Risk Factors for In-hospital Nonhemorrhagic Stroke in Patients With Acute Myocardial Infarction Treated With Thrombolysis : Results From GUSTO-I

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Risk Factors for In-hospital Nonhemorrhagic Stroke in Patients With Acute Myocardial Infarction Treated With Thrombolysis

Results From GUSTO-I

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Background—Nonhemorrhagic stroke occurs in 0.1% to 1.3% of patients with acute myocardial infarction who are treated with thrombolysis, with substantial associated mortality and morbidity. Little is known about the risk factors for its occurrence.

Methods and Results—We studied the 247 patients with nonhemorrhagic stroke who were randomly assigned to one of four thrombolytic regimens within 6 hours of symptom onset in the GUSTO-I trial. We assessed the univariable and multivariable baseline risk factors for nonhemorrhagic stroke and created a scoring nomogram from the baseline multivariable modeling. We used time-dependent Cox modeling to determine multivariable in-hospital predictors of nonhemorrhagic stroke. Baseline and in-hospital predictors were then combined to determine the overall predictors of nonhemorrhagic stroke. Of the 247 patients, 42 (17%) died and another 98 (40%) were disabled by 30-day follow-up. Older age was the most important baseline clinical predictor of nonhemorrhagic stroke, followed by higher heart rate, history of stroke or transient ischemic attack, diabetes, previous angina, and history of hypertension. These factors remained statistically significant predictors in the combined model, along with worse Killip class, coronary angiography, bypass surgery, and atrial fibrillation/flutter.

Conclusions—Nonhemorrhagic stroke is a serious event in patients with acute myocardial infarction who are treated with thrombolytic, antithrombin, and antiplatelet therapy. We developed a simple nomogram that can predict the risk of nonhemorrhagic stroke on the basis of baseline clinical characteristics. Prophylactic anticoagulation may be an important treatment strategy for patients with high probability for nonhemorrhagic stroke, but further study is needed. **(*Circulation*. 1998;97:757-764.)**

Key Words: thrombolysis ■ myocardial infarction ■ stroke ■ cerebral infarction

Stroke is one of the most feared complications in patients with acute myocardial infarction. In the era before the routine use of thrombolytic therapy and anticoagulation, stroke was observed in 1.7% to 3.2% of patients.[1–5] Intracranial hemorrhage was exceedingly rare. In the thrombolytic era, the overall incidence of stroke in large clinical trials is lower, but the types of strokes have changed. Nonhemorrhagic stroke now occurs in 0.1% to 1.3% of patients, and intracranial hemorrhage occurs in 0.07% to 1.5% of patients.[6–12]

Recently, multivariable regression models have been developed to help identify patients at increased risk for intracranial hemorrhage after thrombolysis, including a model based on the GUSTO-I trial experience.[7–9,13–16] Less is known about the risk factors for nonhemorrhagic stroke in patients with acute myocardial infarction treated with thrombolytic therapy, although several investigators have reported clinical and echocardiographic factors associated with an increased risk for nonhemorrhagic stroke.[7,8,10–12,17–25]

We used prospectively collected information from the GUSTO-I trial for patients with and without nonhemorrhagic stroke to determine independent risk factors associated with in-hospital nonhemorrhagic stroke in patients with acute myocardial infarction treated with thrombolytic therapy.

Methods

Study Population

The study population was the 41 021 patients enrolled in the GUSTO-I trial.[26] In brief, patients presenting with acute myocardial

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Members of the GUSTO-I Stroke Committee are listed in the "Appendix."

