Risks of Intracranial Hemorrhage Among Patients With Acute Ischemic Stroke Receiving Warfarin and Treated With Intravenous Tissue Plasminogen Activator

Ying Xian, MD, PhD
Li Liang, PhD
Eric E. Smith, MD, MPH
Lee H. Schwamm, MD
Mathew J. Reeves, PhD
DaiWai M. Olson, PhD, RN
Adrian F. Hernandez, MD, MHS
Gregg C. Fonarow, MD
Eric D. Peterson, MD, MPH

Context Intravenous tissue plasminogen activator (tPA) is known to improve outcomes in ischemic stroke; however, patients receiving long-term chronic warfarin therapy may face an increased risk for intracranial hemorrhage when treated with tPA. Although current guidelines endorse administering intravenous tPA to warfarin-treated patients if their international normalized ratio (INR) is 1.7 or lower, there are few data on safety of intravenous tPA in warfarin-treated patients in clinical practice.

Objectives To determine the risk of symptomatic intracranial hemorrhage (sICH) among patients with ischemic stroke treated with intravenous tPA who were receiving warfarin vs those who were not and to determine this risk as a function of INR.

Design, Setting, and Patients Observational study, using data from the American Heart Association Get With The Guidelines–Stroke Registry, of 23 437 patients with ischemic stroke and with INR of 1.7 or lower, treated with intravenous tPA in 1203 registry hospitals from April 2009 through June 2011.

Main Outcome Measure Symptomatic intracranial hemorrhage. Secondary end points include life-threatening/serious systemic hemorrhage, any tPA complications, and in-hospital mortality.

Results Overall, 1802 (7.7%) patients with stroke treated with tPA were receiving warfarin (median INR, 1.20; interquartile range [IQR], 1.07-1.40). Warfarin-treated patients were older, had more comorbid conditions, and had more severe strokes. The unadjusted sICH rate in warfarin-treated patients was higher than in non–warfarin-treated patients (5.7% vs 4.6%, $P<.001$), but these differences were not significantly different after adjustment for baseline clinical factors (adjusted odds ratio [OR], 1.01 [95% CI, 0.82-1.25]). Similarly, there were no significant differences between warfarin-treated and non–warfarin-treated patients for serious systemic hemorrhage (0.9% vs 0.9%; adjusted OR, 0.78 [95% CI, 0.49-1.24]), any tPA complications (10.6% vs 8.4%; adjusted OR, 1.09 [95% CI, 0.93-1.29]), or in-hospital mortality (11.4% vs 7.9%; adjusted OR, 0.94 [95% CI, 0.79-1.13]). Among warfarin-treated patients with INRs of 1.7 or lower, the degree of anticoagulation was not statistically significantly associated with sICH risk (adjusted OR, 1.10 per 0.1-unit increase in INR [95% CI, 1.00-1.20]; $P=.06$).

Conclusion Among patients with ischemic stroke, the use of intravenous tPA among warfarin-treated patients (INR ≤1.7) was not associated with increased sICH risk compared with non–warfarin-treated patients.

JAMA. 2012;307(24):2600-2608 www.jama.com

INTRAVENOUS TISSUE PLASMINOGEN activator (tPA) is currently the only effective treatment to improve outcomes for acute ischemic stroke[1,2]; however, treatment with intravenous tPA carries the risk of symptomatic intracranial hemorrhage (sICH). Of patients who receive intravenous tPA for stroke, 2.4% to 8.8% experience this potentially life-threatening complication.[3-6] Warfarin-treated patients may be at an increased risk of sICH, but the true absolute risk of sICH in this population remains a matter of significant debate, because warfarin-treated patients were excluded from major trials of tPA.[3-8] Furthermore, observational studies of bleeding risk among warfarin-treated patients receiving intravenous tPA have been small and inconsistent.[9-13] Based on limited data, current guide-

For editorial comment see p 2637.

CME available online at www.jamaarchivescme.com and questions on p 2646.

Author Affiliations: Duke Clinical Research Institute, Durham, North Carolina (Drs Xian, Liang, Olson, Hernandez, and Peterson); Department of Clinical Neurosciences, University of Calgary, Calgary, Alberta, Canada (Dr Smith); Division of Neurology, Massachusetts General Hospital, Boston (Dr Schwamm); Department of Epidemiology, Michigan State University, East Lansing (Dr Reeves); and Division of Cardiology, University of California, Los Angeles (Dr Fonarow).
Corresponding Author: Eric D. Peterson, MD, MPH, Duke Clinical Research Institute, PO Box 17969, Durham, NC 27715 (peter016@mc.duke.edu).

lines of the American Heart Association/American Stroke Association (AHA/ASA) allow use of intravenous tPA in warfarin-treated patients, provided that the patient's international normalized ratio (INR) is 1.7 or lower.[1,2] Without safety data, however, some investigators have expressed concern regarding administration of intravenous tPA to warfarin-treated patients with stroke.[9,12]

We accessed the AHA Get With The Guidelines–Stroke (GWTG-Stroke) Registry to evaluate the association of warfarin treatment and sICH among patients with stroke receiving intravenous tPA in routine clinical practice. Our specific goals were to (1) determine whether warfarin-treated patients were at an increased risk of sICH following administration of intravenous tPA for acute ischemic stroke; (2) to examine the association between INR and sICH in warfarin-treated patients; and (3) to estimate the percentage of warfarin-treated patients in current clinical practice who were otherwise eligible to receive tPA treatment but who did not receive it.

METHODS

GWTG-Stroke Registry

The primary data source was the GWTG-Stroke Registry, an ongoing, voluntary, national stroke registry and performance improvement program sponsored by the AHA/ASA. Details of the design and conduct of the GWTG-Stroke Registry have been previously described.[14-16] To summarize, the AHA/ASA developed the GWTG-Stroke Registry to improve the quality of care and outcomes for patients hospitalized with stroke. The program includes a set of performance measures to quantify the quality of stroke care and uses the results of those measures to guide the quality improvement efforts at participating centers. As part of this effort, trained hospital personnel are instructed to use an Internet-based patient management tool (Outcome Sciences Inc, Cambridge, Massachusetts) to collect patient-level data on acute stroke care provided to patients enrolled in the GWTG-Stroke Registry. The eligibility of each admission is confirmed through chart review.

