# Stroke After Primary Percutaneous Coronary Intervention in Patients With ST-Segment Elevation Myocardial Infarction

## Timing, Characteristics, and Clinical Outcomes

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***Background***—Stroke is a rare but potentially devastating complication of acute myocardial infarction. Little is known about stroke timing, characteristics, and clinical outcomes in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention (PCI).

***Methods and Results***—We studied 5372 patients enrolled in the Assessment of Pexelizumab in Acute Myocardial Infarction (APEX-AMI) trial. We analyzed stroke incidence, type, timing, and association with the prespecified 90-day clinical outcomes. Cox proportional hazards modeling was performed to assess the relationship between stroke and outcomes, after adjusting baseline characteristics and analyzing stroke as a time-dependent covariate. Stroke occurred in 69 primary patients with PCI (1.3%). A third of strokes were ischemic (n=23; 33%), 12% (n=8) were hemorrhagic, and the remaining 55% (n=38) were of uncertain type. The median (25th, 75th percentile) time of stroke occurrence was 6 (3, 14) days. Overall, 43% of strokes occurred within 48 hours of PCI, and all hemorrhagic strokes occurred within 48 hours. Stroke was associated with an increased risk of 90-day death (unadjusted hazard ratio [HR], 8.0; 95% confidence interval [CI], 4.8–13.5), congestive heart failure (unadjusted HR, 3.2; 95% CI, 1.3–7.8), and 30-day hospital readmission (unadjusted HR, 3.2; 95% CI, 2.0–5.1). After adjustment, stroke was still strongly associated with 90-day death (adjusted HR, 5.6; 95% CI, 3.2–9.8) and the combination end point of death, congestive heart failure, or cardiogenic shock at 90 days (adjusted HR, 2.4; 95% CI, 1.2–4.7).

***Conclusions***—Stroke is an infrequent complication in the setting of ST-segment elevation myocardial infarction treated with primary PCI but is associated with increased morbidity and mortality. Studies to determine mechanisms that may be responsible for strokes that occur >48 hours from primary PCI are warranted.

***Clinical Trial Registration***—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00091637. (***Circ Cardiovasc Interv*. 2013;6:176-183.**)

**Key Words:** myocardial infarction ■ myocardial reperfusion ■ outcomes ■ primary percutaneous coronary intervention ■ stroke

Stroke is a rare procedural complication of primary percutaneous coronary intervention (PCI).[1,2] When stroke occurs, it may result in significant patient morbidity, prolonged hospitalizations, and high medical costs.[1,3,4] Most large studies evaluating the stroke risk associated with PCI have used registry data for all PCI indications, and few have evaluated stroke risk with PCI in the setting of acute coronary syndromes (ACS).[2,3,5,6] A paucity of information exists on the risk and types of stroke, its timing related to primary PCI, and the subsequent clinical outcomes after ST-segment elevation myocardial infarction (STEMI).

Using data from a large, contemporary, prospective, international randomized controlled trial, we investigated the risk of stroke in patients undergoing PCI for STEMI. The objectives of the study were to (1) evaluate the incidence of stroke in patients undergoing primary PCI for STEMI, (2) describe the timing and types of strokes, and (3) evaluate the association between an in-hospital stroke and prespecified and adjudicated 90-day outcomes.

## Methods

We analyzed data from 5372 of the 5745 patients enrolled in the Assessment of Pexelizumab in Acute Myocardial Infarction (APEX-AMI) trial database; 5 patients were excluded because of missing stroke data, and 368 patients who did not have primary PCI were excluded. The trial design and primary endpoints have been reported previously.[7,8] Briefly, APEX-AMI was an international, randomized, double-blind, placebo-controlled trial comparing the complement inhibitor pexelizumab with placebo in conjunction with primary PCI.

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## WHAT IS KNOWN

- Stroke is an infrequent but potentially devastating complication of ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention (PCI).
- In the ST-segment elevation myocardial infarction population treated with primary PCI, the incidence, type, and timing of stroke, as well as subsequent clinical outcomes, have been understudied.

## WHAT THE STUDY ADDS

- Data from the Assessment of Pexelizumab in Acute Myocardial Infarction (APEX-AMI) trial showed that stroke occurred in 1.3% of the patients treated with primary PCI, and stroke was associated with longer hospital stays, more hospital readmissions, and increased 90-day mortality.
- All hemorrhagic strokes occurred within 48 hours of primary PCI, whereas ischemic strokes tended to occur beyond 48 hours.
- Because most of the strokes occurred >48 hours after primary PCI, not all strokes after primary PCI seem to be procedure-related and, therefore, other mechanisms might be responsible for these later events.

