A Multicenter Risk Index for Atrial Fibrillation After Cardiac Surgery

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Context Atrial fibrillation is a common, but potentially preventable, complication following coronary artery bypass graft (CABG) surgery.

Objectives To assess the nature and consequences of atrial fibrillation after CABG surgery and to develop a comprehensive risk index that can better identify patients at risk for atrial fibrillation.

Design, Setting, and Participants Prospective observational study of 4657 patients undergoing CABG surgery between November 1996 and June 2000 at 70 centers located within 17 countries, selected using a systematic sampling technique. From a derivation cohort of 3093 patients, associations between predictor variables and postoperative atrial fibrillation were identified to develop a risk model, which was assessed in a validation cohort of 1564 patients.

Main Outcome Measure New-onset atrial fibrillation after CABG surgery.

Results A total of 1503 patients (32.3%) developed atrial fibrillation after CABG surgery. Postoperative atrial fibrillation was associated with subsequent greater resource use as well as with cognitive changes, renal dysfunction, and infection. Among patients in the derivation cohort, risk factors associated with atrial fibrillation were advanced age (odds ratio [OR] for 10-year increase, 1.75; 95% confidence interval [CI], 1.59-1.93); history of atrial fibrillation (OR, 2.11; 95% CI, 1.57-2.85) or chronic obstructive pulmonary disease (OR, 1.43; 95% CI, 1.09-1.87); valve surgery (OR, 1.74; 95% CI, 1.31-2.32); and postoperative withdrawal of a β-blocker (OR, 1.91; 95% CI, 1.52-2.40) or an angiotensin-converting enzyme (ACE) inhibitor (OR 1.69; 95% CI, 1.38-2.08). Conversely, reduced risk was associated with postoperative administration of β-blockers (OR, 0.32; 95% CI, 0.22-0.46), ACE inhibitors (OR, 0.62; 95% CI, 0.48-0.79), potassium supplementation (OR, 0.53; 95% CI, 0.42-0.68), and nonsteroidal anti-inflammatory drugs (OR, 0.49; 95% CI, 0.40-0.60). The resulting multivariable risk index had adequate discriminative power with an area under the receiver operating characteristic (ROC) curve of 0.77 in the validation sample. Forty-three percent (640/1503) of patients who had atrial fibrillation after CABG surgery experienced more than 1 episode of atrial fibrillation. Predictors of recurrent atrial fibrillation included older age, history of congestive heart failure, left ventricular hypertrophy, aortic atherosclerosis, bicaval venous cannulation, withdrawal of ACE inhibitor or β-blocker therapy, and use of amiodarone or digoxin (area under the ROC curve of 0.66). Patients with recurrent atrial fibrillation had longer hospital stays and experienced greater infectious, renal, and neurological complications than those with a single episode.

Conclusions We have developed and validated models predicting the occurrence of atrial fibrillation after CABG surgery based on an analysis of a large multicenter international cohort. Our findings suggest that treatment with β-blockers, ACE inhibitors, and/or nonsteroidal anti-inflammatory drugs may offer protection. Atrial fibrillation after CABG surgery is associated with important complications.

JAMA. 2004;291:1720-1729 www.jama.com

A NUMBER OF ADVANCES IN anesthetic and surgical techniques have reduced risk in patients undergoing cardiac surgery.[1] However, postoperative atrial fibrillation remains common, with an incidence that is consistently reported to range between 27% and 40%, with little change over the past 2 decades.[2-6] Previous reports have suggested that atrial fibrillation is associated with an increased incidence of congestive heart failure (CHF), renal insufficiency, and stroke,[6,7] which prolong hospitalization[2,6,8,9] and increase rates of rehospitalization after discharge.[8-11]

The intraoperative and postoperative periods are potentially stressful for the heart with extremes in response affecting reperfusion, inflammation, hemostasis, and excitotoxicity. Most previous studies of postoperative atrial fibrillation have primarily focused on chronic disease and risk factors prior to surgery. In addition, many studies are based on single-institution data,

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which limits generalizability. Therefore, using data gathered prospectively from an international multicenter population, we assessed the nature and consequences of atrial fibrillation and developed and validated a comprehensive risk index that defines patients at risk for atrial fibrillation after coronary artery bypass graft (CABG) surgery.

METHODS

Study Design

The Ischemia Research and Education Foundation and the Multicenter Study of Perioperative Ischemia Epidemiology II is a prospective and longitudinal study, which includes 5436 patients from 70 hospitals on 4 continents (17 countries) scheduled for CABG surgery between November 1996 and June 2000. Following institutional review board approval, each center was to enroll 100 patients prospectively according to a systematic sampling scheme among all patients undergoing CABG surgery with or without valve repair or replacement using cardiopulmonary bypass. Eligible patients were aged 18 years or older; willing to provide informed consent and participate in a preoperative interview; and were not simultaneously enrolled in another clinical trial.

Data Collection and Management

More than 7500 fields of data per patient were collected by independent investigators throughout each enrolled patient's index hospitalization; treating physicians were blinded to all research data. Data included demographic, historical, clinical, laboratory, and electrocardiographic information as well as resource use and adverse outcome. All data fields for each patient were queried centrally for completeness and accuracy, with all changes documented prior to database closure. All patient data were entered using ORACLE (Redwood Shores, Calif) at the central analysis unit.