Standardized data collection includes patient demographics, medical history, diagnostic testing, brain imaging, in-hospital treatment, and outcomes. The GWTG-Stroke Registry collects data on medications prior to admission, including use of antithrombotics, type of antithrombotic (eg, antiplatelet agent or anticoagulant), and INR values at presentation, using a new version of the data collection form made available in April 2009. The validity and reliability of data collection in the GWTG-Stroke Registry database has been reported.[17] Outcome Sciences Inc serves as the data collection and coordination center for GWTG-Stroke. The Duke Clinical Research Institute serves as the data analysis center and has an agreement to analyze the aggregate deidentified data for research purposes.

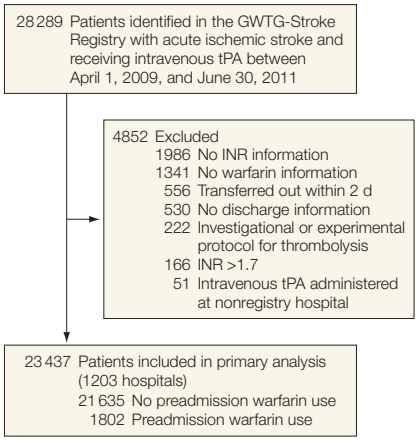
Study Population

Our analyses included patients with acute ischemic stroke receiving intravenous tPA in GWTG-Stroke hospitals between April 1, 2009, and June 30, 2011. We excluded patients who had missing information on warfarin use and INR. We further limited our primary analyses to patients presenting with a baseline INR of 1.7 or lower to conform to the AHA/ASA guideline recommendations. After these exclusions, our primary study population consisted of 23 437 patients from 1203 hospitals (FIGURE 1).

Variables of Interest and Outcomes

Warfarin treatment was defined as a patient taking warfarin within 7 days of the index stroke admission. The baseline INR results refer to the first measurement after presentation to the hospital. The primary outcome measure was sICH, defined as intracerebral hemorrhage within 36 hours, documented by computed tomography or magnetic resonance imaging and by the treating physician's notes indicating clinical deterioration attributable to hemorrhage. This definition is based on the criteria for sICH established in the National Institute of Neurological Disorders and Stroke (NINDS) tPA trials.[3] Secondary end points included life-threatening or serious systemic hemorrhage within 36 hours, any tPA complication within 36 hours, in-hospital mortality, and discharge to skilled nursing facility or inpatient rehabilitation facility. Any tPA complication includes sICH within 36 hours, life-threatening or serious systemic hemorrhage within 36 hours, or other serious complications.

Figure 1. Selection of Study Population



GWTG-Stroke indicates Get With The Guidelines–Stroke; INR, international normalized ratio; tPA, tissue plasminogen activator.

Statistical Analyses

Means, medians, and percentages were used to describe the distribution of continuous and categorical variables, respectively. Baseline characteristics were compared between patients with and without warfarin treatment by Pearson χ^2 test for categorical variables and Wilcoxon rank-sum test for continuous variables. Multivariable logistic regression analyses were performed to investigate the relationships between warfarin use and tPA-related complications of (1) sICH, (2) life-threatening or serious systemic hemorrhage, and (3) any tPA complication. These analyses adjusted for baseline demographic and clinical

variables associated with sICH risk in intravenous tPA–treated patients with stroke and included age, sex, race/ethnicity (determined using GWTG-Stroke Registry categories and assessed because race/ethnicity has been identified in previous studies as a risk factor for sICH), baseline National Institutes of Health Stroke Scale (NIHSS) score (a measure of neurologic deficits ranging from 0-42, with higher score for greater stroke severity), systolic blood pressure, and blood glucose levels.[18] Similar logistic regression analyses were performed to evaluate the relationship between warfarin use and in-hospital mortality. The mortality model adjusted for age, sex, arrival mode, medical history of atrial fibrillation, coronary artery disease, prior stroke or transient ischemic attack (TIA), diabetes mellitus, dyslipidemia, and NIHSS score.[19] A multiple imputation method was used to impute missing NIHSS data for 2327 patients (9.9%). Our analyses also accounted for within-hospital clustering using a generalized estimating equations approach.

The robustness of our findings was assessed in several ways. First, we performed a sensitivity analysis using a logistic regression model with all aforementioned clinical factors except for NIHSS score. Second, we restricted the study population to intravenous tPA–treated patients with complete NIHSS data (N = 21 110). Third, we performed subgroup analyses according to age (<75 and ≥75 years), sex, and NIHSS score (≤14 and >14). Fourth, given that the population of greatest interest may be those with higher INR levels, we performed a subgroup analysis focused on patients presenting with INRs between 1.5 and 1.7 (n = 269). In addition, we extended our study cohort to the entire subtherapeutic INR and included patients with an INR of 2.0 or lower (n = 23 510).

Because of the possibility of confounding by tPA treatment selection, we analyzed data from all tPA-eligible warfarin-treated patients (n = 3554) who arrived within 3.5 hours (potentially eligible for the 4.5-hour treatment window) with INRs of 1.7 or lower and who had no documented contraindication or warning signs except for warfarin use. We compared clinical factors between warfarin-treated patients treated with tPA vs those not. We estimated the risk of sICH for 2 groups based on risk factors associated with sICH and determined whether patients with high risk for sICH or those with low risk received tPA. For warfarin-treated patients who did not receive tPA, the model predicts the expected risk of tPA-related sICH had they received tPA.

The association of INR and risk for sICH among warfarin-treated patients was examined graphically and tested for linearity. We then conducted a multivariable analysis including INR and the aforementioned other intracerebral hemorrhage risk factors to determine whether any association between INR and sICH risk persisted after risk adjustment. Because INR is an exponential measure of the ratio of a patient's prothrombin time to normal, we repeated the analysis based on log INR.

In a separate analysis, we determined the percentage of patients with ischemic stroke receiving warfarin therapy in the GWTG-Stroke Registry who were otherwise eligible for intravenous tPA but did not receive it. Based on the AHA/ASA guidelines, we considered a warfarin-treated patient eligible for intravenous tPA if he or she presented within 0 to 2 or 2 to 3.5 hours (potentially eligible for the 0-3 or 3-4.5–hour time window) with an INR of 1.7 or lower and no contraindications or if the only documented issue for intravenous tPA was use of warfarin.[1,2]

All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc). All *P* values are 2-sided, with $P < .05$ considered statistically significant. Based on sample size and observed sICH rates, our study had more than 84% statistical power to detect a 1% difference in sICH between warfarin-treated and non–warfarin-treated patients.

