Outcomes in Mild or Rapidly Improving Stroke Not Treated With Intravenous Recombinant Tissue-Type Plasminogen Activator : Findings From Get With The Guidelines –Stroke

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Outcomes in Mild or Rapidly Improving Stroke Not Treated With Intravenous Recombinant Tissue-Type Plasminogen Activator

Findings From Get With The Guidelines–Stroke

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Background and Purpose—Mild or rapidly improving stroke is a frequently cited reason for not giving intravenous recombinant tissue-type plasminogen activator (rtPA), but some of these patients may have poor outcomes. We used data from a large nationwide study (Get With The Guidelines–Stroke) to determine risk factors for poor outcomes after mild or improving stroke at hospital discharge.

Methods—Between 2003 and 2009, there were 29 200 ischemic stroke patients (from 1092 hospitals) arriving within 2 hours after symptom onset with mild or rapidly improving stroke symptoms as the only contraindication to rtPA. Logistic regression was used to determine the independent predictors of discharge to home.

Results—Among 93 517 patients arriving within 2 hours, 31.2% (29 200) did not receive rtPA solely because of mild/improving stroke. Among the 29 200 mild/improving cases, 28.3% were not discharged to home, and 28.5% were unable to ambulate without assistance at hospital discharge. The likelihood of home discharge was strongly related to initial National Institutes of Health Stroke Scale score (*P*<0.001). In multivariable-adjusted analysis, patients not discharged to home were more likely to be older, female, and black; have a higher National Institutes of Health Stroke Scale score and vascular risk factors; and were less likely to be taking lipid-lowering medication before admission.

Conclusions—In this large, nationwide study, a sizeable minority of patients who did not receive intravenous rtPA solely because of mild/improving stroke had poor short-term outcomes, raising the possibility that stroke-related disability is relatively common, even in "mild" stroke. A controlled trial of reperfusion therapy in this population may be warranted. (*Stroke*. 2011;42:3110-3115.)

Key Words: acute stroke ■ thrombolysis ■ outcomes

Mild or rapidly improving stroke symptoms are cited as the reason for not using recombinant tissue-type plasminogen activator (rtPA) in 29% to 43% of time-eligible patients.[1,2] Previous studies suggest that not all of these patients have a good recovery or even survive to hospital discharge.[3–6] A limitation of many studies is that they were small or were carried out in single centers or in limited populations, such that the results may not be widely applicable. Here, we used data from the Get With The Guidelines–Stroke (GWTG-Stroke) program to determine the frequency, characteristics, and hospital discharge outcomes of ischemic stroke patients who arrived within 2 hours of symptom onset but who did not receive intravenous (IV) rtPA solely because of mild or rapidly improving stroke.

Methods

Data from the GWTG-Stroke program, a voluntary, nationwide stroke registry and quality improvement initiative sponsored by the American Heart Association, were analyzed. Participating hospitals use an Internet-based patient management tool (Outcome Sciences, Cambridge, MA) to upload data on consecutive ischemic stroke cases. Additional details on the program methods are available in the online Methods Supplement (http://stroke.ahajournals.org) and in previous publications.[7,8]

Between April 1, 2003, and September 25, 2009, there were 1423 hospitals that entered 844 339 ischemic stroke or transient ischemic attack (TIA) patients into the registry. Of these, 150 921 patients

Table 1.   Characteristics of Patients With Mild or Improving Stroke (Whole Cohort and Grouped by Home Discharge Status)

Characteristic	Measure	Overall (n=29 200), %	Discharged to Home (n=20 928), %	Not Discharged to Home (n=8272), %	P Value
Demographics					
Age, y	Median (interquartile range)	72 (60–81)	69 (58–79)	79 (69–85)	<0.001
Sex	Female	47.1	44.5	53.8	<0.001
Race/ethnicity	White	78.1	77.4	79.9	<0.001
	Black	11.2	11.3	10.9	
	Hispanic	4.7	4.9	4.1	
	Other	6.1	6.4	5.1	
Mode of arrival	EMS from scene	65.7	59.7	80.9	<0.001
NIHSS score	Median (interquartile range)	2 (1–5)	2 (1–4)	4 (2–7)	<0.001
Medical history					
Atrial fibrillation	Yes	16.9	14.8	22.1	<0.001
Prosthetic heart valve	Yes	1.6	1.7	1.3	0.04
Previous stroke/transient ischemic attack	Yes	30.5	29.2	33.5	<0.001
Coronary artery disease	Yes	28.2	27.2	30.6	<0.001
Carotid stenosis	Yes	4.5	4.4	4.8	0.13
Diabetes mellitus	Yes	25.7	24.2	29.4	<0.001
Peripheral vascular disease	Yes	4.3	3.9	5.2	<0.001
Hypertension	Yes	76.3	74.9	79.9	<0.001
Smoker	Yes	18.3	20.4	13.3	<0.001
Dyslipidemia	Yes	44.4	45.4	41.9	<0.001
Lipid-lowering drug use	Yes	41.7	41.9	41.4	0.52
Hospital characteristics					
No. of stroke discharges	0–100	8.9	8.9	8.9	0.21
	101–300	45.3	45.0	46.1	
	>301	45.8	46.1	44.9	
No. of beds	Median (interquartile range)	366 (262–530)	369 (262–537)	365 (262–515)	0.004
Region	West	20.5	21.2	18.7	<0.001
	South	34.7	35.2	33.3	
	Midwest	18.5	18.4	18.9	
	Northeast	26.4	25.2	29.2	
Hospital type	Academic	60.0	59.8	60.3	0.47
Discharge status					
Length of stay, d	Median (interquartile range)	3 (2–5)	3 (2–4)	5 (3–7)	<0.001
Ambulation	Independent	66.4	84.3	21.1	<0.001
Discharge destination	Died	1.1	0	3.9	<0.001
	Hospice	0.8	0	2.7	
	Rehabilitation	15.7	0	55.5	
	SNF	10.7	0	37.9	
	Home	71.7	100	0	

