

Original Investigation

Risks and Benefits Associated With Prestroke Antiplatelet Therapy Among Patients With Acute Ischemic Stroke Treated With Intravenous Tissue Plasminogen Activator

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IMPORTANCE Intravenous tissue plasminogen activator (tPA) is known to improve outcomes in ischemic stroke; however, many patients may have been receiving antiplatelet therapy before acute ischemic stroke and could face an increased risk for bleeding when treated with tPA.

OBJECTIVE To assess the risks and benefits associated with prestroke antiplatelet therapy among patients with ischemic stroke who receive intravenous tPA.

DESIGN, SETTING, AND PARTICIPANTS This observational study used data from the American Heart Association and American Stroke Association Get With the Guidelines–Stroke registry, which included 85 072 adult patients with ischemic stroke who received intravenous tPA in 1545 registry hospitals from January 1, 2009, through March 31, 2015. Data were analyzed during the same period.

EXPOSURES Prestroke antiplatelet therapy before tPA administration for acute ischemic stroke.

MAIN OUTCOMES AND MEASURES Symptomatic intracranial hemorrhage (sICH), in-hospital mortality, discharge ambulatory status, and modified Rankin Scale score (range, 0 [no symptoms] to 6 [death]).

RESULTS Of the 85 072 registry patients, 38 844 (45.7%) were receiving antiplatelet therapy before admission; 46 228 patients (54.3%) were not. Patients receiving antiplatelet therapy were older (median [25th-75th percentile] age, 76 [65-84] vs 68 [56-80] years) and had a higher prevalence of cardiovascular risk factors. The unadjusted rate of sICH was higher in patients receiving antiplatelet therapy (5.0% vs 3.7%). After risk adjustment, prior use of antiplatelet agents remained associated with higher odds of sICH compared with no use (adjusted odds ratio [AOR], 1.18 [95% CI, 1.10-1.28]; absolute difference, +0.68% [95% CI, 0.36%-1.01%]; number needed to harm [NNH], 147). Among patients enrolled on October 1, 2012, or later, the highest odds (95% CIs) of sICH were found in 15 116 patients receiving aspirin alone (AOR, 1.19 [1.06-1.34]; absolute difference [95% CI], +0.68% [0.21%-1.20%]; NNH, 147) and 2397 patients receiving dual antiplatelet treatment of aspirin and clopidogrel (AOR, 1.47 [1.16-1.86]; absolute difference, +1.67% [0.58%-3.00%]; NNH, 60). The risk for in-hospital mortality was similar between those who were and were not receiving antiplatelet therapy after adjustment (8.0% vs 6.6%; AOR, 1.00 [0.94-1.06]; nonsignificant absolute difference, -0.01% [-0.37% to 0.36%]). However, patients receiving antiplatelet therapy had a greater risk-adjusted likelihood of independent ambulation (42.1% vs 46.6%; AOR, 1.13 [1.08-1.17]; absolute difference, +2.23% [1.55%-2.92%]; number needed to treat, 43) and better functional outcomes (modified Rankin Scale score, 0-1) at discharge (24.1% vs 27.8%; AOR, 1.14; 1.07-1.22; absolute difference, +1.99% [0.78%-3.22%]; number needed to treat, 50).

CONCLUSIONS AND RELEVANCE Among patients with an acute ischemic stroke treated with intravenous tPA, those receiving antiplatelet therapy before the stroke had a higher risk for sICH but better functional outcomes than those who were not receiving antiplatelet therapy.

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Stroke is the second leading cause of death worldwide, with 5 million people dying of stroke each year and another 5 million left permanently disabled.¹ Intravenous tissue plasminogen activator (tPA) therapy improves outcomes of acute ischemic stroke.² However, the use of tPA also carries the risk for symptomatic intracranial hemorrhage (sICH), the worst complication of thrombolysis for acute ischemic stroke. Approximately 40% of patients receive antiplatelet therapy before their stroke, and these patients may be at risk for increased bleeding with concomitant tPA treatment.³ Although the current US and European guidelines do not preclude administration of intravenous tPA in patients receiving antiplatelet therapy before the stroke,^{2,4} uncertainties remain regarding the safety of thrombolysis in this population.

To date, the question whether patients receiving pre-stroke antiplatelet therapy have a substantially higher risk for sICH remains unanswered.⁵ Secondary analysis from randomized clinical trials and observational studies⁶⁻²² reported conflicting results. Many studies were limited in size and underpowered to draw definite conclusions. Meta-analyses from observational data²³⁻²⁵ were based on crude results without accounting for baseline differences between patients who were and were not receiving antiplatelet therapy before the stroke. Furthermore, data are scarce for various antiplatelet regimens (with most studies analyzing aspirin monotherapy only without including nonaspirin antiplatelet drugs or combination therapy), for clinically relevant subgroups (those older than 80 years; women; and patients with a history of coronary artery disease or prior stroke or with a window of 3.0-4.5 hours for treatment), and for clinical outcomes with tPA after antiplatelet therapy.

