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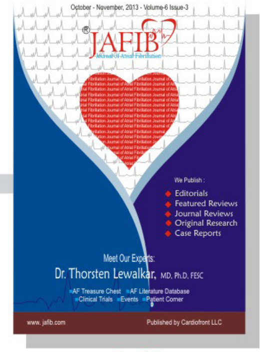

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Atrial Fibrillation and Stroke Risk After Coronary Artery Bypass Grafting Surgery

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Abstract

Background: The present multicentre study was aimed at determining the effect of preoperative atrial fibrillation (preop-AF) as stroke risk factor in coronary artery bypass graft surgery (CABG) during the perioperative period.

Methods: Patients undergoing isolated CABG surgery were enrolled from 21 Spanish centers. Baseline variables related with perioperative stroke risk were recorded and analysed. The Northern New England Cardiovascular Disease Study Group (NNECVDSG) stroke risk schema was used to stratify stroke risk and compare predicted vs observed neurologic outcomes in this study.

Results: 26347 patients were enrolled in the study. Prevalence of preop-AF was 4.2%, and was associated significantly with major cardiovascular comorbidities. The stroke rate was 1.38% (365 strokes), and it was slightly higher for patients with preop-AF vs non preop-AF, 1.82% vs 1.36%, p = 0.2. NNECVDSG schema showed good predictive ability calculating the area under the receiver operating characteristic curve (c-statistic 0.696; 95% CI 0.668 to 0.723). To investigate the associations of baseline preoperative variables with perioperative CABG-stroke a logistic regression model was performed. Preop-AF impact on perioperative stroke was lower that other variables. Preop-AF did not show an adverse impact in the quartiles groups according to NNECVDSG Stroke Risk Index.

Conclusion: Risk of perioperative stroke in isolated CABG surgery patients is not significantly increased by preop-AF.

Key Words:

Atrial Fibrillation, Stroke, Coronary Artery Bypass Grafting.

Disclosures:
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Introduction

Perioperative stroke occurs in 1% to 5% of patients undergoing CABG surgery, and numerous preoperative factors can contribute to patient's stroke risk including atrial fibrillation (AF).[1-7]AF is a significant cardiovascular risk factor for thromboembolic stroke that independently increases mortality. This impact has been reported in: population-based studies,[8] patients with heart failure,[9] patients with known coronary artery disease,[10] and finally in patients with coronary artery bypass graft (CABG) surgery.[11-13] Nevertheless, when compared to other factors, how preop-AF affects the global incidence of the perioperative stroke remains unclear, especially because of the many potential causes of stroke in these patients and the low incidence of this complication in current cardiac surgery practice.

The objective of this multicenter study was to retrospectively examine the effect of preop-AF on perioperative stroke in a series of patients undergoing isolated CABG surgery. We used the validated score of the Northern New England Cardiovascular Disease Study Group (NNECVDSG) Stroke Risk Index to compare predicted vs. observed neurologic outcomes in patients enrolled in this registry.[1]

Methods

Study Setting, Patient Sample, and Data Collection

We designed a retrospective, multicenter, observational study that sought to characterize AF as preoperative stroke risk factor in isolated CABG surgery. Patients were recruited from 21 Spanish National Health System hospitals. Data on 28296 consecutive adult (≥ 18 years of age) patients who underwent CABG surgery as single procedure were retrospectively collected. Patients were identified from hospital administrative databases in reverse chronological order starting from December 31, 2011. In order to meet inclusion criteria only CABG as single surgical procedure was allowed. All other patients who underwent CABG with associated surgical procedures were excluded, including surgical therapy of AF (Maze procedures). Using standardized case report forms, we collected selective preoperative data. Data were entered into a computer database (Microsoft Excel 2002, Redmond, WA). All clinical variables collected had previously shown to have a significant impact in perioperative stroke risk according to the NNECVDSG prediction model.[1] NNECVDSG schema is based in 33,062 consecutive patients undergoing isolated CABG surgery between 1992 and 2001, and has a good predictive accuracy with an area under the relative operating characteristic curve (c-statistic) of 0.70 (95% CI, 0.67 to 0.72).[1] The NNECDSG schema was used to contrast and validate our multicenter study.