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infarction within 6 hours of symptom onset were randomly assigned to one of four thrombolytic strategies: (1) 1.5 million U streptokinase IV over 1 hour and 12 500 heparin U SC BID; (2) 1.5 million U streptokinase IV over 1 hour and 5000 U heparin IV bolus followed by 1000 U/h; (3) alteplase in an accelerated regimen (15-mg IV bolus followed by 0.75 mg/kg over 30 minutes and then 0.5 mg/kg over the next hour) and 5000 U heparin IV bolus followed by 1000 U/h; or (4) both 1 million U streptokinase and 1.0 mg/kg alteplase IV over 1 hour and 5000 U heparin IV bolus followed by 1000 U/h. All patients received aspirin (160 to 325 mg) daily. The overall experience with stroke in the GUSTO-I has been previously reported.[9]

Definitions

Nonhemorrhagic Stroke

Nonhemorrhagic stroke was defined as an acute new neurological deficit resulting in death or lasting for >24 hours without hemorrhage on computed tomography or magnetic resonance imaging, as classified by a physician with supporting documentation from discharge summaries, progress notes, brain images, neurological/neurosurgical evaluation, or autopsy reports.

Sustained Hypotension

Sustained hypotension was defined as systolic blood pressure of <90 mm Hg for >1 hour despite fluid replacement.

Cardiogenic Shock

Cardiogenic shock was defined as systolic blood pressure of <90 mm Hg for ≥1 hour, not responsive to fluid replacement alone, thought to be secondary to cardiac dysfunction, and associated with signs of hypoperfusion (cool, clammy skin, oliguria, or altered sensorium or cardiac index of ≤2.2 $L \cdot min^{-1} \cdot /m^{-2}$). If the systolic blood pressure increased to >90 mm Hg as a result of positive inotropic agents alone within 1 hour, this was still classified as cardiogenic shock.

Congestive Heart Failure

Congestive heart failure was considered to be signs or symptoms of congestion (rales above the lung base, dyspnea, pulmonary edema on chest radiograph, or peripheral edema) or low cardiac output (weakness, fatigue) thought to be secondary to cardiac dysfunction.

Killip Class

Killip class I was defined as the absence of rales over the lung fields and the absence of S3 gallop. Class II included patients who had rales across ≤50% of the lung fields or the presence of an S3 gallop. Class III was defined as rales across >50% of the lung fields, and class IV was defined as pulmonary edema with hypoperfusion (cardiogenic shock).

Ejection Fraction

Ejection fraction was determined by the site investigator at the time of cardiac catheterization and, therefore, is available only for patients undergoing angiography.

Data Collection

The evaluation of patients with stroke and the collection of specific data about stroke treatment and clinical outcomes in the trial were prospectively planned. The protocol specified that all patients with a new focal neurological deficit undergo a complete evaluation including brain imaging. Patients with nonhemorrhagic stroke were identified from the responses to specific questions on the Case Report Form or from a two-page supplemental Stroke Details Form, which was completed for each patient with a suspected stroke. In addition, the study collected available supporting documents, such as physicians' notes, operative reports, discharge summaries, autopsy reports, and results of computed tomographic and magnetic resonance imaging studies.

Nonhemorrhagic Stroke Adjudication

A Stroke Review Committee (see "Appendix") was established to adjudicate and categorize all suspected strokes. For each suspected nonhemorrhagic stroke, the medical records and brain imaging studies were independently reviewed by two teams, each consisting of a cardiologist and neurologist. Each team was responsible for determining whether a nonhemorrhagic stroke had occurred. Disagreements were resolved by a third team.

Patient Functional Assessment

Functional status was determined for all patients with nonhemorrhagic stroke at hospital discharge or 30 days, whichever came first. Patients were classified as not disabled if they had no deficit (no sequelae) or minor deficits (functional status unchanged) and as disabled if they had moderate deficits (significant limitations of activity) or severe deficits (unable to live independently or work).[9]

Statistical Analysis

Continuous variables are shown as medians with 25th, and 75th percentiles; discrete variables are shown as frequencies and percentages. Cox proportional hazards modeling was used to determine the univariable predictors of nonhemorrhagic stroke and determine the multivariable baseline risk factors for nonhemorrhagic stroke. When examining the effect of interventions on nonhemorrhagic stroke, we considered that some patients may have had a nonhemorrhagic stroke before they could receive an intervention or may have had a planned intervention canceled. Crediting the nonintervention group with all of these early events would unfairly inflate the lack of association of the stroke and the intervention. As a result, we used time-dependent Cox modeling to determine multivariable in-hospital predictors of nonhemorrhagic stroke. The interventions included as time-dependent covariates were cardiac catheterization, percutaneous transluminal coronary angioplasty, coronary artery bypass graft surgery, and intra-aortic balloon counterpulsation. In-hospital congestive heart failure and cardiogenic shock were similarly treated as time-dependent covariates. A backward-elimination method was used to determine the significant predictors from the baseline and in-hospital analyses (elimination criterion, $P<.05$). Baseline and in-hospital predictors were then combined to determine the overall predictors of nonhemorrhagic stroke. Predictors in each analysis were tested using the likelihood ratio χ^2 test. Results are also presented as hazard ratios and 95% confidence intervals.

