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Original Article

# Comparison of the effects of bepridil and aprindine for the prevention of atrial fibrillation after cardiac and aortic surgery: A prospective randomized study

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ABSTRACT

*Background:* Approximately one-third of the patients undergoing cardiovascular surgery reportedly experience paroxysmal atrial fibrillation (AF) during the postoperative period. However, the usefulness of antiarrhythmic drugs for preventing postoperative AF recurrence in the Japanese population has not been extensively studied.
*Methods:* From a total of 118 patients who developed postoperative paroxysmal AF between April 2009 and March 2011, 72 patients (45 men, mean age 68 ± 8 years) requiring treatment for postoperative AF due to symptoms lasting ≥ 30 min were enrolled to prospectively investigate the efficacy of oral bepridil (100 mg/day, $n=37$) or aprindine (40 mg/day, $n=35$).
*Result:* The AF recurrence-free survival rates at 1, 3, 7, and 14 days were 100%, 94%, 57%, and 49%, respectively, in the aprindine group, and 100%, 97%, 86%, and 76%, respectively, in the bepridil group ($P=0.028$, aprindine vs. bepridil).
*Conclusion:* Bepridil, at a fixed dose of 100 mg/day, was considered to be more effective than a routine dose of aprindine for the prevention of postoperative AF recurrence.


## 1. Introduction

It has been reported that 30–40% of patients undergoing open heart surgery experience paroxysmal atrial fibrillation (AF) during the postoperative period [1,2]. Postoperative AF may lead to the deterioration of cardiac hemodynamics, and may increase the incidence of serious complications such as ventricular tachyarrhythmia, heart failure, and ischemic stroke [1–3]. This may result in prolonged hospitalization, increased health care costs, and worsening of the clinical course after surgery [4–6]. The prompt treatment of postoperative AF will improve prognoses and decrease health care costs for patients following cardiovascular surgery. However, most previous reports on the efficacy of medical prevention for paroxysmal AF after cardiovascular surgery have focused on the use of amiodarone [6–9], beta blockers [9,10], and sotalol [7,9,11]. Moreover, the efficacy of other anti-arrhythmic drugs for the prevention of AF recurrence remains unclear.

In the present study, we aimed to prospectively compare the efficacy and safety of bepridil and aprindine for the prevention of paroxysmal AF recurrence after cardiovascular surgery.

## 2. Material and methods

### 2.1. Study design

A total of 459 consecutive patients underwent planned heart/aortic surgery at our institution between April 2009 and March 2011. After the exclusion of 31 patients with chronic AF, 428 subjects (279 males and 149 females; mean age, 65 ± 13 years; range, 20–88 years) in whom continuous sinus rhythm was confirmed preoperatively were selected for participation in the study; the Institutional Review Board of our hospital approved the study (Number: H26-113, Date: 17th/November/2014).

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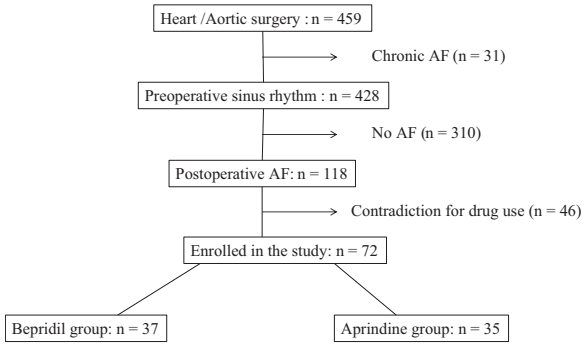


**Fig. 1.** Patient enrollment chart. AF, atrial fibrillation.

Prior to surgery, all patients were evaluated by chest radiography, 12-lead electrocardiography, transthoracic echocardiography, pulmonary function testing, and other noninvasive examinations. When the attending physicians considered it necessary, patients underwent additional examinations such as exercise tolerance testing, transesophageal echocardiography, and cardiac catheterization. Patients were interviewed to determine their history of paroxysmal AF and heart/aortic disease, and the medical records were reviewed to assess the types of drugs that had been used before surgery, C-reactive protein levels, and hepatic/renal function.

During preoperative examinations, the following patients were excluded from the study: those with serious bradyarrhythmia (e.g., sick sinus syndrome, atrioventricular block, or intraventricular conduction defect); those with an ejection fraction of $\leq 40\%$ on transthoracic echocardiography; those with abnormal hepatic/renal function test results; those who might be pregnant; those with urinary retention or glaucoma; and those with a history of drug allergies.

All cases underwent electrical pulmonary vein isolation using cryoablation if paroxysmal or persistent AF was recorded on their 12-lead electrocardiogram before heart/aortic surgery. The decision for performing cryoablation was left to the surgeon.

