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# Antiarrhythmic Effect of Statin Therapy and Atrial Fibrillation

## A Meta-Analysis of Randomized Controlled Trials

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<b>Objectives</b>	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).
<b>Background</b>	The use of statins had been suggested to protect against AF in some clinical observational and experimental studies but remained inadequately explored.
<b>Methods</b>	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.
<b>Results</b>	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 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).
<b>Conclusions</b>	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;xx:xxx) © 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 combined the terms “statin” and “atrial fibrillation” with text searches with the term “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-analysis, 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.

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Manuscript received August 17, 2007; accepted September 19, 2007.

**Abbreviations and Acronyms**

- AF** = atrial fibrillation
- CI** = confidence interval
- CRP** = C-reactive protein
- LDL** = low-density lipoprotein
- OR** = odds ratio

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 previous published data for results published in abstract form (4,9,10). We reviewed the methodological quality of randomized controlled trials by using a scoring system developed by Jadad et al. (11). The numbers 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.

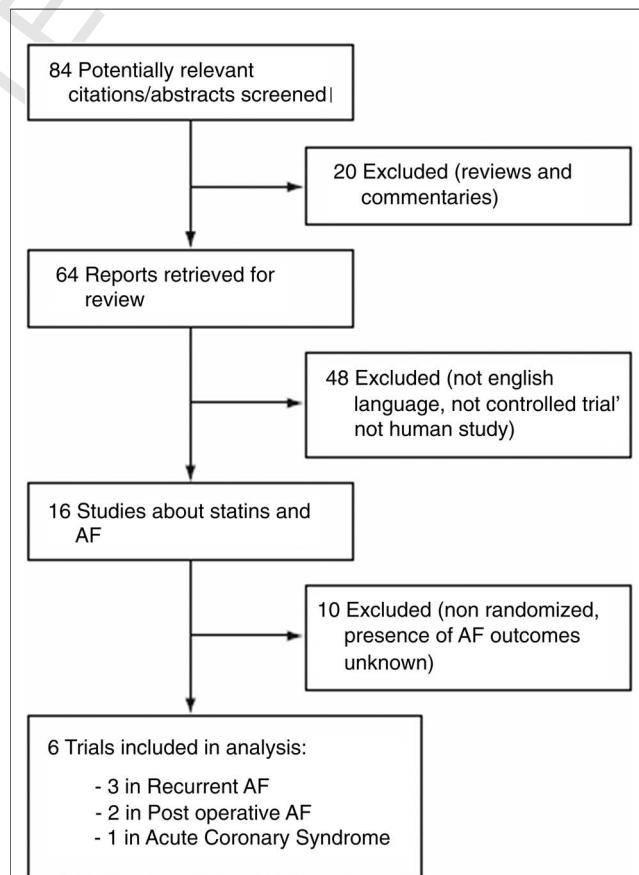
**Statistical analysis.** We calculated values for agreement by using the methods described by Fleiss (13). We calculated an odds ratio (OR) for each study outcome to allow for pooling of similar outcomes. We calculated ORs and 95% confidence intervals (CIs) for incidence or recurrence of AF of each 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 by 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 randomized, controlled trials with estimable ORs for considered end point to assess the presence of publication bias. We plotted the inverse of the standard error of the natural logarithm of the OR against the OR. Statistical calculations were performed by using RevMan, version 4.2.6 (The Cochrane Collaboration, Oxford, United Kingdom). No funding source had a role in the design of the study or in the decision to submit the manuscript for publication.

**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



**Figure 1. Selection Process for Randomized Controlled Trials on Statin and AF**

AF = atrial fibrillation.

