Original Article

Early pharmacologic conversion of atrial fibrillation after off-pump coronary artery bypass grafting

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Background: The aim of this study was to evaluate the efficacy of early amiodarone-based pharmacological cardioversion for postoperative atrial fibrillation (POAF) following off-pump coronary bypass grafting (OPCAB).

Methods: A total of 507 patients who underwent OPCAB between 2015 and 2017 were categorized into POAF (n=94) and no-POAF (n=413) groups. Patients in the POAF group were treated according to the following institutional protocol: 150 mg loading dose of intravenous amiodarone, followed by oral administration with sequential maintenance doses at 600, 400, and 200 mg per day. If sinus rhythm was restored before discharge, patients were discharged without amiodarone or anticoagulants, except for dual antiplatelets.

Results: Before discharge at index hospitalization, 97.8% of POAF patients had restored sinus rhythm. Independent risk factors for POAF were age, unstable angina, prior percutaneous transluminal coronary angioplasty, and left atrial diameter. The mean follow-up duration was 41.1±12.8 months. Freedom from overall mortality and composite events, including mortality, major bleeding requiring admission and cerebrovascular events, were similar between the 2 groups. Results were consistent after propensity-score matching.

Conclusions: Amiodarone-based rapid pharmacological cardioversion of POAF resulted in a high sinus rhythm conversion rate (97.9%). Rate of late adverse cardiovascular events including stroke, were low even without anticoagulation. As optimal treatment and anticoagulation guidelines for POAF after OPCAB have not yet been established, amiodarone-based treatment protocols may be considered as a useful option.

Keywords: Arrhythmia; arrhythmia therapy; atrial fibrillation; coronary artery bypass grafting

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Introduction

Postoperative atrial fibrillation (POAF) is a frequent complication following cardiac surgery, with an incidence of up to 40%. Most studies have ascertained that POAF is associated with adverse clinical outcomes in both the early and late periods (1-5). However, studies regarding the effects of POAF on long-term clinical outcomes have inherent confounding biases and are at risk of misunderstanding. The predictors of POAF were similar to those of long-term mortality (6). POAF may not be the cause of mortality, but likely the result of preoperative risk factors. In addition, POAF may be associated with

various perioperative conditions including transfusion due to bleeding, preconditioned heart fibrosis, inflammatory reaction associated with cardiopulmonary bypass, and poor intraoperative conditions such as myocardial damage. Thus, POAF development may be due to complications of the operation itself rather than underlying conditions (7,8). However, the previously reported risk factors have not been consistent. Furthermore, POAF following off-pump coronary bypass grafting (OPCAB) may be due to an increased susceptibility to triggers of atrial fibrillation (AF) after operation, rather than a structural substrate before operation or surgical trauma (9).

Other criticisms concern the benign and self-limiting nature of POAF (6,10). Considering its high conversion rate and short duration of presentation, the direct impact of POAF on late adverse events is uncertain. Therefore, determining the association between POAF and adverse clinical outcomes can be challenging.

In addition, consensus guidelines on the optimal treatment and anticoagulation strategies for POAF have not yet been established (11-13). Patients indicated for coronary artery bypass grafting (CABG) usually have multiple comorbidities and high risk for cardiovascular events requiring several medications including antiplatelet agents. Additional anticoagulants should therefore be administered cautiously.

In our institution, we proposed an amiodarone-based institutional treatment protocol for POAF after OPCAB. Patients with POAF were treated with amiodarone, and were discharged without anticoagulation when sinus rhythm was achieved.

The aim of our study was to evaluate the efficacy of early amiodarone-based pharmacological cardioversion of POAF following OPCAB.

We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/jtd-21-466).

Methods

Study population

We retrospectively reviewed data from January 2015 through December 2017 of 507 patients who underwent OPCAB in our institution; those with a history of persistent POAF or paroxysmal AF were excluded. Included subjects were then classified into either the POAF (n=94) or the no-POAF (n=413) group. The mean age was 63.8±9 years, and the mean CHA_2DS_2-VAS_C score was 2.5±1.5. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the hospital's institutional review board, which waived the requirement for patient consent (IRB no: 2020-0643, approval date: 11-18-2020).

Operative procedures and routine postoperative managements

The main strategy of CABG in our institution is OPCAB via standard median sternotomy with skeletonized bilateral internal thoracic artery. Composite Y or I grafts were constructed after harvesting. The *in situ* left internal thoracic artery was anastomosed to the left anterior descending artery in most cases; otherwise, the right internal thoracic artery was used. The remaining left circumflex artery or territories were revascularized using a sequential anastomosis technique. Bilateral internal thoracic artery and saphenous vein was used in 1 patient. Single internal thoracic artery and saphenous vein was used in 2 patients.

Routine medication included oral aspirin (100 mg), clopidogrel (75 mg), and statins. Aspirin was administered on the day of operation, and readministered within 6 hours after operation. Clopidogrel and statins were started at postoperative day 1. Prophylactic beta-blockers, calcium channel blockers and amiodarone for preventing POAF were not included as routine medication. Patients were continuously monitored via cardiac telemetry either in the intensive care unit or in the general ward. Twelve-lead electrocardiography (ECG) was performed on patients in whom POAF was detected on telemetry. Those with documented AF were then treated according to the institutional protocol described below. Daily ECGs were taken in patients with POAF. ECGs were also regularly taken at 1, 3 months post-discharge and then every 3 to 6 months.

