Hydroxymethylglutaryl Coenzyme A Inhibitors (Statins) and Arrhythmias: Systematic Review and Meta-Analysis

S Thambidorai, K Anand, T Hee, A Mooss, D Esterbrooks, S Mohiuddin

Citation

Abstract
Hydroxymethylglutaryl coenzyme A inhibitors (statins) reduce mortality in coronary artery disease, heart failure and have been shown to have pleiotropic anti-arrhythmic effects. We performed a meta-analysis to assess the utility of statins in atrial fibrillation (AF) and ventricular tachyarrhythmia (VA). Systematic review of all studies from 1990 until 2006 identified fourteen good quality studies on statins and AF and five studies on statins and VA. Meta-analysis was performed using the random-effects model and the pooled risk ratio (RR) for AF was RR: 0.73 (95% CI: 0.62-0.86) and for long term VA was 0.64 (95% CI: 0.44-0.94). In the sub-group analysis that included only randomized studies, the pooled risk ratio (RR) using random effects model for AF was RR: 0.64 (95% CI: 0.37-1.14). In conclusion, statins decrease the incidence and recurrence of AF and VA, but additional randomized studies are required to confirm this pleiotropic effect of statins.

ABBREVIATIONS LIST
AF- Atrial Fibrillation
HMG CoA inhibitors- Hydroxymethylglutaryl coenzyme-A reductase inhibitors
VA – Ventricular Tachyarrhythmia

INTRODUCTION
Hydroxymethylglutaryl coenzyme-A reductase inhibitors (HMG CoA inhibitors or statins) decrease mortality in patients with coronary artery disease (1) and heart failure (2). While early studies on statins focused on low density lipoprotein (LDL) reduction, more recent studies have shown an early benefit after initiation of statin therapy, suggesting cholesterol independent pleiotropic effects of statins (3-9). Few reports have suggested a role for statins in decreasing atrial fibrillation (AF) (4) and ventricular tachyarrhythmia (VA) (10). AF is the most common arrhythmia in clinical practice and is associated with increased risk of stroke, heart failure and mortality (4). VA accounts for the vast majority of sudden cardiac deaths due to heart disease (4). Current anti-arrhythmic therapy for AF and VA are not very effective and are associated with major side effects (3-9).

There has not been any large-scale prospectively designed clinical trial to examine the efficacy of statins on AF or VA.

A systematic review of all available data is timely and provides the best estimate of effectiveness of statins for AF and VA.

METHODS
Two independent investigators conducted a comprehensive search to identify all human studies of statins and atrial fibrillation or ventricular arrhythmia. Medline, EMBASE, Cochrane databases were searched for any study from 1990 until 2006, using the terms “statin”, all different drug classes of statins, “hmg coa reductase”, “lipid drug”, “atrial fibrillation”, “atrial arrhythmia”, “atrial flutter”, “atrial tachycardia”, “ventricular fibrillation”, “ventricular tachycardia”, “ventricular arrhythmia”, “fibrillation”, “tachycardia”, “arrhythmia”, “flutter”. Additional publications were identified using the reference lists of articles chosen and review articles on statins or atrial fibrillation and ACC/AHA/ESC guidelines on atrial fibrillation. From the articles the methods, results and tables were reviewed to identify the required elements for this study. For secondary analysis of randomized control studies, other publications from the randomized control trial were reviewed to ascertain the number of patients included for the secondary analysis and the number excluded from the original trial. Figure 1 shows the overview of the search.
Study data were independently abstracted, in duplicate, using a standardized form and sensitivity scoring was done using the Newcastle-Ottawa scale (NOS) (9). Any discordance between the reviewers was resolved by consensus.

**INCLUSION CRITERIA**
The following criteria were applied: [1] Human studies assessing the utility of statins on AF and VA. As there were very few randomized studies, we did not allow any restriction on the type of study. All types of AF (incident, recurrent, paroxysmal, chronic) were included as endpoints. [2] The incidence and prevalence rates of AF and VA can be calculated and relative risks obtained. [3] The duration of statin therapy and follow-up for the arrhythmic events is clearly stated. [4] Only studies with a NOS score > 7 were included in the final meta-analysis.

