Prophylactic Oral Amiodarone for the Prevention of Arrhythmias That Begin Early After Revascularization, Valve Replacement, or Repair

PAPABEAR: A Randomized Controlled Trial

L. Brent Mitchell, MD
Derek V. Exner, MD, MPH
D. George Wyse, MD, PhD
Carol J. Connolly, RN
Gregory D. Prystai, MD
Alexander J. Bayes, MD
William T. Kidd, MD
Teresa Kieser, MD
John J. Burgess, MD
André Ferland, MD
Charles L. MacAdams, MD
Andrew Maitland, MD

Context Atrial tachyarrhythmias after cardiac surgery are associated with adverse outcomes and increased costs. Previous trials of amiodarone prophylaxis, while promising, were relatively small and yielded conflicting results.

Objective To determine whether a brief perioperative course of oral amiodarone is an effective and safe prophylaxis for atrial tachyarrhythmias after cardiac surgery overall and in important subgroups.

Design, Setting, and Patients Double-blind randomized controlled trial of 601 patients listed for nonemergent coronary artery bypass graft (CABG) surgery and/or valve replacement/repair surgery between February 1, 1999, and September 26, 2003, at a tertiary care hospital. The patients were followed up for 1 year.

Intervention Oral amiodarone (10 mg/kg daily) or placebo administered 6 days prior to surgery through 6 days after surgery (13 days). Randomization was stratified for subgroups defined by age, type of surgery, and use of preoperative β-blockers.

Main Outcome Measure Incidence of atrial tachyarrhythmias lasting 5 minutes or longer that prompted therapy by the sixth postoperative day.

Results Atrial tachyarrhythmias occurred in fewer amiodarone patients (48/299; 16.1%) than in placebo patients (89/302; 29.5%) overall (hazard ratio [HR], 0.52; 95% confidence interval [CI], 0.34-0.69; $P<.001$); in patients younger than 65 years (19 [11.2%] vs 36 [21.1%]; HR, 0.51 [95% CI, 0.28-0.94]; $P=.02$); in patients aged 65 years or older (28 [21.7%] vs 54 [41.2%]; HR, 0.45 [95% CI, 0.27-0.75]; $P<.001$); in patients who had CABG surgery only (22 [11.3%] vs 46 [23.6%]; HR, 0.45 [95% CI, 0.26-0.79]; $P=.002$); in patients who had valve replacement/repair surgery with or without CABG surgery (25 [23.8%] vs 44 [44.1%]; HR, 0.51 [95% CI, 0.31-0.84; $P=.008$); in patients who received preoperative β-blocker therapy (27 [15.3%] vs 42 [25.0%]; HR, 0.58 [95% CI, 0.34-0.99]; $P=.03$); and in patients who did not receive preoperative β-blocker therapy (20 [16.3%] vs 48 [35.8%]; HR, 0.40 [95% CI, 0.22-0.71]; $P<.001$), respectively. Postoperative sustained ventricular tachyarrhythmias occurred less frequently in amiodarone patients (1/299; 0.3%) than in placebo patients (8/302; 2.6%) ($P=.04$). Dosage reductions of blinded therapy were more common in amiodarone patients (34/299; 11.4%) than in placebo patients (16/302; 5.3%) ($P=.008$). There were no differences in serious postoperative complications, in-hospital mortality, or readmission to the hospital within 6 months of discharge or in 1-year mortality.

Conclusion Oral amiodarone prophylaxis of atrial tachyarrhythmias after cardiac surgery is effective and may be safe overall and in important patient subgroups.

Clinical Trials Registration ClinicalTrials.gov Identifier: NCT00251706

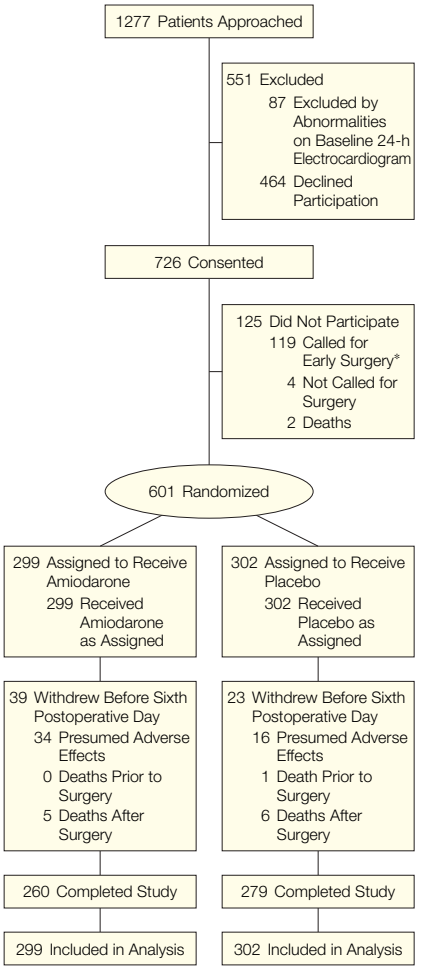
JAMA. 2005;294:3093-3100 www.jama.com

ATRIAL TACHYARRHYTHMIAS, usually atrial fibrillation or atrial flutter, are facilitated by atrial trauma, atrial stretch, atrial ischemia, epicardial inflammation, hypoxia, acidosis, electrolyte disturbances, and electrophysiological changes that accompany sympathetic nervous system discharge.[1] As these factors are common immediately after cardiac surgery, atrial tachyarrhythmia is the most common postoperative complication.[1-5] The incidence of sustained atrial tachyarrhythmias after coronary artery bypass graft (CABG) surgery is approximately 30%; after valve surgery, approximately 40%; and after combined CABG and valve replacement/repair surgery, approximately 50%.[1] The consequences of these atrial tachyarrhythmias include dis-

For editorial comment see p 3140.

Author Affiliations are listed at the end of this article.
Corresponding Author: L. Brent Mitchell, MD, Department of Cardiac Sciences, Foothills Hospital, 1403 29th St NW, Calgary, Alberta, Canada T2N 2T9 (brent.mitchell@calgaryhealthregion.ca).

