Magnitude of and Risk Factors for In-Hospital and Postdischarge Stroke in Patients With Acute Coronary Syndromes
Findings From a Global Registry of Acute Coronary Events
Andrzej Budaj, MD; Katarzyna Flasinska, MD; Joel M. Gore, MD; Frederick A. Anderson, Jr, PhD; Omar H. Dabbous, MD, MPH; Frederick A. Spencer, MD; Robert J. Goldberg, PhD; Keith A.A. Fox, MB, ChB, FRCP; for the GRACE Investigators

Background—Stroke is a recognized complication after acute myocardial infarction, but few studies have investigated the incidence and outcome of stroke in patients with acute coronary syndrome (ACS). This study examined the incidence and outcomes of hemorrhagic and nonhemorrhagic stroke and risk factors associated with stroke in patients with ACS.

Methods and Results—Data were obtained from 35,233 patients enrolled in the Global Registry of Acute Coronary Events (GRACE) with an ACS. In-hospital strokes occurred in 310 patients (0.9%), of which 100 (32.6%) were fatal. The incidence of in-hospital stroke was significantly higher in patients with ST-segment–elevation myocardial infarction than in non–ST-segment myocardial infarction or unstable angina (1.3%, 0.9%, 0.5%, respectively; P<0.001). Overall, 35.5% of in-hospital strokes occurred within 6 days of hospitalization. The strongest risk factor for in-hospital nonhemorrhagic stroke was in-hospital CABG, followed by in-hospital atrial fibrillation, previous stroke, initial enzyme elevation, and advanced age. Prior statin use was a protective factor. After controlling for potential confounders, in-hospital mortality was significantly higher among patients who experienced an in-hospital stroke (adjusted odds ratio, 8.3; 95% CI, 6.0 to 11.4). A total of 269 additional strokes (1.1%) occurred within 6 months after discharge from hospital, of which 56 (20.9%) were fatal. The most important risk factor for postdischarge stroke was the occurrence of an in-hospital stroke.

Conclusions—Stroke is an uncommon event in patients with ACS but is associated with high mortality. Despite current therapy, the incidence of postdischarge stroke is not low. New approaches are warranted to reduce the risk of stroke in patients with ACS. (Circulation. 2005;111:3242-3247.)

Key Words: angina • infarction • myocardial infarction • risk factors • stroke
with ACS. A secondary study goal was to identify risk factors for stroke in these high-risk patients. We used data from the Global Registry of Acute Coronary Events (GRACE), a multinational, observational registry of patients admitted to hospitals with the full spectrum of ACS.

Methods
Full details of the GRACE methods have been published elsewhere. The GRACE study is designed to reflect an unbiased population of patients with ACS regardless of geographic region. Currently, 94 hospitals located in 14 countries (Argentina, Australia, Austria, Belgium, Brazil, Canada, France, Germany, Italy, New Zealand, Poland, Spain, the United Kingdom, and the United States) are participating in this large multinational observational study.

Patients entered in the registry had to be ≥18 years of age and alive at the time of hospital presentation, be admitted for ACS as a presumptive diagnosis (ie, have symptoms consistent with acute ischemia), and have ≥1 of the following: ECG changes consistent with ACS, serial increases in serum biochemical markers of cardiac necrosis, and/or documentation of coronary artery disease. The qualifying ACS must not have been precipitated by significant noncardiovascular comorbidity (eg, trauma or surgery). Approximately 6 months after hospital discharge, patients were followed up to ascertain the occurrence of selected long-term study outcomes. When required, study investigators received approval from their local hospital ethics or institutional review boards.

To ensure the enrollment of an unbiased population, the first 10 to 20 consecutive patients (depending on the patient throughput of each site) were recruited from each site per month. Data were collected by trained coordinators using standardized case report forms. Demo-graphic characteristics, medical history, presenting symptoms, duration of prehospital delay, biochemical and ECG findings, treatment practices, and a variety of hospital outcome data were collected. Standardized definitions of all patient-related variables and clinical diagnoses were used. All cases were assigned to one of the following categories: ST-segment–elevation myocardial infarction (STEMI), non-STEMI (NSTEMI), or unstable angina.

