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Clinical Prediction Rule for Atrial Fibrillation After Coronary Artery Bypass Grafting

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OBJECTIVES This study was designed to devise and validate a practical prediction rule for atrial fibrillation/atrial flutter (AF) after coronary artery bypass grafting (CABG) using easily available clinical and standard electrocardiographic (ECG) criteria.

BACKGROUND Reported prediction rules for postoperative AF have suffered from inconsistent results and controversy surrounding the added predictive value of a prolonged P-wave duration.

METHODS In 1,851 consecutive patients undergoing CABG with cardiopulmonary bypass, preoperative clinical characteristics and standard 12-lead ECG data were examined. Patients were continuously monitored for the occurrence of sustained postoperative AF while hospitalized. Multiple logistic regression was used to determine significant predictors of AF and to develop a prediction rule that was evaluated through jackknifing.

RESULTS Atrial fibrillation occurred in 508 of 1,553 patients (33%). Multivariate analysis showed that greater age (odds ratio [OR] 1.1 per year [95% confidence intervals (CI) 1.0 to 1.1], $p < 0.0001$), prior history of AF (OR 3.7 [95% CI 2.3 to 6.0], $p < 0.0001$), P-wave duration >110 ms (OR 1.3 [95% CI 1.1 to 1.7], $p = 0.02$), and postoperative low cardiac output (OR 3.0 [95% CI 1.7 to 5.2], $p = 0.0001$) were independently associated with AF risk. Using the prediction rule we defined three risk categories for AF: <60 points, 61 of 446 (14%); 60 to 79 points, 330 of 908 (36%); and ≥80 points, 117 of 199 (59%). The area under the receiver-operator characteristic curve for the model was 0.69.

CONCLUSIONS These data show that post-CABG AF can be predicted with moderate accuracy using easily available patient characteristics and may prove useful in prognostic and risk stratification of patients after CABG. The presence of intraatrial conduction delay on ECG contributed least to the prediction model. (J Am Coll Cardiol 2004;44:1248–53) © 2004 by the American College of Cardiology Foundation

Atrial fibrillation/atrial flutter (AF) is seen in 10% to 65% of patients after cardiothoracic operations and are associated with increased morbidity and costs (1–4). The mechanism responsible for postoperative AF in patients with the necessary atrial electrical substrate is not entirely clear and is likely multifactorial (3,5). Narrowing the population susceptible to postoperative AF could lead to more targeted preventive or therapeutic interventions while reducing the potential for antiarrhythmic-related toxicity and drug costs. As in AF unrelated to surgery, age ≥60 years is the only characteristic that has been consistently linked to an increased risk of postoperative AF (1–13). Beyond older age, however, controversy exists as to which preoperative clinical and/or electrocardiographic (ECG) characteristics further distinguish patients who develop postoperative AF. Independent risk factors for AF after cardiac surgery identified in more than one large study with ≥500 patients include male gender (2,9,13), history of AF (2,11), hypertension (9,12), chronic obstructive pulmonary disease (7,8,12), digoxin use (8,12), and longer aortic cross-clamp time (2,8). For ECG characteristics predictive of postoperative AF, equally large studies are lacking. Prolonged P-wave duration, indicating intra-atrial conduction delay, observed by standard or signal-averaged ECG, as well as an increased PR-interval were identified by some (14–17) but not other investigators (18,19) as indpendent risk factors for postoperative AF. Therefore, our goal was to design a prediction rule for postoperative AF risk using both clinical and ECG variables in a prospective cohort of consecutive patients who had coronary artery bypass grafting (CABG).

MATERIALS AND METHODS

With the approval of the institutional review boards of Washington University and Memorial Sloan-Kettering Cancer Center, anonymized data used in this study were obtained from a previously described prospective database of 1,851 patients in sinus rhythm who had CABG from January 1993 to September 1996 at Barnes-Jewish Hospital (St. Louis, Missouri) (8,20). The data were collected daily by trained and experienced research nurses using standardized forms. Data were entered into an institutional computerized database by dedicated research staff. Study patients had no previous cardiac surgery and underwent standard

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Abbreviations and Acronyms

AF	= atrial fibrillation/atrial flutter
CABG	= coronary artery bypass grafting
CI	= confidence interval
ECG	= electrocardiographic/electrocardiogram
MI	= myocardial infarction
OR	= odds ratio
ROC	= receiver operating characteristic

