ORIGINAL RESEARCH

Recent Myocardial Infarction is Associated With Increased Risk in Older Adults With Acute Ischemic Stroke Receiving Thrombolytic Therapy

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***Background*—**Intravenous recombinant tissue-type plasminogen activator (rtPA) remains the only medical therapy to improve outcomes for acute ischemic stroke (AIS), but the safety of rtPA in AIS patients with a history of recent myocardial infarction (MI) remains controversial.

***Methods and Results*—**We sought to determine whether the presence of recent MI would alter the risk of mortality and rtPA-related complications. Multivariate logistic regression models were used to compare in-hospital outcomes between rtPA-treated AIS patients with recent MI within 3 months and those with no history of MI from the Get With The Guidelines-Stroke hospitals between February 2009 and December 2015. Among 40 396 AIS patients aged ≥65 years treated with rtPA, 241 (0.6%) had recent MI, of which 19.5% were ST-segment–elevation myocardial infarction. Patients with recent MI had more severe stroke than those without (median National Institutes of Health Stroke Scale [interquartile range]: 13.0 [7.0–20.0] versus 11.0 [6.0–18.0]). Recent MI was associated with an increased risk of mortality compared with no history of MI (17.4% versus 9.0%; adjusted odds ratio 1.60 [95% CI, 1.10–2.33]; *P*=0.014), but no statistically significant differences in rtPA-related complications (13.5% versus 9.4%; adjusted odds ratio 1.28 [0.88–1.86]; *P*=0.19). Recent ST-segment–elevation myocardial infarction was associated with higher risk of death and rtPA-related complications, but non–ST-segment–elevation myocardial infarction was not.

***Conclusions*—**Among older AIS patients treated with rtPA, recent MI was associated with an increased risk of in-hospital mortality. Further investigations are necessary to determine whether the benefit of rtPA outweighs its risk among AIS patients with recent MI. **(*J Am Heart Assoc*. 2019;8:e012450. DOI: 10.1161/JAHA.119.012450.)**

Key Words: contraindication • eligibility criteria • recombinant tissue plasminogen activator • stroke • thrombolysis

While thrombolysis therapy with intravenous recombinant tissue-type plasminogen activator (rtPA) remains the only medical therapy to improve outcomes in patients with acute ischemic stroke (AIS), use of rtPA in AIS patients with recent myocardial infarction (MI) is controversial.[1] In the 2013 American Heart Association (AHA)/American Stroke Association (ASA) guideline, recent MI within 3 months was listed as a relative exclusion criterion, whereas, in the 2018 AHA/ASA guideline and scientific statement, it is considered reasonable or maybe reasonable with Class IIa or IIb recommendations according to the type and location of MI.[2–4] However, these recommendations are based on consensus of expert opinion (Level of Evidence C). As of today, only a few case reports[5,6] or case series[7] have been reported in the literature. Furthermore, it also remains unclear whether a shorter or longer timeframe than 3 months is safe to give rtPA for AIS patients with a history of MI.

To address this knowledge gap, we evaluated characteristics and clinical outcomes in patients treated with rtPA for AIS who had a recent MI compared with those with no history of MI to determine whether the presence of recent MI alters the risk of mortality and rtPA-related complication in AIS patients treated with rtPA, and to assess whether the safety profiles of rtPA are different according to the type and

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Accompanying Tables S1 through S5 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012450

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Clinical Perspective

What Is New?

- This nationwide registry demonstrated that, among older patients receiving intravenous recombinant tissue-type plasminogen activator for acute ischemic stroke (AIS), a recent history of myocardial infarction (MI) in the past 3 months was associated with higher in-hospital mortality compared with no history of MI in ischemic stroke patients treated with recombinant tissue-type plasminogen activator.
- The association became insignificant, if the timeframe from the onset of MI to the indexed AIS was >3 months or the type of MI was confined to non–ST-segment–elevation myocardial infarction.

What Are the Clinical Implications?

- Given the increased risk of mortality, recombinant tissue-type plasminogen activator should be carefully used for treating AIS patients with a recent history of MI especially in the situations where the timeframe from the onset of MI to the indexed AIS was within 3 months or the type of MI was ST-segment–elevation myocardial infarction.
- Further investigations are necessary to determine whether the benefit of recombinant tissue-type plasminogen activator outweighs its risk among AIS patients with a recent history of MI.

location of the recent MI and the timeframe between MI and the indexed AIS event.

Methods

While data sharing agreements prohibit the AHA from making the data set publicly available, researchers may submit proposals for statistical analysis of the confidential data by the Duke Clinical Research Institute, with approval from the AHA. Details of the application process are available at http:// www.heart.org/en/professional/quality-improvement/quality-research-and-publications/national-level-program-data-research-opportunities.

Data Source

This is a retrospective cohort study using the AHA/ASA GWTG-Stroke (Get With The Guidelines-Stroke) registry, which is an ongoing, voluntary, continuous registry sponsored by the AHA/ASA. Details of GWTG-Stroke registry data collection and variable definitions have been described before.[8] Standardized data collection includes patient demographics, medical history, diagnostic testing, brain imaging, in-hospital treatment, and outcomes. The validity and reliability of data collection in GWTG-Stroke have been reported in previous research.[9]

The in-hospital data from the GWTG-Stroke registry were linked to the Centers for Medicare & Medicaid Services (CMS) claims data to identify recent MI before stroke. Because GWTG-Stroke is an in-patient registry, we link the GWTG-Stroke to CMS claims among Medicare fee-for-services patients aged ≥65 years and determine the timing of the previous MI event. The linked clinical and claims data set (GWTG-Stroke/CMS) was created by matching on a series of indirect identifiers, including admission date, discharge date, patient age or date of birth, and sex.[10] Prior work has shown that patients in the linked GWTG-Stroke/CMS database are representative of the national Medicare AIS population.[11]

The Duke Clinical Research Institute (Durham, NC) serves as the data analysis center and has an agreement to analyze the aggregate de-identified data for research purposes. Each participating hospital received either human research approval to enroll patients without individual patient consent under the Common Rule or a waiver of authorization and exemption from subsequent review by their institutional review board. This study was approved by the institutional review board of Duke University.

