筑　波　大　学

博 士 （ 医 学 ） 学 位 論 文

Impact of coronary artery disease and revascularization on recurrence of atrial fibrillation after catheter ablation: Importance of ischemia in managing atrial fibrillation

(カテーテルアブレーション後の心房細動再発における冠動脈疾患と冠血行再建の影響：心房細動管理における心筋虚血の重要性について)

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謝辞―

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出典―

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Abstract

Introduction: There are few studies analyzing the association between the presence of coronary artery disease (CAD) and recurrence of atrial fibrillation (AF). This study evaluated the clinical impact of concomitant CAD and coronary revascularization on the recurrence of AF after catheter ablation.

Methods and Results: From April 2008 to December 2015, 700 consecutive patients were treated with pulmonary vein isolation for AF as the initial procedure. Of those, 681 patients who simultaneously underwent coronary angiography were investigated. Patients with at least one coronary stenosis (≥70%) were classified as having obstructive CAD. Of 681 patients, 90 patients had CAD and 42 patients underwent percutaneous coronary intervention (PCI) for lesions with perfusion abnormalities on single photon emission tomography. The recurrence of AF was significantly more frequent in patients with CAD (56%) than in those without CAD (39%) (*P*=.0011). On multivariable analysis, the predictors of AF recurrence were persistent or long-standing persistent AF [hazard ratio (HR): 1.36; 95% confidence interval (CI): 1.04-1.77; *P*=.023], left atrial diameter (HR: 1.04; 95% CI: 1.02-1.06; *P*<.0001), and concomitant CAD (HR: 1.45; 95% CI: 1.051.97; *P*=.024). The recurrence of AF in patients with PCI (38%) was significantly lower than in those without PCI (72%) (*P*=.0006), and E/E′ significantly improved in patients with PCI (71%) than in those without PCI (42%; *P*=.001). Performing PCI for concomitant CAD significantly reduced AF recurrence (HR: 0.39; 95% CI: 0.20-0.72;

P=.002).

Conclusion: Patients with CAD had a significantly higher rate of AF recurrence than those without CAD. Coronary revascularization may reduce the recurrence of AF with improvement of left ventricular diastolic function.

Abbreviations:

AF=atrial fibrillation

CAD=coronary artery disease

PVI=pulmonary vein isolation

RFCA= radiofrequency catheter ablation

CAG= coronary angiography

PCI= percutaneous coronary intervention

SPECT=single photon emission computed tomography

AT= atrial tachycardia

PV=pulmonary vein

ECG=electrocardiogram

LV=left ventricular

RCA=right coronary artery

LCX=left circumflex artery

HR=hazard ratio

CI=confidence interval

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia. Miyasaka et al (1) reported that the number of persons with AF in the U.S. will exceed 10 million by the year 2050. The prevalence of AF increases substantially with age (2) (Figure 1). Several previous studies have reported varying estimates of the prevalence of AF ranging from 1.2% to 2.8% in persons aged 60 through 69 years to 7.3% to 13.7% in persons aged 80 years or older (3-6). AF is associated with increased risk of stroke (7,8), heart failure (9), cognitive dysfunction (10,11), and premature death (12-15) and has enormous socioeconomic implications (16,17). Patients with AF have four to five times the risk of stroke and about double the risk of mortality compared with those without AF (18,19).

The clinical risk factors for AF include advancing age, diabetes, hypertension, congestive heart failure, rheumatic and nonrheumatic valve disease, and myocardial infarction (20). Because there is overlap in risk factors for AF and coronary artery disease (CAD), patients with AF often have coexistent CAD (21). Kralev et al (22) reported that the prevalence of CAD in patients with AF ranged between 18% and 46.5% (Figure 2).

Experimental studies and human surgical mapping studies have shown that AF is perpetuated by reentrant wavelets propagating in an abnormal atrial-tissue substrate (23-27). Haïssaguerre et al (28) investigated the mode of initiation of spontaneous paroxysms of human AF by atrial ectopic beats, and the effects of local ablation with radio-frequency energy. And they reported

that the pulmonary veins were an important source of ectopic beats, initiating frequent paroxysms of AF (Figure 3), and these foci responded to treatment with radio-frequency ablation. Radiofrequency catheter ablation (RFCA) using a strategy of pulmonary vein isolation (PVI) (Figure 4) has subsequently become an important treatment option for patients with drug-resistant AF.

A previous meta-analysis found that the single-procedure success rate of PVI for all types of AF without antiarrhythmic drugs was 50% to 64%, and 71% after multiple procedures (29) (Figure 5). It follows that the rate of AF recurrence after successful PVI remains relatively high. AF recurrences are associated with impaired quality of life, and poor clinical outcomes such as increased morbidity and mortality due to cardio- and cerebrovascular events (30,31). On the other hand, the AF Follow-up Investigation of Rhythm Management (AFFIRM) trial revealed that the presence of sinus rhythm was associated with a 47% reduction in mortality and that the use of antiarrhythmic drugs was associated with a significant increase in mortality of 49%, which suggests that restoration and maintenance of sinus rhythm is of potential benefit if it can be done non-pharmacologically (32).

Clinical predictors such as hypertension, hyperlipidemia (33), metabolic syndrome (34), obstructive sleep apnea (35), persistent AF, and enlarged left atrial diameter (36,37) have been shown to be reproducibly associated with AF recurrence after RFCA. However, the impact of coronary atherosclerosis and revascularization on the outcome of rhythm control after PVI for

AF has not been elucidated so far. Therefore, we aimed to investigate the clinical impact of concomitant CAD and coronary revascularization on the recurrence of AF in patients who underwent initial PVI.

Methods

Study Population

This study was approved by the institutional review board of the University of Tsukuba (study no. H29-70), and written informed consent of the ablation and percutaneous coronary intervention (PCI) procedures was obtained from all patients. From April 2008 to December 2015, a total of 700 consecutive patients (61±10 years old,) were treated with PVI for drug-resistant AF as an initial procedure. We recommended coronary angiography (CAG) for all patients because patients with AF often had coexistent CAD. Of those, 15 patients did not undergo CAG and 4 patients refused participation. The remaining 681 patients [455 (67%) with paroxysmal AF, 78 (11%) with persistent AF, and 145 (22%) with long-standing persistent AF] simultaneously underwent CAG at the same time of PVI. Patients with at least one coronary stenosis (≥70%) were classified as having obstructive CAD (38). They underwent classified as having obstructive and PCI for lesions with perfusion abnormalities on single photon emission computed tomography (SPECT) (Figure 6,7). The primary outcome was the recurrence of AF or atrial tachycardia (AT) after PVI. The prevalence of CAD, PCI for CAD, and recurrence of

AF were investigated during follow-up periods (44.0±32.6 months).

Calculation of CHADS2 score

Patients with AF have an increased risk of stroke. CHADS2 score can quantify risk of stroke for patients with AF and may aid in selection of antithrombotic therapy. CHADS2 score is calculated by adding 1 point for each of the following conditions: recent congestive heart failure, hypertension, age at least 75 years, or diabetes mellitus and adding 2 points for having had a prior stroke or transient ischemic attack (Table 1) (39).

Radiofrequency catheter ablation

All antiarrhythmic drugs were discontinued for at least five half-lives before the procedure. A multielectrode catheter was inserted from the subclavian vein or internal jugular vein and placed into the distal coronary sinus. After the trans-septal puncture, an intravenous bolus of heparin was administered. The activated clotting time was evaluated every 30minutes and maintained at ≥300seconds. Intra-pulmonary vein (PV) electrograms were monitored with a decapolar circumferential mapping catheter (Lasso; Biosense Webster, Diamond Bar, CA).

Circumferential ipsilateral PV isolation was performed with a 4-mm-tip irrigated catheter (Navistar ThermoCool; Biosense Webster) or an 8-mm-tip nonirrigated catheter (Ablaze; Japan Lifeline Co, Ltd, Tokyo, Japan). The nonirrigated catheter was used in the former 100 cases

who underwent ablation procedure before March 2009 because an irrigated catheter was not available in Japan during that period. In the latter 600 cases, an irrigated catheter was used. When nonirrigated catheter was used, radiofrequency energy was delivered in the temperature control mode with a maximum output of 35W and a target temperature of 52°C.

When an irrigated catheter was used, a power control mode with an output of 25 to 35W and a temperature limit of 42°C were selected. Encircling radiofrequency lesions surrounding both ipsilateral PVs were created until the PV potentials inside the encircled area disappeared. The endpoint of the PV isolation was the creation of bidirectional conduction block from the atrium to the PVs and vice versa. If AF was sustained after PV isolation, sinus rhythm was restored by cardioversion. Additional ablation including ablation targeting non-PV foci ectopics, linear ablation, ablation of continuous fractionated atrial electrograms, and/or superior vena cava isolation was performed at the operator's discretion.

Management after PVI and definition of AF recurrence

The patients remained hospitalized under continuous rhythm monitoring for 3 days after the procedure. After discharge, patients were followed at 2 to 4 weeks after PVI and then every 1 to 3 months at the outpatient clinic. At each hospital visit, patients underwent a 12-lead electrocardiogram (ECG) and intensive questioning regarding any arrhythmia-related symptoms. Twenty-four-hour Holter monitoring and portable ECG monitoring (HCG-901;

OMRON, Kyoto, Japan) was performed at 2 weeks and 1, 3, 6, and 12 months after PVI. Subsequently, 12-lead ECGs, 24-hour Holter ECGs, and portable ECG monitoring were performed every 12 months. These were also performed anytime patients reported palpitations (Figure 8). A recurrence of AF was defined, regardless of symptoms, as any documentation of AF/AT lasting more than 30seconds on any ECG. If sinus rhythm could be maintained, antiarrhythmic drugs were not resumed during any time after PVI. The recurrence of AF within the first 3 months only after PVI was considered transient since a blanking period of 3 months was applied.