**STATISTICAL ANALYSIS**
Meta-analysis was performed in accordance to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines of observational studies (10). The analyses were conducted based on intention to treat principle. Each study was considered as a single stratum. For studies with a factorial design, we based main results on two-way analyses, that is, all study participants receiving statins were compared with all participants not receiving it.

We obtained the pooled relative risks with 95% confidence interval (CI) for development of AF using the random effects model of DerSimonian and Laird (11). Random effects model was preferred over fixed effects model because of the significant heterogeneity between the included trials. We used the Q test to test for heterogeneity of study results. We used inverse-variance weighting to calculate random effects summary estimates. Thus larger studies, which have smaller standard errors, are given more weight than smaller studies, which have larger standard errors. This choice of weight minimizes the imprecision (uncertainty) of the pooled effect estimate. We performed an influence analysis and assessed the influence of individual studies on the summary effect estimate. All statistical analyses were performed using Stata 8.0 (Stata Corporation, College Station, TX).

**RESULTS**
Most of the excluded studies (~90%) were irrelevant articles, letters, correspondence, reviews and animal studies. One study was excluded because the authors had considered atrial and ventricular arrhythmia as one entity. Three studies were excluded because of inadequate information after contacting primary authors. After carefully reviewing the literature there were a total of 19 studies that qualified based in inclusion criteria (14 studies on AF and 5 on VA). Of these 19 studies, 5 were published as abstracts. The characteristics of the 19 studies included are summarized in Tables 1-4.
Figure 2
Table 1: Study details and demographics- Statins and Atrial fibrillation.

<table>
<thead>
<tr>
<th>Case (Ref. No.)</th>
<th>Author</th>
<th>Age (yr)</th>
<th>Male</th>
<th>HTN</th>
<th>DM</th>
<th>CAD</th>
<th>Past AF</th>
<th>Study withdrawn at crossover follow-up</th>
<th>Exposure period</th>
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<tbody>
<tr>
<td>1 (C01)</td>
<td>Young-Xa</td>
<td>56/71</td>
<td>55/1</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>Ansell</td>
<td>57/71</td>
<td>55/1</td>
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<td></td>
<td></td>
<td></td>
<td>2/3 (80% &lt; 50%)</td>
<td></td>
</tr>
<tr>
<td>3 (C03)</td>
<td>Qin and</td>
<td>59/90</td>
<td>55/1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2/3 (80% &lt; 50%)</td>
<td></td>
</tr>
<tr>
<td>4 (C04)</td>
<td>Dickinson</td>
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<td>55/1</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>55/1</td>
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<tr>
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<tr>
<td>7 (C07)</td>
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<td></td>
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</tr>
<tr>
<td>8 (C08)</td>
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<td>60/71</td>
<td>55/1</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>9 (C09)</td>
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<td>60/71</td>
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<td></td>
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<td>10 (C10)</td>
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<td></td>
<td></td>
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</tr>
<tr>
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<td>Twati</td>
<td>60/71</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
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<tr>
<td>13 (C13)</td>
<td>Demelii</td>
<td>60/71</td>
<td>55/1</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

* Single number represents mean or mean % of entire group and fraction represents mean or mean % in statin / nonstatin group.

AF- Atrial Fibrillation, CAD- Coronary artery disease, DCCV - Direct Current Cardioversion, DM- Diabetes Mellitus, EF - Ejection Fraction, HTN- Hypertension

Figure 3
Table 2: Study details and demographics- Statins and Ventricular tachyarrhythmia.

