

Post-discharge recurrences of new-onset atrial fibrillation following cardiac surgery: impact of low-dose amiodarone and beta-blocker prophylaxis

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Key words:
Amiodarone;
Atrial fibrillation;
Beta-blockers;
Cardiac surgery;
Postoperative
complication.

Background. Atrial fibrillation (AF) is the most frequent complication following cardiac surgery. It occurs mostly between the second and fourth postoperative days and often recurs within 30 days after surgery. While postoperative AF has been well analyzed, post-discharge recurrences of AF have not been clearly described even if they are reported as a frequent cause of re-hospitalization.

Methods. We followed up 185 patients for 10 ± 5 months with the aim of characterizing the post-discharge recurrences of AF. All patients had recently undergone cardiac surgery complicated by AF and were in sinus rhythm at the time of admission to our Center. We also compared the efficacy of the main prophylactic regimens adopted in the referral Centers (amiodarone, beta-blockers, amiodarone plus beta-blockers) during the first postoperative month.

Results. In the first postoperative month AF recurred after discharge in 60 patients. The event rate was not different in patients treated with amiodarone and controls (47 vs 50%, $p = \text{NS}$), while it was significantly lower in patients taking beta-blockers either alone or associated with amiodarone (10 and 9% respectively, $p = 0.002$). At the end of follow up (10 ± 5 months), AF persisted in 3 out of 176 study patients (1.7%).

Conclusions. In patients undergoing cardiac surgery, post-discharge recurrences of AF are frequent during the first postoperative month and have a clinical relevance. Beta-blockers (not amiodarone) seem to be an effective prophylactic measure. The phenomenon tends to vanish in the long term, and a chronic prophylaxis is not justified.

(Ital Heart J 2000; 1 (10): 691-697)

Received May 31, 2000;
revision received August
28, 2000; accepted
September 19, 2000.

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Introduction

Atrial fibrillation (AF) is the most frequent complication of cardiac surgery. The reported incidence of postoperative AF varies considerably, and it has increased in the last few years¹⁻⁷. AF occurs mostly between the second and fourth postoperative days during the stay in the cardiac surgery clinic. It is associated with a higher incidence of systemic thromboembolism⁸⁻¹⁰ and determines longer hospitalization and higher costs^{11,12}. Several studies have shown that, once sinus rhythm has been restored, postoperative AF often recurs after hospital discharge, and it represents one of the main reasons for re-hospitalization during the first postoperative month¹³⁻¹⁵. The post-discharge recurrences of AF following cardiac surgery have never been characterized in the literature, their clinical conse-

quences are not well known and there is no agreement on their prophylaxis.

Accordingly, the main goal of our study was to analyze the prevalence and the clinical characteristics of post-discharge recurrences of AF in a cohort of patients referred to our Rehabilitation Center who had undergone cardiac surgery followed by AF, without any major complication. Our purpose was also to compare the main prophylactic regimens prescribed in the referral Centers.

Methods

Study patients. From January 1997 to January 1998 we enrolled 185 consecutive patients who had recently undergone cardiac surgery with cardioplegic arrest. They were

randomly addressed from the main cardiac surgery clinics in north Italy (which routinely made a protected discharge by referred Rehabilitation Centers) and admitted to our Center.

Criteria for eligibility were: recent coronary artery bypass graft, mitral or aortic valve replacement or mitral valve repair complicated by AF; ascertained sinus rhythm at the time of cardiac surgery and upon admission to our Center.

Criteria for exclusion were: severe postoperative complications requiring a stay in the intensive care unit longer than 1 week; hypotension (systolic blood pressure < 80 mmHg); sick sinus syndrome or advanced atrioventricular block without an artificial pacemaker; history of thyroid dysfunction; electrolytic imbalance. Patients who used amiodarone and/or experienced a documented episode of AF during the 4 months prior to surgery were also excluded.

Postoperative AF was managed by cardiologists at the referral Center. At the onset of the arrhythmia, most patients were treated with amiodarone, by the loading intravenous dose till sinus rhythm was restored. Furthermore, cardiologists decided on prophylactic treatment against recurrences of AF. No pharmacological protocol was routinely applied for preventing recurrences of the arrhythmia after discharge from cardiac surgery clinics. The treatment and the drug selection were based on inferences and intuitions of the attending cardiologists related to the patient's clinical conditions¹⁶.