The institutional review board of the Duke University Health System approved the study; patient informed consent was not required.

RESULTS

Among 23 437 patients receiving intravenous tPA, 1802 (7.7%) were taking warfarin prior to admission. TABLE 1 and TABLE 2 report demographic, clinical, and hospital characteristics. Warfarin-treated patients were older (median age, 77 [interquartile range {IQR}, 68-84] years vs 71 [IQR, 59-82] years); more likely to be women; more often had a medical history of atrial fibrillation or flutter, previous stroke or TIA, coronary artery disease, heart failure, or peripheral vascular disease; and were more likely to present with greater stroke severity as measured by NIHSS score (median, 14 [IQR, 8-20] vs 11 [IQR, 6-17]; $P < .001$ for all). The baseline INR levels were higher in warfarin-treated patients (median, 1.20 [IQR, 1.07-1.40] vs 1.00 [IQR, 1.00-1.10]; $P < .001$). Nearly 15% (269/1802) of warfarin-treated patients presented with INRs between 1.5 and 1.7. Time from symptom onset to administration of intravenous tPA was similar in both groups (median, 148 [IQR, 120-174] minutes vs 145 [IQR, 115-175] minutes; $P = .28$).

We found generally similar demographic, medical history, and clinical characteristics among the tPA-eligible warfarin-treated patients who received tPA vs those who did not (eTable, available at http://www.jama.com). However, patients who received intravenous tPA were less likely to have a history of previous stroke or TIA and more likely to present with greater stroke severity (median NIHSS score, 14 [IQR, 8-20] vs 9 [IQR, 4-16]; $P < .001$). Based on the sICH risk prediction model, tPA-treated patients had significantly higher predicted risk of sICH compared with patients not treated with tPA (mean predicted sICH rate, 5.9%; median, 5.0% [IQR, 2.8%-8.4%] vs mean predicted sICH rate,

4.4%; median, 3.1% [IQR, 1.9%-6.2%]; $P<.001$). Therefore, we found no evidence for preferential treatment of warfarin-treated patients with a lower propensity for tPA-related sICH.

Symptomatic Intracranial Hemorrhage

Overall, 1107 patients (4.7%) developed sICH after intravenous tPA administration. Warfarin-treated patients had a higher overall unadjusted rate of sICH than did non–warfarin-treated patients (5.7% vs 4.6%, $P<.001$; unadjusted odds ratio [OR], 1.22 [95% CI, 0.99-1.51]; $P=.06$) (TABLE 3). However, after risk adjustment, warfarin use was not an independent predictor of sICH risk (adjusted OR, 1.01 [95% CI, 0.82-1.25]; $P=.94$).

These relationships between warfarin use and sICH were consistent in sensitivity analysis (TABLE 4). When NIHSS score was excluded from our multivariable model, we found that warfarin was still not associated with sICH risk (adjusted OR, 1.11 [95% CI, 0.90-1.37]; $P=.32$). Our results also remained essentially unchanged in patients with complete NIHSS data (1617 warfarin-treated and 19 493 non–warfarin-treated patients; unadjusted sICH rates, 5.7% vs 4.6%; adjusted OR, 1.00 [95% CI, 0.79-1.25]; $P=.99$). Further adjustment for use of antiplatelet therapy prior to admission did not substantially alter the association of warfarin and sICH (adjusted OR, 1.04 [95% CI, 0.84-1.29]; $P=.71$). Stratified analyses by age, sex, and NIHSS score found similar results. Warfarin remained unrelated with the risk for sICH in the subgroup analysis of patients with INRs between 1.5 and 1.7 (adjusted OR, 1.32 [95% CI, 0.85-2.04]; $P=.21$) and in the exploratory analysis of those with INRs of 2.0 or lower (adjusted OR, 1.00 [95% CI, 0.81-1.23]; $P=.97$).

Secondary Outcomes

The rates of life-threatening or serious systemic hemorrhage were similar in both groups (0.9% vs 0.9%, $P=.90$) (Table 3), although higher unadjusted rates of any tPA complication (10.6% vs 8.4%, $P=.001$) and mortality (11.4% vs 7.9%, $P<.001$) were observed in warfarin-treated patients. However, after multivariable adjustment, warfarin use was not associated with life-threatening or serious systemic hemorrhage (adjusted OR, 0.78 [95% CI, 0.49-1.24]; $P=.29$), any tPA complication (adjusted OR, 1.09 [95% CI, 0.93-1.29]; $P=.30$), or in-hospital mortality (adjusted OR, 0.94 [95% CI, 0.79-1.13]; $P=.50$). Among patients who survived, there was no significant difference in rates of discharge to a rehabilitation facility (adjusted OR, 1.09 [95% CI, 0.97-1.22]; $P=.16$). However, warfarin-treated patients were more likely to be discharged to a skilled nursing facility (adjusted OR, 1.16 [95% CI, 1.02-1.32]; $P=.02$).

Baseline INR and sICH

Graphical trends of the association between unadjusted admission INR and sICH rates following administration of intravenous tPA are shown in FIGURE 2. International normalized ratio was

Table 1. Demographic, Medical History, and Hospital Characteristics According to Preadmission Warfarin Use

Characteristic	No. (%) Preadmission Warfarin Use (n = 1802)	No. (%) No Preadmission Warfarin Use (n = 21 635)	*P* Value
Demographics			
Age, y			
Mean (SD)	74.1 (13.4)	69.5 (15.1)	<.001
Median (IQR)	77 (68-84)	71 (59-82)	
Women	976 (54.2)	10 920 (50.5)	.003
Race/ethnicity			
White	1309 (72.6)	15 566 (72.0)	.57
Black	256 (14.2)	3226 (14.9)	
Asian	40 (2.2)	514 (2.4)	
Hispanic	129 (7.2)	1519 (7.0)	
Other	68 (3.8)	810 (3.7)	
Medical history			
Atrial fibrillation/flutter	1229 (69.2)	3710 (19.0)	<.001
Prosthetic heart valve	100 (5.6)	166 (0.9)	<.001
Previous stroke/TIA	642 (36.2)	5099 (26.1)	<.001
Carotid stenosis	56 (3.2)	627 (3.2)	.89
CAD/prior MI	658 (37.1)	5417 (27.8)	<.001
Heart failure	320 (18.0)	1744 (8.9)	<.001
Hypertension	1399 (78.8)	15 544 (79.6)	.40
Dyslipidemia	759 (42.7)	8189 (41.9)	.52
Peripheral vascular disease	96 (5.4)	712 (3.7)	<.001
Diabetes mellitus	523 (29.5)	5398 (27.7)	.11
Smoker	173 (9.7)	4147 (21.2)	<.001
Hospital characteristics			
No. of beds, median (IQR)	366 (270-572)	369 (266-567)	.84
Annual ischemic stroke volume			
≥301	826 (45.8)	10 052 (46.5)	.85
101-300	826 (45.8)	9650 (44.6)	
0-100	150 (8.3)	1933 (8.9)	
Annual intravenous tPA cases			
>10	608 (33.7)	6878 (31.8)	.05
7-10	679 (37.7)	7992 (36.9)	
<7	515 (28.6)	6765 (31.3)	
Academic hospital	965 (53.6)	11 881 (54.9)	.20