Coronary revascularization

We decided the indication of PCI and identified the target lesions according to the perfusion abnormalities on stress Tc-99m MIBI SPECT findings, in correspondence with narrowing lesions seen on CAG. All patients received treatment with aspirin (100mg/day) and clopidogrel (75mg/day) before PCI. In addition, anticoagulant therapy was not interrupted in the peri-PCI period. Once the guidewire passed through the culprit lesion, balloon dilatation and stent placement was performed using intravascular ultrasound. The standard of care at discharge for all patients treated with stents was to prescribe clopidogrel for at least 6 months. So that means triple antithrombotic therapy was continued for 6 months. Aspirin was continued indefinitely unless complications occurred.

Stress Tc-99m MIBI SPECT Imaging

SPECT was performed using adenosine stress (0.14mg/kg/min for 6minutes) and intravenously injecting 370 MBq of Tc-99m MIBI after 3minutes of adenosine infusion. Three hours later, resting images were obtained after injection of 740 MBq of Tc-99m MIBI. Myocardial perfusion was analyzed by reconstruction of a standard short- and long-axis projection, perpendicular to the heart axis. SPECT images were assessed using a 17-segment model presented in polar map format (adjusted for peak myocardial activity [100%]) (40). Perfusion defects on stress images were considered present when tracer activity was less than 75% of maximum. When significant fill-in (>10%) of perfusion defects was observed on the resting images, segments were classified as ischemic (shown as Figure 7C). We used percent of peak counts on normalized polar maps within each vascular territory on the stress images as a physiologic measure of quantitative perfusion defects. Stress and resting images were independently analyzed by two nuclear physicians who were blinded to the CAG data. Visual grading was defined as normal (no perfusion defects) or ischemia (stress perfusion defects with fill-in).

Evaluation of left ventricular diastolic function by echocardiography

Diastolic dysfunction represents a combination of impaired left ventricular (LV) relaxation, restoration forces, myocyte lengthening load, and atrial function, culminating in increased LV

filling pressures (41). Echocardiography can be a powerful tool for the diagnosis of diastolic dysfunction and increased LV filling pressures. Current Doppler echocardiography guidelines recommend using early (E) to late (A) diastolic transmitral flow velocity (E/A) to assess diastolic function, and E to early diastolic mitral annular tissue velocity (E/E') to estimate LV filling pressures. The approach starts with transmitral flow pattern (E/A) and is applied in the absence of AF, significant mitral valve disease (at least moderate mitral annular calcification, any mitral stenosis or mitral regurgitation of more than moderate severity, mitral valve repair or prosthetic mitral valve), LV assist devices, left bundle branch block, and ventricular paced rhythm. In the case of AF, beat-to-beat variability and the absence of A waves make the assessment of diastolic dysfunction difficult (42). Other Doppler parameters, such as E' <8 and E/E' >11 are needed to help assess diastolic function and increased left atrial pressure in AF (43). Therefore, E/E' was applied as a parameter of LV diastolic function in this study (Figure 9).

Study Endpoints

Study endpoints were defined as the recurrence of AF after RFCA. A recurrence of AF was defined, regardless of symptoms, as any documentation of AF/AT lasting more than 30seconds on a 12-lead ECG, 24-hour Holter monitoring, or portable ECG monitoring.

Statistical Analysis

All data are expressed as the mean ± standard deviation or in terms of numbers and percentages. Comparisons of continuous variables between two groups were analyzed by analysis of variance. Comparisons of categorical variables between groups were performed by Fisher exact test. Kaplan-Meier curves were made to describe the freedom from AF/AT after initial PVI, and the log-rank test was used to identify significant differences in unadjusted survival rate among groups. Multivariable Cox proportional hazards models were used to calculate variables predictive of the primary endpoint (AF recurrence). Covariates associated with AF recurrence in the univariable analyses (P <.1) were included in the final model. A two-sided P < .05 was considered to be statistically significant throughout the analysis. All statistical analyses were performed with the JMP 11 software package for Macintosh (SAS Inc, Cary, NC).

Results

PVI and CAG were successfully performed in all patients, and no major complications (eg, stroke, atrioesophageal fistula, PV stenosis, coronary dissection, or myocardial infarction) occurred in any of the patients during PVI and CAG. Of 681 patients, 90 patients were identified as having obstructive CAD. We recommended PCI for all 90 patients with obstructive CAD, and patients who agreed on PCI underwent stress Tc-99m MIBI SPECT. All

681 patients were classified into three groups: (a) the non-CAD group (n=591) included patients without obstructive CAD; (b) the non-PCI group (n=48) included patients who refused to receive PCI despite the existence of obstructive CAD (n=26), or who had no ischemia on SPECT (n=22); (c) the PCI group (n=42) included patients who underwent PCI for lesions with perfusion abnormalities on SPECT regardless of symptomatic or asymptomatic myocardial ischemia (Figure 6). Of those 42 patients, only one patient underwent clinically relevant nonmajor bleeding event (bleeding from a brachial artery) soon after PCI during the triple antithrombotic therapy.

Demographic and clinical characteristics of patients with and without CAD

The overall prevalence of obstructive CAD in patients with AF was 13% (90 of 681). The patients with CAD were older and had significantly higher rates of hypertension, diabetes mellitus, and chronic kidney disease than those without CAD (Table 2). Furthermore, the plasma level of brain natriuretic peptide and the left atrial diameter were greater in patients with CAD than in those without CAD. There were no significant differences in the type of AF and left ventricular ejection fraction between the two groups. The patients with CAD were treated more frequently with renin-angiotensin system blockers and statins than those without CAD. We divided 681 patients into three groups according to their CHADS2 score [0, n = 280 (41%); 1, n = 263 (39%); ≥2, n = 138 (20%)]. Importantly, the prevalence of CAD increased

significantly with higher CHADS2 scores ($P < .0001$). In addition, the patients with a higher CHADS2 score underwent PCI more frequently ($P = .006$; Figure 10).

AF recurrence after initial PVI in patients with and without CAD

The overall prevalence of AF recurrence after initial PVI was 41% (283 of 681). The recurrence of AF was significantly more frequent in patients with CAD (56%) than in those without CAD (39%; P=.0011 by the log-rank test; Figure 11). There were no significant differences in the rate of additional ablation between the two groups (Table 3). A multivariable Cox regression analysis revealed that the predictors of AF recurrence after initial PVI were persistent or long-standing persistent AF [hazard ratio (HR): 1.36; 95% confidence interval (CI): 1.04-1.77; P=.023], left atrial diameter (HR: 1.04; 95% CI: 1.02-1.06; P<.0001), and concomitant CAD (HR: 1.45; 95% CI: 1.05-1.97; P=.024; Table 4).

AF recurrence in patients with and without PCI for concomitant CAD

Of 90 patients with obstructive CAD, 42 patients underwent successful PCI for lesions with perfusion abnormalities on SPECT. The left atrial diameter was lower in patients with PCI than in those without PCI. The patients with PCI were treated more frequently with statins than those without PCI. CAD in the right coronary artery (RCA) was more frequently detected in patients with PCI than in those without PCI (64% vs 44%, P=.037), and proximal lesions in

the RCA were more frequently detected in patients with PCI than in those without PCI (35% vs 21%, *P*=.042). The patients with PCI had more multi-vessel disease than those without PCI (57% vs 34%, *P*=.021). ΔE/E′ (calculated as follows: baseline E/E′–follow-up E/E′) was significantly higher in patients with PCI than in those without PCI (2.34±2.78, 1.0±2.34; *P*=.014; Table 5). The rate of patients in whom the E/E′ as a parameter of LV diastolic function improved was significantly higher in PCI group (71%) than in non-PCI group (42%; *P*=.001). The recurrence of AF in patients with PCI (38%) was significantly lower than in those without PCI (72%; *P*=.0006 by the log-rank test; Figure 12). A multivariable Cox regression analysis revealed that performing PCI for concomitant CAD significantly reduced AF recurrence after initial PVI (HR: 0.39; 95% CI: 0.20-0.72; *P*=.002; Table 6). Among the subgroup of 51 patients with AF recurrences after ablation from the overall 90 patients with CAD, 38 patients had reablation, and 35 of 38 patients had PV-reconnection. There were 18 of 51 patients (35%) in non-paroxysmal AF.

Discussion

The major important findings of the present study are as follows: (a) the recurrence of AF after PVI was significantly more frequent in patients with CAD than in those without CAD. On multivariable analysis, it was determined that persistent or long-standing persistent AF, enlarged left atrial diameter, and concomitant CAD remained the independent predictors of AF

recurrence after initial PVI; (b) coronary revascularization for lesions with perfusion abnormalities on SPECT significantly reduced AF recurrence after initial PVI, and performing PCI for concomitant CAD was independent predictor of AF recurrence. Reversal of atrial ischemia may explain part of the apparent benefit observed in patients undergoing PCI, and (c) ischemia-induced diastolic dysfunction might be a mechanism through which CAD contributed to AF recurrence because the E/E′ ratio significantly improved in patients with PCI than in those without PCI. Although previous reports have addressed the recurrence of AF after PVI, this is the first study, to our best knowledge, that assesses the association of concomitant CAD and coronary revascularization with the recurrence of AF after PVI.

