Clinical Investigations

Association of Statin Therapy and the Risk of Atrial Fibrillation in Patients with a Permanent Pacemaker

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Summary

Background: Recent studies have shown conflicting results regarding a protective effect of statin therapy on atrial fibrillation (AF).

Hypothesis: We sought to determine whether statins are effective in reducing the risk of developing arrhythmia in a cohort of 264 patients (49% women, mean age [$\pm$ standard deviation] 71 [$\pm$ 12] years) with permanent pacemakers who are at high risk for AF.

Methods: All patients who underwent implantation of a permanent pacemaker over a 3-year period were eligible for inclusion in the study. We excluded patients with AF at implantation, incomplete medication information, or less than a yearly follow-up visit. Atrial fibrillation was diagnosed by ECG documentation, pacemaker interrogation, and Holter monitoring. Statin treatment was verified through a central pharmacy-computerized database (for most patients) or by chart review. Of the 264 patients, 36% had coronary artery disease.

Results: Atrial fibrillation developed in 70 patients (26%) at a median of 359 days post pacemaker implantation. The incidence rate for the first occurrence of AF post pacemaker implantation among patients treated and not treated with statins was 10.5 versus 9.8 events per 100 patient-years, respectively

($p = 0.81$). Even after controlling for baseline differences, the hazard ratio (HR) for developing AF among statin users did not achieve statistical significance (HR = 0.59 [0.31–1.12]).

Conclusions: We could not demonstrate that statin therapy had a protective effect against the risk of AF in patients implanted with a permanent pacemaker. The low prevalence of coronary artery disease in our patients may partly explain our results.

Key words: atrial fibrillation, statins, pacemaker, prevention, arrhythmia

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia and carries substantial morbidity and mortality risks.¹ The pathogenesis of AF involves an interaction between structural changes in the atria, precipitating electrophysiologic triggers, and underlying anatomical changes facilitating perpetuation of the arrhythmia and possibly inflammation.² In addition to their lipid-modifying properties, statins appear to have anti-inflammatory and other pleiotropic effects³ that may be beneficial in sepsis⁴ and rheumatoid arthritis,⁵ and recently appear to have been associated with a reduced rate of ventricular arrhythmias;⁶ however, their previously suggested benefit in retarding the progression of aortic sclerosis is now debated.⁷ Thus, it is plausible that statins may affect some of the processes involved in the pathogenesis of AF. Recent studies examining the relationship of statin therapy and AF have yielded conflicting results, partly because of small sample size.^{8–10} We set out to evaluate the association of statin therapy and the risk of developing AF in patients implanted with permanent pacemakers, a population with a high incidence of AF.^{11–13}

Methods

All patients undergoing permanent pacemaker implantation at a tertiary care university hospital during the years 1997–2000 were identified and their charts reviewed. Patients were

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excluded if they were in AF at the time of implantation, did not have at least a yearly follow-up visit/hospital admission, and had < 1 year of follow-up or incomplete medication history. At each clinic visit, the patients underwent an electrocardiographic (ECG) study and the pacemaker was interrogated. Atrial fibrillation was diagnosed by one or more of the following: (1) ECG tracing, (2) Holter monitoring, and (3) pacemaker interrogation in which an experienced clinician diagnosed repeated mode-switching episodes to be due to AF. Left ventricular systolic function was assessed by echocardiography.

All prescriptions filled by these patients were extracted from their health maintenance organization's central pharmacy computerized database. Data on medications from patients not registered in the central pharmacy database (10% of the study group) were extracted from the patients' medical charts. First and last statin dispensing/subscription dates, as well as the number of dispensing dates during the follow-up period, were recorded. Patients were considered as "statin-treated" if treatment was continuous from its beginning throughout the end of follow-up. Intermittent treatment was grouped with "no statin treatment."

Statistical Analysis

Continuous and dichotomous variables were compared by Student's *t*-test and chi-square, respectively. The data were analyzed twice: the first analysis assessed the time-dependent risk for developing AF. Kaplan-Meier survival tables were used for AF incidence rates, and Cox regression analysis was used to test the association of statin treatment with the risk for developing AF, with adjustment for covariates known to influence the risk of AF. The hazard for developing AF was compared between patients treated and not treated with statins at the time of implantation. Patients were censored once they developed AF, follow-up was ended, or they were started on statins (for those in the "no-statin" group). Next, patients who developed AF (cases) were matched to patients without AF (controls) by time from implantation (± 30 days) and age (± 5 years). Cases and controls were then retrospectively compared regarding statin use during the time period from pacemaker implantation to AF/censoring date.

