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.

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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). AF is a significant cardiovascular risk factor for thromboembolic stroke that independently increases mortality. This impact has been reported in: population-based studies, patients with heart failure, patients with known coronary artery disease, and finally in patients with...
coronary artery bypass graft (CABG) surgery. 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.

Methods

Study Setting, Patient Sample, and Data Collection

We designed a retrospective, multicenter, observational study that sought to characterize AF as a 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.

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

<table>
<thead>
<tr>
<th>Variables</th>
<th>All cases</th>
<th>AF group</th>
<th>No AF group</th>
<th>Odds ratio</th>
<th>95% IC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>64.8 ± 9.9</td>
<td>68.1 ± 9.3</td>
<td>64.7 ± 9.9</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>≥ 75</td>
<td>4600</td>
<td>17.4</td>
<td>299</td>
<td>4305</td>
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</tr>
<tr>
<td>≥ 80</td>
<td>995</td>
<td>3.8</td>
<td>81</td>
<td>914</td>
<td>3.6</td>
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<tr>
<td>Female</td>
<td>4689</td>
<td>17.8</td>
<td>191</td>
<td>4498</td>
<td>17.8</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9654</td>
<td>36.6</td>
<td>469</td>
<td>9185</td>
<td>36.4</td>
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<tr>
<td>Hypertension</td>
<td>15233</td>
<td>57.8</td>
<td>762</td>
<td>14471</td>
<td>57.3</td>
</tr>
<tr>
<td>Prior stroke /TIA</td>
<td>1282</td>
<td>4.9</td>
<td>88</td>
<td>1194</td>
<td>4.7</td>
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<tr>
<td>Peripheral vascular disease</td>
<td>4148</td>
<td>15.7</td>
<td>242</td>
<td>3906</td>
<td>15.5</td>
</tr>
<tr>
<td>Renal failure (diialysis or Creatinine ≥ 2 mg/dL (%))</td>
<td>2277</td>
<td>8.6</td>
<td>321</td>
<td>1956</td>
<td>7.7</td>
</tr>
<tr>
<td>LVEF &lt; 40%</td>
<td>4000</td>
<td>15.2</td>
<td>279</td>
<td>3721</td>
<td>14.7</td>
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<tr>
<td>Priority of the surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergent</td>
<td>607</td>
<td>2.3</td>
<td>43</td>
<td>564</td>
<td>2.2</td>
</tr>
<tr>
<td>Urgent</td>
<td>2855</td>
<td>10.8</td>
<td>123</td>
<td>2732</td>
<td>10.8</td>
</tr>
</tbody>
</table>

NNECVDSG predictive schema of postoperative stroke

<table>
<thead>
<tr>
<th>Variables</th>
<th>All cases</th>
<th>AF group</th>
<th>No AF group</th>
<th>Odds ratio</th>
<th>95% IC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke risk index</td>
<td>4.50 ± 1.34</td>
<td>5.81 ± 2.52</td>
<td>4.44 ± 2.42</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Probability of stroke</td>
<td>1.34 ± 1.02</td>
<td>1.94 ± 1.43</td>
<td>1.32 ± 0.99</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Off-pump CABG (%)</td>
<td>10634</td>
<td>40.4</td>
<td>454</td>
<td>10180</td>
<td>40.3</td>
</tr>
</tbody>
</table>

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. 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, combative, 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.

Variables of preoperative stroke risk used in this study included only the 18 variables proposed by the NNECVDSG prediction model, although clustered into seven major 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, lower extremity bypass, absent pedal pulses, or lower extremity ulcers), renal failure (requiring dialysis, or preoperative serum creatinine ≥ 2), preoperative left ventricular dysfunction, and prior cerebral (i.e., transient ischemic attack or stroke) or peripheral (i.e., claudication or amputation) vascular disease. We designed a retrospective, multicenter, observational study that sought to characterize AF as a 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.

The NNECVDSG schema is based on 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). The NNECVDSG schema was used to contrast and validate our multicenter study.
dysfunction (left ventricular ejection fraction -LVEF- < 40%, by ventriculography 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 using $\chi^2$ 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 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...
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, 3, 5, 6, 7). 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%. 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 age range of 56-80 years.

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; R² = 0.982).

Figure 2: Prevalence of the preoperative atrial fibrillation by age (solid line) and its exponential line of tendency (y = 1.4131e0.1652x; R² = 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 study).
APPARENT ABSENCE OF PREOP-AF, AND BECAUSE THE UNIVARIATE ANALYSIS SHOWN 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., 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., 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., 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., IN 513 ISOLATED CABG PATIENTS USING OFF-PUMP APPROACH, SHOWN 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 THEMULTICENTER 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, 1.8% 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.

THIRD, THE EFFECTS OF UNKNOWN OR UNMEASURED CONFoundERS ON THE NON-OBSERVED RISK FACTORS DURING THE PREOPERATIVE PERIOD WAS MORE FREQUENT AMONG INCIDENTAL PERIOPERATIVE STROKE PATIENTS.

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

<table>
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<tr>
<th>NNECVDSG stroke index</th>
<th>Preop-AF group</th>
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<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2.5</td>
<td>1115</td>
<td>1121 (9.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>2.5 – 4.9</td>
<td>3488</td>
<td>3079 (9.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>5 – 7.4</td>
<td>892</td>
<td>986 (9.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>≥ 7.5</td>
<td>1137</td>
<td>1119 (9.8%)</td>
<td>NS</td>
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</table>

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References: