Postoperative Atrial Fibrillation Following Coronary Artery Bypass Graft Surgery Predicts Long-Term Atrial Fibrillation and Stroke

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ABSTRACT: **Background:** Atrial fibrillation (AF) is a common complication of coronary artery bypass graft (CABG) surgery, occurring in 20%–40% of patients, mostly during the first week after surgery. It is associated with increased morbidity and mortality, but data are limited.

Objectives: To assess the correlation between new-onset in-hospital AF following CABG and long-term AF, cerebrovascular accident (CVA), or death.

Methods: We conducted an analysis of 161 consecutive patients who underwent isolated CABG surgery in a tertiary center during the period 2002–2003.

Results: Patients' mean age was 72 years, and the majority were males (77%). Approximately half of the patients experienced prior myocardial infarction, and 14% had left ventricular ejection fraction ‹ 40%. Postoperative AF (POAF) occurred in 27% of the patients. Patients were older and had larger left atrium diameter. POAF was strongly correlated with late AF (OR 4.34, 95%CI 1.44–13.1, $P = 0.01$) during a mean follow-up of 8.5 years. It was also correlated with long-term stroke but was not associated with long-term mortality.

Conclusions: POAF is a common complication of CABG surgery, which is correlated with late AF and stroke. Patients with POAF should be *closely* monitored to facilitate early administration of anticoagulant therapy in a high risk population upon recurrence of AF.

IMAJ 2016; 18: 744–748

KEY WORDS: atrial fibrillation (AF), postoperative atrial fibrillation (POAF), coronary artery bypass graft (CABG), long-term, cerebrovascular accident (CVA)

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice. Its prevalence increases with age, affecting approximately 1% of the total population and 8% of individuals over 80 years old [1]. The incidence of postoperative AF (POAF) following coronary artery bypass grafting (CABG) surgery is high and ranges between 20% and 40% of patients. It increases the length of hospital stay and hospital costs, and is associated with increased morbidity and mortality including postoperative stroke, as well as in-hospital and 6 month mortality [2,3].

POAF typically develops within the first week post-surgery, at a median time of 2 days after the operation. It generally resolves within 24–48 hours and most patients are discharged in sinus rhythm [4,5]. Several factors have been found to predict the risk of POAF following CABG, including enlarged left atrial size and prolonged hospitalization post-surgery [6].

Thus far, the majority of studies related to POAF have focused on early and late mortality [7,8]. One of the largest retrospective analyses revealed increased in-hospital and 4 year mortality in patients with POAF [7]. POAF is also associated with increased risk of recurrent AF and stroke [8,9], but data are limited.

Current guidelines do not support long-term anticoagulation in patients with POAF following CABG. The American College of Chest Physicians recommends the use of anticoagulation therapy, particularly for high risk patients in whom AF develops after surgery, for 30 days after return to normal sinus rhythm [10].

The aim of the current analysis was to investigate the correlation between POAF and long-term AF, cerebrovascular accident (CVA) or death over long-term follow-up, and to find predictors of long-term AF after CABG.

PATIENTS AND METHODS

A cohort analysis of 161 consecutive patients who underwent isolated CABG surgery in a tertiary center between the years 2002 and 2003 was performed. Patients who underwent combined CABG and prosthetic heart valve surgery, recent myocardial infarction, or urgent CABG surgery were excluded from the current analysis. Of 161 patients, 11 patients with a prior history of AF and 14 who were lost to follow-up were excluded from the present study. Data were obtained from patients' medical records and computerized database

of the health care provider and included the diagnosis list, medications, outpatient's clinic notes and hospital admissions. Atrial fibrillation was defined according to the International Classification of Diseases (ICD-9 diagnoses 427.3). Any patient designated with this code at least once on hospital discharge, at outpatient clinic visits, or visit to the family physician clinic after discharge from the cardiac surgery department was considered a case of long-term atrial fibrillation. The study was approved by the local ethics committee and a waiver of informed consent was permitted.

STATISTICAL ANALYSIS

Categorical data are expressed as absolute numbers and percentages; continuous parameters are presented as mean ± SD. For univariate analysis the *t*-test for independent samples and chi-square test as well as Kaplan-Meier test were used as appropriate. The Mann-Whitney U test was used when sample data were not normally distributed. For multivariate analysis multivariate logistic regression was performed for the following outcomes: long-term AF, mortality and CVA. Two-sided *P* values < 0.05 were considered statistically significant. All statistical analyses were conducted using SPSS 17.0 statistical software (SPSS Inc., Chicago, IL, USA).

