New-Onset Postoperative Atrial Fibrillation After Isolated Coronary Artery Bypass Graft Surgery and Long-Term Survival

Giovanni Filardo, PhD, MPH; Cody Hamilton, PhD; Robert F. Hebeler, Jr, MD; Baron Hamman, MD; Paul Grayburn, MD

Background—The advancing age and generally increasing risk profile of patients receiving isolated coronary artery bypass graft (CABG) surgery is expected to raise incidence of new-onset postoperative atrial fibrillation (AFIB) resulting in potentially higher risk of adverse outcomes. In the early postoperative course, new-onset post-CABG AFIB is considered relatively easy to treat and is believed to have little impact on patients’ long-term outcome. However, little has been done to determine the effect of new-onset post-CABG AFIB on long-term survival, and this relationship is unclear.

Methods and Results—Survival was assessed in a cohort of 6899 consecutive patients without preoperative AFIB who underwent isolated CABG at Baylor University Medical Center, Dallas, Tex, between January 1, 1997 and December 31, 2006; patients who died during CABG were excluded. Ten-year unadjusted survival was 52.3% (48.4%, 56.0%) for patients with new-onset postoperative AFIB and 69.4% (67.3%, 71.4%) for patients without it. A propensity-adjusted model controlling for risk factors identified by the Society of Thoracic Surgeons and other clinical/nonclinical details was used to investigate the association between new-onset AFIB post-CABG and long-term survival. After adjustment, new-onset AFIB post-CABG was significantly associated (hazard ratio, 1.29; 95% CI, 1.16, 1.45) with increased risk of death.

Conclusions—This study provides evidence that new-onset post-CABG AFIB is significantly associated with increased long-term risk of mortality independent of patient preoperative severity. After controlling for a comprehensive array of risk factors associated with post-CABG adverse outcomes, risk of long-term mortality in patients that developed new-onset post-CABG AFIB was 29% higher than in patients without it. (Circ Cardiovasc Qual Outcomes. 2009;2:000-000.)

Key Words: CABG ■ atrial fibrillation ■ coronary disease ■ mortality ■ survival

Atrial fibrillation (AFIB) is a common complication of cardiac surgery, occurring in 10% to 65% of patients, depending on the study cohort and definition/method of detection used. Incidence of new-onset AFIB after isolated coronary artery bypass graft surgery (CABG) is lower than for valvular cardiac surgery but is still estimated to affect 11% to 40% of patients. As the population of patients undergoing CABG ages, this number is expected to rise as there is an estimated 24% increase in frequency of postoperative AFIB with each additional 5 years of age.

Although early studies appeared to indicate that new-onset postoperative AFIB was a transient event with little impact on short- or long-term outcomes, more recent studies have shown AFIB after cardiac surgery to be associated with increased frequency of intensive-care unit readmission, perioperative myocardial infarction, stroke, ventricular arrhythmias, persistent congestive heart failure, renal dysfunction/failure, cognitive changes, and increased resource use. Moreover, studies examining the impact of postoperative AFIB on survival after cardiac surgery have shown associations with increased mortality in-hospital and at 6 months. Only one study to date has examined long-term survival. It showed that, in low-risk patients undergoing isolated initial CABG between 1994 and 1999, there was an independent association between postoperative AFIB and increased mortality at 4 to 5 years. Over the past decade, there has been a substantial shift toward the use of percutaneous coronary intervention for reperfusion, reducing the “routine” operative CABG workload of cardiothoracic surgeons and transforming the operative list to include many older and higher-risk patients. The increasing risk profile of the population receiving CABG makes the rela-
tionship between postoperative AFIB and survival of even greater interest. For this reason, we examined the relationship between new-onset postoperative AFIB and long-term survival in a recent population who underwent isolated CAGB within the Baylor Health Care System from 1997 to 2006, considering the recently expanded risk factors for postoperative adverse events recognized by the Society of Thoracic Surgeons (STS) to isolate the direct effect of new-onset postoperative AFIB on survival. We hypothesized that patients who did develop new-onset post-CABG AFIB experienced worse long-term survival than patients who did not develop new-onset postoperative AFIB.

WHAT IS KNOWN

- New-onset postcoronary artery bypass graft surgery atrial fibrillation (AFIB) affects 11% to 40% of patients.
- New-onset postcoronary artery bypass graft surgery AFIB is believed to have little impact on patients’ long-term outcome.