Study Population

All patients with a diagnosis of AIS treated with rtPA were identified in GWTG-Stroke/CMS linked data set between February 2009 and December 2015. After excluding (1) patients not treated with rtPA, (2) patients whose onset to treatment time was missing, inaccurate, or >4.5 hours, (3) in-patient onset of AIS, (4) patients transferred in, (5) patients treated with experimental rtPA, (6) discharge status missing, not documented, or discharge against medical advice, and transfer out, and (7) patients who underwent catheter-based treatment, we identified 2 groups of patients: AIS patients with a recent MI who were treated with rtPA and AIS patients with no history of MI who were treated with rtPA. A recent MI was identified using *International Classification of Diseases, Ninth Revision-Clinical Modification* (*ICD-9-CM)* primary diagnosis codes (Table S1) of MI within 3 months before the index admission for AIS. A recent MI was classified according to the type of MI (ST-segment–elevation myocardial infarction [STEMI] versus non–ST-segment–elevation myocardial infarction [NSTEMI]). No history of MI was defined as those without medical history of MI within the past year before AIS. Furthermore, to assess whether the safety profiles of rtPA is different according to the timeframe from the previous MI to the index AIS, a recent MI was further categorized into the subgroups of within 1 to 14, 15 to 30, and 31 to 90 days, and history of MI within 91 to 180 days and within 181 to 365 days before AIS were also identified.

To evaluate potential treatment selection and whether it was rtPA treatment or MI that influence outcomes, we identified a separate cohort of AIS patients who were otherwise eligible but not treated with rtPA. Patients were considered eligible if they arrived within 3.5 hours from symptom onset (potentially eligible for the 0–4.5 hour treatment window) without any documented reasons for no rtPA use except for a recent MI (Figure 1).

Outcome Measures

The primary outcome was in-hospital mortality. Other outcomes included discharge disposition (home versus other), in-hospital mortality or discharge to hospice, ambulatory status at discharge (able to ambulate independently versus not), and modified Rankin Scale at discharge (range of 0 [no symptoms] to 6 [death], with 0–2 as functional independence) and complications related to rtPA, including symptomatic intracranial hemorrhage within 36 hours, life-threatening or serious systemic hemorrhage within 36 hours, any serious complications, hemopericardium and/or cardiac tamponade. Except for hemopericardium and cardiac tamponade which were identified through *ICD-9* secondary diagnosis codes, all other outcomes were reported in the GWTG-Stroke registry (Table S1).

Statistical Analysis

We calculated the medians with 25th and 75th percentiles for continuous variables and counts and percentages for categorical variables in each group. Absolute standardized difference were used to compare the baseline differences in the following cohorts: AIS patients treated with rtPA who have versus do not have a history of recent MI; and AIS patients with recent MI treated with rtPA versus otherwise eligible but not treated with rtPA. An absolute standardized difference >10 indicates significant imbalance between groups. Multivariable logistic regression models were performed to assess the association between a recent MI with each clinical outcome. These analyses adjusted for baseline demographic and clinical variables before the index ischemic stroke event including demographics, enrollment year, medical history, arrival and admission information, National Institutes of Health Stroke Scale score, medications at admission, vital signs and laboratory data, and hospital characteristics. The full list of covariates is described in Table S2. Generalized estimation equations modeling approach was used to account for within-hospital clustering of patients. Subgroup analysis by MI (STEMI versus NSTEMI) was performed. In addition to recent MI within 3 months, the association between a history of MI and clinical outcomes were assessed according to the different timeframes before the indexed AIS (1–14, 15–30, 31–90, 91–180, and 181–365 days).

Although it is still controversial about whether dual antiplatelet therapy is associated with increased risks of intracerebral hemorrhage and subsequent mortality when rtPA is administered,[12,13] we performed a sensitivity analysis in patients who enrolled after October 2012 to account for the impact of dual antiplatelet therapy on bleeding complications, because the detailed information about antiplatelet therapy before admission were added in the data collection form afterwards. In a sensitivity analysis, the model included the number of antiplatelet agent (no antiplatelet agent versus single antiplatelet therapy versus dual antiplatelet therapy)

