Gender Difference in the Long-Term Clinical Implications of New-Onset Atrial Fibrillation after Coronary Artery Bypass Grafting

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Purpose: New-onset postoperative atrial fibrillation (POAF) is associated with poor short- and long-term outcomes after isolated coronary artery bypass graft (CABG) surgery. This study evaluated gender differences in the long-term clinical implications of POAF.
Materials and Methods: After propensity score matching, a gender-based comparison of long-term (>1 year) newly developed atrial fibrillation (LTAF) and mortality between 1664 (480 females) consecutive patients with (POAF) and without POAF (no-POAF) who had undergone CABG was performed.
Results: During a follow-up of 49±28 months, cumulative survival free of LTAF was lower in the POAF group than in the no-POAF group for both males (92.1% vs. 98.2%, *p*<0.001) and females (84.1% vs. 98.0%, *p*<0.001). However, female patients with POAF more frequently developed LTAF than male POAF patients (13.9 % vs. 6.9%, *p*=0.049). In multivariate analysis, POAF was a significant predictor of LTAF among males [hazard ratio (HR) 4.91; 95% confidence interval (CI) 1.22–19.79, *p*=0.031] and females (HR 16.50; 95% CI 4.79–56.78; *p*<0.001). POAF was a predictor of long-term mortality among females (adjusted HR 3.96; 95% CI 1.13–13.87, *p*=0.033), but not among males.
Conclusion: Although POAF was related to LTAF in both genders, cumulative survival free of LTAF was poorer among females than among males. Additionally, a significant correlation with long-term mortality after CABG was observed among female patients with POAF.

Key Words: Atrial fibrillation, coronary artery bypass graft, postoperative complications, survival, gender

INTRODUCTION

The incidence of new-onset postoperative atrial fibrillation (POAF) ranges from 25 to 40% after coronary artery bypass graft (CABG) surgery and up to 62% after a combined CABG

and valve procedure.[1-3] POAF has been shown to be associated with an increased risk of postoperative stroke and an increased length of hospital stay.[4] As the demographic profile of patients undergoing CABG shifts toward adults of older age, the incidence of POAF will increase, because the frequency of this complication sharply increases with age.[5] Although POAF has been commonly regarded as a benign, transient, and self-limited complication after cardiac surgery, it has been found to be associated with perioperative myocardial infarction, renal failure, cognitive dysfunction, infective complications, higher readmission rate, and increasing medical costs.[5-8] It has been demonstrated that long-term mortality is increased in patients with an episode of POAF because of an increased risk of cardiovascular death.[7,9] Recently, we found that POAF is independently associated with long-term (>1 year) newly developed atrial fibrillation (LTAF) and mortality.[10] However, the

gender differences in the long-term prognosis and the effect of POAF has not been fully elucidated. Therefore, we aimed to investigate gender differences in the long-term prognosis and the effect of POAF.

MATERIALS AND METHODS

Patients

The study protocol was approved by the Institutional Review Board of Severance Cardiovascular Hospital, Seoul, Korea and complied with the Declaration of Helsinki. We used International Statistical Classification of Disease and Related Health Problems, 10th revision, codes to identify 1810 consecutive adult patients who underwent an isolated CABG at the Severance Cardiovascular Hospital, Yonsei University Health System, between January 2005 and December 2011. Patients with a history of atrial fibrillation (AF) (n=94) or emergency surgery (n=38) and those who had insufficient medical records (n=8) were excluded. Additionally, patients who died within 10 days after surgery (n=6) were excluded. Finally, we enrolled 1664 patients who were divided into two groups based on their gender (females, n=480 and males, n=1184) (Fig. 1).

