



## Long Term Risk of Recurrent Atrial Fibrillation and Ischemic Stroke After Post-Operative Atrial Fibrillation Complicating Cardiac and Non-Cardiac Surgeries

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### Abstract

**Background:** New onset post-operative atrial fibrillation (POAF) can complicate both non-cardiac(NCS) and cardiac(CS) surgeries. Long term differences in recurrence of atrial fibrillation (AF) and incidence of ischemic stroke/transient ischemic attack(CVA)between these types of POAFare lacking.

**Objective:** To compare the long term recurrence rate of AF and incidence of CVAin patients with new onset POAF after CS and NCS.

**Methods:** All patients who developed POAF between May 2010 and April 2014 were included in this single-center, retrospective study. Exclusion criteria included a prior history of atrial tachyarrhythmias and pre-operative use of anti-arrhythmic drugs. Recurrence of atrial fibrillation and CVA was identified by review of medical records, electrocardiogram and Holter monitor.

**Results:** patients identified by the ICD9 code=523, 112 patients (61 cardiac; 51 non-cardiac) met inclusion criteria. Mean follow up was 943 days (range 32-2052 days). AF recurrence rate within 30 days after hospital discharge was higher in CS compared with NCS(10% vs 0%,  $p=0.03$ ). Kaplan Meier analysis showed a trend towards higher recurrence in NCS compared with CS(HR 2.8; 95% CI 0.78-10.6, log rank  $p=0.03$ ). In long term follow-up, CVA was numerically more common in patients with POAF after CS compared with NCS(10% vs 2%) though this difference was non-significant(HR 3.1 ; 95% CI 0.72-13.3; log rank  $p=0.26$ ).

**Conclusions:** The risk of recurrent AF and ischemic stroke is not different between POAF after CS or NCS. The overall high rate of AF recurrence and risk of ischemic stroke mandate careful long term follow-up.

### Introduction

Post-operative atrial fibrillation (POAF) is often precipitated by adrenergic stimulation and local or systemic inflammation affecting a susceptible atrium in the peri-operative period. It affects approximately 30–60% of patients undergoing cardiac surgery(CS) and 5–10% undergoing non-cardiac surgery(NCS)<sup>[1,2]</sup>. POAF is associated with increased intensive care unit and hospital length of stay, morbidity, mortality, hospital readmission, and long-term risk of stroke<sup>[3-6]</sup>. Estimates of the average annual cost of treatment of POAF and its sequelae approach \$1 billion in the United States alone<sup>[7-9]</sup>. While POAF after CS has been relatively well studied, the long term implications of POAF after NCS are less well understood. The long term risk of recurrent AF may be as high as 20–48% after CS while the long term risk of recurrence after NCS is unknown<sup>[10-14]</sup>.

### Key Words

Post-Operative Atrial Fibrillation, Stroke, Cardiac Surgery, Non Cardiac Surgery, Recurrent Atrial Fibrillation

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Prior studies relied on administrative databases and were limited in the length of follow-up. Since about 50 million NCS are performed each year in the United States alone<sup>[13]</sup>, knowledge of long term implications of POAF after NCS is essential. In addition, differences in long term risk of POAF and cerebro vascular accidents between CS and NCS are unknown.

### Methods

A single-center, retrospective study was designed to include all patients (above 18 years of age) with POAF (confirmed by ECG or telemetry) between May 2010 to April 2014. Exclusion criteria included (1) Patients with a prior history of AF or atrial flutter, (2) use of anti-arrhythmic drugs pre-operatively (since the long half life of amiodarone complicates assessment of recurrent AF) (3) lack of confirmed AF post-operatively. Patients were identified using discharge ICD-9 code “427.31” (atrial fibrillation) among all patients who underwent a surgical procedure during this time period. Demographic data, patient characteristics and procedure information were recorded at the time of the indexed surgery/event from review of the electronic medical record. Primary endpoints of the study were recurrence of AF and ischemic stroke or transient ischemic

attack (CVA). Recurrence of AF was identified by chart review and confirmed by ECG, Holter monitor or device interrogation (when available). Ischemic stroke was defined by the presence of neurological symptoms and supported by radiographic diagnosis (MRI or CT scan) while transient ischemic attack (TIA) was defined by symptoms which resolved spontaneously within 24 hrs with no radiologic evidence of stroke.