Abbreviations: CAD, coronary artery disease; IQR, interquartile range; MI, myocardial infarction; TIA, transient ischemic attack; tPA, tissue plasminogen activator.

modeled as a continuous variable because it did not violate linearity assumptions ($P=.15$). After adjustment for risk factors, INR was not statistically significantly associated with sICH (adjusted OR, 1.10 per 0.1-unit increase in INR [95% CI, 1.00-1.20]; $P=.06$; adjusted relative risk, 1.09 per 0.1-unit increase [95% CI, 1.00-1.19]; $P=.05$). These findings were similar when we repeated the analysis based on log INR (adjusted OR, 1.12 [95% CI, 1.00-1.26]; $P=.06$). We also grouped the INR into 3 categories (0.80-1.19, 1.20-1.49, 1.50-1.70) and found no significant trend of sICH and the degree of anticoagulation ($P=.16$ by Cochran-Mantel-Haenszel trend test).

Table 2. Clinical Characteristics According to Preadmission Warfarin Use

Characteristic	No. (%) Preadmission Warfarin Use (n = 1802)	No. (%) No Preadmission Warfarin Use (n = 21 635)	*P* Value
Medications prior to admission			
Warfarin	1802 (100)	0	NA
Antiplatelet	544 (30.2)	9499 (43.9)	<.001
Antihypertensive	1541 (85.5)	14 253 (65.9)	<.001
Cholesterol reducer	896 (49.7)	8176 (37.8)	<.001
Diabetes medication	411 (22.8)	4150 (19.2)	<.001
Mode of arrival			
EMS from scene	1524 (84.6)	17 393 (80.4)	<.001
Private transport/walk-in	171 (9.5)	2918 (13.5)	
Other	107 (5.9)	1324 (6.1)	
Ambulatory status prior to current event, able to ambulate independently	1427 (79.2)	18 276 (84.5)	<.001
Ambulatory status on admission, unable to ambulate	1005 (55.8)	10 169 (47.0)	<.001
NIHSS score			
Mean (SD)	14.4 (7.7)	12.0 (7.3)	<.001
Median (IQR)	14 (8-20)	11 (6-17)	
Time from symptom onset to intravenous tPA, median (IQR), min	148 (120-174)	145 (115-175)	.28
Heart rate, beats/min			
Mean (SD)	82.9 (19.7)	81.9 (18.4)	.25
Median (IQR)	80 (69-93)	80 (69-92)	
Blood pressure, mm Hg			
Systolic			
Mean (SD)	154.5 (28.2)	157.0 (28.8)	.001
Median (IQR)	153 (136-172)	154 (137-175)	
Diastolic			
Mean (SD)	83.7 (19.1)	84.5 (18.7)	.08
Median (IQR)	82 (71-95)	83 (72-95)	
INR			
Mean (SD)	1.22 (0.20)	1.03 (0.11)	<.001
Median (IQR)	1.20 (1.07-1.40)	1.00 (1.00-1.10)	
Creatinine, mg/dL			
Mean (SD)	1.3 (3.0)	1.4 (5.0)	.32
Median (IQR)	1.0 (0.8-1.3)	1.0 (0.8-1.2)	
Blood glucose, mg/dL			
Mean (SD)	134.6 (53.7)	136.2 (59.1)	.36
Median (IQR)	120 (103-148)	118 (102-147)	
BMI[a]			
Mean (SD)	28.0 (6.8)	28.3 (6.7)	.05
Median (IQR)	27.1 (23.4-31.3)	27.3 (23.8-31.6)	

Abbreviations: BMI, body mass index; EMS, emergency medical services; INR, international normalized ratio; IQR, interquartile range; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator.
SI conversion factors: To convert creatinine values to µmol/L, multiply by 88.4; blood glucose values to mmol/L, multiply by 0.0555.
[a]Calculated as weight in kilograms divided by height in meters squared.

Eligible Warfarin-Treated Patients Not Receiving Intravenous tPA

Among 443 916 patients with acute ischemic stroke in the GWTG-Stroke Registry during in the study period, 47 358 (10.7%) were classified as having taken warfarin prior to admission. More than half of these warfarin-treated patients (25 762/47 358) presented with a baseline INR of 1.7 or lower. The current AHA/ASA guidelines permit administration of intravenous tPA to eligible patients who can be treated in the period of 0 to 3 and 3 to 4.5 hours after symptom onset.[1,2] Accordingly, we identified 5884 warfarin-treated patients presenting within 2 hours (potentially eligible for the 0-3–hours window) and 1826 warfarin-treated patients presenting between 2 and 3.5 hours (potentially eligible for the 3-4.5–hours window) with INRs of 1.7 or lower. Overall, 2489 of the patients in the 0-hours to 3-hours time window and 1065 of the patients in the 3-hours to 4.5-hours time window were reported to have no contraindications for intravenous tPA or the only documented issue was warfarin use. Among these patients, 32.1% (799/2489) in the 0-hours to 3-hours time window and 87.3% (930/1065) in the 3-hours to 4.5-hours time window did not receive intravenous tPA treatment. Collectively, 48.6% (1729/3554) of patients receiving warfarin who were otherwise eligible were not treated.

