Antiarrhythmic Effect of Statin Therapy and Atrial Fibrillation
A Meta-Analysis of Randomized Controlled Trials

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Objectives
To improve the evaluation of the possible antiarrhythmic effect of statins, we performed a meta-analysis of randomized trials with statins on the end point of incidence or recurrence of atrial fibrillation (AF).

Background
The use of statins had been suggested to protect against AF in some clinical observational and experimental studies but has remained inadequately explored.

Methods
A systematic review of controlled trials with statins was performed. Eligible studies had to have been randomized controlled parallel-design human trials with use of statins that collected data on incidence or recurrence of AF.

Results
Six studies with 3,557 patients in sinus rhythm were included in the analysis. Three studies investigated the use of statins in patients with a history of paroxysmal AF (n = 1) or persistent AF undergoing electrical cardioversion (n = 2), and 3 investigated the use of statins in primary prevention of AF in patients undergoing cardiac surgery or after acute coronary syndrome. Incidence or recurrence of AF occurred in 386 patients. Overall, the use of statins was significantly associated with a decreased risk of AF compared with control (odds ratio [OR] 0.39, 95% confidence interval [CI] 0.18 to 0.85, p = 0.02). Benefit of statin therapy seemed more marked in second-ary prevention of AF (OR 0.33, 95% CI 0.10 to 1.03, p = 0.06) than for new-onset or postoperative AF (OR 0.60, 95% CI 0.27 to 1.37, p = 0.23).

Conclusions
Use of statins was significantly associated with a decreased risk of incidence or recurrence of AF in patients in sinus rhythm with a history of previous AF or undergoing cardiac surgery or after acute coronary syndrome. (J Am Coll Cardiol 2008;51:828–35) © 2008 by the American College of Cardiology Foundation

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are hypothesized to have a benefit against arrhythmias in addition to well-established secondary prevention benefits for atherosclerotic coronary artery disease, yet the data are inconsistent. The use of statins had been suggested to protect against atrial fibrillation (AF) in some clinical and experimental studies but remained inadequately explored. Specifically, observational studies provided evidence supporting a protective role of statins against AF. However, insufficient data are available at this time to allow recommendations for prevention of AF with statins (1,2). To improve the evaluation of the possible benefit of statins, we performed a meta-analysis of randomized trials with statins on the end point of incidence or recurrence of AF.

Methods
Data collection. We searched through Medline for all randomized controlled trials published from January 1980 through June 2007 that compared statins with placebo or a control treatment. We conducted text searches with the terms “statin,” “atrial fibrillation,” and “random.” We looked for randomized controlled outcome trials that met all of the following specified criteria: 1) direct comparison between a statin and control treatment or placebo regardless of the background therapy in either group; 2) publication before June 1, 2007 in peer-reviewed journals indexed in Medline; 3) incidence or recurrence of AF as a specified event, although not necessarily a primary end point; and 4) follow-up of at least 3 weeks. We also manually searched
references from selected clinical trials, recent meta-analyses, and review articles. Finally, we reviewed abstracts from the 2001 to 2007 conference proceedings of the American College of Cardiology, American Heart Association, and European Society of Cardiology. The final search identified 6 trials (3–8) that fulfilled all inclusion criteria. We extracted information on study design, sample characteristics, sample size, intervention strategies, outcome measures, and other study characteristics from the included randomized controlled trials and/or previously published data for results published in abstract form (4,9,10). We reviewed the methodologic quality of randomized controlled trials by using a scoring system developed by Jadad et al. (11). The number of events in each trial were extracted when available on the basis of an intention-to-treat approach. All the analysis on the end point of AF was performed at the trial level, and none of the data of the individual studies were obtained from sponsoring institutions. A Quality of Reporting of Meta-Analysis (QUOROM) (12) flow diagram of the study selection process is illustrated in Figure 1.