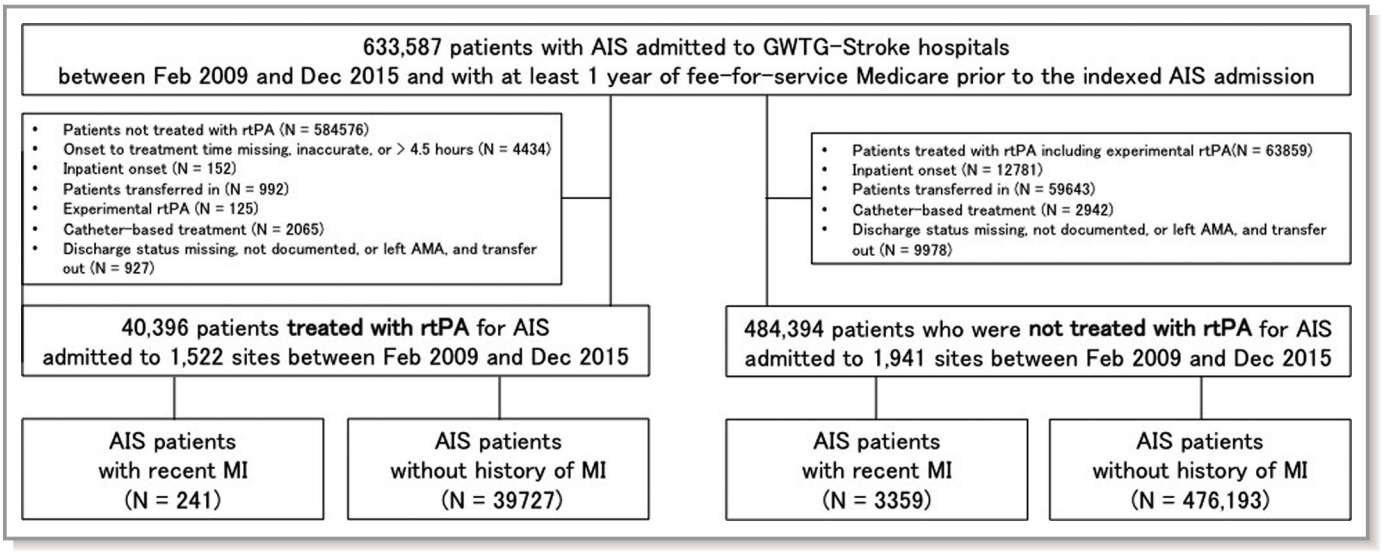

Figure 1. Study cohort creation. AIS indicates acute ischemic stroke; AMA, against medical advice; CMS, Centers for Medicare & Medicaid Services; FFS, fee-for-service; GWTG, Get With The Guidelines; MI, myocardial infarction; rtPA, recombinant tissue-type plasminogen activator.

Table 1. Baseline Characteristics Between AIS Patients Treated With rtPA, With or Without a History of Recent MI

Characteristics	Recent MI Within 3 Mo n=241	No History of MI in the Past Year n=39 727	Absolute Standardized Difference (%)
Age, median (IQR), y	82 (75–88)	81 (74–87)	11.4
Women, n (%)	140 (58.1)	23 053 (58.0)	0.1
Race, n (%)			13.7
Non-Hispanic white	189 (78.4)	32 800 (82.7)	
Non-Hispanic black	26 (10.8)	3265 (8.2)	
Hispanic	11 (4.6)	1498 (3.8)	
Asian	7 (2.9)	817 (2.1)	
Other	8 (3.3)	1284 (3.2)	
Medical history, n (%)			
Atrial flutter	98 (40.8)	12 026 (30.5)	21.8
Previous stroke	44 (18.3)	7974 (20.2)	4.7
Previous transient ischemic attack	22 (9.2)	4062 (10.3)	3.8
Carotid stenosis	11 (4.6)	1370 (3.5)	5.7
Diabetes mellitus	87 (36.3)	10 246 (26.0)	22.4
Peripheral vascular disease	21 (8.8)	1732 (4.4)	17.7
Hypertension	199 (82.9)	31 358 (79.4)	8.9
Smoker	25 (10.4)	2997 (7.6)	9.9
Dyslipidemia	129 (53.8)	18 482 (46.8)	13.9
Heart failure	58 (24.2)	4646 (11.8)	32.7
Obesity or overweight	16 (6.7)	3044 (7.7)	4
Renal insufficiency	10 (4.2)	1602 (4.1)	0.6
Arrival and admission information, n (%)			
Onset to arrival time, median (IQR), min	57 (39–87)	59 (40–90)	7.5
Arrived off-hours	115 (47.7)	18 762 (47.2)	1
NIHSS at presentation, median (IQR)	13 (7–20)	11 (6–18)	20.1
Preadmission medication, n (%)			
Antiplatelet	195 (87.8)	19 913 (53.6)	81.1
Anticoagulant	19 (8.6)	3064 (8.3)	1.2
Antihypertensive	192 (94.6)	25 873 (76.5)	53.1
Cholesterol reducer	178 (73.9)	18 666 (47.2)	56.7
Diabetic medications	59 (30.1)	6575 (19.9)	23.6
Vital signs			
Heart rate, median (IQR), bpm	76 (67–91)	78 (68–90)	2.6
sBP, median (IQR), mm Hg	144 (127–170)	157 (140–177)	34.4
dBP, median (IQR), mm Hg	74 (64–89)	81 (70–93)	27.2
Hospital characteristics			
Bed size, median (IQR), n	395 (275–545)	377 (258–585)	2.7
Academic center, n (%)	185 (78.1)	30 372 (77.5)	1.4
Primary stroke center, n (%)	53 (22.0)	9147 (23.0)	2.5
Rural hospital, n (%)	13 (5.4)	1231 (3.1)	11.5
Annual IV rtPA cases, median (IQR)	25.8 (16.2–37.3)	26.0 (15.9–38.6)	1.7

dBP indicates diastolic blood pressure; EMS, emergency medical services; IQR, interquartile range; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; rtPA, recombinant tissue-type plasminogen activator; sBP, systolic blood pressure.

instead of "antiplatelet therapy" along with the same variables as those in the main model.

