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Amiodarone Versus Propafenone to Treat Atrial Fibrillation after Coronary Artery Bypass Grafting: A Randomized Double Blind Controlled Trial

Mohammad Hassan Nemati, M.D.[1], Behrooz Astaneh, M.D.[2]

Background: Atrial fibrillation (AF) is one of the most common complications after cardiac surgery. Several therapeutic and preventive strategies have been introduced for postoperative AF, but the treatment and prophylaxis of AF remain controversial. We aimed to compare the efficacy of intravenous amiodarone and oral propafenone in the treatment of AF after coronary artery bypass grafting (CABG). ***Methods:*** This was a randomized controlled trial performed in two hospitals in Shiraz, Iran from 2009 to 2012. We included all patients who underwent elective CABG and developed AF postoperatively. The patients were randomly assigned to receive propafenone or amiodarone. The duration of AF, the success rate of the treatment, the need for cardioversion, the frequency of repeated AF, and the need for repeating the treatment were compared. ***Results:*** The duration of the first (p=0.361), second (p=0.832), and third (p=0.298) episodes of AF, the need for cardioversion (p=0.998), and the need to repeat the first and second doses of drugs (p=0.557, 0.699) were comparable between the study groups. Repeated AF was observed in 17 patients (30.9%) in the propafenone group and 23 patients (34.3%) in the amiodarone group (p=0.704). ***Conclusion:*** Oral propafenone and intravenous amiodarone are equally effective in the treatment and conversion of recent-onset AF after CABG.

Key words: 1. Amiodarone
2. Propafenone
3. Coronary artery bypass
4. Atrial fibrillation

INTRODUCTION

Atrial fibrillation (AF) is one of the most common complications observed after cardiac surgery, and is associated with high morbidity, mortality, and increased healthcare expenses [1-3]. Several factors affect the incidence and the characteristics of post-cardiac surgery AF, such as the duration of the operation, the type of the operation, the patients' characteristics, and the method of arrhythmia monitoring [1-5]. The incidence of AF after coronary artery bypass grafting (CABG) has been reported to range from 27% to 33% [1-3]. The incidence increases by age and according to the utilization of more aggressive techniques [3]. The risk factors for AF after CABG have been reported to be higher age, prolonged atrial conduction, hypertension, left ventricular hypertrophy, use of digoxin, history of rheumatic heart disease, peripheral vascular insufficiency and disease, obstructive lung disease, and increased aortic cross-clamp duration [1-3,6,7].

[1]Department of Cardiothoracic Surgery, Shiraz University of Medical Sciences, [2]Medical Journalism Department, Paramedical School, Shiraz University of Medical Sciences
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Corresponding author: Mohammad Hassan Nemati, Cardiac Surgery Department, Shahid Faghihi Hospital, Zand Avenue, Shiraz, Fars, Iran
(Tel) 98-71-32351085 (Fax) 98-71-32351091 (E-mail) nemati_mhs@yahoo.com

Several therapeutic and preventive strategies have been introduced for postoperative AF, but the treatment and prophylaxis of this condition remain controversial [8,9]. The most important step in the treatment of postoperative AF is maintaining sinus rhythm and stabilizing patients' hemodynamic status [10]. Although electrical cardioversion is considered the gold standard for the treatment of recent-onset AF [11,12], the use of intravenous or oral antiarrhythmic drugs is more feasible, accessible, and is associated with fewer complications [2-6]. Previous studies have demonstrated that both propafenone [13,14] and amiodarone [15,16] are highly effective in restoring sinus rhythm in patients with recent-onset AF, especially after cardiac operations. However, data regarding the comparison of these two agents in maintaining sinus rhythm are scarce [17-19]. Previous reports have demonstrated that oral amiodarone and propafenone are equally effective and safe in the termination of chronic [17] as well as acute-onset AF [18,19]. They have also shown that propafenone has a faster effect than amiodarone in terminating recent-onset AF [18]. The aim of this study was to compare the efficacy of intravenous amiodarone and oral propafenone in the termination of recent-onset AF after CABG.

