Milrinone Use Is Associated With Postoperative Atrial Fibrillation After Cardiac Surgery

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Background—Postoperative atrial fibrillation (AF), a frequent complication after cardiac surgery, causes morbidity and prolongs hospitalization. Inotropic drugs are commonly used perioperatively to support ventricular function. This study tested the hypothesis that the use of inotropic drugs is associated with postoperative AF.

Methods and Results—We evaluated perioperative risk factors in 232 patients who underwent elective cardiac surgery. All patients were in sinus rhythm at surgery. Sixty-seven patients (28.9%) developed AF a mean of 2.9±2.1 days after surgery. Patients who developed AF stayed in the hospital longer (P<0.001) and were more likely to die (P=0.02). Milrinone use was associated with an increased risk of postoperative AF (58.2% versus 26.1% in nonusers; P<0.001). Older age (63.4±10.7 versus 56.7±12.3 years; P<0.001), hypertension (P=0.04), lower preoperative ejection fraction (P=0.03), mitral valve surgery (P=0.02), right ventricular dysfunction (P=0.03), and higher mean pulmonary artery pressure (27.1±9.3 versus 21.8±7.5 mm Hg; P=0.001) also were associated with postoperative AF. In multivariable logistic regression, age (P<0.001), ejection fraction (P=0.02), and milrinone use (odds ratio, 4.86; 95% confidence interval, 2.01 to 9.84; P=0.001) independently predicted postoperative AF. When only data from patients with pulmonary artery catheters were analyzed and pulmonary artery pressure was included in the model, age, milrinone use (odds ratio, 4.45; 95% confidence interval, 2.01 to 9.84; P<0.001), and higher pulmonary artery pressure (P=0.02) were associated with an increased risk of postoperative AF. Adding other potential confounders or stratifying analysis by mitral valve surgery did not change the association of milrinone use with postoperative AF.

Conclusion—Milrinone use is an independent risk factor for postoperative AF after elective cardiac surgery. (Circulation. 2008;118:1619-1625.)

Key Words: atrial fibrillation | inotropic agents | surgery

Atrial fibrillation (AF), the most common complication after cardiac surgery, is associated with significant morbidity, increased mortality, longer hospital stay, and higher hospital costs.1-3 Numerous risk factors for developing postoperative AF have been identified, including advanced age, previous history of AF, male gender, decreased left ventricular ejection fraction, left atrial enlargement, mitral valve surgery, chronic obstructive pulmonary disease, chronic renal failure, diabetes mellitus, postoperative withdrawal of β-blockers or angiotensin-converting enzyme (ACE) inhibitors, and obesity.1-7 In contrast, postoperative treatment with β-blockers or amiodarone, potassium supplementation, and preoperative treatment with statins have been associated with a reduced risk of developing postoperative AF.3-8 The complex pathophysiology of postoperative AF involves an interaction between surgical trauma, activation of the inflammatory response, preexisting atrial pathology, and increased adrenergic tone.9 Because ventricular dysfunction is common after cardiac surgery, inotropic drugs are often necessary to improve hemodynamic status; however, the effect of inotropic drugs on postoperative AF has not been studied extensively. For example, the use of low-dose dopamine or dobutamine in the postoperative period has been associated with an increased risk of developing postoperative AF.10,11 Milrinone has been reported to be associated with a lower risk of postoperative AF compared with dobutamine, but milrinone increases the risk of atrial arrhythmias in patients with acute exacerbation of chronic heart failure.11,12

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The aim of this analysis was to test the hypothesis that the use of inotropic drugs is associated with an increased risk of postoperative AF in cardiac surgery patients participating in...
an ongoing randomized, double-blinded, placebo-controlled trial.

