Randomized Trial of Atorvastatin for Reduction of Postoperative Atrial Fibrillation in Patients Undergoing Cardiac Surgery

Results of the ARMYDA-3 (Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery) Study

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Background—Atrial fibrillation (AF) after cardiac surgery is associated with increased risk of complications, length of stay, and cost of care. Observational evidence suggests that patients who have undergone previous statin therapy have a lower incidence of postoperative AF. We tested this observation in a randomized, controlled trial.

Methods and Results—Two hundred patients undergoing elective cardiac surgery with cardiopulmonary bypass, without previous statin treatment or history of AF, were enrolled. Patients were randomized to atorvastatin (40 mg/d, n = 110) or placebo (n = 99) starting 7 days before operation. The primary end point was incidence of postoperative AF; secondary end points were length of stay, 30-day major adverse cardiac and cerebrovascular events, and postoperative C-reactive protein (CRP) variations. Atorvastatin significantly reduced the incidence of AF versus placebo (35% versus 57%, \(P = 0.003\)). Accordingly, length of stay was longer in the placebo versus atorvastatin arm (6.9 ± 1.4 versus 6.3 ± 1.2 days, \(P = 0.001\)). Peak CRP levels were lower in patients without AF (\(P = 0.01\)), irrespective of randomization assignment. Multivariable analysis showed that atorvastatin treatment conferred a 61% reduction in risk of AF (odds ratio 0.39, 95% confidence interval 0.18 to 0.85, \(P = 0.017\)), whereas high postoperative CRP levels were associated with increased risk (odds ratio 2.0, 95% confidence interval 1.2 to 7.0, \(P = 0.01\)). The incidence of major adverse cardiac and cerebrovascular events at 30 days was similar in the 2 arms.

Conclusions—Treatment with atorvastatin 40 mg/d, initiated 7 days before surgery, significantly reduces the incidence of postoperative AF after elective cardiac surgery with cardiopulmonary bypass and shortens hospital stay. These results may influence practice patterns with regard to adjuvant pharmacological therapy before cardiac surgery. (Circulation. 2006;114:1455-1461.)

Key Words: thoracic surgery ■ trials ■ statins ■ atrial fibrillation

Clinical Perspective

Observational evidence has suggested that patients with previous statin treatment undergoing coronary artery bypass surgery have a lower incidence of postoperative atrial fibrillation; these observations have not been validated in a randomized, controlled trial. Thus, the ARMYDA (Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery) study group has designed the first randomized, controlled trial of pretreatment with statins before elective cardiac surgery; in particular, we have evaluated whether administration of atorvastatin 40 mg/d, started 1 week before surgery, prevents postoperative atrial fibrillation versus placebo.
ROME. The design of the study is illustrated in Figure 1. A total of 323 consecutive patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) from March 2003 to October 2005 were evaluated. Exclusion criteria were as follows: emergency cardiac surgery; history of atrial fibrillation; previous or current treatment with statins; elevated liver enzymes (aspartate aminotransferase/alanine aminotransferase); renal failure with creatinine >3 mg/dL; history of liver or muscle disease; and inflammatory diseases that required therapy with steroids or nonsteroidal antiinflammatory drugs. Of the 323 patients evaluated, 123 were excluded (primarily because of current therapy with statins or history of atrial fibrillation); thus, 200 patients represent the study population, 99 of whom were randomized to placebo and 101 to atorvastatin (40 mg/d) beginning 7 days before the scheduled surgery. To assign patients to atorvastatin or placebo, a computer-generated randomization sequence was obtained by a statistical consultant not involved in the study; the randomization assignment for each patient was kept in a sealed envelope, which was opened by a trial investigator at the time of patient enrollment. Randomization was performed in blocks of 20, without taking into account any of the patient’s characteristics (such as age or sex). The assigned therapy was fully blinded; surgeons and investigators performing postoperative assessment were not aware of the randomization assignment, and a hospital pharmacist not involved in the trial supplied the drug/placebo to be administered to patients. Patients were randomized independent of their admission lipid levels.