Patients were diagnosed with STEMI when they had new or presumed-new ST-segment elevation ≥1 mm seen in any location or new left bundle-branch block on the index or qualifying ECG with ≥1 positive cardiac biochemical marker of necrosis (including troponin measurements, whether qualitative or quantitative). In cases of NSTEMI, ≥1 positive cardiac biochemical marker of necrosis without new ST-segment elevation seen on the index or qualifying ECG had to be present. Unstable angina was diagnosed when serum biochemical markers indicative of myocardial necrosis in the laboratory at each hospital were within the normal range. Patients originally admitted because of unstable angina but in whom myocardial infarction evolved during the hospital stay were classified as having had a myocardial infarction. Standardized definitions were also used for selected hospital complications and outcomes. Stroke (hemorrhagic, nonhemorrhagic, or other), diagnosed by the patient’s attending physician, was defined according to the occurrence of typical neurological signs and symptoms. Congestive heart failure (or Killip class II) was defined as bibasilar rales in ≥50% of lung fields or an S3 heart sound. Pulmonary edema (Killip class III) was defined as bibasilar rales in >50% of lung fields. Cardiogenic shock (Killip class IV) was defined as symptomatic hypoperfusion with systolic blood pressure <80 mm Hg. Acute renal failure was defined as oliguria and elevation of serum creatinine ≥2.0 mg/dL or 177 μmol/L. Major bleeding was defined as life-threatening bleeding requiring a transfusion of ≥2 units of packed red cells or resulting in an absolute decrease in hemogtotal of ≥10% or in death. Bleeding after CABG surgery was not included.

Statistical Analysis
The study included 35 233 patients with ACS admitted to 94 hospitals in 14 countries between April 1999 and December 2003. Data for patients with and without stroke were summarized as frequencies and percentages and were tested for differences with the χ² test for categorical data. Continuous variables, reported as median and 25th and 75th percentiles, were compared by means of Wilcoxon rank-sum tests or Kruskal-Wallis tests as appropriate. Kaplan-Meier analysis was used to estimate the probability of experiencing a stroke over the 6-month postdischarge period in hospital survivors of ACS. A multivariable stepwise logistic regression was used to determine the predictors for in-hospital nonhemorrhagic and any postdischarge stroke. The following variables were included as potential predictors: age; gender; medical history of smoking, diabetes, stroke, atrial fibrillation, hypertension, and hyperlipidemia; presenting pulse; initial creatinine; initial serum cholesterol; cardiac arrest at admission; prior aspirin and warfarin; in-hospital procedures (percutaneous coronary intervention and CABG); thrombolytic therapy; in-hospital events (stroke, myocardial infarction, or reinfarction after 24 hours, congestive heart failure, cardiogenic shock, atrial fibrillation, cardiac arrest, renal failure, and AV block); and prior, in-hospital, and discharge medications (aspirin, warfarin, ACE inhibitors, β-blockers, diuretics, and statins) to establish the association between stroke and mortality with adjustment for the GRACE risk score for hospital mortality. Only statistically significant variables were retained in the final models (P<0.05). All tests were double sided and considered statistically significant at α<0.05. The analysis was performed with SAS software package (version 9.1, SAS Institute).

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Characteristics of the Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
</tr>
<tr>
<td>---------</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Median age, y</td>
</tr>
<tr>
<td>Male, n (%)</td>
</tr>
<tr>
<td>Past history, n (%)</td>
</tr>
<tr>
<td>Angina</td>
</tr>
<tr>
<td>MI</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Initial creatinine (median), mg %</td>
</tr>
<tr>
<td>Length of hospital stay (median), d</td>
</tr>
</tbody>
</table>

UA indicates unstable angina.
The incidence of in-hospital stroke was significantly higher in patients with STEMI (1.2%) or unstable angina (0.9%; $P<0.001$; Table 2). Nonhemorrhagic strokes were more common among patients with NSTEMI (1.3%) than in those with STEMI (1.2%) or unstable angina (0.9%; $P<0.001$; Table 2).

**In-Hospital Strokes**

In-hospital strokes occurred in a total of 310 patients (0.88%). The incidence of in-hospital stroke was significantly higher in patients with STEMI than in those with NSTEMI or unstable angina ($P<0.001$; Table 2). Nonhemorrhagic strokes were significantly more common among patients with NSTEMI than in the other groups, whereas hemorrhagic strokes tended to predominate in patients with STEMI ($P<0.001$; Table 2).

Overall, 35.5% of in-hospital strokes occurred within the first 6 days of hospitalization (median length of stay). The cumulative incidence of in-hospital stroke is presented in Figure 1. Of the strokes that occurred within 6 days, 38.2% were hemorrhagic and the remainder were nonhemorrhagic; the corresponding figures for strokes occurring after >6 days were 17.6% and 82.4%, respectively. In-hospital stroke was a relatively infrequent event among other clinical outcomes. In all patients with ACS, as well as in each type of ACS, the incidence of stroke was clearly lower than the incidence of in-hospital death, (re)infarction, heart failure, atrial fibrillation, acute renal failure, or major bleeding (Table 3).