<table>
<thead>
<tr>
<th>Case (Ref. No.)</th>
<th>Author</th>
<th>Age (yr)</th>
<th>Male</th>
<th>HTN</th>
<th>DM</th>
<th>CAD</th>
<th>Past AF</th>
<th>Study withdrawn at crossover follow-up</th>
<th>Exposure period</th>
</tr>
</thead>
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<td>55/1</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>2 (C14)</td>
<td>Ansell</td>
<td>57/71</td>
<td>55/1</td>
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<td></td>
<td></td>
<td></td>
<td>2/3 (80% &lt; 50%)</td>
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</tr>
<tr>
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<td>59/90</td>
<td>55/1</td>
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<td>2/3 (80% &lt; 50%)</td>
<td></td>
</tr>
<tr>
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<td>59/71</td>
<td>55/1</td>
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<td>55/1</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

* Single number represents mean or mean % of entire group and fraction represents mean or mean % in statin / nonstatin group.

DCCV - Direct Current Cardioversion, DM- Diabetes Mellitus, EF - Ejection Fraction, HTN- Hypertension, VT- Ventricular tachyarrhythmia

Figure 4
Table 3: Study details and arrhythmia diagnosis – Atrial Fibrillation

<table>
<thead>
<tr>
<th>Case (Ref. No.)</th>
<th>Author</th>
<th>AF diagnosis*</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Follow-up</th>
<th>Definition of AF</th>
<th>Adjunct variables</th>
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<td>Recurrent</td>
<td>age, HTN, DM, CAD</td>
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<tr>
<td>2 (C02)</td>
<td>Ansell</td>
<td>Permanent</td>
<td>DCCV</td>
<td></td>
<td>2 years</td>
<td>Recurrent</td>
<td>age, DM, CAD, HTN</td>
</tr>
<tr>
<td>3 (C03)</td>
<td>Qin and</td>
<td>DCCV</td>
<td>DCCV</td>
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<td>1 year</td>
<td>Recurrent</td>
<td>age, DM, CAD, HTN</td>
</tr>
<tr>
<td>4 (C04)</td>
<td>Dickinson</td>
<td>DCCV</td>
<td>DCCV</td>
<td></td>
<td>4-5 months</td>
<td>Recurrent</td>
<td>age, DM, CAD, HTN</td>
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<tr>
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<td>Xa</td>
<td>DCCV</td>
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<tr>
<td>6 (C06)</td>
<td>Minna</td>
<td>AF</td>
<td>DCCV</td>
<td></td>
<td>1 month</td>
<td>Recurrent</td>
<td>age, DM, CAD, HTN</td>
</tr>
<tr>
<td>7 (C07)</td>
<td>Aart</td>
<td>AF</td>
<td>DCCV</td>
<td></td>
<td>1 month</td>
<td>Recurrent</td>
<td>age, DM, CAD, HTN</td>
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<td>8 (C08)</td>
<td>Pauls</td>
<td>AF</td>
<td>DCCV</td>
<td></td>
<td>1 month</td>
<td>Recurrent</td>
<td>age, DM, CAD, HTN</td>
</tr>
<tr>
<td>9 (C09)</td>
<td>Cornelia</td>
<td>AF</td>
<td>DCCV</td>
<td></td>
<td>1 month</td>
<td>Recurrent</td>
<td>age, DM, CAD, HTN</td>
</tr>
<tr>
<td>10 (C10)</td>
<td>Cornelia</td>
<td>AF</td>
<td>DCCV</td>
<td></td>
<td>1 month</td>
<td>Recurrent</td>
<td>age, DM, CAD, HTN</td>
</tr>
<tr>
<td>11 (C11)</td>
<td>Twati</td>
<td>AF</td>
<td>DCCV</td>
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<td>1 month</td>
<td>Recurrent</td>
<td>age, DM, CAD, HTN</td>
</tr>
<tr>
<td>12 (C12)</td>
<td>Socrates</td>
<td>AF</td>
<td>DCCV</td>
<td></td>
<td>1 month</td>
<td>Recurrent</td>
<td>age, DM, CAD, HTN</td>
</tr>
<tr>
<td>13 (C13)</td>
<td>Demelii</td>
<td>AF</td>
<td>DCCV</td>
<td></td>
<td>1 month</td>
<td>Recurrent</td>
<td>age, DM, CAD, HTN</td>
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<tr>
<td>14 (C14)</td>
<td>Socrates</td>
<td>AF</td>
<td>DCCV</td>
<td></td>
<td>1 month</td>
<td>Recurrent</td>
<td>age, DM, CAD, HTN</td>
</tr>
</tbody>
</table>

* Single number represents mean or mean % of entire group and fraction represents mean or mean % in statin / nonstatin group.