Figure 1. Flow of Patients Through the PAPABEAR Trial



PAPABEAR indicates Prophylactic Amiodarone for the Prevention of Arrhythmias that Begin Early After Revascularization, Valve Replacement, or Repair. Asterisk indicates outpatients who were called to present for their surgical procedure with fewer than 5 days notice and could not be randomized and start their preoperative medication.

comfort or anxiety, hemodynamic deterioration, stroke, exposure to the risks of tachyarrhythmia treatments, prolongation of hospital stay, and increased health care costs.[2-10] Atrial tachyarrhythmias have recently been reported to increase hospital stay after cardiac surgery by 1.4 days at an additional cost of $6356 per patient.[9]

Accordingly, substantial effort has been invested in finding an effective, safe, and widely applicable prophylactic treatment for atrial tachyarrhythmia occurring after cardiac surgery.[1] The most extensively studied prophylactic therapy is β-blockade.[1] However, the applicability of β-blocker therapy is limited by the frequency of contraindications to its use[11] and its modest efficacy in contemporary cardiac surgery populations.[12] Furthermore, clinical trials have not demonstrated that prevention of postoperative atrial tachyarrhythmias with β-blocker therapy reduces hospital stay or resource use.[12,13]

There have been 4 randomized trials of preoperative oral amiodarone for atrial tachyarrhythmia prophylaxis after cardiac surgery.[14-17] The largest trial[17] randomized only 315 patients. Two trials[14,15] reported a statistically significant reduction in the incidence of postoperative atrial tachyarrhythmias; 2 trials,[16,17] including the largest trial,[17] did not. None were statistically powered to evaluate the efficacy of amiodarone in patient subgroups. Nevertheless, potentially important subgroup differences have been suggested. None of these trials was powered to evaluate the tolerability and safety of oral amiodarone in this setting. Indeed, each trial reported the improbable absence of significant adverse symptoms or signs in patients receiving amiodarone.

Accordingly, the purpose of the Prophylactic Amiodarone for the Prevention of Arrhythmias that Begin Early After Revascularization, Valve Replacement, or Repair (PAPABEAR) trial was to test the hypothesis that amiodarone is an effective, well-tolerated, and safe therapy for prevention of atrial tachyarrhythmias after cardiac surgery in a placebo-controlled, randomized trial in a large patient population using stratified randomization to facilitate separate analysis in younger patients (<65 years) compared with older patients (≥65 years), patients undergoing CABG surgery compared with patients undergoing cardiac valve surgery or combined CABG and valve replacement/repair surgery, and in patients who received preoperative β-blocker therapy compared with those who did not receive preoperative β-blocker therapy.

METHODS

Study Population

Adult patients of either sex and of any age were considered for participation when listed for nonemergent CABG surgery and/or valve replacement/repair surgery without other concomitant procedures. All patients had a baseline 24-hour ambulatory electrocardiogram. Exclusion criteria included myocardial infarction within 2 weeks, any rhythm other than sinus, New York Heart Association class IV congestive heart failure despite treatment, persistent hypotension (systolic blood pressure <80 mm Hg), requirement for antiarrhythmic drug therapy, history of sustained atrial tachyarrhythmias, treatment with amiodarone within 3 months, sinus bradycardia while awake (<50/min^{-1}), PR interval greater than 220 milliseconds, second- or third-degree AV block, corrected QT interval of 480 milliseconds or higher, peripheral neuropathy, aspartate aminotransferase twice the upper limit of normal, interstitial pulmonary disease, clinical hypothyroidism or hyperthyroidism, bleeding diathesis, and women of child-bearing potential. Eligible patients participated after a full-disclosure, written, informed consent process. The study was approved by the Conjoint Medical Ethics Committee of the Calgary Health Region and the University of Calgary.

Study Protocol

The flow of patients through the study appears in FIGURE 1. Participants were randomized to receive amiodarone or matching placebo in a double-blind fashion in a 1:1 ratio, blocked in groups of 10, and stratified for age (<65 years vs ≥65 years), surgical procedure (CABG surgery alone vs valve replacement/repair surgery with or without CABG surgery), and preoperative treatment (with β-blockers vs without β-blockers). The random allocation sequences were computer-generated and were implemented by a hospital pharmacist who was not otherwise involved in the trial. Study personnel

were not aware of the allocation sequences or of patient allocation.

Treatment with amiodarone or placebo was administered 6 days prior to surgery through 6 days after surgery (13 days). The amiodarone dosage was 10 mg/kg daily, divided into 2 doses per day. Continuous telemetry electrocardiographic monitoring began intraoperatively and was continued for the subsequent 6 days. Trough serum amiodarone and desethylamiodarone levels were determined preoperatively on the day of surgery but were not provided to study personnel until after study closure. Patients receiving digoxin had its dosage halved.

Outcome Events

The primary outcome was an atrial tachyarrhythmia during the first 6 days after surgery that lasted for 5 minutes or longer and prompted treatment by the attending physician. Prespecified secondary outcomes included the primary outcome in each subgroup defined by the stratified randomization scheme, the ventricular response rate of atrial tachyarrhythmias that did occur, the postoperative day of an atrial tachyarrhythmia occurrence, the number of atrial tachyarrhythmia episodes, the duration of the longest episode, the tachyarrhythmia "burden" (number of hours of atrial tachyarrhythmia during the first 6 postoperative days), and length of postoperative hospital stay. Adverse events potentially attributable to amiodarone were also prospectively recorded. Because the optimal treatment for atrial tachyarrhythmia after cardiac surgery is unknown, it was not prescribed by protocol.

Sample Size Determination and Data Analyses

Analyses were based on the intention-to-treat principle in all patients as randomized. The sample size required to provide 80% power to detect an absolute difference of 10% in the incidence of postoperative atrial tachyarrhythmia from an estimated control incidence of 30%, allowing for a 5% crossover using a 2-tailed test at the $P<.05$ level, was 600 patients.[18] The observed difference was larger than this conservative estimate and provided greater than 80% power within each of the stratified subgroups.

