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Perioperative Intravenous Amiodarone Does Not Reduce the Burden of Atrial Fibrillation in Patients Undergoing Cardiac Valvular Surgery

Yanick Beaulieu, M.D.,* André Y. Denault, M.D.,†‡ Pierre Couture, M.D.,† Denis Roy, M.D.,§ Mario Talajic, M.D.,§ Eileen O'Meara, M.D.,* Michel Carrier, M.D.,‖ Pierre Pagé, M.D.,‖ Sylvie Levesque, M.Sc.,# Jean Lambert, Ph.D.,** Jean-Claude Tardif, M.D.§

ABSTRACT

Background: Atrial fibrillation is a common complication after cardiac surgery. Postoperative atrial fibrillation is associated with increased risks of morbidity and mortality, and, therefore, preventive strategies using oral amiodarone have been developed but are often unpractical. Intravenous amiodarone administered after the induction of anesthesia and continued postoperatively for 48 h could represent an effective strategy to prevent postoperative atrial fibrillation in patients undergoing cardiac valvular surgery.

Methods: Single-center, double-blinded, double-dummy, randomized controlled trial in patients undergoing valvular surgery. Patients received either an intravenous loading dose of 300 mg of amiodarone or placebo in the operating room, followed by a perfusion of 15 $mg \cdot kg^{-1} \cdot 24\ h^{-1}$ for 2 days. The primary endpoint was the development of atrial fibrillation occurring at any time within the postoperative period.

Results: One hundred twenty patients were randomly assigned (mean age was 65 ± 11 yr). Overall atrial fibrillation occurred more frequently in the perioperative intravenous amiodarone group compared with the placebo group (59.3 *vs*. 40.0%; $P = 0.035$). Four preoperative factors were found to be independently associated with a higher risk of developing postoperative atrial fibrillation: older age ($P = 0.0003$), recent myocardial infarction (<6 months; $P = 0.026$), preoperative angina ($P = 0.0326$), and use of a calcium channel blocker preoperatively ($P = 0.0078$) when controlling for groups.

Conclusion: In patients undergoing cardiac valvular surgery, a strategy using intravenous amiodarone for 48 h is not efficacious in reducing the risk of atrial fibrillation during cardiac valvular surgery.

What We Already Know about This Topic

- New onset atrial fibrillation after cardiac surgery carries significant morbidity.
- The incidence of atrial fibrillation can be reduced with oral amiodarone begun before surgery.

What This Article Tells Us That Is New

- In patients with elective valve surgery, intravenous amiodarone, begun after induction of anesthesia up to 48 h failed to reduce the incidence of atrial fibrillation.

ATRIAL fibrillation (AF) is an important and frequent complication after cardiac surgery occurring in almost one third of patients undergoing coronary artery bypass grafting (CABG)[1] and in up to 44% of patients undergoing a valvular procedure.[2] Heart failure, hypotension, increased risk of stroke, need for anticoagulation, increased length of stay in the hospital, and long-term mortality are some of the various potential consequences of postoperative AF.[3–5] Although valvular surgery poses a greater risk of AF,[2,6,7] most studies in cardiac surgery have been performed in patients undergoing coronary revascularization.[2,6,8–11] Reduction in the incidence of postoperative AF of up to 50% have been demonstrated in some of these studies,[12] when amiodarone was started before entry in the operating room. In several of

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* Assistant Professor, § Professor, Department of Medicine, † Professor, Department of Anesthesiology, ‖ Professor, Department of Cardiac Surgery, Montreal Heart Institute, Université de Montréal, Montreal, Quebec, Canada, ‡ Professor, Division of Critical Care, Centre Hospitalier de l'Université de Montréal, Montreal, Quebec, Canada, # Biostatistician, The Montreal Heart Institute Coordinating Center, Montreal, Quebec, Canada, ** Professor, Department of Preventive and Social Medicine, Université de Montréal.

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Address correspondence to Dr. Denault: Department of Anesthesiology, Montreal Heart Institute, 5000 Belanger Street, Montreal, Quebec H1T 1C8, Canada. denault@videotron.ca.

these protocols, the preoperative loading regimen was administered orally[2,6,9–11]; however, this approach is currently impractical because most patients undergoing elective cardiac surgery are admitted the night before or even on the day of the procedure. However, none of the studies have looked at the hemodynamic safety and efficacy of starting amiodarone loading and infusion after anesthesia induction, before the onset of cardiopulmonary bypass (CPB), without a previous loading dose. Our hypothesis was that perioperative use of intravenous (IV) amiodarone initiated after the induction of anesthesia would be hemodynamically safe and effective in preventing postoperative AF until hospital discharge in patients undergoing cardiac valvular surgery.

Materials and Methods

The study protocol was reviewed and approved by the Ethics and Research Committee of the Montreal Heart Institute, Montreal, Quebec, Canada. All patients gave written informed consent.

