Effects of statin treatment on long-term clinical outcomes in chronic heart failure: a meta-analysis of 15 prospective clinical trials

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Abstract

Purpose
Conflicting results exist now on the clinical utility of statins in CHF patients. The purpose of this study was to conduct a meta-analysis that compared the long-term clinical prognosis of patients with chronic heart failure (CHF) with statin treatment versus no-statin treatment.

Methods
We searched the PubMed, MEDLINE, EMBASE, and Cochrane databases through July 2009. We included prospective clinical studies of subjects who underwent statin therapy or non-statin treatment for established CHF, and provided data on clinical prognosis outcomes with at least 12 months of follow-up. Studies were selected and data were extracted and crosschecked independently by two investigators. Risk ratios (RR) were calculated using a random-effects model.

Results
Fifteen trials involving 45,110 patients with CHF were included in the meta-analysis. The pooling analysis showed that statin treatment was associated with decreased risk of all-cause mortality (RR 0.71; 95% confidence interval [CI], 0.61 to 0.83; p = 0.001), and lower hospitalization rate for heart failure (RR 0.84, 95% CI, 0.74 to 0.96; p = 0.01). However, there were null effects of statin therapy on cardiovascular mortality, pump failure mortality, and sudden cardiac death. Meta-regression demonstrated statistically significant associations between all-cause mortality and study design (p = 0.03), and administration of different statin agents (rosuvastatin, p = 0.03; atorvastatin, p = 0.05), as well as between hospitalization for heart failure and atorvastatin uses (p = 0.04).

Conclusions
Statin administration significantly lowers all-cause mortality, reduces the incidence of hospitalization for heart failure in CHF patients. And different statin agents might share the inconsistent benefits.

Introduction
Despite recent therapeutic advances, clinical prognosis in the growing number of patients with chronic heart failure (CHF) remains poor. There exists an increasing need to define new therapeutic targets to reduce the high mortality and morbidity in this population. Coronary artery disease is a leading cause of heart failure. Hydroxyethylglutaryl-coenzyme A reductase inhibitors (statins), a class of agents for secondary prevention of coronary heart disease, have been shown to reduce adverse cardiovascular events in atherosclerosis related diseases, but their efficacy in patients with CHF remains unknown. Pharmacologically, beyond their lipid-lowering actions, statins have other potentially favorable "pleiotropic" effects, including anti-inflammatory, antithrombotic, antioxidant effects, inhibition of neuronal activation, and prevention of cardiac arrhythmias. Most of these effects can target important components of the complex pathophysiology of heart failure. Base on this hypothesis, concern has been raised about the potential benefits of statin therapy in patients with CHF with other etiologies.

However, uncertainty remains regarding the true benefits afforded by statins treatment in CHF. In an attempt to resolve this issue, we performed a meta-analysis of published prospective trials to examine the effects of statins treatment on long-term clinical outcomes of CHF patients.

Methods
We performed the following literature search to July 21, 2009 using PubMed, MEDLINE, EMBASE, and Cochrane databases. The following complex search formula was used: statin AND (disfunction OR insufficiency OR inadequacy OR failure) AND (heart OR cardiac). The reference lists of studies that met our inclusion criteria were also searched for potential relevant titles. Clinical trials meeting the following criteria were considered eligible for this meta-analysis: (1) prospective and controlled design, (2) CHF patients assigned to statin treatment or control, (3) available data on important clinical outcomes, (4) a minimum follow-up period of 12 months. Two reviewers (S.Z., L.Z.) extracted the data independently.

We pooled treatment effects and calculated risk ratios (RR) with 95% confidence intervals (CI) for all end points in the treatment and control groups by using a random-effects model. Statistical heterogeneity was measured using the I² statistic. To establish the effect of clinical heterogeneity across studies on meta-analysis conclusions, meta-regression analysis was conducted. We quantitatively assessed publication bias using the Beggs adjusted-rank correlation test and Egger regression asymmetry test. Sensitivity analyses were conducted by excluding the studies with intergroup heterogeneity on patient demographics and baseline characteristics, or omitting each trial one at a time from analysis and computing meta-analysis estimates for the remaining studies. For statistical data analysis, Stata software version 8.0 was used. P = 0.05 was set as the level of significance.