All operations were performed by experienced cardiac surgeons using standard techniques; type of surgery and procedural strategies were applied according to the surgeon’s discretion. Induction and maintenance of anesthesia were similar for all patients and consisted of weight-related doses of fentanyl, midazolam, and pancuronium bromide. All operations were performed through exposure of the heart with a median sternotomy incision. CPB was performed in a standard fashion with the use of a hollow-fiber oxygenator and a roller pump, with ascending aortic cannulation added to right atrium cannulation in patients undergoing bypass grafting or aortic valve surgery or added to bicaval cannulation in case of mitral valve surgery. During CPB, hematocrit was maintained between 20% and 25%, and pump flows were kept between 2.0 and 2.5 L/min to maintain mean arterial pressure between 50 and 70 mm Hg. All patients were cooled to moderate hypothermia (mean 32°C), and cardioplegic arrest was achieved with cold blood cardioplegia (4°C) infused into the ascending aorta. No patient received retrograde cardioplegia. Heparin was given at a dose of 300 IU/kg to obtain activated clotting time >400 seconds; on completion of anastomoses, heparin effects were reversed by intravenous protamine sulfate (1 mg/300 IU of heparin) to achieve an activated clotting time similar to preoperative values. All anastomoses were sutured by hand. Postoperative nonhemic volume expanders were routinely used. A standardized protocol for early postoperative care was followed in the intensive care unit. Patients were extubated when the Tobin index (respiratory rate (spontaneous)/tidal volume (L)) was <105, PaO2 was >60 mm Hg with FiO2 <0.4, continuous positive airway pressure <5 mbar, PaCO2 <50 mm Hg, and arterial pH >7.35. Perioperative need for blood products was determined on an individual, patient-by-patient basis; in general, blood transfusions were given when hemoglobin was <9 g/dL. Inotropic agents were used perioperatively in patients with a cardiac index <2.2 L·min⁻¹·m⁻², the target for cardiac index being 2.5 to 3.0 L·min⁻¹·m⁻². Nonsteroidal antiinflammatory drugs, β-blockers, calcium antagonists, and/or angiotensin-converting enzyme inhibitors were given after surgery when clinically indicated. All patients receiving bypass grafting were treated with aspirin (320 mg 24 hours after surgery, followed by a daily dose of 160 mg) and with intravenous nitroglycerin infusion for the first 24 hours, unless contraindicated. From the intensive care unit, patients were transferred to a monitored unit, where 3-lead telemetric monitoring was performed continuously for at least 6 days after the operation; in addition, patients had a 12-lead ECG daily until discharge. The ECG data were stored for 24 hours and reviewed on a daily basis by an investigator blinded to the treatment assignment. Fluid intake and output were monitored hourly throughout the hospital stay. All patients continued the assigned, blinded treatment (atorvastatin 40 mg/d or placebo) from the day after surgery until discharge. Open-label atorvastatin (40 mg/d) was given to all patients on discharge and prescribed indefinitely.

C-reactive protein (CRP) levels were assessed in all patients before surgery and every 24 hours postoperatively until discharge. CRP was measured by the KRYPTOR ultrasensitive immunofluorescent assay (Brahms, Hennigsdorf/Berlin, Germany) with a detection limit of 0.06 mg/L. All patients who had in-hospital atrial fibrillation were treated according to protocol with intravenous amiodarone (bolus 5 mg/kg followed by infusion 15 mg·kg⁻¹·24 h⁻¹) and were discharged with instructions to undergo oral amiodarone therapy for at least 30 days. Patients were scheduled for weekly visits in our outpatient clinic for the first month, where 12-lead ECGs were performed. Each patient gave informed consent to participate in the study. The trial was not supported by any external source of funding.

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**Figure 1.** Design of the ARMYDA-3 trial. MACCE indicates major adverse cardiac and cerebrovascular events (death, stroke, myocardial infarction, and need for coronary revascularization).
End Points
The primary end point of the trial was incidence of postoperative in-hospital atrial fibrillation in the 2 trial arms. Atrial fibrillation was defined as episodes of atrial fibrillation that lasted ≥5 minutes and that was registered by the monitoring system on a rhythm strip or 12-lead ECG, or any episode that required intervention for angina or hemodynamic compromise. For the purpose of the present study, the arrhythmic burden was quantified on the basis of the number of atrial fibrillation episodes per patient, the ventricular response, the postoperative time of occurrence, and total duration of the episodes.