Patient Population

The primary objective of this single-center double-blinded, double-dummy, randomized controlled trial was to demonstrate the efficacy and safety of a 48-h IV infusion of amiodarone in reducing AF prevalence in patients undergoing valvular surgery. From November 2001 to May 2003, patients more than 18 yr old undergoing an isolated cardiac valvular surgery or a valvular surgery combined with a coronary revascularization procedure were screened to be included in the study. To be eligible, they also had to be in sinus rhythm and have a left ventricular ejection fraction more than 20% at the time of screening. Patients were excluded from the study if they met one of the following criteria: amiodarone intake in the previous 6 months, a history of anaphylactic reaction to iodine, a history of severe reaction or toxicity to amiodarone, intake of class I or III antiarrhythmic agents within the previous 48 h before surgery, significant hypotension (systolic blood pressure < 80 mmHg) necessitating sustained treatment with vasoactive agents for more than 1 h preoperatively, urgent surgery, and participation in other investigational trials.

Randomization and Study Protocol

Patients were randomly assigned (1:1 ratio) in a double-blinded fashion, from a computer-generated list implemented by the hospital pharmacists not involved in the trial, to receive either IV amiodarone (Sabex, Boucherville, Quebec, Canada) or placebo (dextrose 5% in normal saline) infused through a central venous access. Because the solvent contained in the amiodarone solution is a soap (Polysorbate 80), shaking the bottle containing the amiodarone solution causes bubbles. To maintain the blind, the bottles containing amiodarone or placebo were covered with opaque or aluminum paper. Induction of anesthesia was performed using a combination of fentanyl (5–10 μg/kg) or sufentanil (0.7–1 μg/kg), midazolam (up to 0.1 mg/kg), and pancuronium (0.1 mg/kg). Isoflurane was used to control blood pressure during maintenance of anesthesia. After anesthesia induction, an IV loading dose of 300 mg of amiodarone (or placebo) was given for more than 10 min followed by an infusion of amiodarone ($15\ mg \cdot kg^{-1} \cdot 24\ h^{-1}$, max 1,500 mg/24 h) or placebo for 48 h. Complete hemodynamic assessment using the pulmonary artery catheter (7.5F 931HF75; Baxter Healthcare, Irvine, CA), transesophageal echocardiographic examination (to verify the adequacy of the valvular procedure), and complete laboratory data including arterial and venous blood gases were obtained just before and after the bolus and after weaning from CPB, during sternal closure. The surgical procedure was performed according to established guidelines. Blood cardioplegia was used in all patients. Induction and maintenance of cardioplegia were cold to tepid (15°–29°C). The blood to crystalloid ratio was 4:1. The pump flow was adjusted to obtain an output of $2.2\ l \cdot min^{-1} \cdot m^{-2}$ of body surface area and was reduced to $0.5\ l \cdot min^{-1} \cdot m^{-2}$ for aortic clamping and unclamping. SIII (Stockert, Munich, Germany) roller pumps were used in all patients. The oxygenator was Sorin Monolyth (Mirandola, Italy). Valve and complex procedures were done with temperatures of 32°–34°C. Weaning from CPB was attempted after systemic temperature (central and vesical) was more than 36°C. All patients in the study had epicardial pacemaker wires (atrial or ventricular) placed at the end of surgery. The use of vasoactive drugs (noradrenaline, adrenaline, vasopressin, and milrinone) and the process of weaning from CPB were done using established protocols[13] (see figs. 1 and 2 for the Vasoactive Protocol Management, Supplemental Digital Content 1, http://links.lww.com/ALN/A562). Temporary pacing was subsequently initiated if judged necessary by the anesthesiologist and the surgeon.

On arrival in the cardiothoracic intensive care unit (CTICU), a Holter monitor (Marquette Electronics Series 8500, Boston, MA) was installed on each patient. Three-lead continuous Holter monitoring was performed for the first 4 postoperative days. The recorded data were stored for 24 h and reviewed by an independent electrophysiologist on a daily basis. Three-lead continuous telemetric monitoring (Fukuda DF 3310 and LW 3100, Fukuda, Japan) was concomitantly performed from the time of admission to the CTICU until hospital discharge. Daily 12-lead electrocardiogram recordings were also performed on all patients. Postoperative AF was treated by the CTICU and surgical teams at their discretion, in accordance with the American College of Cardiology and American Heart Association Guidelines.[14] AF is defined as an uncoordinated atrial activation with consequent deterioration of atrial mechanical function.[14] Rescue amiodarone (IV or oral) could be used for the treatment of an AF episode if judged necessary by the treating physicians. To avoid administering potentially excessive additional doses of amiodarone to patients in the active treatment group, we