Seventeen countries and 296 sites participated in the trial, and patients were enrolled between 2004 and 2006. The inclusion criteria were broad and included age ≥18 years, presentation for primary PCI within 6 hours of symptom onset, and an electrocardiogram (ECG) indicative of STEMI. Exclusion criteria were few and included prior fibrinolytic therapy, complement deficiency, active neisserial infection, isolated low risk inferior myocardial infarction (MI), pregnancy or breastfeeding, or other serious medical condition limiting survival or safety. Informed written consent was obtained from all subjects, and institutional review boards at all participating centers approved the APEX-AMI study protocol.

### Stroke Definition

Stroke was defined as a new focal neurological deficit with residual symptoms after >24 hours. Timing of stroke symptom onset after primary PCI was recorded, and the type of stroke was reported by investigators as ischemic, hemorrhagic, or uncertain. Investigators rated stroke severity as no residual deficit, mild, moderate, severe, or death.

### Clinical Outcomes

The primary study end point was all-cause mortality at 30 days. Prespecified secondary end points included the composite end point of death, cardiogenic shock, or congestive heart failure at 30 and 90 days. Postdischarge outcome information was obtained at 30 and 90 days by phone calls to patients, and if an event occurred, additional information was requested from the site investigator. Congestive heart failure and cardiogenic shock were adjudicated by a blinded clinical events committee. Other data that were collected included in-hospital atrial fibrillation, length of hospitalization, timing of stroke in relation to the index hospitalization, all hospital readmissions, recurrent ischemia, renal failure, and in-hospital mortality. All clinical outcomes were recorded, regardless of whether they occurred before or after stroke.

### Statistical Analysis

Descriptive statistics for baseline and procedural characteristics are presented for patients with and without stroke. Continuous variables are summarized as medians and 25th and 75th percentiles. Categorical variables are expressed as frequencies and percentages. Comparisons between the groups were done using the rank-sum nonparametric test for continuous variables and $\chi^2$ test for categorical. All $P$ values in Tables 1–3 are descriptive and should not be considered as hypothesis testing. Cumulative incidence plots for stroke were constructed using Kaplan–Meier methodology. Cox proportional hazards models were developed to test for associations between stroke and 90-day clinical outcomes. Because stroke was an event that could occur at any time after randomization, it was fit as a time-dependent covariate in these models. Only strokes that occurred after PCI were counted as events in the analysis. Results are expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). As reported previously, a multivariable Cox proportional hazards model was developed using data from the APEX-AMI trial.[9] This model was used to examine the relationship between stroke and death after adjusting for age, systolic blood pressure, Killip class, heart rate, creatinine, sum of ST-segment deviations, and anterior STEMI location. A similar model that was previously developed following the same methods was used to examine the relationship between stroke and the composite end point of death, congestive heart failure, or shock. The threshold for statistical significance was set at $\alpha<0.05$. Statistical analysis was performed using SAS version 8.2 or later (SAS Institute, Cary, NC).

## Results

### Baseline Characteristics

In the overall study population treated with primary PCI, strokes were reported in 69 patients (1.3%). Table 1 shows the baseline characteristics of patients with and without stroke. Patients experiencing a stroke were older and more likely to have a history of stroke or transient ischemic attack. Among the traditional vascular risk factors, diabetes mellitus, hypertension, and hyperlipidemia were more common in the stroke group. More than twice as many stroke patients had a history of atrial fibrillation (10% for stroke patients, 4% for patients without stroke), chronic obstructive pulmonary disease (13% versus 5%), and coronary artery bypass graft surgery (4% versus 2%). More than twice as many patients in the stroke group had documented in-hospital atrial fibrillation (16% versus 7%). Stroke patients also had a higher Killip class at baseline. Vital signs were similar at enrollment, and there was no difference in MI location based on ECG data.

Both patients with and without a stroke were receiving aspirin, and a similar percentage of patients were taking a statin drug (Table 2). More patients in the stroke group received hypoglycemic drugs (15% versus 8%). Fewer patients in the stroke group were taking nitrates compared with the nonstroke group. More stroke patients used calcium channel blockers (20% versus 9%) or were on antiarrhythmic drugs other than Digoxin (9% versus 2%). A similar percentage of patients in each group were taking an oral anticoagulant (3% for patients without stroke and 4% for stroke patients), but glycoprotein IIb/IIIa inhibitors were administered to 49% in the nonstroke group and 20% in the stroke group. Slightly more stroke patients received ticlopidine or clopidogrel (32% versus 26%).