We obtained detailed information regarding patient demographics, preoperative risk factors, operative details, postoperative hospital courses, and morbidity and mortality outcomes from the hospital database and through telephone calls. Renal dysfunction was defined as a serum creatinine level of >1.5 mg/dL for at least 3 months and/or the presence of kidney
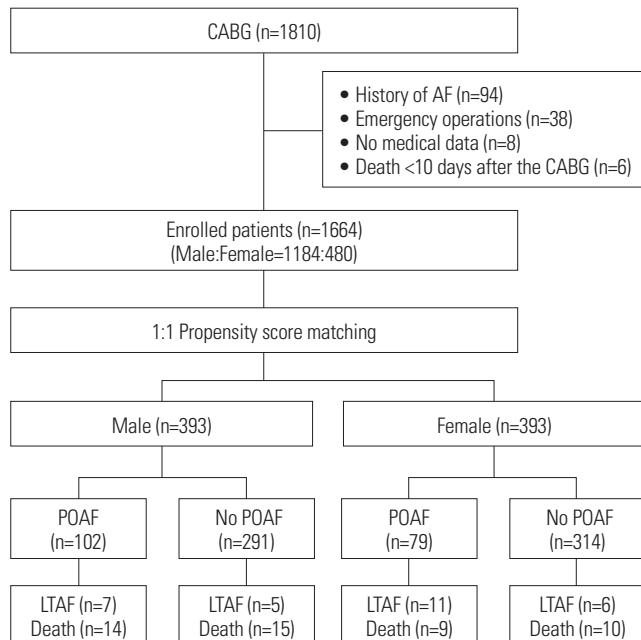
damage (persistent microalbuminuria, proteinuria, or hematuria after the exclusion of urological causes or structural abnormalities detected on kidney imaging tests). Renal failure was defined as a serum creatinine elevation of >three times the baseline or a serum creatinine level of >2.0 mg/dL. Obesity was defined as a body mass index ≥30 kg/m². Significant coronary artery disease was defined as visualized luminal narrowing of each vessel of >50%. Hypercholesterolemia was defined as patients having abnormal preoperative lipid profiles according to the American Heart Association Guidelines or being previously diagnosed and treated by physicians. Before the surgery, the volume of the left atrium (LA) was measured using echocardiography, through the biplane Simpson's method; the LA volume index was calculated as the LA volume/body surface area (mL/m²). Diastolic dysfunction was defined as an E to e' ratio of >15 on echocardiography.

Management and follow-up

POAF was defined as newly developed AF documented using electrocardiography (ECG) or continuous monitoring during the first 10 days after surgery. To restore sinus rhythm in most patients within 24 h after the onset of POAF, electrolyte replacement, antiarrhythmic drugs (AADs), or electrical cardioversion was applied. Patients with AF who were discharged to their home were maintained on warfarin (in the absence of any contraindications) and usually referred for cardioversion after 3–6 weeks. In the absence of any evidence of AF recurrence, AADs were stopped, and this decision was left to the discretion of the treating physician. All patients were followed up with a clinical examination and ECG at 2 weeks, 1 month, 3 months, and every 6 months thereafter. In case of symptom recurrence between follow-up visits, patients were evaluated with a clinical examination, ECG, and Holter monitoring.

Outcomes, including mortality, stroke, renal failure, and AF, were evaluated in the follow-up period. Recurrent AF was defined as any recurrent AF documented in the patients' medical and ECG records. In this study, AF that occurred within 1 year after surgery was not included under LTAF (Supplementary Table 1, only online). Additionally, mortality was defined as death from any cause that occurred at any time after hospital discharge. There were no missing data on preoperative patient characteristics in this study. Long-term follow-up (>1 year) was achieved in 92.3% (1536/1664) of the patients.

Statistical analysis

All continuous data are expressed as a mean±standard deviation (SD), and categorical data are reported as an absolute number or percentage. Student's unpaired t-test or Welch's t-test was adopted based on variance tests for the distribution. Fisher's exact test or Pearson's chi-squared test with Yates' continuity correction (expected frequency >5) was used to compare groups of categorical variables. All calculated p-values were two-sided, and p-values of <0.05 were considered statistically

Fig. 1. Flow diagram and follow-up for new-onset POAF, LTAF, and mortality. CABG, coronary artery bypass graft; AF, atrial fibrillation; POAF, postoperative atrial fibrillation; LTAF, long-term (>1 year) newly developed atrial fibrillation.

significant. Statistical analyzes were performed using R Statistical Software, version 3.0.1 (Foundation for Statistical Computing, Vienna, Austria).

The clinical characteristic variables were compared between males and females before matching, which showed significant differences. To reduce the effect of selection bias and heterogeneity of the gender subgroup in this retrospective cohort study, estimated propensity scores were used to match the patients according to gender, using R Statistical Software with the MatchIt package.[11] Propensity scores were computed for each of the patients using a logistic regression model comprising all 20 variables of baseline characteristics that could have been confounders of AF, such as age, stroke, chronic obstructive pulmonary disease (COPD), renal dysfunction, diabetes, hypercholesterolemia, hypertension, congestive heart failure, peripheral artery occlusive disease, history of percutaneous coronary intervention, recent myocardial infarction, three-vessel disease, left main disease, left ventricular ejection fraction, E/e' ratio, LA volume index, and preoperative medications. A nearest-neighbor matching algorithm was used to match participants, with matches occurring if the difference in the logits of the propensity scores was >0.2 times the SD of the scores. The propensity score model was well calibrated (Hosmer-Lemeshow goodness-of-fit test, p=0.3562), with good discrimination (Harrell's c index=0.76). Based on the propensi-

ty scores, 393 male patients were matched to 393 female patients (Fig. 1).

