Review

Statins as Antiarrhythmics: A Systematic Review Part II: Effects on Risk of Ventricular Arrhythmias

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ABSTRACT

Background: Recent studies have demonstrated that statins may possess antiarrhythmic properties in addition to their lipid-lowering effects.
Methods: Studies which reported the association of statins with the incidence of ventricular arrhythmias were identified through a systematic review of the published literature.
Results: Statins have been associated with significant reduction in ventricular arrhythmia in cardiomyopathy patients with an implantable cardioverter defibrillator, although randomized trials have not been completed.
Conclusions: Published data suggest that statins may possess antiarrhythmic properties that reduce the propensity for ventricular arrhythmias. Most of this data is observational; more randomized, placebo-controlled trials are needed.

Background

Hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins) reduce mortality and cardiac death in patients with coronary artery disease (CAD)[1] and prevent cardiovascular events in patients without clinically evident coronary disease.[2] In addition to their lipid-lowering effects, statins exhibit pleiotropic properties which are thought to play a role in cardiovascular protection, including modulation of inflammation,[3] inhibition of platelet activation and thrombosis,[4] and improvement of endothelial function.[5] Additionally, statins have been shown to reduce ischemia-induced myocardial necrosis and ischemia-reperfusion injury in animal models[6,7] and to favorably influence markers of cardiovascular autonomic regulation such as heart rate variability.[8,9]

Interestingly, recent studies have demonstrated that statins may also possess antiarrhythmic properties. Current data suggests that statins may be useful in the prevention of ventricular arrhythmias. The purpose of this paper is to provide a better understanding of the potential of statins to reduce arrhythmic risk by systematically reviewing the available published data regarding potential antiarrhythmic properties of these medications.

Methods

Studies which reported the association between statins and the incidence of ventricular arrhythmias were identified through a systematic review of the published literature from January 1990 to December 2007 using MEDLINE, EMBASE and the Cochrane Library. The following indexing terms were used to identify potentially pertinent articles: ventricular arrhythmia (VA), statin, hydroxymethylglutaryl-coenzyme A reductase inhibitors, implantable cardioverter defibrillator (ICD), cardiomyopathy. A manual review of the bibliographies of primary and review articles was also performed to identify any additional relevant studies. Observational and randomized clinical trials were included. Retrieved clinical studies are shown in table 1.[10–15]

Results

Several observational studies have evaluated the relationship between statin usage and the incidence of VA and sudden cardiac death (SCD) in those with cardiomyopathy and ICD. De Sutter and colleagues[10] examined 78 patients with CAD and life-threatening VA treated with ICD therapy. Patients who received lipid-lowering therapy had fewer VA episodes compared with those who did not (22% vs. 57%, $p < 0.05$). Mitchell and colleagues,[11] in a subanalysis from the Antiarrhythmics Versus Implantable Defibrillators (AVID) study, examined VA recurrence rates in patients who had CAD and near-fatal VA and had received an ICD. There was an observed 40% reduction in the relative hazard for VA recurrence in the group that received lipid-lowering therapy ($n = 83$; 79% statins) compared with the group that did not ($n = 279$) (hazard ratio 0.40, 95% CI 0.15–0.58, after adjusting for baseline differences, adjusted $p = 0.003$). Chiu

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Table 1. Summary of studies evaluating therapy with statins for prevention of ventricular arrhythmias

No	Study	Type of Study	Setting	Statin	Arrhythmia	No. of Patients	Follow Up	Risk Ratio (95% CI)
1	De Sutter[10]	Observational	CAD	Any	Recurrent VA	78	490 days	RR 0.46, p = 0.004
2	AVID[11]	Sub-analysis from original study	Atherosclerotic heart disease	Any	Recurrent VA	713	3 years	HR 0.40 (0.15–0.58)
3	Chiu[12]	Observational	CAD	Any	First ICD therapy	281	10.2 months	HR 0.60 (0.41–0.89)
4	MADIT-II[13]	Sub-analysis from original study	LVSD	Any	Cardiac death or ICD therapy	654	17 months	HR 0.65 (0.49–0.87)
5	DEFINITE[14]	Sub-analysis from original study	LVSD	Any	Arrhythmic sudden death	229	29 months	HR 0.16 (0.022–1.21)
6	CORONA[15]	Sub-analysis from original study	LVSD	Rosuv.	Arrhythmic sudden death	5011	32.8 months	HR 0.96 (0.82–1.12)