Follow-up ended on 1/1/2016 and duration of follow up was defined as the time between 30 days of hospital discharge (to distinguish between early and late recurrence) to either the last recorded clinical encounter or till a study endpoint was met. Local practice pattern for management of POAF during the study period was as follows: patients with a clearly defined onset of POAF received an attempt at rhythm control with a combination of intravenous and oral amiodarone (total loading dose of 2.5gms in 24 hrs) for a day followed by oral amiodarone (400mg a day) for at least a month. If patients achieved sinus rhythm within 24-48 hrs. of onset, anticoagulation was not started (unless patient had another indication such as prosthetic valve). At discharge, 30 day follow-up was scheduled in the cardiac electrophysiology clinic where the drug was stopped if ECG documented sinus rhythm. A Holter monitor was repeated at 6 months to rule out asymptomatic recurrences. Patients who received rate control strategy were followed up either in the cardiac electrophysiology clinic or primary care physician's office. The study was approved by the institutional review board.

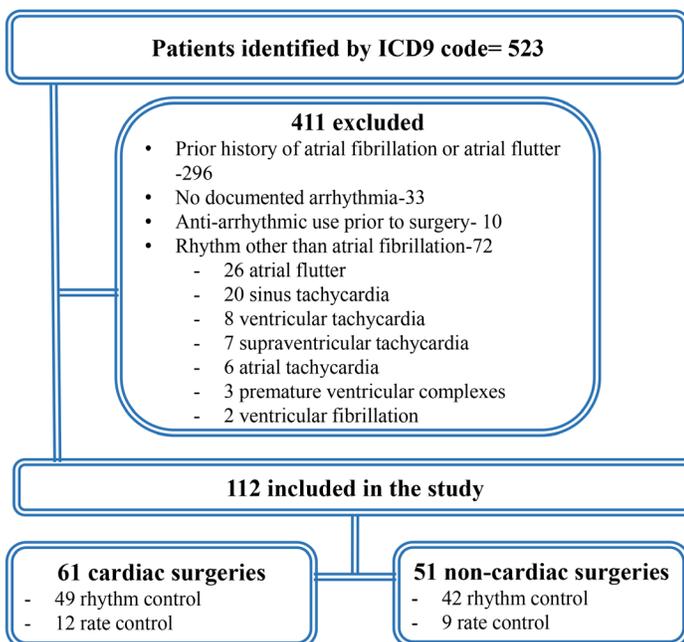
### Statistical analysis

Student t tests were used to compare continuous variables while Chi-square test was used for comparing categorical variables. Mann Whitney U test was used to compare medians. Differences in event rates (long term risk of recurrent AF and ischemic stroke) between CS and NCS were estimated using Kaplan-Meier analysis and log rank tests. All statistical analyses were performed with MedCalc

(version 14, Ostend, Belgium). Statistical significance was defined by a 2-tailed  $p < 0.05$ . All authors had full access to the data and assume responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Table 1:** Clinical characteristics of patients in the cohort. POAF = post-operative atrial fibrillation; COPD= chronic obstructive pulmonary disease; ACEI- angiotensin converting enzyme inhibitor; CCB= calcium channel blocker.

	Total(n=112)	Cardiac POAF(n=61)	Non-Cardiac POAF(n=51)	P value
Age(years)	65.9± 7.7	65.8± 8.2	66±7.1	0.690
Female, n (%)	24 (21%)	3 (5%)	21 (41%)	0.001
Hypertension, n (%)	83 (74%)	52 (85%)	31 (61%)	0.003
Diabetes Mellitus, n (%)	35 (31%)	25 (41%)	10 (20%)	0.015
Dyslipidemia, n (%)	68 (61%)	50 (82%)	18 (35%)	0.001
COPD, n (%)	23 (21%)	11 (18%)	12 (24%)	0.433
Smoking, n (%)	54 (48%)	29 (48%)	25 (49%)	0.971
Congestive Heart Failure, n (%)	18 (16%)	10 (16%)	8 (16%)	0.955
Coronary Artery Disease, n (%)	65 (58%)	54 (89%)	11 (22%)	0.001
Vascular disease history, n (%)	21 (19%)	16 (26%)	5 (10%)	0.024
History of Ischemic Stroke, n (%)	9 (8%)	5 (8%)	4 (8%)	0.949
<b>Medications Prior to Surgery</b>				
Statins, n (%)	66 (59%)	50 (82%)	16 (31%)	0.001
Beta-Blockers, n (%)	56 (50%)	40 (66%)	16 (31%)	0.003
ACEI, n (%)	46 (41%)	32 (52%)	14 (27%)	0.031
CCB, n (%)	32 (29%)	20 (33%)	12 (24%)	0.532
Electrical Cardioversion, n (%)	5 (4%)	4 (7%)	1 (2%)	0.374
Ibutilide, n (%)	8 (7%)	6 (9.8%)	2 (3.9%)	0.287
<b>Medications at discharge(n=108)</b>				
Aspirin, n (%)	78 (72%)	56 (92%)	22 (46%)	0.001
Anticoagulants, n (%)	13 (12%)	8 (13%)	5 (10%)	0.643
Beta blockers, n (%)	83 (79%)	54 (90%)	29(59%)	0.001
CCB, n (%)	27 (25%)	13 (23%)	14 (27%)	0.398
ACEI, n (%)	52 (47%)	38 (64%)	14 (27%)	0.001
Digoxin, n (%)	6 (6%)	4 (7%)	2 (4%)	0.691
Amiodarone, n (%)	81 (72%)	45 (74%)	36 (71%)	1.0
Rhythm control strategy, n (%)	91 (81%)	49 (80%)	42 (82%)	0.785
Median CHA2DS2-VASc(interquartile range)	3(2-4)	3(2-4)	2.5(2-4)	0.75
Length of stay(days, mean SD)	11.6±7.9	10.1±5.9	13.6± 9.5	0.007



