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Effect of Prior Stroke on the Use of Evidence-Based Therapies and In-Hospital Outcomes in Patients With Myocardial Infarction (from the NCDR ACTION GWTG Registry)

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Abstract

Patients with previous stroke are at high-risk for myocardial infarction (MI). Concern regarding increased risk of bleeding or recurrent stroke in this patient population might alter therapeutic decisions. Data were collected from 281 hospitals in the United States in the NCDR ACTION Registry. Patients with ST-segment elevation MI (STEMI; n = 15,997) or non-STEMI (NSTEMI; n = 25,514) entered into the registry from January 1, 2007 through December 31, 2007 were included. We assessed use of evidence-based medications and procedures in patients with and without previous stroke. Risk-adjusted odds ratio of death, major bleeding not related to coronary artery bypass grafting, and a composite outcome (major adverse cardiac events [MACEs], i.e., death/MI/stroke/cardiogenic shock/congestive heart failure) were calculated using logistic regression. Previous stroke was reported in 5.1% of patients with STEMI and 9.3% of those with NSTEMI. Of patients with STEMI eligible for reperfusion therapy, those with previous stroke were less likely to receive reperfusion therapy compared to patients without previous stroke. Patients with previous stroke had longer door-to-needle and door-to-balloon times. Of patients with STEMI and NSTEMI, those with previous stroke were less likely to receive evidence-based therapies. Death, MACEs, and major bleeding were more common with previous stroke. When adjusted for baseline risk, patients with previous stroke were at increased risk of death (only those with STEMI) and MACEs but not bleeding. In conclusion, patients with STEMI and previous stroke are at increased risk for death and patients with STEMI and NSTEMI are at increased risk of MACE. Despite this, previous stroke patients are less likely to receive guideline-based MI therapies.

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The purpose of this analysis was to characterize in-hospital treatment and outcomes related to previous stroke in a large community-based sample of patients with myocardial infarction (MI). We hypothesized that patients with a history of stroke would have worse outcomes, more bleeding, and would be less likely to receive procedures and medications known to be beneficial for patients with MI.

Methods

Data for this study were obtained from the National Cardiovascular Data Registry (NCDR) Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Registry, a nationally representative, quality improvement registry of ST-segment elevation MI (STEMI) and non-STEMI (NSTEMI). Data were derived from records of patients presenting from January 1, 2007 through December 31, 2007 at 195 participating hospitals within 24 hours of onset of symptoms and a primary diagnosis of MI. Exclusion criteria included patients admitted into a nontertiary ACTION hospital, patients with cardiogenic shock on presentation, and patients for whom information on previous stroke was missing. Trained data collectors extracted data from medical records to a Web-based case record without direct patient contact.

Patients presenting with STEMI were analyzed separately from those with NSTEMI. Previous stroke was determined by a patient's medical record and defined as any confirmed neurologic deficit of abrupt onset caused by a disturbance in cerebral blood supply that did not resolve within 24 hours. A listing of specific data fields and their definitions is available (http://www.ncdr.com/WebNCDR/ACTION/Elements.aspx).

Primary outcomes of interest were in-hospital death, death or stroke, death/MI/stroke, and major adverse cardiac events (MACEs; death/MI/stroke/cardiogenic shock/congestive heart failure [CHF]), and major bleeding unrelated to coronary artery bypass grafting (CABG). Major bleeding was defined as an absolute hematocrit decrease ≥12%, intracranial hemorrhage, retroperitoneal hemorrhage, or transfusion (with baseline hematocrit ≥28% or baseline hematocrit <28% and witnessed bleeding event). We analyzed use of in-hospital procedures (thrombolysis and primary percutaneous coronary intervention [PCI] for patients presenting with STEMI or PCI within 48 hours for patients with NSTEMI). Furthermore, we determined the rate of use for known cardioprotective medications acutely in hospital and at discharge. For all analyses, the denominator consisted of eligible patients without a contraindication documented. Contraindications for receiving fibrinolytic therapy included stroke within 3 months or previous hemorrhagic stroke.