POWER AND SAMPLE SIZE

Sample size was determined by the estimated prevalence of long-term AF in patients with or without POAF. In POAF patients, 49.3% are expected to have atrial fibrillation at follow-up of 8 years, compared with 13.6% of patients without POAF [11]. Hence, 31 patients with POAF and 52 patients without POAF (controls) are required to achieve a power of 90% (alpha = 0.05). The present analysis included 37 experimental subjects and 99 control subjects. The probability of exposure among controls was 0.07. Since the true probability of exposure among cases was 0.3, we are able to reject the null hypothesis that the exposure rates for cases and control are equal with a probability (power) of 90%. Type I error probability associated with this test of this null hypothesis is 0.05.

RESULTS

COHORT CHARACTERISTICS

Patient's mean age was 72 years, and the majority were males (77%). Approximately half of the patients experienced prior myocardial infarction, and 14% had left ventricular ejection fraction < 40%. Cardiovascular risk factors included hypertension (70%), dyslipidemia (87%), diabetes mellitus (62%), smoking history (34%), and peripheral vascular disease (PVD) (13%). Of 136 patients enrolled, 37 developed POAF during the first week after surgery (27%). Patients with POAF were older and had larger left atrium diameter as compared to patients without POAF. They also had higher body mass index (BMI) and higher prevalence of hypertension and hyperlipidemia. Notably, treatment with angiotensin-converting enzyme inhibitors was associated with a lower incidence of POAF (*P* = 0.05) [Table 1].

Table 1. Characteristics of patients with or without POAF

	Patients with POAF (37) Mean ± SD N (%)	Patients without POAF (99) Mean ± SD N (%)	*P* value
Follow-up (yrs)	8.5 ± 2	8.4 ± 2	0.86
Age (yrs)	76 ± 7	70 ± 9	0.04
Male gender	25 (68)	80 (81)	0.15
BMI	29 ± 4	28 ± 5	0.04
Prior MI	18 (49)	48 (49)	1.00
Moderate to severe LV dysfunction	5 (13)	13 (14)	1.00
Left atrial size (anteroposterior, mm)	47 ± 6.7	44 ± 5	0.01
Hypertension	31 (84)	66 (67)	0.08
Hyperlipidemia	37 (100)	83 (84)	0.006
Smoking history	8 (22)	38 (39)	0.10
Diabetes mellitus	13 (35)	38 (39)	0.88
PVD	7 (19)	11 (11)	0.26
COPD	6 (16)	12 (12)	0.60
Perioperative medical treatment			
Beta-blockers	31 (84)	84 (85)	1.00
Aspirin	35 (95)	90 (91)	0.50
ACE I	19 (51)	70 (71)	0.05
Statins	34 (92)	84 (85)	0.40
Anticoagulation	7 (19)	5 (5)	0.02
Anti-arrhythmic	7 (19)	5 (5)	0.02

ACE I = angiotensin-converting enzyme inhibitors, BMI = body mass index, CABG = coronary artery bypass grafting, COPD = chronic obstructive pulmonary disease, LV = left ventricular, MI = myocardial infarction, POAF = postoperative atrial fibrillation, PVD = peripheral vascular disease

The extent of coronary artery disease was classified into six groups: left main (LM) disease, 2 vessel coronary artery disease (CAD), 3 vessel CAD, LM + 1 vessel CAD, LM + 2 vessel CAD, or LM + 3 vessel CAD. Since sample data were not normally distributed, the Mann-Whitney test was performed, without evidence of any significant difference in the extent of CAD between patients with POAF vs. those without (*P* = 0.26). We could not find any significant difference between the number of grafts (3.7 ± 1 vs. 3.6 ± 1, *P* = 0.67) or bypass time (104 ± 35 vs. 107 ± 34 minutes, *P* = 0.65) between patients with or without POAF appropriately. The extent of CAD, number of grafts and bypass time were also not found to correlate with long-term AF, stroke or death. Notably, as patients who underwent valve surgery were excluded from the current analysis, none of the patients had significant valvular disease or significant pulmonary hypertension. Only two patients had mild-moderate mitral regurgitation, two other patients had

Table 2. Differences in long-term AF, CVA or death among patients with or without POAF

	Patients with POAF (37) N (%)	Patients without POAF (99) N (%)	*P* value
Long-term AF	11 (30%)	7 (7%)	0.001
CVA	6 (16%)	6 (6%)	0.087
Mortality	10 (27%)	22 (22%)	0.65

AF = atrial fibrillation, CABG = coronary artery bypass grafting, CVA = cerebrovascular accident, POAF = postoperative atrial fibrillation

mild-moderate aortic stenosis, and one patient had moderate pulmonary hypertension. As such, the significance of mitral/aortic or tricuspid disease and pulmonary hypertension were not included in the statistical analysis.