**Figure 1:** Depicting search strategy to identify patients with post-operative atrial fibrillation

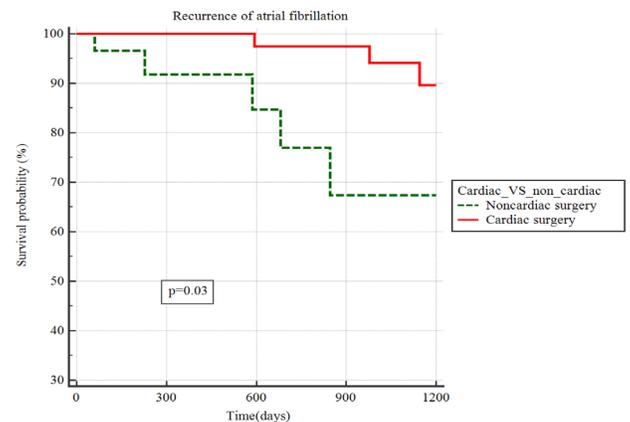
**Results and outcomes**

[Figure 1] delineates the search strategy. Patients identified by ICD9 code= 523, 59.6% had a prior history of AF while 13.8% had other arrhythmias that were wrongly coded and had no evidence of AF. The final cohort consisted of 112 patients ; 61 patients with POAF after CS and 51 after NCS. [Table 1] describes characteristics of the cohort. Patients who had POAF after CS had a significantly higher incidence of diabetes, hypertension and coronary artery disease. In the CS group, 27% underwent valve surgery while the rest were coronary artery bypass surgeries. The NCS group was comprised mostly of thoracic (39%) and abdominal surgeries(37%).

POAF occurred around the 2nd to 3rd post-operative day (mean post-operative day of occurrence 2.4 days CS vs. 2.6 days NCS ;p=0.29). Rhythm control (using a combination of intravenous and oral amiodarone) was the treatment strategy in 81% of the entire cohort (80% CS vs. 82% NCS, p= NS). Ibutilide and electrical cardioversion were used to achieve sinus rhythm in 47% and 4% of patients respectively. Length of hospital stay was significantly longer in NCS compared with CS (13.6 ± 9.5 vs. 10.1±5.9 days ; p=0.007). In hospital mortality was 3.5% (5.8% NCS vs 1.6% CS, p =0.32). [Table 2] At hospital discharge, all patients were in sinus rhythm. A majority of patients were discharged on a single antiplatelet agent (43% of the entire cohort-37% aspirin alone, 6% clopidogrel alone), 22% on aspirin and clopidogrel, 2% on warfarin alone, and 9% on combined warfarin and aspirin (all after valve surgery).