AF- Atrial Fibrillation, CAD- Coronary artery disease, DCCV - Direct Current Cardioversion, DM- Diabetes Mellitus, ECG- Electrocardiogram, EF- Ejection Fraction, HF- Heart failure, HTN-Hypertension, ICD- Implantable cardioverter-defibrillator, LAD- Left atrial diameter, MI- Myocardial infarction, NCI- noncardiac illness, NYHA- New York Heart Class, PCI- Prior coronary revascularization, SHD- Structural Heart Disease, SR- Sinus Rhythm, Sx- AF diagnosis by ECG when symptoms occurred, VHD- valvular heart disease.
Hydroxymethylglutaryl Coenzyme A Inhibitors (Statins) and Arrhythmias: Systematic Review and Meta-Analysis

Figure 5
Table 4: Study details and arrhythmia diagnosis- Ventricular tachyarrhythmia

<table>
<thead>
<tr>
<th>Study (Ref No)</th>
<th>Author</th>
<th>VA Diagnosis</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Follow-up</th>
<th>Definition of VA</th>
<th>Adjusted variables</th>
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<td>12 months</td>
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<td>qrs, NYHA, EF, medication, BDI diagnosis</td>
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<tr>
<td>2(20)</td>
<td>1972</td>
<td>Q3 months</td>
<td>NMLR&lt;45%</td>
<td>NYHA III</td>
<td>24 months</td>
<td>Incident</td>
<td>Medication</td>
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<td>3(20)</td>
<td>1973</td>
<td>CAD, IHD</td>
<td>10.4 months</td>
<td>Incident</td>
<td>qrs, EF, medication, medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4(20)</td>
<td>1974</td>
<td>CAD, ICD</td>
<td>DM, EF, IHD</td>
<td>12 months</td>
<td>Incident</td>
<td>-</td>
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<tr>
<td>5(20)</td>
<td>1975</td>
<td>CAD, IHD</td>
<td>NCI, MI</td>
<td>60 days</td>
<td>Restored</td>
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</table>


We did an overall meta-analysis on statins and AF (14 studies; Figure 2) and another meta-analysis on statins and VA (5 studies: Figure 5). We also performed 5 sub-group analysis in the AF studies, [1] 9 studies that included only published manuscripts (excluded 5 abstracts) (Figure 3a) [2] 3 studies that included only randomized studies (Figure 3b). [3] Statins and Incident AF (5 studies; Figure 3a) [4] Statins and postoperative AF (4 studies; Figure 3b) [5] Statins and postcardioversion recurrence of AF (3 studies; Figure 3c).

STATINS AND AF- META-ANALYSIS

Overall there were 3843 patients on statin and 4292 patients not on statin of which 580 and 971 had AF respectively. The pooled risk ratio (RR) using random effects model for AF was RR: 0.73 (95% CI: 0.62-0.86) (Figure 2).

In the sub-group analysis that included only published manuscripts (excluded abstracts), there were a total of 9 studies with 951 patients on statin and 860 patients not on statin of which 158 and 227 had AF respectively. The pooled risk ratio (RR) using random effects model for AF was RR: 0.67 (95% CI: 0.49-0.90) (Figure 3a). In the sub-group analysis that included only randomized studies, there were a total of 3 studies with 176 patients on statin and 174 patients not on statin of which 55 and 84 had AF respectively. The pooled risk ratio (RR) using random effects model for AF was RR: 0.64 (95% CI: 0.37-1.14) (Figure 3b).