Outcome Measures

All outcomes were prespecified, defined by protocol, and determined by independent investigators blinded to the study question. Postoperative atrial fibrillation was defined by entry into the case report form or by detection on the postoperative electrocardiogram of atrial fibrillation or flutter. A diagnosis of myocardial infarction (MI) was made if there were either new Q waves (Minnesota codes 1-1-1 to 1-2-7); new persistent ST-segment or T-wave changes (Minnesota codes 4-1, 4-2, 5-1, 5-2, or 9-2) and elevated values for the myocardial band isoenzyme of creatine kinase; or evidence of acute MI on autopsy. A diagnosis of heart failure was made if a ventricular assist device was used; if continuous inotropic support was required for at least 24 hours; or if there was evidence of heart failure on autopsy. Stroke was diagnosed on the basis of a focal or global defect on physical examinaton, tomographic scan, magnetic resonance imaging, or autopsy. A decline in score on the Mini-Mental State Examination of 3 points or more and an increase in score on the National Institutes of Health Stroke Scale score of 4 points or more was considered significant. Renal dysfunction was defined by a serum creatinine level of at least 2.0 mg/dL (177 μmol/L), accompanied by an increase of at least 0.70 mg/dL (61.9 μmol/L) from baseline. Renal failure was defined by either renal dysfunction and dialysis or evidence of renal failure on autopsy. Atrial fibrillation was considered to have preceded a complication if it occurred prior to the first day of diagnosis of the complication.

Study Sample

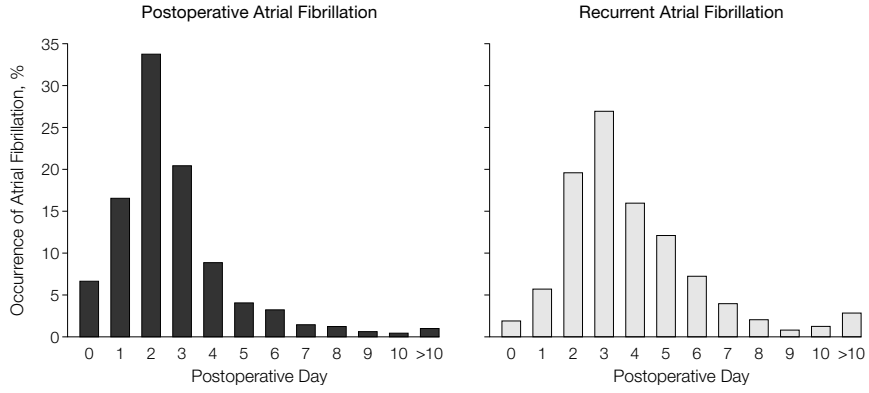
Because clinical decisions were not controlled by study protocol, all patients qualifying within the prespecified enrollment period were entered. Of the 5436 patients enrolled, 372 were excluded because the patient withdrew from the study prior to its completion (n=32), death prior to surgery (n=2), cancelled or rescheduled surgery (n=97), a change in scheduled surgical procedure (n=132), inadvertent enrollment in another study (n=11), incomplete data (n=87), or incomplete blood sampling, shipping, or storage (n=11). Patients were also excluded because they concurrently underwent additional procedures (n=256), such as carotid endarterectomy or had chronic atrial fibrillation (n=151). A total of 4657 patients were included in this analysis.

Predictors of Atrial Fibrillation

Potential predictors of atrial fibrillation were chosen based on a review of the literature. Candidate variables prior to surgery included age; sex; right coronary artery stenosis of 90% or higher; ejection fraction; left atrial enlargement; left ventricular hypertrophy; left ventricular dilation based on a combination of methods including echocardiography, electrocardiography, and/or ventriculography; aortic atherosclerosis based on echocardiogram; hypokalemia; a history of atrial fibrillation, valvular disease, CHF, vascular disease, neurological event, diabetes, any MI, hypertension or chronic obstructive pulmonary disease (COPD); prior CABG surgery or valve surgery; and current treatment with β-blockers, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, amiodarone, or nonsteroidal anti-inflammatory drugs (NSAIDs).

Potential intraoperative predictors of atrial fibrillation included valve surgery, bicaval cannulation, pulmonary vein venting (a surgical procedure performed during cardiopulmonary bypass to keep the left ventricle empty), moderate or severe aortic atherosclerosis, duration of cross-clamp and cardiopulmonary bypass, myocardial and cardiopulmonary bypass temperature, volume and type of cardioplegia (blood, crystalloid), retrograde cardioplegia, adenosine or procainamide in cardioplegia, ejection fraction by transesophageal echocardiography, asynchronous atrial or atrioventricular pacing, occurrence of atrial fibrillation or ventricular tachycardia or fibrillation, and treatment with β-blockers, calcium channel blockers, magnesium, amiodarone, digoxin, aminocaproic acid, aprotinin, NSAIDs, or inotropic drugs.

Figure 1. Day of Initial Occurrence for Postoperative and Recurrent Atrial Fibrillation



The denominators are 1503 patients for postoperative atrial fibrillation and 640 for recurrent atrial fibrillation.

Postoperative predictors of atrial fibrillation included asynchronous atrial or atrioventricular pacing, intra-aortic balloon pump use, Q-wave MI, pericarditis, CHF, hypokalemia (<3.5 mEq/L), hypomagnesemia (<2 mg/dL), β-blocker or ACE-inhibitor withdrawal, and treatment with inotropic drugs, β-blockers, ACE inhibitors, calcium channel blockers, NSAIDs, amiodarone, or supplementation with potassium or magnesium. For patients experiencing postoperative atrial fibrillation, postoperative variables were defined by their occurrence before the onset of atrial fibrillation.

