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Heart Rhythm Disorders

New-Onset Atrial Fibrillation Predicts Long-Term Mortality After Coronary Artery Bypass Graft

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Objectives	We sought to investigate the association between new-onset atrial fibrillation after coronary artery bypass graft (CABG) (post-operative atrial fibrillation [POAF]) and long-term mortality in patients with no history of atrial fibrillation.
Background	POAF predicts longer hospital stay and greater post-operative mortality.
Methods	A total of 16,169 consecutive patients with no history of AF who underwent isolated CABG at our institution between January 1, 1996, and December 31, 2007, were included in the study. All-cause mortality data were obtained from Social Security Administration death records. A multivariable Cox proportional hazards regression model was constructed to determine the independent impact of new-onset POAF on long-term survival after adjusting for several covariates. The covariates included age, sex, race, pre-operative risk factors (ejection fraction, New York Heart Association functional class, history of myocardial infarction, index myocardial infarction, stroke, chronic obstructive pulmonary disease, peripheral arterial disease, smoking, diabetes, renal failure, hypertension, dyslipidemia, creatinine level, dialysis, redo surgery, elective versus emergent CABG, any valvular disorder) and post-operative adverse events (stroke, myocardial infarction, acute respiratory distress syndrome, and renal failure), and discharge cardiac medications known to affect survival in patients with coronary disease.
Results	New-onset AF occurred in 2,985 (18.5%) patients undergoing CABG. POAF independently predicted long-term mortality (hazard ratio: 1.21; 95% confidence interval: 1.12 to 1.32) during a mean follow-up of 6 years (range 0 to 12.5 years). This association remained true after excluding from the analysis those patients who died in-hospital after surgery (hazard ratio: 1.21; 95% confidence interval: 1.11 to 1.32). Patients with POAF discharged on warfarin experienced reduced mortality during follow-up.
Conclusions	In this large cohort of patients, POAF predicted long-term mortality. Warfarin anticoagulation may improve survival in POAF. (J Am Coll Cardiol 2010;55:1370–6) © 2010 by the American College of Cardiology Foundation

Atrial fibrillation (AF) develops in 15% to 30% of patients undergoing isolated coronary artery bypass graft (CABG) (1–5). Post-CABG AF is associated with a longer hospital stay and increased perioperative morbidity and early mortality (6–8). Other studies have also suggested that post-CABG AF affects long-term survival (5,9). The impact of new-onset AF after CABG has not been thoroughly addressed because many of these analyses did not exclude patients with pre-existing paroxysmal AF (5,9). A history of AF predicts increased mortality in population-based studies

(10), in patients with heart failure (11), and in patients with known coronary artery disease (12). Therefore, a history of AF before undergoing CABG may also be a risk factor for mortality (13,14) after surgery. Whether new-onset AF after CABG, often considered a transient phenomenon (15), really predicts long-term mortality remains unanswered. We analyzed the effect of new-onset AF in patients undergoing CABG to determine whether it has an impact on long-term mortality.

Methods

Study protocol. We searched the Society of Thoracic Surgeons Adult Cardiac Database to identify consecutive patients with no history of AF or flutter who underwent isolated CABG at Emory University Hospital or Emory Crawford Long Hospital between January 1, 1996, and

December 31, 2007. The study sample consists of 16,169 patients. Extracted records include demographic data, pre-existing comorbidities, and clinical outcomes. The Emory University Institutional Review Board approved the protocol in compliance with Health Insurance Portability and Accountability Act standards and the Declaration of Helsinki. The Institutional Review Board waived obtaining individual informed consent before obtaining the data on these patients.

We identified the primary study variable as the new onset of AF after CABG (post-operative atrial fibrillation [POAF]). Therefore, we excluded any patient with a pre-operative history of paroxysmal or persistent AF. Pre-operative history of AF is a variable entered into the Society of Thoracic Surgeons (STS) database and obtained by chart review and patient interview. The study defines POAF according to the established STS definition, which defines new-onset AF as the occurrence of POAF or atrial flutter requiring treatment (i.e., beta-blockers, calcium-channel blockers, amiodarone, anticoagulation, or cardioversion).