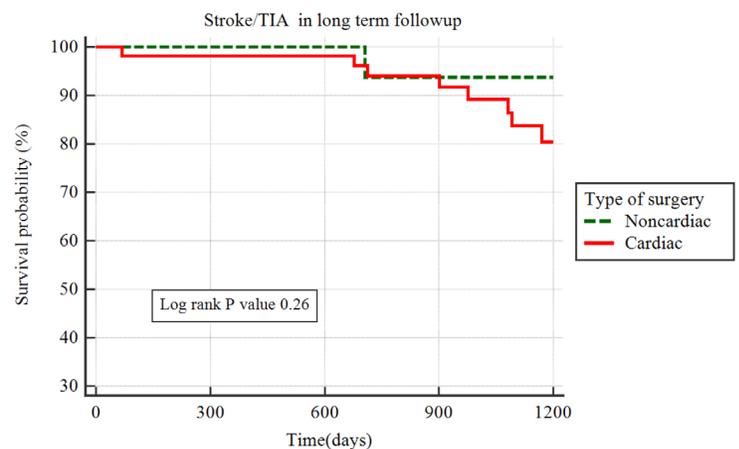
At 30 day follow-up, AF recurrence was more common in CS group (10% vs 0%, p=0.03) and was no different in those treated with rate or rhythm control strategy (8.3% vs 10%; p = 0.9). [Table 2] Among those treated with rhythm control, mean duration of amiodarone therapy was 2.3 months (1.87 ±1.5 in CS VS 2.88± 2.89 in NCS, p= 0.004).

A Mean follow up duration was 943 days (range 32-2052 days). Median time to AF recurrence was 724 days (IQR 229-1157 days). AF recurred in 11 patients(12.5%; CS 9.4% vs NCS 17.1%). These patients were started on anticoagulation and there was no strokes within the study period. By Kaplan Meier analysis, there was a trend to significantly higher recurrence of AF after NCS compared with CS [Figure 2], HR 2.8; 95% CI 0.78-10.6, p =0.03) though the 95% confidence intervals crossed unity. Nine CVAs (including three TIAs) occurred during the follow-up period at a median time of 901 days (IQR681-1093). Survival analysis by Kaplan Meier method showed no significant difference between CS and NCS (HR 3.1; 95% CI 0.72-13.3; p =0.26, [Figure 3]). Two patients were in atrial fibrillation



**Figure 2:** Kaplan Meier analysis of difference in survival probability free of recurrent AF between POAF after cardiac and non-cardiac surgeries.

at the time of the stroke (1 each in CS and NCS). Since paroxysmal AF can remain undetected at the time of the stroke, we reviewed data on all patients with CVA to the last available clinical date (after the end of the study-designated follow-up period) and found that 2 additional patients (both CS) were diagnosed with AF in clinical follow-up.



**Figure 3:** Kaplan Meier analysis of difference in survival probability free of ischemic stroke/TIA between POAF after cardiac and non-cardiac surgeries. TIA= Transient Ischemic Attack.

**Table 2:** Difference in early outcomes in patients with POAF treated with rate or rhythm control after cardiac and non-cardiac surgeries. POAF= Post-operative Atrial Fibrillation

	Cardiac POAF			Non-Cardiac POAF		
	Total(n=61)	Rhythm(n=49)	Rate(n=12)	Total(n=51)	Rhythm(n=42)	Rate(n=9)
In hospital mortality	1(1.6%)	1/49(2%)	0/12(0%)	3/51(5.8%)	3/42(7.1%)	0/9(0%)
Sinus rhythm at discharge	60/60(100%)	48/48	12/12	48/48(100%)	39/39	9/9
30 day mortality	0/60(0%)	0/48	0/48(0%)	0/39	16.2±0.3	0/9
Readmission in 30 days	10/60(16.7%)	8/48(16.7%)	2/12(16.7%)	4/48(8.3%)	4/39(10.3%)*	0/9(0%)
Sinus rhythm at 30 days	54/60(90%)	43/48(89.6%)	11/12(91.7%)	48/48(100%)	39/39	9/9

\*The only statistically significant different outcome was increased risk of readmission in rhythm control compared with rate control in POAF after non-cardiac surgery (p=0.001)

## Discussion

In this study, we found a 15% AF recurrence rate in patients who develop POAF (with no prior history of AF) after both CS and NCS. Early recurrence (within 30 days of hospital discharge) was common after CS. Interestingly, among patients who were in sinus rhythm at 30 day follow-up, AF recurrence was numerically higher in NCS group though the confidence intervals crossed unity. This likely reflects larger arrhythmic substrate as well as local atrial injury in patients undergoing CS which predisposes them to early recurrence. On the other hand, POAF after NCS may reflect systemic factors at the time of surgery (and thus a lower short term recurrence rate between discharge and 30 day follow-up). The risk of CVA was not statistically different. Among patients with stroke, 22% were in atrial fibrillation at the time of the stroke and another 22% were diagnosed with AF in follow-up after the CVA. Overall, three years after POAF, 1 in 6 patients developed recurrent AF and 1 in 10 suffered a CVA. Thus, POAF should not be considered a benign post-operative complication and is an important predictor for recurrent AF and related complications.