Protocol for POAF

When POAF was documented, patients were treated with an amiodarone-based institutional protocol as in the following description. (I) An initial loading dose of 150 mg intravenous amiodarone. If patients had heart rate >120/min with palpitations, an additional bolus of 150 mg amiodarone was considered. (II) Sequential maintenance doses at 600, 400, 200 mg oral amiodarone per day. If heart rate <60/min, maintenance therapy was omitted. (III) In patients with prolonged POAF of >6 hours, anticoagulation with

low molecular weight heparin or unfractionated heparin was initiated (target activated thromboplastin time: 40–50 sec in patients with chronic kidney disease). Oral aspirin and new oral anticoagulants (NOAC) were considered when AF persisted until the day of discharge. (IV) Amiodarone and oral anticoagulation agents were discontinued unless AF was present at discharge.

Electrical cardioversion was considered if patients were symptomatic with systolic blood pressure <80 mmHg.

Follow-up

Hospital records were reviewed retrospectively. The primary endpoint was recurrence of AF during follow-up. The secondary endpoints were all-cause mortality and cerebrovascular events (CVA). Early mortality was defined as death during hospitalization. Composite endpoints included mortality, major bleeding requiring admission, and CVA.

Follow-up survival data were available for all patients (85.8% from our hospital, 14.2% from the national registry). The mean follow-up duration for all patients was 41.1±12.8 [median (Q1–Q3), 41.5 (32.7–51.1)] months; while that for the POAF and the no-POAF group was 38.5±13.8 [39.5 (29.0–49.1)] months and 41.7±12.5 [42.8 (33.5–51.3)] months, respectively (P=0.028).

Statistical analysis

Categorical variables are presented as frequencies and percentages, while continuous variables are presented as means with standard deviations, or medians and Q1–Q3 quartiles. Inter-group differences were assessed using the *t*-test (or the Mann-Whitney test when the normality assumption was in doubt) and the Chi-square test (or the Fisher's exact test when the expected cell frequency was <5). To balance the distribution of baseline risk factors between the groups, inverse probability of treatment weighting (IPTW)-adjusted analysis was performed. Propensity score (PS) was obtained by multiple logistic regression, which was based on preoperative baseline characteristics including age, sex, body surface area, body mass index, hypertension, diabetes mellitus, stroke, New York Heart Association functional class, Canadian Cardiovascular Society class 4 angina, preoperative beta-blocker use, hyperthyroidism, chronic renal failure, chronic obstructive pulmonary disease, CHA_2DS_2-VAS_C score, peripheral occlusive arterial disease, cancer history, old myocardial infarction, percutaneous transluminal coronary angioplasty (PTCA), left ventricular ejection fraction of <40%, left atrial (LA) enlargement (LA diameter ≥40 mm), preoperative intra-aortic ballooning pump support, unstable angina, stable angina, non-ST elevation myocardial infarction, triple vessel disease, left main disease, and the number of anastomoses. Weights for POAF patients were the inverse of the PS, and those for patients without POAF were the inverse of 1-PS. To reduce variability in the IPTW models, stabilized weights were used (14). We also analyzed the PS matching as an added robust analysis result. For PS matching, ninety-one patients with POAF were matched 1:1 with patients without POAF using the nearest-neighbor matching without replacement method, with a matching tolerance (caliper) of 0.25. Survival curves were generated using the Kaplan-Meier method, and survival rates were compared between the 2 groups using the log-rank test. The Cox proportional hazards model analysis was employed to estimate the treatment effect of POAF versus no-POAF on long-term clinical outcomes in terms of overall mortality and composite endpoints. Hazard ratios (HRs) of late clinical outcomes between the 2 groups were compared based on original unmatched data, IPTW models, and matched data. P values <0.05 were considered statistically significant. Rates of missingness for data in our models were <1%, and no imputation was performed for missing data. All statistical analyses were performed using the R3.6.3 software (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics and operative data

Table 1 summarizes the baseline characteristics of the study population before and after IPTW adjustments. Patients with POAF tended to have older age, lower rates of dyslipidemia, higher PTCA history, larger LA diameter, higher prevalence of diabetes mellitus, and higher history of CVA as compared with no-POAF patients. After IPTW adjustment, no differences in the demographic data were observed. Based on operative data, POAF patients showed higher incidences of unstable and stable angina. However, no differences were observed after IPTW adjustment (*Table 2*). It was consistent in matched data, described in the supplementary appendix (Tables S1,S2).