CABG requiring cardiopulmonary bypass without concurrent valvular surgery. Cardiopulmonary bypass was performed with membrane oxygenators and arterial line filters using mild hypothermia (28°C to 32°C). Excluded from this study were 211 patients who had prior cardiac surgery (29% of whom developed postoperative AF) and 87 patients who were not in sinus rhythm before surgery. In addition to common clinical characteristics, we evaluated the standard preoperative 12-lead ECG recorded at a paper speed of 25 mm/s obtained for each patient from the hospital's computerized ECG database. Heart rate and PR-interval were recorded and P-wave duration (lead II) was measured manually after magnification (4×). We used previously defined values for prolonged P-wave duration (>110 ms) or PR-interval (>180 ms) (21). Additional intraoperative and early postoperative characteristics studied were cardiopulmonary bypass time; aortic cross-clamp time; postoperative myocardial infarction (MI) occurrence, defined as new Q waves on the 12-lead ECG; and low cardiac output, defined as having a cardiac index <2.0 $l/min/m^2$ for >8 h after surgery regardless of treatment (20). Preoperative beta-blockers were continued postoperatively to avoid withdrawal. The primary clinical end point of this study was the new onset of sustained (>5 min) postoperative AF requiring drug treatment or cardioversion and detected by continuous ECG until the time of discharge from the hospital. Atrial fibrillation was defined by an irregularly irregular cardiac rhythm other than sinus confirmed by either ambulatory or 12-lead ECG. Based on extensive review of the literature of risk factors for post-CABG AF, we selected 13 clinical variables that were reported in more than one study that included >500 patients: age, gender, history of AF, chronic obstructive pulmonary disease, hypertension, prior MI, peripheral vascular disease, diabetes mellitus, preoperative use of beta-blockers, aortic cross-clamp time, cardiopulmonary bypass time, and postoperative MI or low cardiac output and three ECG variables: preoperative heart rate, P-wave duration (>110 ms), and PR interval (>180 ms) (1–19).

Statistics. Univariate characteristics between patients with and without AF were compared using the Student *t* test for continuous variables and/or chi-square tests for categorical variables. A model was built using stepwise logistic regression to identify the subset of variables that jointly predicted post-CABG AF risk. All variables whose univariate tests resulted in a p value < 0.2 were considered in the multiple logistic regression model. Concordance index and area under the receiver operating characteristic (ROC) curve were computed as descriptive tools for measuring the discrimination of the model. Hosmer-Lemeshow goodness-of-fit statistic was computed for examining the calibration of the model. Internal validation of the predictive model was performed using jackknifing as follows. Logistic regression analysis was performed leaving out one patient at a time, and the results of that regression were used to compute a predicted probability of AF for that patient. These predicted values were then used to compute an adjusted ROC curve, with the area under the curve (AUC) as an indicator of overall discrimination. A simple point score was computed for each individual in the patient population by choosing a formula with whole numbers that were approximately proportional to the logistic regression coefficients of the variables significant in the final model. A nomogram was generated to translate the point score into an estimate of the likelihood of having post-CABG AF. The SAS release 8.2 (SAS Institute, Cary, North Carolina) was used for all analyses. Data are presented as mean value ± SD or number (%). All statistical tests were two-tailed, and $p < 0.05$ was regarded as significant.

RESULTS

Patient characteristics and surgical data are presented in Table 1. Sustained postoperative AF occurred in 508 of 1,553 patients (33%) while in the hospital. On univariate analysis age, prior AF, and history of peripheral vascular disease were significantly associated with AF occurrence (Table 1). Patients with AF had significantly greater values