**Table 1. Baseline Clinical Characteristics in Patients With and Without Stroke (n=5372)**

| Characteristics | No Stroke (n=5303) | Stroke (n=69) | *P* Value |
|---|---|---|---|
| Age,* y | 61 (52, 71) | 73 (61, 78) | <0.001 |
| Men, n, % | 4100 (77) | 50 (73) | 0.340 |
| White, n, % | 5028 (95) | 68 (99) | 0.163 |
| Weight,* kg | 80 (70, 91) | 75 (65, 85) | 0.020 |
| Height,* cm | 173 (166, 178) | 170 (165, 175) | 0.029 |
| Body mass index,* kg/m$^2$ | 27 (24, 30) | 26 (23, 30) | 0.148 |
| Current smoker, n, % | 1748 (33) | 25 (37) | 0.516 |
| History of hypertension, n, % | 2596 (49) | 40 (58) | 0.137 |
| Atrial fibrillation, n, % | 210 (4) | 7 (10) | 0.010 |
| TIA, n, % | 76 (1) | 2 (3) | 0.312 |
| Stroke, n, % | 182 (3) | 8 (12) | <0.001 |
| Ischemic stroke, n, % | 70 (1) | 2 (3) | 0.257 |
| Hemorrhagic stroke, n, % | 15 (0) | 1 (1) | … |
| Stroke of unknown type, n, % | 97 (2) | 5 (7) | 0.001 |
| CHF, n, % | 180 (3) | 3 (4) | 0.664 |
| COPD, n, % | 242 (5) | 9 (13) | 0.001 |
| Hyperlipidemia, n, % | 2004 (50) | 29 (54) | 0.544 |
| Diabetes mellitus, n, % | 814 (15) | 22 (32) | <0.001 |
| CAD, n, % | 834 (16) | 13 (19) | 0.481 |
| Chronic inflammatory condition, n, % | 93 (2) | 4 (6) | 0.012 |
| Current renal dialysis, n, % | 12 (0) | 0 (0) | … |
| Prior CABG, n, % | 98 (2) | 3 (4) | 0.129 |
| Prior MI, n, % | 614 (12) | 7 (10) | 0.711 |
| Killip class, n, % | | | 0.006 |
| I | 4763 (90) | 54 (79) | |
| II | 441 (8) | 10 (15) | |
| III | 50 (1) | 3 (4) | |
| IV | 47 (1) | 1 (2) | |
| Time from symptom onset to hospital arrival,* h | 2.2 (1.3, 3.3) | 2.2 (1.4, 3.3) | 0.575 |
| Time from symptom onset to randomization,* h | 2.8 (2.0, 3.9) | 3.3 (2.1, 4.1) | 0.157 |
| Creatinine clearance,* mL/min | 88 (80, 106) | 93 (82, 106) | 0.287 |
| Baseline CK,* U/L | 144 (90, 280) | 156 (97, 350) | 0.464 |
| Baseline CK-MB,* ng/mL | 5 (2, 15) | 4 (2, 11) | 0.920 |
| Baseline heart rate,* bpm | 75 (65, 86) | 72 (57, 88) | 0.268 |
| Systolic blood pressure,* mm Hg | 133 (117, 150) | 130 (115, 141) | 0.100 |
| Diastolic blood pressure,* mm Hg | 80 (70, 90) | 78 (69, 89) | 0.098 |
| MI location, n, % | | | |
| Anterior | 3049 (59) | 36 (53) | 0.336 |
| Inferior | 2143 (41) | 32 (47) | 0.336 |
| Other | 3662 (69) | 47 (68) | 0.865 |

CABG indicates coronary artery bypass graft surgery; CAD, coronary artery disease; CHF, congestive heart failure; CK, creatine kinase; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; and TIA, transient ischemic attack. *Median (25th, 75th percentile).

## Procedural Characteristics

Primary PCI procedural characteristics are shown in Table 3. In the stroke group, 66 patients received stents, and 4 patients (6%) underwent angioplasty only; a similar pattern was seen in the patients without stroke (5135 stents placed, 214 [4%] angioplasty only). Time to reperfusion was similar in both groups (median, 2.0 hours). In both groups, 7% of patients underwent repeat PCI (379 procedures in the nonstroke group, 5 in the stroke group), and in all cases a stroke occurred after the second PCI.

