Stroke in Relation to Cardiac Procedures in Patients With Non–ST-Elevation Acute Coronary Syndrome

A Study Involving >18 000 Patients

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Background—There are few published data on risk factors for stroke in patients with non–ST-elevation acute coronary syndrome (ACS). We investigated prognostic factors for stroke in 2 large cohorts of patients from the Organization to Assess Strategies for Ischemic Syndromes (OASIS) registry (8010) and the OASIS-2 trial (10 141)

Methods and Results—A total of 18 151 patients with non–ST-elevation ACS were enrolled in the OASIS program. Data from these 2 studies were pooled (a test for heterogeneity was nonsignificant, \( P = 0.34 \)). Overall, 238 patients (1.3%) had a stroke over a 6-month follow-up. Those who experienced stroke had a 4-fold increase in 6-month mortality (27.0% versus 6.3%, \( P < 0.001 \)). A Cox multivariate regression analysis identified CABG surgery as the most important predictor of stroke (hazard ratio [HR], 4.6), followed by history of stroke (HR, 2.3), diabetes mellitus (HR, 1.7), older age (HR, 1.6 per 10-year increase), higher heart rate (HR, 1.1 per 10-bpm increase), and on-site catheterization facility (HR, 1.4). There was no significant excess in stroke in patients undergoing percutaneous coronary intervention (\( P = 0.21 \)). Patients who underwent early CABG surgery were at a substantially increased risk compared with those who had later CABG (3.3% versus 1.6%; HR, 2.1; \( P = 0.003 \)) or who had no surgery (3.3% versus 1.1%; HR, 3.95; \( P = 0.0001 \)).

Conclusions—In this large cohort of patients with ACS, stroke was an uncommon but serious event associated with high mortality. The performance of early CABG surgery was a powerful independent predictor of stroke. (Circulation. 2001; 104:269-274.)

Key Words: stroke ■ coronary disease ■ angina ■ risk factors ■ prognosis

Although numerous studies have examined the incidence of and risk factors for stroke in patients with acute myocardial infarction (MI) receiving thrombolytic therapy, 1–7 there are relatively few data examining its impact in patients with non–ST-elevation acute coronary syndrome (ACS). 8 Over the last decade, the management of patients with non–ST-elevation ACS has increasingly evolved toward a strategy of aggressive antithrombotic treatments, followed by high rates of early angiography and revascularization. Although randomized trials have demonstrated that a routine invasive strategy may be as effective as or superior to a more conservative management strategy in preventing death or MI in the long term, 9–15 it is at the cost of an increased early hazard. Stroke is a rare but potentially devastating complication of cardiac procedures, and although the randomized trials have been too small to detect important differences, large registry studies have demonstrated an increased risk. 16,17

To explore stroke risk and its relationship to cardiac procedures in patients with non–ST-elevation ACS, we studied 18 151 patients who were recruited into the Organization to Assess Strategies for Ischemic Syndromes (OASIS) program. We present here the largest experience of stroke in patients with non–ST-segment-elevation ACS.

Methods

Study Population

The study cohort consisted of 18 151 patients who were diagnosed with unstable angina (UA) or non–Q-wave MI (NQMI) during the initial hospitalization. A detailed description of the study protocol, methods, and results from the registry and trial have been published. 17,18 Briefly, the OASIS registry was conducted between 1995 and 1997 and involved consecutive enrollment of 8010 patients with UA or NQMI who were followed up prospectively for 2 years. OASIS-2 was a double-blind randomized trial of hirudin versus heparin that enrolled 10 141 patients with suspected UA and NQMI. The clinical diagnosis had to be supported by either ECG changes compatible with myocardial ischemia or a history of previous coronary artery disease (for patients >60 years of age). Eligibility criteria were similar to those used in the registry. 17

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Definition of Stroke
Stroke was defined prospectively and actively sought in all patients. The definitions were identical in the registry and trial. Stroke was defined as the presence of a new focal neurological deficit thought to be vascular in origin with signs or symptoms lasting ≥24 hours. It was strongly recommended that an imaging procedure such as CT or MRI be performed in each case of stroke. These reports were further reviewed to classify stroke as definite hemorrhage or ischemic infarction (or unknown). In addition, all strokes that occurred in the OASIS-2 trial were adjudicated by an independent Adjudication Committee blinded to the treatment allocation.