METHODS

1) Study population

This study was a randomized double-blind controlled trial, and was performed in the Ordibehesht and Central Hospitals, both private subspecialty healthcare centers in Shiraz, southern Iran, from November 2009 to March 2012. The protocol of the study was approved by the institutional review board and the Ethics Committee of Shiraz University of Medical Sciences. All patients provided written informed consent before being included in the study. The clinical trial protocol was registered with the Iranian Registry of Clinical Trials (IRCT138809092795N1; http://www.irct.ir).

All patients who were scheduled for elective CABG due to ischemic heart disease diagnosed by coronary artery angiography were examined and evaluated for postoperative AF. The patients who developed AF after CABG were included in the study.

Patients who underwent emergency CABG, those undergoing concomitant cardiac operations such as valvular procedures, those with bradycardia (＜50 beats/min in resting position), and those with more than type I second-degree heart block were excluded from the study. We also excluded patients with symptomatic sick sinus syndrome without a permanent pacemaker, those taking class I or III antiarrhythmic medications, those who had a history of AF within the previous six months, and those with a history of sensitivity to propafenone. Patients with cardiogenic shock, an ejection fraction ＜30%, marked hypotension (systolic blood pressure ＜90 mmHg), and electrolyte imbalances were also excluded from the study. The concomitant use of digoxin, calcium channel blockers, and β-blockers was not controlled for.

2) Randomization and intervention

The patients were randomized to two study groups using a random-digit table after developing post-CABG AF. Those who were assigned to the propafenone group received 600 mg of oral propafenone (ShahreDaru, Tehran, Iran) as a loading dose and 150 mg every eight hours for 10 days after the onset of AF (n=55). Those who were assigned to the amiodarone group received 300 mg as an intravenous loading dose of amiodarone (EBEWE Pharma, Unterach, Austria) followed by a continuous intravenous infusion of 600 mg over 12～24 hours after the occurrence of AF (n=67). In cases where AF continued after the first dose, the protocol shown in Fig. 1 was followed.

3) Study protocol

All patients who were found to be eligible for the study were visited the day before the operation. All patients underwent a complete history and physical examination by the cardiac surgeon and the baseline information (demographic characteristics, risk factors, medications, concomitant medical conditions, and history of previous admissions and operations) were recorded in the data-gathering form. Baseline laboratory tests were also performed in all patients.

All patients underwent on-pump CABG performed by a single cardiothoracic surgeon with cold-potassium cardioplegia and aortic-root venting. The patients were then transferred to the cardiac surgery intensive care unit (ICU) for postoperative care. Postoperatively, continuous electrocardiographic monitor-