The primary end point, the survival time after surgery, used the date of death of patients in the cohort, as identified by the Social Security Death Index (SSDI), a publicly available national database of death records extracted from the U.S. Social Security Administration's Death Master File Extract. The SSDI provided the date of death for each patient who died before the cutoff date of June 30, 2008, allowing computation of the Kaplan-Meier product-limit estimates and associated Cox regressions. Because the SSDI does not describe the cause of death, the analysis describes all-cause long-term mortality.

To better ascertain the isolated effect of POAF on long-term survival, 32 covariates of long-term mortality risk were identified and harvested from the STS database for use in a risk-adjustment analysis, using standard STS definitions for each risk factor and outcome. The covariates analyzed included age, sex, race, left ventricular ejection fraction, history of myocardial infarction, index myocardial infarction, congestive heart failure (CHF), New York Heart Association functional class, stroke, hypertension, diabetes mellitus, renal failure, dyslipidemia, smoking, chronic obstructive lung disease, peripheral vascular disease, the presence of left main disease (≥50%), last creatinine level, dialysis status, elective versus nonelective CABG, redo surgery, and the presence of any valvular disorder or post-operative complications (myocardial infarction, stroke, intra-aortic balloon pump, and post-operative respiratory distress syndrome). We also analyzed the effect of any discharge medications known to influence survival in patients with coronary artery disease. These included angiotensin-converting enzyme inhibitors, beta-blockers, lipid-lowering agents, amiodarone, aspirin, clopidogrel, and warfarin.

We also examined the use and impact of warfarin anticoagulation after discharge on survival.

Management of patients with POAF. It is our practice to restore sinus rhythm in the majority of patients within 24 to 48 hours after the onset of POAF with the use of antiarrhythmic drugs (AADs) or by electrical cardioversion. Patients who are discharged home in AF are maintained on warfarin (in the absence of any contraindication) and referred for cardioversion in 4 to 6 weeks. Patients discharged home on AADs are followed up in the cardiology clinic in 3 months. In the absence of evidence of AF recurrence, their AADs are stopped. The decision to stop warfarin in this case is left to the cardiologist's discretion. Thirty-day event recorder is performed on these patients after stopping their AADs and on any symptoms suggestive of AF recurrence. Initiation of warfarin therapy in a patient with POAF is a decision left to the cardiologist and the cardiovascular surgery team caring for the patient.

Statistical analysis. Trained personnel devoted exclusively to the task created and maintained a medical records database. Data were 100% complete for POAF and survival time. Data were missing for the following pre-operative characteristics: ejection fraction (n = 2,120, 13.1%); race (n = 348, 2.2%); and last creatinine level (n = 3,971, 24.6%). Multiple checks for data quality were performed both at the institutional level and before final entry into the STS national adult cardiac database.

A multiple imputation algorithm was used to impute missing values so that the whole sample could be analyzed to avoid selection bias that can occur by deleting cases with missing covariates. Ten datasets were imputed and estimates from these datasets were combined using methods described by Molenberghs et al. (16). Values that were missing were assumed to be missing at random.

To statistically evaluate the isolated effect of POAF on mortality, a multivariate Cox proportional hazards regression model was constructed that related survival time as a function of POAF, adjusting for the 32 covariates. Adjusted hazard ratios (HRs), along with 95% confidence intervals (CIs), were computed for POAF and the 32 covariates. The proportional hazards assumption was verified by a correlation analysis between the Schoenfeld residuals and ranked follow-up time.

Additionally, Kaplan-Meier product-limit estimates were generated to provide survival estimates at post-operative points in time. The Kaplan-Meier estimates for POAF status were compared for equality using log-rank tests.