EMS indicates emergency medical services; NIHSS, National Institutes of Health Stroke Scale; SNF, skilled nursing facility.

(17.9%) were excluded for the following reasons: entered by sites with <75% completeness in documentation of medical history (11 288), missing information on rtPA treatment and reasons for nontreatment (341), missing discharge destination (9769) or left against medical advice (5252), transferred from another hospital (15 489), symptom onset while admitted at another acute-care facility (49 197) or during hospital admission for another cause (in-hospital stroke, 9087), not admitted through the Emergency Department (ED) (35 362), and transferred to another acute-care facility (16 364). Therefore, in total there were 693 418 patients with ischemic stroke or TIA directly admitted through the ED with complete information. Next, we selected patients whose arrival had been documented to within 2 hours of symptom onset (148 068, 21.3%) because these patients should be time-eligible for rtPA therapy based on the recommended door-to-needle time of 60 minutes or less: 93 517 of these patients had a final diagnosis of ischemic stroke and 54 551 had a final diagnosis of TIA. Patients with a final diagnosis of TIA (n=54 441), defined as complete resolution of neurologic symptoms within 24 hours without evidence of brain infarction on neuroimaging,[9] were excluded.

When rtPA is not administered, hospital abstractors review the medical record to classify the reasons for nontreatment. Contraindications, warnings, and system reasons (including in-hospital delays)

must be specifically documented by the treating healthcare providers in the medical record as the reason for nontreatment; inference on the part of the abstractor is not allowed. The list of acceptable reasons for nontreatment is derived from professional guidelines and the US Food and Drug Administration labeling (see online-only Table I) and includes a specific checkbox for "mild or rapidly improving stroke."

"Mild/improving stroke" was defined in this analysis for patients with a final discharge diagnosis of ischemic stroke who had "mild or rapidly improving stroke" checked as the sole reason for not providing rtPA, with no other reasons checked, and who were documented to have arrived within 2 hours of symptom onset (n=29 200). Therefore, these patients likely would have received rtPA had more severe or persistent symptoms been present. We also performed a sensitivity analysis wherein patients with symptoms present on ED arrival but who had a final diagnosis of TIA were reclassified as "mild or rapidly improving" stroke; this analysis was limited to patients admitted from January 2008 onward. The National Institutes of Health Stroke Scale (NIHSS) score was the initial score recorded in the ED.

The primary outcome was discharge destination, analyzed as discharge to home versus discharge to another inpatient facility or death. The proportion capable of independent ambulation at hospital discharge, defined as ambulation without needing another person's assistance (with or without use of a walking aid such as a cane), was analyzed as a secondary outcome. Information on independent ambulation was missing for 2073 of 29 200 (7.1%). Because patients with a final diagnosis of TIA are expected to have relatively benign, short-term outcomes, similar to those of mild/improving stroke, we present outcomes of the 54 551 TIA patients for comparison purposes.

Patient characteristics according to discharge outcome status were compared by the Pearson χ^2 test for categorical variables and the χ^2 rank-based group means score statistic (equivalent to the Kruskal-Wallis test) for continuous or ordinal variables. Logistic regression was used to determine the independent predictors of outcome by using generalized estimating equations to account for clustering of patients by hospital. Models were adjusted for all of the patient and hospital characteristics displayed in Table 1, as well as for calendar time (per year) and the number of years spent in the GWTG-Stroke program, to account for secular trends over time. Data were missing for <4% of mild/improving stroke patients for all variables except for past medical history (6.7%), NIHSS score (38.1%), and the number of stroke discharges per year at the admitting hospital (14.5%, predominantly because they were admitted to hospitals with <1 year of participation in the GWTG-Stroke). For the purpose of multivariable modeling, missing data were imputed as follows: age was imputed to the median, categorical variables were imputed to the most common category, and absent past medical history was imputed to "no." Patients with missing data on hospital characteristics were excluded. Because the number with missing NIHSS score was large, yet NIHSS score appeared to be a critical determinant of outcomes, models were run with and without NIHSS score. Because of the large size of the dataset, all variables were included in the final models without elimination of nonsignificant variables; however, only the significant variables are tabulated. Statistical analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC). A probability value of 0.05 was considered significant.

