Postoperative atrial fibrillation prediction following isolated surgical aortic valve replacement

Alina Cristina Iliescu[1], Delia Lidia Salaru[1,2], Ionut Achitei[1], Mihaela Grecu[1], Mariana Floria[2,3], Grigore Tinica[1,2]

[1]Institute of Cardiovascular Disease; Iaşi-*Romania*
[2]Grigore T. Popa University of Medicine and Pharmacy; Iaşi-*Romania*
[3]Sf. Spiridon Emergency Hospital; Iaşi-*Romania*

Abstract

Objective: Postoperative atrial fibrillation (POAF) is the most common complication following cardiac surgery, with increased risk of stroke and high mortality. Our aim was to identify patients at risk and to design a model that could predict POAF.
Methods: In this single center study, we evaluated 1191 patients requiring isolated surgical aortic valve replacement between January 2000 and June 2014. The patients were followed during the early postoperative period until discharge.
Results: AF occurred in 342 patients (28.71%). Six variables associated with high arrhythmic risk [advanced age, body mass index, tricuspid regurgitation, prolonged ventilation, longer intensive care unit stay, and dilated left atrium (LA; volume ≥35 ml/m^2)] were selected to create a multivariate prediction model. This model predicted POAF in 64.7% of cases, with a moderate discriminative power (AUC=0.65; p=0.001; 95% CI, 0.571-0.771). We also developed the CHAID (Chi-square automatic interaction detection) model showing multilevel interactions among risk factors for POAF. Age had the greatest discriminative power, with patients aged >68 years at a higher risk for POAF. In low-risk patients, the subgroup with dilated LA (volume ≥40 ml) was more prone to develop POAF. For the intermediate-risk group, history of AF was the next deciding variable, whereas for the high-risk group, it was tricuspid regurgitation (at least moderate).
Conclusion: The multivariate logistic model has an acceptable predictive value. CHAID-derived model is a new tool that could be easily applied to identify patients requiring prophylactic regimens. *(Anatol J Cardiol 2018; 19: 394-400)*
Keywords: atrial fibrillation, postoperative, aortic valve replacement, prediction score

Introduction

Postoperative atrial fibrillation (POAF) is the most common complication following cardiac surgery. Its incidence depends on the surgery type and is estimated to be 40%–50% in valve surgery cases (1). Arrhythmia is associated with a high risk of stroke, increased early and late mortality, and considerable cost (2). Advanced age has been consistently reported as an independent risk factor for arrhythmic complications (3, 4). Increasing life expectancy has resulted in growing number of aortic valve replacements. Such patients often have considerable comorbidity with cumulative arrhythmic risk; therefore, prophylactic management is needed.

Most proposed preventive resources include the administration of antiarrhythmic or anti-inflammatory medications (5) or intraoperative procedures, such as atrial pacing (6, 7). Despite the efficacy of the prophylactic regimens for POAF, routine prevention protocols are not used in many cardiac surgery units, probably due to the drug regimens and their side effects (7-9). In addition, the etiology of POAF is not clearly understood, which can impacts the surgeon's willingness to practice various types of proposed prophylactic treatments. However, recently, prophylaxis has been considered only in high-risk patients, considering the risk-benefit ratio (10).

Our aim was to identify the patients at risk who require prophylactic strategies. We aimed to determine the pre- and perioperative risk factors in patients undergoing surgical aortic valve

Address for correspondence: Mariana Floria, MD, Grigore T. Popa University of Medicine and Pharmacy, and Sf. Spiridon Emergency Hospital; 1 Universitatii Street, 700111, Iaşi-*Romania*
Phone: 04 0232 240 822 Fax: 04 0232 217 781 E-mail: floria_mariana@yahoo.com
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replacement (SAVR) and to design a model that could predict the postoperative arrhythmic event.

Methods

Patients

We performed a cross-sectional analysis in this retrospective study. We included the patients admitted between January 2000 and June 2014 in our hospital. A total of 8740 cardiac surgeries were performed at our center during this period (Fig. 1). Of these, 1191 patients who underwent cardiac aortic surgery required isolated SAVR.