We created a scoring nomogram on the basis of coefficients from the baseline multivariable regression modeling. Each independent predictor was assigned a particular score according to its predictive value. The sum of the scores indicates the probability of a nonhemorrhagic stroke based on baseline predictors for individual patients (F. E. Harrell: Design S plus functions for biostatistical/epidemiological modeling, testing, estimation, validation, graphics, prediction, and typesetting by storing enhanced model design attributes in the fit. UNIX version available from statlib@lib.stat.cmu.edu; 1996).

Results

There were 247 patients with nonhemorrhagic stroke in the GUSTO-I population (0.6%), of whom 42 (17%) died. In all, 56.7% of patients with nonhemorrhagic stroke died or were disabled at the time of hospital discharge (Table 1).

The baseline clinical characteristics for the 246 patients with in-hospital nonhemorrhagic stroke (1 patient had a nonhemorrhagic stroke after hospital discharge and 30-day follow-up and is not included in the analyses) and the 40 688 patients without nonhemorrhagic stroke are shown in Table 2. Patients with nonhemorrhagic stroke were older and more often female and had a higher incidence of previous coronary disease, hypertension, and diabetes. They also tended to have a worse baseline Killip class and more often had atrial fibrillation/flutter and anterior infarcts at enrollment.

TABLE 1. Clinical Outcomes

Outcome	No. of Patients (%) (N=247)
Death	42 (17.0)
Severe deficit	39 (15.8)
Moderate deficit	59 (23.9)
Mild deficit	70 (28.3)
No deficit	23 (9.3)
Unknown	14 (5.7)

Patients with nonhemorrhagic stroke were more likely to have adverse in-hospital events and bypass surgery (Table 3). The univariable χ^2 values and hazard ratios for the baseline and in-hospital factors associated with in-hospital nonhemorrhagic stroke are shown in Tables 4 and 5.

Baseline Multivariable Predictors

Six baseline clinical and historical characteristics were significant independent predictors of in-hospital nonhemorrhagic stroke (Table 6). Age was the most important baseline clinical predictor. Higher heart rate, history of stroke or transient ischemic attack, diabetes, previous angina, and history of hypertension were the other statistically significant baseline predictors. Atrial fibrillation/flutter on the baseline ECG and Killip class at the time of enrollment were not statistically significant independent predictors of nonhemorrhagic stroke (χ^2=3.13, P=.08; and χ^2=5.23, P=.16, respectively). The predicted probability of nonhemorrhagic stroke based on baseline clinical and historical data can be calculated for individual patients with the nomogram shown in Fig. 1.

In-hospital Multivariable Predictors

Worse Killip class was the most potent predictor for nonhemorrhagic stroke, followed by atrial fibrillation/flutter and performance of coronary artery bypass surgery and cardiac catheterization (Table 7). In the analysis of in-hospital factors, patients with atrial fibrillation/flutter at baseline were compared with those who did not have atrial fibrillation/flutter at baseline and did not develop the arrhythmia during the hospital stay. In addition, patients who develop atrial fibrillation/flutter during hospitalization were compared with patients without atrial fibrillation at baseline or in-hospital. Patients developing atrial fibrillation/flutter after enrollment had a greater than twofold higher incidence of nonhemorrhagic stroke than patients who did not have atrial fibrillation/flutter at baseline or during hospitalization (hazard ratio, 2.08; 95% confidence interval, 1.52 to 2.86). Patients with atrial fibrillation/flutter at baseline also had a higher likelihood of nonhemorrhagic stroke than patients who never had atrial fibrillation/flutter during the hospital stay (hazard ratio, 2.44; 95% confidence interval, 1.43 to 4.16).