Statistical Methods

For categorical variables, a 2-tailed χ^2 or Fisher exact test was used to compare patients with and without postoperative atrial fibrillation. For continuous variables, a *t* test or Wilcoxon rank sum test was applied. To evaluate the effect of atrial fibrillation alone on length of intensive care unit (ICU) stay and postsurgical hospitalization, 875 patients with complications other than atrial fibrillation were excluded. Patients with complications were included in all other analyses.

To develop an atrial fibrillation risk index, patients were assigned to a derivation cohort (first 66.4% of patients enrolled at each site; n=3093) or to a validation cohort (last 33.6% enrolled; n=1564). Because enrollment continued for 3.5 years, this sampling scheme provided temporal validity. Univariate associations between potential predictors and atrial fibrillation in the derivation cohort were investigated using the χ^2 test, Fisher exact test, and logistic regression modeling. All variables significant at a nominal 2-tailed $P \leq .20$ were then entered into multivariable logistic models using a combination stepwise selection method. A preoperative model was first developed using only preoperative factors. Subsequently, intraoperative factors were added to create an intraoperative model, followed by addition of postoperative factors to develop a final model. Model entry and retention criteria were set at $P \leq .20$ and $P \leq .01$. The final model was evaluated using the Hosmer-Lemeshow goodness-of-fit test[12] and the area under the receiver operating characteristic (ROC) curve in which an area of more than 0.75 represents a model with good discriminate power.

To develop relative weights for the predictors in the Multicenter Study of Perioperative Ischemia risk index, the parameter estimates of the final logistic model were multiplied by 10 and rounded to the nearest integer.[13] The relative weight was then assigned to each binary predictor, as well as to each age category (10-year increments). The Multicenter Study of Perioperative Ischemia Atrial Fibrillation risk index for each patient was calculated by summing the relative weights across the predictors present for a particular patient. Four risk groups were preplanned based on quartiles. Because both the observed and the predicted incidence rates were similar between the second and the third quartiles, 3 risk groups were defined. The low risk group contained scores below the 25th percentile; the medium risk group contained scores in the 25th to 75th percentile; and the high risk group contained scores higher than the 75th percentile.

In secondary analyses, similar sequential steps and techniques were adopted for the development of a risk index for recurrent (>1 episode during the index hospitalization) atrial fibrillation. Model entry and retention criteria were set at $P \leq .20$ and $P < .05$. All analyses were performed using SAS statistical software (version 8.2, SAS Institute Inc, Cary, NC).

RESULTS

Incidence of Atrial Fibrillation

In the entire study population, the incidence of postoperative atrial fibrillation after CABG surgery and prior to hospital discharge was 32.3% (1503/4657). This incidence was similar among patients in the United States (33.7%), Canada (36.6%), Europe (34.0%), United Kingdom (31.6%), and the Middle East (41.6%), but the incidence was lower in South America (17.4%) and Asia (15.7%) ($P < .001$). Atrial fibrillation was first detected by continuous monitoring (telemetry) in 76.8% (1155/1503); by 12-lead electrocardiogram in 17.5% (263/1503); and by physical examination in 12.8% (193/1503). Forty-three percent of patients (640/1503) experienced more than 1 episode of atrial fibrillation. Atrial fibrillation was most common on postoperative day 2 while recurrence was most common on postoperative day 3 with more than 60% of initial recurrence occurring within 2 days of first onset (FIGURE 1). However, only 22% of patients (326/1503) experienced more than 2 episodes.

Risk Indices

The incidence of postoperative atrial fibrillation was similar in both the deri-

Table 1. Demographic Characteristics

Characteristic	Derivation Cohort (n = 3093)		Validation Cohort (n = 1564)		*P* Value*
	Atrial Fibrillation (n = 976)	No Atrial Fibrillation (n = 2117)	Atrial Fibrillation (n = 527)	No Atrial Fibrillation (n = 1037)	
Age, mean (SD), y	67.8 (8.2)	61.8 (9.8)	67.8 (8.6)	61.9 (9.9)	.56
Men, No. (%)	770 (78.9)	1682 (79.5)	415 (78.8)	849 (81.9)	.22
Prior CABG surgery, No. (%)	63 (6.5)	120 (5.7)	21 (4.0)	66 (6.4)	.63
History, No. (%)					
Atrial fibrillation	142 (14.6)	126 (6.0)	87 (16.5)	65 (6.3)	.24
Valvular disease	271 (27.8)	316 (14.9)	142 (26.9)	163 (15.7)	.67
Congestive heart failure	391 (40.1)	677 (32.0)	221 (41.9)	352 (33.9)	.16
Vascular disease	196 (20.1)	310 (14.6)	102 (19.4)	166 (16.0)	.50
Neurological event	127 (13.0)	196 (9.3)	72 (13.7)	86 (8.3)	.72
Myocardial infarction	612 (62.7)	1334 (63.0)	341 (64.7)	665 (64.1)	.35
Chronic obstructive pulmonary disease	137 (14.0)	183 (8.6)	76 (14.4)	136 (13.1)	.001
Hypertension	668 (68.4)	1348 (63.7)	390 (74.0)	709 (68.4)	<.001
Diabetes	303 (31.1)	660 (31.2)	160 (30.4)	319 (30.8)	.72
Preoperative treatment, No. (%)					
β-Blockers	645 (66.1)	1480 (69.9)	367 (69.6)	743 (71.7)	.11
Calcium channel blockers	391 (40.1)	768 (36.3)	185 (35.1)	348 (33.6)	.02
ACE inhibitors	447 (45.8)	875 (41.3)	261 (49.5)	450 (43.4)	.08
Cross-clamp time, mean (SD), min	69.5 (35.1)	61.8 (29.3)	67.8 (34.7)	61.8 (28.3)	.70
Cardiopulmonary bypass time, mean (SD), min	108.6 (45.7)	98.7 (39.8)	106.2 (43.6)	98.0 (39.4)	.41

Abbreviations: ACE, angiotensin-converting enzyme; CABG, coronary artery bypass graft.
*χ^2 Test comparing the prevalence of risk factors between cohorts.

vation cohort (31.6%; 976/3093) and the validation cohort (33.7%; 527/1564). In the derivation cohort, 43.7% (426/976) experienced multiple episodes of atrial fibrillation, and 40.6% (214/527) in the validation cohort had multiple episodes. Hypertension and COPD were more frequent in the validation cohort, while preoperative calcium-channel blockade was more common in the derivation cohort (TABLE 1).