The inclusion criteria were patients aged >18 years who were referred to our center for SAVR and who signed the informed consent.

The exclusion criteria included patients with a history of AF, those with other cardiac rhythms than normal sinus rhythm, those with implanted cardiac devices such as a pacemaker or defibrillator, those who also needed an aorto-coronary bypass or mitral valve surgery, and those who refused to be included in this study.

All the patients were preoperatively assessed using 24-h ECG Holter monitoring, echocardiography, and coronary angiography. The left ventricular systolic function was classified as normal (ejection fraction >50%), reduced (30%–50%), or severely reduced (<30%). All the data were included in an extensive database, including biological, preoperative, perioperative and early postoperative parameters.

The main outcome was new-onset POAF recorded using electrocardiography and/or telemetry. According to the definition of the 2014 Guidelines on Atrial Fibrillation of the American College of Cardiology/American Heart Association (11), POAF is defined as at least 15 min of arrhythmia. Patients were continuously monitored for at least 72 h postoperatively; subsequently, they were examined twice a day or when symptomatic. The patients were followed during the early postoperative period until discharge.

Ethics statement

The Hospital Ethics Committee approved this study. Each patient was enrolled after signing the informed consent.

Statistical analysis

Continuous variables are presented as the mean±standard deviation and categorical variables as numbers and percentages. Quantitative variables were tested for normality of distribution using the Kolmogorov-Smirnov test and are presented as the median and percentile or mean and standard deviation as applicable. The frequencies of nominal variables were compared using the Fisher's exact test and chi-square test. Differences in the means and medians or between the groups were analyzed using the t-test or Mann-Whitney U test as applicable. For the non-normally distributed data, we used the Spearman's coefficient.

SPSS 17.0 (SPSS Inc., Chicago, IL, USA) statistical software package and Microsoft Office Excel 2013 were used for all calculations. A p value of <0.05 was considered statistically significant.

The logistic regression analysis was used to describe a model that could predict POAF and identify patients at high risk. We tried to use variables with the highest predictive value. The logistic regression model was derived by forward or backward approach selection, with a p value of 0.02, and removed if p was >0.05. The significance of the model was evaluated using the Wald test, and the strength of association of variables with arrhythmia was estimated by calculating the 95% CIs. Discrimination of the models was assessed using the area under the curve (AUC) of the receiver operating characteristic (ROC) determined by logistic regression.

Chi-square automatic interaction detection classification tree

Chi-square automatic interaction detection (CHAID) is a technique that represents a series of decision rules used for prediction. It begins with a root node including all the cases, followed by division into different child nodes containing subgroups of cases. Partitioning is done after examining all possible values of all available predictive variables. In the terminal nodes, the subgroups obtained contain homogenous cases, as possible with respect to the value of the dependent variable (12, 13). The advantage of CHAID decision trees over alternatives is that it is nonparametric. It can detect how independent variables (continuous and/or categorical) best combine, obtaining subgroups based on data homogeneity. For this study, the dependent variable was POAF.

Results

The most frequent intervention performed in our hospital during the study period was the isolated coronary bypass (40.46%), followed by isolated valve surgery (29.08%). A total of 1191 (13.62%) isolated SAVRs were performed (Fig. 1). Patients were divided into two groups depending on the postoperative rhythm: the POAF group (342 patients, 28.7%) and sinus rhythm