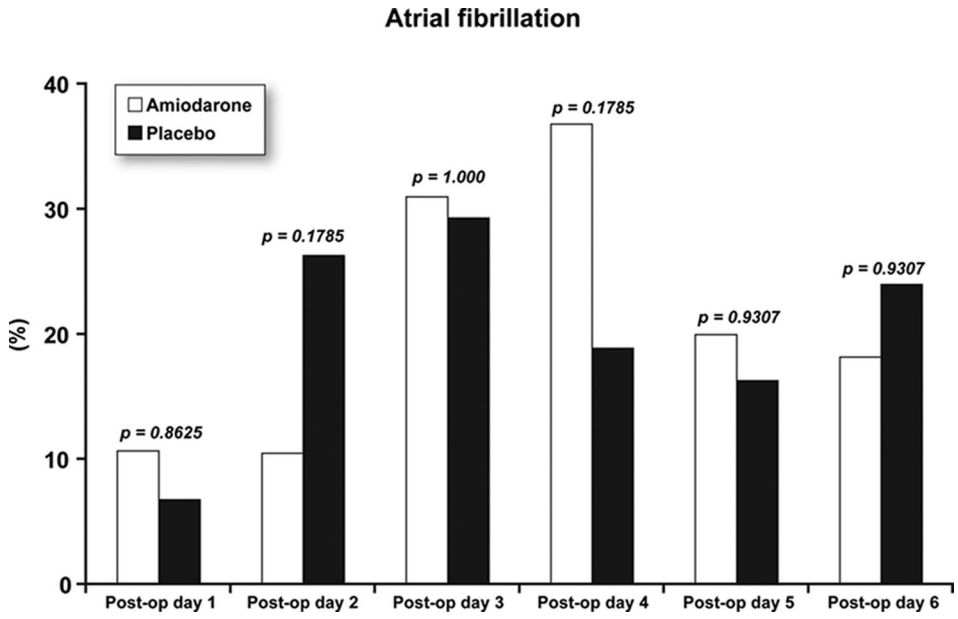

Fig. 1. Incidence of postoperative atrial fibrillation from postoperative days 1 to 6 in the amiodarone group compared with the placebo group. The drug or placebo infusion was administered for 48 h after surgery. Postop = postoperative.

developed a weight-based chart, indicating the maximal amount of additional amiodarone a patient was allowed to receive during the first 24 and 48 h after the surgery. The chart was made so as not to exceed a total IV amiodarone dose of 2,000 mg/24 h (appendix). Hemodynamic assessment, electrocardiographic, and laboratory data were systematically recorded for the first 6 postoperative days and then were recorded if an event occurred. Assessment of clinical variables was performed daily for the entire hospitalization period until the day of discharge. One-month telephone follow-up was performed to assess AF recurrences necessitating hospitalization.

The primary endpoint was the development of AF occurring at any time within the postoperative period (defined as the interval from the time of sternal closure to hospital discharge). AF was defined as an irregular rhythm with episode lasting more than 30 min or any episode requiring urgent treatment because of associated hemodynamic compromise (heart failure, hypotension, and ischemia) or symptomatic discomfort (shortness of breath, palpitations, and chest pain). Secondary endpoints consisted in adverse hemodynamic and electrophysiologic effects of IV amiodarone, temporary pacemaker requirement, length of CTICU and hospital stay, morbidity and mortality rates, and the rate of recurrent AF necessitating hospitalization at 1 month. The relationship between IV amiodarone use and postoperative nausea, the time of AF onset, and the mean heart rate re-

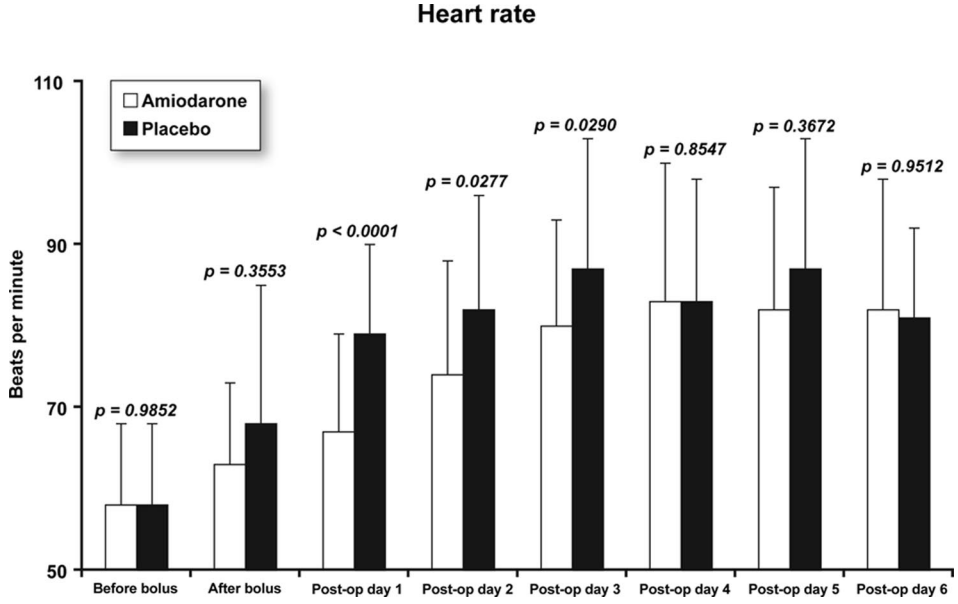

Fig. 2. Heart rate evolution in the amiodarone group compared with the placebo group. The amiodarone group had lower heart rate from postoperative days 1 to 3. Postop = postoperative.