Data were managed and analyzed using SAS Version 9.2 (SAS Institute Cary, North Carolina). The chi-square tests and 2-sample *t* tests for categorical and continuous predic-

Abbreviations and Acronyms

AAD = antiarrhythmic drug

AF = atrial fibrillation

CABG = coronary artery bypass graft

CHF = congestive heart failure

CI = confidence interval

HR = hazard ratio

POAF = post-operative atrial fibrillation

SSDI = Social Security Death Index

STS = Society of Thoracic Surgeons

Table 1	Cohort Characteristics	
n		16,196
Mean age, yrs (SD)		61.7 (10)
White		13,352 (82.6)
Male		11,638 (72.0)
Mean ejection fraction, % (SD)		50 (12.5)
Congestive heart failure		2,505 (15.5)
Diabetes		5,709 (35.3)
Hypertension		12,148 (75.1)

Values are n (%) unless otherwise indicated.

Table 3	Post-Operative Risk Factors by Presence of Atrial Fibrillation		
Parameters	No POAF (n = 13,184)	POAF (n = 2,985)	p Value
Post-operative myocardial infarction	121 (0.9)	37 (1.2)	0.11
Post-operative stroke	174 (1.3)	94 (3.2)	<0.001
Post-operative intra-aortic balloon pump	22 (0.2)	12 (0.4)	0.011
Post-operative acute respiratory distress syndrome	50 (0.4)	37 (1.2)	<0.001
Post-operative renal failure	57 (0.4)	64 (2.1)	<0.001

Values are n (%).
  Abbreviation as in **Table 2**.

tors, respectively, performed unadjusted comparisons. All statistical tests were 2 sided using an α = 0.05 level of significance. No adjustments for multiple tests were made.

Results

Cohort characteristics. Table 1 summarizes the characteristics of the study population. The group consists of a majority of white men, mean age 61.7 years, of whom 75% had hypertension, 35% had diabetes, and 15% had a diagnosis of CHF. The CABG procedure was performed without cardiopulmonary bypass in 41.5% of patients.

POAF occurred in 2,985 (18.5%) patients. Tables 2 and 3 summarize the characteristics of the cohort based on the presence or absence of POAF. Patients with POAF were older and more likely to have known pre-operative risk factors for AF or increased mortality (Table 2). They were

also more likely to have post-operative complications, including stroke, renal failure, and respiratory failure, and more likely to require an intra-aortic balloon pump for hemodynamic support (Table 3). The patients with POAF had a longer hospital stays than patients in whom AF did not develop (9.1 days vs. 5.4 days, p < 0.001).

Assessment of the medications upon discharge shows that patients with POAF were less likely to be discharged and receiving a beta-blocker, statin, or antiplatelet agent and were more likely to be discharged and receiving amiodarone and warfarin (Table 4). Only 20.5% of patients with AF were discharged and receiving warfarin.

Survival analysis. POAF was associated with an increased risk of mortality over a mean follow-up period of 6 years (range 0 to 12 years). The unadjusted HR estimate for the effect of POAF on mortality measured 1.85 (95% CI: 1.71 to 1.99; p < 0.001). As shown previously, patients with POAF are a sicker cohort with more comorbid conditions and post-operative complications. The adjusted HR for POAF was still statistically significant after adjusting for the effect of 32 different covariates (HR: 1.21, 95% CI: 1.12 to 1.32; p < 0.001). The Kaplan-Meier survival curves (Fig. 1) diverge early and are increasingly separate over time. Of the patients without POAF, 96.3% were alive 1 year after surgery compared with 90.1% of patients with POAF. The difference in survival persisted at 10 years after surgery (70.2% vs. 55.2%, respectively). The survival difference