COMMENT

In this large nationwide contemporary registry of patients with acute ischemic stroke, we found that use of intravenous tPA among warfarin-treated patients with a baseline INR of 1.7 or lower was not associated with increased risk of sICH. These findings were robust across several subgroup analyses and risk-adjustment methods. Warfarin use was also not associated with life-threatening or serious systemic hemorrhage, any tPA complication, or in-hospital mortality. Therefore, although the risk of sICH increases marginally with higher INR levels, intravenous tPA appears to be

safe in warfarin-treated patients with a baseline INR of 1.7 or lower. Collectively, these findings provide empirical support for current AHA/ASA guideline recommendations and confirm the safety profile of intravenous tPA in warfarin-treated patients with INRs of 1.7 or lower in routine clinical practice.

Symptomatic intracranial hemorrhage is the most feared complication of thrombolysis for acute ischemic stroke. The NINDS tPA study and the European Cooperative Acute Stroke Study trials (ECASS I-III) excluded patients receiving oral anticoagulant treatment, regardless of INR.[3-6] The Safe Implementation of Thrombolysis in Stroke–Monitoring Study (SITS-MOST), an observational study to assess the safety profile of intravenous tPA in routine clinical practice, also excluded warfarin-treated patients to conform with the European product license.[7,8] Although the use of an anticoagulant was not an exclusion criterion in the Standard Treatment With Alteplase to Reverse Stroke (STARS) study (a phase 4 postmarketing study of tPA mandated by the US Food and Drug Administration), the outcome of sICH has not been reported separately in this patient group.[20]

Despite lack of safety data, intravenous tPA has been used in patients receiving warfarin in clinical practice. To date, only a few studies have investigated the safety of tPA treatment among warfarin-treated patients, with conflicting and inconclusive results.[9-13,21] Two single-center studies involving a total of 27 warfarin-treated patients reported a 6- to 10-fold increased risk of intracranial hemorrhage in patients with preadmission use of warfarin treated with intravenous tPA.[9,12] In contrast, observational studies from Canada, Finland, Korea, and Switzerland (intra-arterial therapy) did not find significantly increased risk of intracranial hemorrhage associated with preadmission warfarin use.[10,11,13,21] How-

Table 3. Primary and Secondary Outcomes Measures According to Preadmission Warfarin Use

Outcome	No. of Events/Total No. of Patients (%)		OR (95% CI)		*P* Value
	Preadmission Warfarin Use	No Preadmission Warfarin Use	Unadjusted	Adjusted	
Symptomatic intracranial hemorrhage	102/1802 (5.7)	1005/21 635 (4.6)	1.22 (0.99-1.51)	1.01 (0.82-1.25)[a]	.94
Life-threatening or serious systemic hemorrhage	16/1802 (0.9)	199/21 635 (0.9)	0.99 (0.62-1.56)	0.78 (0.49-1.24)[a]	.29
Any tPA complication[b]	191/1802 (10.6)	1824/21 635 (8.4)	1.29 (1.10-1.52)	1.09 (0.93-1.29)[a]	.30
In-hospital mortality[c]	202/1772 (11.4)	1676/21 304 (7.9)	1.50 (1.29-1.75)	0.94 (0.79-1.13)[d]	.50
Discharge to skilled nursing facility[e]	414/1406 (29.5)	3720/18 464 (20.1)	1.60 (1.43-1.80)	1.16 (1.02-1.32)	.02
Discharge to inpatient rehabilitation facility[e]	518/1406 (36.8)	6113/18 464 (33.1)	1.19 (1.06-1.33)	1.09 (0.97-1.22)	.16

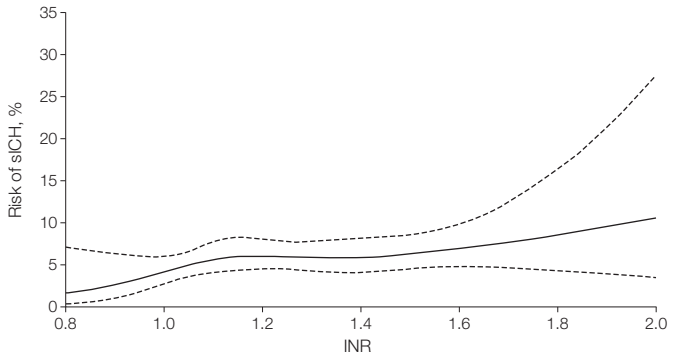
Abbreviations: OR, odds ratio; tPA, intravenous tissue plasminogen activator.
[a] Adjusted for age, sex, race, systolic blood pressure, blood glucose level, and baseline National Institutes of Health Stroke Scale (NIHSS) score from previously established symptomatic intracranial hemorrhage prediction model. Multiple imputations were performed for missing NIHSS data (2327 [9.9%]).
[b] Symptomatic intracranial hemorrhage within 36 hours, life-threatening or serious systemic hemorrhage within 36 hours, or other serious complications.
[c] Excluded transferred out.
[d] Adjusted for age, sex, arrival mode, previous stroke or transient ischemic attack, history of atrial fibrillation, coronary artery disease, diabetes mellitus, dyslipidemia, and baseline NIHSS score from previously established mortality prediction model. Multiple imputations were performed for missing NIHSS data (2327 [9.9%]).
[e] Excluded in-hospital death, left against medical advice, discharge to hospice, and transferred out.

Table 4. Sensitivity Analysis: Preadmission Warfarin Use and Symptomatic Intracranial Hemorrhage

Variable	No. With Hemorrhage/ Total No. of Patients (%)		OR (95% CI)		*P* Value
	Preadmission Warfarin Use	No Preadmission Warfarin Use	Unadjusted	Adjusted[a]	
Risk adjustment					
Without NIHSS adjustment	102/1802 (5.7)	1005/21 635 (4.6)	1.22 (0.99-1.51)	1.11 (0.90-1.37)	.32
Excluding NIHSS missing data	92/1617 (5.7)	902/19 493 (4.6)	1.24 (0.99-1.54)	1.00 (0.79-1.25)	.99
Age, y					
<75	30/743 (4.0)	408/12 337 (3.3)	1.21 (0.84-1.74)	1.12 (0.77-1.62)	.54
≥75	72/1059 (6.8)	597/9298 (6.4)	1.07 (0.82-1.38)	0.96 (0.74-1.25)	.76
Sex					
Women	52/976 (5.3)	532/10 920 (4.9)	1.09 (0.81-1.47)	0.89 (0.66-1.19)	.42
Men	50/826 (6.1)	473/10 715 (4.4)	1.39 (1.03-1.86)	1.17 (0.87-1.59)	.30
NIHSS score					
≤14	34/850 (4.0)	400/12 861 (3.1)	1.28 (0.91-1.80)	1.20 (0.86-1.69)	.29
>14	58/767 (7.6)	502/6632 (7.6)	1.00 (0.75-1.34)	0.94 (0.70-1.26)	.68
Subgroup analysis of INR 1.5-1.7	21/269 (7.8)	1005/21 635 (4.6)	1.73 (1.13-2.64)	1.32 (0.85-2.04)	.21
Exploratory analysis of those with INR ≤2.0	103/1835 (5.6)	1009/21 675 (4.7)	1.21 (0.98-1.49)	1.00 (0.81-1.23)	.97