Follow-up. As common practice, patients were transferred after the operation from cardiac surgery clinics to our Center to make a protected discharge and an expected period of early postoperative controlled rehabilitation lasting 3 weeks ("short-term" follow up). We divided the patients into four groups according to the medical treatment followed at the beginning of our observation:

- group A (n = 62): amiodarone,
- group B (n = 42): beta-blockers,
- group AB (n = 22) amiodarone and beta-blockers,
- group C (n = 50): no amiodarone; no beta-blockers (control group).

In patients of groups A and AB amiodarone was started in the early stages after cardioversion and given during the short-term follow-up at a dosage of 200 mg/day. The beta-blockers used in groups B and AB were atenolol, metoprolol or bisoprolol, and were administered during the follow-up in order to maintain heart rate in a range between 50 and 80 b/min. Due to the small number of patients taking any antiarrhythmic drug other than beta-blockers and/or amiodarone, we excluded from the analysis the 6 patients treated with sotalol and propafenone.

Anticoagulant therapy (warfarin) was routinely given to all patients who had undergone valve replacement or surgical repair, while antiplatelet agents were administered to those who had undergone coronary artery bypass graft. The dose of anticoagulant was titrat-

ed in order to keep the prothrombin time level between 2 and 3.5 of the International Normalized Ratio.

At the beginning of the short-term follow-up, a complete clinical evaluation and a standard 12-lead ECG were performed. The attending physician evaluated the patients daily. Standard ECG was repeated once a week, and every time arrhythmia was suspected. One ECG lead (D2) was continuously recorded using a telemetric system during the daily session of scheduled exercise training.

Twenty-four-hour Holter monitoring was performed routinely 14 ± 4 days after surgery using a two-trace (V₁ and V₅ leads) Traker Recorder (Reinolds Medical System). Recordings were subsequently analyzed by the Autosurveyor Lector, Reinolds Medical Model (Hertford, UK).

A standard echocardiographic study was performed on all patients 11 ± 2 days after surgery by sonographers using a SIM 7050 CFM Challenge System (Esaote Biomedica, Florence, Italy) equipped with a 2.5-3.5 MHz annular-array transducer, and recorded on Super-VHS Panasonic videotape for subsequent analysis. Left atrial and left ventricular diameters were measured by M-mode echocardiography according to the recommendations of the American Society of Echocardiography¹⁷. The Penn Convention was used to calculate the left ventricular mass from two-dimensional-guided M-mode echocardiogram¹⁸. Left ventricular volumes and ejection fraction were computed from apical 2- and 4-chamber views by the area-length method¹⁹.

During the short-term follow-up, the administration of amiodarone and beta-blockers was interrupted for side effects in 3 patients (bradycardia in 2 patients and acute obstructive pulmonary syndrome in 1 patient, respectively). These patients were then excluded from the statistical analysis. At the end of short-term follow-up amiodarone was discontinued in patients of groups A and AB, except in cases of the persistence of the arrhythmia, while beta-blocker treatment was continued.

All patients were re-evaluated in our Center after 3 and 12 months ("long-term" follow-up). At both these time intervals a standard 12-lead ECG and a 24-hour Holter monitoring were performed and information about intercurrent episodes of arrhythmia and/or hospitalizations were asked for. Five patients were excluded.

Definition and management of recurrences of atrial fibrillation. In accordance with Levy et al.²⁰ we considered as events all documented episodes of AF lasting more than 2 min. Once the arrhythmia was diagnosed, the telemetric system was used in order to determine the maximal ventricular rate and the length of event.

No medical treatment was administered during 24 hours in asymptomatic patients. In the case of symptoms or when AF persisted for more than 1 day, quinidine or propafenone was given in an attempt to restore sinus rhythm. Anticoagulant therapy (warfarin) was routinely started when AF persisted for more than 24 hours.

Statistical analysis. The main goal of this study was related to the number of patients who experienced at least one episode of documented AF during the short-term follow-up.

Data are reported as mean value \pm 1 SD. Median values were used in case a variable was non-uniformly distributed. For the comparison of groups, continuous and normally distributed variables were tested using the analysis of variance (breakdown and one-way ANOVA). Considering that the study groups were similar for all examined variables but the type of cardiac surgery, analysis of variance was adjusted for surgical procedure. Clinical characteristics of events could be compared only between groups A and C because of the small number that occurred in groups B and AB.