**Table 1 Trial Design and Baseline Characteristics of the 6 Trials Included in the Meta-Analysis**

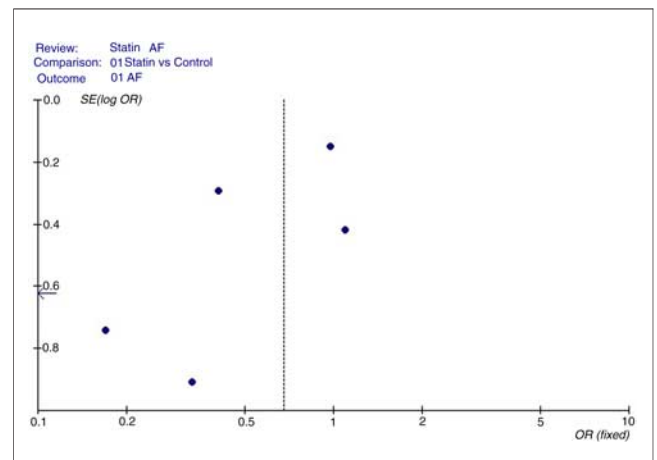
Study, Year (Ref. #)	n	Population	Treatment Arms	Duration	Specified End Point	Documentation of AF	Quality Score*
Tveit et al., 2004 (3)	114	AF >48 h and scheduled EC	40 mg pravastatin vs. standard therapy	6 weeks	Recurrence of AF (primary end point)	Clinical follow-up with ECG	2
MIRACL, 2004 (4)	3,086	Acute coronary syndrome	80 mg atorvastatin vs. placebo	16 weeks	Incidence or recurrence of AF (secondary end point)	Clinical follow-up with ECG	5
Cheilo et al., 2006 (5)	40	Scheduled coronary bypass surgery	20 mg atorvastatin vs. placebo	3 weeks	Incidence of postoperative AF (secondary end point)	ECG monitoring during ICU stay	4
Ozaydin et al., 2006 (6)	48	Persistent AF and scheduled EC	10 mg atorvastatin vs. standard therapy	3 months	Recurrence of AF >10 min (primary end point)	24-h ambulatory ECG monitoring	2
ARMYDA-3, 2006 (7)	200	Scheduled cardiac surgery without history of AF	40 mg atorvastatin vs. placebo	30 days	Incidence of postoperative AF (primary end point)	ECG monitoring during hospital stay and clinical follow-up with ECG	5
Dernellis and Panaretou, 2006 (8)	130	Paroxysmal AF	20-40 mg atorvastatin vs. placebo	4-6 months	Recurrence of AF ≥1 min (primary end point)	48-h ambulatory ECG monitoring	3

\* On a scale of 0 to 5; see Methods section.  
AF = atrial fibrillation; ARMYDA-3 = Atorvastatin for Reduction of Myocardial Dysrhythmia After cardiac surgery study; EC = electrical cardioversion; ECG = electrocardiography; ICU = intensive care unit; MIRACL = Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering study.

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). 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 postoperative AF might in part explain the lack of signifi-



**Figure 2 Funnel Plot of the Meta-Analysis**

Review: statins versus placebo or control regimen for the end point of first episode (new-onset or post-operative) or recurrence of atrial fibrillation (AF). Funnel plot allows assessment of publication bias. Bias is suspected if the plots are asymmetric on each side of the dashed line. Present plot shows no clear evidence of bias. OR = odds ratio.

**Table 2 Baseline Characteristics of the Patients in the 6 Trials Included in the Meta-Analysis**

Study, Year (Ref. #)	n	Mean Age (yrs)	Hypertension (%)	Diabetes (%)	CAD (%)	History of MI (%)	LV EF (%)	Beta-Blocker Use (%)	ACEI Use (%)	Amiodarone Use (%)	Digoxine Use (%)	Class 1 AA Use (%)
Tveit et al., 2004 (3)	114	68	43	6	11	—	—	66	—	3	24	9
MIRACL, 2004 (4)	3,086	65	55	23	100	25	—	78	49	—	11	—
Chello et al., 2006 (5)	40	65	45	—	100	—	—	7	—	—	—	—
Ozaydin et al., 2006 (6)	48	61	40	23	0	0	—	29	—	6	4	8
ARMYDA-3, 2006 (7)	200	66	87	37	84	43	52	66	49	1	7	—
Dernellis and Panaretou, 2006 (8)	130	54	65	20	0	0	—	28	43	—	25	28