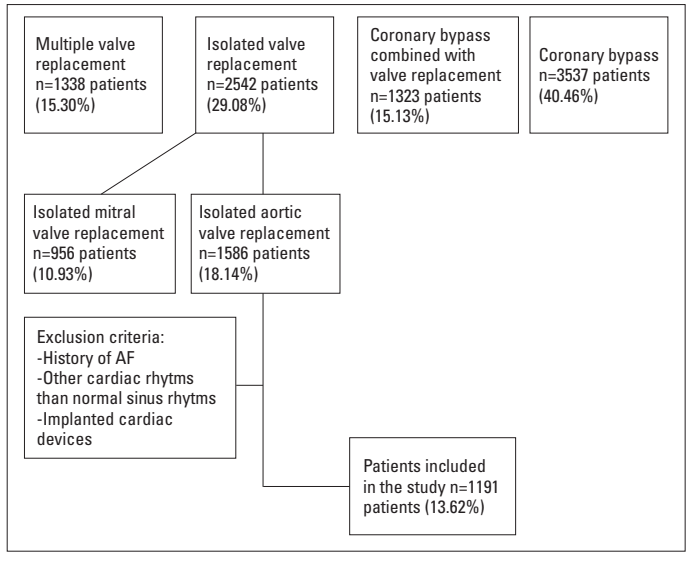

Figure 1. Flow chart of patients with isolated aortic valve replacement included in the study

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Table 1. Preoperative characteristics of patients with postoperative atrial fibrillation compared with patients with sinus rhythm

Parameter	POAF group n=342 patients (28.7%)	Sinus rhythm group n=849 patients (71.3%)	*P* value
Age (years; median±SD)	69.03±10.57	64.47±14.11	**0.005**
Male (%)	63.2	69.8	0.52
Smoker (%)	49.1	39.1	0.059
Arterial hypertension (%)	25.6	28.3	0.76
Hyperlipidemia (mg/dL)	129.98±95.47	148.84±87.50	**0.02**
Diabetes mellitus (%)	12	12	0.725
EuroScore II	9.00±2.87	5.78±1.97	**0.001**
Serum creatinine >200 μmol/L (%)	45.3	26.7	**0.002**
Preoperative medical treatment			
Beta-blocker (%)	23.4	21.7	0.12
Calcium blocker (%)	7.8	5.8	0.091
ACEI (%)	17.7	18.9	0.523
ARB (%)	5.2	7.2	0.34
Diuretics (%)	6.1	5.4	0.71

ACEI - angiotensin converting enzyme inhibitor; ARB - angiotensin II receptor blocker; NS - non-statistically significant; POAF - postoperative atrial fibrillation; SD - standard deviation

Table 2. Preoperative echocardiographic parameters

Parameter	POAF group n=342 patients (28.7%)	Sinus rhythm group n=849 patients (71.3%)	*P* value
LVEF <30% (%)	37	38	**0.039**
LVEF=30%–50% (%)	52	110	**0.041**
LVEF >50% (%)	359	746	0.16
LVED volume (mm)	54.70±9.71	54.61±10.47	0.072
LA volume (mL)	49.42±11.70	47.30±10.37	0.091
Indexed LA volume (mL/m^2)	26.71±12.30	26.27±11.52	**0.007**
Indexed LA volume ≥35 mL/m^2 (%)	36.25	9.62	**<0.001**
IVS (mm)	14.55±2.87	14.38±2.55	**0.032**
Aortic annulus (mm)	23.42±5.55	23.55±5.31	0.43
Aortic regurgitation severity			
Mild	88 (30.24%)	203 (69.75%)	0.72
Moderate	113 (34.45%)	215 (65.54%)	0.54
Severe	97 (26.50%)	259 (70.76%)	0.91
PAP (mm Hg)	47±14	43±12	0.52

IVS - interventricular septum; LA - left atrium; LVEF - left ventricular ejection fraction, LVED - left ventricular end diastolic; NS - non-statistically significant; PAP - systolic pulmonary artery pressure

group (849 patients, 71.3%). The study group had an average age of 64±13 years, and 67.8% were male. The demographic data are presented in Table 1. Five hypertensive patients had a history of stroke, but not AF. Comparing the two groups, variables age and chronic kidney disease showed statistical significance. Arterial hypertension was more frequently encountered in the sinus rhythm group than in the POAF group, without being statistically significant. There were no statistically significant differences between the preoperative and early postoperative medical treatment regimens between the two groups.