Secondary end points were (1) comparison of length of postoperative hospital stay in the treatment versus placebo arm; (2) incidence of major adverse cardiac and cerebrovascular events (death, stroke, myocardial infarction, or need for coronary revascularization) from the time of the operation up to 30 days; (3) correlation of postoperative peak CRP levels with occurrence of atrial fibrillation in the treatment and placebo arms; and (4) identification of variables that were predictors of the outcome. Perioperative myocardial infarction was defined as new Q waves >40 ms or a reduction in R waves >25% in at least 2 contiguous leads, new akinetidyskinetic segments at echocardiogram, and troponin I levels >3.1 μg/L at 12 hours.13

Statistical Analysis
If an overall incidence of postoperative atrial fibrillation of 40% is expected1,6 and a 60% reduction in risk of atrial fibrillation is hypothesized in the treatment arm, a total sample size of at least 137 and 198 patients would provide 90% power to detect this difference with an α-level of 0.05 and 0.01, respectively. This expected reduction in risk of atrial fibrillation is similar to the clinical benefit reported in a recent observational study that described a lower incidence of postoperative atrial fibrillation in patients already taking statins (odds ratio [OR] 0.52).10

Demographic, clinical, and perioperative variables were compared between groups with a t test for normally distributed values; otherwise, the Mann-Whitney U test was used. Proportions were compared by χ2 test or Fisher exact test when appropriate. In particular, CRP levels were analyzed by nonparametric tests. Correlations were assessed by Spearman rank correlation test. ORs and 95% confidence intervals (CIs) to assess the risk of the primary end point according to treatment and potential confounding variables were determined by logistic regression. All clinical and perioperative variables indicated in Tables 1 and 2 were evaluated first in a single-predictor model, and those with P<0.15 were then entered into a multivariable logistic regression analysis. Event-free survival analysis was performed by the Kaplan-Meier method with log-rank test for group comparisons. Results are expressed as mean±SD, unless otherwise specified. A probability value <0.05 (2-tailed) was considered significant. Analysis was performed with GB-STAT version 6 software (Dynamic Microsystems, Inc, Silver Spring, Md).

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
Study Population
Demographic, clinical, and perioperative variables were similar in the atorvastatin versus placebo groups and are illustrated in Tables 1 and 2. An increase above the normal upper limit of liver enzymes (aspartate aminotransferase/alanine aminotransferase) was observed in 1 patient in the atorvastatin group on admission for operation; in this patient, the drug was then discontinued.

Primary End Point
Postoperative atrial fibrillation occurred in 35 (35%) of 101 patients in the atorvastatin arm versus 56 (57%) of 99 patients in the placebo arm (P=0.003). Mean ventricular response was 115±12 bpm in the atorvastatin arm and 118±15 bpm in the placebo group (P=0.12). Atrial fibrillation occurred at a mean of 51±15 hours after surgery in the atorvastatin group and 50±17 hours after surgery in the placebo group (P=0.59), and the total duration of episodes of atrial fibrillation was similar (24±4 versus 24±5 hours, P=0.88). Intravenous infusion of amiodarone restored normal sinus rhythm in all patients. No patient had recurrence of the arrhythmia after cessation of the first episode. During the first month of follow-up, all patients remained in normal sinus rhythm.
TABLE 2. Perioperative Features

