Coronary artery bypass grafting (CABG) is associated with adverse neurological complications, of which stroke is the most debilitating. Previous studies have attempted to identify clinical predictors of stroke after CABG. However, the low frequency of the index event (<5%) limits the power of most published investigations. In addition to a wide variability in the sample sizes studied, previous studies have evaluated many different variables in a nonuniform manner. To systematically investigate the incidence, predictors, and early clinical outcome of stroke after CABG in a large, unselected, clinical setting, we conducted the present study, which includes our 10-year cumulative experience of CABG surgery.

Subjects and Methods

The computerized database of the Division of Cardiac Surgery of the Washington Hospital Center was queried to identify all patients who had undergone CABG and received <4 grafts between September 1989 and July 1999 (n=19 512). Patients who had undergone CABG with concurrent valve replacement (n=1811), aneurysmectomy (n=22), or carotid endarterectomy (n=79) were excluded. Patients who had CABG without cardiopulmonary bypass (n=1072) were also excluded from the study. The remaining 16 528 consecutive patients who underwent CABG during the study period constituted the population of the present study. Baseline demographics, proce-
Strokes were confirmed by an independent neurologist and/or appropriate brain imaging.

**Statistical Analysis**

Primary comparisons were performed between the patients with and without stroke (stroke and no-stroke patients, respectively). Data were expressed as percentages or as mean ± SD. Categorical variables were compared by using a 2-tailed Fisher exact test. Continuous variables were compared by using 2-tailed unpaired Student t tests for variables with normal distributions and 2-tailed Mann-Whitney U tests for variables with nonnormal distributions. Univariate relative risks and 95% CIs were calculated.

A multivariate, stepwise, forward logistic regression analysis was conducted to determine independent predictors of postoperative in-hospital stroke. The variables included in the univariate risk analysis are presented in Table 1. The criterion for a variable entry into the logistic model was a univariate probability level of P < 0.2. A value of P ≤ 0.05 was considered statistically significant. The quality of the fit of the logistic model was tested with the Hosmer-Lemeshow goodness-of-fit test. The area under the receiver operating characteristic curve was used to assess how well the model could discriminate between patients with stroke versus those without stroke. All statistical analyses were performed by using the program SPSS 9.0 for Windows 95 (Statistical Package for the Social Sciences, Inc).

**Results**

A total of 16 528 consecutive patients undergoing CABG were included in the present study. Postoperative stroke occurred in 333 patients (2.0%). The baseline clinical characteristics of patients with and without stroke are summarized in Table 1. Patients with postoperative stroke were significantly older; they were more frequently female; and they were more likely to have diabetes, hypertension, congestive heart failure, recent myocardial infarction, previous cerebrovascular accident, carotid artery disease, chronic renal insufficiency, ejection fraction < 34%, and unstable angina than were patients without stroke (Table 1). Patients who had emergent CABG were also more likely to develop postoperative stroke.

Of patients who had carotid artery disease and developed stroke after surgery (n = 21), 16 had stroke ipsilateral to the location of carotid artery disease, whereas 5 developed stroke in a contralateral location (n = 3) or bilateral (n = 2) relative to the site of carotid artery disease.

Operative and postoperative characteristics of patients are presented in Table 2 (univariate analysis). Aortic atherosclerosis was more frequent in stroke patients. Cross-clamp time was significantly higher in those who developed postoperative stroke (46 ± 19 minutes for stroke patients versus 42 ± 25 minutes for no-stroke patients, P < 0.001). Similarly, cardiopulmonary bypass time was also significantly prolonged for stroke patients (77 ± 59 minutes for stroke patients versus

### Table 1. Baseline Clinical Characteristics (Univariate Analysis)

<table>
<thead>
<tr>
<th></th>
<th>Stroke Patients (N=333)</th>
<th>No-Stroke Patients (N=16 195)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;75 y</td>
<td>90 (27)</td>
<td>2 629 (16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>117 (35)</td>
<td>4 298 (26)</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>143 (43)</td>
<td>4 874 (30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>224 (67)</td>
<td>9 055 (56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>36 (11)</td>
<td>1 072 (7)</td>
<td>0.005</td>
</tr>
<tr>
<td>Recent myocardial infarction</td>
<td>10 (3)</td>
<td>116 (1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preoperative atrial fibrillation</td>
<td>9 (3)</td>
<td>312 (2)</td>
<td>0.34</td>
</tr>
<tr>
<td>Previous cerebrovascular accident</td>
<td>64 (19)</td>
<td>1 328 (8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Carotid artery disease</td>
<td>21 (6)</td>
<td>407 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>137 (41)</td>
<td>3 868 (24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ejection fraction &lt;34%</td>
<td>140 (42)</td>
<td>4 592 (28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>246 (74)</td>
<td>10 913 (67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Emergent CABG</td>
<td>47 (14)</td>
<td>1 530 (9)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Variables are expressed as n (%).

