

## Does Stopping Amiodarone after Successfully Treating Atrial Fibrillation Occurring after Cardiac Surgery Increase the Risk of Recurrence?

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### ABSTRACT

**Objectives:** Atrial fibrillation (AF) following cardiac surgery is common and can complicate postoperative recovery. Amiodarone is a drug frequently used for cardioversion. Some clinicians advocate only in-hospital use of amiodarone until cardioversion, whereas others continue its use for several weeks following cardiac surgery. Inadvertent long-term administration of the drug could be harmful. This study assessed the risk of AF recurrence under 2 different regimens of amiodarone treatment.

**Methods:** From January 2005 to July 2007, we reviewed 296 patients who developed postoperative AF. Group A consisted of 198 patients who were discharged on amiodarone treatment, and group B consisted of 98 patients who were discharged without amiodarone treatment. The patients were followed for 8 weeks after cardiac surgery and were observed for the development of symptoms such as palpitations, transient ischemic attack (TIA), stroke, and recurrence of or readmission for AF. In addition, we evaluated a control group of 145 patients with similar characteristics and no postoperative AF for the incidence of stroke and AF and compared the results with their rates in the study groups.

**Results:** Patients discharged on amiodarone therapy were more likely to experience episodes of palpitations than those not on amiodarone (13% versus 10%); however, the rates of AF recurrence were almost the same for the 2 groups (8% and 9%, respectively). The 2 groups also showed no difference in the incidence of TIA and stroke (5% versus 4%). A low incidence of stroke and AF (1%-2%) was observed in patients with no perioperative AF.

**Conclusions:** Long-term treatment of patients with amiodarone should be reconsidered, because it may not be as effective as previously thought in preventing symptoms and AF recurrence. The surprising incidence of neurologic events requires further investigation.

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### INTRODUCTION

Despite all the advances in cardiology and cardiac surgery, atrial fibrillation (AF) remains a common postoperative complication. Its incidence has been reported to be as high as 15%-50%, depending on patient profile, type of surgery, method of arrhythmia surveillance, and definition of arrhythmia [Maisel 2001; Bradley 2005; Martinez 2005].

The pathophysiology of AF is not yet fully understood. It has been suggested that after open cardiac surgery patients experience an increase in sympathetic tone, leading to an increase in premature atrial contractions and triggering AF [Chung 2000; Jayam 2002]. Furthermore, risk factors such as a history of AF, valvular heart disease, heart failure, vascular disease, chronic obstructive pulmonary disease, stroke, myocardial infarction, advanced age, and nonuse of  $\beta$ -blockers are all preoperative characteristics that have been shown in univariate analyses to increase the risk of postoperative AF [Creswell 1993; Mathew 1995; Weber 1998; Kim 2001; Kwatra 2006].

Postoperative AF is often a short-lived, self-limiting complication. Spontaneous cardioversion is common, and the correction of electrolyte imbalances only and no antiarrhythmic therapy have been reported to lead to the conversion of 15% to 30% of patients within 2 hours and 25% to 80% of patients within 24 hours [Campbell 1980; Gavaghan 1985; Cochrane 1994; VanderLugt 1999]. AF can lead not only to longer hospital stays, admission to the intensive care unit, higher morbidity rates, and higher hospitalization costs but also to potentially debilitating and even lethal conditions, such as stroke, perioperative myocardial infarction, or heart failure [Crosby 1990; Almassi 1997; Abreu 1999; DiDomenico 2005; Martinez 2005]. Hence, various medical and therapeutic strategies have been used in common practice to prevent and treat AF. One of the drugs most commonly used to treat AF is amiodarone, a benzofuran derivative. Amiodarone was approved as an antiarrhythmic agent in 1985 and has been classified as a unique class III antiarrhythmic agent [Mason 1987]. Amiodarone inhibits multiple ion channels (ie, potassium and calcium) as well as adrenergic receptors [Bradley 2005]. Amiodarone generally can be administered safely, especially over the short term (a few days to several weeks) [Maisel 2001]; however, adverse effects have been reported in