A Kaplan-Meier estimate of survival was obtained to investigate the differences in mortality and survival free from AF between the male and female groups. Cox proportional hazard models were used to test the significance of POAF in survival free from LTAF and long-term mortality. We selected the most appropriate model according to the Akaike Information Criteria and principal of parsimony. The assessment of model adequacy was confirmed using scaled Schoenfeld residuals for each variable interaction with time (log). The hazard ratios (HRs), 95% confidence intervals (CIs), and p-values were also reported. In this study, the estimated AF incidence differences between the study groups might have been biased because patients who died during the follow-up might not have survived long enough to develop AF. Therefore, we calculated the HR of competing risk regression using death as a competing event.

RESULTS

Gender differences in pre- and postoperative characteristics, including POAF
Among 1664 enrolled patients, 480 (28.8%) were female, and >90% of the patients had undergone off-pump surgery in this

Table 1. Preoperative Characteristics and Operation Data Stratified by Gender

Variable	Overall series			Propensity score-matched pairs		
	Male (n=1184)	Female (n=480)	*p* value	Male (n=393)	Female (n=393)	*p* value
Age (yr, mean±SD)	63±9	66±7	<0.001	66±8	66±7	0.731
Stroke, n (%)	28 (2.4)	7 (1.5)	0.328	9 (2.3)	7 (1.8)	0.801
Chronic obstructive pulmonary disease, n (%)	30 (2.5)	8 (1.7)	0.373	7 (1.8)	8 (2.0)	1.000
Renal dysfunction, n (%)	122 (10.3)	26 (5.4)	0.002	27 (6.9)	21 (5.3)	0.456
Diabetes mellitus, n (%)	461 (38.9)	231 (48.1)	0.001	173 (44.0)	182 (46.3)	0.566
Hypercholesterolemia, n (%)	686 (57.9)	252 (52.5)	0.049	202 (51.4)	214 (54.5)	0.432
Hypertension, n (%)	774 (65.4)	363 (75.6)	<0.001	285 (72.5)	290 (73.8)	0.747
Congestive heart failure, n (%)	68 (5.7)	33 (6.9)	0.446	31 (7.9)	25 (6.4)	0.488
Peripheral vascular disease, n (%)	92 (7.8)	21 (4.4)	0.017	17 (4.3)	18 (4.6)	1.000
Recent myocardial infarction, n (%)	168 (14.2)	58 (12.1)	0.291	55 (14.0)	42 (10.7)	0.193
Three-vessel disease, n (%)	792 (66.9)	320 (66.7)	0.975	271 (69.0)	261 (66.4)	0.492
Left main disease, n (%)	271 (22.9)	87 (18.1)	0.038	69 (17.6)	70 (17.8)	1.000
LV ejection fraction (%)	55.0±14.2	59.6±14.0	<0.001	58.4±14.0	59.1±14.0	0.490
E/e'	13.0±5.5	16.2±7.1	<0.001	14.9±6.5	14.7±5.3	0.624
LA volume index (mL/m²)	26.9±9.4	29.7±9.9	<0.001	30.0±10.5	28.4±9.2	0.382
Medication, n (%)						
Statin	460 (38.9)	194 (40.4)	0.591	155 (39.4)	159 (40.5)	0.827
Beta-blocker	583 (49.2)	256 (53.3)	0.145	196 (49.9)	198 (50.4)	0.943
ACEI+ARB	400 (33.8)	184 (38.3)	0.088	143 (36.4)	142 (36.1)	1.000
Calcium antagonist	433 (36.6)	192 (40.0)	0.210	152 (38.7)	155 (39.4)	0.884
POAF	306 (25.8)	107 (22.3)	0.145	102 (26.0)	79 (20.1)	0.062

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blocker; LA, left atrial; LV, left ventricular; POAF, postoperative atrial fibrillation; SD, standard deviation.

study. The preoperative characteristics and operative data of the male and female groups are presented in Table 1. Compared with the male patients, the female patients were older (63±9 years vs. 66±7 years, *p*<0.001) and more frequently had diabetes (38.9% vs. 48.1%, *p*=0.001), hypertension (65.4% vs. 75.6%, *p*<0.001), a higher E/e' ratio (13.0±5.5 vs. 16.2±7.1, *p*<0.001), and a larger LA volume index (26.9±9.4 mL/m² vs. 29.7±9.9 mL/m², *p*<0.001). However, renal dysfunction (10.3% vs. 5.4%, *p*=0.002), peripheral vascular disease (7.8% vs. 4.4%, *p*=0.017), and hypercholesterolemia (57.9% vs. 52.5%, *p*=0.049) were more common among the male patients. Except for POAF, no gender differences were found in the postoperative data of both overall and propensity score-matched pairs (Supplementary Table 1, only online). The incidence of POAF exhibited no statistical differences between males and females among the overall patients. However, after propensity score matching, the male group exhibited a trend of higher POAF incidence (26.0% vs. 20.1%, *p*=0.062), compared with the female group.