Variables

Perioperative stroke was defined as any new temporary or permanent, focal or global neurologic deficit, within 30 days after surgery or, later than 30 days if still in hospital, in accordance with published guidelines.[14] Temporary stroke included transient ischemic attack, defined as fully reversible neurologic deficit lasting less than 24 hours, and prolonged reversible ischemic neurologic deficit, defined as an event lasting more than 24 hours and less than 3 weeks. All stroke outcomes included in this study were diagnosed by a neurologist and in most cases brain computed tomography-scan or MRI was used for diagnosis. The study excluded cases with diffuse postoperative brain encephalopathy, presented as delirium, confusion, seizures, prolonged alteration in mental status, combativeness, and agitation in the immediate postoperative period, which could have a relationship with circulatory bypass time and might also reflect a longer exposure to anesthesia.[15]

Variables of preoperative stroke risk used in this study included only the 18 variables proposed by the NNECVDSG prediction model, although clustered into seven mayor factors: age, female, diabetes mellitus, vascular disease (include variables of cerebrovascular disease: prior stroke, prior transient ischemic attack, prior carotid surgery, carotid stenosis or bruit; variables of lower extremity disease: claudication, amputation, prior lower extremity bypass, absent pedal pulses, or lower extremity ulcers), renal failure (requiring dialysis, or preoperative serum creatinine ≥ 2), preoperative left ventricular

Table 1: Comparative Characteristics of the Patients with Preoperative Atrial Fibrillation in a Cohort of 26347 Isolated Coronary Artery Bypass Graft Surgery.

	All cases		AF group		No AF group			Odds ratio	95% IC
	n = 26347	%	n = 1098	%	n = 25249	%	p		
Age (y)	64.8 ± 9.9		68.1 ± 9.3		64.7 ± 9.9		< 0.001		
≥ 75	4600	17.4	295	26.9	4305	17.1	< 0.001	1.7	1.5 – 2.0
≥ 80	995	3.8	81	7.4	914	3.6	< 0.001	2.1	1.6 – 2.6
Female	4689	17.8	191	17.4	4498	17.8	NS	1	0.8 – 1.1
Diabetes mellitus	9654	36.6	469	42.7	9185	36.4	< 0.001	1.3	1.1 – 1.4
Hypertension	15233	57.8	762	69.4	14471	57.3	< 0.001	1.7	1.4 – 1.9
Prior stroke /TIA	1282	4.9	88	8.0	1194	4.7	< 0.001	1.7	1.4 – 2.2
Peripheral vascular disease	4148	15.7	242	22.0	3906	15.5	< 0.001	1.5	1.3 – 1.8
Renal failure (dialysis or Creatinine ≥ 2 mg/dL (%)	2277	8.6	321	29.2	1956	7.7	< 0.001	4.9	4.2 – 5.6
LVEF < 40%	4000	15.2	279	25.4	3721	14.7	< 0.001	2	1.7 – 2.2
Priority of the surgery									
Emergent	607	2.3	43	3.9	564	2.2	<0.001	1.7	1.3 – 2.4
Urgent	2855	10.8	123	11.2	2732	10.8	NS	1	0.8 – 1.2
NNECVDSG predictive schema of postoperative stroke[1]									
Stroke risk index	4.50 ± 1.34		5.81 ± 2.52		4.44 ± 2.42		< 0.001		
Probability of stroke	1.34 ± 1.02		1.94 ± 1.43		1.32 ± 0.99		< 0.001		
Off-pump CABG (%)	10634	40.4	454	41.3	10180	40.3	NS	1	0.9 – 1.1

Variable peripheral vascular disease includes the variable prior stroke/TIA. TIA = transient ischemic attack. LVEF = left ventricular ejection fraction. CABG = coronary artery bypass graft. Northern New England Cardiovascular Disease Study Group = NNECVDSG. IC = interval confidence. Data are presented as percentages, mean ± standard deviation.