Patient characteristics were summarized by standard descriptive statistics and were compared between groups using paired or unpaired *t* tests or the Fisher exact test as appropriate. The Kaplan-Meier method[19] was used to construct time-to-event curves. Adjustment for differences between groups with respect to baseline characteristics was accomplished using the Cox proportional hazards model.[20] The proportional hazards assumption was confirmed to be valid using log-log plots. All comparisons were 2-tailed and significance was ascribed to $P<.05$. Analyses were performed using STATA statistical soft-

Table 1. Baseline Characteristics of Patients and Operative Procedures*

	Amiodarone (n = 299)	Placebo (n = 302)	*P* Value
Characteristic			
Age, mean (SD), y	61.3 (11.3)	61.9 (11.2)	.49
Men	247 (82.6)	247 (81.8)	.83
Left ventricular ejection fraction, mean (SD), %	57 (11)	58 (12)	.76
NYHA functional class			
I	242 (81.0)	246 (81.5)	>.99
II	20 (6.7)	20 (6.6)	
III/IV	34 (11.5)	36 (11.9)	
History			
Congestive heart failure	74 (24.7)	74 (24.5)	>.99
Myocardial infarction	56 (18.7)	55 (18.2)	.92
Hypertension	157 (52.5)	161 (53.3)	.87
Diabetes mellitus	76 (25.4)	62 (20.5)	.18
Chronic obstructive pulmonary disease	4 (1.3)	7 (2.3)	.55
Cerebrovascular accident/TIA	28 (9.4)	22 (7.3)	.38
Preoperative use			
β-Blocker	176 (58.9)	168 (55.6)	.46
ACE inhibitor	141 (47.2)	138 (45.7)	.81
Angiotensin receptor blocker	26 (8.7)	30 (9.9)	.67
NSAID	23 (7.7)	26 (8.6)	.77
Postoperative use of β-blocker	148 (49.5)	150 (49.7)	.94
Operative Procedure			
CABG surgery by No. of vessels			
1	26 (8.7)	27 (9.0)	.29
2	57 (19.1)	45 (14.9)	
3	82 (27.4)	108 (35.9)	
≥4	53 (17.7)	49 (16.3)	
Type/No. of valves repaired/replaced			
Mitral	25 (8.4)	28 (9.3)	.99
Aortic	68 (22.7)	65 (21.6)	
Other	1 (0.3)	1 (0.3)	
Multiple	8 (2.7)	8 (2.7)	
Type of surgery			
CABG only	194 (64.9)	195 (64.6)	>.99
Valve repair/replacement with or without CABG	105 (35.1)	107 (35.4)	>.99
Valve repair/replacement only	81 (27.1)	72 (23.8)	.40
Time, mean (SD), min			
Procedure	158 (49)	161 (52)	.51
Pump	74 (40)	77 (44)	.29
Cross-clamp	53 (31)	56 (34)	.29

Abbreviations: ACE, angiotensin-converting enzyme; CABG, coronary artery bypass graft; NSAID, nonsteroidal anti-inflammatory drug; NYHA, New York Heart Association; TIA, transient ischemic attack.
*Values are expressed as number (percentage) unless otherwise indicated.

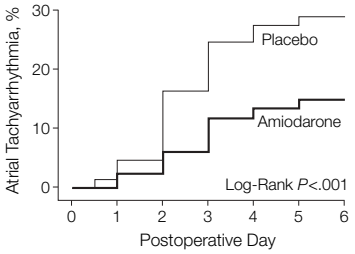
ware version 8.2 (STATA Corp, College Station, Tex).

RESULTS

Study Population

Between February 1, 1999, and September 26, 2003, a total of 601 patients were randomized in the PAPABEAR trial. One patient (assigned to the placebo group) died after study therapy initiation but before surgery subsequent to a monitored electromechanical dissociation arrest. The remaining 600 patients had surgery; of the total group, 299 were assigned to the amiodarone group and 302 were assigned to the placebo group. Patients in the 2 groups were well matched (TABLE 1). The mean (SD) age of the patients was 61.6 (11.2) years; 494 (82%) were male. The mean age, sex, type of heart disease, New York Heart Association functional class, and mean systolic and diastolic blood pressure values were similar in patients who agreed to participate compared with those who declined to participate. No patients were lost to follow-up.

Figure 2. Kaplan-Meier Cumulative Incidence of Atrial Tachyarrhythmia



No. at Risk

Placebo	301	295	284	249	223	199	138
Amiodarone	299	298	291	278	260	238	169

Atrial tachyarrhythmia lasting 5 minutes or longer that prompted specific antiarrhythmic therapy for the patients randomized to amiodarone treatment and for the patients randomized to placebo treatment.

Study Therapy

The mean (SD) durations of preoperative treatment with amiodarone (5.6 [1.7] days) or placebo (5.6 [1.4] days) were equivalent. The mean (SD) duration of postoperative treatment with amiodarone (5.4 [1.8] days) was slightly shorter than with placebo (5.9 [1.7] days) ($P<.001$). On the day of surgery, patients receiving amiodarone had mean (SD) trough serum concentrations of amiodarone of 1.62 (0.78) µmol/L and of desethylamiodarone of 0.80 (0.09) µmol/L.

Atrial Tachyarrhythmia: All Patients

Of the 137 patients experiencing postoperative atrial tachyarrhythmia, 128 (93.4%) had atrial fibrillation and 9 (6.6%) had atrial flutter. Postoperative atrial tachyarrhythmia occurred in fewer amiodarone patients (48/299; 16.1%) than placebo patients (89/302; 29.5%) (hazard ratio [HR], 0.52 [95% confidence interval {CI}, 0.34-0.69]; $P<.001$; FIGURE 2). The absolute reduction in the incidence of postoperative atrial tachyarrhythmia of 13.4% translates into a number needed to treat to prevent 1 patient from developing a postoperative atrial tachyarrhythmia of 7.5 (95% CI, 4.8-14.7).