WHAT THIS STUDY ADDS

- Our findings provide evidence that new-onset postcoronary artery bypass graft surgery AFIB has a significant effect on long-term mortality.
- Our findings encourage implementation of the recommendations within the American College of Cardiology/American Heart Association-European Society of Cardiology guidelines regarding the management of new-onset AFIB.
- Further research should focus on the development of more effective preventive therapeutic strategies.
- Future research should identify high-risk patients for new-onset postoperative AFIB so that they can be targeted for potential prophylaxis.

Methods

Patient Data

All consecutive patients who underwent isolated CAGB surgery at Baylor University Medical Center (Dallas, Tex) between January 1, 1997 and December 31, 2006 without preoperative AFIB were considered for this study. Study data included clinical and nonclinical details collected by Baylor University Medical Center’s and the STS Adult Cardiac Surgery Database.4 Methods regarding data abstraction have been described elsewhere.4,15 Key risk factors for post-CABG adverse outcomes16 recognized by the STS form the core elements for this study. These included age, gender, race, body surface area, diabetes, ejection fraction, left main disease, urgency of operation, heart failure, preoperative revascularization procedure, myocardial infarction timing (hours since myocardial infarction), preoperative endocarditis, previous valve surgery, or missing myocardial infarction timing.

Exposure and Outcome Definition

New-onset postoperative AFIB was defined as new AFIB during hospitalization after isolated CAGB as classified by the STS Adult Cardiac Surgery Database and indicates whether the patient had a new onset of AFIB/flutter requiring treatment. Survival was measured as time (in days) to either death or last follow-up (November 1, 2007) from date of surgery. Vital status was assessed using the National Death Index data from January 1, 1997 to November 1, 2007.

Table 1. Cohort of Patients Without Preoperative AFIB Who Underwent CAGB Surgery and Survived Past the Day of Surgery at Baylor University Medical Center Between January 1997 and December 2006

<table>
<thead>
<tr>
<th>Patients in the initial cohort</th>
<th>Patients without preoperative AFIB that underwent isolated CAGB between January 1, 1997 and 31 December, 2006 at Baylor University Medical Center with a valid Social Security No.</th>
<th>7025 (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients in the final cohort</td>
<td>Patients with preoperative endocarditis, previous valve surgery, or missing myocardial infarction timing</td>
<td>101 (1.4%)</td>
</tr>
<tr>
<td>Patients expiring on day of surgery</td>
<td>Patients with other missing variables were considered for the present investigation and, as recommended by the STS workforce evidence-based surgery report, multiple imputation was performed for continuous and ordinal missing variables via predictive mean matching.</td>
<td>25 (0.4%)</td>
</tr>
</tbody>
</table>

Cardiac Surgery Database and indicates whether the patient had a new onset of AFIB/flutter requiring treatment.

Survival was measured as time (in days) to either death or last follow-up (November 1, 2007) from date of surgery. Vital status was assessed using the National Death Index data from January 1, 1997 to November 1, 2007.

Statistical Analysis

Differences in the continuous factors in Table 2 between the patients that experienced new-onset postoperative AFIB and those that did not were tested via a Wilcoxon-Mann-Whitney test. Categorical factors were tested via a χ² test. To account for multiple comparisons, the presented probability values were adjusted via the method of Bonferroni. A Kaplan-Meier analysis was executed to investigate the unadjusted association of postoperative AFIB and survival. To account for possible confounders of this association, a propensity score approach was used.17 Specifically, a logistic regression model was fit to estimate the likelihood of postoperative AFIB. Covariates for this logistic model included established risk factors identified by the STS,16 and other clinical and demographic factors (see Table 2). Restricted cubic splines were used for all continuous predictors.15,18,19 Missing data were present in only 4 of the 22 variables included in the propensity score (new-onset post-CABG AFIB group: body surface area, 0.6%; creatinine, 32.0%; ejection fraction, 4.2%; and status, 0.3%; no new-onset post-CABG AFIB group: body surface area, 0.6%; diabetes, 30.2%; ejection fraction, 6.9%; and status, 0.3%) and were accounted for via multiple imputation using predictive mean matching.20,21 To ensure a proper estimation for the missing values, a large number of imputations (200) were performed for each missing value. Further details regarding the imputation procedure can be found from the documentation for the aregImpute function from the Hmisc library for the R software.22