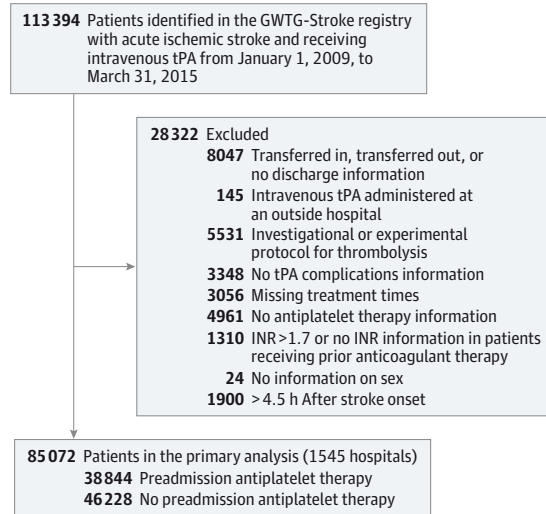
Using data from the American Heart Association and American Stroke Association Get With the Guidelines-Stroke (GWTG-Stroke) program, we evaluated the safety and clinical outcomes among patients with intravenous tPA who received antiplatelet therapy in routine clinical practice. Our specific goals were to (1) determine whether patients receiving antiplatelet therapy were at an increased risk for sICH after tPA, (2) evaluate the safety profile in clinically relevant subgroups, and (3) investigate the association of prior antiplatelet therapy with clinical outcomes.

Methods

GWTG-Stroke Registry

The GWTG-Stroke program includes an ongoing, voluntary, national stroke registry sponsored by the American Heart Association and American Stroke Association. Details of the design and conduct of the GWTG-Stroke registry have been described previously.^{26,27} Standardized data collection in the GWTG-Stroke registry includes patient demographics, medical history, diagnostic testing, brain imaging, in-hospital treatment, and outcomes. As of January 1, 2009, the GWTG-Stroke registry collects data on medications used before admission, including antiplatelet agents or anticoagulants. The validity and reliability of data collection in the GWTG-Stroke registry has been reported in previous research.²⁸ Quintiles,

Figure 1. Study Population



INR indicates international normalized ratio; GWTG-Stroke, American Heart Association and American Stroke Association Get With the Guidelines-Stroke program; and tPA, tissue plasminogen activator.

Inc serves as the data collection and coordination center for the GWTG-Stroke registry. The Duke Clinical Research Institute serves as the data analysis center and has an agreement to analyze the aggregate deidentified data for research purposes. This study was approved by the institutional review board of Duke University.

Study Population

The initial population included 113 394 patients with acute ischemic stroke who received intravenous tPA alone and not combined with endovascular treatment in GWTG-Stroke hospitals from January 1, 2009, through March 31, 2015. We excluded patients who had missing information on the use of antiplatelet agents before admission, patients who had received tPA beyond (>4.5 hours after onset of stroke symptoms) the guideline-recommended treatment window,² and patients who were transferred in or out because in-hospital care and outcomes could not be tracked after interhospital transfer. After these exclusions, our primary study population consisted of 85 072 patients from 1545 hospitals in the United States (Figure 1). The characteristics of patients included and excluded are shown in eTable 1 in the Supplement.

Study Variables

Antiplatelet therapy was defined as documentation of patients taking an antiplatelet medication within 7 days before hospital arrival. Starting with the October 2012 version of the data collection form, specific antiplatelet agents, such as aspirin or the combination of aspirin and dipyridamole, clopidogrel, ticlopidine, or others, were recorded. Prasugrel and ticagrelor were added to the October 2013 version of the data collection form. Based on these data, we further categorized antiplatelet therapy in these later years into the following 4 mutually exclusive groups: (1) aspirin alone, (2) a combination of

aspirin and dipyridamole, (3) clopidogrel alone, and (4) dual antiplatelet therapy with aspirin and clopidogrel. Ticlopidine, prasugrel, ticagrelor, unknown antiplatelet agents, or other combinations were not analyzed separately owing to the small sample size ($n = 278$).

The primary end points were sICH, in-hospital mortality, discharge ambulatory status, and the modified Rankin Scale (mRS) score (range, 0 [no symptoms] to 6 [death]). The sICH was defined as an intracranial hemorrhage within 36 hours, documented by computed tomography or magnetic resonance imaging and the treating physician's notes indicating clinical deterioration attributable to hemorrhage.^{29,30} Functional outcome measured by the mRS score was reported among patients treated with intravenous tPA from October 1, 2012, to March 31, 2015, and further dichotomized as 0 to 1 for excellent recovery and 0 to 2 for functional independence.^{31,32} The characteristics of patients with or without a documented mRS score at discharge are shown in eTable 2 in the [Supplement](#). Secondary end points included life-threatening or serious systemic hemorrhage within 36 hours, any tPA complication within 36 hours (sICH, life-threatening or serious systemic hemorrhage, or other serious complications), and discharge destination (home, hospice, inpatient rehabilitation facility, or skilled nursing facility).