Results

Patients were transferred from cardiac surgery clinics to the Rehabilitation Center at a mean time from surgery of 7.9 ± 2.4 days. Their principal baseline characteristics are summarized in table I. The average amiodarone total dose administered orally during the stay in cardiac surgery clinics in patients of groups A and AB was 900 mg per patient. At the time of recruitment, the dosing regimen of amiodarone was 250 ± 50 mg/day. The mean dose of beta-blockers given to the patients was: atenolol 40 ± 15 mg/day, metoprolol 50 mg/day, and bisoprolol 5 mg/day.

Short-term follow-up. The mean duration of short-term follow-up was 21 ± 2 days. The average time of AF recurrences from surgery was 12 ± 5 days (Fig. 1). The clinical features of the four groups are listed in table II. Patients were perfectly matched for all considered variables (including sex, age, left atrial diameter, left ventricular ejection fraction, and mass) except for the type of surgical procedure and baseline heart rate.

Table I. Principal characteristics of the study population (176 patients).

<i>Clinical</i>	
Male gender	119 (68%)
Age (years)	65 ± 9
Diabetes mellitus	20 (11%)
<i>Preoperative variables</i>	
Systemic thromboembolism	3 (2%)
NYHA functional class (score 1-4)	2.2 ± 0.6
Myocardial infarction	24 (27%)
Acute pulmonary edema	16 (9%)
<i>Postoperative variables</i>	
Heart rate (b/min)	77 ± 12
Hemoglobin (g/dl)	10.4 ± 1.4
Left ventricular ejection fraction (%)	56 ± 9
<i>Surgical</i>	
Coronary artery bypass graft	82 (47%)
Valvular procedure	94 (53%)
Aortic replacement	71 (40%)
Mitral replacement	11 (6%)
Double valve replacement	5 (3%)
Mitral repair	7 (4%)
Perioperative myocardial infarction	2 (1%)

At least one episode of AF was documented in 60 patients (34% of the study population). Figure 2 shows the distribution of patients with events among the study groups. There was no difference between groups A and C (29 of 62 patients = 50% vs 25 of 50 patients = 47%, respectively). On the contrary, the number of patients with events in groups B (4 of 42 patients = 10%) and AB (2 of 22 patients = 9%) was significantly lower than in group C ($p = 0.0002$). Analysis of variance was therefore adjusted for the type of surgical procedure, and the difference in the event rate between groups ($p < 0.001$) remained relevant. Clinical characteristics of AF recurrences are reported in table III. There was no difference in duration, maximal ventricular rate, number of episodes

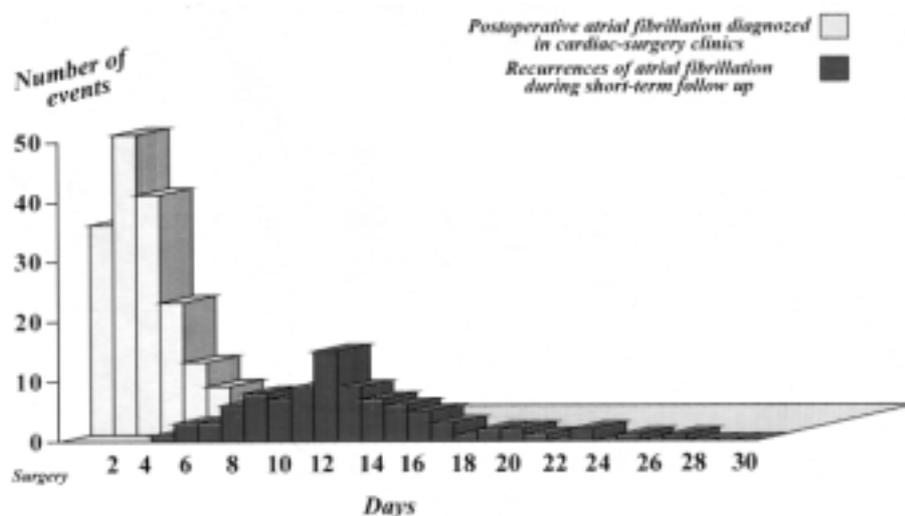


Figure 1. Time distribution of episodes of atrial fibrillation following cardiac surgery during the first postoperative month.

Table II. Characteristics of patients subdivided in the four study groups.