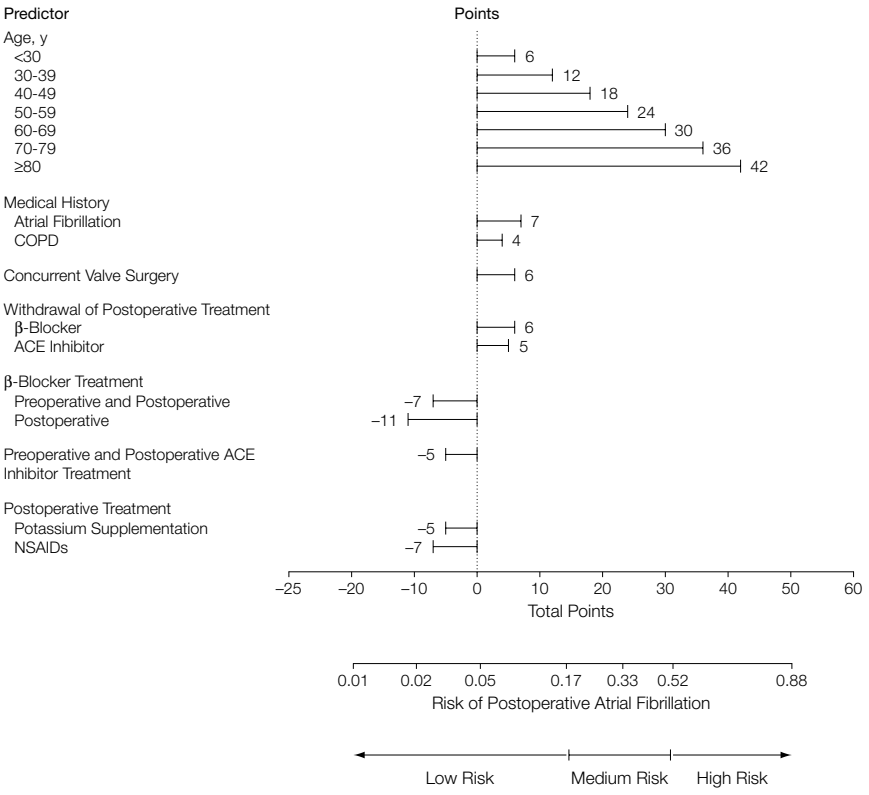
Among patients in the derivation cohort, significant independent predictors of atrial fibrillation were advanced age, history of atrial fibrillation or COPD, valve surgery, and withdrawal of β-blockers or ACE inhibitors (TABLE 2). Conversely, treating patients with β-blockers preoperatively and postoperatively or postoperatively only was associated with a reduced incidence of atrial fibrillation. Similarly, treatment with ACE inhibitors preoperatively and postoperatively and postoperative potassium supplementation and NSAID administration were associated with a reduced incidence of atrial fibrillation. The area under the ROC curve for this model was

Table 2. Multivariable Predictors of Postoperative Atrial Fibrillation Among Patients in the Derivation Cohort

Predictor	Incidence of Postoperative Atrial Fibrillation, No./Total (%)	Risk Score*	OR (95% CI)†	*P* Value
Age, y				
<30	0	6	1.75 (1.59-1.93)‡	<.001
30-39	2/36 (5.6)	12		
40-49	19/229 (8.3)	18		
50-59	160/795 (20.1)	24		
60-69	378/1145 (33.0)	30		
70-79	377/817 (46.1)	36		
≥80	40/68 (58.8)	42		
Medical history				
Atrial fibrillation	142/268 (53.0)	7	2.11 (1.57-2.85)	<.001
Chronic obstructive pulmonary disease	137/320 (42.8)	4	1.43 (1.09-1.87)	.009
Concurrent valve surgery	154/286 (53.9)	6	1.74 (1.31-2.32)	<.001
Withdrawal of treatment				
β-Blockers	396/784 (50.5)	6	1.91 (1.52-2.40)	<.001
ACE inhibitors	320/692 (46.2)	5	1.69 (1.38-2.08)	<.001
Preoperative and postoperative treatment				
β-Blockers	228/1289 (17.7)	–7	0.49 (0.39-0.61)	<.001
ACE inhibitors	126/626 (20.1)	–5	0.62 (0.48-0.79)	<.001
Postoperative β-blocker treatment	51/228 (17.7)	–11	0.32 (0.22-0.46)	<.001
Other treatment				
Potassium supplementation	774/2688 (28.8)	–5	0.53 (0.42-0.68)	<.001
NSAIDs	173/934 (18.5)	–7	0.49 (0.40-0.60)	<.001

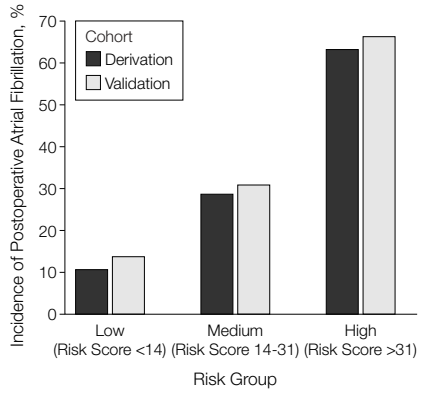
Abbreviations: ACE, angiotensin-converting enzyme; CI, confidence interval; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio.
*A score of less than 14 indicates low risk; a score of 14 to 31, medium risk; and a score higher than 31, high risk.
†The ORs are adjusted for the factors included in the final model and presented in this table.
‡The OR is for a 10-year change and may be extrapolated.