TABLE 2. Baseline Clinical Characteristics

	Nonhemorrhagic Stroke (n=246)	No Nonhemorrhagic Stroke (n=40 688)
Median age, y	69 (62, 75)	61 (52, 70)
Female, n (%)	77 (31.3)	10 227 (25.1)
Systolic blood pressure, mm Hg	130 (115, 148)	130 (112, 144)
Diastolic blood pressure, mm Hg	80 (69, 90)	80 (70, 90)
Killip class		
I	188 (76.4)	34 585 (85.4)
II	43 (17.5)	5073 (12.5)
III	10 (4.1)	537 (1.3)
IV	5 (2.0)	309 (0.8)
Heart rate, bpm	77 (64, 93)	74 (62, 86)
Anterior infarction, n (%)	109 (44.5)	15 825 (39.0)
Previous infarction, n (%)	67 (27.5)	6627 (16.3)
Height, cm	171 (165, 177)	172 (165, 178)
Time to treatment, h	3 (2, 4)	3 (2, 4)
History of smoking, n (%)	162 (66.9)	28 023 (69.5)
Current smoking, n (%)	76 (30.9)	17 416 (43.0)
Diabetes mellitus, n (%)	66 (26.9)	5935 (14.6)
Median weight, kg	76 (68, 85)	78 (70, 88)
Previous bypass surgery, n (%)	22 (8.9)	1757 (4.3)
Previous angioplasty, n (%)	11 (4.5)	1629 (4.0)
Previous angina, n (%)	128 (52.5)	14 903 (36.8)
History of hypertension, n (%)	131 (53.3)	15 398 (38.0)
Hyperlipidemia, n (%)	78 (32.4)	13 497 (34.3)
Atrial fibrillation/flutter, n (%)	15 (6.3)	967 (2.5)

Values are given as median (25th and 75th percentiles) or frequency (percentages).

TABLE 3. In-hospital Coronary Events and Procedures

	Nonhemorrhagic Stroke (n=246)	No Nonhemorrhagic Stroke (n=40 688)
Ejection fraction, %	45 (35, 53)*	51 (43, 60)†
Sustained hypotension, n (%)	52 (21.2)	4824 (11.9)
Worse Killip class, n (%)		
I	75 (30.7)	26 618 (65.9)
II	104 (42.6)	10 177 (25.2)
III	35 (14.3)	1774 (4.4)
IV	30 (12.3)	1854 (4.6)
Atrial fibrillation/flutter, n (%)‡	59 (24.0)	3214 (7.9)
Cardiac catheterization, n (%)		
Total	136 (55.5)	22 169 (54.6)
Before stroke onset§	109 (44.7)	
Angioplasty, n (%)		
Total	38 (15.6)	8701 (21.5)
Before stroke onset§	27 (11.1)	
Bypass surgery, n (%)		
Total	48 (19.5)	3433 (8.5)
Before stroke onset§	40 (16.3)	
Intra-aortic balloon counterpulsation, n (%)		
Total	21 (8.6)	1458 (3.6)
Before stroke onset§	20 (8.2)	
Congestive heart failure, n (%)		
Total	95 (38.6)	6535 (16.1)
Before stroke onset§	71 (29.7)	
Cardiogenic shock, n (%)		
Total	29 (11.8)	2412 (5.9)
Before stroke onset§	25 (10.2)	

*n=94, †n=15 956, ‡after enrollment, §occurring on same day as or before stroke onset.

Combined Multivariable Predictors

All 10 independent predictors from the baseline and in-hospital multivariable analyses except history of hypertension remained statistically significant, independent predictors of nonhemorrhagic stroke in the combined analysis (Table 8). Worse Killip class and older age were the two most important predictors, followed by performance of cardiac catheterization and bypass surgery. A second combined analysis included only the 15 220 (37.1%) patients undergoing angiography who had a documented ejection fraction (Table 9). Age, performance of cardiac catheterization, and bypass surgery were significant and potent independent predictors of nonhemorrhagic stroke. Lower ejection fraction, higher heart rate, diabetes, and worse Killip class had borderline statistical significance as predictors of nonhemorrhagic stroke in the combined model of patients with known ejection fraction. Atrial fibrillation/flutter, previous angina, previous hypertension, and stroke or transient ischemic attack were no longer statistically significant independent predictors.