As an exploratory analysis, among patients with a diagnosis of AIS who did not receive rtPA, we compared in-hospital clinical outcomes of those who had recent MI versus those had no history of MI. This analysis was adjusted for the same covariates as for the main analysis.

All statistical analyses were performed by the Duke Clinical Research Institute using SAS software version 9.4 (SAS Institute, Inc., Cary, NC). All *P*-values are 2-sided, and $P<0.05$ was considered statistically significant and 95% CI was reported.

Results

After the exclusion criteria was applied, a total of 40 396 patients presenting with AIS who were treated with rtPA at any of 1522 GWTG-Stroke hospitals (mean age [standard deviation] 81.0 [8.1] years; 58.0% women) (Figure 1). Of these, 241 had a recent MI within 3 months before AIS, of which 19.5% were STEMI, and 39 727 had no history of MI within 1 year to AIS. The distribution of a history of MI by the type of MI and the timeframe from the onset of MI to AIS is shown in Table S3. Patients with a recent MI were more likely to have atrial fibrillation, dyslipidemia, diabetes mellitus, and heart failure than those without, and the severity of AIS at admission, as measured by National Institutes of Health Stroke Scale, was greater in patients with a recent MI than those without (median 13 [interquartile range: 7–20] versus median 11 [6–18]) (Table 1).

Among AIS patients with a recent MI who arrived within the 3.5 hour time window, 130 were otherwise eligible but did not receive rtPA. When compared with those treated with rtPA, patients not receiving rtPA were more likely to arrive later, be on oral anticoagulants before AIS, have less severe AIS, and be treated in less experienced institutes for rtPA use (Table S4).

History of Recent MI and Outcome Measures

The unadjusted rates of in-hospital mortality and any serious rtPA-related complications were 17.4% and 13.5% for those with a recent MI, and 9.0% and 9.4% for those without, respectively. Hemopericardium was observed in 1 (0.4%) patient with recent MI. After risk adjustment, recent MI was associated with a significant increased risk of mortality (adjusted odds ratio [OR] 1.60, 95% CI [1.10–2.33], $P=0.014$). While numerically higher, there were no statistically significant differences in any serious rtPA-related complications (adjusted OR 1.28, 95% CI [0.88–1.86], $P=0.193$) (Table 2). To account for the potential association of dual antiplatelet therapy with bleeding complications, sensitivity analyses in patients who admitted after October 2012 (N=22 947) were performed and were consistent with the main findings (Table S5).

Subgroup Analysis by the Type of MI

Regardless of the type of MI, the unadjusted rates of in-hospital mortality and any serious rtPA-related complications

Table 2. Clinical Outcomes in rtPA Treated Patients With a Recent MI Versus rtPA Treated Patients Without History of MI

	Recent MI Within 3 Mo	No History of MI in the Past Year		
	n=241	n=39 727	Adjusted OR (95% CI)	*P* Value
In-hospital outcomes				
In-hospital mortality	42 (17.4%)	3561 (9.0%)	1.60 (1.10–2.33)	0.014
In-hospital death or discharge to hospice	69 (28.6%)	6997 (17.6%)	1.50 (1.07–2.11)	0.020
Able to ambulate independently at discharge	45 (28.0%)	11 268 (38.1%)	0.74 (0.53–1.05)	0.094
Discharge home	51 (21.2%)	12 512 (31.5%)	0.70 (0.49–1.02)	0.063
Modified Rankin Scale 0 to 2*	11 (11.8%)	4132 (25.9%)	0.47 (0.24–0.90)	0.023
rtPA-related complication				
Symptomatic intracranial hemorrhage†	19 (8.0%)	1958 (5.1%)	1.43 (0.89–2.31)	0.142
Life-threatening systemic hemorrhage†	4 (1.7%)	460 (1.2%)	1.13 (0.41–3.10)	0.817
Any serious complication related to rtPA†‡	32 (13.5%)	3627 (9.4%)	1.28 (0.88–1.86)	0.193

MI indicates myocardial infarction; OR, odds ratio; rtPA, recombinant tissue-type plasminogen activator.
*Modified Rankin Scale was missing for 11 181 patients (41.1%).
†Complications of rtPA was missing for 1157 patients (2.9%).
‡Any serious rtPA complication was a composite measure of symptomatic intracranial hemorrhage within 36 hours, life-threatening or serious systemic hemorrhage, or other serious complications. Other serious complications were those that required additional medical interventions or prolonged length of stay. Serious complications included those that were unexpected or out of proportion to the patient's expected course and that were documented as complications of reperfusion therapy.

were numerically higher in patients with a recent MI than those without. After risk adjustment, recent STEMI was associated with higher risk of in-hospital mortality and rtPA complications, whereas the difference was not statistically significant in those with recent NSTEMI (Table 3).

Association Between the Timing of a History of MI and Outcome Measures

There was a time-dependent relationship between the timing of a history of MI and the increased risk of adverse clinical outcomes. After the adjustment, patients with a history of MI within 3 months had adjusted ORs of >1 for in-hospital mortality (no history of MI as a reference), whereas those with a history of MI beyond 3 months had adjusted ORs of <1, although none of them reached statistical significance (Figure 2). Other end points demonstrated the similar findings; the risks of adverse events increased, as the timeframe from the onset of MI to the indexed AIS got shorter, especially <3 months.