Seven patients in the placebo group and 5 patients in the amiodarone group died before the sixth postoperative day. One patient in each group had already had an atrial tachyarrhythmia. By way of a sensitivity analysis, if the 4 incompletely monitored patients in the amiodarone group and none of the 6 incompletely monitored patients in the placebo group were considered to have had postoperative atrial tachyarrhythmia, the difference in postoperative atrial tachyarrhythmia incidence remains significantly lower in patients randomized to amiodarone compared with those randomized to placebo (HR, 0.54 [95% CI, 0.38-0.75]; $P<.001$).

When atrial tachyarrhythmia did occur, the ventricular response rate was slower in amiodarone patients than in placebo patients but there were no differences in the postoperative day of atrial tachyarrhythmia onset, the duration of the longest atrial tachyarrhythmia episode, the mean number of atrial tachyarrhythmia episodes per patient, or the burden of atrial tachyarrhythmia per patient (TABLE 2).

Three patients from the placebo group and 1 patient from the amiodarone group were readmitted to the hospital within 6 months of surgery with an atrial tachyarrhythmia diagnosis. Of these, 1 patient (randomized to placebo) had not had an atrial tachyarrhythmia prior to hospital discharge.

Atrial Tachyarrhythmia: Subgroups

Amiodarone reduced the incidence of postoperative atrial tachyarrhythmia in each of the patient subgroups created by stratified randomization and, in each instance, the treatment effect was significant (TABLE 3).

The incidence of postoperative atrial tachyarrhythmia was higher in patients aged 65 years or older, in patients who had valve replacement/repair surgery with or without CABG surgery, and in patients not receiving preoperative β-blocking therapy (Table 3).

The HRs for postoperative atrial tachyarrhythmia in amiodarone patients were comparable in the 6 prespecified subgroups. Subgroups with higher probabilities of postoperative atrial tachyarrhythmia had larger absolute risk reductions that translate into lower numbers of patients needed to treat (Table 3).

A total of 153 patients had valve replacement/repair surgery only. In this nonstratified subgroup, the HR for amiodarone prophylaxis was comparable with that of the prespecified subgroups at 0.56 (95% CI, 0.29-1.07). However, the difference did not reach

Table 2. Characteristics of Atrial Tachyarrhythmia*

	Amiodarone (n = 48)	Placebo (n = 89)	*P* Value
Ventricular rate per min, mean (SD)	105 (24)	131 (25)	<.001
Postoperative onset, d	3 (2-4)	2 (2-3)	.34
Longest episode, h	12.2 (4.4-21.5)	12.0 (4.9-23.3)	.58
Episodes per patient	2 (1-3)	2 (1-4)	.98
Burden per patient, h	17.8 (6.5-40.4)	18.7 (7.7-38.2)	.76

*Values are expressed as median (25th and 75th percentiles) unless otherwise indicated.

Table 3. Atrial Tachyarrhythmia by Subgroups

	Total No. of Patients	No. (%) of Patients With Atrial Tachyarrhythmia		Hazard Ratio (95% CI)*	*P* Value	Absolute Risk Reduction (95% CI)*	No. Needed to Treat (95% CI)*
		Amiodarone	Placebo				
Overall	601	48 (16.1)	89 (29.5)	0.52 (0.34-0.69)	<.001	13.4 (6.8-20.7)	7.5 (4.8-14.7)
Age, y							
<65	341	19 (11.2)	36 (21.1)	0.51 (0.28-0.94)	.02	9.9 (1.3-18.4)	10.1 (5.4-75.8)
≥65	260	28 (21.7)	54 (41.2)	0.45 (0.27-0.75)	<.001	19.5 (7.3-31.7)	5.1 (3.2-29.2)
Type of surgery							
CABG	389	22 (11.3)	46 (23.6)	0.45 (0.26-0.79)	.002	12.3 (4.0-20.5)	8.1 (4.9-25.0)
Valve replacement/ repair with or without CABG	212	25 (23.8)	44 (44.1)	0.51 (0.31-0.84)	.008	20.3 (3.6-31.0)	4.9 (3.2-27.8)
Preoperative β-blocker use							
Yes	344	27 (15.3)	42 (25.0)	0.58 (0.34-0.99)	.03	9.7 (0.3-19.0)	10.4 (5.3-312.5)
No	257	20 (16.3)	48 (35.8)	0.40 (0.22-0.71)	<.001	19.6 (8.0-31.1)	5.1 (3.2-12.5)

Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval.
*Indicates 95% CI for the primary outcome and 97% CI for the 3 prespecified subgroups to account for multiple comparisons (Bonferroni correction).

statistical significance in this smaller subgroup (*P*=.08).

Duration of Hospitalization

The durations of postoperative intensive care unit stays were equivalent in the amiodarone and placebo groups. Although the total mean (SD) length of postsurgical hospital stay was shorter for amiodarone patients (8.2 [7.4] days) than for placebo patients (8.9 [8.1] days), this difference did not reach statistical significance (*P*=.11).

Potential Adverse Effects of Amiodarone

Potential adverse effects of amiodarone were assessed in 4 ways: analysis of withdrawal or reduction in the dosage of blinded therapy; analysis of nonfatal postoperative complications; analysis of in-hospital mortality; and analysis of the frequency of hospital readmission after discharge.

Blinded therapy was more often withdrawn or reduced in dosage in amiodarone patients (34/299; 11.4%) than in placebo patients (16/302; 5.3%) due to an increase in bradycardia requiring pacing, QTc interval prolongation longer than 650 milliseconds, and skin rash (*P*=.008; TABLE 4). In contrast, postoperative sustained ventricular tachyarrhythmia occurred less frequently in amiodarone patients (1/299; 0.3%) than in placebo patients (8/302; 2.6%) (*P*=.04). Of these events, 3 were fatal and occurred in patients randomized to placebo (*P*=.25). Other major nonfatal postoperative complications and causes of operative mortality were not different between the 2 treatment groups (TABLE 5). There was no difference between the 2 treatment groups in the incidence of readmission to the hospital for any reason within 6 months of discharge (42 [14.0%] of 299 amiodarone patients vs 37 [12.3%] of 302 placebo patients; *P*=.55) or in 1-year mortality rates (8 [2.7%] of 299 amiodarone patients vs 12 [4.0%] of 302 placebo patients; *P*=.50).