### Table 2. Operative and Postoperative Characteristics (Univariate Analysis)

<table>
<thead>
<tr>
<th></th>
<th>Stroke Patients (N=333)</th>
<th>No-Stroke Patients (N=16 195)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic atherosclerosis</td>
<td>15 (4)</td>
<td>322 (2)</td>
<td>0.005</td>
</tr>
<tr>
<td>Reoperation due to bleeding</td>
<td>11 (3)</td>
<td>225 (1)</td>
<td>0.008</td>
</tr>
<tr>
<td>Low cardiac output syndrome</td>
<td>110 (33)</td>
<td>2248 (14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postoperative myocardial infarction</td>
<td>4 (1.2)</td>
<td>54 (0.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>Postoperative intraaortic balloon pump</td>
<td>29 (9)</td>
<td>618 (4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prolonged ventilation</td>
<td>69 (21)</td>
<td>725 (4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>8 (2)</td>
<td>81 (0.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postoperative atrial fibrillation</td>
<td>156 (47)</td>
<td>4947 (31)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Variables are expressed as n (%).
The number of proximal anastomoses was higher in patients who had a stroke than in those who did not (2.7±1 versus 2.4±1, respectively; P<0.001).

Postoperative cardiovascular, pulmonary, and renal complications were significantly higher in patients with stroke (Table 2). Postoperative new-onset atrial fibrillation occurred in 47% of the patients who developed postoperative stroke and in 31% of the patients without stroke (P<0.001).

### Independent Predictors of Postoperative Stroke

The results of the multivariate logistic regression analysis model are summarized in Table 3 (see also the Figure). Variables that emerged as independent predictors of stroke included chronic renal insufficiency, recent myocardial infarction, previous cerebrovascular accident, carotid artery disease, hypertension, diabetes, advanced age, moderate/severe left ventricular dysfunction, low cardiac output syndrome, and new-onset atrial fibrillation. The area under the receiver operating characteristic curve was 0.92.

### Resource Utilization and In-Hospital Mortality

Postoperative stroke was found to significantly prolong the postoperative hospital stay (11±4 days for stroke patients versus 7±3 days for no-stroke patients, P<0.001) as well as the intensive care unit stay (2±2 days for stroke patients versus 1±1 days for no-stroke patients, P<0.001). In-hospital mortality was also significantly higher in patients with stroke (n=47, 14.4%) than in patients without stroke (n=436, 2.7%; P<0.001).

### Discussion

Stroke was a common complication after CABG in the 1960s (5% to 9%). Despite the improvement in surgical techniques and cardioplegic agents, along with the introduction of membrane oxygenators and in-line filtration, there is a persistent stroke rate associated with CABG ranging from 1% to 5%. It is estimated that 3000 to 15 000 patients each year suffer a stroke in the perioperative period after CABG. In the present study, the incidence of stroke was the same through-out the study period (1.8% from 1989 to 1994 versus 2.0% from 1995 to 1999) despite an increase in the high-risk patients who underwent surgery during the later study period (hypertension, 52% from 1989 to 1994 versus 60% from 1995 to 1999 [P<0.001]; diabetes, 27% versus 33% [P<0.001]; carotid artery disease, 1.1% versus 1.6% [P=0.006]; and age, 64±10 versus 64±11 years [P=0.06]). However, in the multivariate analysis, the period of study has not emerged as an independent predictor of higher risk of stroke.

Cerebral microemboli generated during CABG with cardiopulmonary bypass might be implicated in postoperative neurological impairment. Pathological examination by Moody et al of the brain after conventional CABG revealed the presence of multiple emboli lodged in small cerebral arterioles and capillaries. Additionally, BhaskerRao et al documented in a prospective study that cerebral dysfunction was significantly lower after CABG without cardiopulmonary bypass compared with on-pump CABG. Previous investigators have also found an association between prolonged cardiopulmonary bypass time (>120 minutes) and increased risk of postoperative stroke. Moreover, in patients who had on-pump CABG, proximal anastomoses were performed by use of complete cross-clamping of the aorta versus only a side clamp (used in off-pump CABG), a fact that may also...
to an increased risk of stroke in on-pump CABG. These findings emphasize the unfavorable effects of cardiopulmonary bypass on the subsequent development of stroke.