Baseline characteristics, treatment profiles, procedure use, and clinical outcomes were compared by the presence or absence of a history of stroke. Continuous variables are presented as medians with interquartile ranges and categorical variables are expressed as percentages. Univariate analysis was done using Wilcoxon rank-sum test for continuous variables and Pearson chi square test for categorical variables.

In examining the association between previous stroke and outcome, multivariable logistic regression was used to estimate effects of previous stroke. The generalized estimating equation[1] method with exchangeable working correlation structure was used to account for within-hospital clustering because patients at the same hospital are more likely to have similar responses compared to patients in other hospitals (i.e., within-center correlation for response). The method produces estimates similar to those from ordinary logistic regression, but estimated variances of estimates are adjusted for the correlation of outcomes within each hospital. Variables adjusted in the model are gender, race, body mass index, age, history of hypertension, diabetes mellitus, peripheral artery disease, current or recent smoking,

dyslipidemia, previous MI, previous PCI, previous CABG, previous CHF, current need for dialysis, heart rate, systolic blood pressure on presentation, and sign of CHF at presentation.

Subgroup analysis was done using patients with STEMI who underwent primary PCI. Odds ratios were calculated using the same method described earlier. Variables adjusted in these models are gender, race, and age.

Adjusted associations are displayed as odds ratios (95% confidence intervals). A p value <0.05 was considered statistically significant for all tests. No adjustments were made for multiple comparisons because all analyses were exploratory in nature. All statistical analyses were performed by the Duke Clinical Research Institute using SAS 9.2 (SAS Institute, Cary, North Carolina).

Results

Of a total population of 50,517, 7,522 were excluded because they were transferred into an ACTION hospital after initial care was received, 1,043 were excluded because of cardiogenic shock on admission, and 441 were excluded because of absence of information on previous stroke. Of the 41,511 patients included in the study, 25,514 presented with NSTEMI and 15,997 presented with STEMI. Of patients with NSTEMI, 9.3% (n = 2,365) had previous stroke compared to 5.1% of patients (n = 814) presenting with STEMI. Patients with previous stroke were a decade older, more likely to be non-Caucasian, and more likely to be women (Table 1). As expected, patients with previous stroke also had higher rates of hypertension, diabetes mellitus, and peripheral vascular disease (Table 1). Such patients were more likely to have previously manifested coronary artery disease as evidenced by previous MIs or previous revascularization procedures. On arrival patients with a history of stroke were more likely to be tachycardic, hypotensive, or to have CHF (Table 1).

Patients with previous stroke were less likely to receive cardioprotective medications within 24 hours of presentation (Table 2). Of patients presenting with NSTEMI, those with stroke were less likely to receive aspirin, clopidogrel, and anticoagulants (Table 2). Similarly, aspirin, clopidogrel, and statins were used less frequently in patients with previous stroke presenting with STEMI (Table 2). Most patients received cardioprotective medications on discharge (Table 3) regardless of previous stroke status. In patients with NSTEMI and STEMI, aspirin and β blockers were prescribed at similar rates but patients with previous stroke were less likely to receive clopidogrel and statins but more likely to be prescribed warfarin (Table 3).

Patients with previous stroke presenting with STEMI were less likely to receive thrombolytics or primary PCI (Table 4). The odds ratio for receiving any reperfusion therapy was significantly lower for patients with stroke after adjusting for baseline and presenting characteristics (odds ratio 0.76, 95% confidence interval 0.59 to 0.97). Furthermore, patients with a history of stroke had significantly longer door-to-needle times (Table 4) and door-to-balloon times (Table 4). After adjusting for differences in the 2 patient populations, those with history of stroke were less likely to have a door-to-balloon time <90 minutes (odds ratio 0.76, 0.58 to 0.98, p = 0.037). Of patients presenting with NSTEMI, those with previous stroke were less likely to undergo diagnostic catheterization (Table 4) and were less likely to have PCI overall (Table 4) even after adjusting for baseline and presenting characteristics (odds ratio 0.77, 0.70 to 0.86, p <0.001).