AA = antiarrhythmic agent; ACEI = angiotensin converting enzyme inhibitor; CAD = coronary artery disease; MI = myocardial infarction; LVEF = left ventricular ejection fraction; other abbreviations as in Table 1.

cance 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

**Table 3** Baseline Biochemical Characteristics of the Patients in the 6 Trials Included in the Meta-Analysis and Changes With Statin Therapy

Study, Year (Ref. #)	n	Total Cholesterol (mg/dl)	LDL Cholesterol (mg/dl)	HDL Cholesterol (mg/dl)	Triglycerides (mg/dl)	CRP (mg/dl)	Decrease in LDL With Statin	Change in CRP With Statin*
Tveit et al., 2004 (3)	114	216	139	—	—	—	-33%	—
MIRACL, 2004 (4)	3,086	207	124	46	184	11.25	-55%	-34%
Chello et al., 2006 (5)	40	235	155	48	157	—	—	—
Ozaydin et al., 2006 (6)	48	171	99	44	140	2.85	-9%	-10%
ARMYDA-3, 2006 (7)	200	—	—	—	—	3.65	—	-1%
Dernellis and Panaretou, 2006 (8)	130	224	154	48	110	6.1	-37%	-50%

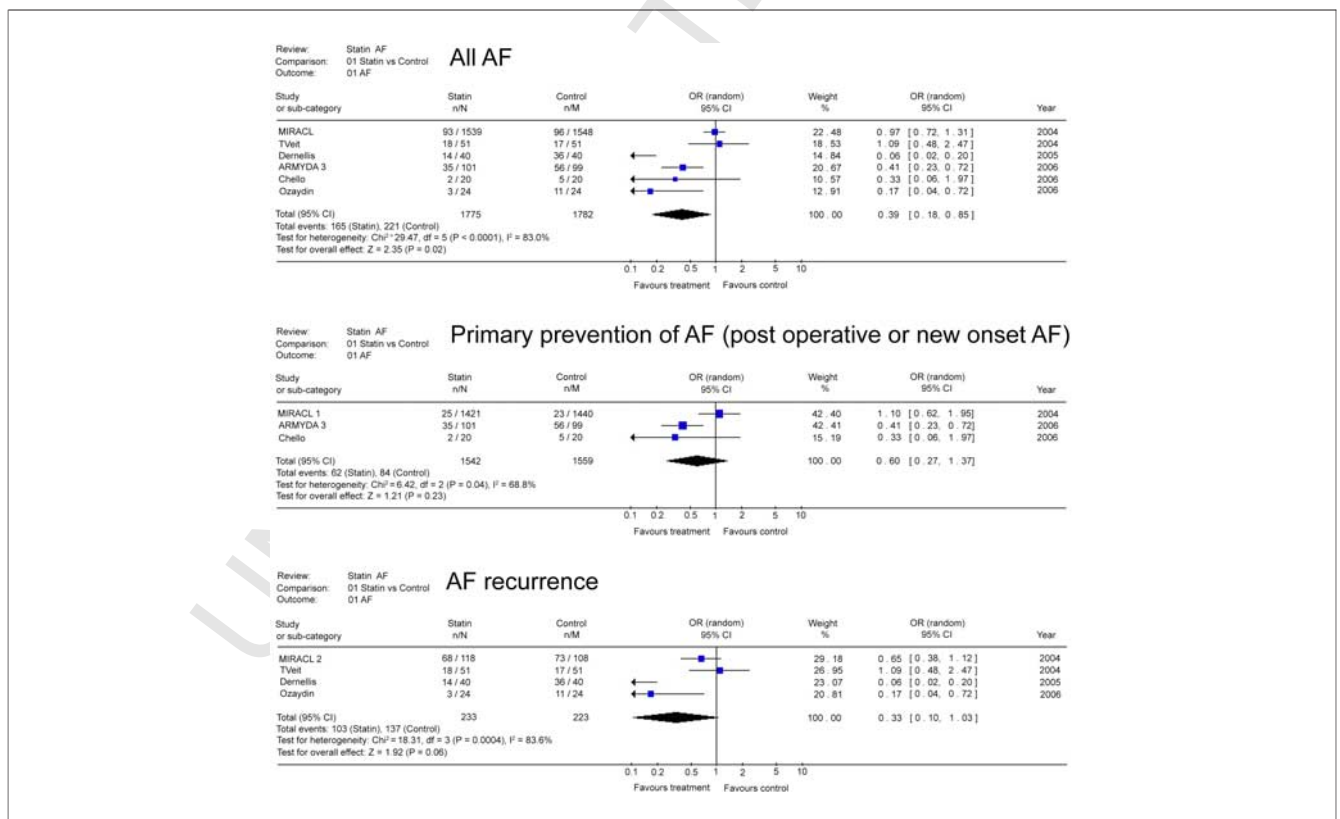
CRP = C-reactive protein; HDL = high-density lipoprotein; LDL = low-density lipoprotein; other abbreviations as in Table 1.  
\*Compared with the control group.