Estimates from the resulting propensity model were then used to adjust the effect of postoperative AFIB on survival in a Cox proportional hazards model. If we let \( y_j \) denote the linear predictor predicted value (Xβ) from the propensity model described previously and AFIB denote whether the patient experienced new-onset post-CABG AFIB, then the final model was as given:

\[
\log(h(t)) = \gamma_0 + \text{AFIB} + \gamma_1 y_j + \cdots + \gamma_p y_j^p.
\]

here

\[
y_j^{p+1} = a_j^p - a_j^p (k_j - k) / (k_j - k) + a_j^p (k_j - k) / (k_j - k).
\]
Table 2. Society of Thoracic Surgeons Operative (In-Hospital) Mortality Risk Factors and Other Clinical/Nonclinical Details for 6899 Patients Without Preoperative AFIB Who Underwent Isolated CABG Surgery and Survived Past the Day of Surgery at Baylor University Medical Center Between January, 1997 and December, 2006

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Postoperative AFIB (n=5085; 74%)</th>
<th>Postoperative AFIB (n=1814; 26%)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>62.2 [54.6, 70.1]†</td>
<td>69.1 [61.6, 75.5]†</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.860</td>
</tr>
<tr>
<td>Male</td>
<td>71.0%</td>
<td>74.0%</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>29.0%</td>
<td>26.0%</td>
<td></td>
</tr>
<tr>
<td>Body surface area</td>
<td>2.0 [1.8, 2.1]†</td>
<td>2.0 [1.9, 2.2]†</td>
<td>0.061</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White</td>
<td>80.0%</td>
<td>84.0%</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>9.0%</td>
<td>6.0%</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>4.0%</td>
<td>3.0%</td>
<td></td>
</tr>
<tr>
<td>Other/unknown</td>
<td>7.0%</td>
<td>7.0%</td>
<td></td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>34.4%</td>
<td>33.2%</td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td>5.2%</td>
<td>5.5%</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.0 [0.8,1.2]†</td>
<td>1.0 [0.8,1.2]†</td>
<td>0.441</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>13.7%</td>
<td>16.4%</td>
<td>0.119</td>
</tr>
<tr>
<td>Hypertension</td>
<td>68.5%</td>
<td>71.2%</td>
<td>0.784</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>15.8%</td>
<td>19.7%</td>
<td>0.003</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>5.1%</td>
<td>6.1%</td>
<td>1.00</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Never</td>
<td>38.0%</td>
<td>41.0%</td>
<td></td>
</tr>
<tr>
<td>Previous</td>
<td>35.0%</td>
<td>39.0%</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>27.0%</td>
<td>20.0%</td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>16.5%</td>
<td>20.8%</td>
<td>0.001</td>
</tr>
<tr>
<td>Previous interventions</td>
<td></td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>14.8%</td>
<td>13.0%</td>
<td></td>
</tr>
<tr>
<td>Previous CABG</td>
<td>6.8%</td>
<td>6.7%</td>
<td></td>
</tr>
<tr>
<td>Preoperative cardiac status</td>
<td></td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>MI timing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>59.0%</td>
<td>56.0%</td>
<td></td>
</tr>
<tr>
<td>≤6 hours</td>
<td>19.0%</td>
<td>20.0%</td>
<td></td>
</tr>
<tr>
<td>&gt;6 hours and &lt;24 hours</td>
<td>18.0%</td>
<td>19.0%</td>
<td></td>
</tr>
<tr>
<td>&gt;24 hours</td>
<td>4.0%</td>
<td>5.0%</td>
<td></td>
</tr>
<tr>
<td>Preoperative angina</td>
<td>66.2%</td>
<td>66.0%</td>
<td>1.00</td>
</tr>
<tr>
<td>Hemodynamics and cath</td>
<td></td>
<td></td>
<td>0.021</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>50.0 [40.0,60.0]†</td>
<td>50.0 [35.0,60.0]†</td>
<td></td>
</tr>
<tr>
<td>Left main disease</td>
<td>21.0%</td>
<td>23.9%</td>
<td>0.296</td>
</tr>
<tr>
<td>Operative</td>
<td></td>
<td></td>
<td>0.654</td>
</tr>
<tr>
<td>Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elective</td>
<td>83.0%</td>
<td>81.0%</td>
<td></td>
</tr>
<tr>
<td>Nonelective</td>
<td>17.0%</td>
<td>19.0%</td>
<td></td>
</tr>
<tr>
<td>Off pump</td>
<td>8.9%</td>
<td>9.2%</td>
<td>1.00</td>
</tr>
<tr>
<td>Preoperative IABP</td>
<td>11.2%</td>
<td>13.6%</td>
<td>0.207</td>
</tr>
</tbody>
</table>

*Bonferroni adjustment.
†Median value [lower quartile, upper quartile].
PCI indicates percutaneous coronary intervention; MI, myocardial infarction; IABP, intra-aortic balloon pump.
for $j = 1$ to $5$, where $k_j$ denotes the $j$th knot for the cubic spline and $a_j = (y_1 - k_j)$ if $y_1 > k_j$ and $= 0$ otherwise. The use of the propensity score as a continuous function in the model avoids some of the dangers involved in using categorizations (e.g., quantiles) of the propensity score. Furthermore, modeling the propensity score with a cubic spline obviates the need to assume a linear effect for the propensity score.