Table 2: Prevalence of preoperative atrial fibrillation within other preoperative stroke risk factors

		n	Prevalence AF (%)	p	Odds ratio	95% IC
Age						
	≥ 75			< 0.001	1.7	1.5 – 2.0
	yes	4600	6.4			
	no	21747	3.7			
	≥ 80			< 0.001	2.1	1.6 – 2.6
	yes	995	8.1			
	no	25352	4.0			
Female				NS	0.97	0.8 – 1.1
	yes	4689	4.1			
	no	21658	4.2			
Diabetes mellitus				< 0.001	1.3	1.1 – 1.4
	yes	9654	4.9			
	no	16693	3.8			
Prior stroke/TIA				< 0.001	1.7	1.4 – 2.2
	yes	1282	6.9			
	no	25065	4.0			
Peripheral vascular disease				< 0.001	1.5	1.3 – 1.8
	yes	4148	5.8			
	no	22199	3.9			
Renal failure				< 0.001	4.9	4.2 – 5.6
	yes	2277	14.1			
	no	24070	3.2			
LVEF < 40%				< 0.001	2	1.7 – 2.2
	yes	4000	7.0			
	no	22347	3.7			
Priority of the surgery non-elective				< 0.001	0.33	0.3 – 0.4
	yes	3295	4.8			
	no	21952	4.1			

Variable peripheral vascular disease includes the variable prior stroke/TIA. Surgery of non-elective includes urgent and emergency surgery. TIA = transient ischemic attack. LVEF = left ventricular ejection fraction. IC = interval confidence. Data are presented as percentages.

dysfunction (left ventricular ejection fraction -LVEF- < 40%, by ventriculograpy or echocardiography), urgent surgery (operation required within 24 hours to minimize the chance of further clinical deterioration) or an emergency (in which there should be no delay in providing an operative intervention). Other variables collected for this study were preop-AF (defined as an ECG or Holter recording showing arrhythmia, paroxysmal o persistent, during the qualifying admission/consultation or in the preceding 12 months), and off-pump beating heart CABG technique.

Statistical Analyses

Continuous variables are presented as mean ± standard deviation (SD) and categorical variables are shown as a percentage (%). All group comparisons were unpaired. Continuous variables were compared using analysis of variance, and categorical variables were compared usingχ^2 analysis or Fisher's exact tests as appropriate. A two-tailed value of p < 0.05 was considered as statistically significant. We first performed a univariate analyses which included the seven major independent variables described in the NNECVDSG schema 1 and preop-AF. Stepwise logistic regression was then performed to determine independent predictors of stroke, and included variables associated with a value of P < 0.3 from the univariate analyses. Results are reported as odds ratios (OR) with associated 95% confidence intervals (CI). We assessed model discrimination using the area under the receiver-operating-characteristic curve, which is also referred to as the c-statistic (Harrell's c), and calibration using the Hosmer-Lemeshow statistic (larger probability value means better calibration). The NNECDSG schema (the score risk index and the probability for preoperative stroke) was used also to stratify the stroke risk of patients and to compare the impact of preop-AF into the categorized strata of risk. IBM SPSS Statistic version 20; SPSS Inc, Chicago [IL], United States) was used for the statistical analysis.

Results

A total of 28296 patients were included in this study. 1949 patients had missing preoperative variables values and were excluded from analysis. Complete information was available in 26347 patients. The prevalence of preop-AF for the entire group was 4.2%, with values ranging from 2.7% to 9.1% at different participating centers. Characteristics of the cohort of patients with preop-AF compared with patients without preop-AF are displayed in table 1. Preop-AF was associated with greater rates of all major preoperative cardiovascular comorbidities, table 2 and figure 1. The prevalence of preop-AF was 2.1% in the younger age group (<50 years) vs 8.7% for the 85-year-older patients, figure 2.

The overall prevalence of perioperative stroke was 1.38% with values ranging from 0.3% to 2.5% at participating centers. Characteristics of the patients with perioperative stroke are displayed in table 3. NNECVDSG showed very good discriminatory ability in predicting perioperative stroke in our cohort.

Effect preop-AF Adjusting by Multivariable Logistic Regression Modeling

Patients with preop-AF had 1.8% of perioperative stroke versus 1.4% in patients without AF (p = 0.23). To assess the relationship between preop-AF and perioperative stroke, all NNECVDSG schema variables and preop-AF were introduced in stepwise logistic regression analysis (Table 3). Renal failure was the strongest predictive variable (OR, 6.4; 95% CI, 5.1 to 8.0; p < 0.001). Other predictive variables, in order of importance, were emergent surgery, preoperative left ventricular dysfunction, urgent surgery, and peripheral vascular disease. Preop-AF association with the perioperative stroke was weak (OR, 1.3; 95% CI, 0.8 to 2.1; p=0,23).