Patients with history of stroke had significantly worse outcomes during hospitalization. Compared to those without stroke, mortality was higher for patients with stroke presenting with STEMI or NSTEMI (Table 5). After adjusting for demographic and clinical differences between the 2 groups, patients with previous stroke presenting with STEMI had higher rates

of death, death/stroke, death/MI/stroke, and MACEs. In contrast, patients with previous stroke presenting with NSTEMI were not at increased odds of death but remained at increased risk of death/stroke, death/MI/stroke, and MACEs (Table 5).

Patients with previous stroke also had greater prevalence of major bleeding that was not significantly different after adjusting for baseline demographic and clinical characteristics when presenting with STEMI or NSTEMI (Table 5). Hemorrhagic stroke was infrequent, during the follow up period. In patients with NSTEMI, those with prior stroke had such events more frequently than those without (0.30 vs 0.06%, unadjusted p value 0.0035). In patients with STEMI, a higher rate was not observed, (0.12 vs 0.20%, unadjusted p value 0.24). Patients with previous stroke presenting with STEMI were more likely to receive excess doses of glycoprotein IIb/IIIa inhibitors (Table 2), whereas those presenting with NSTEMI more frequently received excess doses of glycoprotein IIb/IIIa inhibitors and unfractionated heparin (Table 2).

To address the possibility that some of these differences may have been related to unreported contraindications to fibrinolytic therapy (such as recent stroke or hemorrhagic stroke for reperfusion), we assessed patients with STEMI who underwent PCI during the index hospitalization. The disparity in outcomes persisted in patients with and without previous stroke even in this group of patients with STEMI (Table 6). Compared to those without stroke, mortality, death/MI/stroke, and MACE rates were higher for patients with stroke presenting with STEMI and undergoing primary PCI. After adjusting for demographic differences between the 2 groups, patients with previous stroke presenting with STEMI were at increased odds of death (Table 6), the combined end point of death/MI/stroke, and MACEs. Consistent with the entire cohort, in the subset of patients undergoing PCI, patients with previous stroke were not at a statistically significant increased risk of major bleeding unrelated to CABG.

Discussion

Similar to previous studies we observed that 5% to 10% of patients presenting with MI have a history of stroke. Prevalence of previous stroke is, however, more common in this registry than many clinical trials.[2,3] Previous stroke is more common in patients with NSTEMI than with STEMI,[4] likely reflecting the advanced age and increased frequency of atherosclerosis risk factors in this population. Differences in demographic and clinical characteristics discussed earlier especially age, gender, and history of diabetes may explain some differences seen in medication/procedural use and outcomes between patients with and those without history of stroke.[5–7]

As a consequence of their increased risk of poor outcome, it may be reasonable to predict that patients with a history of stroke might benefit from application of evidence-based interventions to a larger degree than patients without a history of stroke.[6] However, such patients were less likely to receive evidence-based cardioprotective medications. Given the advanced age and multiple co-morbidities of the previous stroke patient population, an increased rate of contraindications is expected. Nonetheless, the lower rate of use of such medications as aspirin and statins, which are unlikely to have a poor risk-to-reward ratio, suggests that there may be underutilization of proved therapies.

There are data to suggest that interventions that may be beneficial in the general population may not be helpful for patients with a history of stroke.[8,9] In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction (TRITON-TIMI-38) study, patients with a history of stroke or transient ischemic attack derived less benefit and were at increased risk of bleeding

from more intensive antiplatelet therapy with prasugrel.[2] The Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischemic Attacks or Ischemic Stroke (MATCH) study revealed that dual antiplatelet therapy imparts a clear increased risk of life-threatening or major bleeding without added benefit in preventing vascular events for patients with recent stroke.[10] The equivalent risk of major bleeding after adjustment for baseline characteristics is of interest and may suggest that providers are attempting to balance the risks and benefits of aggressive treatment across multiple clinical features, not just stroke. A more aggressive strategy may not necessarily improve outcomes if it significantly increases risk of complications.