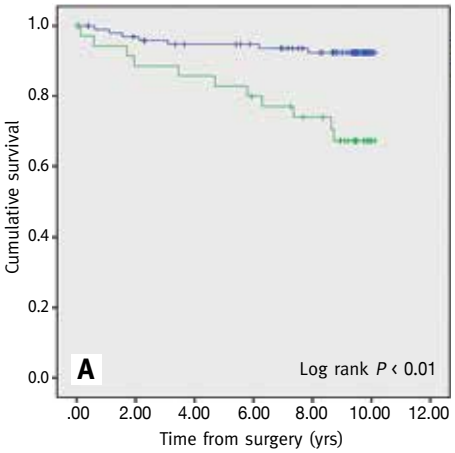
LONG-TERM AF

During the long-term follow-up of 8.5 years, patients who developed POAF were significantly more likely to develop recurrent AF (30% vs. 7%, $P < 0.001$) [Table 2]. In univariate analysis, age ($P = 0.03$) and PVD ($P = 0.01$) were found to predict AF recurrence during follow-up, whereas diabetes, hypertension, BMI, left atrial size, preoperative treatment with beta-blockers, cardiopulmonary bypass time, number of grafts, and atrial fibrillation during surgery were not found to predict future AF. In multivariate analysis, POAF [odds ratio (OR) 4.34, 95% confidence interval (95%CI) 1.44–13.1, $P = 0.01$] and PVD (OR 3.77, 95%CI 1.09–13.05, $P = 0.03$) remained as independent predictors of long-term AF. Notably, 71% of patients who developed AF during the follow-up period were treated with anti-arrhythmic medications and 65% were treated with anticoagulant therapy. As shown in the Kaplan-Meier curves [Figure 1A], POAF was significantly correlated with long-term AF (long rank < 0.01). Not surprisingly, since POAF was correlated with long-term AF, postoperative anticoagulation and anti-arrhythmic therapy, which were mainly administered for POAF [Table 1], were also correlated with long-term AF ($P < 0.01$).

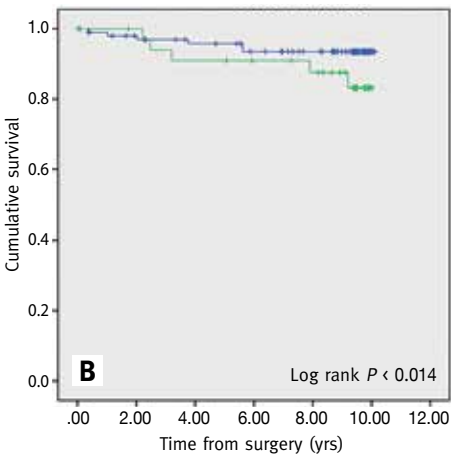
LONG-TERM CEREBRAL-VASCULAR ACCIDENT

Patients with POAF following CABG were more likely to have a CVA during long-term follow-up (16% vs. 6%, $P = 0.087$) [Table 2], although it did not reach statistical significance. Of all factors analyzed – risk factors, BMI, PVD, chronic obstructive pulmonary disease (COPD), LV function, left atrial size and preoperative beta-blocker treatment – only male gender was found to correlate with long-term CVA. Kaplan-Meier curves depicted the cumulative incidence of long-term stroke in patients with or without POAF [Figure 1B]. Importantly, the majority of patients who suffered a stroke during follow-up were not diagnosed with recurrent AF and hence were not treated with anticoagulant therapy.

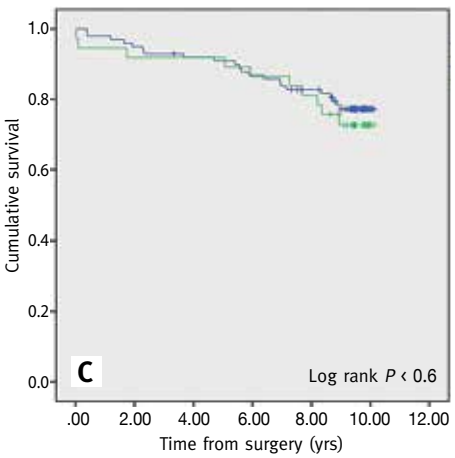
Figure 1. [A] Kaplan-Meier curves of time to first episode of long-term AF in patients with (green line) or without (blue line) POAF



[B] Kaplan-Meier curves of long-term stroke in patients with (green line) or without (blue line) POAF



[C] Kaplan-Meier curves of long-term death in patients with (green line) or without (blue line) POAF



LONG-TERM MORTALITY

The long-term mortality rate was not different between patients who developed POAF following CABG and patients without POAF (27% vs. 22%, $P = 0.65$) [Table 2]. Kaplan-Meier curves depicted the cumulative incidence of long-term death in patients with or without POAF [Figure 1C]. Of 136 patients, 35 patients died during follow-up. Of all factors analyzed (risk factors, BMI, PVD, COPD, LV function, left atrial size, preoperative beta-blocker treatment), diabetes mellitus (56% vs. 32%, $P = 0.02$), PVD (25% vs. 9.6%, $P = 0.03$) and COPD (25% vs. 9.6%, $P = 0.03$) were found to correlate with long-term mortality. Positive correlation remained significant even after multivariate logistic regression analysis: diabetes (OR 3.16, 95%CI 1.33–7.51, $P = 0.009$), PVD (OR 3.04, 95%CI 1.02–9.06, $P = 0.046$), and COPD (OR 3.89, 95%CI 1.28–11.84, $P = 0.017$).