Table 1. Pre- and Intraoperative Baseline and Surgical Characteristics

Characteristics	Amiodarone (n = 60)	Placebo (n = 60)	*P* Value
Age, yr	65 ± 11	65 ± 11	0.8599
Gender			0.5813
Men	32 (53.3)	35 (58.3)	
Women	28 (46.7)	25 (41.7)	
Body mass index	27.2 ± 4.3	27.2 ± 4.9	0.9381
Hypertension	29 (48.3)	28 (46.7)	0.8550
History of stroke	2 (3.3)	1 (1.7)	0.5587
Coronary artery disease	9 (15)	13 (21.7)	0.3453
Myocardial infarction			
<6 mo	1 (1.7)	3 (5)	0.6186
>6 mo	3 (5)	6 (10)	0.4906
Congestive heart failure	12 (20)	21 (35)	0.0658
Left ventricular ejection fraction, %	58 ± 9	61 ± 12	0.1365
Smoking history	10 (16.7)	15 (25)	0.2611
Chronic obstructive pulmonary disease	6 (10)	14 (23.3)	0.0500
Diabetes mellitus	5 (8.3)	14 (23.3)	0.0244
Chronic renal failure	1 (1.7)	4 (6.7)	0.3644
Thyroid disorder	8 (13.3)	5 (8.3)	0.3782
Preoperative medication			
β blockers	19 (31.7)	15 (25)	0.4178
Calcium antagonists	9 (15)	17 (28.3)	0.0763
Angiotensin- converting enzyme inhibitor	17 (28.3)	21 (35)	0.4325
Angiotensin receptor blocker	4 (6.7)	8 (13.3)	0.2235
Diuretics	15 (25)	24 (40)	0.0794
Digitalis	1 (1.7)	1 (1.7)	1.0000
Type of surgery			
Isolated valvular	46 (76.7)	36 (60)	0.0497
Valvular + coronary artery bypass graft	14 (23.3)	24 (40)	
Type of valvular surgery			
Aortic	44 (73.3)	39 (65)	0.3230
Mitral	16 (26.7)	23 (38.3)	0.1725
No. bypass grafts			
1	6 (42.9)	9 (37.5)	0.4464
2	5 (35.7)	6 (25.0)	
3	3 (21.4)	8 (33.3)	
5	0	1 (4.2)	
Use of mammary artery	9 (64.3)	14 (58.3)	0.7173
Total cardiopulmonary bypass time, min	97 ± 32	110 ± 37	0.0426
Aortic crossclamp, min	73 ± 28	85 ± 30	0.0271

Data are presented as n (%) for proportions and as mean ± SD for continuous variables.

sponse were also studied. Finally, the relationship between postoperative AF, and multiple preoperative, intraoperative, or postoperative variables were also studied.

Clinical Variables and Endpoints

Age, gender, body mass index, and body surface area were determined for each patient along with their relevant medications. The presence of hypertension, diabetes, chronic renal failure, smoking history, recent myocardial infarction (MI, before or after 6 months), signs and symptoms of congestive heart failure, chronic obstructive pulmonary disease, previous cerebrovascular disease, thyroid disorders, and left ventricular ejection fraction measured through angiographic ventriculography or echocardiography were also documented. The different types of surgical procedures were classified as isolated valvular or valvular and CABG. The number of bypass grafts and the use of a mammary artery were noted in addition to the CPB time and aortic crossclamping time. The amounts of vasopressor and inotropic support required during and after the procedure were also noted.

Statistical Analyses

On the basis of previous studies, we estimated that 50% of patients undergoing cardiac valvular surgery would develop AF. To detect the expected reduction in AF from 50% to at least 25% in the amiodarone group, 58 patients/group would be necessary to reach a power of 80% with a two-sided chi-square test at an alpha of 5%. Assuming a 3% loss, we recruited 60 patients/group. The results are presented as mean ± SD or median (minimum–maximum) according to the distribution for continuous variables and number (percentage) for categorical variables. The analyses were performed using the intent-to-treat principle. Chi-square tests were used to compare categorical variables between groups

Table 2. Summary of Outcome Data

Characteristics	Amiodarone (n = 59)*	Placebo (n = 60)	*P* Value
Atrial fibrillation	35 (59.3)	24 (40.0)	0.0350
Cardiothoracic intensive care unit duration, h	64 ± 81	51 ± 39	0.4898
Hospitalization duration, h	311 ± 270	253 ± 146	0.1996
Rhythm on discharge			0.6802
Sinus	54 (93.1)	55 (91.7)	
Atrial fibrillation	1 (1.7)	0	
Pacemaker	2 (3.4)	3 (5)	
Other	1 (1.7)	2 (3.3)	
Rescue amiodarone (postop)	23 (39.7)	21 (35)	0.6011
Nonsustained ventricular tachycardia	5 (8.5)	8 (13.3)	0.3956
Acute respiratory distress syndrome	0	0	1.000
Myocardial infarction	1 (1.7)	0	0.3112
Stroke	3 (5.1)	0	0.0769
Acute renal failure	2 (3.4)	2 (3.3)	0.9864
Rehospitalization for atrial fibrillation	3 (5.3)	3 (5.2)	0.9825
Nausea	46 (78)	40 (67.8)	0.2141
Death	1 (1.7)	1 (1.7)	0.9904

Data are presented as n (%) for proportions and as mean ± SD for continuous variables.

* One patient died intraoperatively of right ventricular failure.