Statistical Analysis

Data were analyzed from January 1, 2009, through March 31, 2015. Means (SDs) and medians (25th-75th percentiles) were used to describe the distribution of continuous variables; percentages described categorical variables. We compared baseline characteristics between patients with and without antiplatelet therapy using the Pearson χ^2 test for categorical variables and the Wilcoxon rank sum test for continuous variables. Multivariable logistic regression analyses investigated the associations between prior antiplatelet therapy and each outcome. These analyses adjusted for baseline patient demographic and clinical variables and hospital-level factors that are expected to be predictive of outcome and have been used in prior GWTG-Stroke analyses.^{29,33} Patient-level variables included age; sex; race; baseline National Institutes of Health Stroke Scale (NIHSS) score³⁴ (a measure of neurologic deficits; range, 0-42, with a higher score indicating greater stroke severity); systolic blood pressure; serum glucose level; time from arrival to initiation of tPA (door-to-needle time); medical history of atrial fibrillation, coronary artery disease, prior stroke or transient ischemic attack, carotid stenosis, hypertension, diabetes mellitus, dyslipidemia, or peripheral vascular disease; smoking status; use of emergency medical services transport; arrival time during regular working hours (7 AM to 6 PM Monday through Friday); and use of an anticoagulant before admission. We also examined the interaction between prior use of antiplatelet agents and anticoagulants. Hospital-level factors included hospital bed size, academic status, primary stroke center status, annual ischemic stroke volume, mean number of patients treated with intravenous tPA annually, hospital region, and rural location. These analyses accounted for within-hospital clustering using generalized estimating equations.

The number needed to treat (NNT) or to harm (NNH) was reported to establish the balance of benefits and harms of administering tPA to patients with prior use of antiplatelet agents compared with those treated with tPA without prior use of antiplatelet agents. Calculation of the absolute difference was based on the estimated mean probability of the outcome in the population if all patients received antiplatelet therapy before tPA administration minus the probability of the outcomes if none of them received antiplatelet agents based on the covariates in the logistic regression model.³⁵ A positive absolute difference would indicate that this outcome was more frequent in patients treated with tPA who had received antiplatelet therapy before the stroke. This method has the theoretical advantage of translating the odds ratio (OR) from a relative scale into a clinically meaningful measure of the treatment effect in an absolute scale while adjusting for possible imbalance in prognostically important baseline characteristics.

Because the NIHSS score is a critical predictor of outcomes in acute ischemic stroke and sICH after tPA, we used a multiple imputation method to impute missing NIHSS values. A sensitivity analysis was performed after excluding patients with missing NIHSS data (4229 [5.0%]). The characteristics of all 85 072 patients (including those without NIHSS scores recorded) and only the 80 843 patients with the NIHSS score recorded are shown in eTable 3 in the [Supplement](#). We also evaluated the association with sICH in clinically relevant subgroups by age (≤ 80 and > 80 years) according to the European Cooperative Acute Stroke Study (ECASS) I through III criteria and the European license for the study drug,^{32,36,37} sex, medical history of coronary artery disease, prior stroke and/or transient ischemic attack, guideline-recommended treatment windows (class I level of evidence A, within 3.0 hours; class I level of evidence B, 3.0-4.5 hours),² and various antiplatelet regimens, including aspirin alone, clopidogrel alone, aspirin-dipyridamole, and aspirin-clopidogrel dual antiplatelet therapy.

All P values are 2 sided, with $P < .05$ considered statistically significant. All statistical analyses were performed using STATA software (version 14.0; StataCorp, LP).

Results

Among 85 072 patients receiving intravenous tPA, 38 844 (45.7%) were using antiplatelet therapy before admission and 46 228 (54.3%) were not. **Table 1** displays demographic, clinical, and hospital characteristics according to prestroke antiplatelet use. Patients receiving antiplatelet therapy before admission were older (median [25th-75th percentile] age, 76 [65-84] vs 68 [56-80] years), had a greater prevalence of cardiovascular risk factors, and were more likely to receive antihypertensives or medications to lower cholesterol or glucose levels but were less likely to receive anticoagulants before admission ($P < .001$ for all). The initial NIHSS score (median [25th-75th percentile], 10 [5-17] vs 10 [5-16]; $P < .001$) was slightly higher in patients receiving antiplatelet agents before stroke. Because of the large sample size, the P value was statistically significant, but the measured difference in NIHSS scores was relatively small.

Table 1. Patient and Hospital Characteristics According to Preadmission Use of Antiplatelet Therapy