Effect preop-AF Adjusting by Preoperative Stroke Risk Groups

Preoperative stroke risk groups according to the NNECVDSG schema showed a progressive incremental rate of perioperative stroke that was proportional to the preoperative risk of patients, table 4. Interestingly preop-AF was not associated with a higher risk for stroke at each quartile of the NNECVDSG preoperative stroke risk index. It is remarkable to note that AF shows no significant increase in stroke risk even in the group of patients without preoperative risk factors (NNECVDSG score index = 0).

Discussion

This multicenter study tries to elucidate the impact of preop-AF on perioperative stroke events in relation to isolated CABG surgery. Our results suggest that, (1) Preop-AF prevalence was present in 4.1% of patients undergoing CABG surgery, and increases

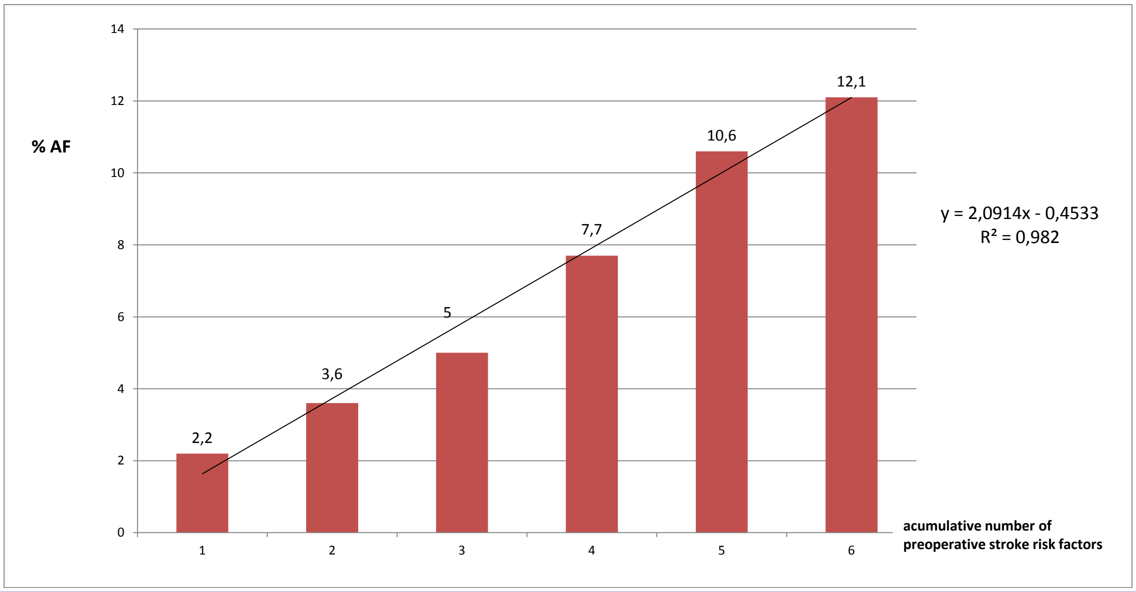

Figure 1: **Bar graph of percentage of preoperative atrial fibrillation (open bars) and perioperative stroke (filled bars) according to presence accumulative of preoperative stroke risk factors (age≥ 75 years-old, female, diabetes mellitus, renal failure, peripheral vascular disease, left ventricular ejection fraction < 40%, urgent and emergent surgery). Line represent tendency of progressive increase of the preoperative prevalence of the atrial fibrillation (y = 2.0914x – 0.4533; R^2 = 0.982).**

proportionality with the number of associated comorbidities and the age; (2) Preop-AF prevalence in CABG surgery was associated with other stroke related variables, particularly, renal failure, OR 4.9(95% IC 4.2 – 5.6), left ventricular dysfunction, OR 2(95% IC 1.7 – 2.2), and age ≥ 75 years-old OR 1.7 (95% IC 1.5 – 2); and (3) Preop-AF has a modest burden on perioperative stroke risk in CABG surgery compared with other preoperative cardiovascular risk factors, with subtle differences between patients with and without preop-AF, 1.8 vs 1.4%, p = 0.2.