Postoperative AF was diagnosed definitively by standard 12-lead electrocardiography, and all cases were confirmed as having a left ventricular ejection fraction of $\geq 40\%$ on preoperative cardiac ultrasonography. Sinus rhythm was then established by electrical cardioversion. Thereafter, subjects were orally administered either bepridil hydrochloride (100 mg/day) or aprindine (40 mg/day) after random sampling using the envelope method. AF recurrence was monitored by continuous electrocardiographic observation and the development of any adverse effects was assessed for two weeks after cardiovascular surgery. Moreover, in patients with recurrent AF after the use of one of these first-line drugs, sinus rhythm was re-established by further electrical defibrillation. We then estimated the preventive efficacy of other drugs that had not been selected as first-line therapies for AF recurrence. Informed consent was obtained from all subjects prior to cardiovascular surgery.

### 2.2. Definitions

Postoperative paroxysmal AF was defined as electrocardiogram findings consistent with AF that continued for at least 5 min during hospitalization [6,12]. Transient ischemic attack was defined as the occurrence of neurological signs/symptoms that disappeared spontaneously within 24 h of onset. Ischemic stroke was diagnosed on the basis of the occurrence of neurological signs/symptoms and the detection of an ischemic lesion, 3 mm in size, on brain computed tomography or magnetic resonance imaging. Patients with paroxysmal AF were classified into the following 3 categories according to when episodes of palpitations developed: diurnal type (episodes occurring 07:00–17:00, when the sympathetic nervous system dominates), nocturnal type (episodes occurring 17:00 –07:00, when the parasympathetic nervous system dominates), and mixed type (episodes occurring irrespective of circadian variation) [13,14]. Hypertension was defined based on the blood pressure value recommended by the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH2009) [15].

### 2.3. Statistics

Continuous data are expressed as mean $\pm$ standard deviation. Inter-group comparisons were performed using the Mann-Whitney U-test for continuous variables, and the chi-square test for non-continuous variables. Survival curves were estimated by the Kaplan-Meier method and compared with the log-rank test (Cox-Mantel). All statistical analyses were performed using the SPSS 13.0 statistical package. In all of these tests, $P$ values of $< 0.05$ were considered statistically significant.

## 3. Results

### 3.1. Comparison of the frequency of postoperative paroxysmal AF and patient background factors

Postoperative AF occurred in 118 (27.6%) of the 428 subjects (males 76, females 42; average age, $68 \pm 10$ years). After excluding patients with drug contradictions such as serious bradyarrhythmia, an ejection fraction of $\leq 40\%$, abnormal hepatic/renal function test results, current pregnancy, urinary retention or glaucoma, or a history of drug allergies, 72 cases were enrolled in this present study and underwent treatment for the prevention of AF using oral anti-arrhythmic drug therapy based on subjective symptoms and cardiac hemodynamics (Fig. 1). The mean follow-up period of the study was $30 \pm 11$ days. Table 1 shows a comparison of patient characteristics in the bepridil ($n=37$) and aprindine groups ($n=35$). There were no significant differences between the two groups in terms of any of the indices (Table 1).

### 3.2. Preventive effect and safety of oral anti-arrhythmic drugs for postoperative AF

The recurrence-free survival rates at 1, 3, 7, and 14 days were 100%, 94%, 57%, and 49%, respectively, in the aprindine group, and 100%, 97%, 86%, and 76%, respectively, in the bepridil group. There was a significant difference in the recurrence-free survival rates between the groups ($P=0.0278$, Fig. 2). In cases where AF was refractory to bepridil as a first-line therapy, the use of aprindine as a second-line therapy yielded a recurrence-free survival rate of 25% (2 of 8 cases). The use of bepridil as a second-line therapy for AF refractory to aprindine was 55% (6 of 11 cases) ($P=0.352$). There was no significant difference in AF recurrence rates between aprindine and bepridil therapy after the second-line therapy. Adverse effects requiring the discontinuation of antiarrhythmic drug therapy were observed in 1 patient (3.0%, sinus arrest) in the bepridil group and none in the aprindine group.