Gender differences in the preoperative characteristics stratified by POAF

Table 2 shows the preoperative characteristics and operative data after a propensity score matching stratified by POAF. Among both genders, the POAF group was older and more frequently had a higher E/e' ratio and a larger LA volume index

(all *p*<0.050).

Gender differences in the perioperative data stratified by POAF

In the female patients, POAF was related to increased hospitalization duration (16±12 days vs. 28±51 days, *p*=0.049). Among the male patients, postoperative complications, including pneumonia (0.3% vs. 6.9%, *p*<0.001) and stroke (1.0% vs. 4.9%, *p*=0.031), were more frequently observed in the POAF group than in the no-POAF group (Table 3). Among both genders, digoxin and amiodarone were more commonly used in the POAF group than in the no-POAF group (all *p*<0.050).

Gender differences in the incidence and risk factors for LTAF

During follow-up of 49±28 months, the POAF group exhibited higher overall AF (2.2% vs. 21.1%, *p*<0.001) and LTAF (1.8% vs. 9.2%, *p*<0.001) rates than the no-POAF group in all patients. After propensity score matching, the POAF group had a higher incidence of overall AF and LTAF than the no-POAF group among both genders (all *p*<0.001). Fig. 2 shows the Kaplan-Meier survival curves for LTAF, according to the presence of POAF in the overall (Fig. 2A) and propensity score-matched patients (Fig. 2B). Regarding the propensity score-matched pairs, the POAF group had a lower cumulative survival free of

Table 2. Preoperative Characteristics after Propensity Score Matching Stratified by POAF

Variable	Males (n=393)			Females (n=393)		
	No-POAF (n=291)	POAF (n=102)	*p* value	No-POAF (n=314)	POAF (n=79)	*p* value
Age (yr, mean±SD)	65±8	69±7	<0.001	65±7	68±7	0.001
Stroke, n (%)	8 (2.7)	1 (1.0)	0.520	6 (1.9)	1 (1.3)	1.000
Chronic obstructive pulmonary disease, n (%)	2 (0.7)	5 (4.9)	0.020	4 (1.3)	4 (5.1)	0.055
Renal dysfunction, n (%)	17 (5.8)	10 (9.8)	0.257	18 (5.7)	3 (3.8)	0.686
Diabetes mellitus, n (%)	125 (43.0)	48 (47.1)	0.547	140 (44.6)	42 (53.2)	0.215
Hypercholesterolemia, n (%)	161 (55.3)	41 (40.2)	0.012	176 (56.1)	38 (21)	0.254
Hypertension, n (%)	211 (72.5)	74 (72.5)	1.000	230 (73.2)	60 (75.9)	0.730
Congestive heart failure, n (%)	25 (8.6)	6 (5.9)	0.509	20 (6.4)	5 (6.3)	1.000
Peripheral vascular disease, n (%)	11 (3.8)	6 (5.9)	0.538	13 (4.1)	5 (6.3)	0.377
History of PCI, n (%)	42 (14.4)	17 (16.7)	0.702	41 (13.1)	12 (15.2)	0.755
Recent myocardial infarction, n (%)	34 (11.7)	21 (20.6)	0.039	29 (9.2)	13 (16.5)	0.098
Three-vessel disease, n (%)	195 (67.0)	76 (74.5)	0.199	207 (65.9)	54 (68.4)	0.783
Left main disease, n (%)	51 (17.5)	18 (17.6)	1.000	53 (16.9)	17 (21.5)	0.424
LV ejection fraction (%)	59.0±13.6	56.6±14.9	0.126	59.3±13.6	58.0±15.6	0.447
E/e'	14.5±6.1	16.2±7.5	0.047	14.5±5.4	15.8±5.0	0.049
LA volume index (mL/m²)	27.3±9.5	33.8±11.7	<0.001	27.3±8.5	32.6±10.5	<0.001
Medication, n (%)						
Statin	117 (40.2)	38 (37.3)	0.684	121 (38.5)	39 (48.1)	0.156
Beta-blocker	138 (47.4)	58 (56.9)	0.127	148 (47.1)	50 (63.3)	0.015
ACEI+ARB	104 (35.7)	39 (38.2)	0.740	104 (33.1)	38 (48.1)	0.019
Calcium antagonist	106 (36.4)	46 (45.1)	0.153	124 (39.5)	31 (39.2)	1.000

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blocker; LA, left atrial; LV, left ventricular; PCI, percutaneous coronary intervention; POAF, postoperative atrial fibrillation; SD, standard deviation.