In-hospital stroke occurred in association with other vascular events, including myocardial infarction, congestive heart failure, and major bleeding (Table 4). The median length of stay in hospital was significantly higher in patients with stroke (11 days) compared with those without stroke (6 days; $P<0.001$).

Multivariate logistic regression analysis revealed that CABG was the most important risk factor for nonhemorrhagic stroke, with an odds ratio (OR) of 3.3, followed by in-hospital atrial fibrillation and previous stroke. Other significant risk factors were initial cardiac enzyme elevation and advancing age. Prehospital use of statin was a protective factor of nonhemorrhagic stroke (Figure 2).

**Postdischarge Stroke**

A total of 269 (1.1%) strokes (all kinds) occurred in the 6 months after discharge from participating hospitals, of which 56 (20.9%) were fatal. The cumulative incidence of postdischarge stroke is presented in Figure 3. The incidence of stroke was higher in patients with NSTEMI (1.3%) than in those with STEMI (1.2%) or unstable angina (0.9%; $P<0.05$; Table 3).

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**TABLE 2. Incidence of In-Hospital and Postdischarge Stroke**

<table>
<thead>
<tr>
<th>Event</th>
<th>Total ACS</th>
<th>STEMI</th>
<th>NSTEMI</th>
<th>UA</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total in-hospital stroke</td>
<td>310 (0.88)</td>
<td>163 (1.3)</td>
<td>92 (0.9)</td>
<td>55 (0.5)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Nonhemorrhagic</td>
<td>138 [55.7]</td>
<td>67 [48.6]</td>
<td>49 [70.0]</td>
<td>22 [55.0]</td>
<td>0.0131</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>72 [25.0]</td>
<td>46 [33.3]</td>
<td>9 [12.9]</td>
<td>7 [17.5]</td>
<td>0.0027</td>
</tr>
<tr>
<td>$P$</td>
<td>$&lt;0.0001$</td>
<td>$&lt;0.001$</td>
<td>$&lt;0.001$</td>
<td>$&lt;0.05$</td>
<td></td>
</tr>
<tr>
<td>Total postdischarge stroke</td>
<td>269 (1.1)</td>
<td>103 (1.2)</td>
<td>93 (1.3)</td>
<td>73 (0.9)</td>
<td>0.0118</td>
</tr>
</tbody>
</table>

UA indicates unstable angina. Values in parentheses indicate the respective population of all ACS, STEMI, NSTEMI, and unstable angina. Values in brackets indicate the respective population of total in-hospital stroke in all ACS, STEMI, NSTEMI, and unstable angina.

* Differences between row percentages.

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**TABLE 3. In-Hospital Events According to Type of ACS**

<table>
<thead>
<tr>
<th>Event</th>
<th>Total, n (%)</th>
<th>STEMI, n (%)</th>
<th>NSTEMI, n (%)</th>
<th>UA, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke (any kind)</td>
<td>310 (0.9)</td>
<td>163 (1.3)</td>
<td>92 (0.9)</td>
<td>55 (0.5)</td>
</tr>
<tr>
<td>Death</td>
<td>1897 (5.4)</td>
<td>1056 (8.2)</td>
<td>502 (4.8)</td>
<td>339 (2.9)</td>
</tr>
<tr>
<td>MI/reinfarctions</td>
<td>3046 (8.7)</td>
<td>1735 (13.5)</td>
<td>1097 (10.5)</td>
<td>214 (1.8)</td>
</tr>
<tr>
<td>CHF/PE</td>
<td>5584 (15.9)</td>
<td>2713 (21.1)</td>
<td>1804 (17.2)</td>
<td>1067 (9.1)</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>1556 (4.4)</td>
<td>1000 (7.8)</td>
<td>340 (3.2)</td>
<td>216 (1.8)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3028 (8.6)</td>
<td>1251 (9.7)</td>
<td>1067 (10.2)</td>
<td>710 (6.0)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>1429 (4.1)</td>
<td>685 (5.3)</td>
<td>516 (4.9)</td>
<td>228 (1.9)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1017 (2.9)</td>
<td>475 (3.7)</td>
<td>364 (3.5)</td>
<td>173 (1.5)</td>
</tr>
</tbody>
</table>

UA indicates unstable angina; CHF, congestive heart failure; and PE, pulmonary edema.
2). In total, 30.6% of postdischarge strokes occurred within the first month after hospital discharge, 30.1% occurred 1 to 3 months after discharge, and 36.6% occurred thereafter.