Table 4. Adverse Events Leading to Withdrawal of Full-Dose Blinded Therapy

Presumed Adverse Event	No. (%) of Patients		*P* Value
	Amiodarone (n = 299)	Placebo (n = 302)	
Any	34 (11.4)	16 (5.3)	.008
Cardiac	21 (7.0)	6 (2.0)	.002
Bradycardia requiring temporary pacing	17 (5.7)	6 (2.0)	.02
QT prolongation >650 ms	4 (1.3)	0	.06
Nausea	8 (2.7)	6 (2.0)	.60
Rash	3 (1.0)	0	.12
Dysphoria	1 (0.3)	2 (0.7)	>.99
Cough	1 (0.3)	0	.50
Headache	0	1 (0.3)	>.99
Hypotension	0	1 (0.3)	>.99

COMMENT

The PAPABEAR trial demonstrates that a 13-day perioperative course of oral amiodarone therapy is associated with a halving of the postoperative incidence of atrial tachyarrhythmias overall, in those patients younger than 65 years, in those aged 65 years or older, in those having CABG surgery, in those having valve replacement/repair surgery with or without CABG surgery, in those receiving concomitant β-blocker therapy, and in those not receiving concomitant β-blocker therapy. The number needed to treat to prevent 1 patient from developing postoperative atrial tachyarrhythmia was only 7.5 overall and was even lower in older patients, in patients having valve surgery, and in patients not receiving concomitant β-blocker therapy. This benefit was associated with a reduction in the incidence of sustained ventricular tachyarrhythmia. Amiodarone had few adverse effects and was not associated with serious postoperative events. These results may be generalizable to any setting performing cardiac surgery.

Table 5. Perioperative Complications

Complication	No. (%) of Patients: Amiodarone (n = 299)	No. (%) of Patients: Placebo (n = 302)	*P* Value
Nonfatal			
Any	28 (9.4)	34 (11.3)	.50
Bleeding requiring reoperation	9 (3.0)	8 (2.6)	.81
Respiratory failure	5 (1.7)	5 (1.7)	>.99
Myocardial infarction	2 (0.7)	6 (2.0)	.39
Sternal dehiscence	2 (0.7)	4 (1.3)	.69
Cerebrovascular accident	2 (0.7)	4 (1.3)	.69
Ventricular tachycardia/fibrillation	1 (0.3)	5 (1.7)	.22
Other	8 (2.7)	8 (2.6)	>.99
Fatal			
Any cause	7 (2.3)	10 (3.3)	.62
Shock/multiorgan system failure	4 (1.3)	4 (1.3)	>.99
Cerebrovascular accident	1 (0.3)	1 (0.3)	>.99
Recurrent emboli	0	2 (0.7)	.50
Ventricular tachycardia/fibrillation	0	3 (1.0)	.25
Bleeding	1 (0.3)	0	.50
Respiratory failure	1 (0.3)	0	.50

Atrial Tachyarrhythmia Prophylaxis

Atrial tachyarrhythmia after cardiac surgery is often transient and causes little morbidity. However, atrial arrhythmia after cardiac surgery may have important consequences including hemodynamic deterioration, stroke, ventricular arrhythmia, permanent pacemaker implantation, longer hospital stays, and exposure to the risks of arrhythmia treatments including anticoagulation.[2-10,21]

Meta-analyses[13,22] of treatments to prevent atrial tachyarrhythmia after cardiac surgery have suggested benefit with standard β-blockers, sotalol, intravenous magnesium, and atrial pacing but not digoxin, verapamil, or procainamide. The most robust data supports treatment with β-blockers. Nevertheless, β-blocker prophylaxis is often not prescribed.[23] Recently, amiodarone has been evaluated as an alternative prophylactic treatment.

Four previous trials[14-17] evaluated preoperative oral amiodarone for atrial tachyarrhythmia prophylaxis after cardiac surgery. Two trials[14,15] showed a significant advantage for amiodarone; 2 trials[16,17] did not. The largest trial[17] involved 315 patients and showed no benefit. None were powered to evaluate the efficacy of amiodarone in subgroups. Nevertheless, potentially important subgroup differences have been suggested. With respect to age, 2 studies[15,17] have reported that the benefits of amiodarone are limited to patients older than 70 years. With respect to the surgical procedure performed, it is noteworthy that the 2 trials[16,17] reporting no benefit enrolled only patients having CABG surgery while the 2 trials[14,15] reporting benefit also enrolled patients having valve replacement/repair surgery. This suggestion that the benefits of amiodarone are limited to those having valve replacement/repair surgery was supported by a post hoc analysis[15] that reported significant benefits in patients without coronary heart disease (who presumably had valve replacement/repair surgery) but not in patients with coronary heart disease (who presumably had CABG surgery). With respect to the effects of concomitant β-blocker therapy, each of these 4 trials reported an interaction in post hoc analyses. However, the results reported were disparate. One trial[14] reported significant benefits from amiodarone in patients receiving concomitant β-blocker therapy but not in patients not receiving β-blocker therapy while another trial[15] reported the reverse interaction. The third trial[17] reported a nonsignificant increase in risk of atrial tachyarrhythmia in patients receiving concomitant β-blocker therapy and a nonsignificant benefit in patients not receiving concomitant β-blocker therapy, while the fourth[16] reported that combined amiodarone and β-blocker therapy was prophylactic but neither amiodarone nor β-blocker therapy was when administered alone. The PAPABEAR trial demonstrates that the atrial tachyarrhythmia risk reduction with amiodarone is comparable in each of these subgroups. However, because the baseline risk of postoperative atrial tachyarrhythmia is higher in older patients, in patients having valve replacement/repair surgery, and in patients not receiving concomitant β-blocker therapy, the absolute benefit in these subgroups is larger, which facilitates their detection in small patient populations.