AF and location of coronary artery stenosis

It is often speculated that atrial ischemia plays an important pathophysiological role in the genesis of AF. Hence, significant stenosis in the proximal RCA and left circumflex artery (LCX) before the take-off of the atrial branches should increase the likelihood of AF in these patients. Kolvekar et al (44) found that obstructive disease in the sinoatrial nodal and atrioventricular nodal arteries is more common in patients developing AF after coronary artery bypass surgery than those who remain in sinus rhythm. In our study, while there were a small number of patients with significant stenosis in the proximal LCX, obstructive CAD and proximal lesions in the RCA was more frequently detected in patients with PCI than in those

without PCI. In addition, the recurrence of AF in patients with PCI was significantly lower than in those without PCI. It is possible that right atrial ischemia induced by RCA disease may promote the recurrence of AF, and reversal of atrial ischemia may explain part of the apparent benefit observed in patients undergoing PCI.

Relationship between AF recurrences and CAD

Previous studies reported the proposed mechanisms of CAD evoking AF. The presence of CAD can cause myocardial ischemia, resulting in impaired relaxation of the left ventricle and leading to higher pressures in the left atrium. High left atrial pressures cause ultrastructural and electrical changes in the atrial tissue, potentially forming the arrhythmogenic substrate for AF (45). In an Olmsted County Study of patients age 65 years and older who were in sinus rhythm at the time of an echocardiographic examination, it was noted that the subsequent development of AF in patients without diastolic dysfunction was only 1% versus approximately 12% in patients with moderate degrees of diastolic dysfunction and 20% in those with restrictive physiology, which is the most severe manifestation of diastolic dysfunction (46). Takagi et al (47) reported that exercise-induced elevated LV filling pressure estimated by raised E/E' ratio after exercise provides significant prognostic information for predicting new-onset AF in elderly patients. Furthermore, the atrial ischemia/infarction resulted in greater atrial electrophysiological changes and propensity for AF forming the dominant substrate for AF

(48-50). Systemic inflammation and oxidative stress have contributed to atrial remodeling, and the initiation and recurrence of AF (51,52). These results provide novel insights into potential AF mechanisms in patients with CAD. However, little is known about the impact of CAD on the efficacy of RFCA for AF. Our study demonstrated that the recurrence of AF after PVI was significantly more frequent in patients with CAD than in those without CAD. In the Leipzig Heart Center AF Ablation Registry of 1310 consecutive patients, the presence, location, and extent of CAD were not associated with AF recurrence (37). Of those patients, 152 (11.6%) with CAD had already undergone coronary revascularization before PVI. In this study, the current revascularization status of the patients was unknown. Interestingly, our data, which showed that the recurrence of AF in patients who underwent PCI (38%) was similar to that in those without CAD (39%), are in agreement with the Leipzig Heart Center study, which demonstrated similar AF recurrence rates in non-CAD (33%) and CAD (35%) groups.

Proposed mechanism for preventing AF recurrence by coronary revascularization

There are only limited, small clinical studies analyzing the association between AF recurrences and coronary revascularization for significant CAD. In our study, coronary revascularization for concomitant CAD significantly reduced AF recurrence after initial PVI. However, PCI was associated with a significantly lower AF recurrence rate—not necessarily a causal relationship. Because the E/E′ as a parameter of LV diastolic function significantly

improved in the patients with PCI than in those without PCI in our study, it is possible that coronary revascularization for concomitant CAD in patients with AF may reduce chronic atrial ischemia, left ventricular end-diastolic pressure, and left atrial pressure, resulting in a lower AF recurrence rate.

Study Limitations

Our study was subject to some limitations. First, this study was based on a non-randomized retrospective design. Therefore, this might have introduced a significant selection bias in the indication for coronary revascularization. Because we did not use the propensity score-matched analysis among two groups (with and without CAD), it is possible that several factors, such as age, hypertension, diabetes mellitus, and left atrial diameter, could not be completely adjusted for in the multivariable analysis. A number of AF patients with CAD had chest discomfort, but it was difficult to distinguish between angina and chest symptom due to arrhythmia. Because the pathophysiology of AF is multifactorial and not completely understood, the pathophysiological reason of the very high percentage of AF recurrences in patients with CAD but no PCI is not clear. It is possible that there are some limitations which SPECT could not detect the ischemic findings of CAD, and it had been reported that atrial ischemia plays an important pathophysiological role in the genesis of AF, but there is no available modality to detect atrial ischemia. It is possible that CAD may be a surrogate marker for the combined

atrial remodeling caused by cardiometabolic risk factors which would be reflected to an extend in the CHADS2 score. Second, any documentation of AT was included in AF recurrences in this study, but the recurrence as organized AT after ablation might be less ischemia-related. And the diagnosis of AF recurrence was based on periodic and occasional ECG recordings and Holter ECG findings in the present study. Therefore, some patients with asymptomatic AF recurrence might have been missed, which might have affected the results. Nevertheless, the present study is the largest to date assessing the association between CAD and AF recurrences after PVI. Third, certain aspects of the AF ablation approach in this study, such as the use of an 8mm-tip ablation catheter and ablation beyond PVI guided by AF inducibility, are currently not considered to be a common practice, because a number of previous patients from 2008 were included in this study. The subgroup of 51 patients with AF recurrences after ablation from the overall 90 patients with CAD is of special importance, and 35 of 38 patients with reablation had PV-reconnection. However, the association of PV-reconnection with the presence of CAD is unclear. Fourth, while we discerned an association between CAD and AF recurrences after PVI rather than a necessary causal relationship, the only way to know for sure would be have a cohort of patients who had inducible ischemia and randomize them to PCI vs no PCI. Further prospective studies with larger sample size, long-term follow-up, and the participation of many hospitals may be needed to resolve these limitations and to enhance the validity of our results.

Conclusion

The prevalence of obstructive CAD in the patients with initial PVI for AF was high. Patients with CAD had a significantly higher rate of AF recurrence than those without CAD. Coronary revascularization for concomitant CAD may reduce the recurrence of AF after PVI with the improvement of LV diastolic function.

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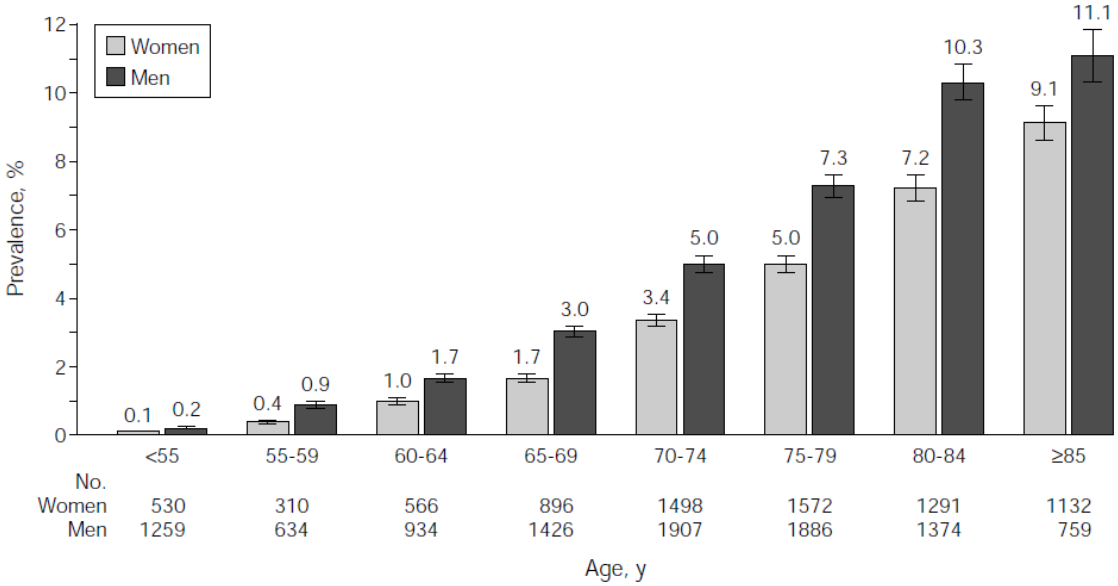


Figure 1. Prevalence of diagnosed atrial fibrillation stratified by age and sex.
The prevalence of atrial fibrillation increased with older age, ranging from 0.1% among persons younger than 55 years to 9.0% among patients 80 years or older; among persons 60 years or older, 3.8% had atrial fibrillation. (Go AS, et al. JAMA. 2001) (2)