Variable	Preadmission Antiplatelet Therapy ^a		P Value
	Yes (n = 38 844)	No (n = 46 228)	
Age, y			
Mean (SD)	73.7 (13.2)	67.2 (15.7)	<.001
Median (25th-75th percentile)	76 (65-84)	68 (56-80)	
Women	19 293 (49.7)	23 768 (51.4)	<.001
Race or ethnicity, No. (%)			
White	29 338 (75.6)	31 219 (67.6)	<.001
Black	4835 (12.5)	7848 (17.0)	
Asian	2352 (6.1)	3824 (8.3)	
Hispanic	894 (2.3)	1380 (3.0)	
Other	1399 (3.6)	1916 (4.1)	
History, No. (%)			
Atrial fibrillation or flutter	9986 (25.7)	7720 (16.7)	<.001
Prosthetic heart valve	496 (1.3)	419 (0.9)	<.001
Previous stroke and/or transient ischemic attack	14 246 (36.7)	7289 (15.8)	<.001
Carotid stenosis	1677 (4.3)	604 (1.3)	<.001
Coronary artery disease and/or myocardial infarction	14 781 (38.1)	6300 (13.6)	<.001
Heart failure	4834 (12.4)	3009 (6.5)	<.001
Hypertension	31 873 (82.1)	30 499 (66.0)	<.001
Dyslipidemia	21 116 (54.4)	14 746 (31.9)	<.001
Peripheral vascular disease	2044 (5.3)	983 (2.1)	<.001
Diabetes mellitus	12 489 (32.2)	10 122 (21.9)	<.001
Smoker	5349 (13.8)	9588 (20.7)	<.001
Medications used before admission, No. (%)			
Antiplatelet agent	38 844 (100)	0	NA
Anticoagulant	1449 (3.7)	3318 (7.2)	<.001
Antihypertensive	29 610 (83.2)	23 373 (53.9)	<.001
Cholesterol level reducer	23 181 (59.7)	11 859 (25.7)	<.001
Glucose level reducer	9258 (26.5)	6503 (15.1)	<.001
Mode of arrival, EMS vs other, No. (%)	31 235 (83.4)	36 722 (82.4)	<.001
Off-hour presentation, No. (%) ^b	18 842 (48.5)	22 634 (49.0)	.19
NIHSS score ^c			
Mean (SD)	11.5 (7.6)	11.2 (7.4)	<.001
Median (25th-75th percentile)	10 (5-17)	10 (5-16)	
Missing	1820 (4.7)	2409 (5.2)	
Time from symptom onset to tPA treatment, median (25th-75th percentile), min	138 (108-170)	138 (107-172)	.11
Door-to-needle time, median (25th-75th percentile), min	68 (52-90)	68 (51-91)	.94
Heart rate, beats/min			
Mean (SD)	80.4 (17.9)	83.4 (18.6)	<.001
Median (25th-75th percentile)	78 (68-90)	81 (70-94)	
Blood pressure, mm Hg			
Systolic			
Mean (SD)	156.8 (28.3)	157.5 (28.9)	.03
Median (25th-75th percentile)	155 (138-175)	155 (138-176)	
Diastolic			
Mean (SD)	83.2 (18.2)	86.4 (18.9)	<.001
Median (25th-75th percentile)	82 (71-94)	85 (74-97)	
Creatinine level, mg/dL			
Mean (SD)	1.4 (4.3)	1.3 (4.0)	<.001
Median (25th-75th percentile)	1.0 (0.9-1.3)	1.0 (0.8-1.2)	

(continued)

Table 1. Patient and Hospital Characteristics According to Preadmission Use of Antiplatelet Therapy (continued)

Variable	Preadmission Antiplatelet Therapy ^a		P Value
	Yes (n = 38 844)	No (n = 46 228)	
Serum glucose level, mg/dL			
Mean (SD)	138.6 (60.8)	135.6 (60.4)	<.001
Median (25th-75th percentile)	120 (103-152)	117 (102-146)	
Body mass index ^d			
Mean (SD)	28.4 (7.4)	28.5 (7.2)	.18
Median (25th-75th percentile)	27.3 (23.9-31.6)	27.4 (23.9-31.8)	
Hospital characteristics			
No. of beds, median (25th-75th percentile)	382 (264-579)	391 (268-584)	.001
Annual ischemic stroke volume, median (25th-75th percentile), No. of patients	227 (156-349)	224 (157-346)	.04
Annual No. of IV tPA cases, median (25th-75th percentile)	21 (12-32)	21 (13-32)	.03
Academic hospital, No. (%)	23 878 (62.5)	28 433 (62.4)	.78
Joint Commission primary stroke center, No. (%)	20 072 (51.7)	23 599 (51.0)	.07
Rural hospital, No. (%)	1341 (3.5)	1273 (2.8)	<.001

Abbreviations: EMS, emergency medical services; IV tPA, intravenous tissue plasminogen activator; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale.

SI conversion factors: To convert creatinine to micromoles per liter, multiply by 88.4; glucose to millimoles per liter, multiply by 0.0555.

^a Owing to missing data, totals may not match the numbers in the column headings.

^b Indicates anytime outside of 7 AM to 6 PM on weekdays.

^c Scores range from 0 to 42, with a higher score indicating greater stroke severity.

^d Calculated as weight in kilograms divided by height in meters squared.

Symptomatic Intracranial Hemorrhage

Overall, 3647 patients (4.3%) developed an sICH after intravenous tPA administration. Patients receiving antiplatelet therapy had a higher crude rate of sICH (5.0%) than those who were not receiving antiplatelet therapy before the stroke (3.7%) (Table 2). After risk adjustment, antiplatelet therapy was independently associated with higher odds of sICH (adjusted OR [AOR], 1.18; 95% CI, 1.10-1.28), although the absolute excess risk was small (absolute difference +0.68% [95% CI, 0.36%-1.01%]; NNH, 147). No interaction effect was found between prior antiplatelet and anticoagulant therapies ($P = .81$). The association between antiplatelet therapy and sICH remained essentially unchanged after excluding patients with missing NIHSS data (AOR, 1.17 [95% CI, 1.09-1.27]; absolute difference, +0.62% [95% CI, 0.30%-0.96%]; NNH, 161). Analyses of clinically relevant subgroups by age (≤ 80 and > 80 years), sex, medical history of coronary artery disease, prior stroke, and treatment window (within 3.0 and 3.0-4.5 hours) found similar trends of higher risk for sICH associated with prior use of antiplatelet agents (Figure 2), although the difference was not statistically significant for patients who received tPA from 3.0 to 4.5 hours after acute ischemic stroke.