Preoperative echocardiographic parameters are presented in Table 2. Preoperatively, there were no statistically significant dif-

Table 3. Predictors of new-onset postoperative atrial fibrillation

Predictor	B	SE	Wald	df	Sig.	Exp (B)	95% CI for Exp (B)	
							Lower	Upper
BMI (kg/m^2)	0.029	0.016	3.179	1	0.075	1.030	0.970	1.032
Tricuspid regurgitation more than mild	0.333	0.157	4.484	1	0.034	1.396	1.194	2.135
Prolonged ventilation	0.168	0.267	0.396	1	0.529	1.183	0.768	1.599
Long intensive care unit stay (>3 days)	2.070	0.800	6.698	1	0.010	7.925	1.770	38.959
LA volume (mL/m^2)	0.020	0.007	7.221	1	0.007	1.020	1.009	1.037
Age ≥65 years	0.280	0.07	17.452	1	0.0001	1.028	1.022	1.047

BMI - body mass index; LA - left atrium

ferences between the number of patients with mild, moderate, or severe aortic regurgitation, mean systolic pulmonary artery pressure, and aortic diameter between the two groups. In the POAF group, the mean interventricular septum thickness was slightly greater than that in the control group.

Aortic calcification was the most common cause of aortic disease (1045 cases, 87.74%); the valve was congenitally bicuspid in 149 patients (12.51%) and unicuspid in one (0.08%). There were 122 cases of endocarditis (10.24%), which was significantly associated with age <65 years (p<0.01).

All prostheses were inserted using separated stitches in the intra-annular position. Mechanical valves were implanted in 931 patients (78.16%): CarboMedics prosthesis in 704 (75.61%), Edwards Mira prosthesis in 220 (23.63%), Medtronic-Hall prosthesis (single-tilting disc) in seven (0.75%), and St. Jude Medical prosthesis in one (0.10%). Bioprostheses were implanted in 260 patients (21.83%): Carpentier Edwards's Lifescience in 13 (5%) and Medtronic Hancock II in 247 (95%).

Of the patients who received bioprosthesis (n=260; 21.83%), 108 (41.53%) developed POAF. In patients who received mechanical valves, arrhythmia developed in 255 (27.46%), and the difference was statistically significant (p<0.001).

The aortic clamping time was 95.00±42.30 min for the AF group and 92.49±24.50 min for the sinus rhythm group (p>0.05). The extracorporeal circulation time was 136.01±57.76 min for the AF group and 128.05±59.70 min for the sinus rhythm group (p=0.085).

Postoperative complications showed statistically significant differences (all p=0.001) between the two groups: endocarditis [95 patients (77.86%) vs. 27 patients (22.13%)], prolonged ventilation [21 (2.47%) vs. 36 (10.52%)]; stroke of >72 h (27 (3.18%) vs. 47 (13.47%)], neurological complications [41 (4.82%) vs. 56 (16.37%)], and acute renal failure (45 (5.3%) vs. 65 (19%)]. For other complications (sepsis, mediastinitis, MSOF, transient ischemic attack, and coma for >24 h), there were no statistically significant differences.

Multivariate analysis identified six variables associated with high arrhythmic risk: advanced age, body mass index (with a cut-off value of 27 kg/m^2), moderate tricuspid regurgitation, prolonged ventilation, longer intensive care unit stay, and increased left atrium (LA) volume (>35 mL/m^2) (Table 3). The model including all these variables predicted POAF in 64.7% of cases (Chi-square value, 62.291; p=0.000) and had a variation of 10.5% for the independent variable. The ROC curve showed that this model had a moderate discriminative power (AUC=0.65; p=0.001; 95% CI, 0.571-0.771) (Fig. 2).