Figure 3: Subgroup analysis in Statins and AF based on study quality.
In the subgroup analysis on incident AF (Figure 4a), postoperative AF (Figure 4b) and postcardioversion recurrence of AF (Figure 4c), the pooled RR were: 0.67 (95% CI: 0.54-0.84), 0.63 (95% CI: 0.52-0.76) and 0.76 (95% CI: 0.45-1.27) respectively.

STATINS AND VENTRICULAR TACHYARRHYTHMIA

There were six studies examining the effect of lipid lowering drugs on VA (12-16) of which one was excluded due to inadequate information. Of the remaining five studies, there were 731 patients on statin and 710 patients not on statin, of which 129 and 155 patients had VA respectively. The pooled risk ratio (RR) using random effects model for VA was RR: 0.62 (95% CI: 0.42-0.92) (Figure 5). One study included fibrates in the final analysis (12). Influence analysis omitting that study did not alter the pooled estimate significantly (table 5).
Overall there were 11 studies that revealed positive associations between statins and decreased AF and 3 studies that revealed no association. The mean age distribution of the patients included in the various studies ranged from 60-70 years of age, with one study by Dernellis et al.\textsuperscript{18} having a younger population (mean age 51-57). Most of the studies had a male predominant population, except one study by Tveit et al.\textsuperscript{19}. There were 5 studies that had greater than 1-year follow-up with 1546 patients on statin and 2223 patients not on statin giving an equal distribution of patients with short-term and long-term follow-up. Of these 5 studies, 3 were published as manuscripts and 2 were abstracts. Among the 3 published manuscripts 2 studies showed that statins decrease AF\textsuperscript{20,21}, while 1 study by Amit et al revealed no association between statins and decreased AF\textsuperscript{22}. In this study by Amit et al, there was relatively lower prevalence of CAD, higher incidence of diabetes and relatively low rate of events resulting in loss of statistical power. Also in this observational study patients with intermittent and no statin use were grouped together with unknown proportions and beta-blocker, ACE inhibitor use was not reported. The advantage of the study was that asymptomatic AF was more commonly diagnosed, as this study included only patients with pacemakers and AF was diagnosed by pacemaker interrogation. Young-Xu et al in an observational study on four hundred forty-nine patients with documented CAD showed that statin therapy was associated with a significantly reduced risk of developing AF after adjustment for potential confounders, including age, hypertension, beta-blocker use, left ventricular systolic function, occurrence of heart failure or acute ischemic events, baseline cholesterol and changes in cholesterol levels (adjusted odds ratio 0.37, 95% confidence interval 0.18 to 0.76)\textsuperscript{23}. For all risk factors statin therapy was associated with reduced incidence of AF. Interestingly in women and normocholesterolemic patients, statin therapy was associated with reduced likelihood of AF. But non-statin anti-hyperlipidemic drugs did not have a reduced incidence of AF suggesting that the reduction in AF incidence to be mediated through a different mechanism than cholesterol reduction. Increased duration of statin and regularity in statin use decreased incidence of AF suggesting a dose response to statins as well. Moreover this effect was independent of beta-blocker use. The other positive study by Siu et al was in a small group of patients (n=62; 10 patients on statin) with lone AF that showed a 70% reduction in recurrent AF at a mean follow-up of 44 months\textsuperscript{21}. At 2 years the recurrence rate was 40% for the statin group (10 patients) as opposed to 84% in the non-statin group (p=0.007). In this study the patients in the statin group were older and had higher cholesterol levels. The authors suggested inflammation and subclinical coronary artery disease causing atrial ischemia as possible mechanisms. The benefit of statins were seen in the few months immediately following cardioversion and on an average patients received statin for 32 ± 6 weeks prior to cardioversion. This study was negative in the meta-analysis due to random-effects and pooling of all data. The 2 studies presented as abstracts with greater than 1-year follow-up showed positive associations in patients with hypertension\textsuperscript{23} and heart failure\textsuperscript{24}. In the SCD-HeFT substudy involving 2521 patients with LVEF < 35%, NYHA class II or III, randomized to amiodarone vs. placebo, statin use was reported in 965 patients at baseline and 1187 patients at follow-up\textsuperscript{24}. In this study statin was associated with a 28% relative risk reduction of AF/flutter incidence at a median follow-up of 45.5 months. Statin was as efficacious as amiodarone and more potent than an ACE inhibitor, beta-blocker or spironolactone in reducing the recurrence of AF. In the study on hypertensive patients with successful DC cardioversion (DCCV) by Colivicchi et al,
stain use was associated with a 25% reduction in AF recurrence by propensity analysis (26). Interestingly this result was obtained in patients without coronary artery disease and hence is independent of its effects of reducing coronary ischemia. In this prospective cohort of 851 patients who had successful cardioversion for persistent atrial fibrillation, the recurrence rate of AF at 1 year was 50.6% in patients taking statins (294) as opposed to 58.5% in the non-statin group.

