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ORIGINAL ARTICLE

Long-term Clinical Outcomes of Statin Use for Chronic Heart Failure: A Meta-analysis of 15 Prospective Studies

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Background The effect of statin treatment on the long-term prognosis in patients with chronic heart failure (CHF) remains uncertain. This study aimed to answer the question by a meta-analysis.

Methods The Cochrane databases, MEDLINE and EMBASE, were systematically searched. The eligibility of prospective studies that assigned CHF patients to receive statin treatment and a control (no statin treatment), had defined prognostic outcomes as primary endpoint, and had a minimal follow-up of 12 months was determined.

Results Fifteen studies involving 45,110 patients were included in the analysis. Additional statin treatment was associated with reduced all-cause mortality (risk ratios [RR] = 0.71, 95% confidence intervals [CI] 0.61–0.83) and reduced rehospitalisation rate for heart failure (RR = 0.84, 95% CI 0.74–0.96). Statin treatment, however, had little impact on pump failure mortality, cardiovascular mortality, and sudden cardiac death. Atorvastatin treatment appeared to facilitate to reduce all-cause mortality (lnRR = 0.61, $p = 0.05$) and rehospitalisation for heart failure (lnRR = 0.44, $p = 0.04$) compared with non-atorvastatin therapy.

Conclusions Based on the available data, statins persistently decreased all-cause mortality and the incidence of rehospitalisation for heart failure in CHF patients, and the benefits might be partially associated with use of specific statin.

Keywords Chronic heart failure • Statin • Long-term • Meta-analysis

Introduction

Mortality and morbidity remain high in patients with chronic heart failure (CHF), despite treatment with contemporary evidence-based pharmacotherapy, such as angiotensin converting enzyme inhibitors, beta blockers, aldosterone antagonists, and angiotensin receptor blockers [1]. Thus, there is a clinical need for further agents that, when added to the best available treatment, will further improve long-term prognosis of CHF patients. Concerns have been raised about the potential benefits of hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins) in patients with CHF of multiple aetiologies [2,3]. Pathophysiologically, statins exert potentially favourable pleiotropic effects beyond lipid-lowering actions and may improve endothelial function, blunt inflammation and neurohormonal activation, and potentiate nitric oxide synthesis, as well as reverse pathologic myocardial remodelling [4–6]. These potential favourable effects would target multiple aspects in the complex pathophysiology of CHF [7]. However, there is emerging evidence both for and against statins exerting beneficial clinical effects in CHF patients.

Although several previous meta-analyses, which aimed to elucidate the efficacy and safety of statin therapy for CHF,

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had demonstrated that additional statin treatment was safe and feasible [8,9], and might improve ejection fraction as well as decrease the serum level of inflammatory factors (e.g. high-sensitivity C-reactive protein, and soluble vascular cell adhesion molecule-1) in patients with CHF [10,11], these agents appeared to have little impact on clinical outcomes of CHF subjects. These conclusions, however, were based on clinical studies that, for the most part, did not designate prognostic outcomes (e.g. mortality or morbidity) as primary or secondary endpoints. Including these studies, consequently, diminishes the ability to make conclusions on statin use in outcomes. Moreover, nearly half of the studies included in these meta-analyses had a follow-up duration of less than six months, further reducing the ability to draw conclusions. As such, uncertainty remains about the long-term efficacy of statin therapy for CHF patients. Accordingly, a meta-analysis of prospective controlled trials was performed to evaluate the true effect of statin therapy on the long-term prognosis of CHF patients.

Materials and Methods

Selection Criteria

Clinical studies that met the following criteria were included in the meta-analysis: (1) studies with a prospective and controlled design, (2) participants with established CHF, regardless of aetiology (ischaemic or non-ischaemic), that received statin and no statin treatment (placebo or guideline-recommended medical therapy), (3) available data including incidence or mortality as well as sample size for analysis, and (4) a minimum follow-up period of 12 months. Retrospective studies and post hoc analysis of randomised controlled trials were excluded from analysis.

Literature Search

We searched MEDLINE, EMBASE, and Cochrane databases (through June 2012) to identify clinical studies pertaining to the use of rosuvastatin, simvastatin, atorvastatin, lovastatin, or pravastatin for treating CHF. Complex search strategies were formulated using the following MESH terms and text words: *statin, heart failure, cardiac dysfunction, cardiac insufficiency, and cardiac inadequacy*. No restrictions were set on year or language of publication. In addition, the reference lists of eligible articles were searched for further relevant studies. All potentially eligible citations were reviewed independently by two investigators (J.W., S.G) using pre-defined selection criteria.

Data Extraction and Quality Assessment

A standardised form was used to extract the data, which included study characteristics, participant characteristics, treatment strategies, and mean follow-up duration. Clinical prognostic endpoints, including all-cause mortality, rehospitalisation for worsening heart failure, nonfatal myocardial infarction, pump failure mortality, cardiovascular mortality, or sudden cardiac death, were also recorded. Any discordance between the reviewers was resolved by discussion. Elements of the STROBE checklist were used to judge quality of prospective cohort studies [12], and the Jadad score (a numerical score between 0 and 5, with 0 being the weakest and 5 designated the strongest) was used as a measure of study design and reporting quality of randomised controlled trials [13].

Statistical Analysis

We used Stata software version 8.0 (Stata Corp., College Station, TX, USA) for meta-analysis and meta-regression analysis. Risk ratios (RR) with 95% confidence intervals (CI) for all outcomes using random-effects models, which provided reassurance for making robust conclusions, were used to present the combined results of the individual studies. Statistical heterogeneity was measured using the I^2 statistic. Meta-regression analysis was conducted to establish the effect of clinical heterogeneity across studies on the conclusions of the meta-analysis. We quantitatively assessed publication bias using the Begg adjusted-rank correlation test [14] and Egger regression asymmetry test [15]. Sensitivity analyses were conducted to examine the robustness of the effect by omitting each trial one at a time from the analysis and computing the overall estimates for the remaining studies. Results were considered statistically significant at $p < 0.05$.

Results

From the initial 2872 citations, 2804 were excluded at the title/abstract level. Reference lists of the remaining 68 articles were reviewed, and one additional relevant study was identified. After full-text reviewing, 54 of the 69 articles were subsequently excluded from the meta-analysis (22 did not include data on clinical outcomes; five did not designate prognostic outcomes as primary or secondary endpoints; 10 were post-hoc analysis of randomised controlled trials; nine were retrospective studies; four lacked control groups; and four had other exclusion reasons). Eventually, 15 controlled studies were included in the analysis [16–30] (Fig. 1).

Table 1 shows the baseline characteristics of the eligible studies. Of them, six adopted randomised design [16–21] and nine were prospective cohort studies [22–30]. The included studies evaluated rosuvastatin ($n = 2$) [16,17], simvastatin ($n = 1$) [18], atorvastatin ($n = 3$) [19–21], multiple statins ($n = 4$) [25,27,29,30] or non-specified statins ($n = 5$) [22–24,26,28] vs. placebo or standard care. A total of 45,110 individuals with CHF were analysed in the meta-analysis: 22,471 patients were treated by statins and 22,639 were not. The mean age of patients in the individual trials ranged from 54 to 73 years. Apart from two studies [25,29] recruiting CHF patients with preserved left ventricular ejection fraction (LVEF), the remaining 13 had the lower LVEFs ranging from 23% to 47%. There was a high prevalence of ischaemic heart failure (66.8%). Clinical events reported by the individual studies were summarised in eTable 1. No adverse effects