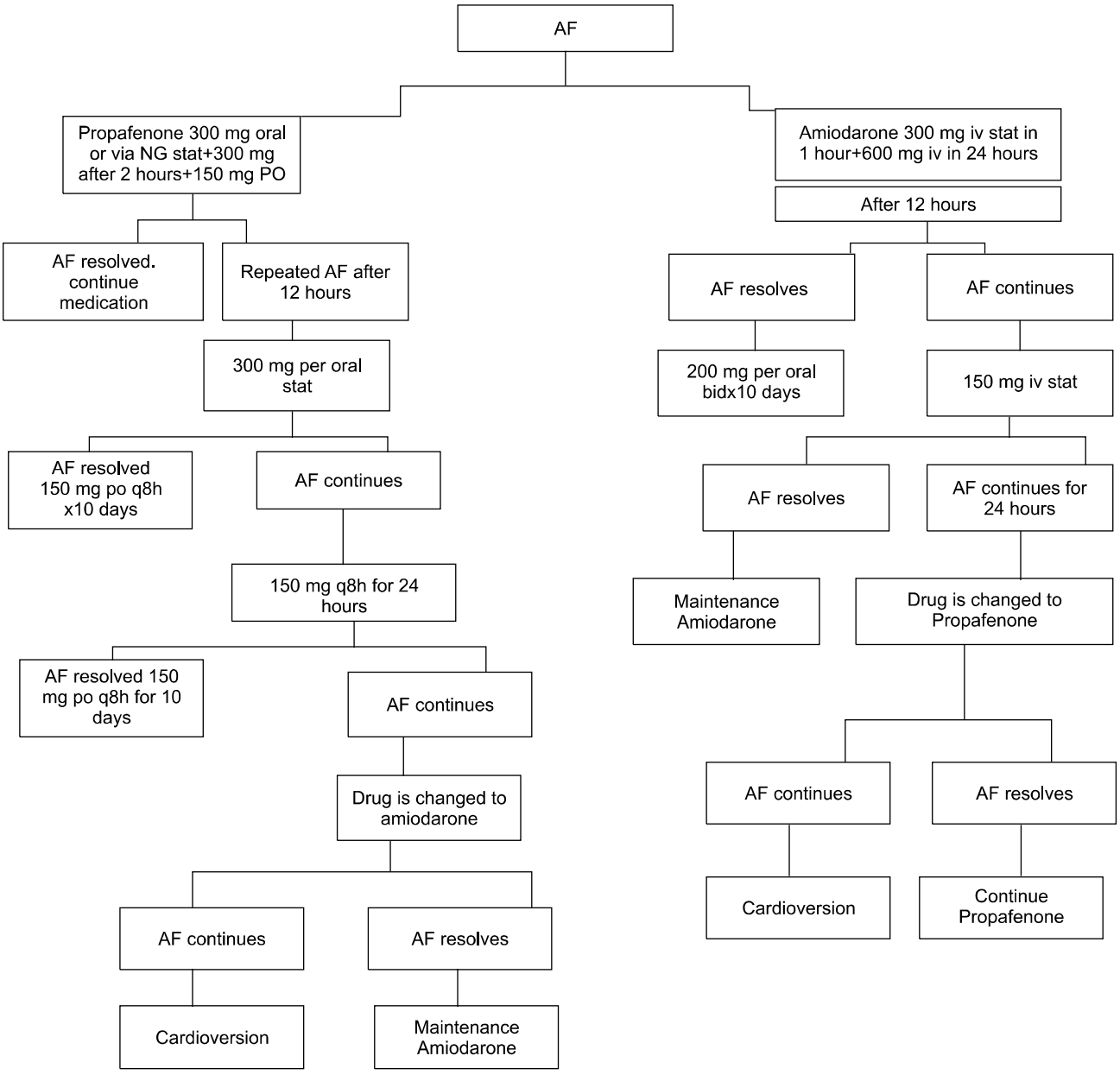

Fig. 1. Study protocol. AF, atrial fibrillation; NG, nasogastric tube; PO, per oral; iv, intravenous; bid, twice a day; q8h, every 8 hours.

ing was performed for at least 96 hours. Postoperative AF was defined as continuous AF for at least 30 minutes or AF requiring treatment for symptoms or hemodynamic compromise. As soon as any abnormal cardiac rhythm developed, a trained ICU nurse differentiated AF from other types of arrhythmia in order to call the designated intensive care physician to visit the patient and diagnose any other accompanying signs such as hypotension. The patients were treated based on their assigned group according to the protocol of the study (Fig. 1).

The success rate of AF treatment and the duration of AF were the primary endpoints of this study. The secondary outcomes included the recurrence of AF, the duration of the recurrent AF, the need for cardioversion, the need for other medical therapies, and the patients' outcome. We also recorded the time of onset and the duration of AF at any stage,