Patients with history of stroke were less likely to undergo thrombolysis or coronary intervention. Even in those patients who receive such therapies, patients with history of stroke also had increased door-to-balloon and door-to-drug times. This delay may result in part from the difficulty in the diagnosis of acute coronary syndrome in a population with advanced age and possibly cognitive impairments.[5] In addition, the increased time to definitive treatment may be in part because of more complex risk–benefit analysis required for patients with previous stroke, which may include use of more frequent consultation or additional imaging.

Underutilization of reperfusion therapy has been documented in the Global Registry of Acute Coronary Events (GRACE) registry for certain clinical subgroups of patients including older patients, women, and patients with diabetes, previous heart failure, or previous MI,[11,12] despite evidence that such patients would benefit from reperfusion.[13] However, even after adjusting for several these demographic and clinical factors, we found that patients with a history of stroke were still less likely to receive reperfusion therapy. Thrombolytics are contraindicated in patients with recent stroke or any previous hemorrhagic stroke. Our data do not identify time of stroke or differentiate between hemorrhagic and ischemic stroke. Therefore, although our analysis is limited to patients without a stated contraindication to a particular procedure or medications, thrombolytics may have been appropriately withheld from patients with known but unrecorded contraindication. However, the lower rate of primary PCI is unlikely to be accounted for by unrecognized contraindications because even patients with recent stroke would usually be candidates for primary PCI. In addition, the finding that patients with stroke who underwent PCI had worse outcomes than patients without stroke who underwent PCI suggests that the varying use of reperfusion did not wholly account for differences in outcomes.

Patients with a stroke history showed significantly worse outcomes during hospitalization. Although the increased risk of death (for patients presenting with STEMI), death/stroke, death/MI/stroke, and MACEs (for patients with STEMI and those with NSTEMI) remained statistically significant after adjustment for multiple baseline characteristics, patients with a stroke history were not at increased risk of major bleeding complications after similar adjustments. A previous study has shown that patients with nonrecent history of stroke presenting with acute coronary syndrome experienced better outcomes when treated with thrombolytics.[14] However, previous stroke is also a predictor of cerebrovascular complications during PCIs.[15] An important area of further study would be determining if the lower rate of reperfusion therapy significantly contributes to the poor outcomes in patients with previous stroke presenting with MI.

The ACTION registry includes all patients presenting with MI at the participating institutions. The strengths of this study include the prospective design and a large contemporary population base that is likely to accurately reflect the current management of patients presenting with MI in the United States. Inclusion of all patients presenting with MI

bypasses a principal limitation of clinical trials, namely exclusion of high-risk patients and those who have contraindications to trial enrollment criteria.

This study is limited by inherent biases of an observation study. Despite controlling for possible confounding demographic and clinical characteristics, residual confounding by unmeasured factors including atrial fibrillation remains possible. Despite standardized definitions, patients may have been misclassified. We included in our study only patients with a history of stroke; therefore patients with cerebrovascular disease (as manifested by transient ischemic attacks or documented carotid artery stenosis without stroke) were not included in the stroke patient population. Most importantly, our data cannot be used to infer causality or to conclude that more aggressive treatment would improve outcomes in patients with a history of stroke.