Discussion

Stroke is a well-documented event in patients with acute myocardial infarction. The routine use of anticoagulant and thrombolytic therapies has reduced the occurrence of nonhemorrhagic stroke but increased the risk of intracranial hemorrhage. Nonhemorrhagic stroke, however, is associated with significant morbidity and mortality.[9] We identified six easily determined baseline patient clinical and historical factors (older age, higher heart rate, history of stroke or transient ischemic attack, diabetes, previous angina, and history of hypertension) that independently predict nonhemorrhagic stroke in patients with acute myocardial infarction treated with thrombolysis, heparin, and aspirin. In addition, four common in-hospital characteristics (worse Killip class, atrial fibrillation/flutter, bypass surgery, and cardiac catheterization) are independently associated with nonhemorrhagic stroke.

Several investigators have reported that patients with increased age,[7,8,10] anterior myocardial infarction,[8,10,11] and worse Killip class[7,10] are at increased risk for nonhemorrhagic stroke. In our analysis, anterior infarct was not a univariable predictor of nonhemorrhagic stroke, although there was a trend toward a higher incidence of anterior infarction in patients with nonhemorrhagic stroke than in those without stroke (44.5% versus 39.0%; $P=.13$). In addition, isolated apical infarct and combined anteroapical infarct also were not statistically significant univariable predictors of nonhemorrhagic stroke ($\chi^2=0.75$, $P=.39$; and $\chi^2=3.23$, $P=.072$, respectively).

TABLE 4. Univariable Baseline Predictors of Nonhemorrhagic Stroke

Patient Characteristic	χ^2	P	Hazard Ratio
Older age (per 10 y)	81.6	<.001	1.7
History of stroke or transient ischemic attack	26.6	<.001	4.3
Diabetes	25.1	<.001	2.2
History of hypertension	21.8	<.001	1.8
Previous angina	20.3	<.001	1.8
Previous infarction	19.6	<.001	2.0
Higher heart rate (per 10 bpm)	19.1	<.001	1.2
Killip class	19.1	<.001	
II vs I			1.5
III vs I			3.4
IV vs I			3.7
Current smoker	13.6	<.001	0.6
Atrial fibrillation/flutter (at enrollment)	9.7	.002	2.6
Previous bypass surgery	8.8	.003	2.1
Higher weight (per 10 kg)	6.1	.01	0.9
Female gender	4.0	.04	1.3
Infarct location (anterior vs other)	2.3	.13	1.2
Systolic blood pressure (per 10 mm Hg)	0.8	.36	1.0
Diastolic blood pressure (per 10 mm Hg)	0.3	.58	1.0
Time to treatment (per 10 minutes)	0.02	.88	0.9

From 28% to 40% of patients with anterior infarction and 0% to 1.5% of patients with inferior infarction have a left ventricular thrombus, according to small echocardiographic studies performed primarily in the era before the routine use of thrombolysis and aggressive anticoagulation.[17–20,23–25] The incidence of systemic embolization was 0% to 33% in patients with documented thrombus, lower in patients receiving anticoagulation, and exceedingly rare in patients with no observed thrombus.[17–25] Echocardiographic features associated with an increased risk of embolization include older age,[19] larger thrombus size,[19] thrombus mobility,[20–23] and pendulousness of the clot.[19–23] Because echocardiography was not mandated by the GUSTO-I protocol, the incidence of left ventricular thrombus in the GUSTO-I population is unknown. In addition, data were not collected on warfarin therapy, which may have influenced these findings. Further study is required to clarify the relationship among location of infarction, incidence of thrombus, impact of anticoagulation, and risk of nonhemorrhagic stroke.