Results

There were 93 517 acute ischemic stroke patients from 1290 hospitals who had a documented time of arrival within 2 hours of symptom onset: 24 292 (26.0%) received IV rtPA, 29 200 (31.2%) did not receive rtPA solely because of mild/improving stroke, 26 891 (28.8%) did not receive rtPA because of other documented reasons, and 13 134 (14.0%) did not receive rtPA and had no reason documented. There was little change from 2003 to 2009 in the proportion with mild/improving stroke as the sole contraindication to rtPA use (Figure 1). The median hospital-specific percentage with mild/improving stroke was 30.4% (interquartile range, 22.6%
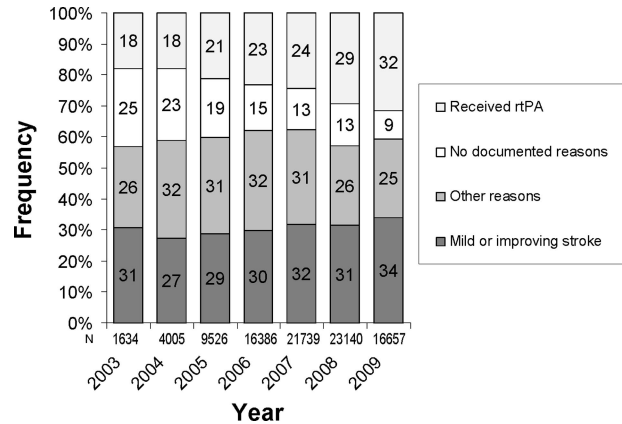

Figure 1. Documentation of recombinant tissue-type plasminogen activator (rtPA) treatment or reasons for nontreatment among ischemic stroke patients arriving at hospital within 2 hours. Numbers within the columns are percentages.

to 37.4%) across 818 hospitals, excluding 503 hospitals submitting <25 patients arriving in <2 hours.

The median age of the patients with mild/improving stroke was 72 years (interquartile range, 62 to 81 years), and 47.1% were women. Compared with those who did receive IV rtPA, patients with mild/improving stroke were more likely to have a history of prior stroke and dyslipidemia and less likely to have a history of atrial fibrillation (online-only Table II). The NIHSS score was documented in 18 067 of 29 200 (61.9%) of the patients with mild/improving stroke; the median score was 2 (interquartile range, 1 to 5). Characteristics of mild/improving stroke patients with versus without a documented NIHSS score are shown in online-only Table III. By comparison, the NIHSS score was documented in 20 095 of 24 292 (82.7%) of the patients given rtPA; the median NIHSS score was 12 (interquartile range, 7 to 18; Figure 2).

Among the 29 200 patients with mild/improving stroke not treated with rtPA, there were 8272 (28.3%) patients who could not be discharged to home, including 323 (1.1%) who died, 224 (0.8%) who were discharged to hospice, 3133 (10.7%) who were discharged to a skilled nursing facility, and 4592 (15.7%) who were discharged to acute rehabilitation. There were 7732 of 27 127 (28.5%) who could not ambulate independently by the time of hospital discharge, including 1621 (6.0%) who were unable to ambulate and 6111 (22.5%) who required assistance to ambulate. The median length of stay was 3 days (interquartile range, 2 to 5 days). Patients with higher initial NIHSS scores had worse outcomes ($P<0.001$, Table 2). By comparison, among 54 551 TIA patients arriving within 2 hours, there were only 4389 (8.0%) who could not be discharged to home, 110 (0.2%) who died in the hospital, and 6448 of 51 408 (12.5%) who could not ambulate independently (all $P<0.001$ compared with mild/improving stroke). In a sensitivity analysis wherein patients with a final diagnosis of TIA but with symptoms present on arrival were reclassified as "mild or improving stroke," the proportion of ischemic stroke patients with mild or rapidly improving stroke increased to 41.9%, and outcomes were somewhat better but still worse than for TIA (online-only Table IV).
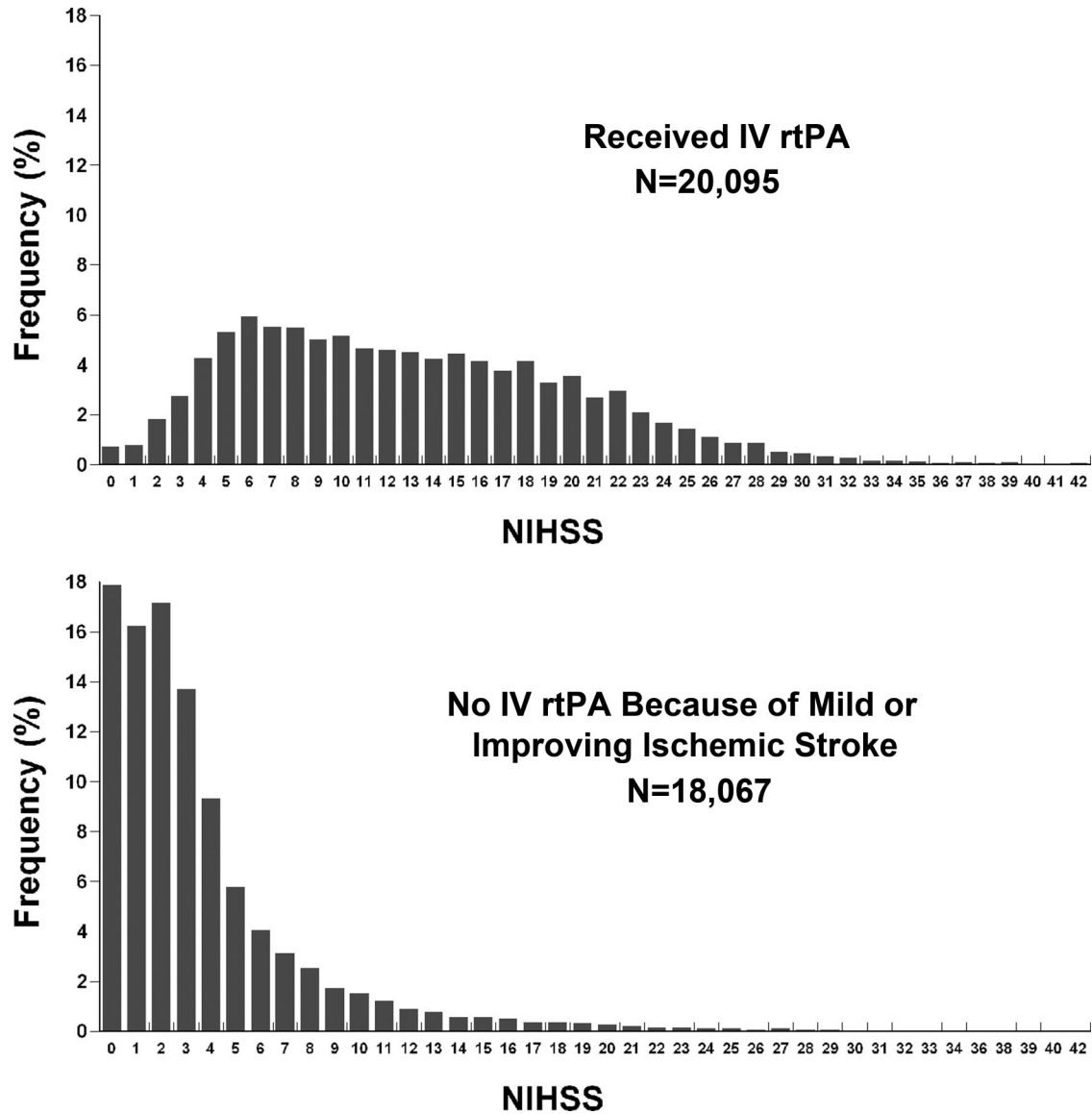
Figure 2. National Institutes of Health Stroke Scale (NIHSS) scores in patients who did or did not receive intravenous recombinant tissue-type plasminogen activator (IV rtPA) treatment because of mild or improving ischemic stroke. Most patients given IV rtPA had NIHSS scores >5 (84.4%), whereas most patients not given IV rtPA because of mild or improving symptoms had NIHSS scores ≤5 (80.1%).