Table 2	Demographic and Pre-Operative Risk Factors by Presence of Atrial Fibrillation		
Parameters	No POAF (n = 13,184)	POAF (n = 2,985)	p Value
Age, yrs (SD)	61.3 (10.9)	67.5 (9.5)	<0.001
Ejection fraction, % (SD)	50.6 (12.5)	49.9 (12.9)	0.008
Male	9,459 (71.7)	2,179 (73)	0.17
White	10,718 (81.3)	2,634 (88.2)	<0.001
Myocardial infarction	6,513 (49.4)	1,545 (51.8)	0.02
Congestive heart failure	1,931 (14.7)	574 (19.2)	<0.001
Chronic obstructive pulmonary disease	1,814 (13.8)	495 (16.6)	<0.001
Peripheral vascular disease	1,047 (7.9)	346 (11.6)	<0.001
Left main coronary artery disease	2,834 (21.5)	757 (25.4)	<0.001
Smoking	3,595 (27.3)	600 (20.1)	<0.001
Hypertension	9,781 (74.2)	2,367 (79.3)	<0.001
Diabetes	4,648 (35.3)	1,061 (35.5)	0.77
Stroke	998 (7.6)	291 (9.8)	<0.001
Creatinine level, mg/dl (SD)	1.2 (1.04)	1.32 (1.1.9)	<0.001
Dialysis	186 (1.4)	66 (2.2)	0.001
Renal failure	765 (5.8)	243 (8.1)	<0.001
Nonelective coronary artery bypass graft	2,547 (19.3)	637 (21.3)	0.012
Dyslipidemia	4,514 (34.2)	1,055 (35.3)	0.25
Previous surgery	741 (5.6)	166 (5.6)	0.9
Any valvular disease	3,084 (23.4)	977 (32.7)	<0.001

Values are n (%) unless otherwise indicated.
  POAF = post-operative atrial fibrillation.

Table 4	Discharge Medications by Presence of Atrial Fibrillation		
Parameters	No POAF (n = 13,184)	POAF (n = 2,985)	p Value
Beta-blockers	11,880 (90.1)	2,332 (78.1)	<0.001
Angiotensin-converting enzyme inhibitor	4,220 (32.0)	935 (31.3)	0.47
Statins	5,575 (42.3)	1,197 (40.1)	0.029
Amiodarone	78 (0.6)	189 (16.4)	<0.001
Aspirin	12,232 (92.8)	2,560 (85.8)	<0.001
Warfarin	545 (4.1)	613 (20.5)	<0.001
Clopidogrel	3,166 (24.0)	587 (19.7)	<0.001