Figure 2. Risk of Postoperative Atrial Fibrillation After Coronary Artery Bypass Graft Surgery



Risk is determined by assigning points from the points scale for each of the predictors listed and then plotting the total points received against the risk score at the bottom of the nomogram. For example, 50 total points predicts a risk of postoperative atrial fibrillation of 88%. ACE indicates angiontensin-converting enzyme; COPD, chronic obstructive pulomonary disease; and NSAIDs, nonsteroidal anti-inflammatory drugs.

Figure 3. Comparison of the Predictive Ability of the Final Risk Index Model for Postoperative Atrial Fibrillation in the Derivation and Validation Cohorts



The denominator is 1503.

0.78, and the Hosmer-Lemeshow goodness-of-fit test was not significant for lack of fit (P=.36). A risk score less than 14 was considered low risk, scores of 14 to 31 were considered medium risk; and scores higher than 31 were considered high risk (Table 2 and FIGURE 2). Comparison of the predictive ability of the model revealed that the incidence of atrial fibrillation was similar in the derivation and validation cohorts stratified across the 3 risk groups (FIGURE 3). The area under the ROC curve when applying the final model in the validation cohort was 0.77.

Among patients who experienced postoperative atrial fibrillation in the derivation cohort, advanced age, left ventricular hypertrophy, moderate or severe aortic atherosclerosis, bicaval venous cannulation, and withdrawal of ACE inhibitor or β-blocker therapy were significant predictors of recurrent atrial fibrillation, while a history of CHF and use of amiodarone or digoxin was associated with a lower odds of recurrence (TABLE 3). The Hosmer-Lemeshow goodness-of-fit test for the model yielded a score of 10.97 (P=.20) and the area under the ROC curve was 0.69. The area under the ROC curve when applying this model in the validation cohort was 0.66. A risk score of less than 9 was considered low risk; scores of 10 to 22 were medium risk; and scores higher than 22 were high risk (Table 3).

Initial Treatment of Atrial Fibrillation

The initial episode was treated pharmacologically in 76.9% (1156/1503) of patients, or electrically by cardioversion in 3.7% (56/1503), and by overdrive pacing in 2.1% (31/1503). No therapy was rendered in 17.3% (260/1503). Digoxin was the most common medication administered during the initial episode of atrial fibrillation, whereas amiodarone, β-blockers, and calcium channel blockers were commonly added for subsequent episodes. Anticoagulation using heparin was started after atrial fibrillation in 56.2% (845/1503) while 17.6% (265/1503) received warfarin.

Sequelae of Atrial Fibrillation

Atrial fibrillation was associated with a greater incidence of subsequent postoperative complications including cognitive changes, renal dysfunction, and infection. This incidence rate was higher in patients with multiple episodes of atrial fibrillation than in patients with a single episode (TABLE 4). The incidence of a composite outcome (encephalopathy, decline in Mini-Mental State Examination score, increase in National Institutes of Health Stroke Scale score, renal dysfunction, renal failure, pneumonia, mediastinitis or deep sternal wound infection, sepsis, harvest site infection, vascular catheter infection, and genitourinary infection) in the patients with atrial fibrillation was 22.6% (340/1503) compared with 15.4% (483/3154) in the patients without atrial fibrillation. Multivariable analysis showed that atrial fibrillation was significantly and independently associated (odds ratio, 1.19 [95% confidence interval, 1.0-1.43];

$P=.049$) with this composite outcome, after adjusting for propensity of risk factors for patients to develop atrial fibrillation. Inhospital mortality in patients with atrial fibrillation was 4.7% (71/1503) compared with 2.1% (66/3154) in patients without atrial fibrillation ($P<.001$).

Resource Use

Patients with atrial fibrillation had longer ICU and hospital stays (TABLE 5). The median difference in postsurgical hospitalization was 2 days. Once discharged from the ICU, patients with atrial fibrillation were also more likely to return to the ICU. After the onset of atrial fibrillation, patients experienced a greater level of testing with computerized axial tomography and ultrasonography. Thirty-five percent of patients (527/1503) with atrial fibrillation were discharged to an extended care facility compared with 28% (882/3154) without atrial fibrillation ($P<.001$). Pa-

Table 3. Multivariable Predictors of Recurrent Atrial Fibrillation Among Patients in the Derivation Cohort