Table 1. Patient Characteristics

	AF (n = 508)	No AF (n = 1,045)	p value
Preoperative			
Age, yrs	68 ± 9	62 ± 11	< 0.0001
Male gender	336 (66)	704 (67)	0.63
COPD	46 (9)	72 (7)	0.13
Hypertension	371 (73)	728 (70)	0.17
Diabetes mellitus	167 (33)	379 (36)	0.19
PVD	92 (18)	141 (14)	0.02
History of MI	265 (52)	525 (50)	0.48
Beta-blocker usage	239 (47)	547 (52)	0.05
History of AF	57 (11)	27 (3)	< 0.0001
Heart rate, beats/min	72 ± 14	72 ± 15	0.55
P-wave duration, ms	117 ± 17	115 ± 18	0.02
P-wave duration >110 ms	318 (63)	550 (53)	0.0002
PR interval, ms	170 ± 29	164 ± 26	< 0.0001
PR interval >180 ms	135 (27)	242 (23)	0.14
Intraoperative			
CPB, min	128 ± 41	127 ± 39	0.49
ACC, min	63 ± 22	64 ± 22	0.33
Postoperative			
MI	6 (1.2)	12 (1.2)	0.96
Low cardiac output	36 (7)	24 (2)	< 0.0001

Data are presented as n (%) or mean ± SD.
ACC = aortic cross-clamp time; AF = atrial fibrillation/atrial flutter; COPD = chronic obstructive pulmonary disease; CPB = cardiopulmonary bypass time; MI = myocardial infarction; PVD = peripheral vascular disease.

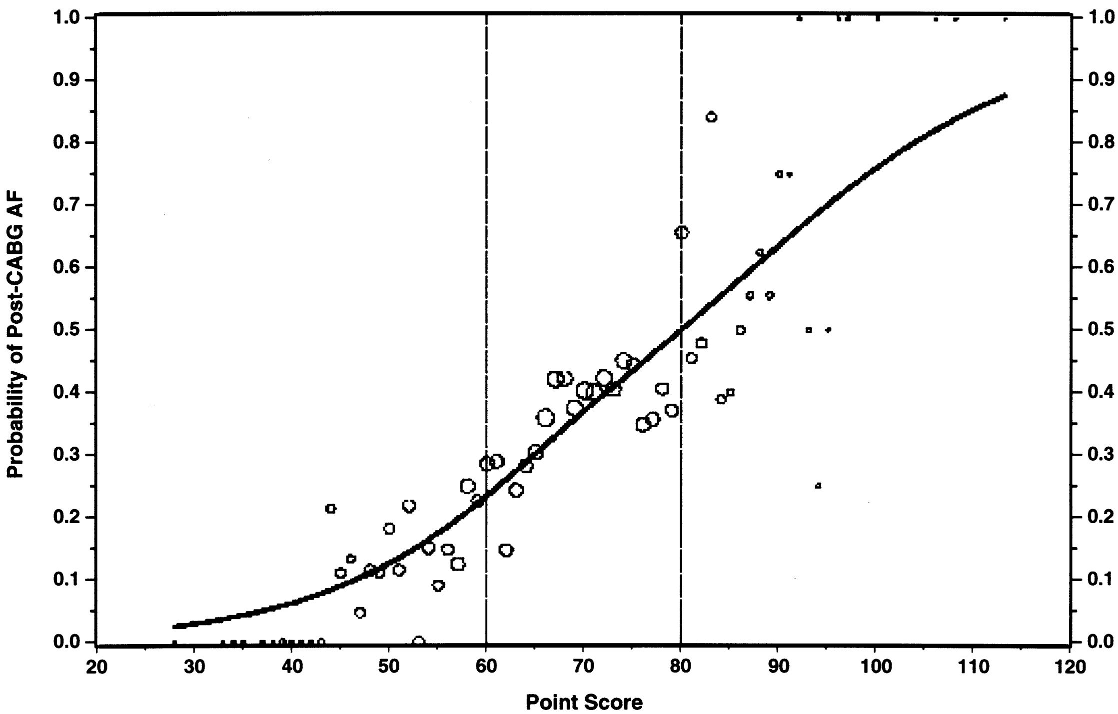

Figure 1. Predicted probability of developing atrial fibrillation/atrial flutter (AF) by the point score. **Circles** = observed probability of post-coronary artery bypass graft (CABG) AF. Areas of the circles are proportional to the number of patients with each score value in the study population. **Curve** = predicted probability of post-CABG AF generated from a spline smooth of the logistic regression model based on point score. **Vertical dash lines** = cutoff of point scores of the three risk categories for AF.