Risk factors for postdischarge stroke are shown in Figure 4. The most powerful risk factor was the occurrence of in-hospital stroke, which was associated with a 6-fold increase in risk. Other significant risk factors were previous stroke, congestive heart failure or pulmonary edema, and increasing age (Figure 4).

Mortality Associated With Stroke
A total of 100 in-hospital strokes (32.6%) were fatal. Of these, 41.0% were hemorrhagic and 42.0% were nonhemorrhagic in origin; type of stroke was not identified or diagnosed in the remaining 17.0% of cases. In contrast, most nonfatal strokes (69.1%) were nonhemorrhagic and 10.1% were hemorrhagic; the type of stroke was not elucidated in the remaining 20.8%.

In-hospital mortality was significantly higher among patients who experienced a stroke while in hospital than in those who did not (32.6% versus 5.1%, respectively; \(P<0.001\)). After adjustment for a variety of potentially confounding variables included in the GRACE risk score (Killip class, age, blood pressure, resuscitated cardiac arrest, positive cardiac markers, creatinine, ST-segment shift, and heart rate), \(^1^3\) in-hospital stroke of any kind was an important independent predictor of in-hospital mortality, with an OR of 8.3 (95% CI, 6.2 to 11.4; Figure 5).

Discussion
These data from the ongoing multinational GRACE registry show that in-hospital stroke occurs in <1% of patients with ACS and is more prevalent in patients with STEMI compared with patients with NSTEMI or unstable angina. Although in-hospital stroke is an uncommon outcome among patients with ACS, it represents an important medical problem because of the high associated mortality. A major risk factor for in-hospital death, stroke is associated with significant morbidity.\(^5\) Approximately one third of hospital strokes and one fifth of those occurring after discharge were fatal, and stroke was the strongest single risk factor for in-hospital death. These findings are consistent with previous studies in patients with ACS.\(^8\)\(^9\) The incidence of 6-month postdischarge stroke is not low in relation to the general population with coronary artery disease.\(^1^4\)

Hemorrhagic and Nonhemorrhagic Strokes
Most in-hospital strokes in this study were nonhemorrhagic in origin, although the proportion of hemorrhagic strokes was higher in patients with STEMI than in other groups. Hemorrhagic strokes, however, accounted for a higher proportion of fatal than nonfatal strokes. This is consistent with the experience in patients with acute STEMI, in whom the introduction of thrombolytic therapy appears to have had little impact on the overall incidence of stroke but the number of stroke deaths has risen as a result of an increase in deaths from intracranial hemorrhage.\(^5\)\(^7\) These findings emphasize the importance of prompt identification of a stroke as ischemic or hemorrhagic to allow appropriate and timely treatment.

In-Hospital Events
In-hospital stroke was associated with a substantial burden of cardiovascular morbidity in this study.
The development of stroke during the acute hospital stay significantly increased the length of hospitalization. The incidence of other vascular events such as myocardial infarction, heart failure, atrial fibrillation, and bleeding was significantly higher in patients with in-hospital stroke than in those without. Similarly, in PURSUIT, patients with stroke were more likely to develop in-hospital heart failure or cardiogenic shock and were more likely to require CABG than those without stroke.

The risk of stroke appeared to increase with the duration of hospitalization; almost two thirds of in-hospital strokes occurred >6 days after admission. In contrast, the risk of stroke after discharge appeared to remain relatively constant over a 6-month follow-up. The reasons for these differences are unclear but may be related to differing risk factors operating in hospital and after discharge.

Risk Factors for Stroke

Our study has identified a number of important risk factors for in-hospital nonhemorrhagic and postdischarge stroke (any kind) in patients with ACS. CABG was the most powerful predictor of in-hospital nonhemorrhagic stroke, a finding consistent with those of previous studies that have shown that stroke is a relatively common complication of CABG, occurring in up to 4% of patients. The risk of stroke in patients undergoing CABG is influenced by a number of patient- and procedure-related factors, and a risk-prediction model has recently been developed that is based on such factors.

Patient-related factors include age, gender, diabetes, recent myocardial infarction, hypertension, renal dysfunction, and impaired cardiac function. Procedural factors include prolonged cardiopulmonary bypass, use of an intra-aortic balloon pump, and prolonged use of inotropic agents.