	Group A (n=62)	Group B (n=42)	Group AB (n=22)	Group C (n=50)	p
<i>Clinical</i>					
Male gender	41 (66%)	32 (76%)	15 (68%)	31 (62%)	NS
Age (years)	66 ± 8	66 ± 8	65 ± 9	64 ± 10	NS
Diabetes mellitus	6 (10%)	7 (17%)	3 (14%)	4 (8%)	NS
<i>Preoperative variables</i>					
Systemic thromboembolism	2 (3%)	0	0	1 (2%)	NS
NYHA functional class (score 1-4)	2.2 ± 0.6	2.2 ± 0.7	2.1 ± 0.8	2.1 ± 0.7	NS
Myocardial infarction	12 (19%)	14 (33%)	4 (18%)	9 (18%)	NS
Acute pulmonary edema	7 (11%)	2 (5%)	2 (9%)	5 (10%)	NS
<i>Postoperative variables</i>					
Heart rate (b/min)	82 ± 8	68 ± 10*§	72 ± 10*§	85 ± 12	<0.000001
Supraventricular ectopic beats (total number in 24 hours)	320 ± 260	281 ± 180	126 ± 93	149 ± 100	NS
Ventricular ectopic beats (total number in 24 hours)	413 ± 321	575 ± 477	103 ± 80	589 ± 407	NS
Complex ventricular ectopic beats	6 (10%)	8 (19%)	0	7 (14%)	NS
Left ventricular end-diastolic diameter (mm)	51 ± 7	49 ± 6	50 ± 7	50 ± 7	NS
Left atrial diameter (mm)	42 ± 5	41 ± 4	40 ± 6	41 ± 6	NS
Left ventricular mass index (g/m ²)	139 ± 44	131 ± 38	145 ± 47	140 ± 45	NS
Left ventricular ejection fraction (%)	54 ± 11	58 ± 7	56 ± 8	56 ± 8	NS
Digoxin therapy	2 (3%)	2 (5%)	2 (9%)	4 (8%)	NS
Anticoagulant therapy (warfarin)	37 (60%)	13 (59%)	11 (50%)	33 (66%)	NS
<i>Surgical</i>					
Coronary artery bypass graft	25 (40%)	29 (69%)*§	11 (50%)	17 (34%)	<0.001
Grafts (n. per patient)	2.3 ± 0.7	2.4 ± 0.6	2.3 ± 0.8	2.1 ± 0.7	NS
<i>Valvular procedure</i>					
Aortic replacement	30 (48%)	10 (24%)*§†	9 (41%)	22 (44%)	<0.001
Mitral replacement	3 (5%)	2 (5%)	1 (5%)	5 (10%)	NS
Double valve replacement	2 (3%)	0	0	3 (6%)	NS
Mitral repair	2 (3%)	1 (2%)	1 (5%)	3 (6%)	NS
Perioperative myocardial infarction	0	1 (2%)	1 (5%)	0	NS

* significant difference vs group C; § significant difference vs group A; † significant difference vs group AB.

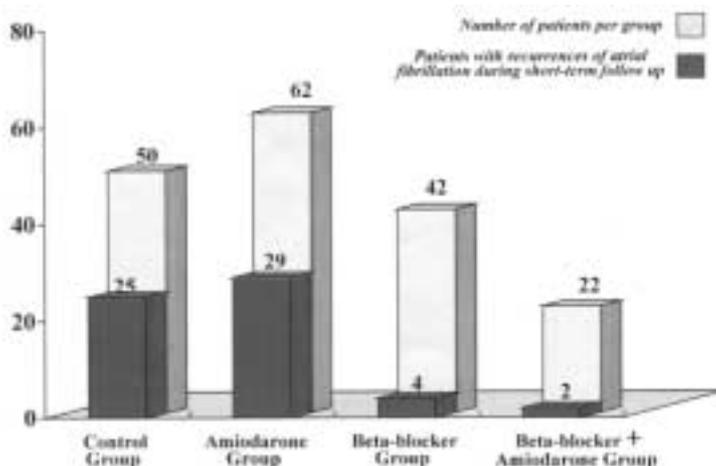


Figure 2. Distribution of patients who experienced at least one episode of post-discharge atrial fibrillation during the short-term follow-up subdivided into the four study groups.

per patient, effect on clinical status and modalities of cardioversion between groups A and C. Arrhythmia was never associated with unstable hemodynamics in groups B and AB while it required urgent cardioversion in 1 and 2 patients of groups A and C, respectively. Neither deaths nor documented episodes of systemic throm-

boembolism were associated with the events. At the end of the short-term follow-up, 167 patients were in sinus rhythm while 9 were in AF: 3 (12%) patients of group C and 6 (21%) patients of group A (p = NS). All these 9 patients had undergone surgical valvular procedure.