Statistical analysis. We calculated values for agreement using the methods described by Fleiss (13). We calculated an odds ratio (OR) for each study outcome to allow for pooling of similar outcomes. We calculated ORs and 95% confidence intervals (CIs) for incidence or recurrence of AF of each trial separately and for combinations of studies according to fixed-effect and random-effect models. We used a chi-square test to assess heterogeneity. In the presence of statistical homogeneity, defined as a chi-square test p value more than 0.10, we analyzed the data using fixed-effects models. Pooled ORs and 95% CIs for fixed-effects models were calculated on the basis of the Mantel-Haenszel method (14). Otherwise, we used random-effects models (15). The p value threshold for statistical significance was set at 0.05 for effect sizes. We also generated a Funnel plot of trials with estimable ORs for considered end point to assess the presence of publication bias (Fig. 2). Coronary artery disease was present in 3,306 of 3,557 patients (93%). Coronary artery

Results

Six studies with 3,557 patients in sinus rhythm were included in the analysis. Three studies investigated the use of statins in patients with a history of paroxysmal AF (n = 1) or persistent AF undergoing electrical cardioversion (n = 2), and 3 investigated the use of statins in primary prevention of AF in patients undergoing cardiac surgery (post-operative AF, n = 2) or after acute coronary syndrome (new-onset AF, n = 1). Table 1 summarizes the characteristics of the 6 trials. All included controlled trials were randomized and received Jadad scores of 2 (n = 2), 3 (n = 1), 4 (n = 1), or 5 (n = 2) points. The 6 eligible trials included 1,542 patients randomized to statins and 1,559 patients randomized to placebo or control regimen. The following statins were studied: atorvastatin (n = 5), and pravastatin (n = 1). Intervention doses for statins were variable. Comparisons were made with placebo (n = 4) or a control regimen (n = 2). In this latter situation, medication and antiarrhythmic use was similar in the control group and in the statin group, particularly for the use of beta-blocker drugs (25% in the study by Ozaydin et al. [6] and 65% in the study by Tveit et al. [3]).

Follow-up durations varied from 3 to 26 weeks. All 6 studies reported AF outcomes. For the considered end point, Funnel plot of trials with estimable ORs appeared to be relatively symmetrical, suggesting the absence of major publication bias (Fig. 2). Coronary artery disease was present in 3,306 of 3,557 patients (93%). Coronary artery
disease was present in 219 of 470 of the patients (47%) when the MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) study published in abstract form was removed. Other characteristics of patients in each study, including concomitant medical treatment, are in Tables 2 and 3. Incidence or recurrence of AF occurred in 386 patients: 165 of 1,775 in patients treated with statin versus 221 of 1,782 in control subjects. Data of the comparison groups for end point were not homogeneous on the basis of the chi-square statistic. Therefore, we assumed random-effects models. Overall, the use of statins was significantly associated with a decreased risk of recurrence of AF compared with control (OR 0.39, 95% CI 0.18 to 0.85, \( p = 0.02 \)) (Fig. 3). The benefit of statin therapy seemed more marked in secondary prevention of AF (OR 0.33, 95% CI 0.10 to 1.03, \( p = 0.06 \)) than for new-onset or postoperative AF (OR 0.60, 95% CI 0.27 to 1.37, \( p = 0.23 \)) (Fig. 3). When atorvastatin was considered alone, benefit was higher (OR 0.30, 95% CI 0.12 to 0.78, \( p = 0.01 \) on the end point of both incidence or recurrence of AF) (Fig. 4). Finally, results were similar when ORs were calculated after exclusion of the MIRACL study, which was only published in abstract form (OR 0.30, 95% CI 0.11 to 0.76, \( p = 0.01 \), on the end point of either incidence or recurrence of AF) or when studies with Jadad score <3 were removed from the analysis (OR 0.34, 95% CI 0.12 to 0.96, \( p = 0.04 \)) (Fig. 5).

**Discussion**

Our systematic analysis suggests that use of statins was significantly associated with a decreased risk of incidence or recurrence of AF in patients in sinus rhythm with a history of previous AF or undergoing cardiac surgery or after acute coronary syndrome. This beneficial effect seemed more...
marked in the prevention of AF recurrences than in primary prevention of AF, although this might not be certain, because none of the subset analyses came out statistically significant. The lower number of patients with new-onset or post-operative AF might in part explain the lack of significance for this subgroup. Of note, although the number of patients in each study was highly variable, we had a relatively well balanced contribution of each of the 6 studies with weight ranging from 10% to 22%.