*Published risk ratios may have been derived from subgroup analyses and/or statistical models and do not necessarily equal crude incidence ratios.
AVID: Antiarrhythmics versus Implantable Defibrillators; CAD: Coronary Artery Disease; CI: Confidence Interval; CORONA: Controlled Rosuvastatin Multinational Trial in Heart Failure; DEFINITE: Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation; HR: Hazard Ratio; ICD: Implantable Cardioverter Defibrillator; LVSD: Left Ventricular Systolic Dysfunction; MADIT: Multicenter Automatic Defibrillator Implantation Trial; RR: Relative Risk; VA: Ventricular Arrhythmia.

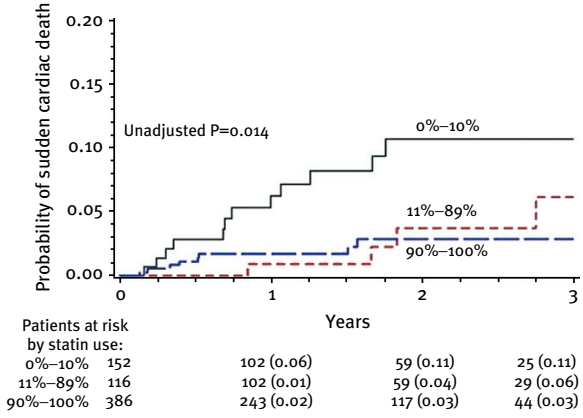

Figure 1. Cumulative probability of death classified as sudden cardiac, by percentage of days that statin therapy was used (≥ 90%, 11% to 89%, and ≤ 10%) during follow-up. Numbers below the graph are the number of patients at risk in the time period; the *p* value assesses differences among the three curves. Results from MADIT II.[13] Reprinted with permission.

and colleagues[12] studied 281 patients who had ischemic cardiomyopathy (left ventricular ejection fraction < 30%) and underwent ICD implantation and observed a reduction in first ICD therapy for VA (adjusted hazard ratio 0.60, p = 0.01) among patients on statin therapy (n = 154) compared with those not on a statin (n = 127).

Over 10,000 statin-treated patients with heart failure have been evaluated in various observational trials examining mortality. Each study has shown a significant reduction in mortality associated with statin use. The second Multicenter Automatic Defibrillator Implantation Trial (MADIT)-II[13] which enrolled patients with ischemic cardiomyopathy and left ventricular ejection fraction ≤ 30% demonstrated that statin use was associated with a 28% reduction in the risk of a first VA event (hazard ratio 0.72, 95% CI 0.52–0.99, p = 0.046). In this analysis, statin use was also associated with a significant reduction in SCD (p < 0.01) in those receiving statin therapy for ≥ 90% of the follow-up period compared with those receiving statin therapy for ≤ 10% of the follow-up period.

Whether statins have a specific effect on life-threatening VA or their effects on reducing these arrhythmias are predominantly mediated by an anti-ischemic mechanism was addressed in a report from the DEFibrillators in Non-ischemic cardiomyopathy Treatment Evaluation (DEFINITE) study which evaluated the benefit of ICD implantation as primary prevention of VA in those with non-ischemic cardiomyopathy and ejection fraction ≤ 35%.[14] The association of statin use and outcomes was analyzed in the 229 patients who were randomized to ICD implantation. Statin use was associated with a 78% reduction in all-cause mortality (hazard ratio 0.22; 95%CI 0.09–0.55, p = 0.001). One patient of 110 (0.9%) on statin therapy died of SCD compared with 18 of 348 (5.2%) not on statin therapy (p = 0.04). Although not statistically significant, patients in the statin group had lower numbers of appropriate shocks (hazard ratio 0.78; 95%CI 0.34–1.82). This data suggests that statins may possess properties that directly suppress VA beyond their anti-ischemic effects.