DISCUSSION

The present study assessed the correlation between new-onset POAF following isolated CABG surgery and long-term AF, CVA and mortality. Thus far, the majority of studies have focused on short-and long-term mortality. POAF was found to be an independent predictor of in-hospital and long-term mortality [6-8]. The current analysis confirms that POAF is also a strong predictor of late AF (30% vs. 7%, $P < 0.001$), even after adjustment for multiple risk factors (OR 4.34, $P = 0.01$). These findings are in line with recently published data on 603 patients, without a history of AF, who underwent CABG and/or valve surgery. In accordance with our findings, after a mean follow-up of 8.3 years, POAF was found to be an independent predictor of late AF, but not of long-term mortality [11]. The authors concluded that patients who develop new-onset POAF should be considered for continuous anticoagulation at least for the first year following cardiac surgery. Postoperative AF was also correlated with late AF among 1171 consecutive patients who had undergone CABG over a shorter follow-up period of 41 months. Accordingly, strict surveillance and routine screening for AF during follow-up after surgery was suggested [12].

However, there are no randomized, controlled clinical trials that specifically address the problem of anticoagulation therapy in POAF. Recommendations are based on the established therapy for non-surgical situations modified by the potential risk of bleeding in the postoperative patient [13]. Based on the knowledge that POAF is a transient and reversible medical condition, the American College of Chest Physicians recommends the use of anticoagulation therapy, particularly for high risk patients in whom AF develops after surgery, for 30 days after return to normal sinus rhythm [10]. The 2014 guidelines of the American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) for the management of patients with atrial fibrillation cautiously recommend that it is reasonable to administer antithrombotic medication in patients who develop postoperative AF following cardiac surgery, as advised for non-surgical patients, yet the length of the treatment is not stated [14].

Another important finding is that POAF was associated with stroke during long-term follow-up, with a trend towards significance (16% vs. 6%, $P = 0.08$). Notably, 11 of 12 patients who suffered a stroke (92%) were not diagnosed with recurrent AF nor treated with anticoagulant therapy. It is possible that the stroke was related to subclinical AF that was misdiagnosed or non-AF related, which suggests that POAF is only a marker for cardiovascular morbidity and future stroke. Careful surveillance with frequent Holter monitoring tests or implantable loop recorder may be required to address this issue and to facilitate early administration of anticoagulant therapy in a high risk population upon AF recurrence.

In addition, PVD was found to be an independent predictor of long-term AF and mortality even after adjustment for multiple risk factors. This finding is in line with data from the REduction of Atherothrombosis for Continued Health (REACH) Registry, which included approximately 4000 patients with PVD and showed that AF is common in patients with PVD and is independently associated with a worse cardiovascular outcome [15].

Analysis of the preoperative medical therapy prior to isolated CABG revealed that angiotensin-converting enzyme (ACE) inhibitor therapy was correlated with a lower incidence of in-hospital AF [Table 1]. Results from a recently published review on the effect of ACE inhibitors on the risk of AF after CABG are conflicting, suggesting that randomized placebo-controlled trials are necessary to determine the risk for AF after CABG associated with preoperative use of ACE inhibitors [16].

In summary, the present study emphasizes that patients who develop POAF after isolated CABG have a fourfold increased risk of AF and increased risk of stroke during long-term follow-up. Current guidelines recommend the use of anticoagulation therapy for high risk patients with POAF for 30 days after return to normal sinus rhythm, considering that POAF is a transient condition that is related to a reversible cause. Given the data presented, a multicenter, prospective randomized trial may be required to determine whether long-term anticoagulant therapy is required to reduce the risk of future stroke in patients with POAF following CABG.

STUDY LIMITATIONS

The main limitation of the present analysis is its retrospective design and the relatively small sample size. Given the retrospective design of the study, patients were not scheduled for routine follow-up visits, neither did they undergo periodic Holter monitoring tests, which suggest that the long-term recurrence rate of AF is underestimated. Therefore, a

prospective study utilizing long-term Holter monitoring or implantable loop recorders are required to assess the precise rate of long-term AF in this patient population, including short AF episodes and asymptomatic AF. Moreover, it should be noted that given the long-term follow-up, the study was sufficiently powered to assess the primary objective of the study: the correlation between POAF and long-term AF.

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