(with or without amiodarone) (tables 1 and 2). For continuous variables, the Student *t* test or Wilcoxon test was used to compare groups (tables 1 and 2). The means and proportions of patients with or without AF were compared using a two-way analysis of variance and the Mantel-Haenszel chi-square test adjusting for treatment group (amiodarone *vs.* placebo), respectively (table 3). To establish which variables predicted the risk of developing AF (overall), multiple logistic regressions were used. Daily contrasts (amiodarone *vs.* placebo) for AF, heart rate, and β blockers as depicted in figures 1 to 3 were estimated using the generalized estimating equation framework because of the presence of correlated data introduced by days (repeated factor). To take into account the multiplicity of testing, the *P* values were corrected using closed multiple testing procedures, that is, the permutational minimum *P* value method for AF and β blockers and the Westfall-Young bootstrap minimum *P* value method for heart rate. To evaluate the long-term effect of AF treatment on mortality, a log-rank test was performed. Statistical analyses were performed using SAS version 8.02 (SAS Institute Inc., Cary, NC). A *P* value $\leq$ 0.05 was considered significant.

Results

Demographic and Surgical Variables

Baseline preoperative and intraoperative characteristics of patients are shown in table 1. A total of 120 patients were randomly assigned, and one patient in the amiodarone group died intraoperatively (right ventricular failure). The final intention-to-treat analysis was performed on the remaining 119 patients (59 amiodarone and 60 placebo). The mean age was 65 ± 11 yr, and 67 (56%) patients were men. Baseline demographic characteristics were similar among groups except for a higher proportion of patients with diabetes (23 *vs.* 8%; $P = 0.0244$) and chronic obstructive pulmonary disease (23 *vs.* 10%; $P = 0.05$) in the placebo group. Two thirds of the total population (68.3%) underwent an isolated valvular surgery and one third (31.7%) underwent combined valvular and CABG surgery. Patients in the amiodarone group underwent more isolated valvular surgeries compared with the placebo group (76.7 *vs.* 60%; $P = 0.0497$). There were no significant differences in the proportion of patients undergoing mitral and/or aortic valve procedures between the two groups. The total CPB time (97 ± 32 *vs.* 110 ± 37 min; $P = 0.0426$) and aortic crossclamp time (73 ± 28 *vs.* 85 ± 30 min; $P = 0.0271$) were shorter in the amiodarone group. There were no differences between the two groups in terms of baseline hemodynamic variables, laboratory, or blood gas data for all the perioperative phases (prebolus, postbolus, and post-CPB).

Primary and Other Endpoints

Postoperative AF occurred in 59 patients (49.6%) and was more frequent in the treatment group (n = 35/59 or 59.3%) compared with the placebo group (n = 24/60 or 40.0%; $P = 0.035$) (table 2). The difference remained significant even after adjusting for diabetes, chronic obstructive pulmonary disease, the duration of CPB, and the use of preoperative β blockers ($P = 0.0292$). AF occurred at a mean of 2.29 days postoperatively in the placebo group and at 3.03 days postoperatively in the amiodarone group ($P = 0.0208$). The median total dose of IV amiodarone administered to patients in the treatment group was 2,444 mg (410–3,790 mg) during the first 48 h.

As depicted in figure 1, both groups had a similarly low incidence of postoperative AF at day 1 (10.7 *vs.* 6.8%; $P = 0.8625$). These incidences increased during the following days, but the frequencies were similar between groups. The proportion of patients in sinus rhythm was similar among groups throughout the study. Figure 2 illustrates the mean heart rate (beats/min) for both groups. Patients in the amiodarone group had a statistically significant reduction in mean heart rate compared with the placebo group on postoperative day 1 (67 ± 12 *vs.* 79 ± 11; $P < 0.0001$), day 2 (74 ± 14 *vs.* 82 ± 14; $P = 0.0277$), and day 3 (80 ± 13 *vs.* 88 ± 16; $P =$

Table 3. Postoperative Outcomes in Patients With or Without Atrial Fibrillation

Postoperative Outcome	Atrial Fibrillation Group	Amiodarone (n = 59)	Placebo (n = 60)	*P* Value (Atrial Fibrillation Group)
Duration of stay in the intensive care unit, h	No atrial fibrillation	65.2 ± 107.2	40.9 ± 21.7	0.3176
	Atrial fibrillation	64.5 ± 60.0	65.5 ± 53.4	
Duration of intubation, h	No atrial fibrillation	10.1 ± 21.1	7.4 ± 12.7	0.0207
	Atrial fibrillation	17.8 ± 27.6	21.1 ± 33.4	
Pacemaker requirement, h	No atrial fibrillation	28.1 ± 45.1	13.7 ± 30.5	0.7806
	Atrial fibrillation	29.5 ± 36.5	16.1 ± 33.6	
Ventricular tachycardia	No atrial fibrillation	1 (4.2)	1 (2.8)	0.0040
	Atrial fibrillation	4 (11.4)	7 (29.2)	
Stroke	No atrial fibrillation	0 (0)	0 (0)	0.1444
	Atrial fibrillation	3 (9)	0 (0)	
Acute renal failure	No atrial fibrillation	0 (0)	0 (0)	0.0384
	Atrial fibrillation	2 (6)	2 (8)	
Duration of sinus rhythm, h	No atrial fibrillation	105.6 ± 42.5	105.8 ± 41	0.4058
	Atrial fibrillation	99.1 ± 29.5	97.7 ± 36.9	
Duration of nausea, h	No atrial fibrillation	37.9 ± 34.6	26.6 ± 23.7	0.0978
	Atrial fibrillation	38.4 ± 30.5	47.0 ± 43.9	
Rhythm on discharge	No atrial fibrillation			0.7955
	Sinus	20 (87)	34 (94)	
	Atrial fibrillation	0 (0)	0 (0)	
	Pacemaker	2 (9)	1 (3)	
	Other	1 (4)	1 (3)	
	Atrial fibrillation			
	Sinus	34 (97)	21 (88)	
	Atrial fibrillation	1 (3)	0 (0)	
	Pacemaker	0 (0)	2 (8)	
	Other	0 (0)	1 (4)	

Data are presented as n (%) for proportions and as mean ± SD for continuous variables.

