alteplase

A retrospective cohort study of patients presenting to GWTG-Stroke participating hospitals between 2003 and 2011 found that 25% of eligible patients who presented within 3 hours of time LKW were not treated with IV alteplase. Increasing age, female sex, non-White race, and mild symptoms were each associated with a reduced likelihood of receiving treatment.[9] Within the present study, the most common reason for withholding IV alteplase in patients presenting within 3 hours since LKW remained rapid improvement (26.7% of patients) and mild symptoms (25.9%). Current AHA/ASA guidelines draw a distinction between mild, disabling and mild, nondisabling symptoms.[2] For patients presenting with mild, disabling symptoms, there is a strong (class 1) recommendation to treat with IV alteplase if presenting within 3 hours of LKW and a weak (class IIb) recommendation to treat with IV alteplase if presenting between 3 and 4.5 hours since LKW. The same guidelines suggest no benefit (class III) to treatment at any point if symptoms are mild and nondisabling. This recommendation is drawn from the Potential of r-tPA for Ischemic Strokes With Mild Symptoms trial[21] wherein patients enrolled only if they had an NIHSS $\leq$5 and symptoms would not interfere with activities of daily living. Thus, these results cannot be extrapolated to a scenario wherein a person may present with deficits that could cause any measurable functional impairment, no matter their NIHSS score. Furthermore, this trial was halted due to slow enrollment and so did not test its primary hypothesis. The current study draws attention to the widespread use of these criteria to exclude patients from IV alteplase.

The Role of Endovascular Thrombectomy

EVT has emerged as a major therapeutic avenue for patients suffering AIS associated with a large vessel occlusion.[4–6] In the present study, 2.1% of patients were treated with EVT and these low numbers prevent further inferences being made. The period of the present study coincided with a period of increasing use of EVT for AIS. However, no more than one third of AISs are associated with a large vessel occlusion.[22] Furthermore, strokes associated with large vessel occlusion present with severe, disabling neurological deficits upfront. Although our study lacks granularity on precisely which patients had large vessel occlusion on presentation and were potentially eligible for EVT, the low median NIHSS (4) in this study sample suggests that only a minority would be eligible. Thus, EVT is not likely to substantially address the unmet need to improve outcomes in this patient population with overall "mild" stroke but nonetheless with relatively high mortality and health care costs.

The Role of Dual Antiplatelet Therapy

Within this study, 83.9% of patients were prescribed aspirin at discharge while only 22.2% were prescribed dual-antiplatelet therapy (DAPT). The high persistent risk of recurrence despite aspirin therapy[23,24] has sparked innovation in the use of DAPT including aspirin/clopidogrel (used for 3 weeks[25] or 3 months[26]) or aspirin/ticagrelor (for 30 days[27]) after a high-risk TIA or minor AIS in patients without a major cardioembolic source or planned carotid endarterectomy. Modern approaches to AIS prevention are centered on a rapidly initiated, short course of DAPT to maximize the upfront benefit while minimizing the longer-term risk of major bleeding. This is supported by a recent meta-analysis[28] and endorsed by the most recent AHA/ASA AIS secondary prevention guidelines.[29] In the present study, the population included falls within the spectrum of patients who may benefit from DAPT because (1) the median NIHSS is low and (2) treatment with IV alteplase was an exclusion criterion in each of the 3 major trials of DAPT. More widespread adoption of DAPT may be one means to improving outcomes in this population, among patients without a major cardioembolic source or planned endarterectomy.

Cost Comparisons

IV alteplase is known to reduce health care costs in the subgroup of patients who receive it whether within 3[30] or 3 to 4.5[31] hours of LKW. The present study highlights the high cost associated with nonalteplase-treated AIS. Using an administrative database including a representative US population, 1 prior study[32] determined that the average inpatient costs in the 1 year post-AIS were $20 140 for patients who were disabled at discharge (ie, discharged to an inpatient nursing facility) and $11 162 for patients not disabled at discharge (discharged home). Patients in the present study who were readmitted thus had costs that approximated those of

the disabled population with AIS at large. The costs seen in our population are higher than in other major cardiovascular conditions. The average 1-year postdischarge costs in patient with ST elevation myocardial infarction treated via percutaneous coronary intervention are only $8037.[33]

Strengths and Limitations

This study has a number of strengths. First, it draws on a large, population-based registry that recruited a diverse patient sample from both academic and community settings. The use of an observational data set such as GWTG-Stroke provides important context supplemental to clinical trials, participants within which are systematically different from real-world practice.[34] Second, the GWTG-Stroke database provides a degree of granularity not afforded by other administrative data sets such as those curated by the Healthcare Utilization Project data or insurance-based registries. Third, linkage with Centers for Medicare and Medicaid Services data using validated methods permits us to obtain long-term follow-up data. There are a number of limitation inherent in this form of study. We limited our study population to individuals over the age of 65, although this does still represent approximately 70% of all AIS discharges.[35] We did not perform a direct comparison with patients during the corresponding time period who did receive IV alteplase, and this is an exciting opportunity for future study. Data quality is strongly dependent on the quality of documentation at each site; however, data in the GWTG-Stroke registry have been shown to have a high degree of fidelity with medical chart review.[16] There may be limitations introduced by excluding those patients not eligible for fee-for-service Medicare; however, the Medicare fee-for-service population within GWTG-Stroke is representative of the general Medicare population.[18]

CONCLUSIONS

In summary, patients within the GWTG-Stroke registry not treated with IV alteplase present with a low median NIHSS across all time spans of treatment yet have a high risk of readmission and mortality and high health care costs. The most common reasons for nontreatment included mild and rapidly improving symptoms. The knowledge gained from this study may inform future efforts to address the unmet need in this vulnerable patient population. In addition to interventions that promote reperfusion, this unmet need could also be addressed by strategies to prevent early recurrence, prevent or treat medical complications, and enhance recovery.

ARTICLE INFORMATION

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None

Author Contributions

BMG aided in study design, interpreted the data, drafted the manuscript, and revised the manuscript for critical intellectual content. YX aided in study design, performed statistical analyses, revised the manuscript for intellectual content, and supervised the study. NCS acquired the data and performed statistical analyses. RAM aided in study design and supervised statistical analyses. MRDP aided in study design and revised the manuscript for intellectual content. GCF, EES, and LHS conceived and designed the study, critically revised the manuscript for intellectual content, and supervised the study.

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Disclosure

YX is funded by the National Institute on Aging (R01AG062770, R01AG066672); has research funding from Genentech, Daiichi Sankyo, and Janssen; and has received honoraria from Boehringer Ingelheim and Portola. MRDP is an employee of Genentech. GCF reports research funding from the Patient Centered Outcome Research Institute, being a member of the GWTG Steering Committee, and an employee of University of California, which has a patent on an endovascular device. This manuscript is not under review at any other journal. There are no redundant publications based on this data set. All coauthors meet the International Committee of Medical Journal Editors requirements for authorship. BMG, NCS, RAM, EES, and LHS have nothing to disclose.

Supplemental Materials

Supporting information.
Table S1. Unadjusted rates and costs according to whether or not EVT was performed.
Table S2. Unadjusted rates and costs by age subgroups (above and below 80 years).
Table S3. Unadjusted rates and costs by gender subgroups.

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