After initiation of oral amiodarone, its electrophysiological effects slowly accumulate. With the dosages used in the PAPABEAR trial, the latency to suppression of atrial arrhythmias is 4 to 6 days[24] but the maximum atrial electrophysiological effects may require 2 weeks.[25] The 6-day preoperative treatment period in the PAPABEAR trial was a compromise between awaiting amiodarone's treatment effects and permitting timely surgery. Although shorter preoperative oral amiodarone treatment periods have been used, it is not clear that they are effective. The 2 trials[14,15] that provided preoperative therapy for 5 days or longer reported positive results for most of their patients while the 2 trials[16,17] that provided preoperative therapy for fewer than 5 days reported negative results. Compared with preoperative amiodarone loading for fewer than 5 days, the effects of preoperative amiodarone loading over 5 days or longer yielded more positive effects.[26] Other trials have attempted to overcome the need for preoperative loading using higher dosages of postoperative oral amiodarone[27] or preoperative and/or postoperative intravenous amioda-

rone.[28-37] These trials with alternative amiodarone dosing approaches almost exclusively enrolled patients having CABG surgery (96%) and ranged in size from 77 patients[29] to 300 patients.[30] Seven trials[27-30,35-37] showed a significant advantage for amiodarone therapy; 4 trials[31-34] did not. Although no study has directly compared preoperative oral amiodarone with any of these alternative amiodarone approaches, their reported effect sizes are comparable with those with preoperative oral amiodarone loading lasting 5 days or longer. Nevertheless, intravenous amiodarone loading may be associated with more adverse effects. None of these trials with alternative amiodarone dosing was large enough to evaluate efficacy in important subgroups.

In the PAPABEAR trial, patients assigned to amiodarone who developed postoperative atrial tachyarrhythmia had a 20% slower mean ventricular response rate. Similar observations were made in the previous preoperative oral amiodarone trials[14-17] and in 6 of the 8 alternative amiodarone dosing trials that reported this measure.[27,28,33,34,36,37] In the PAPABEAR trial, when atrial tachyarrhythmia occurred, the postoperative day of atrial tachyarrhythmia onset and the atrial tachyarrhythmia burden were the same in both treatment groups. Two[15,16] of the 4 previous preoperative oral amiodarone studies and 3 studies[30-32] with alternative amiodarone dosing reported that the day of atrial tachyarrhythmia onset was significantly delayed by treatment with amiodarone. However, a greater number of studies[14,17,27,28,33,36] did not. One[15] of the 4 previous preoperative oral amiodarone studies and 2 studies[28,36] with alternative amiodarone dosing reported a decrease in postoperative atrial tachyarrhythmia burden. However, a greater number of studies[14,16,17,27,31,35,37] did not.

Tolerability and Safety

None of the trials[14-17] of preoperative oral amiodarone was powered to evaluate the tolerability and safety of the therapy in this setting. Indeed, each trial reported the improbable absence of statistically significant adverse symptoms or signs in patients receiving amiodarone. The PAPABEAR trial demonstrates that the incidence of adverse effects leading to a reduction in dosage or discontinuation of amiodarone was 11.4% (approximately double that of placebo: 5.3%). None of the excess adverse effects of amiodarone was serious. Four[31-34] of the 11 trials of alternative amiodarone dosing approaches reported statistically significant adverse effects dominated by hemodynamic instability, sinus bradycardia, and excessive QT interval prolongation.

Early experience with amiodarone included case reports of a possible interaction between long-term amiodarone therapy and cardiac surgery manifest by excessive sinus bradycardia, hemodynamic deterioration, and adult respiratory distress syndrome.[38-40] Subsequently, 2 case-control studies[41,42] found no such interaction. The PAPABEAR trial is the first controlled evaluation of this risk and found no evidence of an association between these adverse outcomes and short-term amiodarone therapy.

The low incidence of adverse effects from a short course of oral amiodarone makes it attractive for atrial tachyarrhythmia prophylaxis. Other advantages of amiodarone include the absence of depression of ventricular function when given orally[43] and a low risk (<1%) of ventricular proarrhythmia.[44] No evidence of either was seen in the PAPABEAR trial.

Other Treatment Effects

The PAPABEAR trial also demonstrates that perioperative oral amiodarone reduces the incidence of postoperative sustained ventricular tachyarrhythmia. This observation also was reported in another trial.[15]

The PAPABEAR trial noted a trend toward a reduction in postoperative hospital stay in patients receiving amiodarone. Two trials[14,36] reported significant reductions in postoperative hospital stay in patients receiving amiodarone. Evidence that amiodarone reduces postoperative hospital stay also has emerged from a meta-analysis.[13]

Limitations

Although the PAPABEAR trial involved twice as many participants as previous amiodarone studies, it is still limited by its power to detect adverse events that occur infrequently.

Use of oral amiodarone prophylaxis for postoperative atrial tachyarrhythmia according to the PAPABEAR algorithm requires a 6-day preoperative treatment period. In many jurisdictions, the waiting period for nonemergent cardiac surgery exceeds this time. However, for those jurisdictions that provide nonemergent cardiac surgery within 6 days of referral, the advantages of amiodarone prophylaxis must be weighed against the risks of delaying surgery. The mortality risk during the preoperative treatment period in the present study was 0.17% (1/601). To justify this risk, the benefits of amiodarone therapy must dominate. In this regard, it is noteworthy that throughout this trial, including after 1 year of follow-up, the mortality difference favored the amiodarone treatment group. Although none of these small mortality differences was statistically significant, their direction suggests that the advantages of amiodarone prophylaxis may be sufficient to delay nonemergent surgery to permit initiation of amiodarone therapy.

CONCLUSIONS

The PAPABEAR trial demonstrates that a 13-day perioperative course of oral amiodarone is an effective, possibly safe, well-tolerated, and widely applicable therapy for the prevention of postoperative atrial tachyarrhythmia after cardiac surgery. This benefit was associated with a reduction in the probability of perioperative sustained ventricular tachyarrhythmia and a trend toward a reduction in postoperative hospital stay.

Author Affiliations: Libin Cardiovascular Institute of Alberta, Calgary; Calgary Health Region, Calgary, Alberta; and the Department of Cardiac Sciences, University of Calgary, Calgary, Alberta.