## 4. Discussion

AF reportedly develops after cardiac surgery due to certain preoperative baseline clinical characteristics such age [1,2,16,17], male sex [2,17], cardiac valvulopathy [1,16], anamnestic AF [1,17], cardiac arrest [1,17], basic pulmonary disease [1,17], and neglecting the internal use of beta blockers [1,16]. In addition, specific perioperative events (inflammation, stress, atrial ischemia, and pulmonary venous blood removal due to surgical stress) and postoperative

**Table 1**
Comparison of clinical characteristics between bepridil and aprindine groups.

| | Bepridil group | Aprindine group | *P* value |
|---|---|---|---|
| Number of patients | 37 | 35 | |
| Observation period (days) | 32 ± 12 | 29 ± 10 | 0.420 |
| Age (years) | 67 ± 9 | 70 ± 8 | 0.200 |
| Body weight (kg) | 56 ± 10 | 60 ± 15 | 0.316 |
| Male:female | 16:21 | 11:24 | 0.301 |
| Hypertension | 22 (59%) | 24 (69%) | 0.421 |
| Diabetes mellitus | 7 (19%) | 12 (34%) | 0.184 |
| Dyslipidemia | 14 (37%) | 12 (34%) | 0.754 |
| Smoking | 5 (13%) | 5 (14%) | 0.925 |
| Alcohol | 2 (5%) | 2 (6%) | 0.954 |
| Hyperuricemia | 1 (3%) | 2 (6%) | 0.523 |
| Underlying heart disease | 32 (86%) | 28 (80%) | 0.460 |
| Old myocardial infarction | 5 (13%) | 4 (11%) | 0.999 |
| Angina pectoris | 8 (22%) | 9 (26%) | 0.784 |
| Cardiac valvular disease | 18 (49%) | 18 (51%) | 0.999 |
| Atrial septal defect | 3 (8%) | 0 (0%) | 0.240 |
| Underlying pulmonary disease | 3 (8%) | 1 (3%) | 0.331 |
| Symptomatic period (months) | 9 ± 12 | 8 ± 11 | 0.380 |
| LVDd (mm) | 47.4 ± 8.7 | 48.6 ± 7.5 | 0.221 |
| LAD (mm) | 41.0 ± 10.1 | 43.6 ± 9.0 | 0.985 |
| LVEF (%) | 61.3 ± 10.9 | 62.1 ± 8.9 | 0.273 |
| IVS (mm) | 12.1 ± 2.4 | 13.3 ± 2.3 | 0.528 |
| LVPW (mm) | 12.1 ± 1.8 | 13.0 ± 2.7 | 0.141 |
| Preoperative RAAS inhibitors | 12 (32%) | 16 (46%) | 0.248 |
| Preoperative statins | 10 (27%) | 10 (29%) | 0.884 |
| Preoperative β-blockers | 20 (54%) | 17 (49%) | 0.642 |
| Days of post-operative | | | |
| AF occurrence | 5.3 ± 3.9 | 4.9 ± 4.5 | 0.788 |
| The onset of paroxysmal AF (diurnal:nocturnal:mixed) | 9:8:20 | 5:11:19 | 0.349 |
| Surgical procedure | | | |
| Coronary artery bypass grafting | 11 (30%) | 16 (46%) | 0.161 |
| Mitral valve replacement | 9 (24%) | 9 (26%) | 0.892 |
| Aortic valve replacement | 12 (32%) | 10 (29%) | 0.722 |
| Tricuspid valve reefing | 1 (3%) | 2 (6%) | 0.523 |
| Pulmonary vein isolation | 8 (22%) | 7 (20%) | 0.866 |
| Thoracic aortic surgery | 8 (22%) | 6 (17%) | 0.631 |
| Abdominal aortic surgery | 1 (3%) | 1 (3%) | 0.968 |
| Peripheral arterial surgery | 4 (11%) | 1 (3%) | 0.185 |
| Postoperative complication | 3 (8%) | 3 (9%) | 0.965 |
| Ischemic stroke | 0 (0%) | 2 (6%) | 0.140 |
| Infection | 2 (5%) | 0 (0%) | 0.163 |
| Cardiac tamponade | 0 (0%) | 1 (3%) | 0.300 |
| Atrioventricular block | 1 (3%) | 0 (0%) | 0.327 |

*Abbreviations*: AF, atrial fibrillation; RAAS, rennin angiotensin aldosterone system; LVDd, left ventricular end-diastolic dimension; LAD, left atrial dimension; LVEF, left ventricular ejection fraction; IVS, intraventricular septum; LVPW, left ventricular posterior wall.