Of the 43 034 patients enrolled from October 1, 2012, to March 31, 2015, 22 813 (53.0%) received no antiplatelet agents. Among the 20 221 patients who received antiplatelet agents, 15 116 (35.1%) received aspirin alone; 2397 (5.6%), aspirin-clopidogrel dual antiplatelet therapy; 2037 (4.7%), clopidogrel alone; 393 (0.9%), aspirin-dipyridamole; and 278 (0.6%), other or unknown antiplatelet agents. The crude rates of sICH were highest among patients receiving aspirin-clopidogrel dual antiplatelet therapy (131 of 2397 [5.5%]), followed by aspirin alone (698 of 15 116 [4.6%]), clopidogrel alone (71 of 2037

[3.5%]), no antiplatelet therapy (760 of 22 813 [3.3%]), and aspirin-dipyridamole (9 of 393 [2.3%]). After risk adjustment, aspirin alone (AOR, 1.19 [95% CI, 1.06-1.34]; absolute difference, +0.68% [95% CI, 0.21%-1.20%]; NNH, 147) and aspirin-clopidogrel dual antiplatelet therapy (AOR, 1.47 [95% CI, 1.16-1.86]; absolute difference, +1.67% [95% CI, 0.58%-3.00%]; NNH, 60) were associated with increased odds for sICH compared with no use of antiplatelet therapy (Figure 2). We found no statistically significant differences in the use of clopidogrel alone (AOR, 0.85 [95% CI, 0.65-1.12]; nonsignificant absolute difference, -0.54% [95% CI, -1.30% to 0.43%]) or aspirin-dipyridamole (AOR, 0.56 [95% CI, 0.28-1.12]; nonsignificant absolute difference, -1.66% [95% CI, -2.76% to 0.42%]) compared with no use of antiplatelet agents.

In-Hospital Mortality, Ambulatory Status, and mRS Score at Discharge

Despite higher bleeding rates, prior antiplatelet therapy was not associated with in-hospital mortality after risk adjustment (unadjusted rates, 8.0% vs 6.6%; AOR, 1.00 [95% CI, 0.94-1.06]; nonsignificant absolute difference, -0.01% [95% CI, -0.37% to 0.36%]) (Table 2). In contrast, patients receiving prestroke antiplatelet therapy had greater odds of being able to ambulate independently at discharge after adjustment (unadjusted rates, 42.1% vs 46.6%; AOR, 1.13 [95% CI, 1.08-1.17]; absolute difference, +2.23% [95% CI, 1.55%-2.92%]; NNT, 43). Among patients with a documented mRS score, prestroke antiplatelet therapy was associated with favorable functional outcomes at discharge after risk adjustment for mRS scores of 0 to 1 (unadjusted rates, 24.1% vs 27.8%; AOR, 1.14 [95% CI, 1.07-1.22]; absolute difference, +1.99% [95% CI, 0.78%-3.22%]; NNT, 50) and for mRS scores of 0 to 2 (unadjusted rates,

Table 2. Primary and Secondary End Points According to Preadmission Use of Antiplatelet Therapy

End Point	No. of Events/Total No. of Patients (%)		OR (95% CI)		P Value
	Preadmission Antiplatelet Therapy	No Preadmission Antiplatelet Therapy	Unadjusted	Adjusted ^a	
Primary					
sICH	1927/38 844 (5.0)	1720/46 228 (3.7)	1.35 (1.26-1.44)	1.18 (1.10-1.28)	<.001
In-hospital mortality	3115/38 844 (8.0)	3061/46 228 (6.6)	1.23 (1.17-1.29)	1.00 (0.94-1.06)	.95
Independent ambulation at discharge ^b	14 277/33 880 (42.1)	18 825/40 432 (46.6)	0.84 (0.81-0.86)	1.13 (1.08-1.17)	<.001
mRS score at discharge ^c					
0-1	3730/15 475 (24.1)	4892/17 613 (27.8)	0.83 (0.79-0.87)	1.14 (1.07-1.22)	<.001
0-2	5081/15 475 (32.8)	6548/17 613 (37.2)	0.83 (0.79-0.86)	1.16 (1.09-1.24)	<.001
Secondary end points					
Life-threatening or serious systemic hemorrhage	451/38 844 (1.2)	314/46 228 (0.7)	1.72 (1.49-1.99)	1.45 (1.23-1.72)	<.001
Any tPA complication ^d	3509/38 844 (9.0)	3497/46 228 (7.6)	1.21 (1.16-1.27)	1.08 (1.02-1.14)	.008
Discharge to home	16 070/38 844 (41.4)	21 098/46 228 (45.6)	0.84 (0.82-0.86)	1.13 (1.09-1.17)	<.001
Discharge to hospice	2446/38 844 (6.3)	2128/46 228 (4.6)	1.39 (1.31-1.48)	0.97 (0.90-1.04)	.37
Discharge to skilled nursing facility ^b	6728/38 784 (17.3)	6398/46 138 (13.9)	1.30 (1.26-1.35)	0.98 (0.94-1.02)	.29
Discharge to inpatient rehabilitation facility ^b	9741/38 784 (25.1)	12 627/46 138 (27.4)	0.89 (0.86-0.92)	0.93 (0.90-0.97)	<.001

Abbreviations: mRS, modified Rankin Scale; OR, odds ratio; sICH, symptomatic intracranial hemorrhage; tPA, tissue plasminogen activator.