Protocol-based treatment for POAF

The time to develop POAF after surgery was 1.9±1.0

Table 1 Baseline characteristics

Variables	Before IPTW				After IPTW*			
	No-POAF (n=413)	POAF (n=94)	P value	SMD	No-POAF (n=413)	POAF (n=93)	P value	SMD
Age, years	62.9±9.5[a]	67.9±8.7[a]	<0.001	0.548	63.8±9.6[a]	62.9±9.5[a]	0.570	0.094
	63.0 (56.0–70.0)[b]	68.1 (62.0–74.2)[b]			63.8 (56.4–71.0)[b]	62.6 (54.9–68.5)[b]		
Sex, female, n (%)	105 (25.4)	25 (26.6)	0.917	0.027	104 (25.2)	16 (17.2)	0.157	0.182
BSA, m^2	1.72±0.17[a]	1.71±0.18[a]	0.494	0.077	1.72±0.17[a]	1.75±0.18[a]	0.254	0.182
	1.73 (1.61–1.83)[b]	1.73 (1.58–1.85)[b]			1.72 (1.61–1.83)[b]	1.75 (1.62–1.87)[b]		
BMI, kg/m^2	24.8±3.1[a]	24.7±2.7[a]	0.725	0.199	24.8±3.0[a]	25.1±2.7[a]	0.539	0.095
	24.6 (22.9–26.5)[b]	24.3 (23.0–26.7)[b]			24.6 (22.9–26.3)[b]	24.5 (23.2–27.3)[b]		
Hypertension, n (%)	243 (58.8)	66 (70.2)	0.054	0.239	250 (60.5)	51 (54.8)	0.503	0.112
Diabetes mellitus, n (%)	208 (50.4)	58 (61.7)	0.061	0.230	217 (52.5)	47 (50.5)	0.786	0.044
Stroke, n (%)	234 (56.7)	61 (68.1)	0.055	0.238	241 (58.4)	49 (52.7)	0.509	0.108
Dyslipidemia, n (%)	132 (32.0)	16 (17.0)	0.006	0.353	121 (29.3)	27 (29.0)	0.892	0.024
NYHA class III–IV, n (%)	18 (4.4)	5 (5.3)	0.897	0.045	18 (4.4)	6 (6.5)	0.595	0.079
CCS class 4, n (%)	20 (4.8)	7 (7.4)	0.447	0.109	22 (5.3)	4 (4.3)	0.745	0.036
Preoperative beta-blocker use, n (%)	310 (75.1)	70 (74.5)	>0.999	0.014	311 (75.3)	71 (76.3)	0.764	0.042
Hyperthyroidism, n (%)	6 (1.5)	0 (0.0)	0.518	0.172	5 (1.2)	0 (0.0)	0.258	0.155
Chronic renal failure, n (%)	17 (4.1)	6 (6.4)	0.497	0.102	20 (4.8)	7 (7.5)	0.519	0.103
COPD, n (%)	10 (2.4)	4 (4.3)	0.528	0.102	12 (2.9)	3 (3.2)	0.986	0.002
Interstitial pneumonia, n (%)	4 (1.0)	0 (0.0)	0.755	0.140	4 (1.0)	0 (0.0)	0.352	0.146
CHA_2DS_2-VAS_C score	2.4±1.4[a]	3.0±1.4[a]	<0.001	0.419	2.5±1.5[a]	2.3±1.5[a]	0.473	0.119
	2.0 (1.0–3.0)[b]	3.0 (2.0–4.0)[b]			1.89 (0.98–2.95)[b]	1.81 (0.55–2.99)[b]		
PAOD, n (%)	134 (32.4)	34 (36.2)	0.568	0.079	135 (32.7)	27 (29.0)	0.608	0.075
Cancer, n (%)	16 (3.9)	8 (8.5)	0.101	0.193	18 (4.3)	3 (3.2)	0.694	0.038
OMI history, n (%)	26 (6.3)	11 (11.7)	0.110	0.190	32 (7.7)	8 (8.6)	0.824	0.029
PTCA history, n (%)	72 (17.4)	30 (31.9)	0.003	0.341	85 (20.6)	18 (19.4)	0.775	0.035
EF <40, n (%)	84 (20.3)	16 (17.0)	0.558	0.085	82 (19.9)	23 (24.7)	0.520	0.120
LA enlargement, n (%)	200 (48.4)	64 (68.1)	0.001	0.407	216 (52.3)	51 (54.8)	0.710	0.061

*, counts in the weighted cohort may not sum up to the expected totals owing to rounding. Percentages may not total to 100 because of rounding. Disagreements between numbers and percentages in the weighted cohort are therefore the result of rounding of non-integer number values. [a]Mean ± standard deviation; [b]Median (Q1–Q3). IPTW, inverse probability of treatment weighting; POAF, postoperative atrial fibrillation; SMD, standardized mean difference; BSA, body surface area; BMI, body mass index; NYHA, New York Heart Association; CCS, Canadian Cardiovascular Society; COPD, chronic obstructive pulmonary disease; POAD, peripheral occlusive arterial disease; OMI, old myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; EF, ejection fraction; LA, left atrial.