History of Recent MI and Outcome Among Those With a Diagnosis of AIS Who Did Not Receive rtPA

Among 484 394 AIS patients who did not receive rtPA, 3359 (0.7%) had a history of recent MI within 3 months (Figure 1). After risk adjustment, recent MI was associated with a significant increased risk of in-hospital mortality and poor outcomes in terms of death or discharge to hospice, discharge home, ambulatory status, and modified Rankin Scale (Table 4).

Discussion

To our knowledge, this study is the first report from a large observational registry evaluating the association between a history of recent MI and clinical outcome in patients treated with rtPA for AIS. Of >40 000 AIS patients treated with rtPA, 0.6% of patients had a history of recent MI within 3 months before AIS. Recent MI within 3 months was associated with the increased odds of mortality and functional disability compared with no history of MI. However, the association became insignificant, if the timeframe from the onset of MI to the indexed AIS was >3 months. In addition, those with recent MI who were not treated with rtPA also had an increased risk of worse outcome in a similar magnitude than those without MI and not treated with rtPA. Furthermore, the increased risk of mortality in a history of recent MI compared with no history of MI was more prominent in patients with STEMI than those with NSTEMI.

The guideline recommendations for rtPA in AIS patients with a history of recent MI have evolved over time. A recent MI within 3 months was listed in a relative contraindication in the 2013 AHA/ASA guideline, while it is considered as reasonable or maybe reasonable with Class IIa or Class IIb recommendation in the 2018 AHA/ASA guideline.[2,3] This

Table 3. Clinical Outcomes by the Type of MI

	No History of MI in the Past Year	Recent STEMI Within 3 Mo	Adjusted OR (95% CI)	*P* Value	Recent NSTEMI Within 3 Mo	Adjusted OR (95% CI)	*P* Value
	n=39 727	n=47			n=194		
In-hospital outcomes							
In-hospital mortality	3561 (9.0%)	13 (27.7%)	2.58 (1.25–5.33)	0.011	29 (15.0%)	1.39 (0.90–2.15)	0.137
In-hospital death or discharge to hospice	6997 (17.6%)	20 (42.6%)	2.65 (1.31–5.35)	0.007	49 (25.3%)	1.27 (0.86–1.88)	0.229
Able to ambulate Independently at discharge	11 268 (38.1%)	4 (16.7%)	0.43 (0.13–1.46)	0.175	41 (29.9%)	0.80 (0.56–1.14)	0.219
Discharge home	12 512 (31.5%)	9 (19.2%)	0.77 (0.32–1.85)	0.559	42 (21.7%)	0.70 (0.48–1.03)	0.068
Modified Rankin Scale 0 to 2*	4132 (25.9%)	0 (0%)			11 (14.5%)	0.58 (0.31–1.10)	0.098
rtPA-related complication							
Symptomatic intracranial hemorrhage†	1958 (5.1%)	6 (12.8%)	2.36 (1.00–5.59)	0.05	13 (6.8%)	1.22 (0.69–2.16)	0.498
Life-threatening systemic hemorrhage†	460 (1.2%)	1 (2.1%)	1.37 (0.19–9.85)	0.757	3 (1.6%)	1.07 (0.34–3.44)	0.905
Any serious complication related to rtPA†‡	3627 (9.4%)	10 (21.3%)	2.14 (1.04–4.41)	0.039	22 (11.6%)	1.09 (0.70–1.69)	0.716

MI indicates myocardial infarction; STEMI, ST-segment–elevation myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction, OR, odds ratio; rtPA, recombinant tissue-type plasminogen activator.

*Modified Rankin Scale was missing for 11 124 patients (41.1%).

†Complications of rtPA was missing for 1153 patients (2.9%).

‡Any serious rtPA complication was a composite measure of symptomatic intracranial hemorrhage within 36 hours, life-threatening or serious systemic hemorrhage, or other serious complications. Other serious complications were those that required additional medical interventions or prolonged length of stay. Serious complications included those that were unexpected or out of proportion to the patient's expected course and that were documented as complications of reperfusion therapy.