The univariate characteristics of patients with mild/improving stroke who were discharged to home are shown in Table 1. The multivariable-adjusted characteristics of those who were discharged to home are shown in Table 3. Patients who were discharged to home had lower initial NIHSS scores and were more likely to be younger, male, and white and to not have diabetes, peripheral vascular disease, or hypertension. Patients taking lipid-lowering medicines before admission were more likely to be discharged to home (Table 3). Covariate estimates were similar when the model was rerun for all patients without including NIHSS score as a covariate, with the exception that the absence of atrial fibrillation, smoking, and previous stroke or TIA were also associated with an increased likelihood of home discharge when not controlling for NIHSS score (online-only Table V). Additional multivariable-adjusted analyses showed that outcomes

for patients with mild/rapidly improving stroke were better than for rtPA–treated patients with mild stroke (defined as an initial NIHSS score of 0 to 5) but worse than for patients with a final diagnosis of TIA (online-only Tables VI and VII).

Discussion

This study shows that many patients not given IV rtPA because of mild or rapidly improving stroke symptoms had poor hospital discharge outcomes. This is the first large, nationwide study to show that patients who do not receive rtPA because of mild or rapidly improving stroke are still at risk for requiring inpatient care or rehabilitation after hospital discharge. Discharge outcomes were significantly worse than for those with TIA. The initial NIHSS score was a strong predictor of outcome, with a graded relation between higher NIHSS score and a lower likelihood of discharge to home or

Table 2. Discharge Outcomes According to Stroke Severity for Patients With Mild or Improving Stroke

Mild/ Improving Stroke, NIHSS Score	Discharge Destination			Ambulatory Status at Discharge		
	Total	Not Discharged Home	Percent	Total	Not Ambulating Independently	Percent
0	3229	500	15.5	3025	488	16.1
1	2932	535	18.2	2757	544	19.7
2	3100	735	23.7	2903	695	23.9
3	2475	715	28.9	2305	641	27.8
4	1682	596	35.4	1557	528	33.9
5	1045	411	39.3	971	370	38.1
6–10	2338	1074	46.0	2165	978	45.2
>10	1266	729	57.6	1155	664	57.5

Stroke patients with NIHSS=0 had either imaging evidence of infarction or stroke symptoms not quantifiable on the NIHSS. Outcomes were strongly associated with initial NIHSS score ($P<0.001$).

NIHSS indicates National Institutes of Health Stroke Scale.

independent ambulation among those with mild or improving ischemic stroke. Other predictors of lower likelihood of discharge to home, based on multivariable-adjusted analysis, were older age, female sex, black race, diabetes, hypertension, and lack of use of lipid-lowering drugs before admission.