Abbreviations: INR, international normalized ratio; NIHSS, National Institutes of Health Stroke Scale.
[a] Adjusted for age, sex, race, systolic blood pressure, blood glucose level, and baseline NIHSS from previously established sICH prediction model. Except for sensitivity analysis excluding NIHSS missing and stratified analysis according to NIHSS, multiple imputations were performed for missing NIHSS data (2327 [9.9%]).

Figure 2. Relationship Between International Normalized Ratio and Risk of Symptomatic Intracranial Hemorrhage in Warfarin-Treated Patients (Baseline INR ≤2.0)



Solid line indicates risk of symptomatic intracranial hemorrhage (sICH); dashed lines, 95% confidence intervals. Logistic regression modeling was conducted to examine the relationship between international normalized ratio (INR) and binary outcome of sICH. The Stone and Koo additive spline method was fitted to generate the plot; adequacy of linearity was tested using likelihood ratio statistic by comparing the linear and nonlinear logistic models.

ever, patterns of stroke care and administration of tPA in the United States may differ from patterns in other nations—especially those with non–United States labeling. Importantly, all of these studies were limited to small samples that included a total of 247 patients receiving oral anticoagulants.

Our study represents the largest clinical experience of the safety of intravenous tPA in warfarin-treated patients who meet clinical guideline eligibility criteria. Among 23 437 patients with ischemic stroke treated with intravenous tPA, 1802 had taken warfarin before stroke onset. The overall sICH rate (4.7%) in this study is slightly lower than pooled results from randomized controlled trials (7.7%) but comparable to rates reported in nonselective patient populations (5.2%).[22,23] Although the unadjusted incidence of sICH was higher in warfarin-treated patients than in non–warfarin-treated patients, these findings appear to be ascribed to the difference in risk profiles between the 2 groups. Age and stroke severity are strong predictors of sICH.[24,25] Warfarin-treated patients were significantly older, and stroke severity assessed by the NIHSS score also tended to be greater in these patients compared with those without prior warfarin use. After adjusting for these factors in the multivariate analysis, warfarin treatment was no longer a significant predictor of sICH. Another explanation may be related to the intensity of anticoagulation. Studies have shown that the bleeding risk of warfarin is associated with the intensity of anticoagulation, as reflected by the INR.[26] Although INR levels were higher in warfarin-treated patients compared with non–warfarin-treated patients (median, 1.2 vs 1.0), the baseline INR was below the therapeutic range (2.0-3.0 or 2.5-3.5), which may explain the low incidence of sICH in our study population.

Our findings also suggest several new directions for outcomes-based stroke research. The NINDS tPA trial suggested a net benefit of intravenous tPA, even after accounting for increased sICH risk among tPA-treated patients.[3] This benefit could be neutralized at some rate of sICH. Although our study supports the safety of intravenous tPA for warfarin-treated patients within the guideline recommendation, it remains unclear how high the INR value could be for this safety to hold. The subgroup analysis of patients with INRs between 1.5 and 1.7 and the exploratory analysis of INRs of 2.0 or lower suggests that intravenous tPA appears to be safe in this population; however, this finding should be interpreted with caution. There were 269 warfarin-treated patients with INRs of 1.5 to 1.7 with 21 sICH events (7.8%) and only 33 patients with subtherapeutic INRs greater than 1.7 with 1 sICH event (3.0%). Further study is warranted to clarify the effectiveness and safety of intravenous tPA for patients beyond the guideline recommended INR range.

In addition, new oral anticoagulants such as dabigatran (a direct thrombin inhibitor) and rivaroxaban (a direct Xa inhibitor) have recently been approved by the US Food and Drug Administration as an alternative to warfarin for the prevention of stroke and thromboembolic disease in patients with nonvalvular atrial fibrillation.[27-29] Yet there is little experience with and no guidelines for the use of intravenous tPA in this population.[30,31] Further study is needed to provide guidance on thrombolytic therapy for patients who developed ischemic stroke while taking new oral anticoagulants.

This study also found that many patients with acute ischemic stroke who were eligible for intravenous tPA did not receive this treatment. Our study found that up to 48.6% of warfarin-treated patients who met AHA/ASA guidelines eligibility criteria did not receive intravenous tPA. In these cases, physician concern about serious adverse effects is one of the main obstacles preventing tPA use.[32] Each year, nearly 800 000 new or recurrent strokes occur in the United States.[33] Based on the prevalence of warfarin use in the GWTG-Stroke Registry, we estimate that at least 2400 warfarin-treated patients with ischemic stroke who presented with a baseline INR of 1.7 or lower are otherwise eligible and currently do not receive tPA.

There are several issues to consider in interpreting the results of our study. First, this was a retrospective observational analysis, and treatment selection may bias outcome comparisons. However, among measured potential confounders, we found that patients re-

ceiving tPA had greater stroke severity and had higher predicted risk of sICH than tPA-eligible warfarin-treated patients who did not receive tPA. Thus, it could be argued that selection bias is more likely to be against warfarin-treated patients. Second, NIHSS score, a critical determinant of stroke outcomes,[34] was missing in 10% of our cohort. Consequently, we performed multiple imputation to fill in missing data with plausible values. Importantly, our findings were consistent for the entire cohort, the subgroup analyses that excluded NIHSS missing data, and the stratified analyses by NIHSS groups.

