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***Original Article** / Özgün Makale*

Validation of SYNTAX and clinical SYNTAX scores in predicting atrial fibrillation following on-pump coronary artery bypass grafting

Pompa destekli koroner arter baypas greftleme sonrası gelişen atriyal fibrilasyonu öngörmede SYNTAX ve klinik SYNTAX skorlarının validasyonu

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ABSTRACT

Background: This study aims to evaluate the role of SYNTAX and clinical SYNTAX scores in predicting postoperative atrial fibrillation in patients undergoing coronary artery bypass grafting.

Methods: In this prospective, single-center, observational study, 123 patients (92 males, 31 females; mean age 60 years; range 40 to 84 years) who underwent coronary artery bypass grafting in our hospital between September 2015 and July 2016 were included. Preoperative demographic and clinical characteristics were recorded and SYNTAX and clinical SYNTAX scores were calculated. Univariate and multivariate logistic regression analyses with correlation analysis were used to identify the predictors of postoperative atrial fibrillation.

Results: Postoperative atrial fibrillation developed in 39 patients (31.7%). The second day of surgery was the peak time of the complication. SYNTAX [18(9-32) vs 24(10-45), p=0.001] and clinical SYNTAX scores [18(7-44) vs 30(11-89), p<0.001] were statistically significantly higher in patients who developed postoperative atrial fibrillation. In the correlation analysis, age, SYNTAX, clinical SYNTAX scores, CHADSVASc scores, hemoglobin A1c, and C-reactive protein values were positively associated with the frequency of postoperative atrial fibrillation, while hemoglobin showed a negative correlation (p<0.05). Clinical SYNTAX scores [(β=0.077, p=0.003, OR=1.080, 95% CI (confidence interval) (1.026-1.137)], SYNTAX [(β=0.081, p=0.028, OR=1.084, 95% CI (1.009-1.165)], and age [(β=0.054, p=0.034, OR=1.056, 95% CI (1.004-1.110)] were found to be independent predictors of postoperative atrial fibrillation in multivariate logistic regression analysis. The receiver operating characteristic analysis showed an area under the curve of 0.68 and 0.75 for SYNTAX and clinical SYNTAX scores, respectively (p=0.01, p<0.001, respectively). Clinical SYNTAX scores >17.59 had 84.6% sensitivity and 54.8% specificity to predict postoperative atrial fibrillation (area under curve: 0.754, p<0.001, 95% CI (0.658-0.850).

Conclusion: This study showed that age, SYNTAX, and clinical SYNTAX scores were independent predictors of postoperative atrial fibrillation. Clinical SYNTAX scores may be better than the SYNTAX scores in predicting postoperative atrial fibrillation in patients undergoing coronary artery bypass grafting.

Keywords: Atrial fibrillation; clinical SYNTAX score; coronary artery bypass grafting; SYNTAX score.

ÖZ

Amaç: Bu çalışmada koroner arter baypas greftleme yapılan hastalarda ameliyat sonrası atriyal fibrilasyonun öngörülmesinde SYNTAX ve klinik SYNTAX skorunun rolü değerlendirildi.

Çalışma planı: Bu prospektif, tek merkezli, gözlemsel çalışmaya hastanemizde Eylül 2015 - Temmuz 2016 tarihleri arasında koroner arter baypas greftleme yapılan 123 hasta (92 erkek, 31 kadın; ort. yaş 60 yıl; dağılım 40 to 84 yıl) dahil edildi. Hastaların ameliyat öncesi demografik ve klinik özellikleri kaydedildi ve SYNTAX ile klinik SYNTAX skorları hesaplandı. Ameliyat sonrası atriyal fibrilasyonun öngördürücülerini belirlemek amacıyla korelasyon analizi ile birlikte tek değişkenli ve çok değişkenli lojistik regresyon analizi yapıldı.