Table 3. Multivariable-Adjusted Predictors of Discharge to Home

Characteristic	OR	Lower 95% CI	Upper 95% CI	P Value
NIHSS score (per 1-point increase)	0.89	0.88	0.90	<0.001
Age (per 10-y increase)	0.63	0.60	0.65	<0.001
Female sex	0.86	0.79	0.93	<0.001
Race/ethnicity				
White (reference)	1.00	. . .	. . .	. . .
Black	0.86	0.74	0.99	0.04
Hispanic, any race	1.22	1.01	1.48	0.04
Other	1.26	1.08	1.47	0.004
Prior stroke or transient ischemic attack	0.93	0.86	1.01	0.11
Diabetes mellitus	0.69	0.63	0.75	<0.001
Peripheral vascular disease	0.82	0.68	0.99	0.03
Hypertension	0.91	0.83	0.99	0.03
Lipid-lowering therapy	1.14	1.04	1.24	0.006
Region				
West (reference)	1.00	. . .	. . .	. . .
Northeast	0.72	0.63	0.84	<0.001
Midwest	0.78	0.68	0.90	<0.001
South	0.85	0.75	0.97	0.01

Models were also adjusted for other past medical history and hospital characteristics (see Methods).

OR indicates odds ratio; NIHSS, National Institutes of Health Stroke Scale; CI, confidence interval.

The pivotal 1995 National Institute of Neurological Disorders and Stroke rtPA trial excluded patients with specific minor stroke syndromes or rapidly improving symptoms, without giving specific NIHSS thresholds.[10] In this study, there was a relatively similar hospital-specific percentage of patients arriving <2 hours who were documented to have mild or rapidly improving stroke across >800 hospitals. Additionally, this study suggests that the operational definition of "mild or rapidly improving stroke" has not substantially changed over time because the frequency was similar from 2003 to 2009, despite large increases in the proportion of patients who were given rtPA. Most patients with mild or rapidly improving stroke had an initial NIHSS score ≤5, whereas most patients treated with rtPA had NIHSS scores >5. Other factors that probably influence the decision as whether to give rtPA, such as specific features of the neurologic examination and patient preferences, were not measured in this study. Patients with NIHSS scores substantially >5 or 10 probably had rapid improvement on the neurologic examination; however, this cannot be confirmed in the current study, because only NIHSS scores at the time of initial assessment were recorded. These patients also had worse outcomes, suggesting that rapid improvement may be associated with a higher risk of subsequent deterioration.[3,4]

Mild or rapidly improving stroke was the most common reason for not giving rtPA to time-eligible patients, occurring in 31.2% of ischemic stroke patient who arrived within 2 hours, consistent with findings from previous registries[1,11] and a population–based study.[2] More patients were not given rtPA because of mild or improving stroke than were actually given rtPA. The proportion of mild or rapidly improving stroke patients may be underestimated because we could not distinguish whether patients with TIA had symptom resolution after the time of rtPA decision and might have been considered for rtPA; our sensitivity analysis suggests that the true proportion of mild or rapidly improving stroke may be as high as 41.9%.

There are some limitations to this study. Hospital participation in GWTG-Stroke is voluntary, and therefore, participating hospitals may not be representative of the entire US hospital population, although a large number of both community and academic hospitals are included. NIHSS information was missing for many participants, reflecting its incomplete use in routine medical practice. Information on postdischarge outcome or global disability was unavailable. Discharge to home is considered an important outcome for patients, however, and the number of days spent at home within the first 90 days after stroke has been shown to correlate well with disability status.[12] A study of postdischarge 90-day outcomes in patients not given rtPA because of mild or rapidly improving stroke symptoms showed that disabling stroke symptoms (modified Rankin scores ≥2) were present in 24.7%,[4] suggesting that many patients who cannot be discharged to home or who are not ambulating independently at discharge may have residual permanent disability. Discharge to home also depends on factors unrelated to stroke severity, such as social support, prestroke function, local practice patterns, and insurance status, which were not measured in this study. Information on prestroke

place of residence was unavailable in this study; therefore, some of the patients not discharged to home may have been residing in another healthcare facility, such as a nursing home, before admission and could not have been discharged to home regardless of their stroke outcomes. Finally, the risk of neurologic deterioration in mild or rapidly improving stroke has been associated with the presence of vascular occlusion[3,4,6] or initial severe symptoms followed by dramatic improvement[3,4]; however, information on these characteristics is unavailable in GWTG-Stroke. During the study period, mild stroke was not discriminated from rapidly improving stroke. Further prospective studies with serial assessments of stroke severity at the scene and in the ED will be needed to determine the relation between timing and the degree of symptom improvement and the risk of subsequent deterioration.

These data suggest that physicians should not assume that patients with initially mild or rapidly improving ischemic stroke symptoms are at low risk for requiring inpatient care or rehabilitation after hospital discharge. The reasons for poor outcomes cannot be determined from this study but could include persistent stroke-related deficits, recurrent stroke, or medical complications of stroke. A re-examination of the criteria for excluding patients from rtPA because of mild or rapidly improving symptoms may be warranted, pending further studies. Previous subgroup analyses of the 1995 National Institute of Neurological Disorders and Stroke study[10] and the ECASS III study[13] suggest that rtPA is similarly effective in milder strokes as in more severe strokes. A randomized, controlled trial of rtPA for treatment of mild or rapidly improving stroke should be considered.