Values are n (%).
  Abbreviation as in **Table 2**.
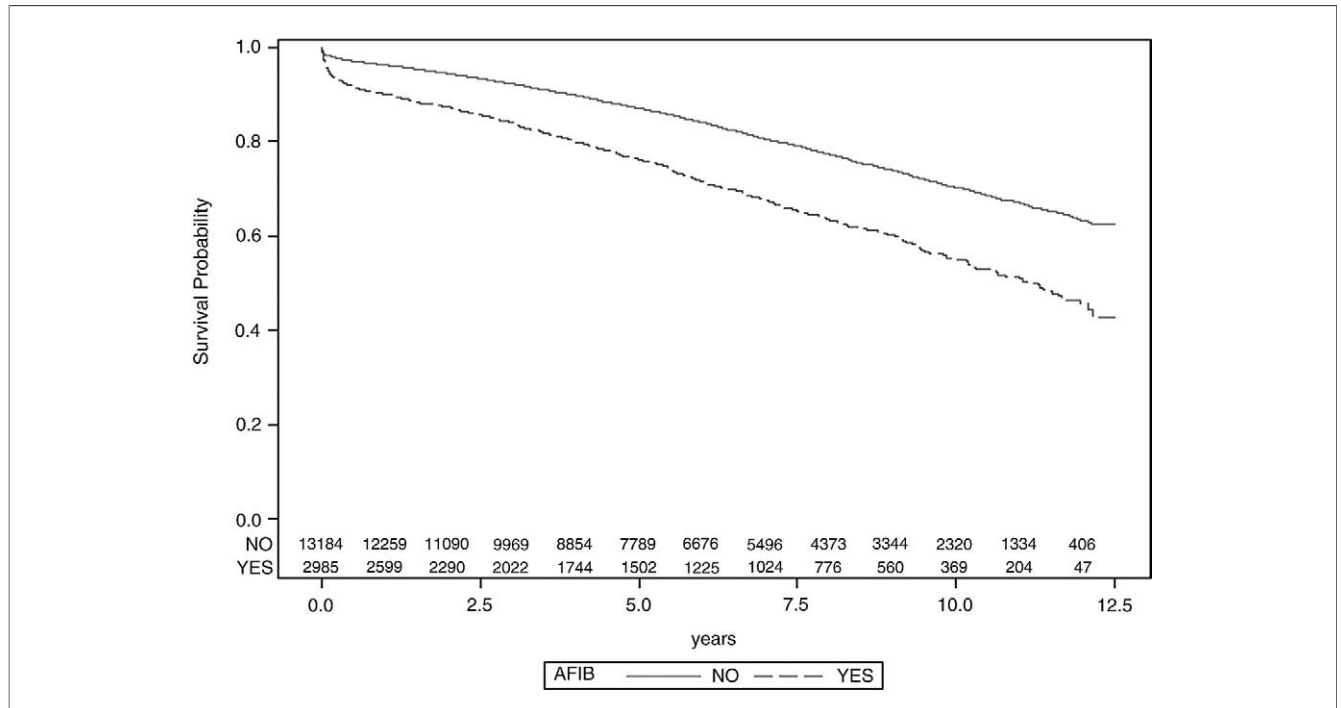
Figure 1 **Kaplan-Meier Survival Curve**

Continuous divergence in survival over time between patients with post-operative atrial fibrillation and those with no post-operative atrial fibrillation. The numbers represent patients at risk over time. AFIB = atrial fibrillation.

appears early and increases with time (6% at 1 year and 15% at 10 years). The initial analysis includes all patients who died during the initial hospitalization. To further elucidate the role of POAF on long-term survival and to exclude the confounding effect of in-hospital mortality possibly associated with POAF, the patients who died before discharge were deleted from a secondary analysis. The negative impact of POAF on survival remained unchanged in this selected sample of patients who survived the initial hospitalization (HR: 1.21, 95% CI: 1.11 to 1.32; p < 0.001). As mentioned previously, 20.5% of patients in whom POAF developed were discharged and receiving warfarin anticoagulation. Adjusting for the same 32 covariates, the adjusted effect of warfarin on mortality in POAF patients seems to be protective (HR: 0.78, 95% CI: 0.66 to 0.92). Therefore, patients with POAF discharged and receiving warfarin experienced a 22% relative reduction in mortality compared with POAF patients not receiving warfarin at discharge. Patients with POAF receiving warfarin on discharge were more likely to have an ejection fraction <30%, CHF, peripheral vascular disease, hypertension, dyslipidemia, and diabetes (Table 5). The analysis did not address continual use of warfarin during the follow-up period.

Discussion

This retrospective evaluation of more than 16,000 consecutive patients undergoing CABG finds an association be-

Table 5 Demographic and Pre-Operative Risk Factors for POAF Patients by Warfarin Use