Bulgular: Ameliyat sonrası atriyal fibrilasyon hastaların 39'unda (%31.7) gelişti. Ameliyatın ikinci günü komplikasyonun pik yaptığı zamandı. Ameliyat sonrası atriyal fibrilasyon gelişen hastalarda SYNTAX [18(9-32)'ye kıyasla 24(10-45), p=0.001] ve klinik SYNTAX skorları [18(7-44)'e kıyasla 30(11-89), p<0.001], istatistiksel olarak anlamlı düzeyde yüksekti. Korelasyon analizinde yaş, SYNTAX, klinik SYNTAX skoru, CHADSVASc skoru, hemoglobin A1c ve C-reaktif protein düzeyleri ameliyat sonrası atriyal fibrilasyon sıklığı ile pozitif ilişkili iken, hemoglobin negatif ilişki gösterdi (p<0.05). Çok değişkenli lojistik regresyon analizinde klinik SYNTAX skoru [(β=0.077, p=0.003, OR=1.080, %95 GA (güven aralığı) (1.026-1.137)], SYNTAX [(β=0.081, p=0.028, OR=1.084, %95 GA (1.009-1.165)] ve yaş [(β=0.054, p=0.034, OR=1.056, %95 GA (1.004-1.110)] ameliyat sonrası atriyal fibrilasyonun bağımsız öngördürücüleri olarak bulundu. Alıcı işletim karakteristiği analizinde eğri altında kalan alan SYNTAX ve klinik SYNTAX skoru için sırasıyla 0.68 ve 0.75 olarak hesaplandı (sırasıyla, p=0.01, p<0.001). Klinik SYNTAX skorunun 17.59 üstünde olması, ameliyat sonrası atriyal fibrilasyonun öngörülmesinde %84.6 duyarlılığa ve %54.8 özgüllüğe (eğri altındaki alan: 0.754, p<0.001, %95 GA (0.658-0.850) sahipti.

Sonuç: Çalışmamızda yaş, SYNTAX ve klinik SYNTAX skoru ameliyat sonrası atriyal fibrilasyonun bağımsız öngördürücüleri olarak bulundu. Klinik SYNTAX skoru, koroner arter baypas greftleme yapılan hastalarda ameliyat sonrası atriyal fibrilasyonun öngörülmesinde daha iyi olabilir.

Anahtar sözcükler: Atriyal fibrilasyon; klinik SYNTAX skoru; koroner arter baypas greftleme; SYNTAX skoru.

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New-onset atrial fibrillation (AF) is the most common rhythm disturbance following cardiac surgery and is associated with thromboembolic events, myocardial ischemia, heart failure, prolonged hospital stay, and increased cost.[1,2] Although several risk factors have been suggested to explain the triggers of postoperative atrial fibrillation (PoAF), the exact underlying mechanisms have not been elucidated, yet.[3] SYNTAX score (SS) is a tool to determine the coronary artery disease (CAD) according to qualitative and quantitative angiographic variables.[4] Clinical SYNTAX score (CSS) is also a risk stratification tool to select optimal revascularization strategy in patients diagnosed with stable CAD and non-ST-segment elevation acute coronary syndromes.[5] It comprises not only anatomic characteristics, but also clinical variables such as age, serum creatinine, and left ventricular ejection fraction. In previous studies, CSS has been found to be superior in predicting the 30-day and one-year clinical outcomes, compared to the SS in patients undergoing percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG).[6] In clinical practice, it is important to develop preoperative risk scoring systems or diagnostic algorithms to reduce the adverse outcomes of PoAF by applying preventive prophylactic measurements. The widening application of CSS in many clinical settings and its association with significant cardiac adverse events has led us to design this study to validate its ability in predicting new-onset AF following CABG.

In the present study, we aimed to evaluate the role of SS and CSS in predicting PoAF in patients undergoing CABG.

PATIENTS AND METHODS

This prospective, single-center, observational study included 123 patients (92 males, 31 females; mean age 60 years; range 40 to 84 years) with sinus rhythm who underwent isolated on-pump CABG in our hospital between September 2015 and July 2016. The study protocol was approved by the Istanbul University, Cerrahpasa Faculty of Medicine, Ethics Committee and a written informed consent was obtained from each participant. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient selection

Patients with a history of preoperative AF, ST-segment-elevation myocardial infarction (STEMI), previous cardiac surgery, chronic obstructive pulmonary disease (COPD), concomitant valve surgery, thyroid disease, electrolyte imbalance, chronic inflammatory disease, ejection fraction (EF) <35%, and peripheral artery disease were excluded. Preoperative demographic and clinical characteristics of the patients were recorded.