Author Contributions: Drs Mitchell and Exner and Ms Connolly had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Mitchell, Exner, Wyse, Maitland.
Acquisition of data: Mitchell, Exner, Connolly, Prystai, Bayes, Kidd, Kieser, Burgess, Ferland, MacAdams, Maitland.
Analysis and interpretation of data: Mitchell, Exner, Wyse, Connolly.
Drafting of the manuscript: Mitchell, Exner, Connolly.
Critical revision of the manuscript for important intellectual content: Mitchell, Exner, Wyse, Connolly, Prystai, Bayes, Kidd, Kieser, Burgess, Ferland, MacAdams, Maitland.
Statistical analysis: Mitchell, Exner, Connolly.
Obtained funding: Mitchell, Exner, Connolly.
Administrative, technical, or material support: Mitchell, Wyse, Connolly, Prystai, Bayes, Kidd, Kieser, Burgess, Ferland, MacAdams, Maitland.
Study supervision: Mitchell, Exner, Wyse, Connolly.
Financial Disclosures: Dr Wyse has been a consultant to Sanofi-Aventis and Biovail Pharma; served on the scientific advisory board for Medtronic and Boehringer Ingelheim; served as a speaker for Cardiome/Astellas, Medtronic, Sanofi-Aventis, Chugai Pharma, Biovail Pharma, Daiichi Pharma; and owns stock in Cardiome. None of the other authors reported disclosures.
Funding/Support: The PAPABEAR pilot study was funded by the Heart and Stroke Foundation of Alberta, NWT, and Nunavut. The main PAPABEAR trial was funded by grant MCT-14764 from the Canadian Institutes for Health Research. Amiodarone and it matching placebo were supplied by Wyeth-Ayerst Canada Inc. Dr Exner is a clinician-scientist for the Canadian Institutes of Health Research and a clinical investigator for the Alberta Heritage Foundation for Medical Research.
Role of the Sponsor: The funding agencies had no role in the design or conduct of the study, in the collection, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript.
Acknowledgment: We are indebted to the staff of the cardiac surgery preoperative clinic, cardiac surgery operating rooms, cardiac surgery intensive care unit, and cardiac surgery ward for their major contributions to the PAPABEAR trial.