0.0290). At the onset of AF, mean heart rate did not differ between groups (amiodarone group [84 ± 21], placebo group [86 ± 21]; $P = 0.9851$). Figure 3 illustrates the use of β blocker from days 1 to 6.

Other postoperative outcomes are shown in table 2. There were no differences in the length of stay in the CTICU (64 ± 81 *vs.* 51 ± 39 h; $P = 0.4898$) or total hospitalization duration (311 ± 270 [median 228] *vs.* 253 ± 146 [median 192] h; $P = 0.1996$) between groups. No differences were observed in terms of rhythm on discharge, use of rescue oral and IV amiodarone, nonsustained ventricular tachycardia, acute respiratory distress syndrome, MI, stroke, acute renal failure, and rehospitalization

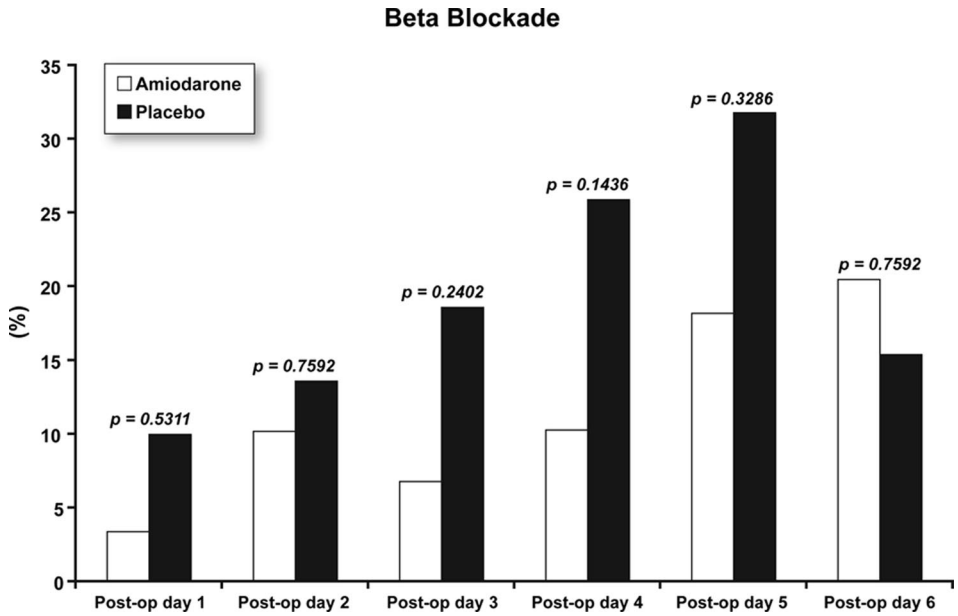

Fig. 3. Use of β blockers in the amiodarone group compared with the placebo group. Postop = postoperative.

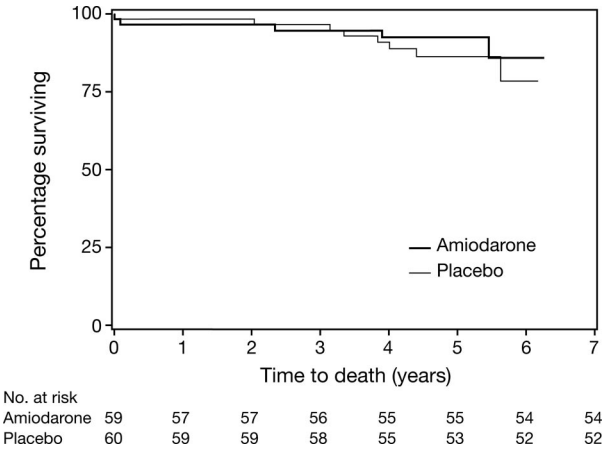

Fig. 4. Probability of survival at 6 yr. There were no differences between the groups in the analysis of death of the 119 patients at 6 yr ($P = 0.4307$).

for AF. The overall mortality was 2.5% (3 of 120). Excluding the patient who died intraoperatively, one patient in each group died during hospitalization. One patient in the control group died the next day after acute tamponade secondary to a rupture of the atrioventricular groove. The other patient in the amiodarone group died also the next day after repair through laparotomy of an accidental rupture of an iliac artery during the insertion of an intraaortic balloon pump. At 6 yr, 107 patients were still alive (89.2% survival rate), and one amiodarone patient was lost to follow-up. Survival at 6 yr was not different among groups. There were five deaths in the amiodarone group and eight deaths in the placebo group ($P = 0.4307$) (fig. 4).