Surgical technique

All patients were operated under the same anesthetic protocol. General anesthesia was induced with 1 to 3 mg midazolam, 5 to 10 µg/kg fentanyl, and 0.3 mg/kg etomidate. Anesthesia was maintained with fentanyl and analgesia with propofol. All procedures were performed by the same surgery team. Standard median sternotomy was employed and left internal mammary artery (LIMA) was preferred for the distal left anterior descending coronary artery (LAD) anastomosis.

Atrial fibrillation

Postoperative AF was defined as an arrhythmia which lasts longer than 60 seconds with irregular RR intervals, showing no distinct P waves on the surface electrocardiography (ECG) during the first seven postoperative days.[7] Following surgery, all patients were followed by continuous telemetry in the intensive care unit and a 12-lead ECG was obtained from the patients every 12 hours, until the discharge of the patients from hospital. Additional 12-lead ECG was taken, when the patients complained of dyspnea, palpitation, or angina.

SYNTAX and Clinical SYNTAX Score Calculation

SYNTAX was calculated for each patient using the SYNTAX score calculator, version 2.11[8] by two experienced cardiologists who were blinded to the procedural data and the clinical outcome on angiograms. In case of disagreement, a third observer was obtained and final decision was made by consensus. The CSS was calculated using the following formula: CSS= SYNTAX score x modified ACEF (age, creatinine clearance, ejection fraction) score. The modified ACEF score was calculated using the formula: age/ejection fraction + 1 point for every 10 mL/min reduction in CrCl <60 mL/min/1.73 m^2 (up to a maximum of 6 points).[9]

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). All data were expressed in mean ± standard deviation and median (range) for continuous variables and in percentage for categorical variables. The Kolmogorov-Smirnov test was used to identify distribution of variables. The Student's t-test or Mann-Whitney U test was used to compare continuous variables, while the chi-square test was used to compare categorical data. The Pearson test was used to analyze correlation of parametric variables and the Spearman test was used for non-parametric variables in PoAF. Univariate and multivariate logistic regression analyses were performed to identify the independent predictors of PoAF. The receiver operating characteristic (ROC) analysis was used to determine the discriminative ability of the CSS and SS for PoAF development. A *p* value of <0.05 was considered statistically significant.

RESULTS

Of a total of 123 patients, PoAF developed in 39 patients (31%). It was most common within the second day of CABG. Patients' clinical, demographic, laboratory, echocardiographic, and perioperative features are shown in Table 1. Age (59±10 vs 63±9, p=0.023), hemoglobin levels (13±1.6 vs 12±1.4, p=0.047), CSS [18(7-44) vs 30(11-89), p<0.001], SS [18(9-32) vs 24(10-45), p=0.001], CHADSVASc [Congestive heart failure or left ventricular systolic dysfunction, Hypertension (blood pressure consistently above 140/90 mmHg or

Table 1. Comparison of variables between postoperative atrial fibrillation negative/positive groups

	PoAF (-) (n=84)					PoAF (+) (n=39)					
	n	%	Mean±SD	Median	Range	n	%	Mean±SD	Median	Range	*p*
Demographic characteristics											
Age (year)			59±10					63±9			0.023
Gender											
Female	19	23				12	31				0.333
Hypertension	64	76				31	79				0.685
Diabetes mellitus	35	42				23	59				0.074
Current smoking	53	63				26	67				0.701
CHADSVASc score			1.8±1.1					2.4±1.3			0.021
SS (*)				18	9-32				24	10-45	0.001
CSS (*)				18	4-47				30	11-89	<0.001
Laboratory findings											
Hemoglobin (g/dL)			13±1.6					12±1.4			0.047
White blood cell (µL)			8.3±2.6					8.7±2			0.452
Platelet (10^3 /µL)			244±61					245±66			0.894
Total cholesterol (mg/dL)			189±45					182±53			0.405
Low-density lipoprotein-C (mg/d)			129±37					128±44			0.854
High-density lipoprotein-C (mg/dL)			39±10					39±11			0.916
Creatinine (mg/dL)			0.90±0.18					0.93±0.28			0.468
Glomerular filtration rate (mL/min)			84±16					80±23			0.243
Potassium (mEq/L)			4.3±0.4					4.4±0.3			0.295
Body mass index (kg/m^2)			28±4					29.5±4			0.213
Fasting blood glucose (mg/dL)*				103	77-417				120	65-395	0.108
Hemoglobin A1c (%)			6.6±1.6					7.2±1.7			0.040
C-reactive protein (mg/dL)*				3	0-418				7	1-47	0.004
Medications											
Beta blocker	53	63				24	62				0.868
ACEI/ARB	63	75				27	69				0.502
Statin	46	55				25	64				0.329
Intraoperative variables											
Aortic cross-clamp time (min)			75±30					83±38			0.236
Total bypass time (min)			125±37					146±66			0.078
Usage of LIMA	78	93				35	90				0.724
Total graft number			2.9±1					3±0.8			0.949
Echocardiographic measurement											
Left ventricle ejection fraction (%)			54±8					53±7			0.812
Left ventricle diastolic dysfunction (%)	60	71				32	82				0.207
Left atrium diameter (cm)			3.6±0.4					3.8±0.4			0.060
Postoperative features											
Length of stay in hospital (day)*				6	4-10				7	5-70	<0.001
Length of stay in intensive care unit (day)*				2	1-5				3	1-58	<0.001
Complications	3	10				11	13				0.315
- Wound infection	2					5					
- Acute renal failure	1					4					
- Ischemic stroke	0					1					
- Peripheral embolism	0					1					