There were 9 studies with less than 1-year follow-up with a range from 1 week to 6 months. Of these, there were 3 post-cardioversion studies (26), 4 postoperative studies (20,27,28,29) and 2 studies on patients with acute coronary syndromes (ACS) (30). Both studies on ACS were subgroup analysis of the MIRACL trial which compared 80mg atorvastatin with placebo in 3086 patients with ACS and looked at short term AF incidence and recurrence at 16 weeks (31). This intensive statin therapy did not prevent new AF and did not clearly promote resolution of AF present during the ACS. There was no correlation between CRP and AF either. This trial showed reduction in recurrent ischemic events and stroke after ACS, but no effect on incident or recurrent AF.

STATINS AND INCIDENT AF

Overall statins showed a decrease in new-onset AF. Three studies were in post-operative patients (20,28,29) and two studies were in patients in CAD (20,30). While all the post-operative studies showed decrease in AF incidence, the two studies in CAD showed differing results. As outlined above the observational study by Young-Xu et al (30) showed decrease AF incidence in long-term follow-up (5 years) and the MIRACL trial (31) showed no benefit in reduction of AF incidence in short-term follow-up (4 months). The only randomized trial by Patti et al showed reduction in new onset AF in 1-month follow-up (30).

STATINS AND POSTOPERATIVE AF

Marin et al studied 234 patients undergoing CABG and had continuous electrocardiogram monitoring for 48 hours post surgery and daily EKG for 1 month (32). The statin pretreatment group had 144 patients and median statin use duration prior to surgery was 31 days (range 10 to 420). 66 patients developed AF post operatively and statin use was significantly associated with decreased postoperative AF. Moreover in a subset of patients with matrix metalloproteinases measurements, higher levels of tissue inhibitor to the metalloproteinases were found in the statin group suggesting a possible mechanism for the protective role of statins. In the SPPAF posthoc analysis, in addition to antiarrhythmics and beta blockers, use of statins reduced postoperative AF significantly (33). Statins were significantly associated with decreased AF after adjusting for age, heart valve surgery, beta-blocker and antiarrhythmic drug use. Postoperative AF, defined as lasting greater than 5 minutes or resulting in significant hemodynamic compromise, was seen in 39.1% of patients and 95% of the episodes were within the first week. In another recent study on 362 consecutive patients undergoing bypass surgery, postoperative AF was shorter and less frequent in the statin group (8.2% vs 16.8%, p=0.03) (33). Follow-up was for 1 week postoperatively. ARMYDA-3 is the only randomized double blinded placebo controlled postoperative trial comparing atorvastatin 40mg and placebo started 7 days before the cardiac surgery (33). Atorvastatin had 61% reduction of postoperative AF at 1 month and reduced CRP levels were associated with decreased incidence of AF. Length of stay was decreased in the statin group as well. In addition, atorvastatin and beta-blockers had a 90% reduction of AF. Only age, hypertension and aortic atherosclerosis were stronger predictors of AF than CRP levels. Total AF duration and mean time to AF episode were similar in both groups.