^a Adjustment for patient-level characteristics includes age; sex; race; systolic blood pressure; serum glucose level; baseline National Institutes of Health Stroke Scale score; door-to-needle time; medical history of atrial fibrillation or flutter, prior stroke and/or transient ischemic attack, coronary artery disease and/or myocardial infarction, heart failure, carotid stenosis, hypertension, dyslipidemia, diabetes mellitus, or peripheral vascular disease; smoking status; emergency medical services arrival; on- or off-hour presentation; and preadmission anticoagulant use. Adjustment for hospital-level characteristics includes number of beds, academic status, primary stroke center, annual

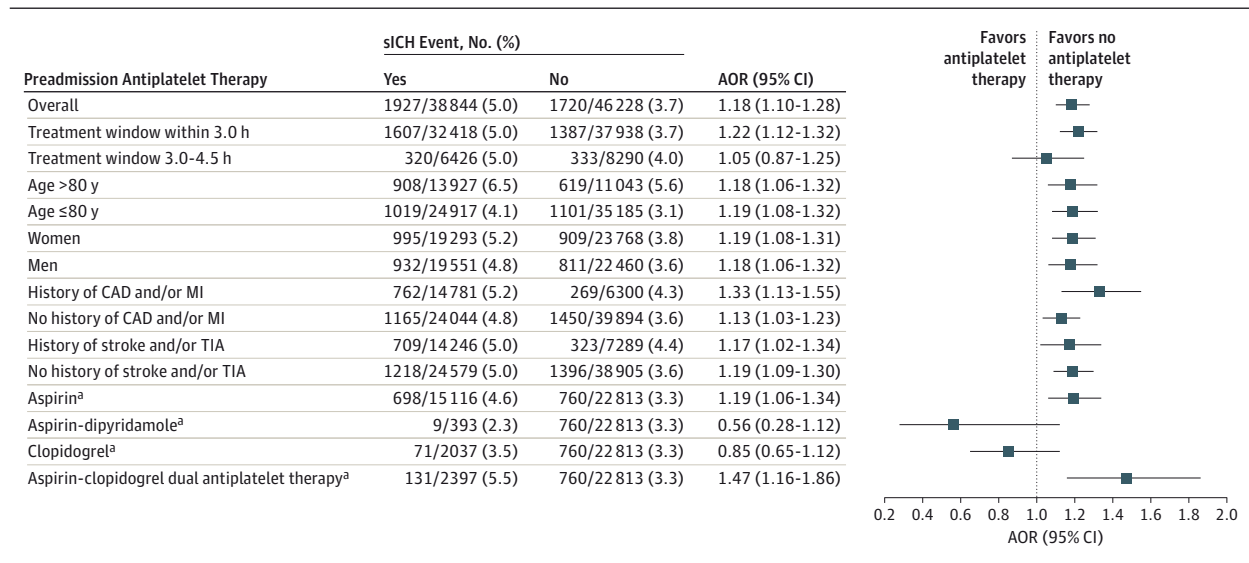
ischemic stroke volume, annual tPA volume, hospital region, and rural location. No significant interaction between preadmission anticoagulant and antiplatelet agent use was observed.

^b Excludes missing data.

^c Indicates from October 1, 2012, through March 31, 2015. Scores range from 0 (no symptoms) to 6 (death). Excludes patients with missing mRS scores. Characteristics between patients with and without documented mRS scores are shown in eTable 1 in the Supplement.

^d Includes sICH within 36 hours, life-threatening or serious systemic hemorrhage within 36 hours, or other serious complications.

Figure 2. Preadmission Antiplatelet Therapy and Symptomatic Intracranial Hemorrhage (sICH)



Data are given overall and in clinically relevant subgroups. AOR indicates adjusted odds ratio; CAD, coronary artery disease; MI, myocardial infarction; and TIA, transient ischemic attack.

^a Includes patients admitted October 1, 2012, or later.

32.8% vs 37.3%; AOR, 1.16 [95% CI, 1.09-1.24]; absolute difference, +2.54% [95% CI, 1.33%-3.77%]; NNT, 39). These associated benefits in functional outcomes were consistent in

patients receiving aspirin alone (Table 3). Similar improvements in ambulatory status and mRS scores were also observed after risk adjustment among patients receiving clopi-

Table 3. Primary End Points According to Various Preadmission Antiplatelet Therapy Regimens^a

Outcome ^b	Antiplatelet Therapy, OR (95% CI)			
	Aspirin Alone	Aspirin-Dipyridamole	Clopidogrel Alone	Aspirin-Clopidogrel Dual Antiplatelet Therapy
sICH	1.19 (1.06-1.34)	0.56 (0.28-1.12)	0.85 (0.65-1.12)	1.47 (1.16-1.86)
In-hospital mortality	0.97 (0.88-1.07)	1.10 (0.72-1.69)	1.04 (0.85-1.27)	0.98 (0.80-1.19)
Independent ambulation at discharge	1.09 (1.03-1.15)	1.04 (0.82-1.33)	1.13 (1.00-1.28)	1.08 (0.96-1.21)
mRS score at discharge ^c				
0-1	1.16 (1.07-1.26)	0.59 (0.40-0.85)	1.09 (0.92-1.29)	1.07 (0.91-1.25)
0-2	1.16 (1.08-1.25)	0.80 (0.58-1.11)	1.11 (0.95-1.30)	1.15 (0.98-1.34)

Abbreviations: mRS, modified Rankin Scale; OR, odds ratio; sICH, symptomatic intracranial hemorrhage; tPA, tissue plasminogen activator.