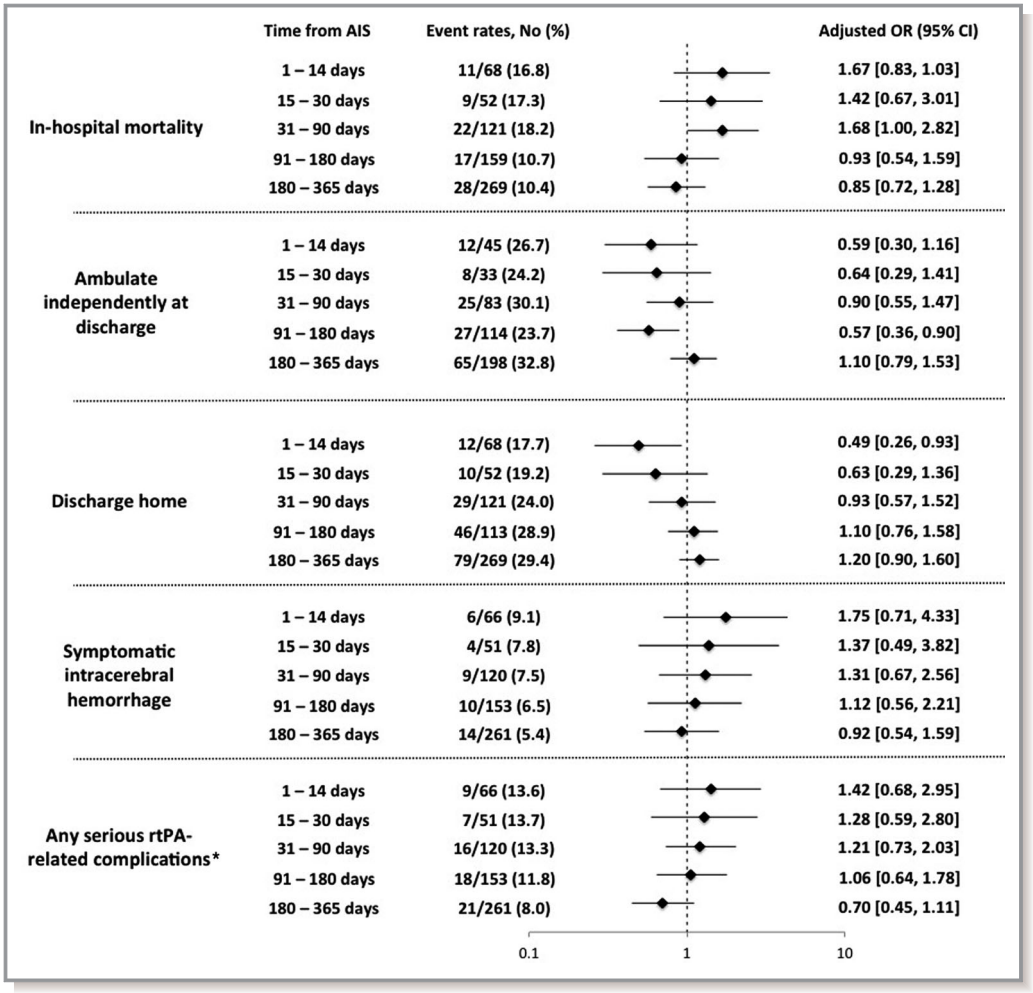

Figure 2. Association between the timing of a history of MI and outcome. AIS indicates acute ischemic stroke; MI, myocardial infarction; OR, odds ratio; rtPA, recombinant tissue-type plasminogen activator. *Complications of rtPA were missing for 1157 patients (2.9%).

inconsistency is mainly because of a lack of evidence beyond case reports or case series.[5–7] While the total number of cases is relatively small, our report is the first of its kind from large observational registry including a total of 241 patients treated with rtPA who had a history of recent MI. Our study indicated that a history of recent MI within 3 months was associated with increased risk of mortality and functional disability, and its prognostic impact might vary according to the type and timing of the recent MI. Given the similar magnitude of the adjusted odds ratio in those who did not receive rtPA to those who received rtPA, the association between a recent history of MI and worse outcomes was consistent regardless of rtPA use, suggesting the higher risk of worse outcome may be mainly driven by MI itself. That being said, our analysis was not designed to evaluate the efficacy or clinical effectiveness of the treatment. Functional outcome such as modified Rankin Scale at 90 days are not available in the registry.

Beyond bleeding complications, the main concerns about giving rtPA to patients with a history of recent MI are (1) the potential for thrombolysis-induced myocardial hemorrhage predisposing to myocardial wall rupture, (2) post-myocardial infarction pericarditis that may become hemopericardium, and (3) possible ventricular thrombi that could embolize because of thrombolysis.[1] Thrombolytic agents activate plasminogen to plasmin, which stimulate the breakdown of collagen, increasing the risk of hemorrhagic complications such as cardiac rupture.[14] Since rtPA for treating AIS became commercially available in the United States in 2006, there have been at least 3 published reports describing 5 elderly women with recent MI developing hemopericardium after receiving stroke thrombolytic therapy.[5–7] While it was likely underreported because of use of *ICD-9* diagnosis, we only observed 1 case of hemopericardium and/or cardiac tamponade in patients with recent MI who were treated with rtPA. The widespread use of percutaneous revascularization

Table 4. Clinical Outcomes in Patients Not Treated With rtPA Who Had a Recent MI Versus Not

	Recent MI Within 3 Mo	No History of MI in the Past Year		
	n=3359	n=476 193	Adjusted OR (95% CI)	*P* Value
In-hospital outcomes				
In-hospital mortality	307 (9.1%)	22 106 (4.6%)	1.52 (1.34–1.73)	<0.001
In-hospital death or discharge to hospice	675 (20.1%)	53 430 (11.2%)	1.66 (1.49–1.85)	<0.001
Able to ambulate independently at discharge	869 (36.1%)	156 760 (43.5%)	0.86 (0.79–0.95)	0.003
Discharge home	1036 (30.8%)	187 005 (39.3%)	0.81 (0.74–0.88)	<0.001
Modified Rankin Scale 0 to 2*	215 (20.1%)	42 056 (29.6%)	0.72 (0.60–0.88)	0.001

AIS indicates acute ischemic stroke; MI, myocardial infarction; OR, odds ratio; rtPA, recombinant tissue-type plasminogen activator.
*Modified Rankin Scale was missing for 146 098 out of 479 552 patients (50.5%).

for patients with STEMI has reduced the incidence of cardiac rupture[15] and ventricular thrombi,[16] but it is well-known that STEMI, especially with left anterior myocardium involvement, is an important factor related to these complications,[17–19] resulting in the downgraded recommendation of rtPA for patients with recent left anterior myocardium-involved STEMI (Class IIb). The favorable recommendation (Class IIa) for patients with a recent history of NSTEMI is based on the idea that they may be at lower risk of rtPA-related complications than those with STEMI, but there were no solid data to estimate risks or guide treatment in this subset of patients. In our analysis, the rates of mortality and rtPA-related complications in patients with a history of recent NSTEMI were not significantly higher than that in patients without a history of MI, suggesting that the current Class IIa recommendation of giving rtPA in this specific population may be reasonable.