PoAF: Postoperative atrial fibrillation; SD: Standard deviation; CHADSVASc: Congestive heart failure or left ventricular systolic dysfunction; SS: SYNTAX score; CSS: Clinical SYNTAX score; ACEI: ACEI: Angiotensin-converting-enzyme inhibitor; ARB: Angiotensin-receptor blocker; LIMA: Left internal mammary artery; * Mann-Whitney U-test was used for non-normally distributed variables and expressed by the median (range) ranges.

Table 2. Correlation analysis between clinical variables and postoperative atrial fibrillation

Clinical variables	r value	*p*
Age	0.190	0.035
Hemoglobin	0.179	0.036
SYNTAX score	0.291	0.001
Clinical SYNTAX score	0.409	<0.001
CHADSVASc score	0.210	0.020
Hemoglobin A1c	0.186	0.039
C-reactive protein	0.263	0.003

SYNTAX: Synergy between PCI with Taxus and Cardiac Surgery; CHADSVASc score: Congestive heart failure or left ventricular systolic dysfunction; Hypertension (blood pressure consistently above 140/90 mmHg or treated hypertension on medication), Age ≥75 years, Diabetes Mellitus, Prior Stroke or thromboembolism, Vascular disease (peripheral artery disease, myocardial infarction, aortic plaque), Age 65-74 years, Sex category (female sex)].

treated hypertension on medication), Age ≥75 years, Diabetes mellitus, Prior stroke or thromboembolism, Vascular disease (peripheral artery disease, myocardial infarction, aortic plaque), Age 65-74 years, sex category (female sex)] score [1.8±1.1 vs 2.4±1.3 p=0.021], hemoglobin A1c (HbA1c) levels (6.6±1.6 vs 7.2±1.7 p=0.040), C-reactive protein (CRP) levels [3(0-418) vs 7(1-47) p=0.004)], length of stay in the intensive care unit [6(4-10) vs 7(5-70) p<0.001], and length of stay in hospital [2(1-5) vs 3(1-58) p<0.001] were different between the patients with and without PoAF. The rate of postoperative complications were similar (13% vs 10%, p=0.315) between the two groups. Correlation analysis showed that age (r=0.205, p=0.023), CSS (r=0.461, p<0.001), SS (r=0.327, p<0.001), and CHADSVASc score (r=0.200, p=0.026) were positively associated with PoAF development, while hemoglobin level (r=0.179, p=0.047) was negatively correlated with PoAF (Table 2). Univariate and multivariate logistic regression analyses revealed that CSS [(β=0.077, p=0.003, OR=1.080, 95% CI (1.026-1.137)], SS [(β:0.081, p=0.028, OR=1.084, 95% CI (1.009-1.165)], and age [(β=0.054, p=0.034, OR=1.056, 95% CI (1.004-1.110)] were independent predictors of PoAF (Tables 3 and 4). The ROC analysis showed an area under the curve of 0.68 and 0.75 for SS and CSS, respectively (p=0.01, p<0.001, respectively) (Figure 1). In addition, CSS >17.59 had 84.6% sensitivity and 54.8% specificity in predicting PoAF (area under curve (AUC): 0.754, p<0.001, 95% CI (0.658-0.850).