STATINS AND POSTCARDIOVERSION RECURRENT AF

Of the 2 post cardioversion randomized studies with conflicting results, the study with pravastatin showed no benefit at 6 weeks (19) while the study with atorvastatin significantly reduced AF at 3 months (19). In the pravastatin study, 114 patients with AF scheduled for external cardioversion were randomized to receive 40 mg of pravastatin once daily for 3 weeks before and 6 weeks after cardioversion. There was no reduction in the recurrence rate of AF at 6 weeks. Patients with previous statin therapy were not included. This study showed that short term statin therapy did not affect AF recurrence rate. There was an under representation of coronary artery disease in this population and the duration of statin therapy might have been short. (19). In the other postcardioversion randomized control trial of 48 patients on atorvastatin 10mg/day starting 2 days prior to cardioversion, recurrence of AF was significantly reduced in the statin group (33). Even after adjusting for age, male sex, body mass index, AF duration, diabetes, left atrial diameter, ejection fraction and serum
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cholesterol, the association was significant. Additionally CRP levels were measured and were reduced in the statin group 48 hours post cardioversion. Short lived asymptomatic episodes were not noted and only AF recurrences> 10 minutes were considered significant which could have underestimated the true incidence of atrial fibrillation. Dernellis et al studied the effect of Atorvastatin 20 to 40mg aiming at a target of 20% reduction in C-reactive protein on AF recurrence (43). Patients with symptoms of AF, ECG evidence of PAF, previous persistent AF successfully treated with DCCV and subsequent PAF were included in this study. CRP levels and 48hr ambulatory ECG monitoring were done and follow up was done at 6 weeks, 3 months and 6 months. There was significant improvement in the number of AF episodes in the atorvastatin group compared to the placebo (odds ratio 13.5). Improvement in CRP levels (odds ratio 7.2) was associated with lower AF recurrence. None of the patients in the atorvastatin group had any worsening of AF. Plasma CRP was closely related to clinical manifestations of AF. This study showed that CRP lowering strategy can improve AF over a short period of time and statin is useful in this regard.

STATINS AND VENTRICULAR ARRHYTHMIA

Beneficial effects of statins were seen in ischemic (14,15) and non-ischemic heart disease (16). In heart failure patients the effect of statins was independent of lipid profile and beta-blocker usage (16). Dose response effect was also seen in the study by Vyas et al (14). The two negative studies by Goldberger et al (16) and Riahi et al (17) were limited by lack of statistical power due to the low event rates.

DISCUSSION

The results of this systematic review and meta-analysis indicate that HMG CoA inhibitors (statins) are associated with decreased incidence and recurrence of atrial fibrillation (AF) and ventricular tachyarrhythmia (VA). As with most meta-analysis of observational studies, publication bias against negative studies might cause overestimation of the effect of statins on AF. In our meta-analysis there were 3 studies with a total of 1521 patients on statin (40% of the total patients on statin) and 1704 patients not on statin (40% of the total patients not on statin) that showed no association between statin and decreased AF recurrence. It is apparent that there were a good proportion of the patients in the negative studies. While none of the negative studies reviewed were excluded, there were 5 positive studies with low NOS score (<7) that were excluded. This limits the overestimation effect, although it does not abolish it. In most of the studies included in our meta-analysis, statin decreased AF recurrence independent of age, hypertension, diabetes, CAD, inflammatory markers, hypercholesterolemia, atrial dimension and medications. But potential confounding variables not addressed in the primary analysis will be accentuated in a meta-analysis resulting in significant study heterogeneity, which was present in our study. Therefore inverse-variance weighting was used to calculate random effects summary estimates for each trial and the summary pooled estimate. The pooled estimate using random and fixed effects model were similar. We performed an influence analysis, in which the meta-analysis estimates were computed omitting one study at a time. The random effects estimates were similar after sequential omission of each study, suggesting that none of the study had a dominating effect on pooled estimate (Table 5). Moreover publication bias was assessed using a Begg’s test and it revealed no significant publication bias (figure 6). There is also the issue of confounding by indication that was impractical to control when including observational studies with various indications for statin use. Meta-analysis of only the randomized studies showed a positive trend towards decreased AF recurrence with statins, with comparable risk estimate, but was limited by the fact that there were only 3 randomized studies with a total of 330 patients.