Third, baseline INR was determined as the first measurement on presentation to the hospital. We were unable to verify whether it was before or after the tPA treatment. Although plausible, the latter seems less likely, because clinical guidelines require an INR result before giving tPA in patients receiving warfarin or in those whose use of anticoagulants is not known.[1] A related issue is the definition of sICH. Computed tomography or magnetic resonance imaging scans were interpreted locally and not centrally adjudicated. The GWTG-Stroke Registry does not have the actual images for review; therefore, we cannot determine the hemorrhage type according to the commonly used ECASS grading system.[5] Nonetheless, our overall sICH rate (4.7%) is comparable to rates reported in nonselective patient populations outside of randomized controlled trials (5.2%).[23] However, it should be noted that because various definitions are used, it might be difficult to compare our incidence of sICH with incidences from other studies. Fourth, the GWTG-Stroke Registry did not have information on causes of death, so that deaths related to tPA complications could not be determined.

Last, the GWTG-Stroke Registry is a voluntary program. Hospitals participate based on their level of interest in quality improvement in stroke care and their capacity to fulfill the requirements. Therefore, the generalizability of our findings to non–GWTG-Stroke Registry hospitals remains to be established. Regardless, the GWTG-Stroke Registry is the largest stroke registry in the world, representing nearly 25% of all ischemic stroke cases in the United States in 2008.[16] In parallel with increasing rates of hospital participation, this number is expected to increase in later years. Thus, our findings are likely to represent routine clinical practice.

In summary, this study represents the largest clinical experience of the safety of thrombolysis in warfarin-treated patients with acute ischemic stroke who meet clinical guideline eligibility criteria. The use of intravenous tPA among warfarin-treated (INR $\leq$1.7) patients with ischemic stroke was not associated with increased sICH risk compared with the use of intravenous tPA among non–warfarin-treated patients in routine clinical practice. We found the potential for substantial undertreatment, because up to 50% of warfarin-treated patients who might have been eligible for reperfusion therapy did not receive intravenous tPA. These data provide empirical support of current AHA/ASA guideline recommendations and may help support future stroke quality improvement efforts.

Author Contributions: Drs Xian, Liang, and Peterson had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Xian, Peterson.
Acquisition of data: Xian, Peterson.
Analysis and interpretation of data: Xian, Liang, Smith, Schwamm, Reeves, Olson, Hernandez, Fonarow, Peterson.
Drafting of the manuscript: Xian, Peterson.
Critical revision of the manuscript for important intellectual content: Xian, Liang, Smith, Schwamm, Reeves, Olson, Hernandez, Fonarow, Peterson.
Statistical analysis: Liang.
Administrative, technical, or material support: Xian, Peterson.
Study supervision: Peterson.
Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Smith reported serving as a volunteer for the American Heart Association (AHA) Get With The Guidelines (GWTG) Steering Committee and serving on the advisory board for Genentech. Dr Schwamm reported serving as the chair of the AHA GWTG Steering Committee; serving as a consultant to the Massachusetts Department of Public Health; providing expert review of medical records for malpractice claims against neurologists regarding care of acute stroke; and serving as principal investigator of a phase 2 multicenter study of extended-window intravenous thrombolysis (alteplase provided at no cost to Massachusetts General Hospital). Dr Olson reported receiving a grant from the American Heart Association (Duke Clinical Research Institute serves as the statistical coordinating center for AHA GWTG). Dr Hernandez reported serving as a consultant for Johnson & Johnson, AstraZeneca, sanofi, and Corthera; receiving research grants or grants pending from Johnson & Johnson, Amylin, Portola, and Preventis; and serving as a consultant to Corthera. Dr Fonarow reported serving as a consultant to Pfizer, Merck, Schering-Plough, Bristol-Myers Squibb, and sanofi-aventis; receiving research grants or grants pending from the National Institutes of Health; receiving speakers honoraria from Pfizer, Merck, Schering-Plough, Bristol-Myers Squibb, and sanofi-aventis; and that he is an employee of the University of California, which holds a patent on retriever devices for stroke. Dr Peterson reported receiving research grants from Johnson & Johnson, Eli Lilly, and Janssen Pharmaceuticals and serving as a consultant to Boehringer Ingelheim, Johnson & Johnson, Medscape, Merck, Novartis, Ortho-McNeil-Janssen, Pfizer, Westat, the Cardiovascular Research Foundation, WebMD, and United Healthcare. No other authors reported disclosures.
Funding/Support: This study received an award from the American Heart Association–Pharmaceutical Roundtable and from David and Stevie Spina. The Get With The Guidelines–Stroke (GWTG-Stroke) program is provided by the American Heart Association/American Stroke Association. The GWTG-Stroke Program is currently supported in part by a charitable contribution from Janssen Pharmaceutical Companies of Johnson & Johnson. GWTG-Stroke has been funded in the past through support from Boehringer Ingelheim, Merck, Bristol-Myers Squibb/Sanofi Pharmaceutical Partnership, and the AHA Pharmaceutical Roundtable.
Role of the Sponsor: The funding organizations had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation of the manuscript. Representatives from the AHA reviewed and approved a draft of the manuscript.
Disclaimer: This study used the GWTG-Stroke database. The interpretation and reporting of these data are the sole responsibility of the authors and do not necessarily represent the official views of the AHA. Dr Peterson, Contributing Editor for *JAMA*, was not involved in the editorial review of or the decision to publish this article.
Previous Presentation: Presented in part at the Quality of Care and Outcomes Research 2012 Scientific Sessions, Atlanta, Georgia, May 10, 2012.
Online-Only Material: The eTable is available at http://www.jama.com.
Additional Contributions: We thank Erin Lofrese, MS, Duke Clinical Research Institute, for editorial assistance and manuscript preparation. Ms Lofrese did not receive compensation for her assistance apart from her employment at the institution where the study was conducted.