^a Indicates from October 1, 2012, to March 31, 2015.

^b Compared with patients treated with tPA without prior use of antiplatelet therapy.

^c Scores range from 0 (no symptoms) to 6 (death).

dogrel alone or aspirin-clopidogrel dual antiplatelet therapy, although none of these differences reached statistical significance.

Secondary Outcomes

The rates of life-threatening or serious sICH and any tPA complications were higher in patients receiving prior antiplatelet therapy (Table 2). In the unadjusted analysis, fewer patients who received antiplatelet therapy were discharged home (41.4% vs 45.6%). However, they had higher AORs for being discharged home than patients without antiplatelet use (1.13 [95% CI, 1.09-1.17]). No statistically significant differences were seen in discharge to hospice (unadjusted rates, 6.3% vs 4.6%; AOR, 0.97 [95% CI, 0.90-1.04]) or a skilled nursing facility (unadjusted rates, 17.3% vs 13.9%; AOR, 0.98 [95% CI, 0.94-1.02]) between the two groups.

Discussion

In this large, nationwide, contemporary registry of patients with acute ischemic stroke, we found that the use of intravenous tPA in patients receiving prestroke antiplatelet therapy was associated with an increased risk for sICH compared with tPA-treated patients without prior antiplatelet therapy. Despite higher rates of intracranial bleeding, the overall excess risk appeared small (absolute difference, +0.68%; NNH, 147) and did not translate into higher in-hospital mortality. In contrast, patients treated with tPA after antiplatelet therapy appeared to have better functional outcomes in terms of ambulatory status (NNT, 43) and mRS scores of 0 to 1 (NNT, 50) and 0 to 2 (NNT, 39) than those not receiving antiplatelet therapy. Collectively, these findings demonstrate that the risk for sICH among patients with stroke who receive antiplatelet therapy before the stroke and are treated with intravenous tPA is relatively low and must be weighed against the potential benefits in terms of improved functional outcomes.

Intravenous tPA remains the only available pharmacologic therapy to improve the outcomes for acute ischemic stroke. However, experience with tPA in patients with acute ischemic stroke who receive antiplatelet therapy has been limited. Subgroup analyses of the National Institute of Neurological Disorder and Stroke tPA Stroke Trial⁶ (ORs not reported) and the ECASS III Trial⁷ (unadjusted OR, 1.12) showed no association between preadmission antiplatelet therapy and sICH.

In contrast, rates of sICH were significantly higher among antiplatelet therapy users in the Stroke-Acute Ischemic NXY Treatment (SAINT I and II) trials⁹ (AORs, 2.04 for single and 9.19 for double antiplatelet therapy) and the Third International Stroke Trial⁸ (IST-3; AOR, 1.62). Patients were not randomized based on their antiplatelet drug use in any of these secondary analyses of the trial data. These post hoc trial analyses were performed in relatively small numbers of patients compared with our study, in highly selected clinical trial participants, and in an era when aspirin monotherapy would have been the predominant antiplatelet drug used. Findings from small and moderately powered observational studies showed that the odds of sICH range from 0.6 to 6.0.¹¹⁻²⁰ However, the reported sICH risk might have been underestimated or overestimated, especially when the sample size was small and no risk adjustment was made. A previous GWTG-Stroke analysis²⁹ failed to identify antiplatelet therapy as an independent predictor of sICH, likely owing to its smaller sample size. This result highlights the need for large studies to obtain stable estimates of bleeding risks in patients treated with tPA after use of antiplatelet therapy.

This study represents, to our knowledge, one of the largest clinical experiences of intravenous tPA available so far. Among 85 072 patients with ischemic stroke treated with tPA, 38 844 had received antiplatelet drugs before stroke onset. In accordance with other multicenter registry reports, such as the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST)¹⁴ and the International Stroke Thrombolysis Registry (SITS-ISTR),¹¹ we found that antiplatelet therapy was associated with a higher incidence of sICH. However, patterns of care and administration of tPA in the United States may differ from those of other nations. Although the off-label use of tPA in the elderly is increasing in Europe after publication of the findings of the IST-3 trial,³⁸ the European license still excludes patients older than 80 years. The SITS-ISTR included a subgroup of patients who were treated off-label; however, patients older than 80 years or those who received treatment beyond the 3.0-hour time window were specifically excluded from the analysis.¹¹ We included patients with a class I level of evidence B recommendation for tPA (treatment window, 3.0-4.5 hours), those 80 years or older, women, and those with a medical history of coronary artery disease or a prior stroke and found similar associations between prestroke antiplatelet therapy and sICH in each clinically relevant subgroup.

Given the high prevalence of coronary artery disease and the widespread use of percutaneous coronary intervention, many patients are receiving aspirin or dual antiplatelet therapy at the time of stroke onset. To date, only a few studies have investigated the association between sICH and different antiplatelet regimens.^{9-11,16,18} In our analysis of 20 221 patients receiving different antiplatelet regimens, the incidence of sICH was the highest in patients using dual antiplatelet therapy. This observation may not be surprising given that aspirin and clopidogrel decrease platelet aggregation and inhibit thrombus formation by targeting more than 1 pathway in the hemostatic cascade and hence likely increase the risk for bleeding after tPA administration. Despite higher sICH rates, the overall excess risk appeared to be small. For every 147 patients receiving long-term antiplatelet drugs and treated with tPA, only 1 additional sICH occurred compared with those without prior antiplatelet therapy. Even among patients receiving dual antiplatelet therapy, only 1 more sICH occurred for every 60 patients treated with tPA. The relatively small excess risk did not translate into higher mortality. In contrast, we found preadmission antiplatelet use was associated with better functional outcomes as measured by discharge ambulatory status and mRS scores. The NNTs were 43 for independent ambulation and 50 for excellent functional recovery (mRS scores, 0-1). Therefore, the overall benefit of tPA likely will outweigh any risk for excess bleeding associated with antiplatelet therapy.