Methods

Subjects included in this analysis were participants in the ongoing Atrial Fibrillation and Renin Angiotensin Aldosterone System (RAAS) study. This study is approved by the Vanderbilt University Institutional Review Board for Research on Human Subjects and is conducted according to the Declaration of Helsinki. All patients provided written informed consent. Briefly, the trial is designed to test the hypothesis that interruption of the RAAS by either ACE inhibition (ramipril) or aldosterone receptor antagonism (spironolactone) decreases the incidence of AF after elective cardiac surgery. Patients are eligible for the study if they are undergoing elective coronary artery bypass graft or valvular surgery and are in sinus rhythm. Exclusion criteria include chronic AF, an ejection fraction <30%, evidence of coagulopathy, emergency surgery, serum creatinine >1.6 mg/dL, and hyperkalemia with potassium >5.0 mEq/L. One week to 4 days before surgery, patients are randomized to treatment with placebo, spironolactone (25 mg/d), or ramipril (1.25 mg the first 2 days, followed by 2.5 mg/d). Randomization is stratified by age and prior statin, prior ACE inhibitor, angiotensin receptor blocker, or mineralocorticoid receptor antagonist use. Pre-existing ACE inhibitor, angiotensin receptor blocker, or mineralocorticoid receptor antagonist use is stopped at randomization. The primary end point of the study is the occurrence of ECG-confirmed AF at any time after the end of surgery until hospital discharge. Secondary end points include intraoperative and postoperative requirements for vasopressors, death, length of hospital stay, and serum potassium and creatinine concentrations.

Study Population

The analysis population comprises all subjects included in the first interim analysis of the Atrial Fibrillation and RAAS study. Before the analysis, 328 subjects gave consent and were screened for the study. Fifty-eight subjects were excluded from the study for the following reasons: 24 subjects had surgery emergently at another location or did not require surgery; 4 subjects had an ejection fraction <30%; 9 subjects were unable to stop their current medications; 3 subjects had hyperkalemia; 2 subjects had an elevated serum creatinine; 2 subjects had chronic AF; 1 subject previously had angioedema with an angiotensin receptor blocker; and the remaining 9 subjects were judged unable to follow the protocol. Thirty-eight subjects withdrew from the study for personal reasons before starting the study drug. Thus, 236 subjects were randomized. Of these, an additional 4 subjects did not undergo surgery, so the final data set consisted of 232 adult subjects.

No differences were found in age, gender, race, body mass index, blood pressure, heart rate, history of diabetes mellitus, history of hypertension, history of smoking, types of procedures, or prestudy use of ACE inhibitors, angiotensin receptor blocker, β-blockers, or statins between those subjects who consented and not studied and the 232 subjects studied. Those not studied were more likely to be taking spironolactone (P < 0.001), had a significantly lower ejection fraction (P = 0.049), and had a higher baseline serum potassium (P = 0.03), reflecting the exclusion criteria of the study.

Patient Treatment

Anesthetic management and surgical management were conducted according to institutional protocols. Briefly, patients received general endotracheal anesthesia, consisting of induction with a combination of thiopental, midazolam, fentanyl, or etomidate and maintenance with isoflurane, pancuronium, and fentanyl. Monitoring included standard modalities (ECG, temperature, invasive blood pressure, pulse oximetry, and gas monitoring), central venous pressure or pulmonary artery catheter monitoring, and transesophageal echocardiography. Aprotinin was used for repeat sternotomy procedures and those involving >1 open-chamber procedure, but its use was discontinued after release of study results by Mangano et al.10 showing increased mortality in patients treated with aprotinin. ε-Aminocaproic acid was used for first-time sternotomy operations in patients without a history of venous thrombosis or unstable coronary syndromes. Anticoagulation for cardiopulmonary bypass (CPB) consisted of 400 U/kg unfractionated porcine heparin. Temperature management involved cooling to 28°C to 30°C, temperature-uncorrected blood gas management (α stat), and cold antegrade and retrograde cardioplegia techniques. At the conclusion of CPB, anticoagulation was reversed with 250 mg protamine, with an additional 50 mg administered in the next 10 minutes in the presence of ongoing microvascular bleeding. Vasopressors and inotropes were used for separation from CPB for the following criteria: left ventricular ejection fraction <40%, CPB time >120 minutes, a cardiac index <2 L·min⁻¹·m⁻², or evidence of new-onset left ventricular dysfunction by transesophageal echocardiogram. Use of inotropes and/or vasopressor in the postoperative period was at the discretion of the intensive care physicians. Milrinone was used preferentially if the postbypass left ventricular ejection fraction was <30%, for evidence of right ventricular dysfunction, or for pulmonary hypertension. Milrinone was started as a continuous infusion at a dose of 0.5 μg·kg⁻¹·min⁻¹ and adjusted at the discretion of the supervising physician. Norepinephrine was used to offset milrinone-induced vasodilation. Metoprolol 12.5 mg twice a day was given if heart rate was >60 and systolic blood pressure was >100 mm Hg starting on postoperative day 1. Patients were monitored continuously on telemetry throughout the postoperative period until discharge. ECGs were obtained for any rhythm changes detected on telemetry monitoring; in addition, ECGs were performed preoperatively and daily starting on postoperative day 1. All ECGs and rhythm strips were reviewed in a blinded fashion by a cardiac electrophysiologist.