Additionally, recent myocardial infarction (within 24 hours before CABG) was associated with a 3 times higher risk of stroke. Moore et al.\(^\text{10}\) reported a higher incidence of stroke after recent myocardial infarction that is probably related to the hemodynamic instability, increased blood thrombogenicity, and pronounced sympathetic activation in post–myocardial infarction patients. Comorbid conditions, such as chronic renal insufficiency,\(^\text{11}\) previous cerebrovascular accident,\(^\text{3,4}\) carotid artery disease,\(^\text{12}\) hypertension,\(^\text{13}\) diabetes mellitus,\(^\text{14}\) advanced age,\(^\text{15}\) and depressed ejection fraction,\(^\text{6}\) have been found in this and previous studies to predict postoperative stroke.

Among the postoperative variables, new-onset atrial fibrillation was associated with a higher risk of postoperative stroke. Atrial fibrillation has consistently been found to increase stroke rate in various clinical settings.\(^\text{3,16}\) Postoperative low cardiac output syndrome was associated with a 2-fold higher risk of stroke. Wide fluctuations in arterial blood pressure, as well as increased thrombogenicity and cerebral hypoperfusion, are implicated in the pathophysiology of stroke in this subset of patients.\(^\text{3,6}\) Atrial fibrillation most probably is related to the development of postoperative atrial fibrillation combined with low cardiac output was correlated only with late (postoperative) stroke because early (intraoperative) strokes precede the onset of postoperative atrial fibrillation.\(^\text{3}\)

In the present study, stroke significantly increased the length of hospital and intensive care unit stay, as previously reported.\(^\text{2}\) Moreover, patients who developed stroke after CABG had a 5-fold higher rate of in-hospital mortality than did patients without stroke (14.4% versus 2.7%, respectively). This is in accordance with previous studies that have also reported a high mortality rate (13% to 41%) in patients with stroke after CABG.\(^\text{2}\)

Clinical Implications

The typically poor postoperative course of patients who develop stroke after CABG underlines the need for timely recognition and prevention/modification of factors that predispose to stroke. Carotid duplex ultrasonography may identify significant carotid disease in high-risk patients. An alternative therapeutic approach in this subset of patients may be concomitant CABG with carotid endarterectomy or a staged approach with carotid endarterectomy preceding CABG.\(^\text{17}\)

A modification of the surgical strategy, such as the “no-touch technique” described by Mills and Everson,\(^\text{18}\) might also be important in these patients. Furthermore, the increasing recognition of the role played by aortic atheroma, the innovative steps taken to minimize this risk (including epiaortic scanning), and the potential for intra-aortic filtration are all currently undergoing large-scale prospective evaluations.\(^\text{19}\) Royse et al.\(^\text{20}\) have demonstrated that the use of epiaortic scanning and of a Y graft, which uses the radial artery joined to the pedicled left internal mammary artery in a Y-graft fashion, is associated with a significantly decreased incidence of cerebral embolization secondary to aortic instrumentation. CABG without cardiopulmonary bypass requires further investigation as an approach for decreasing the incidence of stroke and should potentially be considered in patients with carotid artery disease or other high-risk characteristics for stroke. However, the benefits of this technique have not been evaluated in a prospective randomized setting.

In addition, pharmaceutical agents, such as gangliosides,\(^\text{21}\) glutamate receptor antagonists, and antioxidants, may potentially minimize neuronal damage and decrease the occurrence of stroke.\(^\text{23}\) It has also been suggested that prostaedylin infusion during cardiopulmonary bypass may lower the incidence of encephalopathy and stroke during CABG by preventing the adhesion of platelets to the extracorporeal tubing and the subsequent microembolization.\(^\text{22}\) Further studies are needed to prospectively investigate the potential benefits of pharmaceutical agents in reducing the incidence of stroke after CABG.

Study Limitations

We studied an unselected cohort of CABG patients that enabled the documentation of 333 index events and allowed the creation of a statistically powerful regression model to identify predictors of postoperative stroke. Limitations of the present study include limitations inherent in any retrospective analysis. However, all data elements were prospectively recorded according to specific definitions. Although evaluation by an independent neurologist and/or brain imaging was routinely performed in patients with suspected neurological events, there was no neuropsychological testing that would have enabled the assessment of more subtle changes in mentation and behavior.