Statistical Analysis
A test for heterogeneity was conducted to determine whether the 2 patient populations in the OASIS registry and the OASIS-2 trial were significantly different with respect to important prognostic factors. The databases were then combined, and univariate comparisons of baseline patient characteristics, use of medications, and cardiac procedures in hospital were made between those patients who developed stroke and those who did not. A Cox regression analysis was used to estimate the multivariate hazard ratio (HR) and 95% CI for independent predictors. Cardiac procedures were treated as time-dependent covariates.

From the results of previous studies7,15 and data from the OASIS registry,17 we postulated that early CABG surgery might significantly increase the incidence of stroke. To determine whether there was a trend in relation to timing of cardiac procedures, we examined the crude rates of stroke within 48 hours of the procedure. We also compared stroke incidence for each procedure before and after 14 days of initial hospitalization (“early” and “late” procedures). The choice of a 14-day cutoff point was made arbitrarily. A separate Cox regression analysis was used to estimate multivariate HRs and 95% CIs for early procedures versus delayed or no procedures.

Because analysis of the registry data showed an excess of strokes in patients initially treated in hospitals with cardiac-catheterization facilities, results were adjusted for availability of these facilities at each center. Missing 6-month data were treated as censored. All computations were performed with SAS. The probability values provided in the tables are 2 sided and uncorrected for multiple comparisons.

Results
A total of 18151 patients with ACS were recruited from 1995 to 1998. Forty-three patients were excluded from the analysis because of missing data. The 6-month follow-up was completed for 98.3% of all patients (98.1% in the registry and 98.4% in the trial).

Baseline Characteristics
Overall, baseline characteristics and use of in-hospital medications were similar among the registry and trial patients. Detailed descriptions of the baseline characteristics have been published elsewhere.17,18 There were small differences in the proportion of patients with previous history of stroke, heart failure, or cardiac interventions (percutaneous coronary interventions [PCI] or CABG). Most patients in the registry were treated with heparin (98%). In the trial, patients were assigned to either heparin or hirudin by study design; however, there was no significant difference between treatment groups with respect to stroke patients. The overall test for heterogeneity showed that the patient populations were not significantly different in relation to important prognostic variables such as patient age, history, baseline characteristics, and hospital treatment (P = 0.34). Therefore, data from the OASIS registry and the OASIS-2 trial were combined for further analyses.

Incidence of Stroke
The overall incidence of stroke during the 6 months of follow-up was 1.3% (238 of 18151). There was a marked early increase in strokes during the first month after admission, followed by a lower rate of increase over the next 5 months (Figure 1). Of the 238 strokes, 27 (11%) were hemorrhagic, and 211 (89%) were ischemic (or presumably ischemic) strokes. Of all strokes, 21% and 53% occurred within the first 7 and 35 days of initial hospitalization, respectively.

Six-month mortality among patients who experienced a stroke was significantly higher than in those who did not have a stroke (27% [65 of 238] versus 6.3% [1123 of 17913]; HR, 4.3; 95% CI, 3.49 to 5.38; P < 0.0001). Compared with patients without stroke, mortality rates in those with a hemorrhagic stroke (48% versus 6.3%; HR, 7.8; 95% CI, 5.17 to 11.4; P < 0.0001) and those with nonhemorrhagic stroke (25% versus 6.3%; HR, 3.9; 95% CI, 3.07 to 4.99) were increased by 8- and 4-fold, respectively. Forty-six of 238 patients (about one fifth) experienced a fatal stroke.

Prognostic Importance of Patient Baseline and In-Hospital Characteristics
Compared with patients without stroke, those who had a stroke were older and were more likely to have higher heart rate, higher systolic blood pressure, diabetes mellitus, and a history of stroke and to undergo CABG surgery (Table 1). The availability of an on-site cardiac catheterization facility was also associated with an increased risk of stroke.