Statistical Analysis

A total of 67 AF events occurred in the study cohort. Initial univariate analysis was performed to determine risk factors associated with the development of postoperative AF and risk factors associated with treatment with milrinone on the day of surgery. Univariate analyses were performed with the Student t test or Mann-Whitney U test, when data were not normally distributed, for continuous variables, and the χ² test was used for categorical variables. Data are presented as mean ± SD. Risk for developing AF was then evaluated by logistic regression. Variables with values of P < 0.1 by univariate analysis, as well as known risk factors for AF, were considered for logistic regression modeling. The number of variables included in the model was based on the criteria of 1 variable per 10 events,14 which allowed 7 variables in the final model. Only variables considered to be the most important confounders were used. Although current smoking showed a trend toward association with postoperative AF (P < 0.1) by univariate analysis, it was not thought to be a strong confounder on the effect of milrinone on AF. The final model included age, gender, history of hypertension, mitral valve surgery, baseline ejection fraction, preoperative β-blocker use, and treatment with milrinone on the day of surgery. An additional model was performed that included mean pulmonary artery pressure (PAP) in addition to the previous variables; however, because not all patients underwent pulmonary artery catheter placement, this model excluded 45 patients. Potentially significant confounding variables, including right ventricular dysfunction, postoperative left ventricular dysfunction, statin use, perioperative treatment with norepinephrine, and perioperative treatment with dobutamine, were analyzed with the main logistic regression model by adding each variable, 1 at a time, to the main model. Because of the large number of potential confounding variables associated with milrinone treatment, we also conducted a propensity score analysis using logistic regression on age, gender, hypertension, baseline ejection fraction, mitral valve surgery, preoperative use of β-blockers, preoperative use of statins, CPB time, perioperative treatment with dobutamine, and perioperative treatment with norepinephrine. Because the number of patients treated perioperatively with dopamine and epinephrine was small and no association was found between the use of these pressors and AF in this study, we did not include these variables in our logistic regression or propensity
score analyses. Data are reported as the estimated odds ratios (ORs) and 95% confidence intervals (CIs) (with a value of \( P < 0.05 \) considered statistically significant). Data were analyzed with SPSS (version 15.1, SPSS Inc, Chicago, Ill), and the propensity score analyses were performed with SAS for Windows (version 9, SAS Institute Inc, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

## Results

### Subject Characteristics Associated With Milrinone Use

Baseline characteristics of patients according to treatment with milrinone on the day of surgery are presented in Table 1. A trend was found toward increased milrinone use in women. Patients treated with milrinone were less likely to be diabetic. Preoperative statin use was significantly lower in patients treated with milrinone, but the use of other preoperative medications was similar between patients treated with milrinone and those not treated with milrinone. The rate of milrinone use was not significantly different among the mock-unblinded study groups (data not shown).

Table 2 presents intraoperative characteristics in patients according to whether they were treated with milrinone on the day of surgery. Milrinone was started in the operating room in 28.4% of patients and was used in a total of 35.3% of patients on the day of surgery. Patients who received milrinone perioperatively were more likely to have had on-pump surgery, were more likely to have had mitral valve surgery, had longer pump times, were more likely to be treated with norepinephrine and epinephrine postoperatively, and were less likely to be treated with dobutamine and dopamine postoperatively. The mean PAP at the end of surgery was significantly higher in patients who received milrinone. Data from intraoperative transesophageal echocardiography were available for 192 subjects.

### Subject Characteristics Associated With Postoperative AF

Sixty-seven patients (28.9%) developed postoperative AF at a mean of 2.9 ± 2.1 days (median, 2 days) after surgery. Patients who developed postoperative AF stayed in the hospital longer (8.5 ± 11.6 days versus 5.1 ± 2.0 days; \( P < 0.001 \)) and were more likely to die in the hospital (4.5% versus 0%; \( P < 0.001 \)) and were more likely to develop left ventricular ejection fraction \(<35\% \) than those who did not develop postoperative AF. Patients who developed postoperative AF were more likely to have had mitral valve surgery, and had lower preoperative left ventricular ejection fraction. Women tended to be overrepresented in the AF group. Preoperative medications were similar between groups, with a trend toward higher preoperative \( \beta \)-blocker use in the AF group. Race, blood pressure,
body mass index, and preoperative laboratory measurements were similar between groups.