REFERENCES

1. Adams HP Jr, del Zoppo G, Alberts MJ, et al; American Heart Association; American Stroke Association Stroke Council; Clinical Cardiology Council; Cardiovascular Radiology and Intervention Council; Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups. 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: the American Academy of Neurol-

ogy affirms the value of this guideline as an educational tool for neurologists. *Stroke*. 2007;38(5):1655-1711.
2. del Zoppo GJ, Saver JL, Jauch EC, Adams HP Jr; American Heart Association Stroke Council. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator: a science advisory from the American Heart Association/American Stroke Association. *Stroke*. 2009;40(8):2945-2948.
3. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333(24):1581-1587.
4. Hacke W, Kaste M, Fieschi C, et al; The European Cooperative Acute Stroke Study (ECASS). Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. *JAMA*. 1995;274(13):1017-1025.
5. Hacke W, Kaste M, Fieschi C, et al; Second European-Australasian Acute Stroke Study Investigators. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). *Lancet*. 1998;352(9136):1245-1251.
6. Hacke W, Kaste M, Bluhmki E, et al; ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359(13):1317-1329.
7. Wahlgren N, Ahmed N, Dávalos A, et al; SITS-MOST Investigators. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke–Monitoring Study (SITS-MOST): an observational study. *Lancet*. 2007;369(9558):275-282.
8. Wahlgren N, Ahmed N, Dávalos A, et al; SITS Investigators. Thrombolysis with alteplase 3-4.5 h after acute ischaemic stroke (SITS-ISTR): an observational study. *Lancet*. 2008;372(9646):1303-1309.
9. Prabhakaran S, Rivolta J, Vieira JR, et al. Symptomatic intracerebral hemorrhage among eligible warfarin-treated patients receiving intravenous tissue plasminogen activator for acute ischemic stroke. *Arch Neurol*. 2010;67(5):559-563.
10. Meretoja A, Putaala J, Tatlisumak T, et al. Off-label thrombolysis is not associated with poor outcome in patients with stroke. *Stroke*. 2010;41(7):1450-1458.
11. Kim YD, Lee JH, Jung YH, et al. Safety and outcome after thrombolytic treatment in ischemic stroke patients with high-risk cardioembolic sources and prior subtherapeutic warfarin use. *J Neurol Sci*. 2010;298(1-2):101-105.
12. Seet RC, Zhang Y, Moore SA, Wijdicks EF, Rabinstein AA. Subtherapeutic international normalized ratio in warfarin-treated patients increases the risk for symptomatic intracerebral hemorrhage after intravenous thrombolysis. *Stroke*. 2011;42(8):2333-2335.
13. Vergouwen MD, Casaubon LK, Swartz RH, et al; Investigators of the Registry of the Canadian Stroke Network. Subtherapeutic warfarin is not associated with increased hemorrhage rates in ischemic strokes treated with tissue plasminogen activator. *Stroke*. 2011;42(4):1041-1045.
14. 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.
15. Schwamm LH, Fonarow GC, Reeves MJ, et al. Get With The Guidelines–Stroke is associated with sustained improvement in care for patients hospitalized with acute stroke or transient ischemic attack. *Circulation*. 2009;119(1):107-115.
16. Fonarow GC, Reeves MJ, Smith EE, et al; GWTG-Stroke Steering Committee and Investigators. Characteristics, performance measures, and in-hospital outcomes of the first one million stroke and transient ischemic attack admissions in Get With The Guidelines–Stroke. *Circ Cardiovasc Qual Outcomes*. 2010;3(3):291-302.
17. Xian Y, Fonarow GC, Reeves MJ, et al. Data quality in the American Heart Association Get With The Guidelines–Stroke (GWTG-Stroke): results from a national data validation audit. *Am Heart J*. 2012;163(3):392-398.
18. Menon BK, Saver JL, Prabhakaran S, et al. Risk score for intracranial hemorrhage in patients with acute ischemic stroke treated with intravenous t-PA [abstract]. *Stroke*. 2012;43(2):A68.
19. Smith EE, Shobha N, Dai D, et al. Risk score for in-hospital ischemic stroke mortality derived and validated within the Get With The Guidelines–Stroke Program. *Circulation*. 2010;122(15):1496-1504.
20. Albers GW, Bates VE, Clark WM, Bell R, Verro P, Hamilton SA. Intravenous tissue-type plasminogen activator for treatment of acute stroke: the Standard Treatment with Alteplase to Reverse Stroke (STARS) study. *JAMA*. 2000;283(9):1145-1150.
21. De Marchis GM, Jung S, Colucci G, et al. Intracranial hemorrhage, outcome, and mortality after intra-arterial therapy for acute ischemic stroke in patients under oral anticoagulants. *Stroke*. 2011;42(11):3061-3066.
22. Wardlaw JM, Murray V, Berge E, del Zoppo GJ. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2009;(4):CD000213.
23. Graham GD. Tissue plasminogen activator for acute ischemic stroke in clinical practice: a meta-analysis of safety data. *Stroke*. 2003;34(12):2847-2850.
24. NINDS t-PA Stroke Study Group. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. *Stroke*. 1997;28(11):2109-2118.
25. Tanne D, Kasner SE, Demchuk AM, et al. Markers of increased risk of intracerebral hemorrhage after intravenous recombinant tissue plasminogen activator therapy for acute ischemic stroke in clinical practice: the Multicenter rt-PA Stroke Survey. *Circulation*. 2002;105(14):1679-1685.
26. Fuster V, Rydén LE, Cannom DS, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; European Society of Cardiology Committee for Practice Guidelines; European Heart Rhythm Association; Heart Rhythm Society. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation*. 2006;114(7):e257-e354.
27. Wann LS, Curtis AB, Ellenbogen KA, et al; American College of Cardiology Foundation/American Heart Association Task Force. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (update on dabigatran): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011;123(10):1144-1150.
28. Patel MR, Mahaffey KW, Garg J, et al; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883-891.
29. Connolly SJ, Ezekowitz MD, Yusuf S, et al; RELY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139-1151.
30. De Smedt A, De Raedt S, Nieboer K, De Keyser J, Brouns R. Intravenous thrombolysis with recombinant tissue plasminogen activator in a stroke patient treated with dabigatran. *Cerebrovasc Dis*. 2010;30(5):533-534.
31. Matute MC, Guillán M, García-Caldentey J, et al. Thrombolysis treatment for acute ischaemic stroke in a patient on treatment with dabigatran. *Thromb Haemost*. 2011;106(1):178-179.
32. Bambauer KZ, Johnston SC, Bambauer DE, Zivin JA. Reasons why few patients with acute stroke receive tissue plasminogen activator. *Arch Neurol*. 2006;63(5):661-664.
33. Lloyd-Jones D, Adams RJ, Brown TM, et al; Writing Group Members; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2010 update: a report from the American Heart Association [published correction appears in *Circulation*. 2010;121(12):e260]. *Circulation*. 2010;121(7):e46-e215.
34. Fonarow GC, Saver JL, Smith EE, et al. Relationship of National Institutes of Health Stroke Scale to 30-day mortality in Medicare beneficiaries with acute ischemic stroke. *J Am Heart Assoc*. 2012;1(1):42-50.