The number of stents deployed in each patient was similar in both groups, and distal protection devices were rarely used (1% of procedures in the nonstroke group, and none in the stroke patients). Cardiac surgery occurred in twice as many patients in the stroke group (4% versus 2% for patients without stroke), and intra-aortic balloon pumps were used more commonly (16% versus 7%). Patients with stroke were much more likely to require mechanical ventilation (17% versus 3%). Intra-aortic balloon pumps were used predominantly before stroke (82%), whereas cardiac surgery occurred mostly after stroke (67%). The timing of mechanical ventilation was not captured in this study.

## Stroke Characteristics and Timing

Patients experienced ischemic or hemorrhagic strokes in 33% (n=23) and 12% (n=8) of cases, respectively (Table 4). The type of stroke was uncertain in a large percentage of patients (55%; n=38). Twenty-nine percent of strokes were rated as moderate to severe, whereas severity was unknown in 44%. The median (25th, 75th percentile) time of stroke occurrence was 6 days (3, 14). Only 27% of all strokes occurred within 24 hours of PCI, and 43% occurred within 48 hours (Figure 1). Timing stroke from randomization or primary PCI yielded very similar results. However, 6 (75%) of the hemorrhagic strokes occurred within 24 hours of PCI and 100% within 48 hours. All hemorrhagic stroke patients were stented, and 7 of the 8 received heparin and ticlopidine/clopidogrel during the first 24 hours of their initial hospitalization. Glycoprotein IIb/IIIa inhibitors were given to 5 of 8 patients with hemorrhagic stroke.

Fifty-six percent of all strokes occurred during the index hospitalization, and most (75%) had occurred within 30 days (Figure 2).

## Clinical Outcomes

Compared with mortality in patients without stroke, mortality at 90 days in patients experiencing a stroke was substantially higher, rising from 14% at 30 days to 25% at 90 days. Three of the 8 patients (38%) with a hemorrhagic stroke died. The median (25th, 75th percentile) length of stay for patients who experienced an in-hospital stroke and survived was 10 days (7, 13), whereas it was 5 days (3, 7) for those without a stroke. No particular pattern between the timing of outcomes and the occurrence of stroke was evident, with the exceptions of shock, which occurred before stroke in all cases (n=9), and atrial fibrillation, which occurred before stroke in 64% of cases (n=11).

When fitted as a time-dependent covariate (Figure 3), stroke was associated with an increased risk of 30-day death (HR, 8.0; 95% CI, 4.2–12.8; $P<0.001$) and 90-day death (HR, 8.0; 95% CI, 4.8–13.5; $P<0.001$). Stroke was also independently associated with cardiogenic shock (HR, 4.4; 95% CI, 1.6–11.9;

**Table 2. Baseline Medications in Patients With and Without Stroke (n=5372)**

| Medications | No Stroke (n=5303) n, % | Stroke (n=69) n, % | *P* Value |
|---|---|---|---|
| Aspirin | 3690 (70) | 51 (74) | 0.437 |
| β-Blocker | 1828 (35) | 24 (35) | 0.957 |
| Nitrates | 2400 (45) | 26 (38) | 0.209 |
| Oral anticoagulant | 149 (3) | 3 (4) | 0.444 |
| Ticlopidine or clopidogrel | 1377 (26) | 22 (32) | 0.266 |
| ACE inhibitor | 984 (19) | 16 (23) | 0.326 |
| ARB | 275 (5) | 5 (7) | 0.444 |
| Aldosterone inhibitor | 49 (1) | 1 (1) | 0.652 |
| Calcium channel blocker | 481 (9) | 14 (20) | 0.001 |
| Digoxin | 75 (1) | 3 (4) | 0.043 |
| Other antiarrhythmic | 120 (2) | 6 (9) | 0.001 |
| Oral diuretic | 437 (8) | 11 (16) | 0.022 |
| Statin | 1022 (19) | 14 (20) | 0.831 |
| Hormone replacement therapy | 74 (1) | 0 (0) | 0.323 |
| Insulin | 156 (3) | 5 (7) | 0.037 |
| Oral hypoglycemic | 422 (8) | 10 (15) | 0.047 |

ACE indicates angiotensin-converting enzyme inhibitor; and ARB, angiotensin II receptor blocker.

*P*=0.003); congestive heart failure (HR, 3.2; 95% CI, 1.3–7.8; *P*=0.010); the combination end point of death, cardiogenic shock, or congestive heart failure (HR, 4.0; 95% CI, 2.1–7.7; *P*<0.001); and 30-day hospital readmission (HR, 3.2; 95% CI, 2.0–5.1; *P*<0.001). After adjusting for baseline covariates, stroke remained significantly associated with 90-day death (adjusted HR, 5.6; 95% CI, 3.2–9.8; *P*<0.001) and the combination end point of death, congestive heart failure, or shock at 90-days (adjusted HR, 2.4; 95% CI, 1.2–4.7; *P*<0.012).