Table 4 indicates intraoperative patient characteristics in patients with or without postoperative AF. Milrinone use on the day of surgery was associated with an increased risk of postoperative AF (58.2% versus 26.1%; P<0.001). Milrinone use on the day of surgery also was associated with an increased risk of postoperative amiodarone or sotalol use (37.8% versus 11.3%; P=0.001). In addition, mitral valve surgery and a higher mean PAP measured at the end of surgery on CPB or off pump. Blood product transfusions were similar between groups.

### Logistic Regression Models

In a multivariate logistic regression model that included age, gender, history of hypertension, baseline ejection fraction, mitral valve surgery, and treatment with milrinone on the day of surgery, only milrinone use, increasing age, and lower baseline ejection fraction were significantly associated with the development of postoperative AF (Table 5). The Hosmer and Lemeshow goodness-of-fit test accepted this model and postoperative AF.

### Table 3. Preoperative Subject Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No AF (n=165)</th>
<th>AF (n=67)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>56.7±12.3</td>
<td>63.4±10.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>52 (31.5)</td>
<td>30 (44.8)</td>
<td>0.06</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>151 (91.0)</td>
<td>62 (91.2)</td>
<td>0.96</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29.6±6.6</td>
<td>28.9±5.7</td>
<td>0.51</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>92.8±11.0</td>
<td>91.7±11.1</td>
<td>0.51</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>65.5±12.9</td>
<td>65.8±14.9</td>
<td>0.89</td>
</tr>
<tr>
<td>Medical history, n (%)</td>
<td>1622 Circulation October 14, 2008</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 4. Intraoperative Subject Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No AF (n=165)</th>
<th>AF (n=67)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>On-pump surgery, n (%)</td>
<td>143 (86.7)</td>
<td>62 (92.5)</td>
<td>0.21</td>
</tr>
<tr>
<td>CABG surgery, n (%)</td>
<td>72 (43.6)</td>
<td>25 (37.3)</td>
<td>0.38</td>
</tr>
<tr>
<td>Blood product transfusion in OR, U</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRBC</td>
<td>1.2±1.9</td>
<td>1.7±2.3</td>
<td>0.13</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>0.5±1.7</td>
<td>0.7±1.7</td>
<td>0.10</td>
</tr>
<tr>
<td>Random donor platelets</td>
<td>0.6±1.8</td>
<td>0.6±1.9</td>
<td>0.99</td>
</tr>
<tr>
<td>Pheresed platelets</td>
<td>0.1±0.4</td>
<td>0.2±0.4</td>
<td>0.18</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>0.1±0.8</td>
<td>0.1±0.7</td>
<td>0.54</td>
</tr>
<tr>
<td>Mean PAP at end of surgery, mm Hg</td>
<td>21.8±7.5</td>
<td>27.1±9.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Right ventricular dysfunction,* n (%)</td>
<td>13 (9.6)</td>
<td>12 (21.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>Left ventricular dysfunction,* n (%)</td>
<td>5 (3.8)</td>
<td>3 (5.6)</td>
<td>0.69</td>
</tr>
</tbody>
</table>

### Table 5. Multivariate Logistic Regression Model for Postoperative AF

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>P</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milrinone use</td>
<td>4.86</td>
<td>&lt;0.001</td>
<td>2.31–10.25</td>
</tr>
<tr>
<td>Age</td>
<td>1.06</td>
<td>&lt;0.001</td>
<td>1.03–1.10</td>
</tr>
<tr>
<td>Baseline ejection fraction</td>
<td>0.96</td>
<td>0.02</td>
<td>0.93–0.99</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.63</td>
<td>0.23</td>
<td>0.74–3.58</td>
</tr>
<tr>
<td>Gender, male vs female</td>
<td>0.63</td>
<td>0.19</td>
<td>0.31–1.26</td>
</tr>
<tr>
<td>Mitral valve surgery</td>
<td>1.34</td>
<td>0.40</td>
<td>0.64–2.99</td>
</tr>
<tr>
<td>Preoperative β-blocker use</td>
<td>1.33</td>
<td>0.42</td>
<td>0.66–2.67</td>
</tr>
</tbody>
</table>

Including mean pulmonary artery pressure, right ventricular dysfunction, perioperative dobutamine, perioperative norepinephrine, or perioperative statin use in the multivariate model did not change the association between milrinone and postoperative AF.
inhibition or aldosterone receptor antagonism versus placebo on postoperative AF. The data confirm previous studies indicating an association of increased age, decreased ejection fraction, and pulmonary hypertension with postoperative AF. Perioperative milrinone use was associated with a 2- to 4-fold increased risk of postoperative AF, even after controlling for potential confounders.