Preop-AF prevalence is variable in the different populations published in literature, ranging from 3.2% to 14.6% 2-7,16. In the report of the STS National Adult Cardiac Surgery Database, that included 774,881 isolated CABG procedures, with 819 participating centers, preop-AF prevalence is 5.0%.[16] In our study preop-AF prevalence was 4.1%, and clearly associated with the number of the major preoperative stroke risk factors (atherosclerosis comorbidities). Not surprisingly any analysis of the impact of the preop-AF is masked by other severe atherosclerotic preoperative factors. Our data indicate that preop-AF might be considered a surrogate marker of cardiovascular illness, particularly atherothrombotic disease, which predisposes to AF and stroke. An initial suggestion of this is noted in our study because the vast majority of strokes (94.5%) occur in the

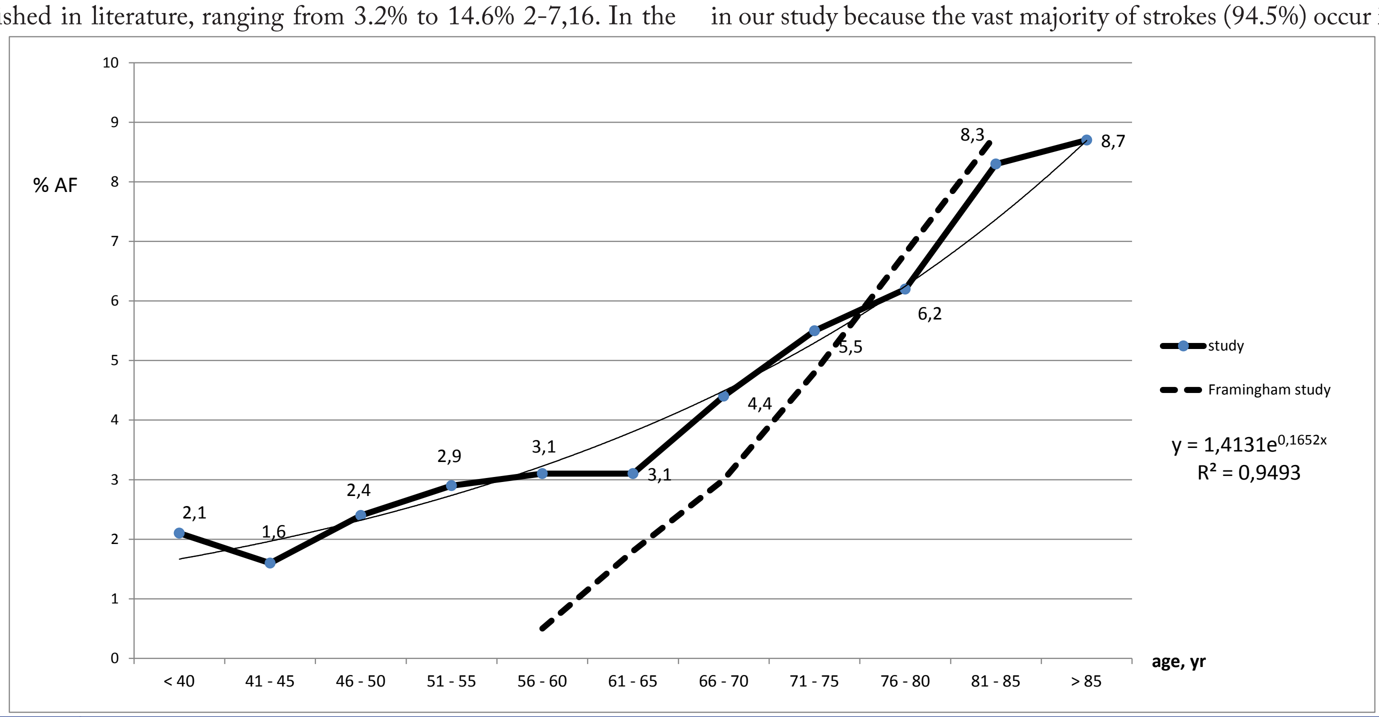

Figure 2: **Prevalence of the preoperative atrial fibrillation by age (solid line) and its exponential line of tendency (y = 1.4131e0.1652x ; R^2 = 0.9493) in the cohort of 26347 isolated coronary artery bypass graft surgery. Dotted line showed prevalence atrial fibrillation in population-based study (data from Framingham study8).**

apparent absence of preop-AF, and because the univariate analysis showed that the presence of cardiovascular disease and cardiovascular risk factors during the preoperative period was more frequent among incidental perioperative stroke patients.