Sources of Funding

Disclosures

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ONLINE SUPPLEMENT

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Supplemental Methods

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Supplemental Table 2 (Table S2): Characteristics of Patients with Mild or Improving Stroke Compared
to Patients that Received IV rt-PA

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Supplemental Table 4 (Table S4): Sensitivity Analysis—Discharge Outcomes According to Different
Definitions of Mild or Improving Ischemic Stroke

Supplemental Table 5 (Table S5): Multivariable-adjusted Predictors of Discharge to Home in the Entire
Cohort (Including Patients Missing NIH Stroke Scale Score)

Supplemental Table 6 (Table S6): Hospital Discharge Outcomes in Patients Not Treated with rt-PA
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Supplemental Table 7 (Table S7): Hospital Discharge Outcomes in Mild or Rapidly Improving Stroke
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Supplemental Methods

Characteristics of the GWTG-Stroke program have been previously described.[1, 2] Participating hospitals use an internet-based Patient Management Tool (Outcome Sciences Inc, Cambridge Mass) to enter data, receive decision support, and obtain feedback via on-demand reports of performance on quality measures. Hospitals were instructed to record data from consecutive stroke and TIA admissions. Case ascertainment was through clinical identification during hospitalization, retrospective identification by ICD-9 codes (including 433.x, 434.x and 436), or both. The eligibility of each case was confirmed at chart review prior to abstraction. Trained hospital personnel abstracted data using the internet-based Patient Management Tool with standardized data definitions and detailed coding instructions. The internet-based system performs checks to ensure that the reported data is complete and internally consistent. In addition, data quality is monitored for completeness and accuracy. Hospital characteristics (i.e., academic teaching status, bed size) were based on American Hospital Association data.[3] Past medical history was defined based on pre-existing conditions, excluding newly diagnosed conditions during the hospital stay.

All participating institutions were required to comply with local regulatory and privacy guidelines and, if required, to secure institutional review board approval. Because data were used primarily at the local site for quality improvement, sites were granted a waiver of informed consent under the common rule. Outcome Sciences, Inc (Cambridge, Massachusetts) served as the registry coordinating center. The Duke Clinical Research Institute (Durham, North Carolina) served as the data analysis center and institutional review board approval was granted to analyze aggregate de-identified data for research purposes.

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Supplemental Table 1 (S1). Categories of Reasons for Non-treatment with IV rt-PA

Contraindications:
- SBP > 185 or DBP > 110 mmHg despite treatment
- Seizure at onset
- Recent surgery/trauma (<15 days)
- Recent intracranial or spinal surgery, head trauma, or stroke (<3 mo.)
- History of intracranial hemorrhage or brain aneurysm or vascular malformation or brain tumor
- Active internal bleeding (<22 days)
- Platelets <100,000, PTT> 40 sec after heparin use, or PT > 15 or INR > 1.7, or known bleeding diathesis
- Suspicion of subarachnoid hemorrhage
- CT findings (ICH, SAH, or major infarct signs)

Warnings:
- Advanced age
- Care-team unable to determine eligibility
- Glucose < 50 or > 400 mg/dl
- Increased risk of bleeding due to comorbid conditions (see coding instructions)
- IV or IA rt-PA given at outside hospital
- Left heart thrombus
- Life expectancy < 1 year or severe co-morbid illness or CMO on admission
- Pregnancy
- Pt./Family refused
- Rapid improvement or stroke severity too mild
- Stroke severity – Too severe (e.g., NIHSS >22)

Hospital or other related factors:
- Delay in Stroke diagnosis
- Inhospital Time Delay
- No IV access
- Other

Supplement Table 1 Legend

List of contraindications, warnings, and system reasons for not administering rt-PA that can be checked in the Get With The Guidelines-Stroke case report form. Chart abstractors are instructed that the reason for not giving rt-PA must be specifically documented in the medical record in order to be abstracted; inference on the part of the abstractor is not allowed. These categories were derived from professional guidelines[1, 2] and the approved use labeling for alteplase by the U.S. Food and Drug Administration.[3]

References

[1]Adams HP, Jr., Adams RJ, Brott T, del Zoppo GJ, Furlan A, Goldstein LB, Grubb RL, Higashida R, Kidwell C, Kwiatkowski TG, Marler JR, Hademenos GJ. Guidelines for the early management of patients with ischemic stroke: A scientific statement from the Stroke council of the American Stroke Association. *Stroke*. 2003;34:1056-1083.

[2]Adams HP, Jr., del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, Grubb RL, Higashida RT, Jauch EC, Kidwell C, Lyden PD, Morgenstern LB, Qureshi AI, Rosenwasser RH, Scott PA, Wijdicks EF. Guidelines for the early management of adults with ischemic stroke: A guideline from the American Heart Association/American Stroke association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups. *Stroke*. 2007;38:1655-1711.

[3]Available on line at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandAppro ved/ApprovalApplications/TherapeuticBiologicApplications/ucm080871.pdf. Accessed November 14, 2010.