There were no differences among groups in the number of patients requiring defibrillation to restore sinus rhythm after aortic crossclamp release (35 [58%] *vs.* 32 [53%]; $P = 0.58$) and in the use of vasoactive agents in the immediate postoperative period. The only significant difference in postoperative hemodynamics between the amiodarone and placebo groups observed during the hospitalization was that patients in the amiodarone group developed lower cardiac indices on the first postoperative day (2.5 ± 0.52 *vs.* 2.9 ± 0.67 $l \cdot min^{-1} \cdot m^{-2}$; $P = 0.0003$), with associated higher pulmonary vascular resistance indices (283 ± 104 *vs.* 247 ± 87 dynes $\cdot s \cdot cm^{-5} \cdot m^2$; $P = 0.0441$). Prescribed postoperative medications were not different among groups, except for a higher number of patients on vasoactive agents on postoperative day 2, which was higher in the placebo group (13 [22%] *vs.* 4 [6.8%]; $P = 0.018$). There were no differences in laboratory data and blood gas values between groups. Temporary pacemaker use was approximately twice as frequent in the amiodarone group compared with the placebo group, but this difference was only statistically significant for the first postoperative day (24 [41%] *vs.* 11 [18%]; $P = 0.0075$).

Outcome of Patients with AF Compared with Those without AF

Patients who developed AF presented with more complications, even adjusting for therapies received (table 3). A longer duration of postoperative mechanical ventilation ($P = 0.0207$), more frequent ventricular tachycardia ($P = 0.004$), and acute renal failure ($P = 0.0384$) were observed in patients with postoperative AF. Lengths of CTICU and hospital stays were similar in patients who developed AF compared with those who did not. At hospital discharge, a majority of patients were in sinus rhythm with no differences between groups.

Predictors of Postoperative AF and Outcome with AF

Four preoperative factors were found to be independently associated with a higher risk of developing postoperative AF: older age ($P = 0.0003$), recent MI (< 6 months; $P = 0.026$), preoperative angina ($P = 0.0326$), and use of a calcium channel blocker (CCB) preoperatively ($P = 0.0078$) when controlling for groups. Eighteen of 26 patients (69%) who were receiving a CCB preoperatively and 15 of 19 patients (80%) who were put on a CCB after surgery developed AF ($P = 0.0078$ and 0.0065, respectively). Preoperative use of β blockers was similar in the amiodarone and placebo group (19 [31.7%] *vs.* 15 [25%]; $P = 0.42$) and not correlated with the development of postoperative AF. Figure 3 illustrates the use of β blockers postoperatively. No intraoperative (type of surgery, total CPB time, and aortic crossclamp time) or postoperative factors were found to be predictive of postoperative AF.

Discussion

In this double-blinded, randomized, controlled trial on AF prevention in patients undergoing cardiac valvular surgery, we observed that a strategy using IV amiodarone initiated in the operating room before CPB followed by an infusion for 48 h is hemodynamically safe. There was a trend in reduction of the risk of AF while patients were receiving the medication but was no longer effective after the infusion was stopped. However, this potential benefit was lost at 4 days when the trend was reversed, and the amiodarone group had more AF than the placebo group. Therefore, this 48-h IV strategy resulted in an overall occurrence of AF that was higher in the patients who received perioperative IV amiodarone compared with placebo.

Most of the studies using amiodarone to prevent incident AF have been conducted in patients undergoing CABG with very few including patients undergoing isolated valvular surgery or combined with CABG.[12] Only six studies have included valvular surgical patients.[2,6,8–11] In addition, only four studies involved IV amiodarone only in the perioperative period[8,11,15,16] and only two studies included valvular patients.[8,11]

Our results are similar to those observed in a study by Daoud *et al.*[6] in which 71 patients (57% incident AF) underwent valvular surgery. AF occurred in 46% of patients undergoing valvular surgery, and incidence was reduced by approximately 50% in the amiodarone-treated patients. However, Daoud *et al.* used pre- and postoperative oral ami-

odarone. Guarnieri *et al.* [8] used IV amiodarone, which was started postoperatively for 48 h and observed a 26% reduction in AF; however, only 42 patients (14%) underwent valvular surgery in that study. The largest and most recent Prophylactic Amiodarone for Prevention of Arrhythmias that Begin Early After Revascularization (PAPABEAR) trial included 212 patients (35.3% of total population) undergoing valvular surgery.[2] Using a 12-day strategy of oral amiodarone (6 days before and 6 days after surgery), the investigators observed a 13.4% absolute risk reduction in the incidence of AF. In patients undergoing valvular surgery with or without CABG, AF occurred in 23.8% in the amiodarone group compared with 44.1% in the placebo group. We observed similar rates of AF in the placebo group (40.1%) in our study. The PAPABEAR trial patients were younger, the majority were men, the use of angiotensin-converting enzyme inhibitors and β blockers was almost twice more frequent, and the duration of CPB was shorter. The larger proportion of patients undergoing revascularization explains to some extent the latter difference. Despite a 50% reduction in the occurrence of postoperative AF with the use of oral amiodarone in the PAPABEAR study, the authors observed that the total burden of AF was similar in both the amiodarone and the placebo groups (25.1 *vs.* 23.7 h; P = not significant).