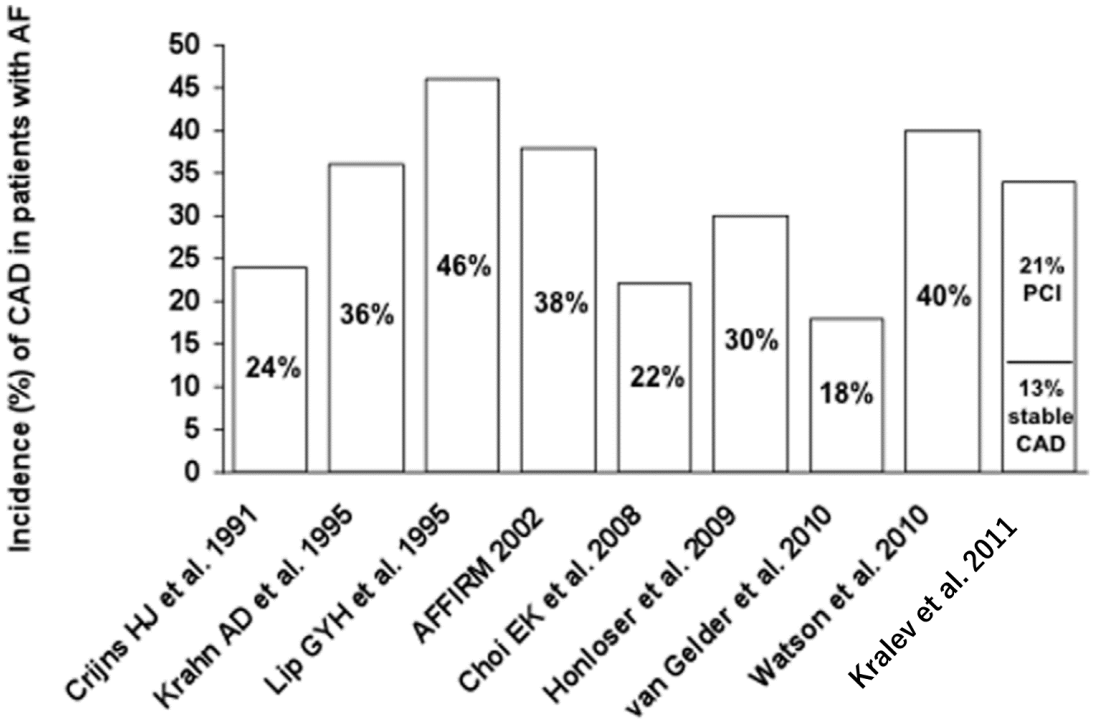


Figure 2. Overview of reported incidences of coronary artery disease in patients presenting with atrial fibrillation.

AF=atrial fibrillation, CAD=coronary artery disease, PCI=percutaneous coronary intervention. (Kralev S, et al. PLoS ONE. 2011) (22)

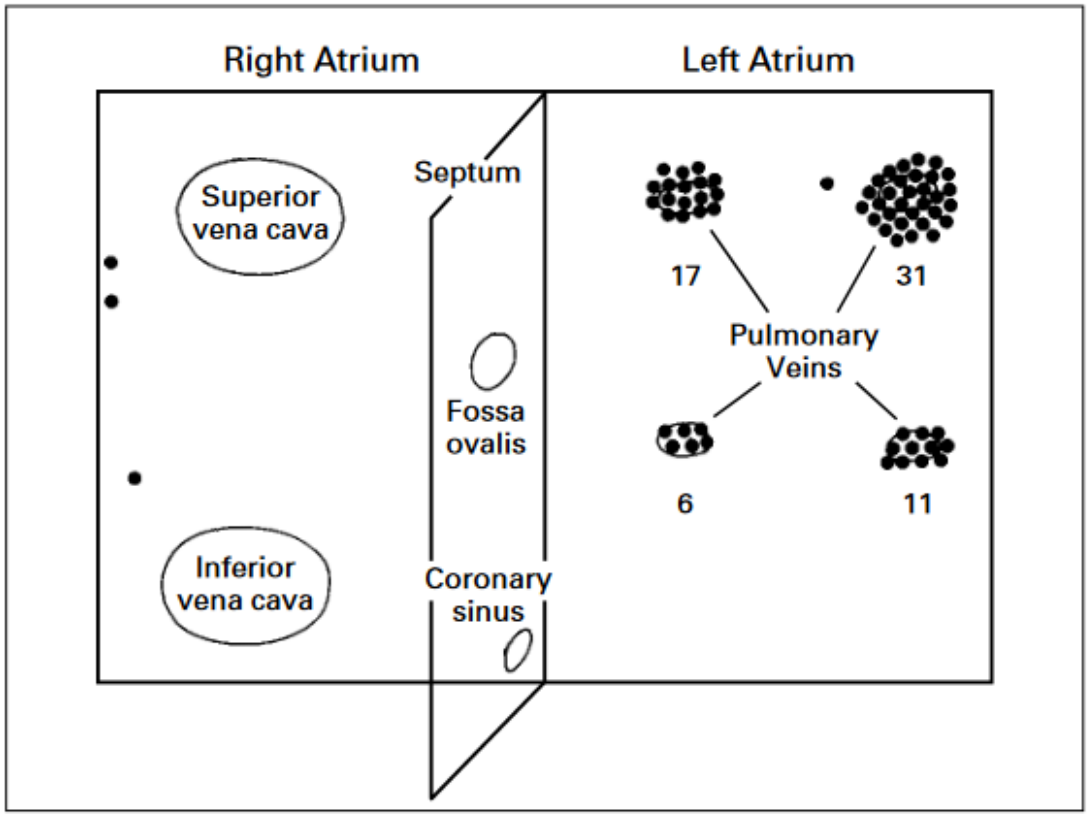


Figure 3. Diagram of the sites of 69 foci triggering atrial fibrillation in 45 patients. Ectopic beats originated in atrial muscle in 4 patients and in the pulmonary veins in 41 patients (a total of 65 foci [94 percent]): 31 foci in the left superior, 17 in the right superior, 11 in the left inferior, and 6 in the right inferior pulmonary vein. (Haïssaguerre M, et al. N Engl J Med. 1998) (28)

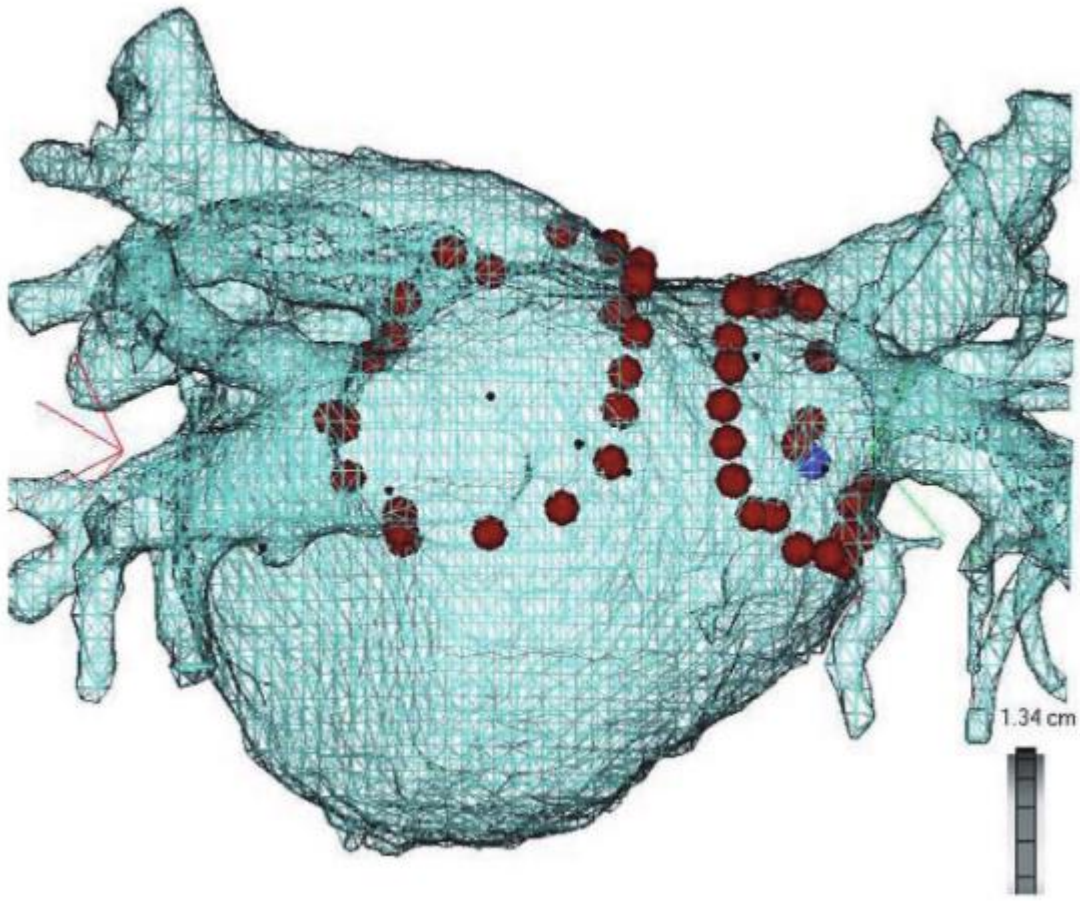


Figure 4. Anatomical pulmonary vein ablation for atrial fibrillation.
In this study, circumferential ipsilateral PV isolation was performed with a 4-mm-tip irrigated catheter (Navistar ThermoCool; Biosense Webster) or an 8-mm-tip nonirrigated catheter (Ablaze; Japan Lifeline Co, Ltd, Tokyo, Japan). The nonirrigated catheter was used in the former 100 cases who underwent ablation procedure before March 2009 because an irrigated catheter was not available in Japan during that period. In the latter 600 cases, an irrigated catheter was used. When nonirrigated catheter was used, radiofrequency energy was delivered in the temperature control mode with a maximum output of 35W and a target temperature of 52°C. When an irrigated catheter was used, a power control mode with an output of 25 to 35W and a temperature limit of 42°C were selected. Encircling radiofrequency lesions surrounding both ipsilateral PVs were created until the PV potentials inside the encircled area disappeared. PV=pulmonary vein. (Guidelines for indications and procedural techniques of catheter ablation. JCS 2012）