patients receiving long-term amiodarone therapy. These effects include pulmonary fibrosis, prolonged hypotension related to resistant peripheral vasodilatation, low cardiac output, bradycardia requiring pacing, toxicity to such organs as the liver and the thyroid gland, and ocular or neurologic symptoms [Lieberman 1985; Terada 1994; Dimopoulou 1997; Crystal 2003]. Persistence or recurrence of the arrhythmia for longer than 4 to 6 weeks after operation is also believed to be rare in postoperative AF. Long-term therapy therefore is generally unnecessary; however, no study has ever compared the rates of recurrence in postoperative AF patients with and without long-term amiodarone treatment [DiDomenico 2005].

The aim of this study was to examine whether continuation of amiodarone after cardioversion for 6 to 8 weeks until the follow-up visit would decrease the incidence of AF recurrence or stroke.

## MATERIALS AND METHODS

We studied 360 patients who developed postoperative AF between January 2005 and July 2007. We excluded 54 patients with chronic AF (or a history of paroxysmal AF or any other cardiac arrhythmias), 3 patients whose AF continued despite treatment, and 7 patients who died within 4 weeks of discharge (Figure 1). Overall, we included 296 patients with AF in the study. In addition, we included a group of 145 patients with similar characteristics who underwent cardiac surgery and did not develop AF.

This study was carried out with the permission of our research ethics committee. With the patients' consent, one of the leading surgeons (J.D.) discontinued amiodarone treatment in 95 patients after the restoration of sinus rhythm. Amiodarone was stopped in another 3 patients because of bradycardia.

Patients who developed AF received a 1.2-g loading dose of either oral or intravenous amiodarone, followed by a tapering dose of oral amiodarone (200 mg 3 times a day for 1 week, 200 mg twice a day for 1 week, and finally 200 mg once a day). Group A ( $n = 198$ ) received oral amiodarone therapy for 6 to 8 weeks despite reverting back to sinus

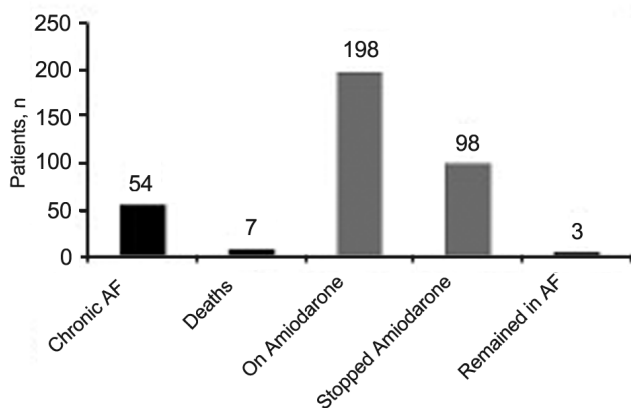


Figure 1. Breakdown of patients with atrial fibrillation (AF).

rhythm, and the patients in group B ( $n = 98$ ) had their amiodarone treatment discontinued in the hospital soon after the restoration of sinus rhythm. Table 1 summarizes the characteristics of the 2 patient groups.

Sinus rhythm was confirmed in our patients by electrocardiography at the time of discharge. Patients also received a phone call after 4 weeks, when they were requested to respond to a questionnaire. The patients were asked (a) whether they had experienced any palpitations during the weeks after discharge, (b) whether they had experienced any stroke or transient ischemic attack (TIA), and (c) whether they had experienced any AF recurrence or readmission for AF. In addition, their heart rhythm and electrocardiogram were assessed in the clinic 6 to 8 weeks after the operation, and the patients' responses to a similar questionnaire were recorded.

The mean age of the patients was 68.5 years (range, 24-86 years) in group A and 69.5 years (range, 36-89 years) in group B, with approximately 70% male patients in both groups. The mean age of the patients in the group with no AF was 67.5 years (range, 60-75 years).