Table 3. Univariate analysis of clinical variables in terms of postoperative atrial fibrillation development

Clinical parameters	*p*
Age	0.026
Hemoglobin (g/dL)	0.051
SYNTAX score	0.001
Clinical SYNTAX score	<0.001
CHADSVASc score	0.029
Hemoglobin A1c (%)	0.069
C-reactive protein	0.947
Glomerular filtration rate (mL/min)	0.242
Ejection fraction (%)	0.725
Body mass index (kg/m^2)	0.215
Total bypass time (minute)	0.931
Aortic cross-clamp time (minute)	0.239

SYNTAX: Synergy between PCI with Taxus and Cardiac Surgery; CHADSVASc score: Congestive heart failure or left ventricular systolic dysfunction; Hypertension (blood pressure consistently above 140/90 mmHg or treated hypertension on medication), Age ≥75 years, Diabetes Mellitus, Prior Stroke or thromboembolism, Vascular disease (peripheral artery disease, myocardial infarction, aortic plaque), Age 65-74 years, Sex category (female sex)].

DISCUSSION

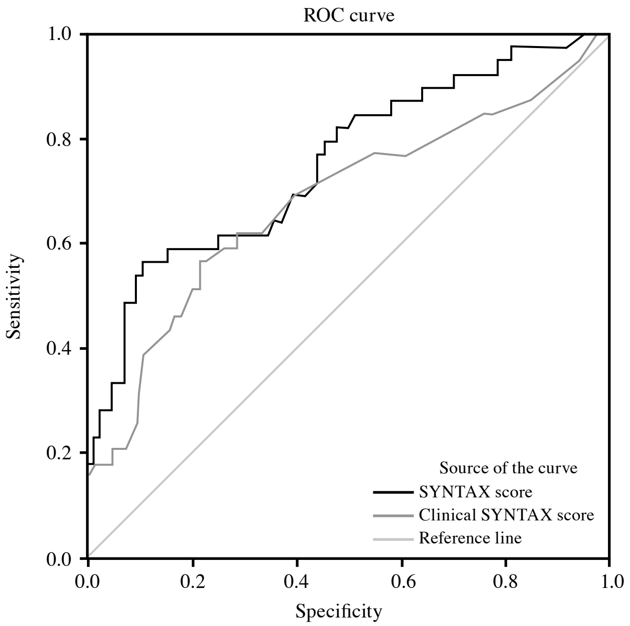
This study showed that advanced age, CSS, and SS were the independent predictors of PoAF development following isolated on-pump CABG and CSS performed better than SS for indicating PoAF. To the best of our knowledge, this is the first study reporting that the CSS is associated with PoAF incidence in this patient population.

New-onset AF following cardiac surgery is associated with an increased hospital stay, stroke risk, health care costs, and mortality.[10] It typically occurs within the first four postoperative days.[11] Although numerous risk factors predisposing to PoAF development have been identified such as advanced age, anemia, hypoxia, left atrial dilatation, left ventricular dysfunction, severe CAD, hypertension, type of cardiac surgery, increased sympathetic activation, oxidative stress and inflammation, the main pathophysiology of PoAF has not been well-understood completely and it is likely multi-factorial in cause.[12-14] Postoperative complications including congestive heart failure, myocardial infarction, renal insufficiency, infection,

Table 4. Independent predictors of postoperative atrial fibrillation after coronary artery bypass grafting in multivariate analysis

Clinical parameters	Beta	*p*	OR (95% CI)
Age	0.054	0.034	1.056 (1.004-1.110)
SS	0.081	0.028	1.084 (1.009-1.165)
CSS	0.077	0.003	1.080 (1.026-1.137)

Beta: Standardized coefficient; OR: Odds ratio; CI: Confidence interval; SS: SYNTAX score; CSS: Clinical SYNTAX score; SYNTAX: Synergy between PCI with Taxus and Cardiac Surgery.