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Table 1

Baseline characteristics

Demographics and Medical History	STEMI			NSTEMI		
	Previous Stroke (n = 818)	No Previous Stroke (n = 15,179)	p Value	Previous Stroke (n = 2,365)	No Previous Stroke (n = 23,149)	p Value
Age (years)	72.0 (61.0–81.0)	60.0 (51.0–71.0)	<0.0001	75.0 (66.0–83.0)	66.0 (55.0–77.0)	<0.0001
Women	44.5%	29.2%	<0.0001	47.1%	37.7%	<0.0001
Body mass index (kg/m^2)	27.4 (23.9–31.3)	28.2 (25.1–32.0)	<0.0001	27.4 (23.8–31.6)	28.3 (24.9–32.7)	<0.0001
Ethnicity						
Caucasian	81.5%	85.2%	<0.0001	82.2%	84.2%	<0.0001
Black	11.4%	7.0%		11.3%	8.8%	
Asian	2.1%	1.3%		1.7%	1.4%	
Hispanic	2.9%	3.5%		2.5%	3.3%	
Other	1.8%	2.7%		1.8%	1.9%	
Hypertension	84.0%	59.1%	<0.0001	86.8%	71.5%	<0.0001
Diabetes mellitus	38.1%	21.3%	<0.0001	47.7%	32.1%	<0.0001
Peripheral arterial disease	15.4%	5.2%	<0.0001	24.2%	10.1%	<0.0001
Current/recent smoker	29.6%	43.5%	<0.0001	19.4%	30.5%	<0.0001
Previous myocardial infarction	33.0%	17.8%	<0.0001	40.0%	25.9%	<0.0001
Previous coronary intervention	24.3%	18.6%	<0.0001	25.8%	23.2%	0.005
Previous coronary artery bypass grafting	12.7%	7.0%	<0.0001	26.9%	17.7%	<0.0001
Previous congestive heart failure	16.3%	4.5%	<0.0001	30.1%	13.8%	<0.0001
Home medications						
Aspirin	51.0%	33.8%	<0.0001	59.9%	47.2%	<0.0001
Clopidogrel	22.3%	8.7%	<0.0001	29.1%	14.9%	<0.0001
Warfarin	12.5%	2.7%	<0.0001	15.3%	5.7%	<0.0001
Presentation features						
Onset to arrival (hours)	3.1 (1.5–6.3)	2.9 (1.4–5.5)	0.0207	4.1 (1.7–10.0)	4.9 (1.9–11.5)	<0.0001
Heart failure on presentation	20.8%	8.6%	<0.0001	33.3%	18.8%	<0.0001
Heart rate (beats/min)	81.0 (66.0–88.0)	77.0 (65.0–92.0)	<0.0001	86.0 (72.0–103.0)	82.0 (70.0–97.0)	<0.0001
Systolic blood pressure (mm Hg)	136.0 (115.0–158.0)	138.0 (119.0–158.0)	0.1489	142.0 (121.0–166.0)	144.0 (124.0–164.0)	0.0283
Baseline laboratory values						
Creatinine clearance, Modification of Diet in Renal Disease (ml/min)	59.2	72.5	<0.0001	54.78	67.42	<0.0001
Hematocrit (%)	40.0	42.7	<0.0001	38.2	41.0	<0.0001

Values are presented as median (interquartile range) or percentage of patients.

Table 2

Medications received within 24 hours of presentation and medication overdose during hospitalization

	STEMI			NSTEMI		
	Previous Stroke	**No Previous Stroke**	**p Value**	**Previous Stroke**	**No Previous Stroke**	**p Value**
Aspirin	97.3%	98.5%	0.0420	95.0%	97.0%	<0.0001
Clopidogrel	81.2%	88.0%	<0.0001	57.1%	61.6%	0.0002
β Blocker	95.2%	96.6%	0.0561	92.5%	93.6%	0.0741
Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker	54.7%	58.4%	0.0744	55.1%	51.0%	0.0002
Statin	62.4%	68.9%	0.0001	57.2%	59.2%	0.0994
Glycoprotein Iib/IIIa inhibitor	60.9%	76.2%	<0.0001	32.0%	46.8%	<0.0001
Unfractionated heparin	72.6%	79.2%	<0.0001	54.2%	56.9%	0.0139
Low-molecular-weight heparin	19.9%	16.0%	0.0035	40.7%	40.6%	0.8937
Direct thrombin inhibitor	12.2%	10.9%	0.1444	9.7%	11.9%	0.0051
Medication overdose						
Unfractionated heparin	—	—	—	30.3%	27.2	0.0231
Low-molecular-weight heparin	—	—	—	13.8%	13.5%	0.8271
Glycoprotein IIb/IIIa inhibitor	24.1%	8.2%	<0.0001	20.6%	9.7%	<0.0001