Our study has limitations. First, we performed a retrospective observational analysis. Unmeasured confounding and treatment selection may bias outcome comparisons. However, patients receiving antiplatelet drugs were older and had more cardiovascular risk factors than those not receiving antiplatelet therapy before the stroke. Therefore, selection bias, if it exists, might be more likely to be against patients receiving antiplatelet therapy. Second, stroke severity is a critical determinant of stroke outcomes.³⁵ We may have introduced bias by using a multiple imputation method for patients without a record of NIHSS scores (5.0%). Nonetheless, NIHSS scores appeared to be missing at random because patients with documented NIHSS scores were comparable to those patients without docu-

mented NIHSS scores with respect to most characteristics. A sensitivity analysis of the tPA cohort with complete NIHSS data found consistent results.

Third, we did not have access to data on the time and the last dose of the antiplatelet drug or the medication indication for which the antiplatelet drug was prescribed before the stroke. As a result, the bleeding risks might be underestimated for patients taking antiplatelet drugs up to the day of the stroke or overestimated for patients who stopped therapy for reasons such as surgical procedures or nonadherence and subsequently had an ischemic stroke event. Fourth, sICH was not centrally adjudicated and was based on locally interpreted computed tomographic or magnetic resonance imaging findings. The GWTG-Stroke registry does not have the actual images for review. Therefore, comparing the incidence of sICH with that of other studies may be difficult. Fifth, we were unable to report long-term functional outcomes because these measures are not currently collected in the GWTG-Stroke registry. Nonetheless, our study was able to report discharge destination, ambulatory status, and mRS scores, which have strong associations with long-term functional outcomes at 90 days.³⁹ Last, the GWTG-Stroke registry is a voluntary program. These results might not be extrapolated to patients treated in non-GWTG-Stroke registry hospitals or in other countries.

Conclusions

This study represents the largest clinical experience of stroke thrombolysis in patients receiving antiplatelet therapy before stroke onset. The use of intravenous tPA in patients receiving antiplatelet therapy was associated with slight increased risk for sICH, especially among patients receiving aspirin or dual antiplatelet therapy. However, the relatively small excess risk did not translate into higher mortality and appeared to be associated with favorable functional outcomes at discharge. Therefore, the overall benefits of thrombolytic therapy may outweigh the risks in eligible patients with ischemic stroke receiving antiplatelet therapy before stroke onset.

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per-patient payments to participating sites; serving as chair of the AHA and American Stroke Association (ASA) Get With The Guidelines–Stroke (GWTG-Stroke) clinical work group; serving as a stroke systems consultant to the Massachusetts Department of Public Health; and serving as a scientific consultant regarding trial design and conduct to H. Lundbeck A/S (international steering committee, Efficacy and Safety Study of Desmoteplase to Treat Acute Ischemic Stroke [DIAS-3 and DIAS-4] trials) and Penumbra (data and safety monitoring committee, Randomized Concurrent Controlled Trial to Assess the Safety and Effectiveness of the Separator 3D as a Component of the Penumbra System in the Revascularization of Large Vessel Occlusion in Acute Ischemic Stroke trial). Dr Bhatt reported serving on the advisory boards of Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, and Regado Biosciences; serving on the boards of directors of the Boston Veterans Affairs Research Institute and Society of Cardiovascular Patient Care; serving as the chairperson for the GWTG-Stroke steering committee; serving on the data monitoring committees of the Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, and Population Health Research Institute; receiving honoraria from the American College of Cardiology (senior associate editor, *Clinical Trials and News*, ACC.org), Belvoir Publications (editor-in-chief, *Harvard Heart Letter*), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (editor-in-chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (associate editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (chief medical editor, *Cardiology Today's Intervention*), and *WebMD* (continuing medical education steering committees); serving as deputy editor of *Clinical Cardiology* without compensation; receiving research funding from Amarin, AstraZeneca, Biotronik, Bristol-Myers Squibb, Eisai, Ethicon, Forest Laboratories, Ischemix, Medtronic, Pfizer, Roche, Sanofi, St Jude Medical, and The Medicines Company; serving as a trustee for the American College of Cardiology; and performing unfunded research for FlowCo, PLx Pharma, and Takeda. Dr Fonarow reported serving as a member of the GWTG-Stroke steering committee, receiving significant research support from the National Institutes of Health and Patient Centered Outcomes Research Institute, and being an employee of the University of California, which holds a patent on retriever devices for stroke. Dr Peterson reported receiving research grants from Eli Lilly, Johnson & Johnson, Bristol-Myers Squibb, Sanofi, and Merck-Schering Plough partnership and serving as principal investigator of the data analytic center for the GWTG-Stroke. No other disclosures were reported.

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