Figure 11
Table 5: Influence Analysis: Studies on long-term atrial fibrillation (AF) and ventricular tachyarrhythmia (VA) with one study omitted at a time
Most of the observational studies that showed a positive association between statins and decreased AF have a male sex predominance and normal left ventricular systolic function. 2 major populations not consistently represented in the various studies were female sex and heart failure patients. There were 2 studies where more than 45% of the patients on statins were female and both these studies showed no beneficial effect in reduction of AF (19, 22). Only 3 studies included patients with documented low ejection fraction (22, 24, 27), whereas most studies excluded patients with heart failure and hence restricting the generalization of these results in heart failure patients. Also the effects of statins seem to have been studied only on post-cardiac surgeries and no data of good quality was available on non-cardiac surgeries. While studies on statins and sudden cardiac death were reviewed, we excluded them from this analysis. Hence all five studies chosen for the statins and VA were from a patient population with implantable cardioverter defibrillators (ICD) and had documented VA as an endpoint. This included both primary and secondary prevention studies in ischemic and non-ischemic heart failure patients. Due to the limited number of studies further subgroup analysis was not attempted.

AF was diagnosed at the time of symptom onset or at scheduled intervals in all studies (except one) and hence the true reduction of asymptomatic paroxysmal AF episodes by statins is unknown leading to ascertainment bias. The one study where pacemaker interrogation was undertaken did not show any reduction in overall AF, but the event rates were low. Hence the utility of statins in altering the underlying pathophysiology of AF is still debatable, although symptomatic AF recurrences are decreased. The diagnosis of VA was not subject to ascertainment bias as they were all ICD recorded events, increasing the strength of the analysis.

Statin use was recorded at enrollment and follow-up and all studies in our review reported statin use for at least one month except one postoperative study by Auer et al reporting 1 week postoperatively with previous duration unknown (26). Large randomized studies have shown that statin therapy improves inflammatory mediators and alters endothelial function as early as 1-2 months (31). This suggests that in most of the studies selected there was adequate duration of statin use for the early effects of statin to occur. Moreover in more than 50% of the patients in overall analysis, there was more than 1 year follow-up on statins and hence by combining both these populations for an overall analysis was a way of performing sensitivity analysis.

Possible biological mechanisms that can mediate the anti-arrhythmic effects of statins include anti-inflammatory, anti-hyperlipidemia and autonomic modulation (Figure 7). There is increasing evidence for the inflammatory etiology for AF and statins have been shown to reduce the levels of inflammatory markers (CRP, Interleukin–6) in 2-4 weeks (31). This is seen in animal studies (33), in our post-cardioversion (18, 25) and post-operative patient population (29). Additionally by inhibition of mevalonate synthesis, statins have endothelial stabilizing function, increasing nitric oxide activity and thereby decreasing coronary ischemia (33). Animal studies also show that statins reduce arrhythmia burden by reduction in coronary ischemia (34). Statins decrease the catecholamine response and normalizes the sympathovagal response in heart failure and improves heart rate variability in as early as 2 weeks (35, 36).
CONCLUSIONS

Our systematic review and meta-analysis suggest that there is evidence that statins decrease the incidence and recurrence of atrial fibrillation and incidence of ventricular tachyarrhythmias. These results are complementary to the current AHA/ACC/ESC guidelines on atrial fibrillation and ventricular tachyarrhythmias and the prevention of sudden cardiac death. J Am Coll Cardiol 2006;48:e247-346.

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