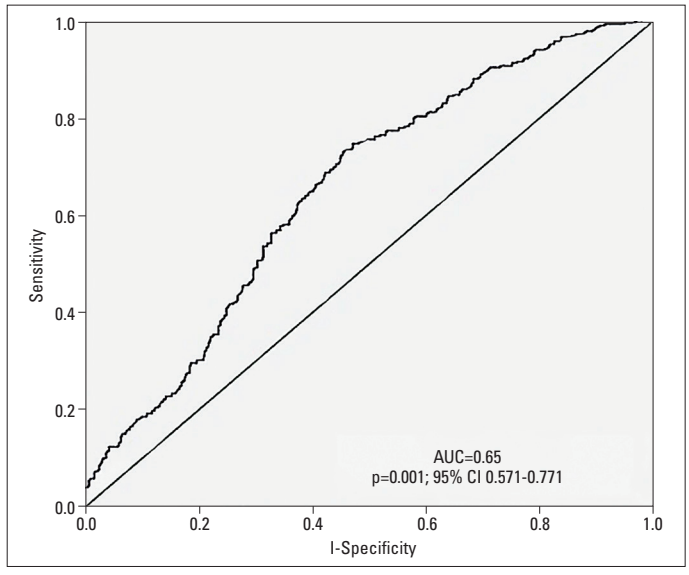

Figure 2. Receiver operator characteristic curve of point score as a predictor for new-onset postoperative atrial fibrillation in patients undergoing aortic surgery

CHAID classification tree

In the analysis using the CHAID decision tree (Fig. 3), in which POAF was the dependent variable, age, history of arrhythmia, body mass index, left atrial volume, left ventricle ejection fraction, tricuspid regurgitation more than mild, prolonged ventilation, long intensive care unit stay, diabetes, and EuroScore were the independent variables. The maximum tree depth was four. The analysis showed that age was the most important variable, with four levels of risk for POAF: 1) very low risk (age <46.8 years); 2) low risk (age between 46.8 and 57 years); 3) intermediate risk (age between 57

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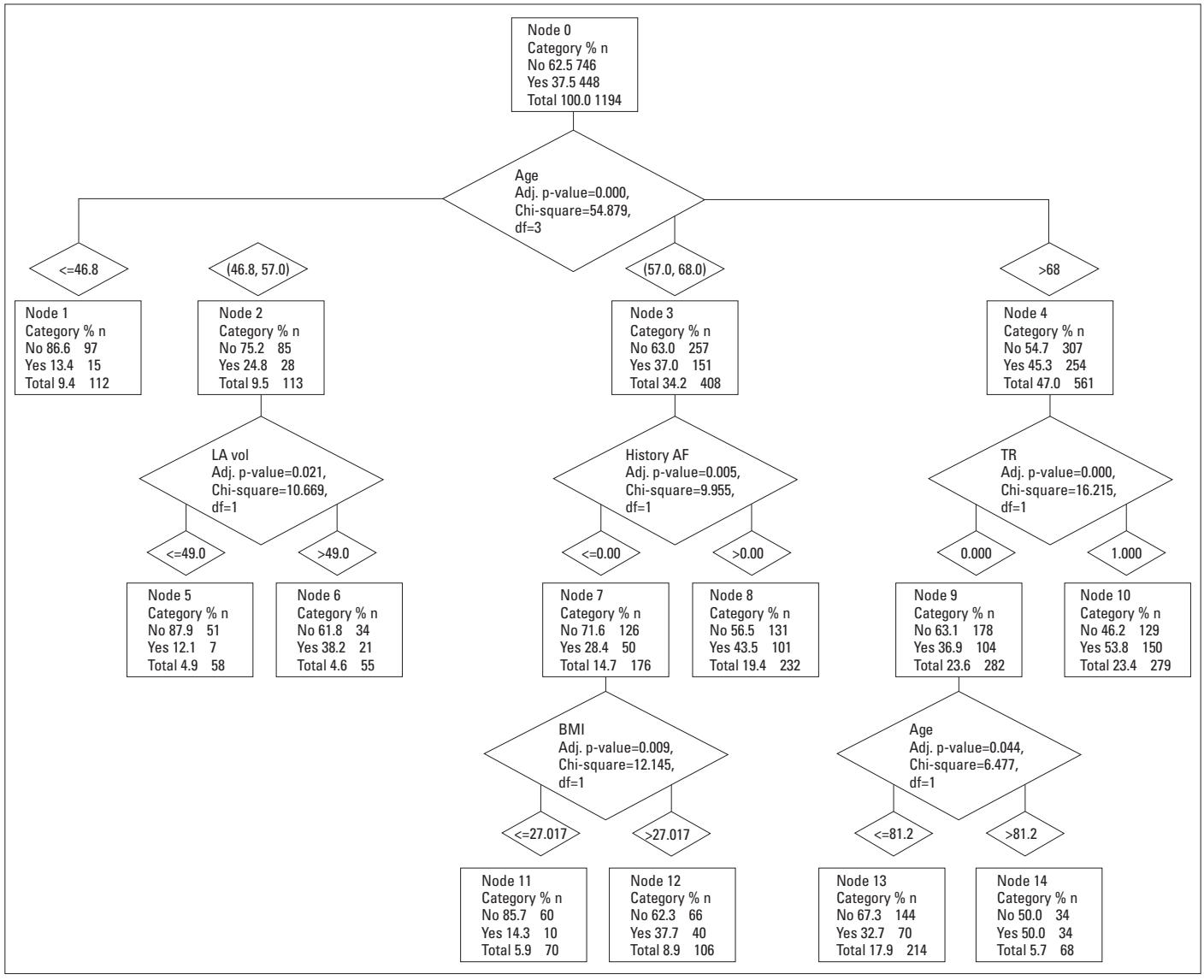