Results
Detailed steps are described in Figure 1. Of 15 eligible studies, 6 adopted randomized design, and 9 were prospective cohort studies. The included studies evaluated atorvastatin (n = 3), rosuvastatin (n = 2), simvastatin (n = 1), multiple statins (n = 4) or non-specific statins (n = 5) vs. placebo or standard care. All 15 studies reported all-cause mortality and 11 of them regarded it as primary end point. A total of 45,110 individuals with CHF were analyzed in the meta-analysis: 22,471 of them were treated by statins, and 22,639 were not. The age range between 50 and 73 years and participants were mostly male (65%). Moreover, they had low average LVEF of approximately 34%, and there was a high prevalence of ischemic heart failure in the meta-analysis (66%).

Despite these patients were younger and were mostly male (65%), there was a high prevalence of ischemic heart failure (66%). Nonetheless, they had low average LVEF (34%) of approximately 34%. Therefore, we performed a meta-analysis of published prospective trials to examine the effects of statins treatment on long-term clinical outcomes of CHF patients.

Conclusion
The present study indicates that administration of statins is associated with lower all-cause mortality, and reduced hospitalization rate for worsening heart failure in patients with CHF. These arguments provide a basis to recommend statin therapy in patients with CHF. Our results support the efficacy of current guidelines and may help to improve prevailing practices of insufficient statin therapy in CHF patients.

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Figure 1. Flowchart of selection of studies for inclusion in meta-analysis.

Figure 2. Meta-analysis and pooled risk ratio of all-cause mortality: CI = confidence interval; RR = risk ratio.

Figure 3. Meta-analysis and pooled risk ratio of rehospitalization for worsening heart failure.

Figure 4. Meta-analysis and pooled risk ratio of nonfatal myocardial infarction.

Table 1. Meta-analysis and pooled risk ratio of nonfatal myocardial infarction.

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>p Value</th>
</tr>
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<tbody>
<tr>
<td>Avera-EMD</td>
<td>0.80 (0.66 to 0.97)</td>
<td>0.02; I² = 0%</td>
</tr>
<tr>
<td>CORONAS-CHF</td>
<td>0.77 (0.68 to 0.88)</td>
<td>0.00; I² = 0%</td>
</tr>
<tr>
<td>CREST-CHF</td>
<td>0.87 (0.75 to 1.02)</td>
<td>0.32; I² = 0%</td>
</tr>
<tr>
<td>FAMOUS-CHF</td>
<td>0.80 (0.46 to 0.96)</td>
<td>0.01; I² = 63.7%</td>
</tr>
<tr>
<td>OASIS-5-CHF</td>
<td>0.79 (0.64 to 0.98)</td>
<td>0.07; I² = 0%</td>
</tr>
</tbody>
</table>

Figure 2. Meta-analysis and pooled risk ratio of all-cause mortality: CI = confidence intervals; RR = risk ratios.

Results
Statin therapy was similarly found to have benefit concerning significantly reducing the risk of rehospitalization for worsening heart failure (RR 0.84, 95% CI 0.74 to 0.96, p = 0.01, I² = 83.7%) (Figure 3), and decreasing the incidence of nonfatal myocardial infarction (RR 0.80, 95% CI 0.66 to 0.97, p = 0.02; I² = 0%) (Figure 4). In addition, statin therapy tended to be associated, albeit nonsignificantly, with reduction in pump failure mortality (RR 0.94, 95% CI 0.82 to 1.07, p = 0.32; I² = 0%). With respect to other prognostic variables, pooling the data yielded neutral results (cardiovascular mortality: RR 0.97, p = 0.60; I² = 16.8%; sudden cardiac death: RR 0.98, p = 0.06; I² = 63.9%; nonfatal stroke: RR 0.96, p = 0.82; I² = 36.1%). Egger’s test showed that there was no publication bias existing among the included studies.