Table III. Clinical characteristics of post-discharge recurrences of atrial fibrillation developed during the short-term follow-up in the four study groups.

	Group A (n=29)	Group B (n=4)	Group AB (n=2)	Group C (n=25)	p
Onset (postoperative day)	13 ± 7	15 ± 9	12 ± 4	12 ± 4	NS
Mean duration (hours)	28 ± 26	26 ± 20	10 ± 9	26 ± 22	NS
Maximal heart rate (b/min)	105 ± 25	87 ± 15	120 ± 35	112 ± 22	NS
More than one episode	10 (34%)	0	1 (50%)	7 (28%)	NS
Overall episodes (n. per patient)	43 (1.5)	0	1 (0.5)	35 (1.4)	NS
Effect on clinical status					
No symptoms	17 (59%)	4 (100%)	1 (50%)	10 (40%)	NS
Symptoms with stable hemodynamics	11 (38%)	0	1 (50%)	13 (52%)	NS
Symptoms with unstable hemodynamics	1 (3%)	0	0	2 (8%)	NS
Modalities of restoration to sinus rhythm					
Spontaneous	12 (41%)	2 (50%)	1 (50%)	7 (28%)	NS
Pharmacological	11 (38%)	2 (50%)	1 (50%)	14 (56%)	NS
Electrical	0	0	0	1 (4%)	NS
Persistent at the end of short-term follow-up	6 (21%)	0	0	3 (12%)	NS

Analysis of variance was performed only between groups A and C.

Long-term follow-up. The mean duration of the long-term follow-up was 10 ± 5 months. During this period DC shock was performed in all the 9 patients in whom AF persisted at the end of the short-term follow-up (mean time from surgery 60 ± 15 days), and sinus rhythm could be restored in 6 of them. Among the 167 patients who were in sinus rhythm at the end of the short-term follow-up, 3 experienced an episode of AF. None of these patients was taking beta-blockers. In all the 3 cases sinus rhythm was restored by pharmacological therapy. Hence, at the end of the long-term follow up, AF persisted in 3 of 176 study patients (1.7%).

Discussion

It is commonly believed that AF determines an adverse hemodynamic effect, predisposes to systemic thromboembolism and increases duration and cost of hospitalization. AF occurs frequently after cardiac surgery and often recurs within the first postoperative month¹³⁻¹⁵. Such a post-discharge postoperative complication has never been clarified in the literature. What can be safely gathered from the few available data is that it is a frequent reason for re-hospitalization within 30 days of discharge after cardiac surgery^{14,15}.

To our knowledge, this is the first study aimed at characterizing the post-discharge recurrences of postoperative AF in a large cohort of patients undergoing cardiac surgery without any major complication. We underline that the seriousness of the baseline cardiac disease and the postoperative clinical conditions were not the main criteria for patient admission, but rather enrollment was based on the well-known demographic, financial and logistical aspects (the distribution of the cardiac surgery clinics in our country, the internal migration of patients

undergoing cardiac surgery, etc.). Therefore, the patients considered in the present study are perfectly representative of the general population discharged from Italian cardiac surgery clinics.

Our principal finding is that AF recurrences are a frequent, important clinical event, when the first postoperative month is considered. During this critical period, indeed, 50% of patients taking no prophylactic treatment had events, and 60% of them had symptoms during the arrhythmia. Due to the difficulty in recording short and asymptomatic episodes, the event rate was probably even higher. Hence, these patients have to be considered at high risk for AF recurrences. However, our results also suggested that the phenomenon tends to lose its clinical relevance in the long term according to the results obtained by Landymore and Howell²¹ who demonstrated that AF seldom recurs 3 weeks after surgery.

In clinical practice there is no agreement on the approach to this problem^{22,23}. Thus, it is not surprising that we received patients who had been very differently managed: about one third were treated with amiodarone, one fourth with beta-blockers, and the two drugs were concomitantly given in 13% of patients. A very small number of them received propafenone and sotalol. It is noteworthy that 28% of these patients did not receive any antiarrhythmic prophylaxis.