Six baseline and in-hospital characteristics were identified as independent predictors of stroke in patients with ACS without ST elevation (Table 2). The most important independent predictors were performance of CABG surgery (HR, 4.6; 95% CI, 3.39 to 6.34; P < 0.0001), followed by history of stroke (HR, 2.3; 95% CI, 1.53 to 3.36; P = 0.0001), diabetes mellitus (HR, 1.7; 95% CI, 1.31 to 2.26; P < 0.0001), older age (HR, 1.6 for 10-year increase; 95% CI, 1.42 to 1.87; P < 0.0001), a higher heart rate (HR, 1.1 for 10-bpm increase; 95% CI, 1.01 to 1.16; P = 0.038), and availability of catheterization facilities (HR, 1.4; 95% CI, 1.09 to 1.91; P = 0.01).
A history of CABG surgery, higher systolic blood pressure, and performance of PCI were not statistically significant.

Cardiac Procedures and Perioperative Risk of Stroke

The incidence of strokes after CABG surgery was 0.93% (29 of 3118) and 1.4% (45 of 3073) at 48 hours and 7 days, respectively. The 6-month incidence of stroke among patients who had CABG surgery was 2.45%.

There were significant differences in stroke rates depending on the timing of CABG surgery. Patients who underwent early CABG surgery (within the first 14 days of initial hospitalization) were twice as likely to develop a stroke compared with those patients who underwent late CABG surgery (adjusted HR, 2.1; 95% CI, 1.28 to 3.35; \(P\) = 0.003) and almost 4 times as likely compared with those who did not have CABG surgery (adjusted HR, 3.95; 95% CI, 2.63 to 5.92; \(P\) = 0.0001) (Table 3 and Figure 2). In patients who had late surgery, the risk of developing stroke remained significant compared with those who did not have surgery (HR, 2.88; 95% CI, 1.82 to 4.54; \(P\) = 0.0001).

The rates of stroke in patients who underwent early CABG surgery were also related to the number of risk factors present (Figure 3). If patients had \(\geq 2\) risk factors (other than CABG surgery) and underwent early CABG surgery, they had a 2-fold increase in risk of stroke compared with those who had late or no CABG surgery (2.5% versus 1.1%; 95% CI, 1.15 to 4.62; \(P\) = 0.019). If \(\geq 3\) risk factors were present, the rate of stroke increased almost 3-fold in patients who underwent early CABG surgery versus those who had late or no CABG surgery (4.0% versus 1.7%; 95% CI, 1.67 to 3.74; \(P\) < 0.0001).

The 6-month incidence of stroke among patients who underwent PCI was much lower (0.9%) than for those who underwent CABG surgery. There was no significant excess in stroke in patients undergoing PCI compared with those who did not have a cardiac procedure (adjusted HR, 1.03; 95% CI, 0.65 to 1.65; \(P\) = 0.89). The risk of stroke was not significantly different in those who underwent early PCI compared with those who underwent late PCI (adjusted HR, 0.9; 95% CI, 0.39 to 2.06; \(P\) = 0.8).

| TABLE 1. Univariate Baseline and In-Hospital Predictors of Stroke |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Variable                    | With Stroke (n=238)         | Without Stroke (n=17 870)   | Unadjusted HR               | \(P\)                        |
| Age, y                      | 69±9                       | 64±11                       | 1.49*                      | 0.0001                      |
| SBP, mm Hg                  | 147±27                     | 141±25                      | 1.24†                      | 0.002                       |
| Heart rate, bpm             | 79±19                      | 76±17                       | 1.35‡                      | 0.01                        |
| History, n (%)              |                            |                             |                            |                             |
| Diabetes mellitus           | 83 (2.2)                   | 3766 (97.8)                 | 2.05                       | 0.002                       |
| Stroke                      | 29 (3.4)                   | 835 (96.6)                  | 2.88                       | 0.0001                      |
| PCI                         | 29 (1.5)                   | 1974 (98.5)                 | 1.35                       | 0.07                        |
| CABG surgery                | 43 (1.7)                   | 2521 (98.3)                 | 1.19                       | 0.08                        |
| Smoking                     | 141 (1.3)                  | 11 100 (98.7)               | 1.09                       | 0.39                        |
| In-hospital procedures, n (%)|                            |                             |                            |                             |
| PCI                         | 22 (0.8)                   | 2644 (99.01)                | 0.71                       | 0.25                        |
| CABG surgery                | 70 (2.3)                   | 3048 (97.7)                 | 4.42                       | 0.0001                      |
| Catheterization facility‡   | ...                        | ...                         | 1.72                       | 0.0001                      |