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 99)</th>
<th>Atorvastatin (n = 101)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of operation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG only</td>
<td>74 (75)</td>
<td>84 (83)</td>
<td>0.20</td>
</tr>
<tr>
<td>Valve surgery with or without CABG</td>
<td>25 (25)</td>
<td>16 (16)</td>
<td>0.14</td>
</tr>
<tr>
<td>Aortic aneurysm repair</td>
<td>. . .</td>
<td>1 (1)</td>
<td>1</td>
</tr>
<tr>
<td>On-pump surgery</td>
<td>99 (100)</td>
<td>101 (100)</td>
<td>1</td>
</tr>
<tr>
<td>Distal anastomoses</td>
<td>2.3 ± 0.7</td>
<td>2.4 ± 0.8</td>
<td>0.32</td>
</tr>
<tr>
<td>CPB duration, min</td>
<td>105.5 ± 30</td>
<td>113.3 ± 37</td>
<td>0.09</td>
</tr>
<tr>
<td>Cross-clamp duration, min</td>
<td>73 ± 27</td>
<td>76 ± 34</td>
<td>0.9</td>
</tr>
<tr>
<td>Blood cardioplegia</td>
<td>99 (100)</td>
<td>101 (100)</td>
<td>1</td>
</tr>
<tr>
<td>Atrial or atrioventricular pacing</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>1</td>
</tr>
<tr>
<td>Bicaval cannulation</td>
<td>7 (7)</td>
<td>2 (2)</td>
<td>0.10</td>
</tr>
<tr>
<td>Pulmonary vein venting</td>
<td>23 (23)</td>
<td>14 (14)</td>
<td>0.13</td>
</tr>
<tr>
<td>Postoperative use of inotropic agents</td>
<td>25 (25)</td>
<td>30 (30)</td>
<td>0.58</td>
</tr>
<tr>
<td>Postoperative magnesium &lt;2 mg/dL</td>
<td>26 (26)</td>
<td>32 (32)</td>
<td>0.49</td>
</tr>
<tr>
<td>Postoperative potassium &lt;3.5 mEq/L</td>
<td>12 (12)</td>
<td>9 (9)</td>
<td>0.61</td>
</tr>
<tr>
<td>Postoperative hemoglobin &lt;9 g/dL</td>
<td>10 (10)</td>
<td>13 (13)</td>
<td>0.69</td>
</tr>
<tr>
<td>Postoperative body temperature &gt;38°C</td>
<td>20 (20)</td>
<td>18 (18)</td>
<td>0.80</td>
</tr>
<tr>
<td>Postpericardiotomy syndrome</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1</td>
</tr>
<tr>
<td>Postoperative myocardial infarction</td>
<td>3 (3)</td>
<td>3 (3)</td>
<td>1</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass graft. Values are number (%) unless otherwise indicated.

rhythm, and no further episodes of atrial fibrillation occurred in either group. Kaplan-Meier curves confirmed a significantly better atrial fibrillation–free survival at 30 days in the treatment arm (Figure 2).

Secondary End Points

Mean postoperative hospital stay was significantly lower in the atorvastatin versus placebo arm (6.3 ± 1.2 versus 6.9 ± 1.4 days, P = 0.001). Occurrence of major adverse cardiac and cerebrovascular events was as follows: 4 patients (2 in the atorvastatin and 2 in the placebo arm) died after the operation; cause of death was ischemic stroke in 1 patient, respiratory failure in 1, and multiorgan failure in 2 patients with valvular heart disease. The incidence of postoperative myocardial infarction was 3% in patients in the atorvastatin arm (3/101) and 3% in those randomized to placebo (3/99); all had troponin I elevation >3.1 μg/L at 12 hours, without ST-segment elevation on the ECG or new wall-motion abnormalities on the echocardiogram. No correlation was found between postoperative peak levels of troponin I or creatine kinase-MB and occurrence of atrial fibrillation (P = 0.41). No further major adverse cardiac and cerebrovascular events were observed at 30 days of follow-up; thus, the occurrence of the composite secondary end point at 1 month was 5% in both groups, and it was due entirely to in-hospital events.

Baseline preoperative CRP levels were not different (2.8 ± 2.4 mg/L in the statin group versus 4.5 ± 10 mg/L in the placebo group, P = 0.40), nor were peak CRP levels after the operation (164 ± 37 versus 166 ± 51 mg/L, P = 0.75); CRP levels were significantly lower in patients without versus those with atrial fibrillation (P = 0.01; Figure 3). Patients with atrial fibrillation had the highest postoperative peak levels of CRP, irrespective of the randomization assignment (atorvastatin 186 ± 39 mg/L, placebo 187 ± 45 mg/L).

Multivariable Analysis

Multivariable analysis (Figure 4) revealed that treatment with atorvastatin was associated with a 61% reduction in risk of atrial fibrillation after cardiac surgery (OR 0.39, 95% CI 0.18 to 0.85, P = 0.017), and postoperative peak CRP levels above the median value (166 mg/L) were associated with a higher risk (OR 2.0, 95% CI 1.2 to 7.0, P = 0.01). Age >65 years, systemic hypertension, and aortic atherosclerosis were also predictors of increased risk, whereas use of β-blockers had a protective effect (OR 0.19, 95% CI 0.08 to 0.44, P = 0.0001). Patients randomized to atorvastatin who were taking β-blockers showed a 90% risk reduction of postoperative atrial fibrillation (OR 0.10, 95% CI 0.02 to 0.25, P < 0.0001). Subgroup analysis showed that atorvastatin treatment resulted in a lower risk of atrial fibrillation in patients irrespective of age (>65 and ≤65 years), sex, presence of diabetes mellitus, hypertension, and chronic obstructive pulmonary disease (P ≤ 0.033 for the beneficial effect of atorvastatin in each subgroup, by logistic regression). Treatment benefit was more evident in patients undergoing coronary bypass operations (OR 0.24, 95% CI 0.13 to 0.47, P = 0.0001) and in those with a normal-sized left atrium (OR 0.22, 95% CI 0.10 to 0.47, P = 0.0001), whereas it was absent after noncoronary surgery (OR 0.98, 95% CI 0.30 to 3.9, P = 0.89) and in patients with left atrial enlargement (OR 0.64, 95% CI 0.27 to 1.6, P = 0.33).