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.

There is evidence suggesting an association between AF and enhanced renin angiotensin system activity. Angioten-

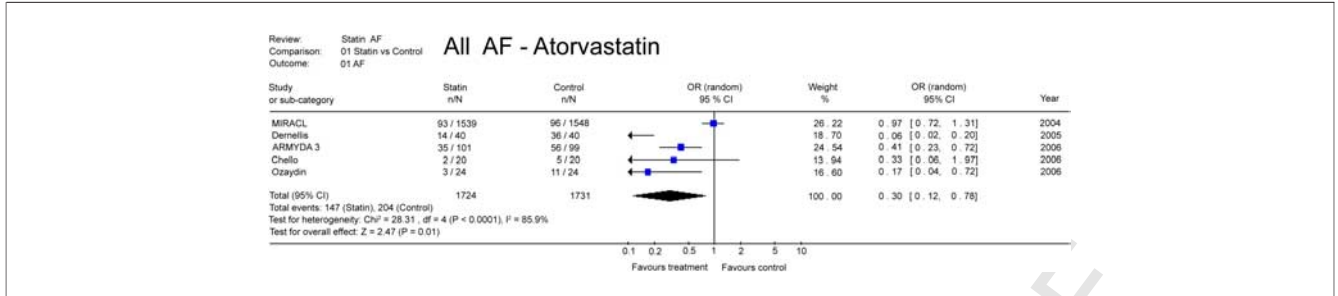
sin II has a growth-enhancing effect on cardiac myocytes, vascular smooth muscle cells, and fibroblasts, thus resulting in remodeling and fibrosis of the atria that could also provide a potential arrhythmogenic substrate for the development of AF (21). This association is supported by the fact that inhibition 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 mecha-



**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 postoperative AF, middle panel), or prevention of recurrence of AF (lower panel). MIRACL 1 and 2 indicate effect of statin in subgroups of patients in the MIRACL study without or with a previous AF, respectively. CI = confidence interval; OR = odds ratio.

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**Figure 4** Effect of Atorvastatin on the Occurrence of AF

Effect of atorvastatin versus placebo or control regimen on the occurrence of first AF episode (new-onset or postoperative AF) or recurrence of AF. Abbreviations as in Figure 3.

nism might explain a possible antiarrhythmic effect of statins against AF (23).