of P-wave duration and PR interval; however, the mean differences in both of these characteristics were small (Table 1). Lower use of preoperative beta-blockers was near significant for AF risk. Multivariate analysis showed that greater age (odds ratio [OR] 1.1 per year increment [95% confidence intervals (CI) 1.0 to 1.1], $p < 0.0001$; estimated coefficient 0.054, point score 1 per one-year increment), history of AF (OR 3.7 [95% CI 2.3 to 6.0], $p < 0.0001$; estimated coefficient 0.654, point score 12), P-wave duration >110 ms (OR 1.3 [95% CI 1.1 to 1.7], $p = 0.02$; estimated coefficient 0.142, point score 3), and postoperative low cardiac output (OR 3.0 [95% CI 1.7 to 5.2], $p = 0.0001$; estimated coefficient 0.547, point score 10) were independently associated with AF risk. Point score was assigned to be whole numbers approximately proportional to the estimated coefficients of the multivariate logistic regression model.

The predictive model based on these variables had a concordance index of 0.69, and an AUC of 0.69; the Hosmer-Lemeshow goodness-of-fit statistic suggested good calibration ($p = 0.11$). The results from jackknife analysis show that the model is mildly overfitted (area under the jackknife-adjusted ROC curve = 0.62). Figure 1 presents observed and predicted probabilities of postoperative AF based on the computed point score from the final model. Figure 2 plots the ROC curve for the point score as a predictor of AF (AUC = 0.69). The prediction rule using the point score is displayed graphically in the nomogram (Fig. 3). Using this point scoring system we defined three overall risk categories for AF: <60 points, 61 of 446 (14%); 60 to 79 points, 330 of 908 (36%); ≥80 points, 117 of 199 (59%).

DISCUSSION

The main findings of this study are that in addition to older age, prior history of AF, presence of P-wave duration >110 ms on the standard preoperative ECG, and a low postoperative cardiac output independently contribute to the risk for postoperative AF. Using these four risk factors, we were able to develop a simple prediction rule and scoring system to estimate the likelihood of postoperative AF occurrence. Three out of four risk factors are easily available before surgery, with age (1 point per year) and prior history of AF (12 points) carrying the most weight in the point scoring system. Presence of P-wave duration >110 ms before surgery scored the least (3 points), whereas the development of a low cardiac output after surgery conferred significant risk (10 points). For example, a 68-year-old patient with history of prior AF and P-wave duration >110 ms (83 points total) had a probability of 0.54 for developing postoperative AF, compared with a patient at the same age but without the other two risk factors (68 points total), who had a 0.35 chance for AF. Alternatively, a 73-year-old patient with no other risk factors (73 points) who developed postoperative low cardiac output had a probability to de-