Though the effect of POAF on immediate post-operative outcomes has been previously studied, its effect on long term outcomes remains largely unknown. Most POAF converts to sinus rhythm with or without treatment and approximately 80% are in sinus rhythm at discharge<sup>[3,8-10]</sup>. Long term follow-up of patients with POAF after CS suggests a 20-48% risk of recurrence (depending upon the duration of follow-up)<sup>[10-12]</sup>. In a single center study of 305 patients after CABG, POAF occurred in 88 (28.9%) patients<sup>[10]</sup>. Post-discharge symptomatic AF occurred in 25 (8.2%) patients with an annual incidence of 2% during a mean follow-up of 48 + 30 months and recurrence was more common in those with POAF compared with those without POAF (20.4% vs 3.2%,  $p < 0.0003$ )<sup>[10]</sup>. Similarly in another single center experience, recurrent AF after POAF was 18.9% after a mean follow-up duration of 41 + 23 months<sup>[11]</sup>. In a community based study from Olmsted County with the longest available follow-up (8.3 + 2.3 years), the rate of AF was as high as 42.6%<sup>[13]</sup>. In all these studies, POAF was a significant predictor of future AF. The recurrence rate of AF likely depends on the follow-up strategy employed. Many clinicians follow patients clinically and with periodic electrocardiograms and Holter monitoring as was performed in the current study. An intriguing approach would be the implantation of loop recorders for long term follow-up. In a recent nonrandomized study using this approach, the recurrence rate after CS was as high as 61%<sup>[15]</sup>.

To our knowledge, there are no long term follow-up studies after POAF complicating NCS with the longest available follow-up of 1 year (in an administrative database)<sup>[14]</sup>. Data on the risk of long term ischemic stroke after POAF is even more limited. In the study by Gialdini et al, 1 year incidence of CVA was 1.47% in patients with POAF after NCS compared to 0.36% in patients who did not develop POAF<sup>[14]</sup>. POAF was associated with subsequent stroke both after CS (hazard ratio, 1.3; 95% CI, 1.1-1.6) and NCS (hazard ratio, 2.0; 95% CI, 1.7-2.3) and interestingly, the association was stronger for POAF after NCS ( $P < .001$  for interaction). Despite the large number of patients studied, the lack of detailed medical history and relatively short term duration of follow-up were limiting factors

to this analysis.

The current study provides the most comprehensive data (albeit in a small sample) on the risk of recurrent AF and incidence of ischemic stroke in long term follow-up after NCS. In contrast to the study by Gialdini et al. we found no significant difference in risk of stroke after CS and NCS. Mean CHA2DS2-VASc scores were similar in these groups at baseline and in more than half the cases, CVA occurred in the absence of recurrent AF. This suggests that in addition to AF, other vascular risk factors may play a role in causing ischemic stroke in long term follow-up.

Despite the small size of the cohort, this study has several strengths. This is the first study to provide long term follow-up of patients who achieved sinus rhythm after POAF complicating NCS. We systematically eliminated all patients who had a history of AF or were on anti-arrhythmic therapy prior to surgery. The search strategy employed, excluded close to 14% of patients who were miscoded as AF. This emphasizes the limitation of using large administrative databases in studying POAF where individual medical records and ECG recordings are unavailable for review. The current study also provides insight into the optimal management of POAF. Similar to a recent large randomized study in patients after CS<sup>[16]</sup>, there was no significant difference in early recurrence between those treated with rhythm control vs rate control after NCS.

There are several limitations of the study. The management and anticoagulation strategy in this small cohort reflects practice patterns in a single center. The small number of patients and the large number of baseline differences between patients undergoing CS and NCS precluded propensity matching. Follow-up was limited to those who survived index hospitalization; was based on chart and ECG review and there was no continuous rhythm monitoring. The event rate may be higher than found in this study since small, clinically silent strokes and a symptomatic paroxysmal AF may have remained undiagnosed during the study period. The absence of a control group without POAF prevents the assessment of the relative risk of developing recurrent AF and CVA.

## Conflict of Interests

None.

## Conclusions

Despite achieving sinus rhythm, there is a significant risk of long term recurrence of AF and CVA among patients with new onset POAF. The risk of recurrent AF is similar between CS and NCS. These preliminary results should be verified prospectively in a larger, multi-center cohort. In addition, the optimal anticoagulation strategy at hospital discharge and clinical follow-up in this population remain to be determined.

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