Figure 3. Tree model based on Chi-squared automatic interaction detection for patients with postoperative atrial fibrillation.
AF - atrial fibrillation; BMI - body mass index; LA vol - left atrial volume; TR - tricuspid regurgitation

and 68 years); and 4) high risk (age >68 years). For patients with low risk, the left atrial volume was the next predictive variable, the cut-off value being 40 mL. In patients with intermediate risk, history of AF was the next variable predicting arrhythmia, and in patients without arrhythmic history, body mass index (with a cut-off value of 27 kg/m^2) was the next predictive variable. In the high-risk group, tricuspid regurgitation (at least moderate) was the next predictive variable. Patients aged >81 years had the highest risk of POAF.

Discussion

The overall incidence of POAF in our group was 28.71%, which was consistent with that reported in the literature (1-3). We used logistic regression to determine a predictive model for POAF. The predictive value of different analyzed models was influenced by the variables involved and the number of patients included. Studies reporting risk factors for POAF have described different variables, but there are only a few prediction models, mainly for patients undergoing coronary artery bypass grafting (CABG) or combined surgical procedures (9, 10, 14-16). Our aim was to test a population of patients undergoing SAVR, excluding other surgical procedures such as CABG or mitral valve surgery. For more reliable results, the multivariate logistic regression excluded patients with preexisting AF, wherein preventive management is already justified. Estimating individual risk for POAF in patients undergoing SAVR is important for applying prophylactic strategies only in patients with high arrhythmic risk, thereby avoiding excessive cost and unwanted side effects in low-risk individuals. Previously proposed predictive models involved different variables that were significant for POAF risk but had several limitations due to small sample size or exclusion of

important factors, such as poor ventricular function and severe renal dysfunction (17-20).

Mahoney et al. (2) described three different models based on the type of cardiac surgery; for valve surgery, the model had two variables: age and chronic obstructive pulmonary disease. Furthermore, the model's predictive value was 0.665. Tran et al. (14) proposed another prediction score including three risk variables (age >65 years, mitral valve disease, and left atrial dilation), with a scoring system based on the regression coefficient, and reported a mean sensitivity of 82% and specificity of 39.2%. Mariscalco et al. (21) published a study including 12,938 patients undergoing cardiac surgery (CABG or/and valve surgery) and proposed a POAF score with seven variables (age, chronic pulmonary obstructive disease, glomerular filtration rate, emergency surgery, preoperative intra-aortic balloon pump use, low systolic ventricular function, and valve surgery), with moderate discriminative power.