Predictor	Incidence of Recurrent Atrial Fibrillation, No./Total (%)	Risk Score*	OR (95% CI)	*P* Value
Age, y				
<40	1/2 (50)	2	1.22 (1.04-1.44)†	<.001
40-49	6/19 (31.6)	4		
50-59	58/160 (36.3)	6		
60-69	163/378 (43.1)	8		
70-79	175/377 (46.4)	10		
≥80	23/40 (57.5)	12		
History				
Congestive heart failure	156/391 (39.9)	–4	0.67 (0.51-0.89)	.006
Left ventricular hypertrophy	164/314 (52.2)	5	1.60 (1.19-2.14)	.002
Moderate or severe aortic atherosclerosis	120/213 (56.3)	5	1.47 (1.02-2.11)	.001
Bicaval cannulation	87/163 (53.4)	4	1.91 (1.52-2.40)	.04
Withdrawal of treatment				
ACE inhibitors	126/226 (55.8)	6	1.80 (1.30-2.48)	<.001
β-Blockers	136/246 (55.3)	7	1.93 (1.41-2.64)	<.001
Postoperative treatment				
Amiodarone	70/217 (32.3)	–7	0.50 (0.36-0.71)	<.001
Digoxin	169/458 (36.9)	–6	0.57 (0.44-0.75)	<.001

Abbreviations: ACE, angiotensin-converting enzyme; CI, confidence interval; OR, odds ratio.
*A score of less than 9 indicates low risk; a score of 10 to 22, medium risk; and a score higher than 22, high risk.
†The OR is for a 10-year change and may be extrapolated.

Table 4. Inhospital Outcome and Its Association With Postoperative Atrial Fibrillation

Outcome	No./Total (%) of Patients With Atrial Fibrillation		No./Total (%) of Patients Without Atrial Fibrillation	*P* Value Comparison*		
	1 Episode	>1 Episode		No Atrial Fibrillation vs 1 Episode	No Atrial Fibrillation vs >1 Episode	1 Episode vs >1 Episode
Angina	13/863 (1.51)	24/640 (3.75)	138/3147 (4.4)	<.001	.47	.006
Myocardial infarction	27/863 (3.13)	30/640 (4.69)	231/3154 (7.3)	<.001	.02	.12
Congestive heart failure	35/863 (4.06)	48/640 (7.50)	226/3154 (7.2)	.001	.77	.004
Pulmonary edema	28/863 (3.24)	41/640 (6.41)	199/3147 (6.3)	<.001	.94	.004
Intra-aortic ballon pump used	14/863 (1.62)	15/640 (2.34)	97/3154 (3.1)	.02	.32	.32
Stroke	8/863 (0.93)	9/640 (1.41)	37/3154 (1.2)	.54	.62	.39
Encephalopathy	12/863 (1.39)	27/640 (4.22)	22/3154 (0.7)	.049	<.001	<.001
Seizures	3/863 (0.35)	3/640 (0.47)	7/3147 (0.2)	.51	.27	.71
Decline of >3 points in Mini-Mental State Examination score	55/520 (10.58)	61/364 (16.76)	191/1970 (9.7)	.55	<.001	.007
Increase of >4 points in National Institutes of Health Stroke Scale score	13/752 (1.73)	21/543 (3.87)	32/2775 (1.2)	.21	<.001	.02
Renal dysfunction	20/863 (2.32)	25/640 (3.91)	61/3154 (1.9)	.48	.002	.07
Renal failure	14/863 (1.62)	30/640 (4.69)	38/3154 (1.2)	.34	<.001	<.001
Adult respiratory distress syndrome	5/863 (0.58)	21/640 (3.28)	35/3147 (1.1)	.16	<.001	<.001
Type of infection						
Pneumonia	28/863 (3.24)	56/640 (8.75)	106/3147 (3.4)	.86	<.001	<.001
Sepsis	22/863 (2.55)	32/640 (5.00)	23/3147 (0.7)	<.001	<.001	.01
Mediastinitis or deep sternal wound	17/863 (1.97)	11/640 (1.72)	24/3147 (0.8)	.002	.02	.72
Harvest site	18/863 (2.09)	19/640 (2.97)	42/3147 (1.3)	.11	.003	.28
Vascular catheter	7/863 (0.81)	25/640 (3.91)	18/3147 (0.6)	.43	<.001	<.001
Genitourinary tract	19/863 (2.20)	36/640 (5.63)	65/3147 (2.1)	.81	<.001	<.001

*Bonferroni correction for multiple testing requires $P<.017$ for significance.

Table 5. Resource Use in Patients With and Without Atrial Fibrillation

Resource Use	Atrial Fibrillation* With (n = 1503)	Atrial Fibrillation* Without (n = 3154)	*P* Value
Intensive care unit stay, h			
Mean (SD)	56.8 (73.9)	44.7 (177)	<.001
Median (interquartile range)	36.3 (21.7-68.2)	25.5 (21.0-47.3)	
Postsurgical hospitalization, d			
Mean (SD)	10.5 (6.5)	8.5 (4.3)	<.001
Median (interquartile range)	9 (7-12)	7 (6-10)	
Resource duplication			
Intensive care unit	146/1503 (9.7)	179/3154 (5.7)	<.001
Operating room	94/1503 (6.3)	168/3154 (5.3)	.20
Electrocardiographic monitoring	69/1491 (4.6)	161/3093 (5.2)	.40
Computed axial tomographic scan	69/1473 (4.7)	93/3097 (3.0)	.004
Magnetic resonance imaging	6/1498 (0.4)	8/3138 (0.3)	.40
Electroencephalography	8/1500 (0.5)	70/3107 (2.3)	<.001
Noncardiac angiography	9/1481 (0.6)	10/3107 (0.3)	.16
Cardiac catheterization	17/1139 (1.5)	35/2274 (1.5)	.92
Ultrasound			
Cardiac	389/1432 (27.2)	1590/2899 (54.9)	<.001
Noncardiac	134/1458 (9.2)	180/3025 (6)	<.001
Drug level testing†	366/1503 (24.4)	197/3154 (6.3)	<.001

*Values are expressed as number/total (percentage) unless otherwise indicated.
†Not timed to the onset of atrial fibrillation.

tients with more than 1 episode of atrial fibrillation experienced longer ICU (mean [SD], 65.1 [85.6] vs 51.3 [64.6] hours; median [interquartile range], 43 [22.4-71.4] vs 28.3 [21.3-64.0] hours; $P = .001$) and hospital (mean [SD], 11.2 [7.5] vs 9.9 [5.6] hours; median [interquartile range], 9 [8-12] vs 9 [7-11] days; $P < .001$) stays than those with a single episode.