## Discussion

In our study, stroke occurred in 1.3% of the patients who were treated with primary PCI. The majority of strokes were labeled as uncertain type, one third were classified as ischemic, and a minority (12%) were hemorrhagic. More ischemic strokes tended to occur beyond 48 hours after primary PCI, whereas all hemorrhagic strokes occurred within 48 hours. Stroke was associated with greater resource use as a result of longer hospital stays and more hospital readmissions, and, after adjusting for baseline covariates, greatly increased 90-day mortality and other adverse events.

We found a median time to stroke of 6 days, and only 43% of strokes occurred within 48 hours. An abrupt increase in stroke incidence was not observed during the first 48 hours after PCI as might be expected with factors directly related to the procedure. Instead, there was a linear increase in stroke incidence, with the highest risk in the first 3 weeks after STEMI. However, all hemorrhagic strokes occurred within 48 hours of PCI, possibly related to the contemporary use of aggressive periprocedural antithrombotic regimens. Our results seem to show that not all stroke events in the setting of STEMI are PCI-related. Beyond 48 hours after MI, additional mechanisms for stroke might include heart failure and atrial fibrillation–related cardiogenic emboli or proinflammatory conditions that extend beyond the coronary artery to the systemic vasculature. A prior analysis of APEX trial data demonstrated that 6.3% of patients developed new onset atrial fibrillation, occurring within 4 days of randomization in 88% of patients.[10] Not surprisingly, atrial fibrillation was associated with stroke and provides support for this mechanism as a potential cause of later strokes in this population.

**Table 3. Primary Percutaneous Coronary Intervention Procedural Characteristics**

| Characteristics | No Stroke (n=5303) | Stroke (n=69) | *P* Value |
|---|---|---|---|
| Time to reperfusion,* h | 2.0 (1.0, 2.0) | 2.0 (1.0, 2.0) | 0.382 |
| Glycoprotein IIb/IIIa inhibitors, n, % | 2623 (49) | 14 (20) | <0.001 |
| Atherectomy/thrombectomy, n, % | 250 (5) | 1 (1) | 0.202 |
| Angioplasty only, n, % | 214 (4) | 4 (6) | 0.461 |
| Bare metal stents, n, % | 2934 (55) | 46 (67) | 0.060 |
| Per patient* | 1.0 (1.0, 1.0) | 1.0 (1.0, 1.0) | 0.035 |
| Drug-eluting stents, n, % | 2201 (42) | 20 (29) | 0.0359 |
| Per patient* | 1.0 (1.0, 2.0) | 1.0 (1.0, 1.5) | 0.521 |
| Distal protection device, n, % | 27 (1) | 0 (0) | … |
| Cardiac surgery, n, % | 93 (2) | 3 (4) | 0.106 |
| Intra-aortic balloon pump, n, % | 351 (7) | 11 (16) | 0.002 |
| Mechanical ventilation, n, % | 175 (3) | 12 (17) | <0.001 |
| Repeat PCI, n, % | 379 (7) | 5† (7) | 0.975 |
| Repeat PCI on culprit artery, n, % | 55 (1) | 2 (3) | 0.111 |

PCI indicates percutaneous coronary intervention.
*Median (25th, 75th percentile).
†All strokes occurred after the repeat procedure.

### Stroke in STEMI Patients Undergoing PCI

Although the association of stroke and acute MI has been long established,[11] a higher risk of stroke among ACS patients receiving primary PCI compared with other PCI indications has recently been recognized.[1,5,12] An early analysis of data from the Global Registry of Acute Coronary Events (GRACE) demonstrated a 2.0% stroke incidence in STEMI patients.[13] A subsequent analysis using data from 1999 to 2003 reported

**Table 4. Stroke Characteristics in 69 Patients**

| Characteristics | No. of Patients, % |
|---|---|
| Stroke type | |
| Hemorrhagic stroke | 8 (12) |
| Ischemic stroke | 23 (33) |
| Uncertain | 38 (55) |
| Stroke severity* | |
| No sequelae | 5 (7) |
| Mild | 14 (20) |
| Moderate | 9 (13) |
| Severe | 10 (15) |
| Death | 1 (1) |
| Unknown | 30 (44) |

*Rated by investigators.