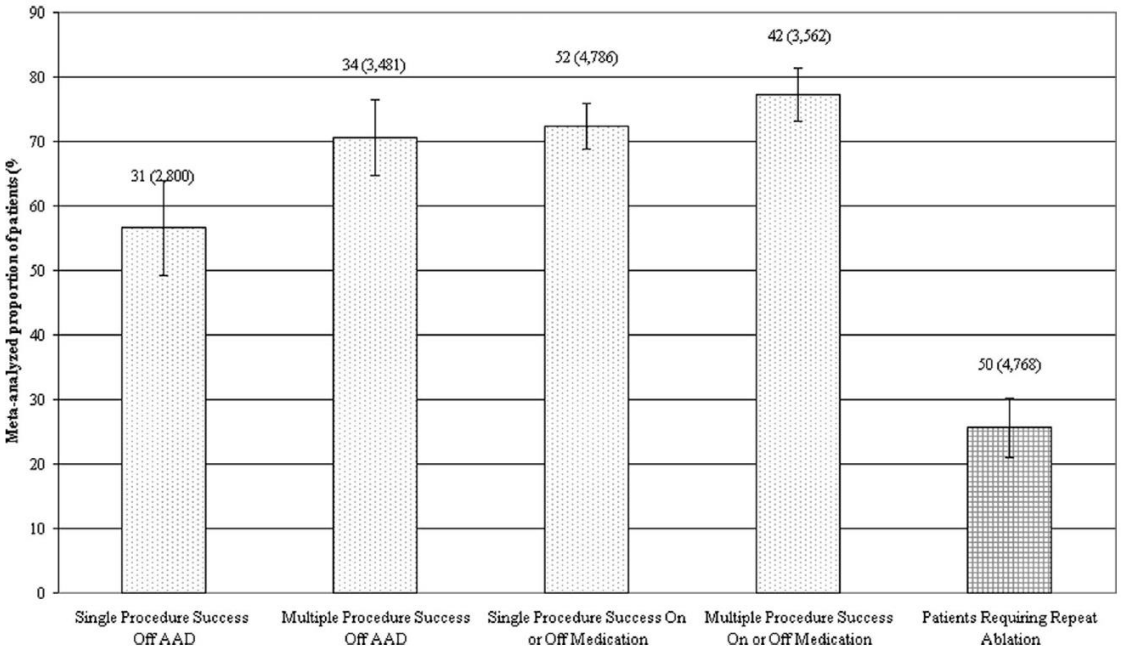


Figure 5. Efficacy of catheter ablation in patients with atrial fibrillation.
The single procedure success rate of catheter ablation of atrial fibrillation off antiarrhythmic drugs (AAD) therapy was 57% (50% to 64%) in 31 arms with 2800 patients. After multiple or uncertain number of procedures, the off-AAD success rate increased to 71% (65% to 77%) in 34 arms with 3481 patients. The ablation success rate was 77% (73% to 81%) in 3562 patients in 42 arms after multiple or uncertain number of procedures in patients on AAD therapy and 72% in 4786 patients in 52 arms after a single procedure on AAD therapy. AAD=antiarrhythmic drugs. (Calkins H, et al. Circ Arrhythm Electrophysiol. 2009) (29)

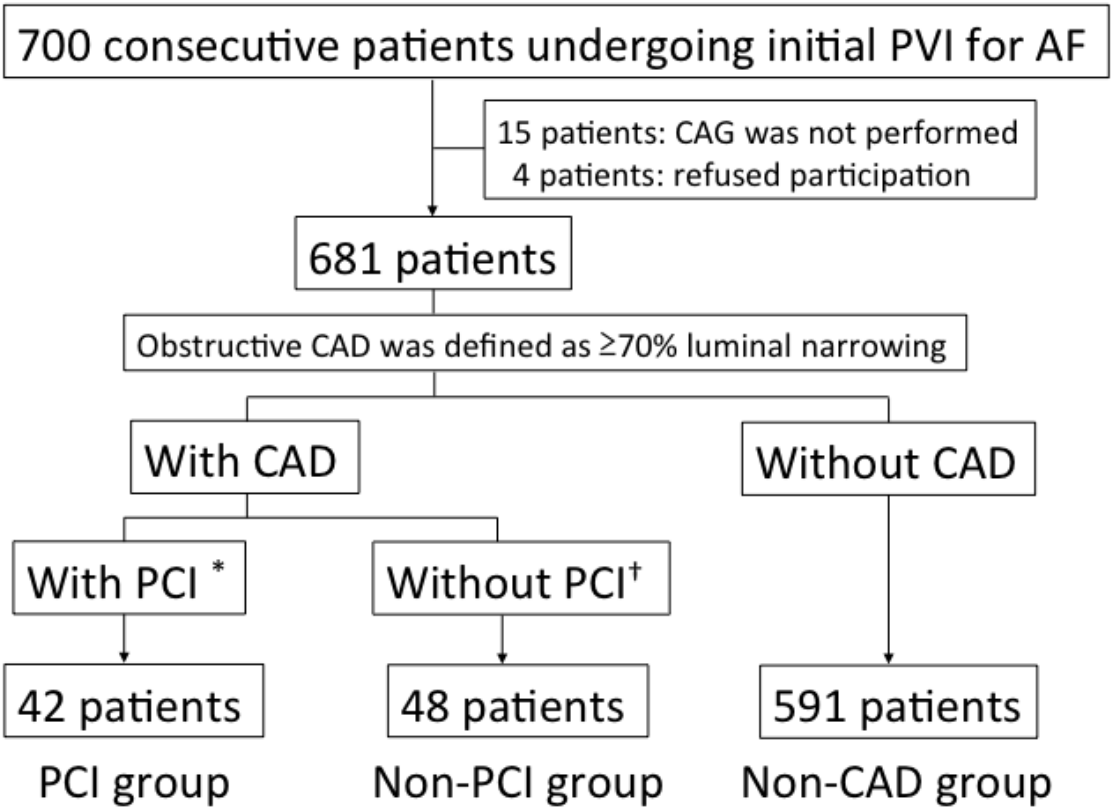


Figure 6. Patient flow chart in this study.

*PCI was performed for patients who demonstrated myocardial ischemia on SPECT. †PCI was not performed for patients who refused to receive PCI despite the existence of obstructive CAD (n=26), or who had no ischemia on SPECT (n=22). AF=atrial fibrillation, PVI=pulmonary vein isolation, CAG= coronary angiography, CAD=coronary artery disease, PCI= percutaneous coronary intervention.

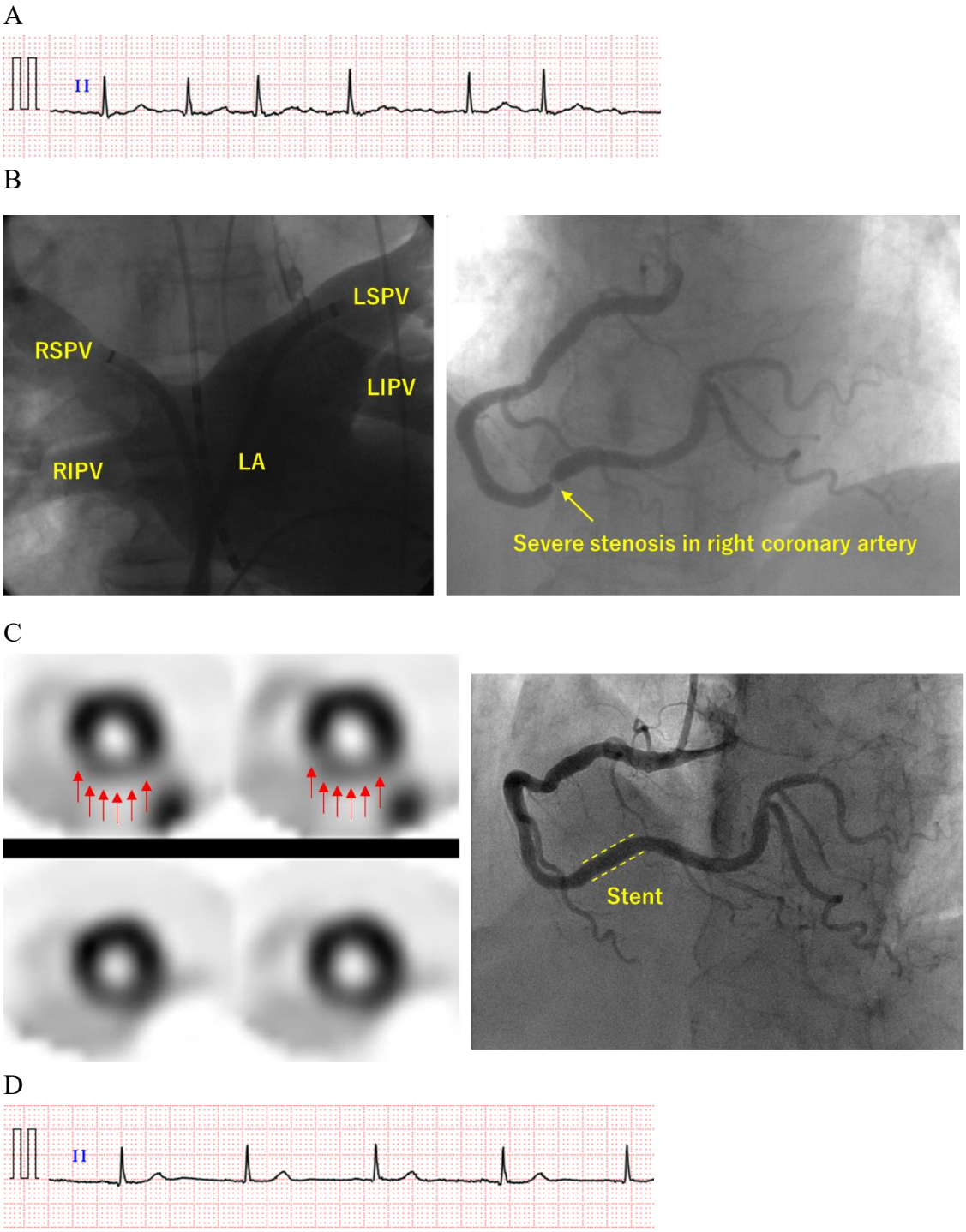


Figure 7. Representative case in this study.