Table 2 Operative data

Variables	Before IPTW				After IPTW*			
	No-POAF (n=413)	POAF (n=94)	P value	SMD	No-POAF (n=413)	POAF (n=93)	P value	SMD
Unstable angina, n (%)	71 (17.2)	27 (28.7)	0.016	0.277	80 (19.4)	19 (20.4)	0.811	0.033
Stable angina, n (%)	165 (40.0)	27 (28.7)	0.056	0.238	157 (38.0)	37 (40.0)	0.855	0.030
NSTEMI, n (%)	167 (40.4)	40 (42.6)	0.794	0.043	168 (40.7)	37 (40.0)	0.920	0.016
STEMI, n (%)	10 (2.4)	0 (0.0)	0.266	0.223	8 (1.9)	0 (0.0)	0.150	0.200
Triple vessel disease, n (%)	300 (72.6)	68 (72.3)	>0.999	0.007	300 (72.6)	66 (71.0)	0.893	0.023
Left main disease, n (%)	111 (26.9)	30 (31.9)	0.392	0.111	116 (28.1)	27 (29.0)	0.869	0.026
Emergency operation, n (%)	1 (0.2)	1 (1.1)	0.814	0.102	1 (0.2)	0 (0.0)	0.991	0.001
No. of anastomosis, n (%)	3.7±1.0	3.5±1.1	0.157	0.159	3.6±1.0	3.6±1.2	0.947	0.013
Preoperative IABP support, n (%)	3 (0.7)	2 (2.1)	0.508	0.118	3 (0.7)	1 (1.1)	0.810	0.019
Intraoperative IABP insertion, n (%)	7 (1.7)	4 (4.3)	0.252	0.151	9 (2.2)	3 (3.2)	0.619	0.054

*, counts in the weighted cohort may not sum up to the expected totals owing to rounding. Percentages may not total to 100 because of rounding. Disagreements between numbers and percentages in the weighted cohort are therefore the result of rounding of non-integer number value. IPTW, inverse probability of treatment weighting; POAF, postoperative atrial fibrillation; SMD, standardized mean difference; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; IABP, intra-aortic balloon pump.

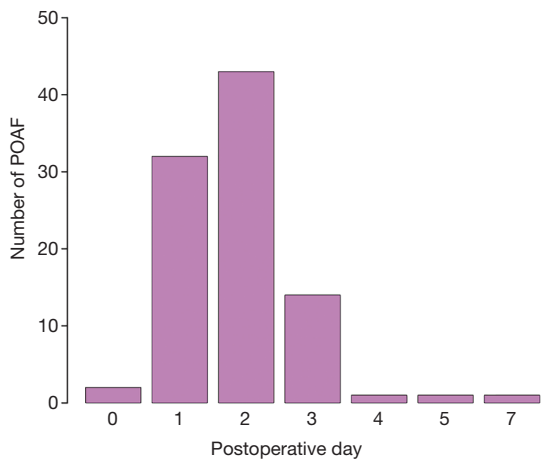

Figure 1 Incidence of postoperative atrial fibrillation according to postoperative days. POAF, postoperative atrial fibrillation.

{2 [1–2]} days, with postoperative day 2 being the most common time for POAF development (*Figure 1*). A total of 94.7% of POAF patients (n=89) were treated according to the amiodarone-based institutional protocol. Among them, sinus rhythm was achieved in 97.9%, and the time to sinus rhythm conversion was 1.6±2.4 {1 [0–2.75]} days. Only 2 POAF patients (2.1%) were discharged without sinus rhythm conversion, and were administered NOAC, respectively, upon discharge. Among them, AF was persisted in one patient, sinus rhythm conversion was occurred in the other patient. During follow-up, AF recurrence was occurred in two patients. Consequently, persistent AF was noted in 3 patients.

Early outcomes

Before IPTW adjustment, 8 early deaths (1.9%) in the no-POAF group and 1 (1.1%) in the POAF group were reported (P>0.999). Early postoperative mortality and morbidity rates were not significantly different between the 2 groups both before and after IPTW adjustment (*Table 3*).

Late outcomes

Three-year freedom from overall mortality did not differ between the no-POAF and POAF groups (93.2% *vs.* 89.0%, respectively, P=0.374). Three-year freedom from composite events also did not differ between groups (88.8% *vs.* 83.7%, respectively, P=0.356) (*Figure 2*).

The IPTW-weighted Kaplan-Meier analysis also showed no difference in freedom from overall mortality and composite events (P=0.397 and P=0.716, respectively, *Figure 3*).

Figure 4 summarizes the HRs for clinical outcomes

Table 3 Early outcomes

Variables	Before IPTW				After IPTW*			
	No-POAF (n=413)	POAF (n=94)	P value	SMD	No-POAF (n=413)	POAF (n=93)	P value	SMD
Early mortality, n (%)	7 (1.7)	1 (1.1)	>0.999	0.054	8 (1.9)	1 (1.1)	0.272	0.112
Stroke, n (%)	11 (2.7)	3 (3.2)	>0.999	0.031	11 (2.7)	3 (3.2)	0.813	0.028
PMI, n (%)	3 (0.7)	0 (0.0)	0.933	0.121	3 (0.7)	0 (0.0)	0.418	0.123
LCOS, n (%)	5 (1.2)	3 (3.2)	0.351	0.135	5 (1.2)	2 (2.2)	0.357	0.092
Bleeding reoperation, n (%)	3 (0.7)	2 (2.1)	0.508	0.118	4 (0.9)	1 (1.1)	0.666	0.042
Mediastinitis, n (%)	7 (1.7)	3 (3.2)	0.596	0.097	7 (1.7)	4 (4.3)	0.256	0.134

*, counts in the weighted cohort may not sum up to the expected totals owing to rounding. Percentages may not total to 100 because of rounding. Disagreements between numbers and percentages in the weighted cohort are therefore the result of rounding of non-integer number values. IPTW, inverse probability of treatment weighting; POAF, postoperative atrial fibrillation; SMD, standardized mean difference; PMI, perioperative myocardial infarction; LCOS, low cardiac output syndrome.