Supplemental Table 2 (S2). Characteristics of Patients with Mild or Improving Stroke Compared to Patients that Received IV rt-PA

Characteristic	Level	Mild/Improving Stroke N=29,200 %	tPA N=24,292 %	P-value
Demographics				
Age	Median [IQR]	72 [60-81]	72 [59-81]	<0.001
Gender	Female	47.1	49.1	<0.001
Race/Ethnicity	White/Caucasian	78.1	75.5	<0.001
	African American	11.2	12.8	
	Hispanic	4.7	5.4	
	Other	6.1	6.3	
Mode of Arrival	Private transport	34.3	12.8	<0.001
	EMS	65.7	87.2	
NIHSS	Median [IQR]	2 [1-5]	12 [7-18]	<0.001
Medical History				
Atrial Fibrillation	Yes	16.9	23.6	<0.001
Prosthetic Heart Valve	Yes	1.6	1.3	<0.001
Previous Stroke or TIA	Yes	30.5	24.2	<0.001
Coronary Artery Disease	Yes	28.2	28.7	<0.001
Carotid Stenosis	Yes	4.5	3.3	<0.001
Diabetes Mellitus	Yes	25.7	24.4	<0.001
PVD	Yes	4.3	3.6	<0.001
Hypertension	Yes	76.3	76.4	<0.001
Smoker	Yes	18.3	21.0	<0.001
Dyslipidemia	Yes	44.4	39.1	<0.001
Hospital Characteristics				
Number of Stroke Discharges	0 - 100	8.9	8.0	
	101 - 300	45.3	44.0	
	301+	45.8	48.0	<0.001
Number of Beds	Median [IQR]	366 [262-530]	394 [278-571]	<0.001
Region	West	20.5	21.0	<0.001
	South	34.7	33.9	
	Midwest	18.5	18.0	
	Northeast	26.4	27.1	

Hospital Type	Academic	40.0	35.9	<0.001
Discharge Status				
Length of Stay	Median [IQR]	3 [2-5]	5 [3-8]	
Discharge Destination	Died	1.1	10.0	
	Hospice	0.8	4.3	<0.001
	Rehabilitation	15.7	31.4	
	Skilled Nursing Facility	10.7	17.2	
	Home	71.7	37.2	
Ambulatory Status	Independent	71.5	41.9	<0.001

Supplemental Table 2 Legend

IQR, interquartile range; PVD, peripheral vascular disease.

Supplemental Table 3 (S3). Characteristics of Mild or Rapidly Improving Stroke Patients With vs. Without NIHSS Recorded

Characteristic	Level	NIHSS Recorded (N=18067)	NIHSS Not Recorded (N=11133)	P-value
Demographics				
Age	Median [IQR]	72 [60-81]	73 [61-81]	0.01
Gender	Female	46.7	47.9	0.05
Race/ethnicity	White	77.7	78.8	<0.001
	Black	11.1	11.3	
	Hispanic	4.7	4.6	
	Other	6.5	5.4	
Mode of Arrival	Ambulance from scene	67.3	63.2	<0.001
Medical History				
Atrial Fibrillation	Yes	17.0	16.8	0.62
Prosthetic Heart Valve	Yes	1.5	1.7	0.24
Previous Stroke/TIA	Yes	29.9	31.4	0.009
Coronary Artery Disease	Yes	27.9	28.7	0.16
Carotid Stenosis	Yes	4.3	4.9	0.04
Diabetes Mellitus	Yes	25.7	25.9	0.69
Peripheral Vascular Disease	Yes	4.2	4.4	0.37
Hypertension	Yes	76.2	76.5	0.59
Smoker	Yes	18.9	17.3	<0.001
Dyslipidemia	Yes	44.2	44.7	0.41
Lipid Lowering Drug	Yes	41.4	42.3	0.34

Supplemental Table 3 Legend
IQR, interquartile range.

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Supplemental Table 4 (S4): Sensitivity Analysis—Discharge Outcomes According to Different Definitions of Mild or Improving Ischemic Stroke

	Definition of Mild or Rapidly Improving Stroke		Final diagnosis TIA with resolved symptoms on ED arrival (%)
	Excluding all with final diagnosis of TIA (%)	Including patients with final diagnosis of TIA who had symptoms on ED arrival (%)	
	n=12,912	n=19,412	(n=17,563)
Discharge status			
Not discharged home	27.3	20.2	6.5
Died	1.0	0.7	0.2
Length of Stay			
Median (interquartile range)	3 (2-5)	3 (2-4)	2 (1-3)
Ambulation			
Not independent	26.7	21.3	11.3

Table Legend

In primary analyses we excluded patients with a final diagnosis of TIA, even though some patients may have had neurological symptoms at the time of tPA decision and could have been clinically treated as mild or improving stroke. To determine the impact of including TIA patients with neurological symptoms at the time of ED arrival, we performed a sensitivity analysis limited to the 63,860 patients included since January 2008, when information on the presence or absence of symptoms on ED arrival was collected. Among 24,063 patients with final diagnosis of TIA, 6,500 (27.0%) had symptoms present on ED arrival and were reclassified as mild or improving stroke in this sensitivity analysis. In the sensitivity analysis the prevalence of mild or improving stroke among all ischemic stroke patients was 41.9% (19,412/46,297) when using the revised definition, compared to 32.4% (12,912/39,797) when using the primary definition. Because we do not have information on when symptoms resolved in patients with symptoms on ED arrival but final diagnosis of TIA, we are unable to determine how many of these patients had symptom resolution prior to the time of tPA decision and would have been clinically treated as TIA. Therefore the true proportion of mild or improving stroke, as ascertained at the time of tPA decision, is somewhere between 32.4% and 41.9%.