Table 3

Discharge medications

	STEMI			NSTEMI		
	Previous Stroke	**No Previous Stroke**	**p Value**	**Previous Stroke**	**No Previous Stroke**	**p Value**
Aspirin	98.3%	98.7%	0.5749	96.5%	97.3%	0.0258
Clopidogrel	85.9%	90.7%	0.0001	70.1%	74.5%	<0.0001
Warfarin	15.2%	7.2%	<0.0001	15.0%	8.3%	<0.0001
β Blocker	96.2%	97.1%	0.1729	95.3%	95.5%	0.4334
Angiotensin-eonverting enzyme inhibitor or angiotensin II receptor blocker	81.3%	86.7%	0.0645	74.3%	74.3%	0.8410
Statin	87.1%	91.7%	<0.0001	82.8%	86.6%	<0.0001

Table 4

In-hospital procedures

	Previous Stroke	No Previous Stroke	p Value
ST-segment elevation myocardial infarction			
Reperfusion (any method)	87.3%	94.9%	<0.0001
Thrombolytic therapy	10.0%	16.3%	0.0023
Door to drug ≤30 minutes	22.8%	37.3%	0.0179
Arrival to thrombolytic (minutes)	47.5 (30.0–72.0)	35.00 (23.0–55.0)	0.0042
Primary percutaneous coronary intervention	82.0%	85.7%	0.0480
Door to balloon ≤90 minutes	57.9%	68.6%	<0.0001
Arrival to primary percutaneous coronary intervention (minutes)	81.0 (64.0–110.0)	75.0 (58.0–97.0)	0.0001
Coronary artery bypass grafting	9.6%	8.2%	0.1846
Non–ST-segment elevation myocardial infarction			
Catheterization	83.3%	92.8%	<0.0001
Percutaneous coronary intervention	42.2%	56.9%	<0.0001
Coronary artery bypass grafting	13.3%	14.1%	0.3289

Values are presented as median (interquartile range) or percentage of patients.

Table 5

In-hospital outcomes

	Previous Stroke	No Previous Stroke	Adjusted OR (95% CI)
ST-segment elevation myocardial infarction			
Death	10.8%	4.1%	1.40 (1.07–1.85)
Death/stroke	12.5%	4.5%	1.53 (1.19–1.96)
Death/myocardial infarction/stroke	13.7%	5.3%	1.49 (1.18–1.89)
Major adverse cardiac events	25.6%	11.9%	1.43 (1.17–1.75)
Noncoronary artery bypass graft major bleeding	14.6%	10.5%	0.99 (0.80–1.22)
Non–ST-segment elevation myocardial infarction			
Death	6.1%	3.4%	1.11 (0.92–1.38)
Death/stroke	7.3%	3.3%	1.21 (1.01–1.46)
Death/myocardial infarction/stroke	8.3%	4.7%	1.21 (1.01–1.44)
Major adverse cardiac events	18.6%	11.1%	1.17 (1.04–1.30)
Noncoronary artery bypass graft major bleeding	13.9%	9.1%	1.10 (0.94–1.30)

CI = confidence interval; OR = odds ratio.

Table 6

In-hospital outcomes in patients with ST-segment elevation myocardial infarction who underwent primary percutaneous coronary intervention

	Previous Stroke	No Previous Stroke	p Value (unadjusted)	Adjusted OR (95 CI)*
Death	7.6%	2.6%	<0.001	2.00 (1.38–2.90)
Death/myocardial infarction/stroke	10.2%	3.6%	<0.001	2.01 (1.44–2.81)
Major adverse cardiac events	22.22%	9.9%	<0.001	1.84 (1.42–2.40)
Noncoronary artery bypass graft major bleeding	15.6%	10.3%	<0.001	1.21 (0.94–1.55)

Abbreviations as in Table 5.

*Adjusted for male gender, Caucasian race, and age.