The definition of AF and the monitoring tool to diagnose the arrhythmia are also important to consider when comparing such studies. Holter monitoring offers a continuous, more reliable beat-to-beat analysis of the cardiac rhythm and may thus be best suited for arrhythmia detection and diagnosis. In our study, we defined AF as an episode lasting more than 30 min or any episode requiring urgent treatment because of associated hemodynamic compromise or symptomatic discomfort. This precise definition, which we used for AF occurrence, may explain in part why our results did not show a reduction in AF occurrence with amiodarone. Holter monitoring was performed on all patients, and the use of a more rigorous diagnostic tool could be partly responsible for better assessment of AF occurrence in both groups. Prevention of any episode of sustained AF should be the primary goal to be achieved.

The higher trend of AF at day 4 in the amiodarone group was associated with 50% less patients taking a β blocker in this group on that day compared with the placebo group. This may suggest that a strategy in which β blockers are introduced in the postoperative phase could represent a potentially effective prophylactic measure, as suggested by a meta-analysis.[12] As a consequence of the lower heart rate in the amiodarone group, temporary pacemaker use was approximately twice as important in the amiodarone group for the first postoperative day compared with the placebo group, which is similar to the AF Suppression Trial study.[10]

Older age, recent MI (< 6 months), angina, and use of a CCB were found to be associated with postoperative AF. Older age has been shown to be a strong predictive factor of postoperative AF in previous studies.[4,17,18] The occurrence of a recent MI has been related to cardiac remodeling and atrial dilatation, which is a risk factor for AF.[9] Preoperative and postoperative use of a CCB was associated with a higher risk of developing postoperative AF. This higher occurrence of AF in patients taking a CCB has previously been described in the literature.[19–22]

Conclusion

In patients undergoing cardiac valvular surgery, a strategy using IV amiodarone perioperatively did not reduce the burden of postoperative AF in patients after cardiac valvular surgery.

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Appendix. Daily Weight-based Amiodarone Dosage

Weight, kg	Total Dose per 24 h (per study protocol), mg	Maximal Allowable Dose in 24 h for Clinical Indication, mg
Postoperative no. 1		
50	1,050	850
51	1,065	835
52	1,080	820
53	1,095	805
54	1,110	790
55	1,125	775
56	1,140	760
57	1,155	745
58	1,170	730
59	1,185	715
60	1,200	700
61	1,215	685
62	1,230	670
63	1,245	655
64	1,260	640
65	1,275	625
66	1,290	610
67	1,305	595
68	1,320	580
69	1,335	565
70	1,350	550
71	1,365	535
72	1,380	520
73	1,395	505
74	1,410	490
75	1,425	475
76	1,440	460
77	1,455	445
78	1,470	430
79	1,485	415
80	1,500	400
81	1,515	385
82	1,530	370
83	1,545	355
84	1,560	340
85	1,575	325
86	1,590	310
87	1,605	295
88	1,620	280
89	1,635	265
90	1,650	250
91	1,665	235
92	1,680	220
93	1,695	205
94	1,710	190
95	1,725	175
96	1,740	160
97	1,755	145
98	1,770	130
99	1,785	115
100	1,800	100
Weight (kg)–based total amiodarone dosage:		
Postoperative no. 2		
50	750	1,150
51	765	1,135
52	780	1,120

(*continued*)

Appendix. Continued

Weight, kg	Total Dose per 24 h (per study protocol), mg	Maximal Allowable Dose in 24 h for Clinical Indication, mg
53	795	1,105
54	810	1,090
55	825	1,075
56	840	1,060
57	855	1,045
58	870	1,030
59	885	1,015
60	900	1,000
61	915	985
62	930	970
63	945	955
64	960	940
65	975	925
66	990	910
67	1,005	895
68	1,020	880
69	1,035	85
70	1,050	850
71	1,065	835
72	1,080	820
73	1,095	805
74	1,110	790
75	1,125	775
76	1,140	760
77	1,155	745
78	1,170	730
79	1,185	715
80	1,200	700
81	1,215	685
82	1,230	670
83	1,245	655
84	1,260	640
85	1,275	625
86	1,290	610
87	1,305	595
88	1,320	580
89	1,335	565
90	1,340	550
91	1,365	535
92	1,380	520
93	1,395	505
94	1,410	490
95	1,425	475
96	1,440	460
97	1,455	445
98	1,470	430
99	1,485	415
100	1,500	400

For example, a patient weighing 70 kg assigned to the amiodarone group would have received an initial bolus of 300 mg followed by 15 mg $\times$ kg^{-1} $\times$ h^{-1} infusion for a total of 1,350 mg of intravenous amiodarone in the first 24 h postoperatively perprotocol. If this patient would develop atrial fibrillation within 24 h and the physician would like to treat it with intravenous amiodarone, he could administer up to 550 mg to this patient according to the weight-based chart (so not to exceed the safety limit of 2,000 mg). On the other hand, if this patient would have been in the placebo group, he/she would have received a potentially subtherapeutic dose of the medication. In a case where the arrhythmia would persist and the physician would want to administer additional amiodarone (exceeding the maximal dose allowed based on the weight-based chart), the blind would have to be broken (by the pharmacist) to ensure that potentially dangerous amiodarone doses would not be used.