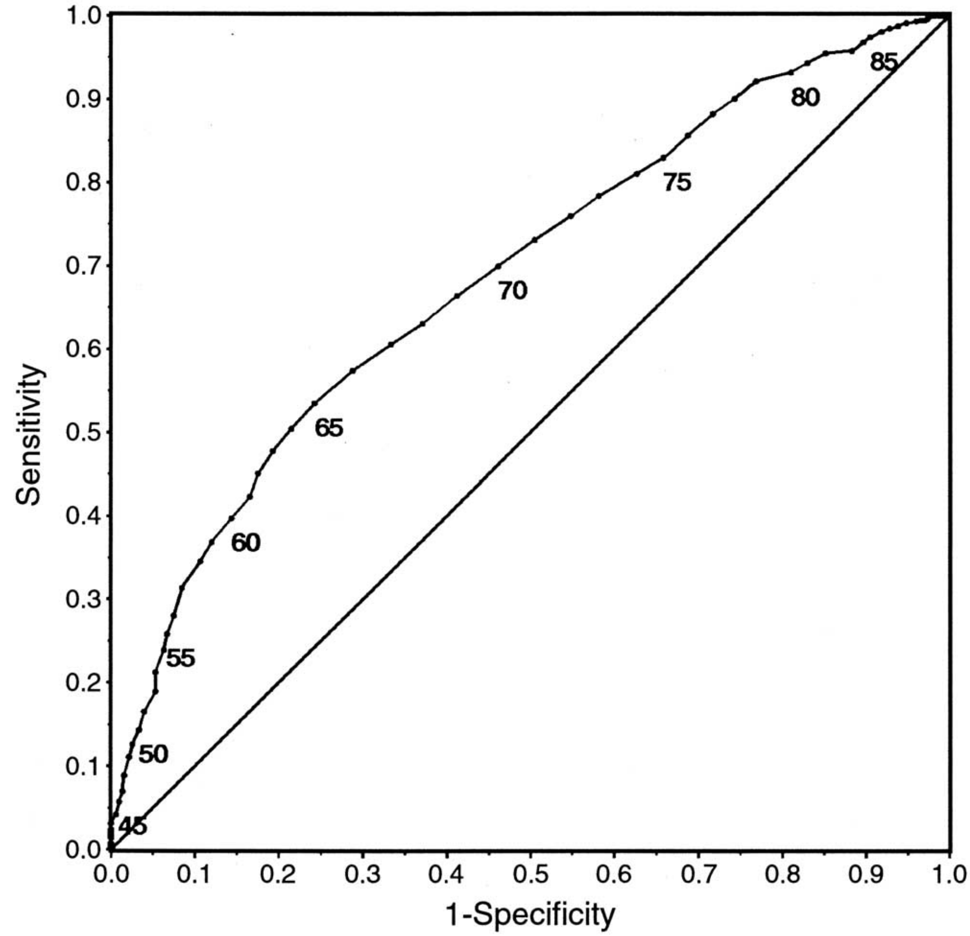

Figure 2. Receiver-operator characteristic (ROC) curve of point score as a predictor of post-coronary artery bypass graft atrial fibrillation/atrial flutter as determined by logistic regression analysis. The area under the ROC curve for the model was 0.69. Every fifth point score value is labeled.

velop AF that increased from 0.42 to 0.54. If one's practice was to limit AF prevention measures to high-risk patients (≥80 points), the patient in the last example would not receive prophylaxis before but rather immediately after surgery.

To date, the only consistent preoperative risk factor for an increased incidence of AF following surgery has been age ≥60 years (1–13). It is well known that aging causes degenerative changes in the atrial myocardium that lead to alterations in electrical properties of the SA and AV nodes and atria, which contribute to fragmentation of the propagating impulse (22,23). The concept of a preexisting anatomic or electrophysiologic substrate for arrhythmias due to aging that may be present in varying severity among individuals who are susceptible to AF possibly explains why some, but not other, patients who undergo the same operation develop postoperative AF (3,5). This theory is supported by the findings of Goette et al. (24) in 259 patients who had right atrial appendage specimens taken during cardiac surgery to determine the relationship between the degree of atrial fibrosis and the occurrence of postoperative AF. This study showed that the combination of older age, greater P-wave duration ≥100 ms from the standard ECG, and degree of atrial fibrosis was associated with postoperative AF occurrence. The amount of atrial fibrosis in patients with and without postoperative AF,

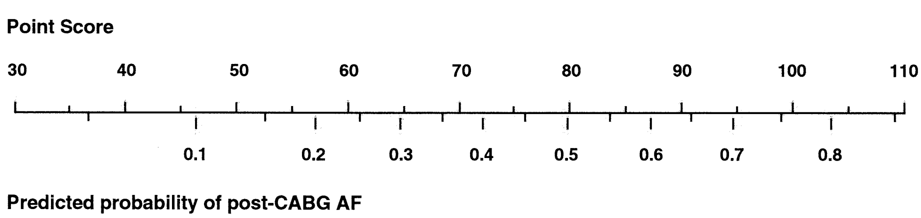

Figure 3. Nomogram for the proposed prediction rule for post-coronary artery bypass graft (CABG) atrial fibrillation/atrial flutter (AF). Point scores are computed by adding one point for each year of age, 12 points for prior history of AF, 3 points for P-wave duration >110 ms, and 10 points for low cardiac output. For any point score on the scale **above the line**, one can read the corresponding estimated probability of AF on the scale **below the line**.

however, overlapped markedly (24). We used an established definition of a prolonged P-wave duration (>110 ms) (21) and found it to be a weak contributor to the model, albeit an independent risk factor. Not surprisingly, prior history of AF carried a significant weight in our model, reinforcing that such patients likely possessed the anatomic substrate for AF. Our observation that a low cardiac output after surgery is an independent predictor of AF is not new (25) and suggests that intraoperative conditions leading to left ventricular systolic and/or diastolic dysfunction and atrial enlargement add to the atrial electrical substrate predisposing to AF.