There is no prior study evaluating whether 3 months interval after the onset of MI is an appropriate time window to give rtPA safely for treating AIS. Our study demonstrated that a history of MI in the past 3 months was associated with increased odds of in-hospital death, but the mortality in patients experienced MI during the time window between 3 months and 1 year before AIS was not different from that in patients with no history of MI within the past year. This finding may provide evidence for the current time interval of 3 months. From the pathological aspect, in general, fibrosis and scarring process is completed around 8 weeks after the onset of MI, which also provides the rationale for the timeframe of 3 months.[20]

The higher mortality in patients with recent MI may not be related to bleeding risk, despite their higher usage of dual antiplatelet therapy. In our main analysis, the rates of rtPA-related complications, including intracranial and life-threatening hemorrhage, were not statistically significant different between those with recent MI and those with no history of MI. Further adjustment for antiplatelet therapy only slightly attenuated the mortality association and the rtPA-related complications remained non-significant (Table S5). In addition, even among AIS patients who did not receive rtPA, recent MI showed the similar magnitude of adjusted OR for mortality (Table 4), suggesting the excess risk of worse outcomes might be driven by recent MI itself rather than rtPA treatment. One potential mechanism could be the different etiology of AIS. In patients with a diagnosis of acute MI treated with PCI, the incidence of left ventricular thrombus was up to 15% in the first 3 months after the onset of acute MI, resulting in thromboembolism.[20] Another explanation could be that recent MI causes reduced systolic function owing to cardiac remodeling, resulting in increased risks of heart failure and death.[21,22] In addition, stroke is known to affect cardiac function[23]; therefore, patients with recent MI are prone to cardiac decompensation, which may increase a risk of death.

Limitations

This study has several limitations. First, despite the use of the largest stroke registry in the United States, statistical power might be insufficient in patients receiving rtPA for AIS with a history of recent MI. In other words, it may be hard to evaluate the true risks of in-hospital mortality and rtPA-related complications, given the small sample size. Second, although we used a large number of characteristics to adjust for potential confounding, residual and/or unmeasured confounding may exist. Third, the data are obtained from hospitals participating in the GWTG-Stroke program and may not be able to be extrapolated to patients treated in hospitals outside the registry. However, given the fact that the registry covers about three-fourths of the United States population, the study population of this investigation is potentially representative of AIS patients in the United States. Fourth, we stratified patients according to the type of a recent MI, but the size of infarcted area was not available for risk adjustment. Fifth, rtPA was used only for highly selected subset in patients with

a recent MI, which may have skewed the results. Patients treated with rtPA were more likely to have more severe AIS than those who were otherwise eligible but not treated with rtPA (Table S4); therefore, this selection bias may have overestimated risks in patients with a recent MI. Sixth, we were unable to evaluate the benefits and risks of rtPA versus no rtPA in patients with recent MI because 90-day modified Rankin Scale and other post-discharge functional outcomes are not collected in the registry. However, the benefit of rtPA versus no rtPA has already been demonstrated in pivotal clinical trials such as the NINDS (National Institute of Neurological Disorders and Stroke) and ECASS (European Cooperative Acute Stroke Study) III,[24,25] albeit patients with recent MI were excluded from the trials. Importantly, we are able to demonstrate the safety and to what degree history of recent MI alters risk of mortality and rtPA-related complications in patients treated with IV rtPA in acute ischemic stroke.

Conclusions

Among older patients receiving rtPA for AIS, a recent history of MI in the past 3 months was associated with higher in-hospital mortality compared with no history of MI in ischemic stroke patients treated with rtPA and the association was more prominent in patients with STEMI than those with NSTEMI. Such an association was not significant, if the timeframe from the onset of MI to the indexed AIS was >3 months. Despite the increasing risk, further studies are needed to evaluate the benefit of rtPA, the only approved medical therapy, in AIS patients with recent MI.

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Supplemental Material

Table S1. Definition of Recent MI.

	International Classification of Disease 9th revision (ICD-9) diagnosis or procedure code
Variable	
Myocardial Infarction*	410.x1
STEMI	410.01, 410.11, 410.21, 410.31, 410.41, 410.51, 410.61, 410.81, 410.91
STEMI involving LAM	410.01 or 410.11
STEMI not involving LAM	410.21, 410.31, 410.41, 410.51, 410.61, 410.81, 410.91
NSTEMI	410.71
PCI†	0066, 3601, 3602, 3603, 3605, 3606, 3607, 3609
CABG†	3610, 3611, 3612, 3613, 3614, 3615, 3616, 3617, 3619
Clinical endpoint	
Hemopericardium‡	423.0
Tamponade‡	423.3

STEMI, ST-elevation myocardial infarction; LAM, left anterior myocardium; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting

* Primary diagnosis code; † either primary or secondary diagnosis code; ‡ secondary diagnosis code

Table S2. List of covariates.

Demographics: age, sex, and race/ethnicity (non-Hispanic black, Hispanic, Asian, and others vs. white)

Enrollment year

Medical history: atrial fibrillation/flutter, prior stroke, previous transient ischemic attack, coronary artery disease, carotid stenosis, diabetes, peripheral vascular disease, hypertension, smoker, dyslipidemia, heart failure, prior percutaneous coronary intervention within the past 1 year, and prior coronary artery bypass grafting within the past 1 year)

Arrival and admission information: emergency medical services arrival and arrived off-hours (vs. regular hours)

National Institutes of Health Stroke Scale (NIHSS) score

Medications at admission: antiplatelet, anticoagulant, antihypertensive, lipid-lowering, and diabetic agents

Vital signs and laboratory data: systolic blood pressure, blood glucose, and international normalized ratio, serum creatinine and body mass index

Hospital characteristics: region, rural vs. urban, teaching hospital, number of beds, certified primary stroke center, annual ischemic stroke volume, annual intravenous rtPA volume

Table S3. Distribution of a history of MI by the type of MI and the timing from the index AIS.