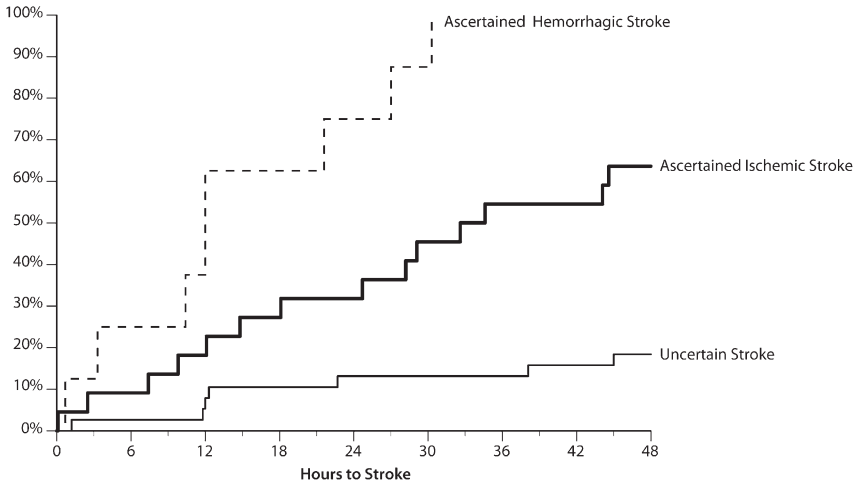


**Figure 1.** Cumulative timing of stroke during the first 48 hours from primary percutaneous coronary intervention (PCI) for ascertained hemorrhagic, ascertained ischemic, and uncertain stroke. Timing of stroke during the first 48 hours demonstrates a gradual linear increase in stroke in the uncertain and ascertained stroke population. All ascertained hemorrhagic strokes occurred within 48 hours from primary PCI. Uncertain strokes tracked more closely with ascertained ischemic strokes rather than hemorrhagic strokes.

that an in-hospital stroke occurred in 1.3% of STEMI patients, identical to what we found in our study. However, many patients did not receive PCI,[3] and reporting bias may have resulted in a lower stroke risk than reality. Finally, a retrospective analysis of >2000 patients who received PCI for ACS between 2001 and 2005 reported a stroke incidence of 0.88%, and STEMI patients had a higher stroke risk (1.08%) than non-STEMI patients (0.71%).[12]

Data from clinical trials of stroke after primary PCI in the setting of STEMI are similarly limited. The Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) study randomized 3602 STEMI patients to heparin plus a glycoprotein IIb/IIIa inhibitor or bivalirudin alone.[14] At 30 days, 0.5% of patients who received primary PCI experienced a stroke in both arms; at 1 year, 1.1% had a stroke.[15] The frequency of ischemic versus hemorrhagic stroke and stroke timing have not been reported. The Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial of eptifibatide in patients with ACS reported a stroke rate of 0.8%, but only 14% of patients had ST-segment elevation on their qualifying ECG, and 60% of patients received PCI.[16]

Data from the APEX-AMI trial suggest an increased risk of stroke in STEMI patients compared with other indications for PCI, such as stable and unstable angina and multivessel coronary disease, and the risk seems similar to treatment with thrombolytics, but fewer intracranial hemorrhages are expected. In our study, the number of hemorrhagic strokes was too small to make a formal comparison of glycoprotein IIb/IIIa inhibitor use and hemorrhagic stroke. However, the relatively high proportion of hemorrhages in patients who received glycoprotein IIb/IIIa inhibitors suggests that special attention should be paid to this drug class in future primary PCI studies in STEMI patients, particularly in certain populations such as patients >75 years, who may be at increased risk for complications.[17]

## Timing of Stroke After MI and PCI

Before thrombolytic therapy, ischemic stroke was a complication that usually occurred several days after an MI, likely related to cardiogenic emboli or cerebral hypoperfusion in