Other prediction rules for post-CABG AF have been proposed. Zaman et al. (16) reported in 326 patients undergoing CABG that the combined ability of age ≥60 years, male gender, and a signal-averaged P-wave duration >155 ms to predict postoperative AF was 59%. Passman et al. (17) studied 287 CABG patients and derived a rule with an AUC of 0.76 using the predictors of age, prior AF, history of heart failure, standard ECG P-wave duration >110 ms, and PR interval >185 ms. The major limitation of these two prediction rules is the relatively small sample size, and in our analyses we found that some of these risk factors are not actually associated with increased risk of AF (16,17). Several studies examined whether the preoperative presence of a prolonged P-wave duration may select those patients who are likely to develop postoperative AF. P-wave duration was measured from the standard preoperative ECG in some studies (14,15,17–19) or by using a computerized signal-averaging system in other studies (15,16,18,19). The latter technique is expensive, requires 20 min to perform, and is not widely available. Furthermore, there is controversy on how a prolonged signal-averaged P-wave duration is defined (16,19) and whether it predicts postoperative AF (15,18). Even those investigators who described its usefulness as a predictor of postoperative AF have proposed different cutoffs of >140 ms and >155 ms to indicate significant intra-atrial conduction delay (16,19). Moreover, the incremental benefit of the signal-averaged P-wave duration over advanced age alone was small.

Mahoney et al. (13) examined clinical but not ECG characteristics in 8,709 patients and derived a prediction rule for post-CABG AF using age, male gender, prior MI, and cardiopulmonary bypass time. In contrast to Mahoney et al. (13), we did not find that gender, prior MI, or cardiopulmonary bypass time were predictive of AF. Such discrepencies are common among large epidemiologic studies (2,7–13) and may reflect one or more of the following: differences in patient charactaeristics and demographics surveyed, study sample size, number of risk factors in the mulitvariate model, and operative techniques The rule proposed by Mahoney et al. (13) is confusing because when the investigators examined patients with ischemic heart disease who underwent CABG with valvular surgery, they found that besides age, renal insufficiency was a risk factor for AF, whereas male gender, prior MI, and cardiopulmonary bypass time were no longer predictive. Despite the large number of patients the discrimination of their model was 0.68, similar to ours (13). For a prediction rule to be adopted into clinical practice it must not only be statistically valid but computationaly simple. We believe that our prediction rule has a simpler scoring system than the other rules and relies less on cumbersome data such as cardiopulmonary bypass time or information that must be obtained from nonstandard tests such as signal-averaged P-wave duration (13,17).

Study limitations. Our results and conclusions are limited to the new onset of in-hospital AF and do not address episodes of AF that occur after discharge. We excluded patients with prior CABG in order to focus on a homogeneous group of patients presenting for their first operation. Although the predictors in our study are highly significant, the overall accuracy of the prediction was moderate (AUC = 0.69). As with other models produced from one institution, ours may suffer performance dropoff when used in a new setting and therefore should undergo outside validation (26).

Conclusions and clinical implications. We present an easy prediction rule to estimate the risk of AF after CABG using four independent predictors: increasing age, prior history of AF, P-wave duration >110 ms, and low cardiac output after CABG. To the best of our knowledge, this is the largest study combining clinical and standard ECG characteristics in designing such a rule. Using this scoring system we were able to establish low-, intermediate-, and high-risk categories for postoperative AF. Although most would agree that the high-risk group should receive prophylaxis either before or immediately following surgery and that the low-risk group should not, for intermediate-risk patients cost-to-benefit analyses for potential prevention or therapeutic strategies would provide evidence-based data on which strategy to pursue to minimize drug related adverse events and costs. Because of the multifactorial etiology of postoperative AF and the high breakthrough rate of AF despite single-drug prophylaxis (27), we speculate that a potential strategy for AF prevention with the use of prediction rules could be that intermediate-risk patients receive a combination of antiarrhythmic drugs with differing sites of action and high-risk patients receive similar drug combinations plus prophylactic pacing as prophylaxis, for example (28).

In conclusion, decision rules that are data-driven have the potential to optimize care by limiting unnecessary variation while maintaining or improving outcomes. As newer drugs or interventions become available for the prevention of postoperative AF, clinical prediction models will be useful to assess their cost-effectiveness among patients at risk for this complication.

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