	Area under the curve (95% CI)	*p*
SYNTAX score	0.681 (0.571-0.790)	0.001
Clinical SYNTAX score	0.754 (0.658-0.850)	<0.001

Figure 1. Receiver operating characteristic analysis comparing the performance and predictive accuracy of SS and CSS for postoperative atrial fibrillation after coronary artery bypass grafting.
ROC: Receiver operating characteristic; SYNTAX: Synergy between PCI with Taxus and Cardiac Surgery; CI: Confidence interval.

prolonged ventilation and re-exploration of the chest for bleeding are also correlated with PoAF.[15-17] It is, therefore, important to develop new risk prediction models for identifying patients who are most likely to benefit from prophylactic therapies, such as beta blockers, statins, amiodarone, colchicine, and biatrial pacing during the preoperative period.[18]

The SS is an anatomically-based tool to determine the complexity of CAD and to guide decision-making between CABG and PCI in patients with unprotected left main CAD or three-vessel disease. Each coronary lesion with a diameter of stenosis ≥50% in vessels ≥1.5 mm is scored in SS. It was developed during the design of SYNTAX Trial in 2009 and numerous studies confirmed its clinical validity in predicting major cardiac events (MACEs) and mortality after PCI.[19] In addition, CSS which integrates SS with modified ACEF was defined by Garg et al.[9] in 2010. In this study, CSS was found a better discriminatory ability for five-year mortality and MACE than either SS alone or modified ACEF score. Afterwards, the validity and the superiority of CSS to SS was demonstrated by large and small scale clinical studies in predicting cardiovascular end points.[20-22] However, the role of CSS in predicting new-onset AF after CABG has not been investigated extensively, yet.

In our study, CSS, SS, and advanced age were the independent predictors of PoAF after CABG and the predictive power of CSS was also found to be higher than the SS. In previous reports, advanced age has been described as the most significant predictor of new-onset AF after CABG.[23-25] Aging leads to structural changes in heart such as atrial fibrosis, scarring, and dilatation.[26] Increased sympathetic activation and prolonged atrial conduction time by aging are likely responsible for PoAF development.[27] Amar et al.[28] reported that in patients older than 60 years POAF was more common and Hosokawa et al.[29] reported that for every additional 10-year increment in age, there was an associated 1.5 times increased risk for the development of POAF.

Furthermore, the presence of complex coronary artery disease is an additional risk factor involved in the pathophysiology of PoAF following CABG.[30,31] The ischemia of atrial tissue results in PoAF due to altered cardiac conduction system. These alterations include shortening of the atrial wavelength or decreasing the atrial refractory period.[32] Mendes et al.[33] reported that angiographic evidence of right coronary artery stenosis was a predictor of PoAF. Gecmen et al.[34] also found that higher SYNTAX scores were related to more frequent PoAF in patients undergoing isolated on-pump CABG. Contrary to this finding, Fukui et al.[35] found no significant difference between high and low SYNTAX score groups for the development of PoAF in patients undergoing off-pump CABG. In our study, CSS integrating the angiographic findings with clinical variables such as advanced age, left ventricular dysfunction and renal impairment, which were well-known risk factors for the occurrence of PoAF after CABG, was superior to the SS in predicting PoAF.[36] This result may indicate that risk scoring systems in which clinical risk factors and severity of coronary artery disease are validated together provide more accurate information for the prediction of PoAF after CABG.

According to our findings, it is reasonable to calculate CSS in addition to SS preoperatively for identifying high-risk patients in terms of PoAF development. In clinical practice, CSS may be a simple and useful risk scoring system not only validating the mortality and morbidity after CABG surgery, but also predicting the possibility of PoAF occurrence. It should be also kept in mind that risk scoring systems validate certain clinical parameters; therefore, no single risk stratification system can be accepted as the gold standard in predicting PoAF. Furthermore, these models forecast which patients will likely have PoAF after cardiac surgery, although they may not guide about the prediction of serious complications related with PoAF development.

Study limitations

Nonetheless, there were several limitations which should be taken into consideration. Firstly, it was a single-center study and the sample size was relatively small. Secondly, the follow-up period in the in-patients unit electrocardiograms were recorded twice a day, which could have resulted in missing some of the silent AF episodes. Additionally, long-term follow-up data of the patients were not recorded.

In conclusion, our study results suggest that clinical SYNTAX score, which combines clinical parameters with the angiographic complexity of coronary artery disease, can further improve the predictive capability for new-onset postoperative atrial fibrillation following on-pump coronary artery bypass grafting.

Declaration of conflicting interests

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