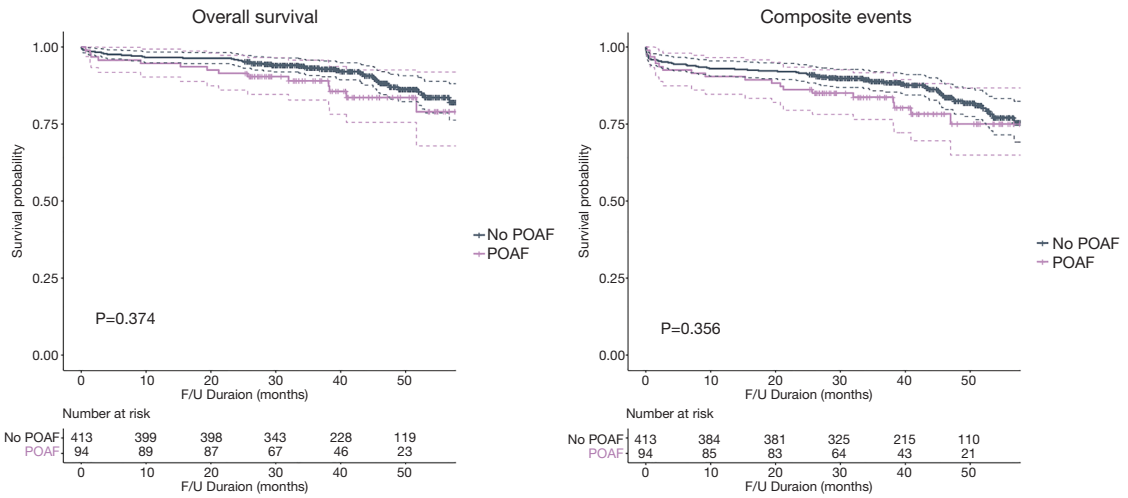

Figure 2 Kaplan-Meier curves of POAF and no-POAF patients in the total population. Kaplan-Meier curves for comparison of overall survival and composite events including mortality, bleeding, and cerebrovascular event between POAF and no-POAF patients after off-pump coronary bypass grafting in the total population. POAF, postoperative atrial fibrillation.

between the 2 groups. Various statistical methods consistently indicated no differences in overall mortality and composite events between the 2 groups.

Risk factors for developing POAF

Table 4 presents the results of the univariable and multivariable logistic regression analyses for the assessment of risk factors for POAF. Multivariable analysis revealed that age [odds ratio, OR=1.054, 95% confidence interval (CI): 1.027–1.083, P<0.001], unstable angina (OR=1.805, 95% CI: 1.036–3.098, P=0.034), PTCA history (OR=2.003, 95% CI: 1.172–3.384, P=0.010), and LA enlargement (OR=2.141, 95% CI: 1.312–3.560, P=0.003) were significant risk factors for POAF. Dyslipidemia showed a preventive effect against POAF (OR=0.472, 95% CI: 0.250–0.844, P=0.014).

Discussion

We found that the incidence of POAF following isolated OPCAB was 18.5% of the entire cohort. Sinus rhythm conversion rate in POAF patients treated according to the amiodarone-based institutional protocol was 97.9%. Only 3 persistent AF cases were observed during follow-up. Even

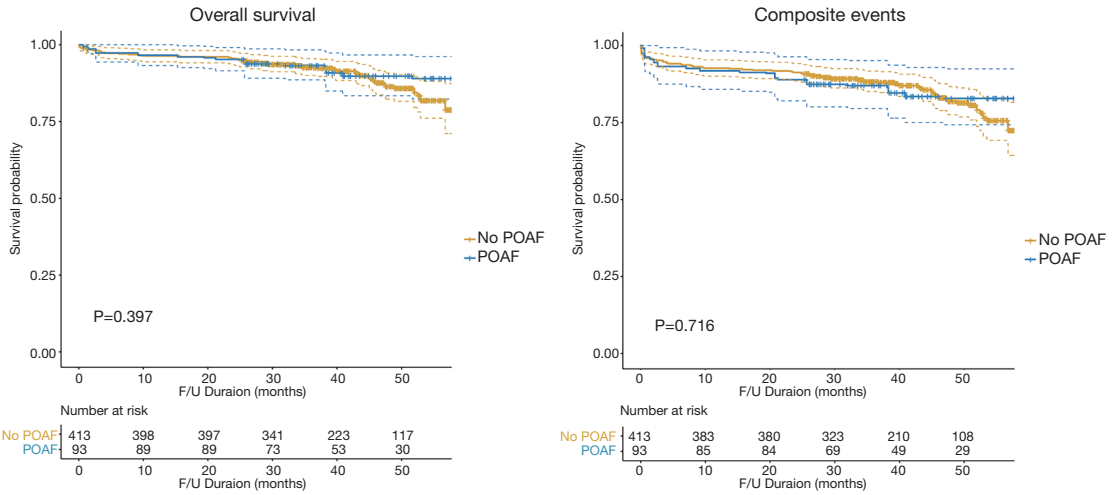

Figure 3 Kaplan-Meier curves of POAF and no-POAF patients in the IPTW adjusted population. Kaplan-Meier curves for comparison of overall survival and composite events including mortality, bleeding, and cerebrovascular event between POAF and no-POAF patients after off-pump coronary bypass grafting in the IPTW adjusted population. POAF, postoperative atrial fibrillation; IPTW, inverse probability of treatment weighting.