Sympathetic activation predicts postoperative AF, whereas \( \beta \)-adrenergic blockers effectively decrease the incidence of postoperative AF.\(^6\)\(^-\)\(^17\) Perioperative use of dopamine or dobutamine is associated with an increased risk of postoperative AF after cardiac surgery.\(^10\)\(^,\)\(^11\) Short-term intravenous milrinone use has been associated with an increased risk of atrial arrhythmias during treatment of acute exacerbation of chronic heart failure.\(^11\) In contrast, Fenech et al\(^11\) reported a decreased incidence of postoperative AF in cardiac surgery patients randomized to milrinone compared with those randomized to dobutamine; however, no placebo control group was included. In addition, AF was not a primary endpoint of this study, and the incidence of postoperative AF, at 5% to 18%, may have been underestimated.

Milrinone and inotropes such as dopamine and dobutamine may increase the risk of AF by increasing cAMP, leading to an increase in intracellular calcium concentration. Dopamine and dobutamine increase cAMP production by activating the \( \beta \)-adrenergic receptor, whereas milrinone decreases cAMP degradation by inhibiting phosphodiesterase. Activation of protein kinase A by cAMP leads to phosphorylation of ion channel subunits involved in multiple cardiac currents, including the slowly activating delayed rectifier (\( I_{Kr} \)) and L-type calcium current.\(^18\)\(^,\)\(^19\) The mechanisms whereby protein kinase A activation promotes AF may include abbreviation of atrial refractoriness and triggered activity in pulmonary veins.\(^18\)\(^,\)\(^20\) Recent data indicate that phosphodiesterase inhibition may significantly enhance protein kinase A–mediated phosphorylation in the heart compared with \( \beta \)-adrenergic stimulation.\(^21\)

Because this study was observational and not randomized, confounding by indication may have contributed to the increased risk of postoperative AF among milrinone-treated patients. Norepinephrine and epinephrine, sympathomimetics often given to counteract the hypotensive effect of milrinone, were administered more often in milrinone-treated patients than in those who did not receive milrinone. In contrast, patients treated with milrinone were less likely to receive dopamine or dobutamine. Patients treated with milrinone had a higher PAP, longer bypass times, and a number of other

### Discussion

We assessed risk factors for postoperative AF in an ongoing randomized clinical trial designed to assess the effect of ACE inhibitors. When the mean PAP, measured at the end of surgery, was added to the model, only milrinone use (OR, 4.44; 95% CI, 2.01 to 9.83; \( P<0.001 \)), higher mean PAP (OR, 1.06; 95% CI, 1.01 to 1.11; \( P=0.02 \)), and older age were associated with an increased risk of postoperative AF. Adding right ventricular dysfunction to the model did not change the effect of milrinone on postoperative AF (OR, 5.59; 95% CI, 2.34 to 13.37; \( P<0.001 \)), and the effect of right ventricular dysfunction was not significant (OR, 1.24; 95% CI, 0.43 to 3.63; \( P=0.69 \)). The addition of left ventricular dysfunction to the model did not change the effect of milrinone on postoperative AF (OR, 6.35; 95% CI, 2.62 to 15.39; \( P<0.001 \)), and the effect of left ventricular dysfunction was not significant (\( P=0.33 \)). When treatment with dobutamine was added to the main logistic regression model, the effect of milrinone on AF was slightly increased (OR, 5.91; 95% CI, 2.65 to 13.17; \( P<0.001 \)), and treatment with dobutamine did not significantly increase the risk of postoperative AF (OR, 2.30; 95% CI, 0.85 to 6.18; \( P=0.10 \)). Adding norepinephrine treatment to the model did not change the effect of milrinone on postoperative AF (OR, 4.56; 95% CI, 2.13 to 9.75; \( P<0.001 \)), and the effect of norepinephrine was not significant (OR, 1.31; 95% CI, 0.59 to 2.93; \( P=0.51 \)). When statin use was added to the model, the effect of milrinone on postoperative AF also did not change significantly (OR, 4.91; 95% CI, 2.31 to 10.43; \( P<0.001 \)). Statin use tended to decrease the risk of postoperative AF (OR, 0.5; 95% CI, 0.23 to 1.07; \( P=0.07 \)).