A. Atrial fibrillation was detected on an electrocardiogram. B. Pulmonary vein isolation (PVI) and coronary angiography were simultaneously performed. C. Percutaneous coronary intervention (PCI) was performed for lesion with perfusion abnormalities (red arrows) on SPECT. D. Sinus rhythm was maintained after PVI and PCI. LA=left atrium, RSPV=right superior pulmonary vein, RIPV=right inferior pulmonary vein, LSPV=left superior pulmonary vein, LIPV=left inferior pulmonary vein.

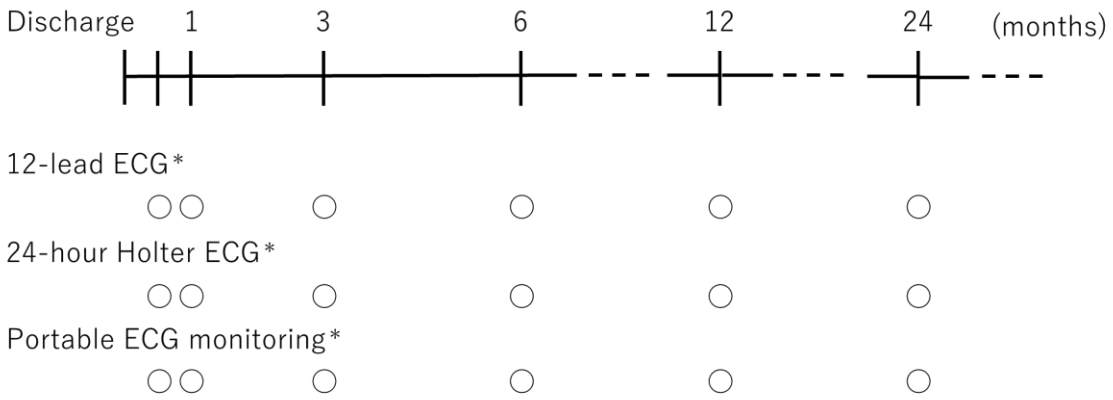
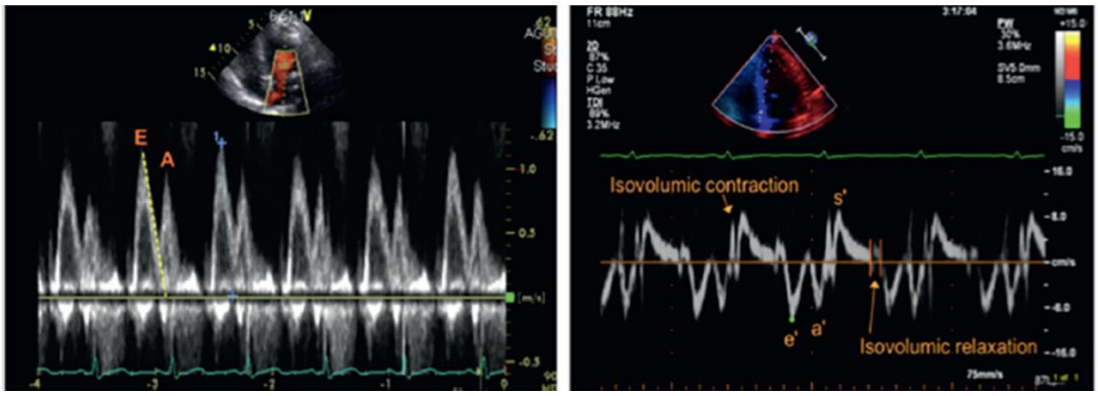


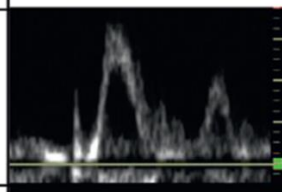
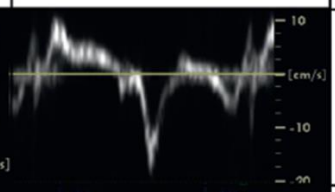
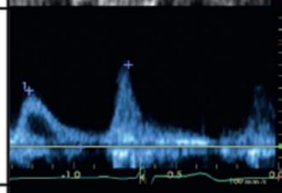
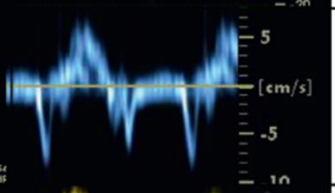
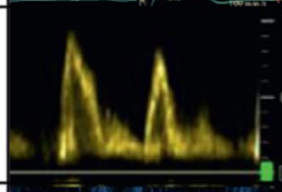
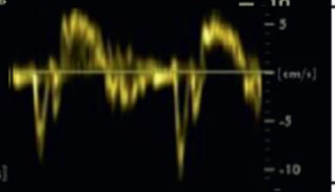
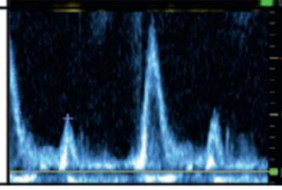
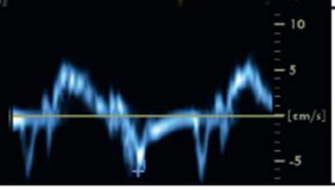
Figure 8. Management after pulmonary vein isolation in this study.

*These were also performed anytime patients reported palpitations. ECG=electrocardiogram.

A



B

	TRANSMITRAL PULSE WAVE DOPPLER	MITRAL ANNULAR TISSUE DOPPLER	PEARLS
NORMAL			• E/A > 0.8 • e' velocity is normal for age • E deceleration time is normal
GRADE I DIASTOLIC DYSFUNCTION			• E/A < 0.8 due to impaired relaxation and inability of LV to untwist* • e' velocity is reduced for age • E deceleration time usually prolonged
GRADE II DIASTOLIC DYSFUNCTION			• E/A > 0.8 (often > 1) as a result of increased left atrial pressure • e' velocity is reduced for age • Look for increased E/e' and/or increased LA size to corroborate the diagnosis of grade II diastolic dysfunction
GRADE III DIASTOLIC DYSFUNCTION			• E/A > 1.5-2.0 with very short E deceleration time (< 140 ms) due to severely reduced LV compliance and high LV filling pressure • e' velocity is severely reduced • A wave and a' velocities are reduced due to LA dysfunction

C

1) Not sinus rhythm (atrial fibrillation*, bigeminy, etc.)
2) Fusion of the E and A waves (tachycardia, atrioventricular block, etc.)
3) Severe mitral regurgitation
4) Mitral stenosis, severe mitral annulus calcification
5) Impaired left atrial muscle