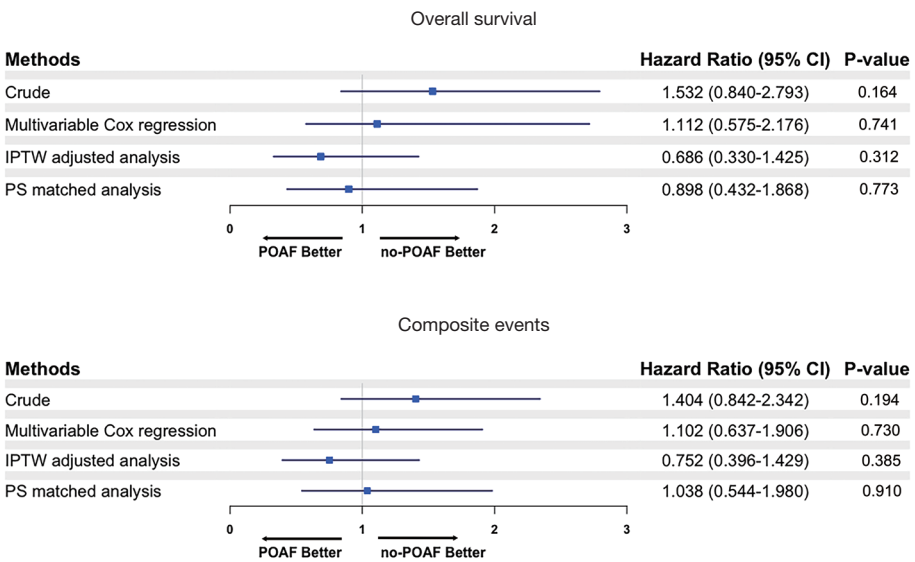

Figure 4 Forest plot of hazard ratios for late clinical outcomes by various methods. Forest plot of hazard ratios for overall survival and composite events including mortality, bleeding, and cerebrovascular event between POAF and no-POAF patients after off-pump coronary bypass grafting by various methods; Univariable Cox regression (Crude), Multivariate Cox regression, Inverse probability of treatment weighting adjusted analysis, Propensity score matched analysis. POAF, postoperative atrial fibrillation.

without anticoagulation or amiodarone medication after discharge, the risk of mid-term outcomes (overall mortality and composite event) of the POAF and no-POAF groups did not differ significantly.

Adverse effects of POAF following CABG have been reported. A recent meta-analysis showed that POAF associated with reduced 10-year survival rates, and significantly higher 30-day mortality, stroke, respiratory failure, pneumonia and hospitalization (1). Villareal *et al.* showed results of 6,475 patients who underwent CABG

Table 4 Multivariable logistic regression for risk factor analysis of POAF

Variables	OR	95% CI	P value
Age	1.054	1.027–1.083	<0.001
Unstable angina	1.805	1.036–3.098	0.034
PTCA history	2.003	1.172–3.384	0.010
LA enlargement	2.141	1.312–3.560	0.003
Dyslipidemia	0.472	0.250–0.844	0.014

POAF, postoperative atrial fibrillation; OR, odds ratio; CI, confidence interval; PTCA, percutaneous transluminal coronary angioplasty; LA, left atrial.

(994 POAF and 5,481 no-POAF) showed that POAF was an independent predictor of long-term mortality (4). In the study by Lee at al. on 1,171 patients who underwent CABG (244 POAF and 927 no POAF), POAF was suggested to be an independent predictor of long-term AF (HR 4.99, 95% CI: 1.68–14.84, P=0.004), and long-term survival was shown to be worse in POAF patients (P=0.01) (5).

However, Levy *et al*. provided a deep insight regarding research conducted on POAF, suggesting that residual confounders may exist in papers reporting on the hazards of POAF (6). Predictors of POAF such as older age, poor comorbidity and intra-aortic balloon pumps requirement, seem to overlap with those of long-term mortality; i.e., patients who developed POAF tend to be sicker than those without POAF. Therefore, determining the effects of POAF on long-term mortality is inherently challenging with susceptibility to selection bias. Moreover, advanced age has been the only established predictor of POAF; other suggested predictors, including the use of cardiopulmonary bypass in CABG, have not been consistent across papers. Another uncertainty involves the mechanisms in which POAF contributes to long-term adverse outcomes. POAF has been suggested as a risk factor for long-term AF and long-term mortality (4,5). Although the authors performed adjustments or matching in these studies, POAF patients had higher postoperative complication rates and longer hospital stays. In addition, the onset of AF after surgery, the specific treatment methods of AF, sinus conversion rates and recurrence rates were not described. Recent study by Benedetto *et al*. also suggested POAF increased risks of late CVA and mortality after isolated CABG. However, the information on the duration of POAF, sinus rhythm conversion rate, recurrence of AF was not described in the study. In addition, patients with or without POAF showed different preoperative characteristics. Early postoperative complications were not described. Patients in each group had different medications at discharge, especially warfarin. And, non-cardiovascular causes of death were higher than cardiovascular causes (15). Furthermore, it were not mentioned and analyzed in the study, various operative (on-pump or off-pump) and graft (use of vein or not, aorta-no touch or not) strategies were applied in the trial (16). Therefore, it is difficult to analyze the association of POAF with long-term AF and long-term mortality. Whereas, in our study, we tried to inform the onset of POAF and the rate of restoration of sinus rhythm clearly. By applying our protocol-based treatment regimen, the duration of POAF following OPCAB was a few days to a few hours (mean 1.6±2.4 days). Sinus conversion rate was high (97.9%) and prevalence of persistent AF was low (n=3). Thus, acute POAF might be a potential risk for early stroke and complications. However, the contributing effects of POAF on long-term adverse outcomes remain uncertain and need to be investigated.