Advanced age strongly associated with POAF is the only consistent finding in all the studies (2, 9-21).

Our model included six variables, and advanced age was a significant predictor in the multivariate analysis. Aging implies considerable remodeling of the atria due to increased fibrous tissue between the myocardial cells. These structural changes trigger arrhythmic mechanisms. Increased age is also most likely to be associated with multiple comorbidities and thus could explain the higher incidence of POAF in patients with biological prosthesis.

We also found that left atrial volume indexed to the body surface was an important predictor for POAF (p=0.007). Moreover, 36.25% of patients with POAF had indexed value of left atrial volume >35 mL/m^2 compared with 9.62% patients who maintained the sinus rhythm. Both, age and left atrial dilation, have well-documented association with arrhythmic mechanisms.

Two of our model variables (significant tricuspid regurgitation and prolonged ventilation) could be related to chronic pulmonary disease, a variable included in previous studies but without significant prediction power in our analysis (2, 21).

Extracorporeal circulation involves a systemic inflammatory response that triggers many postoperative complications. We compared the total aortic clamping time and extracorporeal circulation time between the two groups, but the values were not statistically significant. In our opinion, future studies should include variables that describe the inflammatory response to surgery, such as C-reactive protein or interleukin 6.

Logistic regression models could be useful in predicting POAF and identifying high-risk patients. Prophylactic strategies should be applied only in these patients to avoid unnecessary antiarrhythmic side effects and higher costs. Our CHAID model showed multilevel interactions among risk factors for POAF, age being the first level of partition and with the greatest discriminative power; patients aged >68 years were at higher risk. In patients with low risk, the subgroup with dilated LA (volume ≥40 mL) is more prone to develop POAF. The history of AF helps to identify patients with intermediate risk who may require antiarrhythmic prophylaxis. For patients in the high-risk group, this decision making tree could be applied when the risk-benefit ratio is unclear.

This novel approach has the ability to improve the predictive value of various multivariate models. The interaction of different variables is analyzed, and the hazard ratio is applied to the entire population.

Study limitation

Our study had several limitations. It was a retrospective study, although the data were prospectively included in the database. We only recorded in-hospital episodes of AF, without considering AF episodes that might have occurred after discharge. Although we included variables with high predictive value, the accuracy of the proposed model was only moderate, which may be attributed to the multifactorial arrhythmic etiology or vast variety of comorbidities of different severities and with different pharmacological schemes and multiple effects and interactions (22-24). The 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS (25) recommend perioperative beta-blockers to prevent POAF (class IB), although the moderate bias of the published studies has been underlined. Perioperative amiodarone is recommended in high-risk patients (class IIa, level of evidence B). However, the side effects of existing antiarrhythmic drugs are influencing the clinical decision. A recent study described a prophylactic protocol with intravenous amiodarone for 14 days or until the patient is discharged (26). Unfortunately, the adverse events (severe bradycardia and heart block) could be serious, especially in those with degenerative aortic disease (26).

The underlying mechanisms of POAF are yet to be determined. Future models should include parameters of the inflammatory response and other new variables derived from these findings.

Conclusion

Logistic regression models could be useful in predicting POAF and identifying high-risk patients. Prophylactic strategies should be applied only in these patients to avoid unnecessary antiarrhythmic side effects and higher costs. The models proposed to date have only moderate accuracy, include different variables and traditional pre- and perioperative risk factors, and do not address a specific surgical procedure. Our aim was to describe a predictive model for patients undergoing SAVR. Our model obtained by multivariate analysis has an acceptable predictive value and allows the clinician to vary the threshold for preventive medication. The novelty of this study lies in the CHAID-derived model, a tool that could easily identify patients requiring prophylactic regimens.

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