A recent analysis from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) which enrolled patients with

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ischemic or non-ischemic cardiomyopathy and left ventricular ejection fraction $\leq$ 35% demonstrated that statin use was associated with reduction in all-cause mortality, independent of heart failure etiology.[16] The long duration of follow-up (45.5 months) and the large number of statin-treated patients (1187 on statin at the last visit, including 371 with non-ischemic cardiomyopathy) makes this one of the most significant reports to date on the mortality benefit of statins in heart failure. The association between statins and reduced mortality was strong even in the setting of non-ischemic cardiomyopathy, and was present despite high rates of concomitant use of Angiotensin-Converting Enzyme inhibitors, angiotensin receptor blockers, beta blockers, and ICDs.

Similar results were found by another report looking at hospital discharge diagnosis and prescription data gathered on Medicare patients; those heart failure patients who filled their prescriptions for statins had significantly lower morality rates.[17] An association of statins with lower mortality rates was also noted in the EuroHeart Failure survey.[18]

The Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA)[15] was recently published. In this study, a total of 5011 heart failure patients were randomly assigned to receive 10 mg of rosuvastatin or placebo per day. Rosuvastatin did not reduce the primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. However, this study enrolled older patients (mean age 73 years) with moderate-to-severe heart failure who were in New York Heart Association class III or IV (or who had an ejection fraction of $\leq$ 35% in class II) and whose physicians had not recommended that they should receive a statin. Some have speculated that the patients enrolled in CORONA may have had atherosclerotic or myocardial disease that was too advanced to modify and that rosuvastatin might have had a different effect in patients with milder heart failure. Also, patients with nonischemic heart failure were not studied, which limits the applicability of study findings to a large population of heart failure patients.

A recent meta-analysis of ten randomized clinical trials enrolling a total of 22,275 patients showed that statin treatment was associated with a significant 19% risk reduction for SCD (odds ratio 0.81, 95% CI 0.71–0.93, $p = 0.003$). In subgroup analysis, the benefit of statins was independent from the main characteristics of the studies and changes in patient lipid levels during the study.[19]

Discussion

The totality of data published to date suggests that statins may possess antiarrhythmic properties that reduce the incidence of VA. Although much of the current data is observational in nature, most of the findings from the few and relatively small randomized trials evaluating statins and VA support these observations.

The benefit of statins in reducing VA may relate directly or indirectly to one or more of their pleiotropic effects. For example, the anti-oxidant, anti-inflammatory, and anti-mitogenic properties of these medications may play a role in plaque stabilization and thus contribute to an antiarrhythmic effect by reducing ischemia-related VA. Additionally, statins have been shown to enhance cardiovascular autonomic balance, which may in and of itself reduce the propensity for arrhythmia development,[8,9] and to improve LV systolic function in patients with cardiomyopathy, which may influence the risk of VA in these patients.[20] Of interest, the improved survival noted with statins in nonischemic cardiomyopathy patients with heart failure was reported to be independent of the lipid-lowering effects of these agents[21] and was not related to a significant reduction in appropriate ICD-delivered therapies in one study.[14] However, statin therapy in several other studies has been associated with a reduced risk for SCD.[11,13,14] Further trials are necessary to determine the relative contribution of statin therapy to improvement in arrhythmic and non-arrhythmic mortality in the setting of ischemic and nonischemic cardiomyopathies.

Prior studies have shown that other classes of medications that are not generally considered antiarrhythmic agents also possess antiarrhythmic properties. Angiotensin-Converting Enzyme inhibitors and omega-3 fatty acids, for example, have been shown to decrease the incidence of VA[22] and SCD,[23] respectively.

Limitations to studies presented in this review do exist: most of them are observational in nature and statin use was a time-dependent covariate; and duration of follow up varied significantly among studies and development of VA might have just been delayed and not actually prevented. Despite these limitations and although the exact mechanisms by which statins may exert antiarrhythmic effects are speculative, these medications remain an important cornerstone in the management of patients with, or at risk for, CAD. The potential antiarrhythmic properties, as suggested by the multiple observational as well as randomized studies discussed in this review, may strengthen and extend the indications for the statin class of agents. Future, randomized, long-term studies are still needed to further our understanding of the possible role of statins as antiarrhythmic agents and the underlying mediators of these effects.

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