Multivariable analysis of our study showed that age, diabetes, unstable angina, PTCA history, and large LA diameter represent the risk factors for POAF. As suggested previously (6), these variables may be consistent with possible risk factors for late adverse events. However, sinus rhythm conversion was achieved in most of our POAF patients, and the follow-up course and nature of the disease may be identical with those without POAF. Therefore, such risk factors may not be contributable for late outcomes. Further investigations for the association of risk factors for POAF-associated long-term outcomes are hence required.

Dyslipidemia revealed as preventive factor for POAF. Several studies suggested that dyslipidemia was inverse associations with AF (17-19). The proposed mechanisms include alterations in cardiac ion channel handling by cholesterol and confounding by hyperthyroidism status and by cardiac load through natriuretic peptides. However, inverse association of dyslipidemia and AF remains uncertain (17). Further studies would be required to evaluate the impacts of dyslipidemia on POAF.

The optimal treatment for POAF has not yet been established. Current guidelines for AF have recommended beta-blockers and calcium channel blockers, but consensus for both therapeutic (11) and prophylactic (12) regimens has not been reached. In addition, guidelines have suggested the consideration of not only sinus rhythm restoration, but also of rate control with anticoagulation therapy (both Class IIa recommendation) (11,12). A recent multi-center randomized

controlled trial also showed no difference in clinical outcomes between rhythm control and rate control strategies after cardiac surgery (20). However, these suggestions were not specific for POAF after CABG, but for POAF after cardiac surgery which can have different perioperative courses such as the use of cardiopulmonary bypass (CPB) and administration of warfarin after valve operation. Nevertheless, guidelines for CPB have mentioned the risk and treatment requirements for POAF after CABG, although no specific recommendations have been described (21,22). Our institutional protocol focuses on rhythm control (achieving restoration of sinus rhythm). Patients with documented AF were administrated with amiodarone, and the length of administration was determined by the restoration of sinus rhythm. This protocol worked well in patients with POAF after OPCAB, with up to 98% rate of sinus rhythm restoration achieved in about 2 days (mean 1.6±2.4 days). Long-term outcomes did not differ between the POAF and no-POAF groups. Although similar outcomes between rhythm control and rate control of POAF have been suggested (20), guidelines have warned that POAF has associated with a two-fold increase in cardiovascular mortality, future AF and ischemic stroke compared to patients with sinus rhythm (11). Therefore, we assumed that early sinus rhythm restoration may have contributed to the notable late-outcomes in our study.

Amiodarone is one of the most commonly used medication for AF. However, it may adversely affect various organ systems, including the hepatic, gastrointestinal, pulmonary, thyroid and neurologic systems, the skin and eyes, as well as cause bradycardia (23). Therefore, we proposed the use of lower amiodarone dosages. We used relatively lower doses of amiodarone compared with those used in general practice (20,24), since POAF following OPCAB may be due to increased susceptibility to the triggers of AF after surgery, rather than due to structural substrates present before surgery or surgical trauma (9).

Anticoagulation treatment for POAF is important to prevent thromboembolic events. However, no consensus regimens have been proposed among current guidelines (11-13). The American Association for Thoracic Surgery guidelines have suggested 4–6 weeks of anticoagulation for POAF even after restoration to sinus rhythm (Class I recommendation) (13), to prevent the risk of thromboembolic events due to recurrent AF and LA stunning. Despite these concerns, cardioversion after recent-onset AF (AF duration within 48 hours) did not impair LA velocity (25). Therefore, rapid pharmacological cardioversions may not increase the risk of embolism or recurrent AF. In addition, a proper anticoagulation regimen for POAF after CABG has not been established. At least one antiplatelet therapy is required after CABG. Therefore, the addition of anticoagulants can increase bleeding risks. Investigations on the appropriate regimens for POAF after CABG (such as aspirin and warfarin, or aspirin and NOAC, or dual antiplatelet therapy) are therefore warranted.

Our institutional protocol involves early rhythm control strategies using amiodarone, which achieved successful pharmacological cardioversion in 98% of POAF patients within a mean of 2 days, and with most patients discharged with sinus rhythm. Additional NOAC or warfarin medications were not required, except for antiplatelet agents for coronary diseases. During follow-up, no significant differences in adverse events were observed between POAF and no-POAF patients.