TABLE 5. Univariable In-hospital Predictors of Nonhemorrhagic Stroke

Patient Characteristic	χ^2	P	Hazard Ratio
Killip class	122.3	<.001	
II vs I			3.3
III vs I			5.8
IV vs I			6.5
Atrial fibrillation/flutter	59.4	<.001	
At baseline vs none			3.2
Developed in-hospital vs none			3.4
Congestive heart failure	44.4	<.001	2.8
Bypass surgery	42.2	<.001	4.2
Cardiac catheterization	22.7	<.001	2.0
Sustained hypotension	18.3	<.001	2.1
Lower ejection fraction (per 10%)	17.7	<.001	1.4
Cardiogenic shock	16.3	<.001	2.6
Intra-aortic balloon pump counterpulsation	15.1	<.001	2.9
Angioplasty	0.02	.88	1.0

TABLE 6. Multivariable Baseline Predictors of Nonhemorrhagic Stroke

	χ^{2*}	P	Hazard Ratio (95% CI)
Older age (per 10 y)	60.9	<.001	1.60 (1.41-1.80)
Increased heart rate (per 10 bpm)	15.1	<.001	1.13 (1.07-1.21)
History of stroke or TIA	11.6	.001	2.55 (1.58-4.10)
Diabetes	10.9	.001	1.66 (1.24-2.21)
Previous angina	10.6	.001	1.53 (1.18-1.97)
History of hypertension	6.2	.013	1.39 (1.07-1.80)

TIA indicates transient ischemic attack.
*Model χ^2=147.8; 39 942 patients with 242 events included in modeling.

The incidence of stroke associated with the procedures and events that this study found to correlate with increased risk of nonhemorrhagic stroke—specifically, atrial fibrillation/flutter, cardiac catheterization, and coronary artery bypass surgery—has been well established by previous investigators. The risk of stroke in patients with nonvalvular atrial fibrillation is ≈5% per year, or a fivefold to sevenfold higher incidence compared with patients without the arrhythmia.[27,28] Several large registries have reported that stroke occurs in <0.01% of patients undergoing cardiac catheterization.[29,30] The incidence of stroke in patients undergoing coronary artery bypass surgery has been reported to occur in 0.4% to 5.4% of patients.[31–33] One of the largest most comprehensive multicenter series reported nonfatal stroke in 2.6% of patients after coronary artery bypass surgery.[34]

A unique aspect of this study was the incorporation of in-hospital events in the analysis, to examine not only baseline clinical characteristics but also in-hospital factors common in patients after acute myocardial infarction—such as atrial arrhythmias, coronary interventions, and bypass surgery—that may predict nonhemorrhagic stroke. The finding of the Fibrinolytic Therapy Trialists' Cooperative Group that 62% of the nonhemorrhagic strokes in patients treated with thrombolysis occurred >24 hours after enrollment emphasizes the importance of this analysis.[6] In addition, 60% of nonhemorrhagic strokes in the GUSTO-I trial occurred >48 hours after randomization (Fig. 2).[9]

Study Limitations

Our study has several limitations. An important aspect of the study was the time-dependent analysis of clinical events and procedures in relation to the onset of stroke symptoms. The time of onset for atrial fibrillation or worse Killip class was not known, so only the day of occurrence was used in the time-dependent analysis and compared with the day of stroke

1. Find Points For Each Risk Factor

Age, *y*		Heart rate, per min		Diabetes		Hypertension	
Age	Points	Rate	Points		Points		Points
20	10	0	0	Yes	11	Yes	7
30	20	20	5	No	0	No	0
40	30	40	11				
50	40	60	16				
60	50	80	21				
70	60	100	27				
80	70	120	32				
90	80	140	38	Previous CVD		Previous angina	
100	90	160	43		Points		Points
		180	48	Yes	20	Yes	9
		200	54	No	0	No	0
		220	59				
		240	64				
		260	70				

2. Sum Points For All Risk Factors

_____ + _____ + _____ + _____ + _____ + _____ = _____

Age | Heart rate | Diabetes | Hypertension | Prev. CVD | Prev. Angina | Point Total