Table 3. Operative Data after Propensity Score Matching Stratified by POAF

Variable	Males (n=393)			Females (n=393)		
	No-POAF (n=291)	POAF (n=102)	*p* value	No-POAF (n=314)	POAF (n=79)	*p* value
On-pump procedure, n (%)	19 (6.5)	7 (6.9)	1.000	14 (4.5)	8 (10.1)	0.059
Total pump time (min, mean±SD)	100±31	87±36	0.373	112±29	95±36	0.223
Aortic cross-clamp time (min, mean±SD)	59±36	53±43	0.707	80±40	58±52	0.280
Number of distal anastomoses (mean±SD)	3.2±0.8	3.1±0.8	0.475	3.1±0.8	3.1±0.7	0.741
Internal mammary artery graft used, n (%)	288 (99.0)	100 (98.0)	0.608	308 (98.1)	78 (98.7)	1.000
Radial artery graft used, n (%)	202 (69.4)	66 (64.7)	0.450	214 (68.2)	56 (70.9)	0.739
Perioperative pacing, n (%)	59 (20.3)	18 (17.6)	0.667	61 (19.4)	14 (17.7)	0.854
Postoperative medication, n (%)						
Beta-blocker	276 (94.8)	96 (94.1)	0.980	298 (94.9)	76 (96.2)	0.776
Digoxin	6 (2.1)	26 (25.5)	<0.001	7 (2.2)	25 (31.6)	<0.001
Amiodarone	2 (0.7)	10 (9.8)	<0.001	3 (1.0)	11 (13.9)	<0.001
Calcium antagonist	258 (88.7)	86 (84.3)	0.332	273 (86.9)	65 (82.3)	0.375
Tambocor	0 (0)	2 (2.0)	0.067	0 (0)	0 (0)	
Hospitalization duration (days)	16±17	19±12	0.206	16±12	28±51	0.049
Discharge medication, n (%)						
Beta-blocker	283 (97.3)	97 (95.1)	0.335	300 (95.5)	75 (94.9)	0.767
Digoxin	4 (1.4)	18 (5.7)	<0.001	2 (0.6)	15 (19.0)	<0.001
Amiodarone	1 (0.3)	6 (5.9)	0.002	1 (0.3)	5 (6.3)	<0.001
Calcium antagonist	229 (78.7)	75 (73.5)	0.350	261 (83.1)	62 (78.5)	0.424
Tambocor	0 (0)	1 (1.0)	0.259	0 (0)	0 (0)	
Postoperative complications, n (%)						
Pneumonia	1 (0.3)	7 (6.9)	<0.001	5 (1.6)	3 (3.8)	0.204
Wound infection	4 (1.4)	1 (1.0)	1.000	6 (1.9)	3 (3.8)	0.393
Gastrointestinal complication	11 (3.8)	3 (2.9)	1.000	7 (2.2)	2 (2.5)	1.000
Renal failure	18 (6.2)	13 (12.7)	0.057	17 (5.4)	8 (10.1)	0.202
Stroke	3 (1.0)	5 (4.9)	0.031	3 (1.0)	1 (1.3)	1.000

POAF, postoperative atrial fibrillation; SD, standard deviation.

LTAF than the no-POAF group among male (92.1% vs. 98.2%, *p*<0.001) and female (84.1% vs. 98.0%, *p*<0.001) genders. Furthermore, female patients with POAF more frequently had LTAF than did male patients with POAF, according to Kaplan-Meier survival analysis (6.9% vs. 13.9 %, *p*=0.049) (Fig. 2B).

Table 4 presents the multivariate adjusted HRs of LTAF associated with POAF. In the competing risk model, patients with POAF had a higher risk of LTAF among both male (adjusted HR 4.91; 95% CI 1.22–19.79; *p*=0.031) and female (adjusted HR 16.50; 95% CI 4.79–56.78; *p*<0.001) genders. Additionally, LTAF was associated with COPD in both male (adjusted HR 17.68; 95% CI 1.39–224.58; *p*=0.032) and female patients (adjusted HR 12.71; 95% CI 1.81–89.06; *p*=0.011). Furthermore, congestive heart failure (adjusted HR 16.08; 95% CI 3.17–81.56; *p*<0.001) and renal dysfunction (adjusted HR 14.16; 95% CI 3.62–55.36; *p*<0.001) were significant predictors of LTAF among females, and postoperative beta-blocker usage (adjusted HR 0.05; 95% CI 0.01–0.20; *p*<0.001) was a significant predictor of LTAF among males.