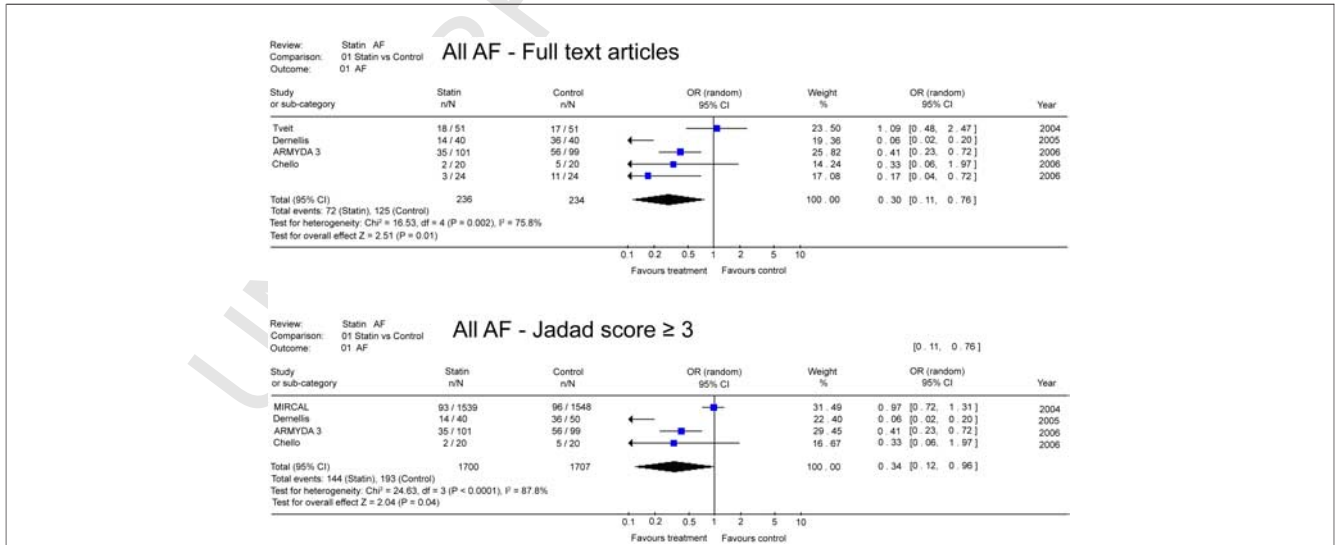
Finally, it has been suggested that a modulation of the autonomic nervous system by statins might have a protective role against AF in the particular setting of postoperative patients with enhanced sympathetic activity (25).

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.** Jadad score was low in some studies, and it is noteworthy that the results of the MIRACL study

COLOR



**Figure 5** Effect of Statins on the Occurrence of AF in Studies Published in Full Text Form and in Studies With Jadad Score  $\geq 3$

Effect of statins versus placebo or control regimen on the occurrence of first AF episode (new-onset or postoperative AF) or recurrence of AF. Odds ratio for occurrence of AF in studies published in full text form is on the top panel and OR in studies with Jadad score  $\geq 3$  is on the lower panel. Jadad score  $\geq 3$  indicates that studies with a lower methodological quality were excluded from the analysis. Abbreviations as in Figure 3.

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 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 were 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. 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.

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## mini-abstract for 4705

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

*Laurent Fauchier, Bertrand Pierre, Axel de Labriolle, Caroline Grimard, Noura Zannad, Dominique Babuty*

A systematic review of randomized controlled trials with statins was performed with analysis on the end point of incidence or recurrence of atrial fibrillation (AF). Six studies with 3,557 patients in sinus rhythm were included in this analysis. 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 0.18 to 0.85,  $p = 0.02$ ). Benefit of statin therapy seemed more marked in secondary prevention of AF (OR 0.33,  $p = 0.06$ ) than for new-onset or postoperative AF (OR 0.60,  $p = 0.23$ ).

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UNCORRECTED PROOF

## AUTHOR QUERIES

### AUTHOR PLEASE ANSWER ALL QUERIES

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AQ1— OK as revised? Alternatively, "We conducted text searches with the terms "statin," "atrial fibrillation," and "random."

AQ2— OK as revised: with number "4" deleted? Alternatively, set as (4) if citation for ref. #4.

AQ3— QUOROM spelled out correctly as Quality of Reporting of Meta-Analysis?

AQ4— OK as revised? Alternatively, "...end point of both incidence and recurrence of AF..."

AQ5— OK as revised: dose of 40 mg/day?

AQ6— OK as revised: "The capacity of statins to reduce inflammation and CRP levels is relatively well established"?

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