SBP indicates systolic blood pressure. Values are mean±SD when appropriate.
*For 10-year increase.
†For 10-mm Hg increase.
‡For 10-bpm increase.
§Availability of on-site cardiac catheterization facility.

| TABLE 2. Independent Baseline and In-Hospital Predictors of Stroke |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Likelihood                  | Ratio \(\chi^2\)            | HR (95% CI)                 | \(P\)                        |
| CABG surgery                | 92.4                       | 4.6 (3.39–6.34)             | <0.0001                     |
| Prior stroke                | 16.7                       | 2.3 (1.54–3.36)             | <0.0001                     |
| Diabetes mellitus           | 15.7                       | 1.7 (1.31–2.26)             | <0.0001                     |
| Age                         | 47.9                       | 1.6* (1.42–1.87)            | <0.0001                     |
| Heart rate                  | 6.7                        | 1.1† (1.01–1.16)            | 0.038                       |
| Catheterization facility‡   | 3.7                        | 1.4 (1.09–1.91)             | 0.01                        |

*For 10-year increase.
†For 10-bpm increase.
‡Availability of on-site cardiac catheterization facility.
had late CABG or those who did not undergo surgery. As expected, the incidence of stroke was higher in the elderly and in those with higher heart rate, diabetes mellitus, and a history of stroke.

Although the value of CABG surgery in high-risk patients has been well established,\(^{19,20}\) the increasing use of coronary interventions may also result in an increase in postoperative complications, including stroke. Stroke remains one of the most devastating and debilitating complications in patients with ACS and is associated with high morbidity and mortality rates.\(^{21}\) Furthermore, stroke often results in long-term physical and psychological disabilities and substantially compromises quality of life.

The 238 strokes reported in the combined OASIS registry and OASIS-2 trial database of 18 151 patients is one of the largest data sets of stroke in patients with non–ST-elevation ACS. The overall incidence of stroke was 1.3%, and more than half of these occurred within the first 35 days of initial hospitalization. We observed a 4-fold increase in mortality among patients with non–ST-elevation ACS who sustained stroke compared with those who did not. Strokes were directly responsible for one fifth of all deaths, yet little attention is paid to this devastating complication in evaluations of therapies in ACS. Other than the present study, there are few data on stroke incidence in patients with non–ST-elevation ACS. In the only other study of stroke in patients with non–ST-elevation ACS, the incidence of ischemic stroke was 0.7%.\(^{8}\) However, this study was based on a small number of events and did not explain the impact of cardiac procedures and strokes.

Unlike non–ST-segment-elevation ACS, there have been several studies of stroke in patients with ST-segment elevation acute MI. In these studies, patients treated with thrombolytic therapy who underwent bypass surgery and cardiac catheterization demonstrated a substantially increased rate of non-hemorrhagic stroke.\(^{2–6}\)

Previous observational studies that included patients undergoing elective and nonelective CABG surgery have re-

![Figure 2](image-url)

**Figure 2.** A, Rates of stroke in patients undergoing early CABG surgery (within 14 days of initial hospitalization) and in those without CABG surgery. For early CABG group, day 1 is day of procedure with day 8 as median day of CABG surgery. For no CABG group, day 1 is the median day of CABG in group of patients with early CABG (day 8). B, Rates of stroke in patients undergoing late CABG surgery (after 14 days of initial hospitalization) and in those without CABG surgery. For late CABG group, day 1 is day of procedure with day 38 as median day of CABG surgery. For no CABG group, day 1 is the median day of CABG in group of patients with late CABG (day 38).