Gender differences in the incidence and risk factors for long-term (>1 year) mortality

During follow-up, the POAF group had a higher overall mortality (3.5% vs. 10.7%, *p*<0.001) than the no-POAF group in all the patients. Fig. 3 shows the Kaplan-Meier survival curves for long-term mortality, according to the presence of POAF in the overall (Fig. 3A) and propensity score-matched (Fig. 3B) patients. After propensity score matching, the POAF group had a lower cumulative survival free of long-term mortality than the no-POAF group among both genders (all *p*<0.05). Unlike patients with LTAF, there were no significant differences in long-term mortality between male and female patients with POAF (13.7% vs. 11.4%, *p*=0.922), according to the Kaplan-Meier survival analysis.

Table 4 presents the multivariate adjusted HRs for long-term mortality associated with POAF. In the Cox proportional hazards model, POAF was a risk factor for long-term mortality among females (adjusted HR 3.96; 95% CI 1.13–13.87; *p*=0.033) but not among males. Diabetes was a significant risk factor for long-term mortality among both male (adjusted HR 3.04; 95% CI 1.05–8.79; *p*=0.043) and female (adjusted HR 4.14;
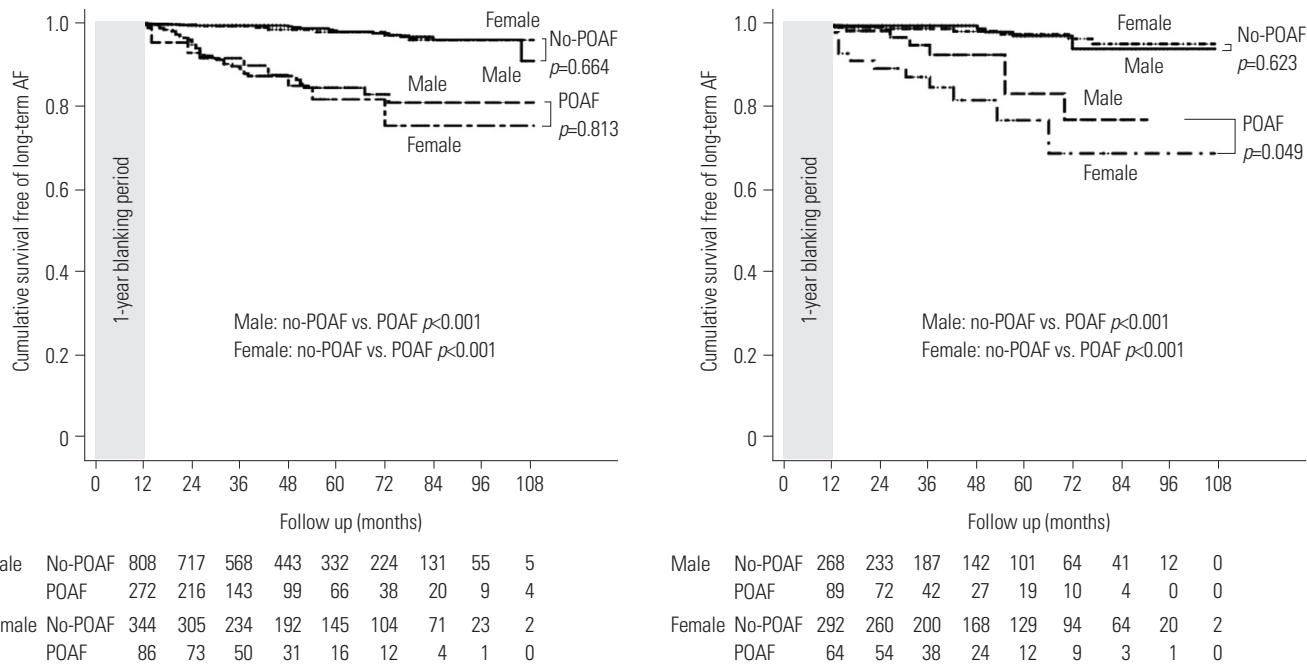
Fig. 2. Kaplan-Meier curves for survival free of LTAF according to the presence of POAF in the overall (A) and propensity score-matched patients (B). The left and right panels show the survival curves in the male and female patients according to POAF, respectively. The POAF group had a lower cumulative survival free of LTAF than the no-POAF group among both the overall and propensity score-matched patients (all $p<0.001$). The female POAF group had a lower cumulative survival free of LTAF than the male POAF group among the propensity score-matched patients ($p=0.049$). LTAF, long-term (>1 year) newly developed atrial fibrillation; POAF, postoperative atrial fibrillation; AF, atrial fibrillation.