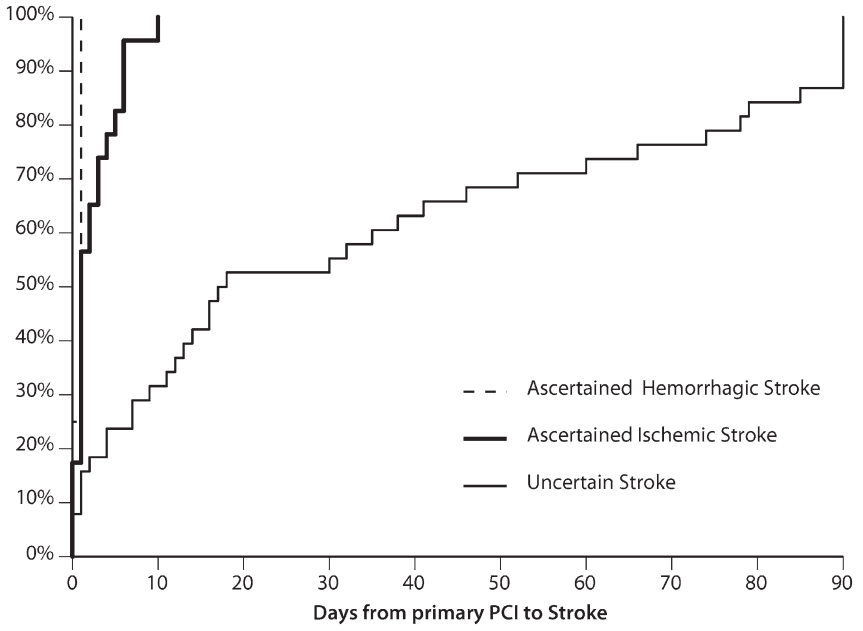


**Figure 2.** Cumulative timing of stroke during the first 90 days from primary percutaneous coronary intervention (PCI) for ascertained hemorrhagic, ascertained ischemic, and ischemic/uncertain stroke. All hemorrhagic strokes occurred within 48 hours of primary PCI.

the setting of coexisting heart failure or cerebrovascular atherosclerotic disease.[9] In the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO-1) trial, nonhemorrhagic stroke was also delayed, whereas hemorrhagic strokes occurred early.[18] The median time to onset of nonhemorrhagic stroke symptoms was 6.5 days in the PURSUIT trial.[19] Similarly, the GRACE registry showed that only 36% of patients hospitalized for ACS (>50% STEMI patients) experienced a stroke within the first 6 days.[3] A single-center study of patients receiving PCI for MI found different stroke risk factors based on the timing of a stroke.[12] Strokes within 24 hours of PCI were associated with the less frequent use of glycoprotein IIb/IIIa inhibitors and PCI of vein grafts. In contrast, strokes after 24 hours were associated with diabetes mellitus and a worse hemodynamic status as suggested by low ejection fraction, elevated serum creatinine, emergency use of intra-aortic balloon pumps, and anterior wall STEMI.

## Stroke and Subsequent Clinical Outcomes

Mortality from stroke in patients with ACS or receiving PCI is quite high. In-hospital mortality between 1999 and 2003 was 32.6% in the GRACE registry,[3] and Fuchs et al[2] reported an in-hospital mortality of 37.2% and 1-year mortality of 56.1%. Investigators from GUSTO-1 reported that 41% of strokes were fatal, although death was driven by the high rate of intracranial hemorrhage.[18] In-hospital mortality for stroke after PCI has been reported to be 25% to 30%.[1,5] In support of these previous studies, we found that stroke was associated with a dramatically increased risk of in-hospital mortality and death at 90 days.

In addition, the in-hospital length of stay among patients experiencing a stroke was higher than those without stroke (median 10 versus 5 days), which naturally results in increased healthcare costs. Budaj et al[3] and Aggarwal et al[5] reported very similar length of stay results for stroke patients. Not surprisingly, stroke was also associated with increased hospital readmissions, possibly related to stroke complications that contribute additional burdens on the healthcare system.

## Clinical Implications

Our data indicate that although the incidence of stroke in patients undergoing primary PCI is small, it is nonetheless associated with significant persistent disability, increased resource use, and worse outcomes compared with patients without stroke. The median age of patients with stroke was 73 years, and recovery may be less satisfactory with advancing age. Thus, every effort should be directed at implementing methods to decrease this event. Our findings question the notion that strokes in patients undergoing primary PCI occur early in the periprocedural period, are mainly related to catheter manipulation, and are mostly ischemic with rarity of hemorrhagic strokes. In fact, more than half of the strokes occurred >48 hours post procedure. Thus, strokes that occur 48 hours after primary PCI may result from other mechanisms, and predictors of late stroke require better characterization and understanding to allow the development of appropriate protective strategies. For example, transient atrial fibrillation may be 1 possible mechanism of late stroke that might require an intensive review of telemetry records to be recognized.