COMMENT

Despite ongoing efforts to decrease its occurrence, postoperative atrial fibrillation remains a frequent complication of CABG surgery. In a large, multicenter, international cohort, we found that the incidence of postoperative atrial fibrillation was remarkably consistent (approximately 32%) across most regions of the world. Second, the majority of the initial episodes of atrial fibrillation occurred within the first 3 days after CABG surgery. Third, atrial fibrillation recurred in 43% of patients with more than 60% of initial recurrence occurring within 2 days of the first episode. Fourth, postoperative atrial fibrillation increased hospital resource use and was associated with greater neurological, renal, and infectious complications. Fifth, patients with recurrent atrial fibrillation experienced a greater complication rate and had longer hospital stays than those with a single episode. Sixth, advancing age, prior history of atrial fibrillation or COPD, valve surgery, and withdrawal from ACE inhibitor or β-blocker therapy were associated with an increased risk of atrial fibrillation. Seventh, use of β-blockers or ACE inhibitors preoperatively and postoperatively or use of β-blockers, potassium supplementation, and NSAIDs postoperatively only was associated with a reduced risk of atrial fibrillation. Eighth, advancing age, left ventricular hypertrophy, significant aortic atherosclerosis, bicaval venous cannulation, and withdrawal of ACE inhibitor or β-blocker therapy were significant predictors of recurrent atrial fibrillation. Finally, a history of CHF and use of amiodarone or digoxin were associated with a lower risk of recurrence.

The Multicenter Study of Perioperative Ischemia atrial fibrillation risk index can be used to accurately assess risk of atrial fibrillation among patients undergoing CABG surgery.

Atrial Fibrillation and Postoperative Complications

To the best of our knowledge, this is the first study to capture the precise day of onset of both atrial fibrillation and postoperative complications, allowing for examination of the temporal relationship between atrial fibrillation and those complications occurring after the onset of atrial fibrillation. This is also the first study to document the frequency of atrial fibrillation recurrence and its significant association with a greater complication rate as well as longer length of stay. Encephalopathy, cognitive decline, increase in National Institutes of Health Stroke Scale score, renal dysfunction and failure, and infection occurred more frequently in patients with recurrent atrial fibrillation but not those with a single episode. Endothelial dysfunction and abnormalities in the prothombotic or hypercoagulable state seen in patients with paroxysmal atrial fibrillation may contribute to this increased risk.[14] Although the stroke rate in our study was not increased in patients with atrial fibrillation, this finding should be interpreted with caution. The lack of association may reflect the current clinical practice of aggressively treating patients at highest risk for stroke (ie, those with persistent atrial fibrillation) with anticoagulants.

Preoperative Risk Factors for Postoperative Atrial Fibrillation

When preoperative factors are considered, advanced age has been the most consistent predictor of postoperative atrial fibrillation.[2,4-6] Our results show that every 10-year increase in age is associated with a 75% increase in the odds of developing atrial fibrillation; thus, on the basis of age alone, anyone older than 70 years is considered to be at high risk for developing atrial fibrillation. Age-related changes in atrial connective tissue, dilation, and nonuniform anisotropic conduction may account for this increased risk.[15] However, these changes in atrial substrate may not be related to

CABG surgery itself because a higher rate of atrial fibrillation in older patients is also seen in the nonsurgical Framingham population.[16]

Changes in the atrial substrate are also a plausible explanation for the importance of a history of atrial fibrillation in its postoperative reoccurrence. The risk of atrial fibrillation is likely to increase when there are preoperative changes in the atrial substrate and when sensitivity to factors that previously triggered atrial fibrillation persist.[17] The final preoperative predictor of atrial fibrillation (prior COPD) has been controversial.[4,6,18] Our study reveals that chronic lung disease produces a 43% increase in the odds of developing atrial fibrillation. A larger sample size of patients with COPD may account for this variation from prior research. While the pathogenesis of atrial fibrillation in patients with COPD is unclear, it is likely multifactorial and partially related to the increased P-wave dispersion present in patients with COPD.[19]

Intraoperative Risk Factors for Postoperative Atrial Fibrillation

Valve surgery was the only intraoperative variable associated with an increased risk of atrial fibrillation. The incidence of atrial fibrillation after valve surgery typically exceeds that in patients undergoing coronary revascularization alone,[4,6,20] with the greater susceptibility believed to result from structural and hemodynamic abnormalities such as left atrial enlargement, pathological changes from rheumatic heart disease, increased left atrial pressure, and surgical trauma.[20] Although left atrial enlargement was not a predictor in our study, pathological changes associated with valvular heart disease at a cellular level are poorly described in our study of clinical predictors. It is possible that these pathological changes are more important than the surgical procedure itself.