Outcomes were somewhat better when using the revised sensitivity definition of mild or improving stroke vs. the primary definition; however, outcomes for mild or rapidly improving stroke patients were significantly worse than TIA ($p<0.001$ for all outcomes) by either definition.

Supplemental Table 5 (S5). Multivariable-adjusted Predictors of Discharge to Home in the Entire Cohort (Including Patients Missing NIH Stroke Scale Score)

Characteristics	Odds Ratio	Lower 95% Confidence Limit	Upper 95% Confidence Limit	P-value
Age (per 10-year increase)	0.61	0.59	0.62	<0.001
Female sex	0.83	0.78	0.89	<0.001
Race/Ethnicity				
White (reference)	1.00			
African-American	0.75	0.68	0.84	<0.001
Hispanic - any race	0.95	0.82	1.11	0.54
Other	1.19	1.04	1.37	0.01
Atrial Fibrillation or Flutter	0.84	0.78	0.91	<0.001
Prior Stroke or TIA	0.90	0.85	0.96	0.002
Diabetes Mellitus	0.69	0.64	0.73	<0.001
Peripheral Vascular Disease	0.82	0.71	0.94	0.006
Hypertension	0.91	0.85	0.98	0.008
Smoker	0.90	0.82	0.97	0.01
Lipid-Lowering Therapy	1.20	1.12	1.29	<0.001
Region				
West (reference)	1.00			
Northeast	0.76	0.68	0.86	<0.001
Midwest	0.79	0.71	0.89	<0.001
South	0.90	0.81	1.01	0.06

Supplemental Table 5 Legend

Models were also adjusted for other past medical history and hospital characteristics (see Methods for details). NIH Stroke Scale score is not included as a covariate because it was missing in 38.1% of all patients.

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Supplemental Table 6 (S6). Hospital Discharge Outcomes in Patients Not Treated with rt-PA Because of Mild or Rapidly Improving Stroke, Compared to rt-PA-treated Patients with Mild Stroke (NIHSS 0-5)

Outcome	Unadjusted OR	Lower 95% CI	Upper 95% CI	P value	Adjusted OR	Lower 95% CI	Upper 95% CI	P value
Not Adjusting for NIHSS								
In-Hospital Death	0.54	0.42	0.71	<0.001	0.46	0.35	0.61	<0.001
Discharged to Home	1.18	1.08	1.28	<0.001	1.48	1.35	1.62	<0.001
Ambulatory at Discharge	1.05	0.95	1.16	0.33	1.32	1.19	1.47	<0.001
LOS >= 4 days	0.69	0.63	0.76	<0.001	0.63	0.58	0.69	<0.001
Adjusting for NIHSS								
In-Hospital Death	0.54	0.42	0.71	<0.001	0.46	0.35	0.62	<0.001
Discharged to Home	1.18	1.08	1.28	<0.001	1.39	1.27	1.52	<0.001
Ambulatory at Discharge	1.05	0.95	1.16	0.33	1.26	1.14	1.40	<0.001
LOS >= 4 days	0.69	0.63	0.76	<0.001	0.65	0.60	0.72	<0.001

Table S6 Legend

Models were adjusted for age, gender, race/ethnicity (white, black, hispanic, other), BMI, atrial fibrillation, revious stroke/TIA, coronary artery disease, carotid stenosis, diabetes, peripheral vascular disease, hypertension, dyslipidemia, and hospital characteristics (hospital region, academic teaching hospital, number of beds).

There were 29,200 patients with mild or rapidly improving stroke and 3,139 patients with admission NIHSS 0-5 who were treated with rt-PA. Adjusted outcomes were better in the patients not treated with rt-PA because of mild or rapidly improving stroke, compared to rt-PA-treated patients with mild stroke (NIHSS 0-5). Caution should be exercised in the interpretation of these results, however. Because rt-PA was used based on physician preference and not randomly assigned, it is possible that the observed apparent deleterious effect of rt-PA may represent residual confounding by poor prognostic features that might have influenced the decision whether to give rt-PA or not.

Supplemental Table 7 (S7). Hospital Discharge Outcomes in Mild or Rapidly Improving Stroke Patients Compared to TIA

Outcome	Unadjusted OR	Lower 95% CI	Upper 95% CI	P value	Adjusted OR	Lower 95% CI	Upper 95% CI	P value
In-Hospital Death	5.49	4.42	6.81	<0.001	5.42	4.38	6.70	<0.001
Discharged to Home	0.22	0.21	0.23	<0.001	0.19	0.18	0.20	<0.001
Ambulatory at Discharge	0.37	0.35	0.38	<0.001	0.31	0.30	0.33	<0.001
LOS >= 4 days	3.23	3.12	3.35	<0.001	3.38	3.25	3.51	<0.001

Table S7 Legend

Models were adjusted for age, gender, race/ethnicity (white, black, hispanic, other), BMI, atrial fibrillation, revious stroke/TIA, coronary artery disease, carotid stenosis, diabetes, peripheral vascular disease, hypertension, dyslipidemia, and hospital characteristics (hospital region, academic teaching hospital, number of beds).

Patients not treated with rt-PA because of mild or improving stroke had an increased risk of death and decreased odds of discharge to home or ambulating independently at discharge, compared to patients with TIA.