Discussion

ARMYDA-3 is the first randomized, controlled trial demonstrating that treatment with atorvastatin significantly reduces the incidence of new-onset postoperative atrial fibrillation and shortens the length of hospital stay in patients undergoing cardiac surgery with CPB. Beneficial effects of statins on atrial fibrillation have been described in a variety of reports. In a retrospective study, statins decreased recurrence after successful external cardioversion for persistent lone atrial fibrillation; in a prospective analysis, statins protected against atrial fibrillation in patients with stable coronary
artery disease. The use of statins has recently been related to a 3-fold decrease in the odds of atrial fibrillation after noncardiac thoracic surgery. To date, there are only observational data that patients taking statins may have a lower incidence of atrial fibrillation or other cardiac arrhythmias after coronary artery bypass surgery. Although those patients were treated with different statins, variable doses, and unknown duration, the present study demonstrates improved clinical outcome with a selected dose of a specific statin given prospectively for a definite period of time within a controlled randomization protocol.

Several factors may contribute to the development of atrial fibrillation after cardiac surgery through alterations in atrial refractoriness and/or local reentry: operative trauma, rise in atrial pressure due to postoperative ventricular stunning, increase of atrial electrical susceptibility from rapid return of temperature after cardioplegic arrest, atrial distension by fluid overload, chemical stimulation during infusion of inotropic drugs, reflex sympathetic activation, and pericardial or respiratory complications. Moreover, advanced age and valve surgery are recognized risk factors for postoperative atrial fibrillation because of hemodynamic, electrical, and histolog-

**Figure 3.** Postoperative peak levels of CRP. AF indicates atrial fibrillation; Atorv, atorvastatin.

**Figure 4.** Multivariable analysis indicating predictors of outcome. CHF indicates congestive heart failure; Rx, prescription; and Atorv, atorvastatin.
Fibrillation in ARMYDA-3 versus other trials may be due to the sensitive definition of atrial fibrillation we used, to the older age of patients in the present study, and to the higher prevalence of chronic obstructive pulmonary disease. Inclusion of patients without a history of atrial fibrillation at any time in the past (previous atrial fibrillation is a predictive factor of postoperative recurrence) and the proportion of only 21% of patients with valvular heart disease may explain the absence of recurrence over a 30-day period. In addition, all patients who had in-hospital atrial fibrillation were discharged on oral amiodarone therapy for at least 30 days, and all patients were given open-label atorvastatin during follow-up. Because the ARMYDA-3 protocol used a follow-up assessment after discharge with 12-lead ECGs at regular intervals, a lack of detection of brief, asymptomatic, self-limiting episodes of paroxysmal atrial fibrillation after hospitalization cannot be excluded, however.

Disclosures

None.

References

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CLINICAL PERSPECTIVE

Atrial fibrillation after cardiac surgery is a relatively common complication that may increase morbidity, length of hospital stay, and cost of care. ARMYDA-3 (Atorvastatin for Reduction of Myocardial Dysrhythmia After Cardiac surgery) is the first randomized, controlled trial demonstrating that atorvastatin significantly reduces the incidence of new-onset postoperative atrial fibrillation and shortens length of stay in patients undergoing cardiac surgery with cardiopulmonary bypass. Administration of atorvastatin 40 mg/d starting 7 days before surgery reduced the risk of postoperative atrial fibrillation by 61% and reduced length of stay by 0.6 days. Whether the mechanism of benefit is due to an antiinflammatory effect is not known. These findings support the administration of atorvastatin to reduce atrial fibrillation in patients undergoing elective cardiac operations.
Randomized Trial of Atorvastatin for Reduction of Postoperative Atrial Fibrillation in Patients Undergoing Cardiac Surgery: Results of the ARMYDA-3 (Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery) Study
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