Postsurgical Predictors of Postoperative Atrial Fibrillation

Postoperative administration of several medications and/or withholding of medications was associated with an alteration in the occurrence of atrial fibrillation. Withdrawal of β-blocker therapy in the immediate postoperative period resulted in a 91% increase in the odds of developing atrial fibrillation. However, when β-blockers were given preoperatively and postoperatively, or even initiated postoperatively only, the odds were significantly reduced by between 51% to 68%. Despite guidelines recommending that early postoperative administration of β-blockers should be standard therapy for the prevention of atrial fibrillation,[21] only 52% of the patients were treated with β-blockers postoperatively; and in 24%, β-blockers were actually withdrawn from therapy. Sympathetic activation or an exaggerated response to adrenergic stimulation may be an important trigger for postoperative atrial fibrillation.[22]

Similarly, ACE inhibitor therapy initiated before and after surgery was associated with a lower risk of atrial fibrillation, while withdrawal from therapy was associated with an increased risk. Recent reports have suggested that atrial fibrillation is associated with an activation of the atrial angiotensin system.[23,24] Atrial expression of ACE is increased in patients with atrial fibrillation,[23] possibly leading to angiotensin II–dependent atrial fibrosis and regulation of angiotensin II–receptor subtypes.[24] Moreover, ACE inhibitor therapy has been shown to reduce the occurrence of atrial fibrillation after MI.[25] Pretreatment with ACE inhibitors decreases the relapse rate of atrial fibrillation after cardioversion.[26] ACE inhibition might thus alter the pathophysiological substrate of the atria to decrease the occurrence of atrial fibrillation. Withdrawal of ACE inhibitor therapy may, in turn, up-regulate receptor subtypes and promote the structural and electrical remodeling of the atria.[23]

Cardiopulmonary bypass is associated with an ischemia-reperfusion injury, inducing a complex inflammatory response. Inflammatory changes have been reported in patients with atrial fibrillation ranging from the presence of inflammatory infiltrates in atrial biopsies[27] to increased concentrations of C-reactive protein.[28,29] Acute inflammation, particularly the development of pericarditis, is thought to alter atrial coupling and lead to transient structural or electrical changes that predispose patients to atrial fibrillation.[30] In our study, postoperative pericarditis was not a significant predictor of atrial fibrillation and was diagnosed in only 1.2% of patients. However, administering NSAIDs was associated with a reduction in the odds of developing atrial fibrillation, suggesting that inflammation may contribute to the pathogenesis of postoperative atrial fibrillation.

Risk Factors for Recurrent Atrial Fibrillation

To the best of our knowledge, our study is also the first to examine the predictors of recurrent in-hospital atrial fibrillation, which was observed commonly in older patients with aortic atherosclerosis and left ventricular hypertrophy. The latter has been shown to correlate with atrial fibrillation and systolic hypertension, which, in turn is associated with increased aortic rigidity from aortic atherosclerosis.[10,16,31] The interaction between these comorbid conditions and atrial fibrillation, whether genetic, inflammatory, or physiological, are poorly defined and often coexist, such that pathophysiological distinctions become difficult. The inverse relationship between CHF and recurrent atrial fibrillation is both surprising and unclear. On the other hand, our findings of increased recurrence of atrial fibrillation following withdrawal of β-blocker or ACE inhibitor therapy and diminished risk of recurrence from treatment with amiodarone or digoxin strengthen existing reports and recommendations for management of atrial fibrillation[32] and, more important, for lowering morbid and fatal perioperative vascular events. Lastly, bicaval venous cannulation (most often performed for mitral valve surgery) may predispose toward recurrent atrial fibrillation as a consequence of greater surgical injury.

Limitations

Limitations to our study include its observational design. Thus, the effects of medications are likely to be overestimated and confounded by treatment bias wherein patients with greater comorbidities may be less likely to receive β-blockers or NSAIDs. However, the described associations of atrial fibrillation with drug therapy were independent of postoperative markers of illness severity such as CHF, MI, and inotropic therapy. Second, episodes of atrial fibrillation may have been missed because of the lack of continuous electrocardiographic monitoring, although the recorded incidence of atrial fibrillation is comparable with other published reports. Third, systematic electrolyte concentrations were not obtained. Thus, the potential for significant temporal variation in serum electrolyte concentrations in patients after CABG surgery makes it difficult to accurately categorize electrolyte abnormalities. Fourth, although our study revealed no effect of amiodarone in reducing postoperative atrial fibrillation, a larger sample of patients treated with preoperative amiodarone is needed. Finally, the model for recurrent atrial fibrillation only has moderate discriminative power (area under the ROC curve, 0.66) and thus, our findings need to be confirmed prior to the widespread application of this risk index.

Conclusions

In summary, the Multicenter Study of Perioperative Ischemia atrial fibrillation risk index may be used to identify patients for whom prophylactic therapy might be most effective,[33] to optimize current therapeutic regimens, and to define patient selection criteria for future interventional trials. Our findings indicate that discontinuation of certain cardiovascular medications may be unwise and that ACE inhibitors and/or NSAIDs may offer protection against postoperative atrial fibrillation. Patients with recurrent atrial fibrillation are at greater risk for postoperative complications and aggressive intervention should be considered.

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Statistical expertise: Fontes, Tudor, Hsu, Mangano.
Obtained funding: Mangano.
Administrative, technical, or material support: Mathew, Fontes, Ramsay, Duke, Barash, Mangano.
Supervision: Mathew, Fontes, Ramsay, Hsu, Mangano.
Funding/Support: This work was supported by a grant from the Ischemia Research and Education Foundation, San Francisco, Calif.
Role of the Sponsor: The Ischemia Research and Education Foundation provided all funding for execution of the study, collection of the data, and analysis and publication of the findings. The foundation is independent and not-for-profit.
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The beginning of knowledge is the discovery of something we do not understand.
—Frank Herbert (1920-1986)