Our study has several limitations. First, it was a retrospective, non-randomized study from a single institution. Therefore, it may have been influenced by selection bias. We therefore performed IPTW adjustment and propensity score matching analyses to compensate for potential biases in patient selection. However, an unidentified confounding bias may have influenced our results. A prospective, randomized, multicenter study would still be necessary. Second, our study only included patients who underwent OPCAB. Our main institutional operative strategy for CABG is via the off-pump technique to ensure homogeneity in the characteristics of our study cohort. However, our results may not be generalizable to patients who underwent CABG with CPB or other cardiac surgeries. Third, we did not perform Holter study during the follow-up period. Therefore, ECGs alone may not capture the full burden of AF.

Conclusions

Our institutional, amiodarone-based treatment protocol for rapid pharmacological cardioversion of POAF resulted in a high sinus rhythm conversion rate (97.9%). The course of POAF after OPCAB are usually benign, and the persistence of AF is rare. Rates of late adverse events, including stroke, were low even without anticoagulation. Regarding the absence of optimal treatment and anticoagulation guidelines for POAF after OPCAB, amiodarone-based treatment protocol may be considered a useful option.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the hospital's institutional review board, which waived the requirement for patient consent (IRB no: 2020-0643, approval date: 11-18-2020).

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Supplementary

Table S1 Baseline characteristics after propensity score-matching

Variables	No-POAF (n=91)	POAF (n=91)	P value	SMD
Age, years	66.6±9.4[a]	67.5±8.6[a]	0.410	0.105
	68.0 (60.5-73.0)[b]	68.0 (62.0-73.5)[b]		
Sex, female, n (%)	26 (28.6)	24 (26.4)	0.874	0.049
BSA, m^2	1.71±0.16[a]	1.71±0.18[a]	0.897	0.018
	1.69 (1.60-1.82)[b]	1.74 (1.58-1.85)[b]		
BMI, kg/m^2	24.6±2.3[a]	24.7±2.7[a]	0.788	0.038
	24.7 (23.0-25.9)[b]	24.3 (23.0-26.6)[b]		
Hypertension, n (%)	60 (65.9)	63 (69.2)	0.742	0.070
Diabetes mellitus, n (%)	52 (57.1)	55 (60.4)	0.749	0.067
Stroke, n (%)	58 (63.7)	61 (67.0)	0.749	0.067
Dyslipidemia, n (%)	19 (20.9)	16 (17.6)	0.663	0.084
NYHA class III–IV, n (%)	4 (4.4)	4 (4.4)	>0.999	<0.001
CCS class 4, n (%)	8 (8.8)	6 (6.6)	0.789	0.083
Preoperative beta-blocker use, n (%)	66 (72.5)	68 (74.7)	0.871	0.050
Hyperthyroidism, n (%)	2 (2.2)	0 (0.0)	0.477	0.212
Chronic renal failure, n (%)	4 (4.4)	6 (6.6)	0.752	0.097
COPD, n (%)	3 (3.3)	4 (4.4)	>0.999	0.057
Interstitial pneumonia, n (%)	2 (2.2)	0 (0.0)	0.477	0.212
CHA_2DS_2-VAS_C score	2.9±1.5[a]	3.0±1.4[a]	0.702	0.053
	3.0 (2.0-4.0)[b]	3.0 (2.0-4.0)[b]		
PAOD, n (%)	33 (36.3)	33 (36.3)	>0.999	<0.001
Cancer, n (%)	4 (4.4)	7 (7.7)	0.505	0.139
OMI history, n (%)	9 (9.9)	10 (11.0)	>0.999	0.036
PTCA history, n (%)	25 (27.5)	29 (31.9)	0.627	0.096
EF<40, n (%)	17 (18.7)	16 (17.6)	>0.999	0.029
LA enlargement, n (%)	61 (67.0)	62 (68.1)	>0.999	0.023

[a]Mean ± standard deviation; [b]Median (Q1–Q3). POAF, postoperative atrial fibrillation; SMD, standardized mean difference; BSA, body surface area; BMI, body mass index; NYHA, New York Heart Association; CCS, Canadian Cardiovascular Society; COPD, chronic obstructive pulmonary disease; POAD, peripheral occlusive arterial disease; OMI, old myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; EF, ejection fraction; LA, left atrial.

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Table S2 Operative data after propensity score-matching

Variables	No-POAF (n=91)	POAF (n=91)	P value	SMD
Unstable angina, n (%)	21 (23.1)	25 (27.5)	0.556	0.101
Stable angina, n (%)	26 (28.6)	27 (29.7)	>0.999	0.024
NSTEMI, n (%)	44 (48.4)	39 (42.9)	0.551	0.110
STEMI, n (%)	0 (0.0)	0 (0.0)	NA	<0.001
Triple vessel disease, n (%)	65 (71.4)	67 (73.6)	0.860	0.049
Left main disease, n (%)	24 (26.4)	28 (30.8)	0.627	0.097
Emergency operation, n (%)	0 (0.0)	0 (0.0)	NA	<0.001
No. of anastomosis, n (%)	3.5±1.0	3.5±1.1	0.875	0.022
Preoperative IABP support, n (%)	0 (0.0)	1 (1.1)	>0.999	0.149
Intraoperative IABP insertion, n (%)	5 (5.5)	4 (4.4)	>0.999	0.051

POAF, postoperative atrial fibrillation; SMD, standardized mean difference; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; IABP, intra-aortic balloon pump.

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