The contribution of postoperative atrial fibrillation to stroke risk may have been underestimated in the present study because the timing of the neurological event was not taken into consideration. Indeed, because early strokes precede the onset of postoperative atrial fibrillation, this arrhythmia cannot be a predictor of these events.\(^\text{3}\)

Another limitation was that we detected aortic atherosclerosis by surgical palpation and not by ultrasonography; however, surgical palpation, when positive, has a high degree of specificity,\(^\text{2}\) as reported by Wolman et al.\(^\text{2}\) in a study involving 24 institutions. The reason we have not used ultrasonography was because it was not always available or considered to be the standard of care at the time the study was performed. Furthermore, long-term morbidity and mortality outcomes in patients who developed stroke after CABG were outside the scope of the present study.

References


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**Editorial Comment**

An estimated 650,000 coronary artery bypass graft operations are performed in the United States each year. The procedure has significantly reduced morbidity related to unstable angina and mortality in certain patients with chronic stable angina. However, the incidence of clinically obvious stroke is reported to be between 0.8% and 5.2%. Those figures suggest that between 5000 and 35,000 new strokes are the result of this procedure, which possibly makes cardiac bypass surgery the single largest cause of iatrogenic stroke in the United States.

The study by Stamou et al focused solely on patients who had cardiopulmonary bypass (so-called on-pump patients) as part of the surgical procedure. Some authors suggest that patients who have coronary bypass surgery without cardiopulmonary bypass (so-called off-pump patients) are at lower risk for stroke. To date, there is no randomized trial evidence to suggest that the hypothesis of reduced strokes in off-pump patients is true. And, even if true, there are other factors to consider between the 2 methods of surgery. For example, graft durability may be better in on-pump surgery, because off-pump surgery can be technically more challenging.

By virtue of the size of the database available to them, Stamou et al were able to identify, with sufficient power, risk factors that are more likely to be associated with this outcome in on-pump patients. A similar analysis of the >1000 off-pump patients in their database would be interesting, to see whether similar factors are related to clinically obvious stroke. Their findings are, at all once, new, confirmatory, and in some instances, surprising. Chronic renal insufficiency (serum creatinine >2.0 mg/dL) emerged as the most potent risk factor while aortic atherosclerosis (as detected by palpation) failed to emerge as an independent risk factor. Other factors such as advanced age, hypertension, diabetes, and postoperative atrial fibrillation seem more obvious. Their research raises important questions. What is the mechanism by which these factors put patients at greater risk? Since the strokes that occur around the time of cardiopulmonary bypass are presumed to be embolic, what is it about chronic renal failure, for example, that might increase the risk of embolism? Or, are these conditions merely markers of other disease states?

The occurrence of clinically obvious stroke, the outcome measure in this study, likely represents only the tip of the iceberg. Postoperative cognitive impairment or delirium, conditions that may not necessarily fall under the rubric of “stroke,” quite possibly represent multiple territory cerebral microinfarcts occurring as a result of an embolic shower. Consider the example of a 73-year-old woman 2 days after on-pump bypass surgery referred for consultation because of “confusion and left arm weakness.” Though the clinical picture suggested only a right hemispheric event, diffusion-weighted imaging suggested a more diffuse pattern of insult (Figure). Similarly, a physician who undergoes bypass surgery and is no longer able to practice 3 months after surgery because of “difficulty concentrating” has possibly also sustained multiterritory cerebral embolism. The 2.0% complica-
tion rate of “stroke” quoted in the current article likely represents an underestimate, because not all patients were independently assessed and patients with strokes might have been classified in other categories, such as delirium, depression, or dementia. Unfortunately, diagnosing these patients radiologically has traditionally been difficult in the past. Newer modalities may show promise in that regard.

Finally, the coronary artery bypass surgery operating room may represent an excellent venue in which to test the efficacy of putative neuroprotectants. In contrast to traditional trials, which are conducted in relatively uncontrolled settings (eg, emergency rooms), trials in bypass patients may more closely mirror those of the preclinical studies (eg, controlled blood pressure, temperature, and blood sugar). Studies such as those of Stamou et al help to identify those at highest risk and may help focus future studies of alleged neuroprotectants so that smaller sample sizes are required.

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Stroke After Coronary Artery Bypass: Incidence, Predictors, and Clinical Outcome
Sotiris C. Stamou, Peter C. Hill, George Dangas, Albert J. Pfister, Steven W. Boyce, Mercedes K.C. Dullum, Ammar S. Bafi and Paul J. Corso

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