REFERENCES

1. Mitchell LB. Incidence, timing and outcome of atrial tachyarrhythmias after cardiac surgery. In: Steinberg JS, ed. *Atrial Fibrillation After Cardiac Surgery*. Boston, Mass: Kluwer Academic Publishers; 2000:37-50.
2. Creswell LL, Schuessler RB. Rosenbloom, Cox JL. Hazards of postoperative atrial arrhythmias. *Ann Thorac Surg*. 1993;56:539-549.
3. Leitch JW, Thomson D, Baird DK, Harris PJ. The importance of age as a predictor of atrial fibrillation and flutter after coronary artery bypass grafting. *J Thorac Cardiovasc Surg*. 1990;100:338-342.
4. Aranki SF, Shaw DP, Adams DH, et al. Predictors of atrial fibrillation after coronary artery surgery: current trends and impact of hospital resources. *Circulation*. 1996;94:390-397.
5. Khaja F, Parker JO. Hemodynamic effects of cardioversion in chronic atrial fibrillation: special reference to coronary artery disease. *Arch Intern Med*. 1972; 129:433-440.
6. Lynn GM, Stefanko K, Reed JF III, Gee W, Nicholas G. Risk factors for stoke after coronary artery bypass. *J Thorac Cardiovasc Surg*. 1992;104:1518-1523.
7. Flaker GC, Blackshear JL, McBride R, Kronmal RA, Halperin JL, Hart RG. Antiarrhythmic drug therapy and cardiac mortality in atrial fibrillation. *J Am Coll Cardiol*. 1992;20:527-532.
8. Hravnak M, Hoffman LA, Saul MI, Zullo TG, Whitman GR, Griffith BP. Predictors and impact of atrial fibrillation after isolated coronary artery bypass grafting. *Crit Care Med*. 2002;30:330-337.
9. Hravnak M, Hoffman LA, Saul MI, Zullo TG, Whitman GR. Resource utilization related to atrial fibrillation after coronary artery bypass grafting. *Am J Crit Care*. 2002;11:228-238.
10. Mathew JP, Fontes ML, Tudor IC, et al. A multicenter risk index for atrial fibrillation after cardiac surgery. *JAMA*. 2004;291:1720-1729.
11. Goldstein S, Byington R; BHAT Research Group. The Beta Blocker Heart Attack Trial: recruitment experience. *Control Clin Trials*. 1987;8:79S-85S.
12. Connolly SJ, Cybulski I, Lamy A, et al. Double-blind, placebo-controlled randomized trial of prophylactic metoprolol for reduction of hospital length of stay after heart surgery: the beta-Blocker Length of Stay (BLOS) study. *Am Heart J*. 2003;145:226-232.
13. Crystal E, Connolly SJ, Sleik K, Ginger TJ, Yusuf S. Interventions on prevention of postoperative atrial fibrillation in patients undergoing heart surgery: a meta-analysis. *Circulation*. 2002;106:75-80.
14. Daoud EG, Strickberger A, Man KC, et al. Preoperative amiodarone as prophylaxis against atrial fibrillation after heart surgery. *N Engl J Med*. 1997;337: 1785-1791.
15. Giri S, White CM, Dunn AB, et al. Oral amiodarone for prevention of atrial fibrillation after open heart surgery: the Atrial Fibrillation Suppression Trial (AFIST): a randomised placebo-controlled trial. *Lancet*. 2001; 357:830-836.
16. Redle JD, Khurana S, Marzan R, et al. Prophylactic oral amiodarone compared with placebo for prevention of atrial fibrillation after coronary artery bypass surgery. *Am Heart J*. 1999;138:144-150.
17. Maraš D, Bošković SD, Popović Z, et al. Single-day loading dose of oral amiodarone for the prevention of new-onset atrial fibrillation after coronary artery bypass surgery. *Am Heart J*. 2001;141:e8.
18. Freedman LS. Tables of the number of patients required in clinical trials using the log-rank test. *Stat Med*. 1982;1:121-129.
19. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53: 457-481.
20. Cox DR. Regression models and life tables (with discussion). *J Roy Stat Soc [Ser B]*. 1972;34:187-220.
21. Malouf JF, Alam S, Gharzeddine W, Stefadouros MA. The role of antiacoagulation in the development of pericardial effusion and late tamponade after cardiac surgery. *Eur Heart J*. 1993;14:1451-1457.
22. Andrews TC, Reinmold SC, Berlin JA, Antman EM. Prevention of supraventricular arrhythmias after coronary artery bypass surgery: a meta-analysis of randomized control trials. *Circulation*. 1991;84: III236-III244.
23. Lauer MS, Eagle KA, Buckley MJ, De Sanctis RW. Atrial fibrillation following coronary artery bypass surgery. *Prog Cardiovasc Dis*. 1989;31:367-378.
24. Rosenbaum MB, Chiale PA, Halpern MS, et al. Clinical efficacy of amiodarone as an antiarrhythmic agent. *Am J Cardiol*. 1976;38:934-944.
25. Mitchell LB, Wyse DG, Gillis AM, Duff HJ. Electropharmacology of amiodarone therapy initiation: time course of onset of electrophysiologic and antiarrhythmic effects. *Circulation*. 1989;80:34-42.
26. White CM, Giri S, Tsikouris JP, et al. A comparison of two individual amiodarone regimens to placebo in open heart surgery patients. *Ann Thorac Surg*. 2002;74:69-74.
27. Yazigi A, Rahbani P, Zeid HA, Madi-Jebara S, Haddad F, Hayek G. Postoperative oral amiodarone as prophylaxis against atrial fibrillation after coronary artery surgery. *J Cardiothorac Vasc Anesth*. 2002;16: 603-606.
28. Lee SH, Chang CM, Lu MJ, et al. Intravenous amiodarone for prevention of atrial fibrillation after coronary artery bypass grafting. *Ann Thorac Surg*. 2000;70: 157-161.
29. Hohnloser SH, Meinertz T, Dammbacher T, et al. Electrocardiographic and antiarrhythmic effects of intravenous amiodarone: results of a prospective, placebo controlled study. *Am Heart J*. 1991;121:89-95.
30. Guarnieri T, Nolan S, Gottlieb SO, Dudek A, Lowry DR. Intravenous amiodarone for the prevention of atrial fibrillation after open heart surgery: the Amiodarone Reduction in Coronary Heart (ARCH) trial. *J Am Coll Cardiol*. 1999;34:343-347.
31. Treggiari-Venzi MM, Waeber JL, Perneger TV, Suter PM, Adamec R, Romand J-A. Intravenous amiodarone or magnesium sulphate is not cost-beneficial prophylaxis for atrial fibrillation after coronary artery bypass surgery. *Br J Anaesth*. 2000;85:690-695.
32. Dörge H, Schoendube FA, Schoberer M, Stellbrink C, Voss M, Messmer BJ. Intraoperative amiodarone as prophylaxis against atrial fibrillation after coronary operations. *Ann Thorac Surg*. 2000;69:1358-1362.
33. Butler J, Harriss DR, Sinclair M, Westaby S. Amiodarone prophylaxis for tachycardias after coronary artery surgery: a randomized, double-blind, placebo controlled trial. *Br Heart J*. 1993;70:56-60.
34. Harahsheh BS, Sawalha WA. Effect of amiodarone on atrial fibrillation after coronary artery bypass surgery. *Saudi Med J*. 2001;22:797-799.
35. Tokmakoglu H, Kandemir O, Gunaydin S, Catav Z, Yorgancioglu C, Zorlutuna Y. Amiodarone versus digoxin and metoprolol combination for the prevention of postcoronary bypass atrial fibrillation. *Eur J Cardiothorac Surg*. 2002;21:401-405.
36. Yagdi T, Nalbantgil S, Ayik F, et al. Amiodarone reduces the incidence of atrial fibrillation after coronary artery bypass grafting. *J Thorac Cardiovasc Surg*. 2003;125:1420-1425.
37. White CM, Caron MF, Kalus JS, et al. Intravenous plus oral amiodarone, atrial septal pacing, or both strategies to prevent post-cardiothoracic surgery atrial fibrillation: the Atrial Fibrillation Suppression Trial II (AFIST II). *Circulation*. 2003;108:II200-II206.
38. Gallagher JD, Lieberman RW, Meranze J, Spielman SR, Ellison N. Amiodarone-induced complications during coronary artery surgery. *Anesthesiology*. 1981;55:186-188.
39. MacKinnon G, Landymore R, Marble A. Should oral amiodarone be used for sustained ventricular tachycardia in patients requiring open-heart surgery? *Can J Surg*. 1983;26:355-357.
40. Nalos PC, Kass RM, Gang ES, Fishbein MC, Mandel WJ, Peter T. Life-threatening postoperative pulmonary complications in patients with previous amiodarone pulmonary toxicity undergoing cardiothoracic operations. *J Thorac Cardiovasc Surg*. 1987;93:904-912.
41. Tuzcu EM, Maloney JD, Sangani BH, et al. Cardiopulmonary effects of chronic amiodarone therapy in the early postoperative course of cardiac surgery patients. *Cleve Clin J Med*. 1987;54:491-495.
42. Elliot PL, Schauble JF, Rogers MC, et al. Risk of decompensation during anesthesia in presence of amiodarone. *Circulation*. 1983;68:iii280.
43. Sheldon RS, Mitchell LB, Duff HJ, Wyse DG, Manyari DE. Right and left ventricular function during chronic amiodarone therapy. *Am J Cardiol*. 1988;62: 736-740.
44. Hohnloser SH, Klingenheben T, Singh BN. Amiodarone-associated proarrhythmic effects: a review with special reference to torsade de pointes tachycardia. *Ann Intern Med*. 1994;121:529-535.