The possibility of effect modification produced by gender and age were investigated. No significant modification was detected.

The proportionality of the hazards in this model was checked using the test statistic of Grambsch and Therneau. Adjusted survival curves were estimated and plotted via the method of Kalbfleisch and Prentice. Results of the final adjusted model were similar to those based on all patients (whether or not they had missing preoperative creatinine). Finally, an unadjusted Cox model (a Cox model containing new-onset AFIB as the sole predictor) was fit to compare the unadjusted hazard ratio (HR) to the final adjusted HR.

All analyses were performed using R software, version 2.7.1. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
The final study cohort included 6899 subjects, 1814 (26%) with postoperative AFIB (median age, 69.1 years), and 5085 patients without postoperative AFIB (median age, 62.2 years).

The Kaplan-Meier analysis suggested a significant unadjusted survival difference (log-rank test: $P < 0.0001$) between patients with and without postoperative AFIB (Figure 1). Five-year survival rates were 75.1% (72.8%, 77.1%) and 85.2% (84.1%, 86.2%) for patients with and without postoperative AFIB, respectively. Ten-year survival was 52.3% (48.4%, 56.0%) for patients with new-onset postoperative AFIB and 69.4% (67.3%, 71.4%) for patients without it. The unadjusted HR was 1.77 (95% CI, 1.59, 1.97).

After propensity adjustment for all the risk factors in Table 2, the difference in the survival curves remained highly significant ($P < 0.001$). The estimated HR for new-onset post-CABG AFIB versus no new-onset post-CABG AFIB was 1.29 (95% CI, 1.16, 1.45). Thus, independently of the patient’s clinical presentation, at least with regard to the risk factors listed in Table 2, the estimated hazard increased by 29% for patients developing AFIB postoperatively. It should be noted that this adjusted HR is quite different in magnitude from the unadjusted HR, indicating the need for statistical adjustment. The adjusted survival curves are presented in Figure 2.

Discussion
Our study provides evidence that new-onset post-CABG AFIB is significantly associated with increased long-term risk of mortality independently of patients’ preoperative severity. After controlling for a comprehensive array of risk factors associated with post-CABG adverse outcomes, risk of long-term mortality in patients who developed new-onset post-CABG AFIB was significantly higher (29%) than in patients without it. In other words, a patient in this cohort who experienced new-onset post-CABG AFIB faced 29% higher risk of mortality than a patient with exactly the same preoperative risk profile who did not.

Early postoperative new-onset post-CABG AFIB is commonly considered relatively easy to treat and is believed to have little effect on patients’ short- and long-term outcomes. The American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology clinical guidelines address management of new-onset postoperative AFIB but do not specifically address...
Our findings augment the established evidence regarding the detrimental effect of new-onset post-CABG AFIB on short-term outcomes\textsuperscript{9–12} with evidence of a direct effect on long-term mortality. Our results are consistent with those of Villareal et al\textsuperscript{6} but also provide novel data regarding the risk of mortality associated with new-onset post-CABG AFIB in elderly and high-risk populations.

Some study limitations should be noted. First, the study was conducted at a single center in Dallas, Tex, which may limit the generalizability of the results. Additionally, we cannot exclude the possibility that new-onset post-CABG AFIB may be a marker of underlying myocardial disease, inflammation, or neurohormonal activity, which may predispose patients to mortality and morbidity.\textsuperscript{28} As for the details regarding the management of postoperative AFIB, information on the preoperative and intraoperative pharmacological management and clinical data concerning possible underlying conditions were not routinely collected, and therefore their confounding effects are not accounted in our study. The possibility that these or other unknown factors confound the relationship between exposure (post-CABG AFIB) and outcome (survival) exists, as is the case in any observational study. However, the multivariable propensity model developed to conduct the statistical analysis considered an extensive list of risk factors identified by the STS in addition to other important variables, providing a rigorous adjustment for potential confounders.

Further research should focus on the development of more effective preventive therapeutic strategies and the vigorous implementation of the recommendations within the American College of Cardiology/American Heart Association/European Society of Cardiology guidelines regarding the postoperative management of new-onset AFIB. Moreover, future research should identify high-risk patients for new-onset postoperative AFIB so that they can be targeted for prophylaxis.

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