AF is a risk factor for stroke and when present before CABG surgery there is an increase of perioperative stroke rate according to numerous studies. However some authors disagree. Ad et al,[3] using data of 281,567 patients from STS National Adult Cardiac Surgery Database, reported higher rates of perioperative stroke in patients with preop-AF vs without preop-AF (2.6% vs 1.4%, p < 0.01). Banach et al,[12] in a study of 3000 patients undergoing isolated CABG demonstrated that preop-AF increased the risk of stroke by two-fold, from 4.4 to 9.2%, p < 0.001. Quader et al,[13] reported a Cleveland Clinic series of 46984 isolated CABG patients, with and without preop-AF, compared in propensity-matched groups, and found that preop-AF was not an independent risk factor for perioperative stroke, rates of 3.1% in AF group vs 1.6% in group without AF, p = 0.1. Fukahara et al,[6] in 513 isolated CABG patients using off-pump approach, showed that preop-AF was not an independent risk factor (stroke rate 3.8% in AF group vs 1.8% in group without AF, p = ns). Similar results are reported by the Multicenter Study of Perioperative Ischemia (McSPI) Research Group 2, with 2017 isolated CABG patients from 24 different institutions in the United States, describing a preoperative stroke risk model where preop-AF was not included as variable of stroke risk in the final study model. In our study the incidence of perioperative stroke with preop-AF was only slightly increased compared without preop-AF, 1.82% vs 1.36% (p = 0.2), but it was not an independent variable of perioperative stroke. Considering the low incidence of this complication and the many potential causes of stroke, we categorized the patients in strata attending its preoperative stroke risks to precise more exactly which is the effect of the preop-AF in CABG surgery. In our study the preoperative stroke risk was assessed by NNECVDSG schema, and found that none of the stroke-risk groups had a higher incidence of stroke when preop-AF was present, even in those with no stroke risk factors. According to our results, therefore, preop-AF seems to have a smaller impact on stroke risk compared with other cardiovascular risk factors.

This study has several limitations to note. First, the retrospective nature of this study may have introduced the inherent selection bias found in this type of design, including potential misclassification of preop-AF status due to clinically unrecognized arrhythmias. Second, many preoperative variables related with perioperative stroke can be collected but we used only those that have showed significant impact in the NNECVDSG predictive model, because we consider that is a representative model created from a large cohort of patients with a good discriminatory accuracy as demonstrated in our study. Third, the effects of unknown or unmeasured confounders on the non-observed

Table 3: Univariate and Multivariate Associations Between Preoperative Risk Factors and Perioperative Stroke

	Stroke	No Stroke		Univariate		Multivariate		
	(n=365)	(n=25982)	p	Odds ratio	95% IC	Odds ratio	95% IC	p
Age (y)	64.7 ± 9.9	67.8 ± 8.6	< 0.001					
55 – 59 (%)	42 (11.5%)	3188 (12.3%)	NS	0.9	0.6 – 1.2			
60 – 64 (%)	62 (17%)	4166 (16%)	NS	1.0	0.8 – 1.4			
65 – 69 (%)	61 (16.7%)	4877 (18.8%)	NS	0.8	0.6 – 1.1			
70 – 74 (%)	71 (19.5%)	5035 (19.4%)	NS	1	0.7 – 1.3			
75 -79 (%)	56 (15.3%)	3549 (13.7%)	NS	1.1	0.8 – 1.5			
≥ 80 (%)	16 (4.4%)	979 (3.8%)	NS	1.1	0.7 – 1.9			
Female (%)	55 (15.1%)	4634 (17.8%)	NS	0.8	0.6 – 1.0			
Diabetes mellitus (%)	174 (47.7%)	9480 (36.5%)	< 0.001	1.5	1.2 – 1.9			
Peripheral vascular disease (%)	121 (33.2%)	4027 (15.5%)	< 0.001	2.7	2.1 – 3.3	1.74	1.38 – 2.20	< 0.001
Renal failure (%)	148 (40.5%)	2129 (8.2%)	< 0.001	7.6	6.1 – 9.4	6.41	5.14 – 8.00	< 0.001
LVEF < 40%	147 (40.3%)	3853 (14.8%)	< 0.001	3.8	3.1 – 4.7	3.04	2.44 – 3.79	< 0.001
Revascularization presentation:								
Urgent (%)	76 (20.8%)	2779 (10.7%)	< 0.001	2.2	1.7 – 2.8	2.07	1.57 – 2.69	< 0.001
Emergent (%)	33 (9.0%)	574 (2.2%)	< 0.001	4.4	3.0 – 6.3	3.48	2.35 – 5.17	< 0.001
Preoperative AF	20 (5.5%)	1078 (4.1%)	0.23	1.3	0.8 – 2.1			
Off-pump CABG (%)	144 (39.5%)	10490 (40.4%)	NS	1.0	0.8 – 1.1			
NNECVDSG predictive schema of postoperative stroke[1]								
Stroke risk index	5.7 ± 2.2	4.4 ± 2.4	< 0.001	1.36	1.3 – 1.4			
Probability of stroke	1.82 ± 1.26	1.32 ± 0.99	< 0.001	1.53	1.4 – 1.6			