3. Look Up Risk Corresponding to Point Total

Points	Risk	Points	Risk	Points	Risk
67	0.5%	116	5%	153	25%
82	1%	132	10%	158	30%
97	2%	141	15%	162	35%
105	3%	148	20%		

Figure 1. Nomogram for the prediction of nonhemorrhagic stroke after thrombolysis for acute myocardial infarction. CVD indicates cerebrovascular disease. In 1, find the value most closely matching the patient's risk factors and circle the corresponding point assignment. In 2, sum the points for all predictive factors. In 3, determine the probability of in-hospital nonhemorrhagic stroke. For example, a 71-year-old nondiabetic patient with previous CVD, a history of hypertension, and previous angina who presents with a heart rate of 121 bpm would have a total score of 60+32+0+20+7+9=128. This score corresponds to a predicted probability of in-hospital nonhemorrhagic stroke of 10%.

symptom onset. Dates and times for cardiac interventions and other in-hospital events were available.

Because information was not collected about the use of warfarin therapy, the impact of anticoagulation in this patient population cannot be assessed. In addition, information was not collected about postdischarge events (other than mortality and procedures that may be associated with nonhemorrhagic stroke). However, only one nonhemorrhagic stroke occurred after hospital discharge and before 30-day follow-up. A proportion of the GUSTO-I population may have had a cerebrovascular event that was pathophysiologically related to the index myocardial infarction >30 days after enrollment.

In the in-hospital model, patients who presented with or developed atrial fibrillation/flutter (compared with those without the arrhythmia) were at higher risk for nonhemorrhagic stroke. However, in the baseline multivariable model, atrial fibrillation/flutter at enrollment did not independently predict nonhemorrhagic stroke. Duration of atrial fibrillation/flutter before enrollment, which we were unable to assess, may have been a contributing factor.

TABLE 7. Multivariable In-hospital Predictors of Nonhemorrhagic Stroke

	χ^{2*}	*P*	Hazard Ratio (95% CI)
Killip class	84.1	<.001	
II vs I			2.95 (2.17-4.01)
III vs I			4.50 (2.94-6.89)
IV vs I			5.01 (3.20-7.84)
Atrial fibrillation/flutter	24.4	<.001	
At baseline vs none			2.44 (1.43-4.16)
Developed in-hospital vs none			2.08 (1.52-2.86)
Bypass surgery	13.0	<.001	2.25 (1.47-3.42)
Cardiac catheterization	8.4	.004	1.60 (1.17-2.19)

*Model χ^2=180.6; 38 417 patients with 235 events.

The GUSTO-I stroke dataset, which included 247 nonhemorrhagic stroke patients, is the largest single-trial experience to date. The systematic review of all suspected strokes by the Stroke Review Committee and the availability of computed axial tomographic, magnetic resonance imaging, or autopsy data for 93% of stroke patients resulted in definitive classification of stroke subtypes; thus, the number of "unknowns" was small. The mechanism of nonhemorrhagic stroke was not determined, and some strokes may not have been related to cardiac events or procedures. Despite the relatively large numbers, the sample size still limited the ability to perform more extensive multivariable regression modeling.

TABLE 8. Combined (Baseline and In-hospital) Multivariable Predictors of Nonhemorrhagic Stroke

	χ^{2*}	*P*	Hazard Ratio (95% CI)
Killip class	46.8	<.001	
II vs I			2.34 (1.71-3.19)
III vs I			3.01 (1.94-4.66)
IV vs I			3.51 (2.22-5.53)
Older age (per 10 y)	35.1	<.001	1.47 (1.29-1.68)
Cardiac catheterization	14.5	<.001	1.87 (1.37-2.57)
Bypass surgery	13.4	<.001	2.28 (1.50-3.48)
Atrial fibrillation/flutter	11.8	.003	
At baseline vs none			1.81 (1.05-3.11)
Developed in-hospital vs none			1.68 (1.22-2.32)
Previous angina	10.0	.002	1.52 (1.17-1.97)
History of stroke or TIA	9.3	.002	2.28 (1.42-3.68)
Diabetes	7.9	.005	1.55 (1.15-2.08)
Higher heart rate (per 10 bpm)	6.1	.014	1.09 (1.02-1.16)
History of hypertension	3.8	.0503	1.30 (1.00-1.69)

TIA indicates transient ischemic attack.