Duration of follow-up in the 6 studies was variable and might seem relatively short. However, different types of AF have varying expected times to development or onset. In each study, patients were appropriately monitored on the basis of the type of AF. Recurrences of paroxysmal AF or AF after cardioversion frequently occur within the first month (1). All of the patients with recurrent AF included in our analysis had a follow-up period >1 month (6 weeks to 6 months). Postoperative AF patients were followed for at least 3 days and up to 30 days. Because the risk of developing postoperative AF is greatest on postoperative days 2 and 3 and lower after day 10, these periods of follow-up were sufficient (16). The MIRACL study was the only one that did not show a clear reduction in AF with atorvastatin use, particularly in the subgroup of patients that had new-onset AF analyzed with a relatively short follow-up of 16 weeks. This shorter duration of follow-up (considering new-onset AF) might explain why a beneficial effect against AF was not observed with statin in the MIRACL study. This relatively inadequate follow-up duration might also explain the lack of benefit of statin use on the primary prevention of AF (postoperative or new-onset AF), because these results were essentially driven by the MIRACL study.

The present analysis ignored in part varying doses of statins and varying durations of therapy, as in most of meta-analyses. Because populations were different, we thought it was inappropriate to compare the OR in each trial and draw precise conclusions on dose effect. However, the benefit against AF did not seem clearly related to statin dose, particularly for atorvastatin use, because OR was not lower in the ARMYDA-3 (Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery) study and the MIRACL studies in which a high dose of atorvastatin was used (40 and 80 mg/day, respectively). A beneficial effect was not found in the only study performed with pravastatin in contrast to those that used atorvastatin. Whether the benefit obtained against AF, at least at some extent, in almost all the populations studied with atorvastatin might be obtained with other statins is unknown.

The mechanisms by which statins might prevent AF have been in part delineated. Inflammation is involved in the development, recurrence, and persistence of AF (17). These conditions are associated with enhanced myocardial tissue inflammation and atrial remodeling that might serve as a substrate for the development of AF (2). Moreover, elevated C-reactive protein (CRP) levels have been shown to be
independently associated with an increased risk for the development or recurrence of AF (18). The capacity of statins to reduce inflammation and CRP levels is relatively well established (19,20). This might explain a potential beneficial effect of statins against AF. However, we were not able to establish a clear relation between the decrease in CRP with statin use and the benefit obtained against AF.

Several risk factors for atherogenesis, such as age, obesity, and hypertension have been associated with increased risk for the development of AF (1), suggesting an association between AF and atherosclerotic vascular disease. Statins are known to improve lipid abnormalities. Whether statins have a protective role against AF development through anti-atherogenic properties remains to be established.

### Table 3

Baseline Biochemical Characteristics of the Patients in the 6 Trials Included in the Meta-Analysis and Changes With Statin Therapy

<table>
<thead>
<tr>
<th>Study, Year (Ref. #)</th>
<th>n</th>
<th>Total Cholesterol (mg/dl)</th>
<th>LDL Cholesterol (mg/dl)</th>
<th>HDL Cholesterol (mg/dl)</th>
<th>Triglycerides (mg/dl)</th>
<th>CRP (mg/dl)</th>
<th>Decrease in LDL With Statin</th>
<th>Change in CRP With Statin*</th>
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</thead>
<tbody>
<tr>
<td>Tveit et al., 2004 (3)</td>
<td>114</td>
<td>216</td>
<td>139</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>MIRACL, 2004 (4)</td>
<td>3,086</td>
<td>207</td>
<td>124</td>
<td>46</td>
<td>184</td>
<td>11.25</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Ozgaid et al., 2006 (6)</td>
<td>48</td>
<td>171</td>
<td>99</td>
<td>44</td>
<td>140</td>
<td>2.85</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>ARMYDA-3, 2006 (7)</td>
<td>200</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Demellis and Panaretou, 2006 (8)</td>
<td>130</td>
<td>224</td>
<td>154</td>
<td>48</td>
<td>110</td>
<td>6.1</td>
<td>—</td>
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</tr>
</tbody>
</table>

*Compared with the control group.