![Figure 3](image-url)

**Figure 3.** Rates of stroke in relation to presence of risk factors in patients undergoing early versus late or no CABG surgery.

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<th>TABLE 3. Stroke Rates in Relation to Timing of CABG Surgery</th>
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<td><strong>Crude Stroke Incidence, n/N (%)</strong></td>
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*Adjusted for prior stroke, diabetes mellitus, age, heart rate, and availability of on-site cardiac catheterization facility.
†CABG surgery within the first 14 days of initial hospitalization.
‡CABG surgery after the first 14 days of initial hospitalization.
§No CABG surgery.
ported that postoperative rates of stroke in patients <80 years of age have ranged from 0.2% to 1.8%. None of these studies separately reported the rates of stroke among those undergoing CABG surgery among ACS patients. We found that in patients with non–ST-elevation ACS who underwent CABG surgery, the rates of stroke were almost 2 times higher (2.5%), with most of this increase in patients undergoing CABG surgery within 14 days of hospitalization. This represented a 3.6-fold increase compared with those patients who did not undergo CABG surgery, which persisted even after adjustment for baseline risk in our multivariable model. Interestingly, we did not find a similar increased risk of stroke in those patients undergoing PCI. However, it is likely that patients undergoing CABG surgery may have more extensive coronary artery disease compared with those undergoing PCI or no intervention at all.

Most strokes in our study were classified as ischemic (82%), with <10% classified as being hemorrhagic. The mechanism by which UA increases the risk of stroke may relate to the severity and extent of underlying atherosclerosis and degree of left ventricular function. Also, patients admitted with UA or NQMI and treated with anticoagulation therapy may already be at increased risk for stroke. In addition, those who undergo CABG surgery could also develop possible microembolization, hemodynamic compromise, hypoxia, hemorrhage, and/or metabolic abnormalities, resulting in stroke. It is possible that because of a combination of these factors and existing comorbidities, patients with ACS may be more likely to experience stroke during or after CABG surgery.

Study Limitations

The main limitation of the present analysis is the potential for selection bias that is inherent in any observational analysis. Selection of patients for cardiac procedures is likely to have been driven largely by clinical circumstances, which include the extent of coronary disease and symptomatic status of the patient. The decision to operate and its timing are also dependent on additional factors that cannot be easily measured or adjusted for, such as variation in regional or center-based practice patterns, skill of the surgeon, and techniques specific to the surgery itself. We attempted to account for this selection bias as much as possible by using multivariable time-dependent covariate adjustment models and by adjusting our analysis for the presence or absence of on-site cardiac catheterization facilities. However, there is no assurance that any statistical adjustment can be guaranteed to be precise. Nevertheless, the very large excess in stroke risk among those undergoing early CABG surgery should be recognized by clinicians when making decisions as to the need, type, and timing of coronary intervention in ACS patients. Minor strokes may be difficult to diagnose in the first few days after CABG surgery because patients may otherwise be ill. We therefore may have missed some minor, nondisabling strokes shortly after CABG surgery. Because we focused only on the clinically important strokes, the risk quoted in our study is therefore a conservative estimate.

Implications

With the increasing use of a routine invasive approach to the management of patients with non–ST-elevation ACS, our study provides important data on the uncommon but potentially devastating complication of stroke in patients with ACS. Although the overall incidence of stroke is low, those patients undergoing early CABG surgery have a substantially increased risk, even after correction for baseline factors. We did not observe a similar increase in risk in patients undergoing early PCI. Nevertheless, there are many valid clinical reasons for performing earlier, rather than delayed, CABG surgery. Future studies are therefore required to address the question of whether it may be preferable to delay CABG surgery in certain high-risk groups (eg, elderly diabetics) to ensure that the benefits outweigh the risks associated with the procedure.

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