The development of atrial fibrillation during the acute hospitalization, history of stroke, and advancing age were also significant risk factors for in-hospital nonhemorrhagic stroke. This is consistent with the findings of the PURSUIT and GUSTO-I studies. Increasing heart rate, diabetes mellitus, prior anterior infarction, previous angina, history of hypertension, Killip class, and coronary angiography were reported to be risk factors in other trials but were not confirmed in our analysis (Table 5). Use of statin before admission was a protective factor of nonhemorrhagic stroke. Beneficial effects of statins on vascular physiology, including plaque stabilization, suppression of inflammation, improvement in endothelial function, and platelet antiaggregant activity, may be responsible for this phenomenon. Reduction of incidence of stroke after myocardial infarction with pravastatin has been reported.

The principal risk factor for any kind of stroke after discharge from hospital was previous stroke, particularly the occurrence of in-hospital stroke. The combined OR for postdischarge stroke in patients with either in-hospital or previous stroke was 22.0 (95% CI, 7.3 to 66.8) compared with 6.2 (95% CI, 2.9 to 13.6) for in-hospital stroke alone. Similarly, in the Euro-Heart Survey, a history of stroke indicated patients with high-risk features.

Given the potentially devastating consequences of stroke, it is important to identify patients with ACS at high risk for this adverse event. The present study provides insights into the major risk factors for both in-hospital and postdischarge stroke. These data should facilitate the development of a risk prediction model suitable for all types of ACS. Prediction models for the development of stroke have previously been described for patients with acute myocardial infarction and for those undergoing CABG.

Clinical Implications

The identification of predictors for stroke in patients with an ACS may help in clinical decision making. Results of this study show that hospitalized patients who require a CABG, patients who develop atrial fibrillation during their ACS event, and individuals with a history of stroke are at particularly high risk of a nonhemorrhagic strokes; treatment for these patients should be adapted accordingly. Furthermore, the apparent protective effect of prehospital use of statins encourages even wider use of this treatment in patients with an ACS.

Study Strengths and Limitations

GRACE is the largest multinational registry to include the complete spectrum of patients with ACS, including >30 000

| TABLE 5. Independent Predictors of In-Hospital Nonhemorrhagic Stroke |

<table>
<thead>
<tr>
<th>Study</th>
<th>Predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRACE</td>
<td>In-hospital CABG, in-hospital atrial fibrillation, history of stroke, initial cardiac enzyme elevation, age, prior statin (protective factor)</td>
</tr>
<tr>
<td>PURSUIT</td>
<td>Heart rate, age, prior anterior MI, prior stroke or TIA, diabetes mellitus</td>
</tr>
<tr>
<td>GUSTO-I</td>
<td>Age, heart rate, history of stroke or TIA, diabetes mellitus, previous angina, history of hypertension, Killip class, coronary angiography, CABG, atrial fibrillation/flutter</td>
</tr>
<tr>
<td>OASIS (model for all strokes)</td>
<td>CABG, history of stroke, diabetes mellitus, older age, heart rate, on-site catheterization facility</td>
</tr>
</tbody>
</table>

TIA indicates transient ischemic attack.
patients from 14 countries. Standardized criteria are used to define ACS and hospital outcomes, and rigorous quality control and audit measures are used. “Real-life” studies like GRACE offer the advantage that they provide data on a heterogeneous patient population that includes groups that are often underrepresented in randomized trials such as women and the elderly, which enhances the generalizability of the study findings. GRACE provides a representative sample of patients with ACS who are treated in a variety of hospital and healthcare systems. Nevertheless, as a nonrandomized observational study, GRACE is subject to certain inherent limitations and potential biases, which must be kept in mind when the study results are interpreted.

Conclusions

Although in-hospital stroke is a relatively uncommon event in patients with ACS, it is an independent risk factor for death. Most strokes occur after 6 days of hospitalization. In contrast, the incidence of stroke occurring within 6 months of hospital discharge is not low. New approaches are needed to reduce the risk of stroke and to improve the in-hospital and long-term outcomes of patients experiencing an acute stroke in the setting of an ACS.

Acknowledgments

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Disclosure

The GRACE study is supported by an unrestricted grant from Sanofi-Aventis to the Center for Outcomes Research, University of Massachusetts Medical School. Sanofi-Aventis had no involvement in the collection, analysis, and interpretation of data; in the writing of the manuscript; or in the decision to submit the paper for publication. The design, conduct, and interpretation of GRACE are undertaken by an independent steering committee.

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References


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