*Model χ^2=267.7; 38 256 patients with 233 events included in modeling.

TABLE 9. Combined (Baseline and In-hospital) Multivariable Predictors of Nonhemorrhagic Stroke Including Ejection Fraction

	χ^{2*}	P	Hazard Ratio (95% CI)
Older age (per 10 y)	28.3	<.001	1.79 (1.43-2.25)
Cardiac catheterization	10.6	.001	2.54 (1.43-4.50)
Bypass surgery	8.3	.004	2.31 (1.33-4.00)
Lower ejection fraction (per 10%)	4.0	.046	1.18 (1.00-1.39)
Higher heart rate (per 10 bpm)	3.9	.047	1.12 (1.01-1.24)
Worse Killip class	7.8	.051	
II vs I			1.54 (0.94-2.54)
III vs I			1.95 (0.96-3.95)
IV vs I			2.64 (1.28-5.43)
Diabetes	3.8	.052	1.61 (1.01-2.56)
Previous angina	3.7	.053	1.51 (0.99-2.29)
Atrial fibrillation/flutter	4.2	.13	
At baseline vs none			2.07 (0.87-4.89)
Developed in-hospital vs none			1.52 (0.91-2.54)
History of hypertension	2.1	.15	1.36 (0.89-2.08)
History of stroke or TIA	0.9	.34	1.61 (0.64-4.00)

TIA indicates transient ischemic attack.
*Model χ^2=128.7; 15 220 patients with 91 events included in modeling.

Finally, these results are only applicable to the patients with acute myocardial infarction treated with thrombolytic therapy and should not be generalized to all patients with acute myocardial infarction.

Conclusions

Nonhemorrhagic stroke remains a serious event in patients with acute myocardial infarction treated with thrombolytic, antithrombin, and antiplatelet therapy and is associated with significant morbidity and mortality. Older age, higher heart rate, history of stroke or transient ischemic attack, diabetes, previous angina, and history of hypertension are independent clinical and historical predictors of nonhemorrhagic stroke; physicians can use these factors to determine the baseline probability of nonhemorrhagic stroke with a simple scoring nomogram (Fig 1). This information may enhance awareness of the potential for nonhemorrhagic stroke early after myocardial infarction. Beyond the baseline characteristics, adverse in-hospital cardiac events, such as worsening Killip class, atrial fibrillation/flutter, and performance of cardiac catheterization or bypass surgery also are potent, independent predictors of nonhemorrhagic stroke.

Patients with several risk factors or a high probability for nonhemorrhagic stroke may benefit from prophylactic anticoagulation, but further study is needed.

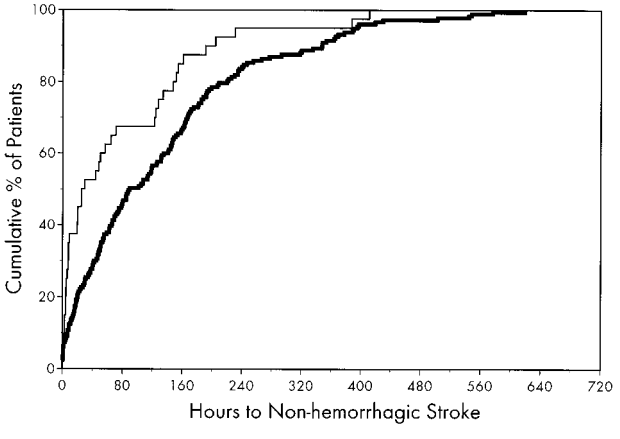

Figure 2. Cumulative frequency distribution of hours from enrollment to onset of nonhemorrhagic stroke in GUSTO-I. Nonfatal nonhemorrhagic stroke is indicated by the heavy line, and fatal nonhemorrhagic stroke is indicated by the light line.

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Appendix

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