CRP = C-reactive protein; HDL = high-density lipoprotein; LDL = low-density lipoprotein; other abbreviations as in Table 1.

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**Figure 3**

Effect of Statins on the Occurrence of AF

Effect of statins versus placebo or control regimen on the occurrence of all types of atrial fibrillation (AF) (i.e., first episode or recurrence of AF, top panel), primary prevention of AF (new-onset or post-operative AF, middle panel), or prevention of recurrence of AF (lower panel). MIRACL 1 and 2 indicate the effect of statin in subgroups of patients in the MIRACL study without or with a previous AF, respectively. CI = confidence interval; OR = odds ratio.
There is evidence suggesting an association between AF and enhanced renin angiotensin system activity. Angiotensin II has a growth-enhancing effect on cardiac myocytes, vascular smooth muscle cells, and fibroblasts, thus resulting in remodeling and fibrosis of the atria that could also provide a potential arrhythmogenic substrate for the development of AF (21). This association is supported by the fact that inhibition of the renin angiotensin system might decrease the incidence of AF (22). There is also evidence suggesting an interaction between dyslipidemia and renin angiotensin system activity (23). Statins decrease both cholesterol levels and oxidative stress (24) and thus might downregulate the renin angiotensin system. This mechanism might explain a possible antiarrhythmic effect of statins against AF (23).

Finally, it has been suggested that a modulation of the autonomic nervous system by statins might have a protective role against AF in the particular setting of postoperative patients with enhanced sympathetic activity (25). Meta-analyses might help the integration of current evidence into clinical practice. There is a need for continually updating meta-analyses when new randomized controlled trials are available and to perform meta-analysis with a sufficient power from all published trials. Findings from meta-analyses change when data from a trial with a substantial number of patients are added, especially when...
previous ORs border on the threshold of statistical significance (26,27). An additional trial comparing 10 mg of rosuvastatin with placebo in heart failure of ischemic etiology, CORONA (Controlled Rosuvastatin Multinational Study in Heart Failure) (28), is ongoing. Atrial fibrillation is a common event in these patients. This trial combined with our meta-analysis should provide further information, if results on the end point of incidence of AF become available. Results about statins and AF from new randomized studies will then be difficult to obtain in the particular population of patients with coronary artery disease, because it will seem unethical to build a study including a control arm without any statin in these patients. Patients with coronary heart disease are currently treated with statins in most cases, and this might not have an impact on their treatment. In contrast but possibly very interestingly, it remains to be determined whether statins might bring some benefit in patients with AF without any type of established atherosclerotic disease or with a low risk of atherogenesis.

**Study limitations.** The Jadad score was low in some studies, and it is noteworthy that the results of the MIRACL study with AF have not been published in a full text article to date. However, results were similar when the MIRACL study was not included in our analysis or when ORs were calculated after studies with Jadad score <3 were removed.

We were not able to assess the degree of low-density lipoprotein cholesterol (LDL)-lowering versus the incidence or recurrence of AF, as was done with other events with statin therapy (29). We cannot determine from our analysis whether the benefit was seen because some type or dose of statins was used or because low LDL levels were achieved. Thus, if a patient achieved a certain goal of LDL (<100 or <70 mg/dl) with moderate-dose statin, we are not able to say whether outcomes would be better if a higher-dose statin was used.

Finally, mechanisms of AF might be varied in different groups of patients. The benefit of intervention therapies might be due to different protective effects, and results cannot be directly extrapolated to specific clinical settings. Significant heterogeneity found in OR calculations might also reflect heterogeneity of different clinical settings included in the study.

**Conclusions**

Use of statins was significantly associated with a decreased risk of incidence or recurrence of AF in patients in sinus rhythm with a history of previous AF, in those undergoing cardiac surgery, or after acute coronary syndrome. These results provide some evidence of the benefit of statins beyond their lipid-lowering activity. However, large-scale, prospective, randomized clinical trials are still needed to establish whether statins bring a similar benefit and are an appropriate therapeutic option in all subgroups of patients for the management of AF.

**REFERENCES**


20. Plenge JK, Hernandez TL, Weil KM, et al. Simvastatin lowers C-reactive protein within 14 days: an effect independent of low-