Table 4. Effect of Gender on LTAF or Mortality According to Significant Risk Factors in a Multivariate Regression Model

Risk factors	Male		Female	
	Adjusted HR (95% CI)	*p* value	Adjusted HR (95% CI)	*p* value
LTAF*				
POAF	4.91 (1.22–19.79)	0.031	16.50 (4.79–56.78)	<0.001
Congestive heart failure	1.97 (0.25–15.50)	0.516	16.08 (3.17–81.56)	<0.001
Renal dysfunction	0.67 (0.02–16.05)	0.813	14.16 (3.62–55.36)	<0.001
Chronic obstructive pulmonary disease	17.68 (1.39–224.58)	0.032	12.71 (1.81–89.06)	0.011
Postoperative beta-blocker usage	0.05 (0.01–0.20)	<0.001	3.66 (0.07–192.20)	0.524
Long-term mortality†				
POAF	2.26 (0.80–6.33)	0.117	3.96 (1.13–13.87)	0.033
Diabetes mellitus	3.04 (1.05–8.79)	0.043	4.14 (1.00–17.12)	0.049

POAF, postoperative atrial fibrillation; LTAF, long-term (>1 year) newly developed atrial fibrillation; HR, hazard ratio; CI, confidence interval.
*Adjusted for age, POAF, ejection fraction, left atrial volume index, on-pump surgery, chronic obstructive pulmonary disease, congestive heart failure, renal dysfunction, recent myocardial infarction, postoperative beta-blocker usage, and the propensity score, †Adjusted for age, POAF, ejection fraction, left atrial volume index, chronic obstructive pulmonary disease, hypercholesterolemia, diabetes mellitus, recent myocardial infarction, renal dysfunction, and the propensity score.

95% CI 1.00–17.12; *p*=0.049) patients.

DISCUSSION

Major findings
The main finding of this study was that, although POAF was related to LTAF among both genders, cumulative survival free of LTAF was poorer in female patients than in male patients. Second, females with LTAF were related to multiple risk factors, including POAF, congestive heart failure, renal dysfunction,

and COPD. Third, POAF was a determinant of long-term mortality in female patients, but not in male patients. These differences suggest a need for more strict surveillance for AF among female patients.

Gender differences in POAF
In both genders, POAF was a common risk factor, along with older age and COPD, and these patients more often presented with comorbidities, including a reduced left ventricular function and increased LA volume index. Although the incidence of POAF according to gender is controversial, several studies
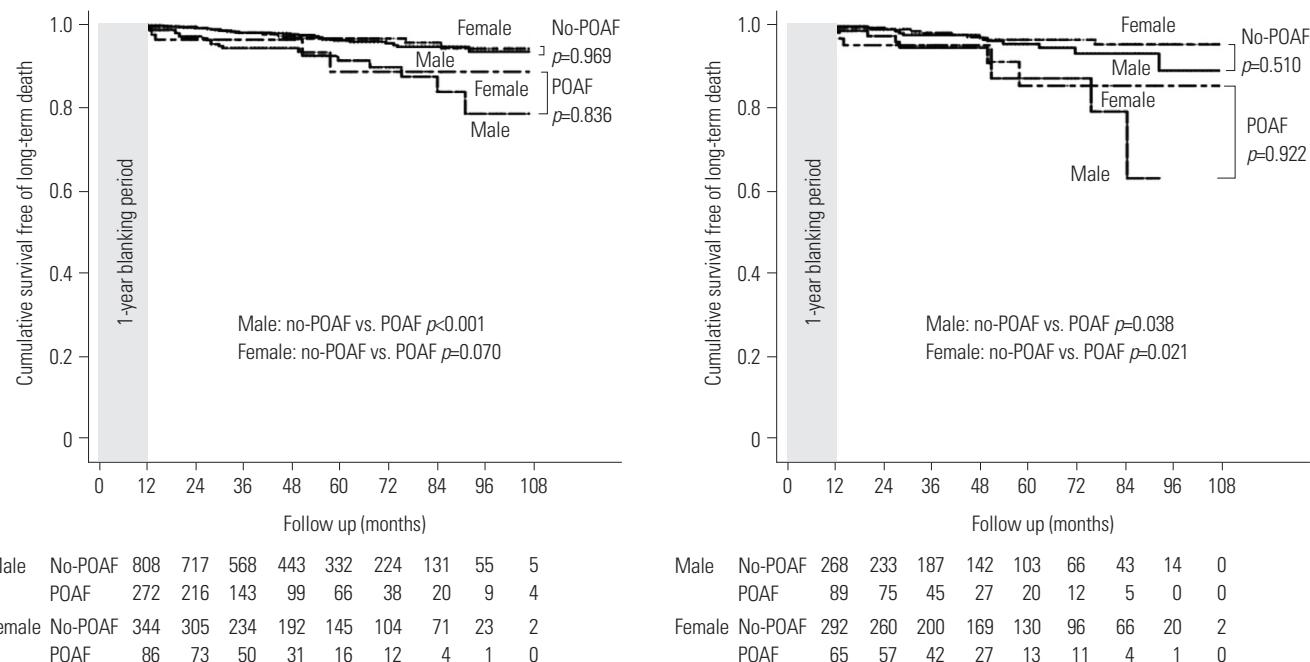
Fig. 3. Kaplan-Meier curves for survival free of long-term mortality according to the presence of POAF in the overall (A) and propensity score-matched patients (B). The left and right panels show the survival curves in the male and female patients according to POAF, respectively. The POAF group had a lower cumulative survival free of long-term mortality than the no-POAF group among both the overall and propensity score-matched patients (all $p<0.050$). POAF, postoperative atrial fibrillation.