LVEF = left ventricular ejection fraction. CABG = coronary artery bypass graft. Northern New England Cardiovascular Disease Study Group = NNECVDSG. IC = interval confidence. Data are presented as percentages, mean ± standard deviation. Discrimination of the model, with c-statistic 0.696 (95% CI 0.668 to 0.723) for the NNECVDSG stroke index, and 0.675 (95% CI 0.646 to 0.704) for the probability calculated (logistic regression model) 1. The Hosmer-Lemeshow goodness-of-fit test indicated good accuracy for the prediction of postoperative stroke with NNECDSG schema (p = 0.40, H-L statistic= 8.31; and p = 0.08, H-L statistic= 14.07, respectively). Percentage of patients correct clasification with the model 98.6%. Age was introduced in the multivariate analysis as categorized variable as showed the table. There were no significative interactions between the variable preoperative AF and other variables included in the model.

Table 4: Quartiles of the NNECVDSG Stroke Risk Index and Incidence of Perioperative Stroke in Groups of Patients with and Without Preoperative Atrial Fibrillation.

		Preop-AF group	No preop-AF group	p
NNECVDSG stroke index[1]	n	Stroke number (rate, %)	Stroke number (rate, %)	
= 0	3406	0 / 32 (0%)	6 / 1913 (0.3%)	NS
2.5 – 4.9	9429	2 / 286 (0.70%)	79 / 9062 (0.87%)	NS
5 – 7.4	8839	7 / 409 (1.71%)	122 / 8301 (1.47%)	NS
≥ 7.5	4673	11 / 302 (3.64%)	121 / 2972 (4.07%)	NS
< 2.5	1951	0 / 81 (0%)	23 / 4569 (0.50%)	NS

Northern New England Cardiovascular Disease Study Group = NNECVDSG. Preop-AF = preoperative atrial fibrillation.

association cannot be ruled out. Owing to the significant impact of the variables included in our multivariable analyses and the robustness of our results, however, the effects of any such confounders are unlikely to be large. Fourth, we could not delineate the mechanisms by which preop-AF may not lead to adverse postoperative stroke. There is clinical evidence that AF is associated with increased risk of stroke, and death.[8,9] Conversely our results support the notion that preop-AF is not associated significantly with perioperative stroke. Nevertheless it is interesting to recall here that the influence of small, unmeasured differences in patient risk factors between preop-AF and no preop-AF groups may account for some of the differences observed in patients´ outcomes. For instance, the perioperative pharmacological treatment is a priori different for patients without preop-AF when compared with patients with preop-AF. The former group will usually take only antiplatelet drugs as stroke prophylaxis whereas the later is usually treated with anticoagulation drugs. We can not elaborate on this because the use of antiplatelet drugs or anticoagulants was not comprehensively recorded for all patients during the perioperative period which constitutes an important limitation for our study. Finally, the relatively low incidence of perioperative stroke after CABG surgery limits the modeling efforts for adjusted outcomes and constrained our efforts when adjusting for the potential confounding influence of factors, and these factors could mask the minor adverse effect of the preop-AF. Although some of these methodological limitations may have been overcame by propensity score matching we opted to validate our series of patients with a robust tool like the NNECVDSG predictive model by quartile of risk stratification. Even in the lowest quartile of preoperative risk factors (NNECVDSG score index = 0), preop-AF has a modest burden on perioperative stroke risk.

Conclusions:

In this retrospective multicenter study we identify preop-AF as a minor predictor of postoperative stroke. Preop-AF in patients undergoing CABG has been associated significantly with most of the major preoperative comorbidities previously described as risk factors for perioperative stroke including advanced age, diabetes, cardiac dysfunction, peripheral artery disease, renal failure, and non-elective surgery.

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