D

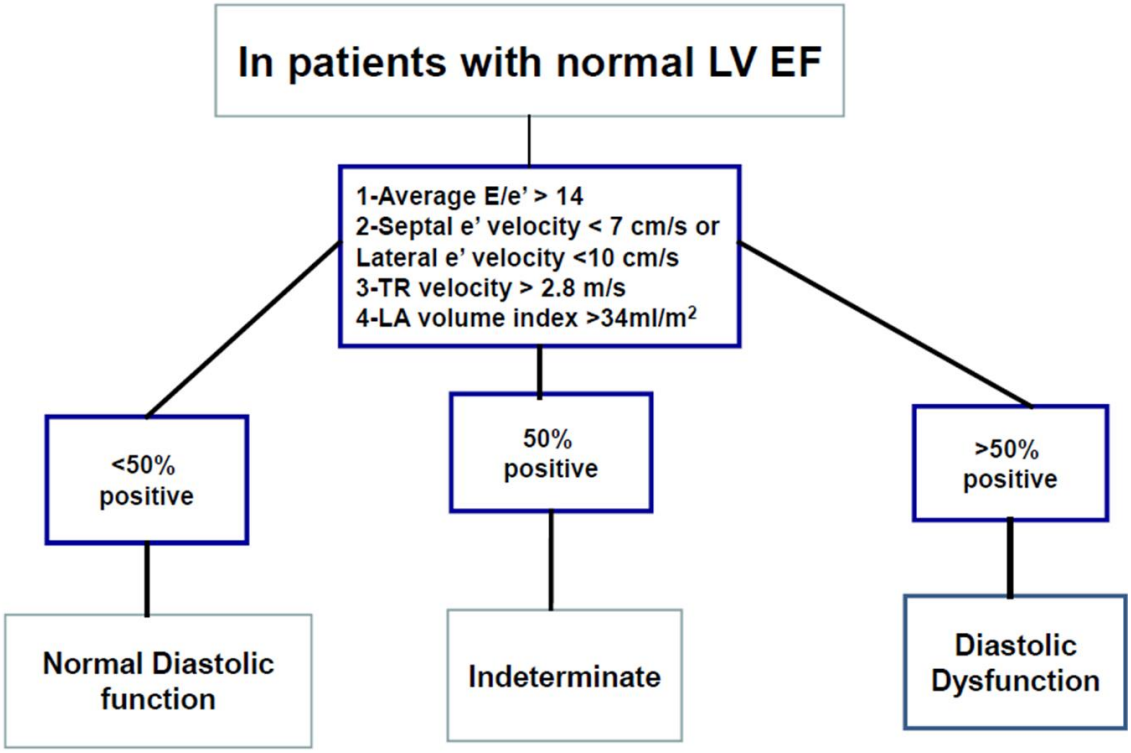


Figure 9. Evaluation of left ventricular diastolic function by echocardiography.
A. Doppler (E/A ratio) and tissue Doppler (e' velocity) profiles for the assessment of left ventricular diastolic function. (Left) Transmitral flow demonstrating early (E) and late/atrial (A) waves on pulsed-wave Doppler imaging at the mitral leaflet tips. (Right) Pulsed-wave tissue Doppler velocities at the septal/lateral mitral annulus. B. Stages of diastolic dysfunction (Mitter SS, et al. J Am Coll Cardiol. 2017) (41). C. Clinical conditions in which it is difficult to assess the left ventricular diastolic function by transmitral flow pattern (E/A ratio) (Hirotsugu Yamada, echocardiography pocket notebook). *In patients with atrial fibrillation, Doppler assessment of left ventricular diastolic function is limited by the variability in cycle length and the absence of organized atrial activity. Other Doppler measurements that can be applied include peak acceleration rate of mitral E velocity and E/e' ratio. D. Algorithm for diagnosis of left ventricular diastolic dysfunction in subjects with normal left ventricular ejection fraction (LVEF). (Nagueh, et al. J Am Soc Echocardiogr. 2016) (42)

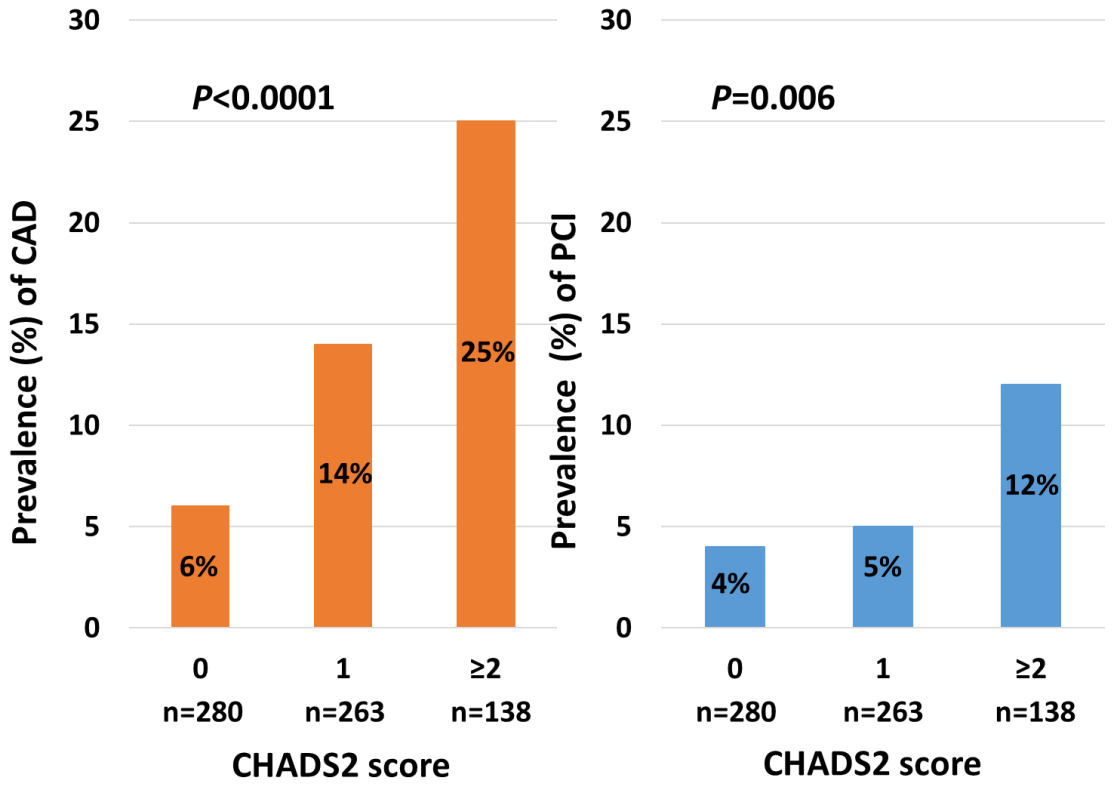
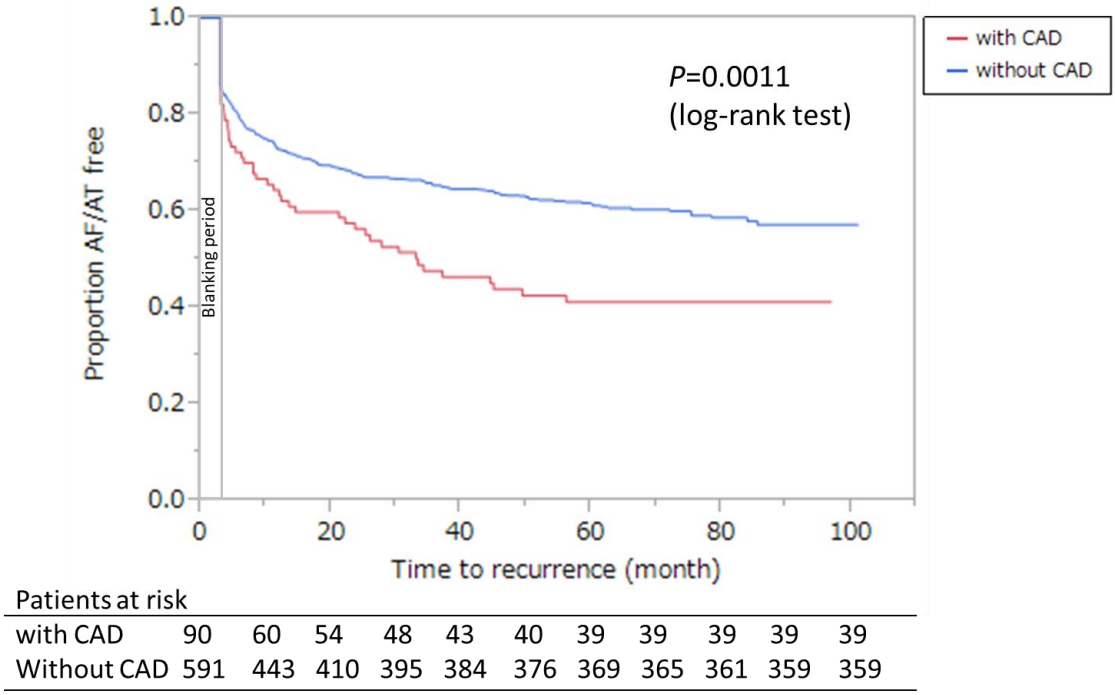


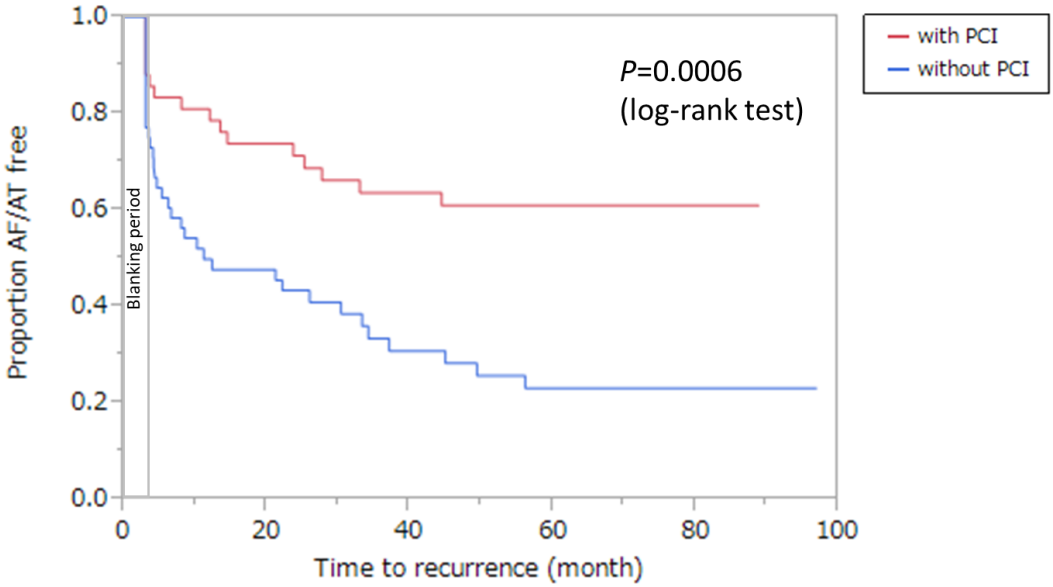
Figure 10. Prevalence of CAD and PCI according to the CHADS2 score.
CAD=coronary artery disease, PCI=percutaneous coronary intervention.