Parameters	No Warfarin (n = 2,372)	Warfarin (n = 613)	p Value
Age, yrs (SD)	67.5 (9.6)	67.8 (9.0)	0.44
Ejection fraction, % (SD)	50.3 (12.7)	48.2 (13.6)	0.001
% of patients with ejection fraction ≤30%	21	25	0.04
Male	1,711 (72.1)	468 (76.4)	0.036
White	2,039 (88.0)	533 (88.0)	0.97
Myocardial infarction	1,209 (51.0)	336 (54.8)	0.09
Congestive heart failure	435 (18.3)	139 (22.7)	0.015
Chronic obstructive pulmonary disease	385 (16.2)	110 (17.9)	0.31
Peripheral vascular disease	250 (10.5)	96 (15.7)	<0.001
Left main coronary artery disease	606 (25.6)	151 (24.6)	0.64
Smoking	478 (20.2)	122 (19.9)	0.89
Hypertension	1,848 (77.9)	519 (84.7)	<0.001
Diabetes	819 (34.5)	242 (39.5)	0.023
Stroke	221 (9.3)	70 (11.4)	0.12
Creatinine level, mg/dl (SD)	1.32 (1.20)	1.30 (1.17)	0.75
Dialysis	51 (2.2)	15 (2.5)	0.66
Renal failure	187 (7.9)	56 (9.1)	0.31
Nonelective coronary artery bypass graft	507 (21.3)	130 (21.2)	0.93
Dyslipidemia	808 (34.1)	247 (40.3)	0.004
Previous surgery	132 (5.6)	34 (5.6)	0.99

Values are n (%) unless otherwise indicated.
Abbreviation as in **Table 2**.

tween POAF and a 21% relative increase in mortality. This increase was true after controlling for multiple demographic variables, pre-operative risk factors, post-operative complications, and use of discharge medications. Of note, the survival difference emerged early and increased over time, with a 10-year survival rate of 55% in the POAF group compared with 70% in the no-AF group. In addition, this survival difference was seen in different identified subgroups (a trend was observed in nonwhite patients and in patients undergoing off-pump coronary bypass) (Table 6). In particular, POAF had the greatest negative impact on long-term survival in women (HR: 1.46, 5% CI: 1.27 to 1.67) (Table 6).

In patients in whom POAF developed, warfarin use at discharge was associated with a lower long-term mortality. The use of warfarin was not controlled, and the difference in mortality in patients with POAF was purely observational. However, the group receiving warfarin seems to be a somewhat sicker population with higher demographic and pre-operative risk factors. The lower long-term mortality in the POAF group receiving warfarin suggests a protective effect, perhaps from prevention of thromboembolism and stroke. The continuing divergence of the POAF and no-POAF survival curves over time should prompt reconsideration of the label given to new-onset POAF as a benign, transient phenomenon. Also, the observed association between use of warfarin at discharge in patients with POAF and reduced long-term mortality should prompt further study of the use of warfarin in POAF, perhaps in a randomized, controlled fashion.

Comparison with previous studies. Our report is not the first analysis of POAF in patients undergoing CABG. Mariscalco et al. (9) addressed new-onset POAF in a study of CABG at 2 Italian centers. They reported findings in 1,832 patients undergoing isolated CABG; POAF occurred in 31% of patients and was associated with increased short- and long-term mortality. However, those investigators did not exclude patients with a history of paroxysmal AF from the analysis of POAF after CABG. Because a history of AF is associated with increased mortality in population studies and in patients with coronary artery disease, their reported association between POAF and mortality could have been biased by the effect of pre-existing AF on long-term mortality in patients with coronary artery disease requiring

CABG. The study also lost 8% of patients to follow-up and therefore potentially lacked mortality data on those individuals. Use of the SSDI made mortality data available for all the patients included in our study. Interestingly, the Italian study determined the cause-specific mortality in POAF and identified the main cause of death in patients with POAF as embolic events. Paradoxically, warfarin therapy was associated with higher long-term mortality. The authors acknowledged that warfarin was prescribed in a sicker cohort of patients. One must note that the total number of patients with POAF discharged on warfarin was relatively small (n = 90) compared with our study, which included more than 600 patients with POAF discharged and receiving warfarin.

Villareal et al. (5) reported an association between POAF and late mortality in 6,475 patients undergoing first-time revascularization surgery at the Texas Heart Institute. POAF occurred in 16% patients. Those patients with POAF appeared to be older and sicker than those without POAF, a finding consistently seen in other studies (17–20) and in ours. Although the investigators adjusted for many comorbid conditions when testing the effect of POAF on mortality, they did not account for the effect of race (21,22), ejection fraction (23), the presence of concomitant valve disease (15), dialysis (24), left main coronary artery disease (25), or creatinine level (26,27). The Texas Heart Institute study did not find an association between warfarin use on discharge and reduced mortality in POAF. The relatively small number of patients studied and discharged receiving warfarin may have prevented meaningful analysis.