Time from the indexed AIS	All MI	STEMI	NSTEMI
	N	N	N
Within 3 months (Recent MI)	241	47	194
Between 1 - 14 days	68	15	53
Between 15 - 30 days	52	11	41
Between 31 - 90 days	121	21	100
Between 91 - 180 days	159	33	126
Between 181 - 365 days	269	47	222

MI, myocardial infarction; AIS, acute ischemic stroke; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction

Table S4. Baseline characteristics in AIS patients with recent MI treated with rtPA vs. otherwise eligible patients but not treated with rtPA.

Characteristics	Patients treated with rtPA (N=241)	Patients not treated with rtPA (N=130)	Absolute standardized difference (%)
Age, median (IQR), y	82 (75-88)	82 (76-87)	2.4
Women, No. (%)	140 (58.1)	78 (60.0)	3.9
Race, No. (%)			31.0
Non-Hispanic white	189 (78.4)	116 (89.2)	
Non-Hispanic black	26 (10.8)	8 (6.2)	
Hispanic	11 (4.6)	2 (1.5)	
Asian	7 (2.9)	1 (0.8)	
Other	8 (3.3)	3 (2.3)	
Medical History, No. (%)			
AF or atrial flutter	98 (40.8)	56 (44.1)	6.6
Previous stroke	44 (18.3)	42 (33.1)	34.2
Previous transient ischemic attack	22 (9.2)	11 (8.7)	1.8
Carotid stenosis	11 (4.6)	5 (3.9)	3.2
Diabetes mellitus	87 (36.3)	47 (37.0)	1.6
Peripheral vascular disease	21 (8.8)	9 (7.1)	6.2
Hypertension	199 (82.9)	99 (78.0)	12.5
Smoker	25 (10.4)	8 (6.3)	14.9
Dyslipidemia	129 (53.8)	71 (55.9)	4.3
Heart failure	58 (24.2)	33 (26.0)	4.2
Arrival and admission information, No. (%)			
Onset to arrival time, median (IQR), minutes	57 (39-87)	141 (88-180)	32.2
Arrived off-hours	115 (47.7)	65 (50.0)	4.6
NIHSS at presentation, median (IQR)	13 (7-20)	8 (3-14)	48.9
Preadmission medication, No. (%)			
Antiplatelet	195 (87.8)	96 (81.4)	18.0
Anticoagulant	19 (8.6)	29 (24.4)	43.5
Antihypertensive	192 (94.6)	98 (93.3)	5.2
Cholesterol reducer	178 (73.9)	100 (77.5)	8.5
Diabetic medications	59 (30.1)	28 (27.7)	5.3
Vital signs			
Heart rate, median (IQR), bpm	76 (67-91)	79 (65-88)	12.3
sBP, median (IQR), mmHg	144 (127-170)	143 (123-164)	11.7
dBP, median (IQR), mmHg	74 (64-89)	77 (63-87)	1.7
Hospital Characteristics			
Bed size, median (IQR), No.	395 (275-545)	316 (199-487)	32.6
Academic center, No. (%)	185 (78.1)	87 (69.1)	20.5

Primary Stroke Center, No. (%)	53 (22.0)	28 (21.5)	1.1
Rural hospital, No. (%)	13 (5.4)	12 (9.3)	14.9
Annual IV rtPA cases, median (IQR)	25.8 (16.2-37.3)	15.6 (9.4-23.8)	56.7

rtPA, recombinant tissue plasminogen activator; MI, myocardial infarction; IQR, interquartile range; EMS, emergency medical services; sBP, systolic blood pressure; dPB, diastolic blood pressure

Table S5. Sensitivity analysis with further adjustment of antiplatelet therapy after October 2012.

	Recent MI within 3 months N=125	No history of MI in the past 1 year N=22822	Adjusted OR (95% CI)	P
In-hospital outcomes				
In-hospital mortality	18 (14.4%)	1862 (8.2%)	1.48 (0.86, 2.57)	0.160
In-hospital death or discharge to hospice	31 (24.8%)	3886 (17.0%)	1.33 (0.82, 2.17)	0.252
Able to ambulate Independently at discharge	28 (29.2%)	7366 (41.7%)	0.64 (0.42, 0.99)	0.045
Discharge home	26 (20.8%)	7674 (33.6%)	0.63 (0.39, 1.03)	0.064
Modified Rankin scale 0-2*	10 (13.3%)	3713 (26.6%)	0.51 (0.25, 1.06)	0.071
rtPA related complication				
Symptomatic intracranial hemorrhage†	11 (8.9%)	1011 (4.6%)	1.77 (0.94, 3.34)	0.079
Any serious complication related to rtPA†	14 (11.4%)	1908 (8.7%)	1.14 (0.66, 1.99)	0.631

MI, myocardial infarction; OR, odds ratio; rtPA, recombinant tissue plasminogen activator

* Modified Rankin scale was missing for 8889 patients (38.7%)

† Complications of rtPA was missing for 964 patients (4.2%)