Results

The study cohort included 264 patients (49% women) with a mean ($\pm$ standard deviation [SD]) age at pacemaker implantation of 71 (± 12) years. Indications for permanent pacing were sinus bradycardia in 81 patients (30%), atrioventricular block in 158 (60%), and other in 26 (10%). The implanted pacemaker types were DDDR, VDD, VVIR, and AAIR in 52, 36, 10, and 2% of patients, respectively.

Atrial fibrillation developed in 70 patients (26%) at a median of 359 days (range–2,171) post pacemaker implantation. Of those, 51 patients (73%) were diagnosed at a clinic visit (41 by ECG tracing, 7 by mode switching, and 3 by Holter moni-

toring) and 19 patients (27%) during subsequent hospital admission (all by ECG tracing). Of the 264 patients, 51 (19.3%) were treated with statins continuously from implantation. The characteristics of patients treated and not treated with statins are presented in Table I. Statin-treated patients had a higher prevalence of hypertension, diabetes, and coronary heart disease, and a trend toward a higher incidence of previous AF and treatment with antiarrhythmic drugs. The incidence rate for the first occurrence of AF post pacemaker implantation was 9.9 events/100 patient-years for the whole cohort (Fig. 1). Among patients not treated with statins, the rate was 9.8 events/100 patient-years versus 10.5 events/100 patient-years among statin-treated patients ($p = 0.81$). After controlling for the variables listed in Table I, the hazard of developing AF for statin users remained nonsignificant (hazard ratio [HR] = 0.59; 95% confidence interval [CI] = 0.31–1.12).

Of the 70 AF cases, 64 could be matched to 101 controls. The rate of statin use among cases was 34.4 versus 37.6% among controls ($p = 0.67$) and the median days on statin were 329 and 190 ($p = 0.43$), respectively.

Discussion

Atrial fibrillation is a frequent arrhythmia in patients implanted with a pacemaker for conduction abnormalities.¹⁴ Prevention of AF in this group of patients in a cost-effective and safe manner has the potential for reducing the complications of pacing. In our cohort of implanted patients, we did not find

TABLE I Baseline characteristics of patients according to statin therapy

	Statin treatment (n = 51)	No statin treatment (n = 213)	p Value
Age (mean + SD)	72 $\pm$ 8	71 $\pm$ 13	0.67
Female (%)	23 (45)	107 (50)	0.53
Past AF (%)	12 (24)	29 (14)	0.08
Hypertension (%)	44 (88)	150 (71)	0.01
Coronary artery disease (%)	35 (69)	61 (29)	<0.01
Diabetes mellitus (%)	21 (42)	54 (26)	0.02
Indication for pacemaker implantation			0.08
Sinus bradycardia (%)	21 (41)	60 (28)	
Other	30 (59)	154 (72)	
Significant LV dysfunction (%) ^a	8 (22)	24 (19)	0.67
Antiarrhythmic drug use (%)	11 (22)	26 (12)	0.08
Pacemaker type (%)			0.44
DDDR	30 (59)	109 (51)	
VDD	18 (35)	77 (36)	
VVIR	3 (6)	23 (11)	
AAIR	0 (0)	5 (2)	

^a Estimated by echocardiography, 30% missing values.

Abbreviations: SD = standard deviation, AF = atrial fibrillation, LV = left ventricular.

FIG. 1 Atrial fibrillation-free survival for statin-treated (dashed line) versus not statin-treated (solid line) patients.

that treatment with a statin was associated with a reduced incidence of subsequent AF.

The strength of our study lies in the relatively long follow-up period in a population with a high incidence of arrhythmia. The prospective analysis has the advantage of comparing the actual incidence rate of AF. Analyzing the data in a “case-control” design has the advantage of controlling for age and time from implantation, the two most important biases. The disadvantage is the inability to compare incidence rate of AF among users and nonusers of statins. Both methods of data analysis failed to demonstrate any significant association between statin treatment and occurrence of AF.