After adjustment for the propensity score, the effect of milrinone on AF remained significant (OR, 3.64; 95% CI, 1.76 to 7.56; \( P<0.001 \)). The balance of the distribution of all the covariates used in constructing the propensity score between milrinone users and nonusers was satisfactory within the lower and upper half of the propensity score subgroups except for mitral valve surgery because of its strong relationship with milrinone use. For this reason, we examined the relationship between milrinone use and postoperative AF after stratifying subjects according to whether they had had mitral valve surgery (the Figure). The results were consistent with the multivariate logistic regression model (Cochran-Mantel-Haenszel common OR for milrinone use, 3.88; 95% CI, 1.97 to 7.66; \( P<0.001 \); OR for milrinone use in the mitral valve surgery stratum, 5.00; 95% CI, 1.67 to 15.00; \( P=0.003 \); and OR for milrinone use in the non–mitral valve surgery stratum, 3.16; 95% CI, 1.32 to 7.59; \( P=0.008 \)).
clinical characteristics that may have predisposed them to postoperative AF. For example, pulmonary hypertension is associated with increased morbidity and mortality after cardiac surgery.\textsuperscript{22,23} PAP predicts risk of AF after mitral valve surgery in patients with a history of AF and in patients after closure of secundum atrial septal defects.\textsuperscript{24,25} Milrinone-treated patients were less likely to have taken statins before surgery. Statin use has been reported to protect against postoperative AF in observational studies and in a randomized, placebo-controlled trial.\textsuperscript{26} We also observed a trend toward a protective effect of preoperative statin use. Controlling for each of these confounding variables using multivariate regression, using propensity score analysis, and stratifying by mitral valve surgery did not change the association between perioperative milrinone use and postoperative AF. Nevertheless, other factors may exist that are associated with the use of milrinone in certain patients that were not measured and were not controlled for in our analysis.

Despite the limitations presented by an observational study, the absolute rate of postoperative AF among patients treated with milrinone in the perioperative period raises concern. Approximately 500,000 patients undergo cardiac surgery each year in the United States, and milrinone is commonly used to treat postoperative ventricular failure.\textsuperscript{27,28} In this single-center study, 35% of patients received milrinone in the perioperative period. On the basis of the incidence of postoperative AF observed in the milrinone-treated versus nonexposed patients, similar rates of treatment with milrinone nationally could result in an excess of 56,000 cases of postoperative AF per year. If even a fraction of these are attributable to milrinone use rather than to underlying disease, this represents a significant health concern.

Conclusions
Milrinone, a phosphodiesterase inhibitor that increases cardiac cAMP, has been associated with an increased risk of AF in a randomized trial in patients with congestive heart failure.\textsuperscript{12} In the present study, we found that perioperative milrinone use was associated with an increased incidence of postoperative AF, even after controlling for potential confounders. Because of the possible impact of selection bias on these observational data, randomized clinical trials are needed to confirm or refute this finding. Given the magnitude of the effect of milrinone on AF risk, however, the potential impact on morbidity and healthcare costs is large.

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Disclosures
None.

References
CLINICAL PERSPECTIVE

Approximately 500,000 patients undergo cardiac surgery in the United States each year. Postoperative atrial fibrillation is a common complication after surgery that causes morbidity and prolongs hospitalization. Milrinone use on the day of surgery was associated with an increased risk of postoperative atrial fibrillation even after controlling for other risk factors such as age, ejection fraction, and increased pulmonary artery pressure. These findings have clinical and financial implications. Milrinone was administered in 35% of patients in this single-center study. On the basis of the incidence of postoperative atrial fibrillation in the milrinone-treated versus nonexposed patients, similar rates of milrinone use nationally could result in an excess of 56,000 cases of postoperative atrial fibrillation per year, with an attendant excess in postoperative stroke and prolongation of hospital stay. Randomized, prospective studies are needed to assess further the risk of postoperative atrial fibrillation associated with milrinone use.
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