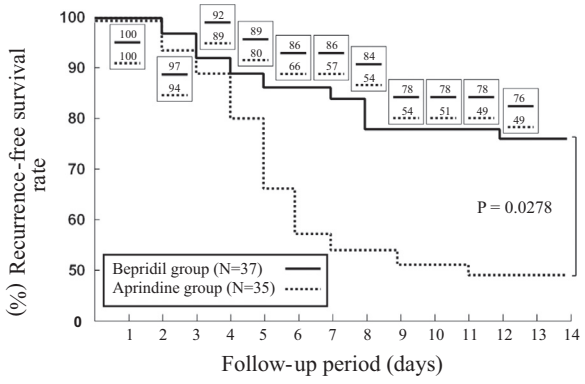


**Fig. 2.** Survival curves of atrial fibrillation recurrence-free survival between the bepridil and aprindine groups.

events (volume overload, increases in afterload, reductions in blood pressure, and electrolyte abnormalities) might be important factors inducing postoperative AF [18]. Thus, the underlying mechanisms involved in postoperative AF development are multifactorial, and are currently not fully understood. However, some other causative mechanisms have been proposed, including pericardial inflammation, myocardial ischemia, excessive production of catecholamines, autonomic imbalances during the postoperative period, and neurohumoral environments. The mechanisms of AF occurrence between postoperative AF and ordinary AF may be different.

According to the ACC/AHA/ESC guidelines for the prevention of paroxysmal AF after cardiac surgery, oral beta blockers are a Class I indication and oral amiodarone or preoperative oral antiarrhythmic drugs are a Class IIa indication [19]. On the other hand, according to the Japanese Circulation Society's guidelines (JCS 2008), bepridil, aprindine, sotalol, and amiodarone are recommended as first-line drugs for preventing paroxysmal AF in the presence of underlying cardiac disease [20]. In Japan, the use of sotalol and amiodarone for the prevention of AF after cardiac surgery is not covered by insurance. Therefore, this study compared the pharmacological efficacy of bepridil and aprindine for the prevention of paroxysmal AF after cardiac surgery. Our results show that bepridil is superior to aprindine for this purpose.

Bepridil is a multichannel blocker, suggesting that its pharmacological effects on cardiac myocytes are exerted by blocking Na [21], Ca [22], and K [23–25] channels. It has recently been reported

that bepridil has a cardioprotective effect [26] by opening ATP-dependent K channels in mitochondria and suppressing ATP-dependent K channels in sarcomeres. In addition, it attenuates Ca overload by blocking the $Na^{+}$-$Ca^{2+}$ interchange mechanism [27–28] and increases $Ca^{2+}$ susceptibility [29,30], thus maintaining cardiac hemodynamics. Furthermore, bepridil has been shown to have a reverse remodeling effect on atrial myocytes in a frequent pacing experimental model [31], and reportedly attenuates the premature contractions that trigger AF via suppression of the stretch-activated channels of cardiac myocytes [32]. Thus, it is probable that the anti-arrhythmic efficacy of bepridil and its pleiotropic actions such as myocardial protection, atrial pressure load reduction, reverse remodeling, and attenuation of premature contractions contribute to its efficacy in preventing postoperative AF, where the underlying cardiac disease is strongly correlated with AF development. In addition, aprindine requires several days to reach a stable and effective blood concentration. It is thus probable that the rapid pharmacological efficacy of bepridil influenced the results of the present study.

The predictors of AF recurrence and chronicity after anti-arrhythmic treatment for maintaining sinus rhythm reportedly include the duration of AF [33], AF history [34], left atrial dimension [35], underlying cardiac disease [36], aging [37], and development of the mixed type [38]. In this prospective randomized study, these factors did not differ significantly between the bepridil and aprindine groups. There is thus a low probability that these factors significantly influenced our results.

### 4.1. Study limitations

The present study was prospective in nature, but did not utilize a placebo group for evaluating the efficacy of AF recurrence prevention. It cannot be completely denied that AF may recur without medication. According to reports of multicenter trials in Europe and the US, the cumulative recurrence-free survival rate was as low as 7% [39] after 1 month of follow-up. The mean follow-up period in the present study was also short (approximately 1 month). We suggest that the placebo effect had little impact on our results. Second, the incidence of postoperative paroxysmal AF was similar to that in previous reports [7,8]. We may have overlooked asymptomatic AF [40] because we did not perform continuous electrocardiographic monitoring in all cases for 2 weeks postoperatively. Third, as we did not assess the refractory period and conduction time in atrial muscle before and after administering the anti-arrhythmic drugs, we did not determine the electrophysiologic mechanism underlying postoperative paroxysmal AF. However, Workman et al. reported no significant difference in action potential duration, maximal action potential rate of rise, and effective refractory period between patients who developed preoperative paroxysmal AF and those who did not [41]. Finally, our sample size was relatively small, and therefore, multi-center trials will be needed in the future to more fully evaluate the efficacy of anti-arrhythmic drugs for the prevention of postoperative paroxysmal AF.

## 5. Conclusion

Bepridil appears to be more effective than aprindine in preventing postoperative AF recurrence.

## Conflict of interest

All authors declare that they have no conflict of interest.

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