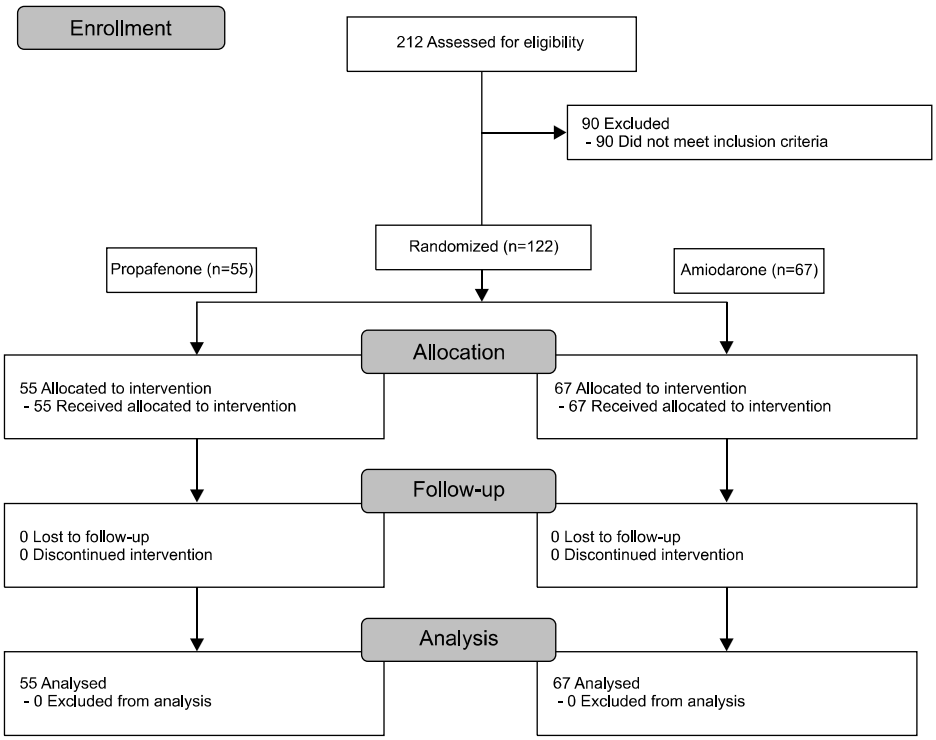

Fig. 2. Consolidated Standards for Reporting Randomized Trials flow diagram.

the AF recovery time after administering the drugs, and the response rate to each drug. All the staff involved in this trial including the cardiothoracic surgeon, intensive care physicians, the physicians performing randomization and allocation, and those recording the results and outcomes were blinded to the study group of the patients. As the intervention was given by the ICU nurses, they were not blinded to the patients' groups, but they were blinded regarding the outcome of each patient. Only the statistician was aware of the study groups.

4) Statistical analysis

For this trial, all eligible patients were recruited. All statistical analyses were performed using the SPSS for Windows ver. 16.0 (SPSS Inc., Chicago, IL, USA). The independent t-test was used to compare the results between the groups; and the chi-square test or Fisher's exact test was used to compare the proportions. The Mann-Whitney U-test was used to compare the parametric data without a normal distribution between the two study groups. The data are reported as means±standard deviations or proportions as appropriate. Two-sided p-values <0.05 were considered to indicate statistical significance.

RESULTS

Overall, 1,991 patients underwent CABG in these two centers between 2009 and 2012, of whom 212 developed post-CABG AF and were eligible to be included in the study. The number of patients who were excluded from the study was 90; thus, the number of patients who were randomized to the two study groups was 122 (55 in the propafenone group and 67 in the amiodarone group). None of the patients were lost to follow-up or were further excluded from the study; therefore, the final number of the patients included in the final analysis was 122, with 55 in the propafenone group and 67 in the amiodarone group (Fig. 2).

Table 1 summarizes the baseline characteristics of the patients in the two study groups. No significant differences were found between the two study groups regarding demographic characteristics and risk factors for AF. Serum levels of potassium as well as the patients' drugs were also comparable between the two study groups (Table 1).

The results of AF treatment and the success rate are presented in Table 2. The mean interval between the onset of AF and the initiation of the treatment was comparable be-

Table 1. Baseline characteristics of 122 patients who developed post-coronary artery bypass grafting atrial fibrillation according to treatment group

Characteristic	Propafenone (n=55)	Amiodarone (n=67)	p-value
Age (yr)	66.7±8.7	68.1±9.9	0.437
Risk factors			
Hypertension	39 (70.9)	52 (77.6)	0.412
Hyperlipidemia	38 (69.1)	45 (67.2)	0.848
Diabetes mellitus	28 (50.9)	33 (49.3)	0.999
Congestive heart failure	0	2 (3.1)	0.501
Chronic obstructive pulmonary disease	9 (16.4)	21 (31.8)	0.059
Right atrium enlargement	0	1 (1.6)	0.998
Intra-aortic balloon pump	5 (9.1)	6 (9.1)	0.999
Previous atrial fibrillation	5 (9.1)	2 (3.2)	0.245
Drugs			
β-blocker	48 (87.3)	54 (80.6)	0.462
Calcium channel blocker	5 (9.1)	8 (12.5)	0.769
Angiotensin converting enzyme inhibitor	19 (34.5)	16 (25.8)	0.320
Preoperative K^+ (meq/L)	4.21±0.51	4.23±0.71	0.830

Values are presented as mean±standard deviation or number (%).