Patients at risk											
with CAD	90	60	54	48	43	40	39	39	39	39	39
Without CAD	591	443	410	395	384	376	369	365	361	359	359

Figure 11. Kaplan-Meier curves of the freedom from AF/AT after initial PVI in all patients.

AF=atrial fibrillation, AT=atrial tachycardia, PVI=pulmonary vein isolation, CAD=coronary artery disease.



Patients at risk											
with PCI	42	34	31	28	27	26	26	26	26	26	26
Without PCI	48	26	23	20	16	14	13	13	13	13	13

Figure 12. Kaplan-Meier curves of the freedom from AF/AT after initial PVI in the patients with CAD.

AF=atrial fibrillation, AT=atrial tachycardia, PVI=pulmonary vein isolation, CAD=coronary artery disease, PCI=percutaneous coronary intervention.

Table 1. Risk of stroke in National Registry of Atrial Fibrillation (NRAF) participants, stratified by CHADS2 score.

$CHADS_2$ Score	No. of Patients (n = 1733)	No. of Strokes (n = 94)	NRAF Crude Stroke Rate per 100 Patient-Years	NRAF Adjusted Stroke Rate, (95% CI)†
0	120	2	1.2	1.9 (1.2-3.0)
1	463	17	2.8	2.8 (2.0-3.8)
2	523	23	3.6	4.0 (3.1-5.1)
3	337	25	6.4	5.9 (4.6-7.3)
4	220	19	8.0	8.5 (6.3-11.1)
5	65	6	7.7	12.5 (8.2-17.5)
6	5	2	44.0	18.2 (10.5-27.4)

*CHADS2 score is calculated by adding 1 point for each of the following conditions: recent heart failure, hypertension, age at least 75 years, or diabetes mellitus and adding 2 points for having had a prior stroke or transient ischemic attack. †The adjusted stroke rate is the expected stroke rate per 100 patient-years from the exponential survival model, assuming that aspirin was not taken. (Gage BF, et al. JAMA. 2001) (39)

Table 2. Demographic and clinical characteristics of the patients with and without coronary artery disease.

	All (n=681)	With CAD (n=90)	Without CAD (n=591)	P Value
Age	61±10	66±7	60±10	<0.0001
Sex (male)	555 (81%)	73 (81%)	482 (81%)	0.919
BMI, kg/m^2	23.9±2.8	23.1±2.9	24.0±3.1	0.0091
Type of AF				
Paroxysmal	455 (67%)	64 (71%)	391 (66%)	0.347
Persistent	78 (11%)	9 (10%)	69 (12%)	0.636
Long-standing persistent	145 (22%)	15 (17%)	130 (22%)	0.238
Risk factors				
Hypertension	341 (50%)	62 (69%)	279 (47%)	0.0001
Dyslipidemia	325 (48%)	49 (54%)	276 (47%)	0.171
Diabetes mellitus	106 (16%)	26 (29%)	80 (13%)	0.0005
CKD	138 (20%)	27 (30%)	111 (19%)	0.018
CHADS2 score				<0.0001
0	280 (41%)	17 (19%)	263 (45%)	
1	263 (39%)	38 (42%)	225 (38%)	
≥2	138 (20%)	35 (39%)	103 (17%)	
BNP, pg/ml	81.9±17.6	101±110	76.9±96.6	0.033
Echocardiography				
Left atrial diameter, mm	39.4±6.9	40.9±6.4	39.1±6.9	0.024
LVEF, %	65.7±8.5	64.8±10.9	65.9±8.8	0.306
Medication				
Beta-blockers	437 (64%)	58 (64%)	379 (64%)	0.953
ACE-I/ARB	327 (48%)	61 (68%)	266 (45%)	<0.0001
Statins	213 (31%)	52 (58%)	161 (27%)	<0.0001

Values are reported as the means ± standard deviation, medians [interquartile range], or n (%). CAD=coronary artery disease, BMI=body mass index, AF=atrial fibrillation, CKD=chronic kidney disease, BNP=brain natriuretic peptide, LVEF=left ventricular ejection fraction, ACE-I=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker.

Table 3. Additional ablation of the patients with and without coronary artery disease.

	All (n=681)	With CAD (n=90)	Without CAD (n=591)	P Value
Linear ablation	221 (32%)	31 (34%)	190 (32%)	0.666
CFAE	125 (18%)	14 (16%)	111 (19%)	0.453
SVC	103 (15%)	9 (10%)	94 (16%)	0.086

CFAE=continuous fractionated atrial electrograms, SVC=superior vena cava.

Table 4. Univariable and multivariable cox regression analyses of the recurrence of atrial fibrillation.

Variables	Univariable		Multivariable	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Age	1.01 (0.99-1.02)	0.291	—	—
Male	1.05 (0.78-1.44)	0.729	—	—
Hypertension	1.07 (0.85-1.36)	0.530	—	—
Dyslipidemia	1.26 (0.99-1.59)	0.053	1.15 (0.90-1.47)	0.247
Diabetes mellitus	1.13 (0.82-1.53)	0.431	—	—
CKD	1.38 (1.04-1.80)	0.024	1.12 (0.83-1.48)	0.436
CHADS2 score ≥2	1.18 (0.88-1.55)	0.251		
Persistent/ Long-standing persistent	1.77 (1.39-2.24)	<0.0001	1.36 (1.04-1.77)	0.023
Left atrial diameter	1.05 (1.04-1.07)	<0.0001	1.04 (1.02-1.06)	<0.0001
CAD	1.62 (1.18-2.18)	0.002	1.45 (1.05-1.97)	0.024

HR=hazard ratio, CI=confidence interval, CKD=chronic kidney disease, CAD=coronary artery disease.

Table 5. Demographic and clinical characteristics of the patients with and without percutaneous coronary intervention for concomitant coronary artery disease.

	With PCI (n=42)	Without PCI (n=48)	P Value
Age	65±7	66±7	0.658
Sex (male)	36 (85%)	37 (77%)	0.293
BMI, kg/m^2	22.6±2.8	23.5±2.9	0.139
Type of AF			
Paroxysmal	31 (74%)	33 (69%)	0.596
Persistent	3 (7%)	6 (12%)	0.392
Long-standing persistent	6 (14%)	9 (19%)	0.569
Risk factors			
Hypertension	26 (62%)	36 (75%)	0.181
Dyslipidemia	24 (57%)	25 (52%)	0.631
Diabetes mellitus	15 (36%)	11 (23%)	0.181
CKD	12 (28%)	15 (31%)	0.782
CHADS2 score			0.151
0	11 (26%)	6 (12%)	
1	14 (33%)	24 (50%)	
≥2	17 (40%)	18 (38%)	
BNP, pg/ml	110±130	92.3±90	0.439
Echocardiography			
Left atrial diameter, mm	39.2±5.7	42.6±6.7	0.014
LVEF, %	63.7±10.3	65.8±11.3	0.362
E/E' baseline	10.2±5.7	8.4±3.5	0.109
⊿E/E'	2.34±2.78	1.0±2.34	0.014
Coronary Vessels			
LAD	27 (64%)	28 (58%)	0.466
LCX	18 (43%)	22 (46%)	0.855
RCA	27 (64%)	21 (44%)	0.037
Multi-vessel disease	24 (57%)	16 (34%)	0.021
Medication			
Beta-blockers	28 (67%)	30 (62%)	0.680
ACE-I/ARB	26 (62%)	35 (73%)	0.264
Statins	29 (69%)	23 (48%)	0.041

Values are reported as the means ± standard deviation, medians [interquartile range], or n (%).

⊿ E/E' was calculated as follows: baseline E/E' – follow-up E/E'. PCI=percutaneous coronary intervention, BMI=body mass index, AF=atrial fibrillation, CKD=chronic kidney disease, BNP=brain natriuretic peptide, LVEF=left ventricular ejection fraction, LAD=left anterior descending artery, LCX=left circumflex artery, RCA=right coronary artery, ACE-I=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker.

Table 6. Univariable and multivariable cox regression analyses of the recurrence of atrial fibrillation in the patients with coronary artery disease.

Variables	Univariable		Multivariable	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Age	0.99 (0.95-1.04)	0.986	—	—
Male	1.23 (0.62-2.70)	0.561	—	—
Hypertension	0.96 (0.54-1.79)	0.912	—	—
Dyslipidemia	0.97 (0.56-1.71)	0.935	—	—
Diabetes mellitus	0.89 (0.46-1.61)	0.712	—	—
CKD	0.99 (0.52-1.77)	0.979	—	—
Persistent/ Long-standing persistent	1.36 (0.75-2.39)	0.297	—	—
Left atrial diameter	1.04 (0.99-1.09)	0.052	1.02 (0.98-1.07)	0.234
PCI	0.37 (0.20-0.66)	0.0008	0.39 (0.20-0.72)	0.002

HR=hazard ratio, CI=confidence interval, CKD=chronic kidney disease, PCI=percutaneous coronary intervention.