Contradictory data have been collected about the role of amiodarone in preventing AF after cardiac surgery²⁴⁻²⁷. In our population amiodarone was administered intravenously with a loading dose at the onset of the postoperative AF to restore sinus rhythm and it was continued with oral administration according to a low-dose regimen. Our study demonstrated that amiodarone was not effective in preventing events after discharge. The loading intravenous dose administered varied over a wide range. However, the average total dose received

orally before the recruitment was only 900 mg and the maintaining dose was low. Therefore, we can speculate that the lack of effectiveness of amiodarone was due to an insufficient serum concentration of the drug. This hypothesis seems to have been confirmed by Daoud et al.²⁴ who showed that preoperative prophylaxis with amiodarone reduced the overall incidence of postoperative AF at a 24-day follow-up.

The effectiveness of beta-blockers in preventing postoperative AF has been clearly reported by a lot of investigators^{6,28-31}. Our study showed that for patients in whom beta-blocker treatment (either alone or in combination with amiodarone) is continued after discharge from the cardiac surgery clinics, the incidence of AF recurrences in the critical 3-week period after surgery was very low, and that the beneficial effect was independent of the surgical procedure.

Many reasons could be given to explain this behavior. The postoperative period is indeed characterized by an increase in adrenergic tone^{32,33} that can produce the activation of an arrhythmogenic substrate^{34,35}. The very low rate of events in the subgroup of patients taking beta-blockers strongly suggests that the documented postoperative variations of autonomic tone might persist for a relatively long time after cardiac surgery and that also post-discharge postoperative AF might be primarily triggered by an increased sympathetic tone. In our study the dose regimen of beta-blockers was low and managed in order to maintain heart rate in a wide range (between 50 and 80 b/min). The mean heart rate of the two groups treated with beta-blockers was relatively high (68 ± 10 and 72 ± 10 b/min, respectively) and suggests that the block of beta-receptors might not be the only involved mechanism.

The phenomenon tended to be self-limiting in the long-term period. In our population, indeed, the arrhythmia relapsed in only 3 patients at the long-term follow-up. Sinus rhythm was easily restored and in no case was DC shock needed. Many reasons could be taken into account to explain this finding. Firstly, the progressive normalization of the adrenergic tone over the time should be considered. Furthermore, both an electrical and structural atrial remodeling could be suggested in patients submitted to valvular procedure.

Unfortunately, a precise cost analysis to assess the financial impact of AF recurrences in our patients is not feasible. The postoperative discharge was "protected" by the presence of cardiologists in our Rehabilitation Center, who managed arrhythmic events *in loco* without the need of re-hospitalization. However, some speculations can be made. The reported prevalence of hospital readmission within 1 month after cardiac operation caused by AF is about 13%^{14,15}, and it is retained a costly event that exceeds any other complication^{11,12}. Our study demonstrated that in the subgroups of patients taking no prophylactic treatment or amiodarone alone the prevalence of symptomatic AF recurrences requiring medical assistance, and potentially re-hospitalization, was

even higher (24%). Considering that most of the cost analysis regarding the complications of cardiac surgery excluded patients at higher risk for AF such as those with valve disease, and that the mean age of current surgical patients is rapidly increasing, we can speculate that the impact of postoperative AF on hospital resources will be higher in the future, and any reduction in its rate of occurrence will result in an enormous saving.

In conclusion, the present study demonstrated that in a cohort of patients who had undergone cardiac surgery followed by AF and no major complication, the post-discharge recurrences of the arrhythmia are frequent during the first postoperative month and have a clinical relevance. In such patients prophylactic treatment should be retained as beneficial and indicated in order to reduce postoperative morbidity and early re-hospitalization. The phenomenon vanishes in the long term and a chronic prophylaxis seems unnecessary.

Oral low-dose amiodarone seems to be ineffective for the prevention of recurrences after discharge. On the contrary, beta-blocker treatment is associated with a reduced incidence of events and might be proposed as pharmacological prophylactic strategy in this group of patients at high risk.

Acknowledgments

We are indebted to Dr. Elio Braitto for his effort in the organization of our work and for useful conversations and suggestions for this study. We thank Dr. Alessandra Ricchi for her help in the preparation of the manuscript.

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