Study implications. The possible impact of POAF on long-term mortality undermines the notion that newly diagnosed, seemingly transient, post-CABG AF represents a benign event in these patients. Furthermore, the association between warfarin use and decreased long-term mortality in POAF patients suggests that a protective effect against thromboembolic stroke, the major cause of death attributable to AF, may have been responsible for the benefit. We detected a greater association between POAF and mortality in women (HR: 1.46, 95% CI: 1.27 to 1.67 vs. the general population estimated HR of 1.21), consistent with the observation that women with AF have a higher risk of stroke compared with men (28).

The notion that POAF can be attributed to post-operative inflammation and oxidative stress (29–31) may suggest that it is a transient phenomenon and may explain the low use of warfarin in patients with POAF. The rates of warfarin use reported in this setting in Europe (16%) (9) and the U.S. (14%) (5) were slightly below that of our cohort. Patients receiving warfarin on discharge in our population exhibited greatest risk of stroke based on the presence of diabetes, hypertension, or CHF (Table 5), suggesting recognition of a greater need for anticoagulation at the time of discharge.

These results support other recent observations that POAF should not be considered a transient phenomenon and may herald a continuing risk of recurrent AF with all its manifestations and complications, particularly stroke and death. The limited data on the effect of warfarin use

Table 6	Atrial Fibrillation as a Predictor of Mortality Among Different Subgroups	
Group	**Adjusted POAF Hazard Ratio (95% CI)**	**p Value**
All patients	1.21 (1.12–1.32)	<0.001
Females	1.46 (1.27–1.67)	<0.001
Male	1.13 (1.02–1.24)	<0.019
White	1.23 (1.12–1.34)	<0.001
Nonwhite	1.18 (0.93–1.48)	0.17
Off-pump	1.12 (0.96–1.31)	0.14
On-pump	1.24 (1.13–1.36)	<0.001

Abbreviation as in Table 2.

in our population suggest the need for controlled, randomized analysis of warfarin use in newly diagnosed POAF. Our observations suggest that in the absence of data from controlled trials, one should consider the need for warfarin therapy in patients with newly diagnosed post-CABG AF and known risk factors for stroke (CHF, hypertension, age older than 75 years, diabetes, or previous stroke).

Study limitations. This report involves a retrospective and observational analysis of single-center data on post-CABG. Our regression model contains 32 covariates that pose a potential for model overfitting and other associated estimation problems. The STS database was not designed to assess the effect of POAF on long-term mortality, so some unknown variables that confound this association may not have been analyzed. Furthermore, the STS database defines AF as requiring specific therapy such as medication or direct current cardioversion. Clearly, shorter episodes of AF for which therapy is not administered would not have been classified and would have been excluded from the analysis. Whether AF not requiring therapy affects long-term mortality cannot be answered by this analysis. Use of warfarin for POAF was not controlled or randomized. Physician discretion, based on individual patient characteristics, led to its prescription. We also cannot determine the duration of warfarin therapy or its effectiveness based on therapeutic international normalized ratio targets, nor do we have specific data on bleeding and stroke occurrence during follow-up. However, our observations do suggest that in a large cohort of patients without previous AF, the new onset of AF after CABG is associated with increased long-term mortality.

Conclusions

In this large cohort of patients undergoing isolated CABG, POAF is associated with greater long-term mortality. Warfarin use in patients with POAF was associated with 22% relative risk reduction of adjusted mortality. These findings implicate embolic events as a potential cause of death in patients with newly diagnosed POAF. Anticoagulation should be considered for patients with POAF and known risk factors for stroke.

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