Table 2. Comparison of the characteristics and outcomes of atrial fibrillation therapy with propafenone and amiodarone in 122 patients who underwent coronary artery bypass grafting

	Propafenone (n=55)	Amiodarone (n=67)	p-value
AF therapy interval (min)	22.8±34.5	14.2±12.1	0.803
AF duration, first episode (min)	262.5±321.5	384.1±428.4	0.361
AF duration, second episode (min)	62.5±201.8	85.2±254.8	0.832
AF duration, third episode (min)	17.1±62.3	13.8±86.3	0.298
Cardioversion	2 (3.6)	3 (4.5)	0.998
Repeated AF	17 (30.9)	23 (34.3)	0.704
Repeat of the first drug	15 (27.3)	22 (32.8)	0.557
Repeat of the second drug	4 (7.4)	3 (4.5)	0.699

Values are presented as mean±standard deviation or number (%).
AF, atrial fibrillation.

tween the groups (22.8±34.5 minutes vs. 14.2±12.1 minutes, p=0.803). Likewise, the durations of the first (p=0.361), second (p=0.832), and third (p=0.298) episodes of AF were comparable between those who received amiodarone and those who received propafenone. Repeated AF was recorded in 17 patients (30.9%) in the propafenone group and 23 patients (34.3%) in the amiodarone group, which was comparable (p=0.704). The need for cardioversion (p=0.998), the need to repeat the first dose of the drug (p=0.557), and the need to repeat the second dose of the drug (p=0.699) were also comparable between the study groups. Table 2 additionally shows how many patients developed repeated AF after receiving different rounds of drug administration. As shown in the table, for example, 55 patients who developed AF received propafenone, of whom only 17 patients were not converted to sinus rhythm and the drug was administered repeatedly. Again, if AF did not convert, according to the protocol in Fig. 1, the same drug was either continued or the patient was changed to the other drug. Ultimately, only two patients in the propafenone group and three patients in the amiodarone group needed cardioversion, and all of them eventually recovered from AF. Finally, all patients recovered, showing the efficacy of management using these two drugs to treat AF.

DISCUSSION

Despite advances in cardiovascular surgery, AF after CABG remains a common and disruptive complication associated with increased morbidities, such as coronary ischemia, ventricular arrhythmias, infection, thromboembolic events, and congestive heart failure [2,3]. These complications increase the duration of the hospital stay as well as the costs and expenses of care [3,4]. Amiodarone and propafenone are considered to be potent and effective antiarrhythmic drugs. In recent-onset AF, the potency and effectiveness of both drugs are similar to that of electrical cardioversion [1-3]. Some studies have shown oral propafenone [13,14] and amiodarone [15,16] to be effective agents in converting recent-onset or chronic AF. It has also been reported that oral propafenone or intravenous amiodarone can be used for the prophylaxis of AF after cardiac operations, including CABG [20-22]. However, very few studies have compared the efficacy of amiodarone and propafenone in the treatment of post-CABG AF [23-25]. In the current study, we attempted to compare the efficacy of oral propafenone with intravenous amiodarone in the treatment of recent-onset AF after CABG. We found that the duration of AF, the recurrence of AF, and the need for cardioversion and repeating the first and second doses of the drug were all comparable between the two study groups. Therefore, intravenous amiodarone and oral propafenone were found to be equally effective in the conversion and treatment of recent-onset AF after CABG.

Propafenone and amiodarone share similar characteristics, although they have different mechanisms of action. Propafenone is classified as class Ic antiarrhythmic drug that prolongs the conduction of electrical impulses in the atrial myocardium [26]. Amiodarone, however, is a class III antiarrhythmic drug that prolongs the refractory period in the cells of the atrial myocardium [26,27]. The mechanism of AF after CABG is believed to be atrial re-entry, meaning that drugs that cut the circuit of re-entry could be used in the management of AF.