## Statistical Analysis

We used a chi-square test with Analyse-it for Microsoft Excel (Analyse-it, Leeds, UK) to evaluate the proportions of the patients in groups A and B in each category. In addition, we performed a multivariate stepwise logistic regression analysis with SPSS software (version 15.0; SPSS,

Table 1. Clinical Details of the Patients\*

Variable	Group A (n = 198)	Group B (n = 98)	P
Age, y†	68.5 (24-86)	69.5 (36-89)	.97
Female sex, n (%)	58 (29)	32 (32)	.64
Diabetes, n (%)	31 (15)	21 (21)	.29
Hypertension, n (%)	150 (75)	80 (81)	.32
Previous TIA/stroke, n (%)	17 (8)	7 (7)	.84
PVD, n (%)	48 (24)	23 (23)	.99
Carotid disease, n (%)	24 (12)	11 (11)	.97
Left ventricular function, n (%)			
Good (>50%)	130 (65)	58 (59)	.34
Fair (30%-50%)	52 (26)	35 (35)	.12
Poor (<30%)	16 (8)	5 (5)	.48
Operation, n (%)			
CABG	118 (60)	59 (59)	.98
AVR/MVR	36 (18)	15 (16)	.65
CABG + valve	24 (12)	15 (16)	.75
Aortic root replacement	15 (7)	6 (6)	.51
Dissection	4 (2)	1 (1)	.88
ASD	0 (0)	2 (2)	.21
Myxoma	1 (1)	0 (0)	.72

\*Group A was discharged on amiodarone therapy, and group B was discharged without amiodarone therapy. TIA indicates transient ischemic attack; PVD, peripheral vascular disease; CABG, coronary artery bypass graft; AVR, aortic valve replacement; MVR, mitral valve replacement; ASD, atrial septal defect.

†Data are presented as the mean (range).

Chicago, IL, USA) to identify the independent predictors of postoperative AF. The fit of the model was assessed with the Hosmer-Lemeshow goodness-of-fit test. The results were reported as a *P* value and an odds ratio with a 95% confidence interval. Statistical significance was set at the .05 level.

## RESULTS

Amiodarone was well tolerated in group A (long-term amiodarone). Adverse effects, including sickness, skin rash, and bradycardia, were reported in fewer than 10 patients. At the baseline evaluation, no significant differences were found between the 2 groups in the recurrence of symptoms (Table 2). Patients in group A, however, complained of symptoms of palpitation more frequently than those in group B (13% versus 10%). This finding could be related to having a higher threshold for prescribing  $\beta$ -blockers in group A than in group B (45% versus 64%). Documented AF was almost the same for the 2 groups (8% versus 9%). The only statistically significant difference between the 2 groups was  $\beta$ -blocker administration, which was higher in group B ( $P < .003$ ). Of the patients who did not develop AF during their postoperative period, only 3 developed AF within 4 weeks after surgery; AF occurred in one of these patients soon after the discontinuation of  $\beta$ -blockers.

Multivariate logistic regression analysis did not show any preoperative and operative characteristics to be significantly correlated with AF recurrence after cardioversion and discharge. The Nagelkerke-adjusted  $R^2$  value was 0.75. The results of a Pearson goodness-of-fit test were not statistically significant.

Another important finding in this study was the high incidences of TIA (2%) and stroke (2%-3%), which were similar in groups A and B but higher than the incidences in the patients with no postoperative AF ( $n = 2$ , 1.3%). In group A, 7 cases of new-onset stroke and 4 cases of TIA were recorded. Three of these patients were known preoperatively to have carotid artery stenosis or peripheral vascular disease; however, none of the patients in group B who developed TIA or stroke had carotid artery stenosis or peripheral vascular disease preoperatively. Only 1 patient in group A with stroke was receiving warfarin treatment at the time of discharge, and none of the patients who developed TIA were receiving warfarin (Table 2).