The lack of association in this study between statin use and development of AF is not in accordance with other reported evidence. Siu *et al.*⁸ found that in patients treated with a statin for a mean of 44 months, and who underwent cardioversion for lone AF, the recurrence rate of arrhythmia was significantly reduced compared with nontreated patients. Young-Xu *et al.*⁹ followed a cohort of patients with coronary artery disease and found that only among patients with continuous use of

statins (vs. intermittent or no use) did the drugs have a protective effect against AF. On the other hand, Tveit *et al.*¹⁰ conducted an open-label study randomizing patients to pravastatin or placebo beginning 3 weeks before and continued for 6 weeks after AF electrical cardioversion. No difference was found between the two groups in the rate of successful cardioversion or recurrence of AF. We are not aware of previous published studies relating the use of statins and AF in patients with permanent pacemakers.

We can suggest several explanations for the lack of association in this study. First, as can be seen from Table I, statin users were at a higher risk for developing AF, probably not entirely controlled for by the regression model. Indeed, although not significant, there was a 40% theoretical reduction in risk. This hypothetical risk reduction might suggest that if the groups had been more similar, a true difference could have been shown, probably with larger sample size or a longer follow-up. Second, patients were treated with various statin formulations and dosages for which we could not adjust. Third, some patients in the no-treatment group were treated intermittently with statins. Fourth, the effect of statins seen in previous studies may be limited to patients with coronary artery disease, as a result of their antiatherosclerotic properties. In this regard, statins may ameliorate atrial ischemia and thus protect from AF, or indirectly reduce left ventricular ischemia, which will lead to a reduction in left ventricular diastolic pressures known to affect AF. Table II summarizes the major points of difference among the previous studies and the current study. Although all patients in the positive study of Young-Xu *et al.*⁹ had coronary disease, only about 10% in the negative trial of Tveit *et al.*¹⁰ and about 36% in our study had a history of coronary bypass or myocardial infarction. In the positive study of Siu *et al.*,⁸ the subjects had a much higher blood cholesterol level, again suggesting that statins exert their effect on AF through hypolipidemic and anti-ischemic properties and only 10 patients were treated with statins. Thus, different populations yield diverse results regarding the statin effect on AF. It

TABLE II Comparison with previous studies

	Young-Xu <i>et al.</i> (9)	Siu <i>et al.</i> (8)	Tveit <i>et al.</i> (10)	Current study
No. of subjects (statin / no statin)	186 / 128	10 / 52	57 / 57	51 / 213
Age, mean $\pm$ SD	66 $\pm$ 9 /	68 $\pm$ 4 /	68 $\pm$ 10 /	72 $\pm$ 8 /
(statin / no statin)	71 $\pm$ 9	59 $\pm$ 2	68 $\pm$ 10	71 $\pm$ 13
History of AF (%)	0	100	100	16
AF incidence rate per 1,000 person-years (statin / no statin)	15 / 37			97 / 99
Rate of AF at 2 years of follow-up, % (statin / no statin)	0 / 20	40 / 84	35 ^a / 33	20 / 22
Coronary artery disease (%)	100	?	11	36
Total cholesterol level mean $\pm$ SD	199 $\pm$ 40 /	257 $\pm$ 27 /	218 $\pm$ 44 /	214 $\pm$ 47 /
in mg/dl (statin / no statin)	193 $\pm$ 34	206 $\pm$ 4	218 $\pm$ 44	210 $\pm$ 45
RR of AF + 95% CI	0.37	0.31	1.06	0.59
(statin vs. no statin)	(0.18–0.76)	(0.10–0.91)	(0.64–1.77)	(0.31–1.12)

^a At 6 weeks.

Abbreviations: RR = relative risk, CI = confidence interval. Other abbreviations as in Table I.

appears that the higher the atherosclerosis/ischemic risk of the population, the more positive the effect of the medications. Finally, statins may have no effect or a significantly smaller effect on AF than previously thought, as was recently found pertaining to the progression of aortic stenosis.⁷

Limitations

Our study has several limitations, most of which are related to its retrospective nature. Excluding patients because of incomplete follow-up or medication data may have biased the results in an unknown direction. Due to the numerous types and doses of statins used by our study patients, it was not practical to look for a dose–response relationship. Diagnosing AF by atrial mode switching may overestimate its incidence because of oversensing;¹⁵ however, excluding this small proportion of patients from the analysis did not change the results. Finally, the retrospective nature of the study did not enable us to adjust for the amount of time of ventricular pacing.

Conclusion

Contrary to recently published data, we found no relationship between statin therapy and the subsequent development of AF in patients implanted with pacemakers who have a high incidence of AF. Only a randomized clinical trial might settle the study question.

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