The effectiveness of these two drugs has been widely studied for both recent-onset or chronic AF [13-16]. However their effectiveness for the treatment of AF after CABG has not been adequately studied. Eremenko et al. [23] compared the antiarrhythmic activity of amiodarone and propafenone used to prevent AF after CABG. They started antiarrhythmic therapy within 24 hours after CABG. They gave the first group intravenous amiodarone at a dosage of 6 mg/kg/day, whereas the second group received oral propafenone at a dosage of 6.6 mg/kg/day. The results of their study demonstrated that propafenone was more effective for the prevention of AF after CABG [23]. In another study, Larbuisson et al. [24] compared the efficacy and safety of amiodarone and propafenone in the conversion of AF or atrial flutter after CABG. The patients received intravenous propafenone (1–2 mg/kg in a 10-minute bolus dose, followed by an infusion of 420 mg over 24 hours), or amiodarone (2.5–5 mg/kg in a 10-minute bolus dose followed by an infusion of 900 mg in 24 hours). They likewise found that propafenone produced a more prompt effect in converting AF or flutter to normal sinus rhythm [24]. Di Biasi et al. [25] also compared the efficacy and safety of amiodarone and propafenone for treating AF after CABG. They treated the patients with amiodarone (46 patients; 5 mg/kg over 15 minutes and then 15 mg/kg over the subsequent 24 hours for non-converting patients) or propafenone (38 patients; 2 mg/kg over 15 minutes and then 10 mg/kg over the subsequent 24 hours for non-converting patients). They found that the two drugs were equally effective in converting postoperative AF or flutter after 24 hours, although propafenone was superior within the first hour [25]. The results of these studies are contrary to ours. We found that both drugs were equally effective in treating and converting AF after CABG.

Several risk factors have been reported for AF after CABG, including the perioperative use of β-blockers, chronic obstructive pulmonary disease, congestive heart failure, left ventricular end-diastolic pressure, the type of cardioplegia, the type of cardiac venting, and perioperative pacing [2,3]. Among these, advanced age is the only independent predictor of AF after CABG [28]. A previous study demonstrated that patients in whom AF developed after CABG were an average of 5.7 years older than those who remained in sinus rhythm [29]. Currently, no standard prophylaxis regimen has been established for AF after CABG. Digoxin, calcium blockers, magnesium, glucose-insulin-potassium solution, and various cardioplegia are ineffective in preventing AF after CABG

[1-3,30-32]. However, propafenone and amiodarone may be successfully used for preventing AF after CABG [20-22].

In our study, propafenone and amiodarone were well tolerated by all patients and no significant side effects were recorded. However, previous reports have shown several adverse effects to be associated with treatment with these two drugs. Amiodarone is associated with several adverse effects, most of which are dose-dependent, which could explain why our patients did not experience the side effects of amiodarone, as they received a low dose with a short duration [26]. Propafenone has significant proarrhythmic effects, especially in those with structural heart disease. As we excluded patients with multiple types of organic heart disease, none of our patients developed side effects after being treated with propafenone. However, another report has also shown that both drugs are safe for treating AF after CABG [27].

We note some limitations to our study. First, the number of patients included in this study was limited. The incidence of AF after CABG is relatively low, and we therefore included all patients who met the inclusion criteria during our study period. Second, we did not measure the atrial dimensions, and data regarding the ejection fraction or the number of grafts were not collected, which may be another limitation of our study. The main strength of this study is the use of strict inclusion and exclusion criteria, which limited the role of confounding factors.

In conclusion, as we found that intravenous amiodarone and oral propafenone were equally effective and safe when used to treat and convert AF after CABG, it can be concluded that oral propafenone is a safe alternative for amiodarone in routine AF treatment after CABG. In light of the problems involved in the intravenous infusion of drugs and the fact that oral medications are tolerated by more patients, the results of this study may be worth considering by cardiac surgeons treating AF after CABG. More clinical trials with larger sample sizes are recommended.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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