Table 2. Atrial Fibrillation (AF)-Related Symptoms in the 2 Groups\*

Variable	Group A (n = 198), n (%)	Group B (n = 98), n (%)	<i>P</i>
Palpitation	28 (13)	10 (10)	.44
AF recurrence	17 (8)	9 (9)	.96
Stroke	7 (3)	2 (2)	.73
TIA	4 (2)	2 (2)	.67
PE, DVT	1 (<1)	0 (0)	.99

\*TIA indicates transient ischemic attack; PE, pulmonary embolism; DVT, deep vein thrombosis.

## DISCUSSION

Amiodarone is the most widely used antiarrhythmic drug. To date, many studies describing the role of amiodarone in the treatment and prevention of AF after cardiac surgery have been published; however, no study has demonstrated the true value of continuing amiodarone treatment after cardioversion following cardiac surgery. We know that amiodarone may be efficacious in rhythm control for patients with postoperative AF, but the evidence for this effect is both indirect and weak. In addition, we know from previous studies that AF arising de novo after cardiac surgery rarely requires long-term therapy [Maisel 2001; Jayam 2002; Bradley 2005; Martinez 2005].

Thus far, no study has investigated whether continuing amiodarone treatment after cardioversion following cardiac surgery is actually necessary. Our findings did not show any major differences between the 2 groups in the prevention of AF recurrence, palpitations, or even embolic events. In other words, the study failed to establish that long-term amiodarone treatment will avert AF in such patients. We therefore conclude that the practice of extending amiodarone treatment after cardioversion needs to be reassessed, because it may not be as effective as previously thought. Further statistical analysis failed to show any correlation between the preoperative and operative characteristics and the recurrence of AF after discharge. Even the use of  $\beta$ -blockers failed to prevent recurrence, but it did decrease the incidence of palpitations (Table 3).

In our study, we also found a higher-than-expected incidence of neurologic events in patients with a history of AF after cardiac surgery. This finding raises the question of whether we need to anticoagulate patients with postsurgical AF, even if they have cardioverted. Some studies have suggested that patients who have AF for more than 48 hours should be strongly considered for anticoagulation therapy; however, specific data are lacking to guide the management of anticoagulation treatment in patients with AF after cardiac surgery [Maisel 2001].

Our study has some limitations, the major one being that a Holter monitor was not used to record the heart rate and

Table 3. Results of Multivariate Logistic Regression Analysis Displayed with Likelihood Ratio Tests on Preoperative Characteristics and Recurrence of Atrial Fibrillation after Discharge

Effect	Likelihood Ratio Tests		
	Chi-square	Degrees of Freedom	<i>P</i>
Sex	0.831	1	.362
Diabetes mellitus	1.799	1	.180
Blood pressure	0.774	1	.379
Cardiac procedures	6.645	6	.355
$\beta$ -Blocker use	0.101	1	.751
Continuing amiodarone	0.006	1	.936
Left ventricular function	1.089	2	.580
Peripheral vascular disease	0.709	1	.400
Age at surgery	0.139	1	.709

rhythm after discharge. The results of our study are mainly based on the development of symptoms, such as palpitation and stroke or symptomatic AF, that would have encouraged the patient to seek medical attention. Therefore, episodes of asymptomatic AF have not been taken into account. Furthermore, the follow-up period in this study was relatively short (less than 2 months), and any development of AF after the postoperative follow-up clinic would have been missed. Otherwise, our study is original and raises the possibility that the value of amiodarone in treating AF occurring after cardiac surgery is overestimated.

In conclusion, more research is needed on a larger scale and in a double-blind randomized fashion to investigate the 3 questions raised in this study: (a) Should we continue amiodarone therapy after patient cardioversion following cardiac surgery; (b) should we anticoagulate every patient who develops AF following cardiac surgery, irrespective of AF duration; and (c) what are the main causes of AF recurrence after discharge?

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