have reported that male patients more frequently have POAF after CABG.[8,12] After propensity score matching, our results were also consistent with those of recent studies. However, women with AF generally had a lower quality of life and frequently had more comorbidities than did men.[13] Moreover, the significantly longer length of hospital stays among the female patients with POAF in our study could be similarly explained.

Gender differences in the Role of POAF for LTAF

Previously, new-onset POAF was commonly considered as being relatively easy to treat,[14-16] and it rarely recurred after discharge from the hospital.[15] Other studies have reported that POAF is self-limiting, with a total prevalence of AF of 1–4% at 1 year.[15,17,18] On the contrary, recent studies have reported that patients with POAF are at an increased risk of developing overall AF[19,20] and LTAF.[10] However, the effects of gender differences in POAF on long-term follow-up are not fully elucidated. In this study, female patients had a poorer cumulative survival free of LTAF than did male patients.

POAF was a significant predictor of LTAF in both genders in our multivariate competing risk-adjusted model. However, the other covariates significantly differed according to gender. Postoperative beta-blocker use and COPD were significant predictors of LTAF in males, whereas congestive heart failure, COPD, and renal dysfunction were predictors in females. These results indicate that, for reducing LTAF, gender-specific risk assessment should be considered during pre- and perioperative periods.

Gender differences in POAF as a risk factor for long-term mortality

In general, AF is a well-established risk factor for mortality, stroke, and heart failure.[21] Previous studies have reported that worse preoperative risk profiles in patients with POAF accounted for higher observed early and late mortality.[14,20,22,23] In the present study, interestingly, the multivariate regression analysis showed that POAF was a significant predictor of long-term mortality in females but not in males. Therefore, POAF in females should be treated as a severe complication with close follow-up. There are some points to be considered regarding these results. First, the contributing factors for POAF might differ according to gender. Second, other confounding factors that were not addressed in this study, such as diet, exercise, and family history, might also have affected the results. Among patients of both genders, diabetes was recognized as a risk factor for long-term mortality after CABG. This finding is consistent with previous studies.[24,25]

Limitations of the study

First, we performed a risk adjustment in the overall patients by using the propensity score matching method. Therefore, a smaller number of patients were included in the analyses, and a decreased statistical power was inevitable. However, propensity score matching has been shown to provide unbiased and more reliable results.[26] Second, the prevalence of AF and other long-term complications at follow-up might have been underestimated because of the retrospective study design. Third, the older age of patients in this study could lead to a

bias, because old age affects the incidence of AF and absolute mortality.[27] Fourth, despite the convincing findings, it is necessary to interpret the results with caution, because POAF and other cardiovascular risk factors may not be completely independent. Indeed, further large prospective cohort studies are necessary to determine the role of gender in long-term clinical implications. Although our results could hardly be generalized to all patients, it may reveal a relationship between POAF and long-term prognosis according to gender in off-pump CABG patients of older age.

Conclusions

After isolated CABG, POAF was a significant predictor of LTAF regardless of gender, and cumulative survival free of LTAF was poorer in female than in male patients. Furthermore, male and female patients had different risk predictors of LTAF. POAF was related to long-term mortality in only female patients. These gender differences in the clinical implications of POAF should be considered in careful postoperative surveillance aimed at reducing AF and its complications.

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