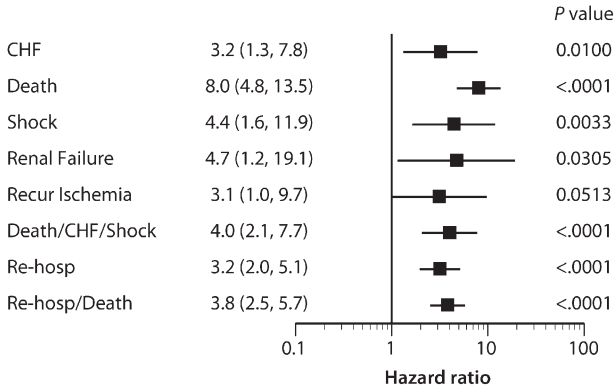


**Figure 3.** Forest plot of unadjusted hazard ratios for stroke at 90 days, showing increased risk of outcomes after a stroke versus without a stroke. CHF indicates congestive heart failure; Recur, recurrent; and Re-hosp, hospital readmission.

In addition, 1 of every 8 strokes was hemorrhagic, and three fourths of these strokes occurred early within 24 hours. Whether the occurrence of hemorrhagic stroke early after primary PCI may be decreased by careful avoidance of overanticoagulation still needs to be proven. A meta-analysis of trials evaluating thrombus aspiration devices has suggested that while significantly improving parameters of myocardial tissue reperfusion (ST resolution >70%, TIMI 3 flow, myocardial blush grade 3), they caused a 2.8-fold increase in risk of stroke.[20] Careful engagement and frequent repeated aspiration of the guide-catheter may help minimize the risk of this adverse event during the use of thrombus aspiration devices in patients undergoing primary PCI. Ongoing studies that compare thrombus aspiration before angioplasty with conventional angioplasty should clarify whether this approach improves outcomes.[21,22]

The presence of ischemic stroke risk far beyond the time of catheter manipulation also raises questions regarding the value of anticoagulation for the first 3 to 6 months among patients with large STEMI, as in the era of fibrinolytic therapy, for prevention of ischemic stroke. Among patients with large infarcts, clot formation in the left ventricle occurs as early as the first 24 hours, and the risk of clot formation may be significantly reduced with anticoagulation. In our study, oral anticoagulation with warfarin was used in <3% of patients undergoing primary PCI. This may have been a result of current American College of Cardiology/American Heart Association guidelines that provide a Class IIa indication for oral anticoagulation in patients with large anterior STEMI undergoing primary PCI, due to the absence of any study that evaluated the role of anticoagulation in this subset of patients. In addition, the perceived risk of bleeding with triple therapy (aspirin, thienopyridines, and warfarin), including among those patients with documented in-hospital atrial fibrillation, may have resulted in low use of these agents and contributed to the risk of ischemic stroke. The benefits of triple therapy for reducing the risk of stroke versus the risk of bleeding in these high-risk subsets need to be evaluated in future studies.

## Limitations

Our study has several limitations. First, our study is observational, and therefore a cause-and-effect relationship cannot be

established. We assessed the association between in-hospital stroke and 90-day clinical outcomes, and not causality. Second, stroke was a variable collected in the case report form assessed by the investigator. Thus, we did not use a central adjudication process to identify and determine stroke and its type and severity. Furthermore, the type and severity of stroke were not reported in a significant number of patients. Third, imaging studies were not available for review, and we were unable to confirm the location of strokes or categorize strokes by probable pathogenesis. It is possible that mild or transient neurological symptoms were not reported. Because of the devastating nature of hemorrhagic strokes and simple diagnosis with computed tomography of the head, we assume that most of the unclassified strokes classified were ischemic. Fourth, the cause of readmission at 30 days could not be determined from our data. Finally, our results should be interpreted cautiously because they were derived from a selected clinical trial population in which STEMI patients were randomized within 6 hours from hospital presentation to intervention, and thus the results may not be generalizable to the broader population that has been previously described in registries.[3,5,13]

Distinct strengths of this study were the use of prospectively collected data, the quality of the data collection, and large sample size. Despite the limitations addressed above, this study provides some of the best data currently available for stroke in STEMI patients during the modern era of PCI.

## Conclusions

Stroke occurred in 1.3% of patients treated with primary PCI. Many strokes occurred >48 hours after PCI, whereas all hemorrhagic strokes occurred within 48 hours. Our study suggests that not all strokes are directly related to PCI. The optimal strategy to reduce primary PCI stroke risk may ultimately entail a dual approach that focuses on appropriate anticoagulation and PCI procedural techniques to reduce early strokes and strategies directed at additional potential mechanisms involved in later, post-PCI strokes. Understanding factors associated with stroke in patients with ACS could also aid in the safety evaluation of novel pharmaceutical and interventional strategies, such as newer antithrombotic agents, advancing through further clinical studies.

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