Heart, Lung and Circulation (2014) **23,** 970–977
1443-9506/04/$36.00
http://dx.doi.org/10.1016/j.hlc.2014.05.005

ORIGINAL ARTICLE

Effects of Lipophilic Statins for Heart Failure: A Meta-analysis of 13 Randomised Controlled Trials

Gang Liu, MD PhD, Xin-Xin Zheng, MD PhD, Yan-Lu Xu, MD PhD, Jie Lu, MD, Ru-Tai Hui, MD PhD, Xiao-Hong Huang, MD PhD *

Department of Special Medical Treatment Center, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, People's Republic of China

Received 18 February 2014; received in revised form 31 March 2014; accepted 8 May 2014; online published-ahead-of-print 28 May 2014

Background The effects of lipophilic statins in heart failure (HF) were controversial. The goal of the present study was to systematically review all randomised controlled trials evaluating the effects of lipophilic statins in patients with HF.

Methods We performed a comprehensive literature search to identify eligible trials that prospectively randomised patients with HF to lipophilic statins or control. Primary end points were all-cause mortality, cardiovascular mortality, hospitalisation for worsening HF, left ventricular ejection fraction (LVEF), and low-density lipoprotein cholesterol. Risk ratios (RRs) and Weighted mean differences (WMDs) were calculated using fixed-effects models or random-effects models.

Results A total of 13 randomised trials with 1,532 subjects were included in this analysis. Ten trials randomised patients to atorvastatin, two to simvastatin, and one to pitavastatin. Overall, lipophilic statins significantly decreased all-cause mortality (RR 0.53, $P < 0.001$), cardiovascular mortality (RR 0.66, $P = 0.04$), and hospitalisation for worsening HF (RR 0.60, $P < 0.001$). Subgroup analyses showed that the effects of lipophilic statins in HF were not modified by age, baseline LVEF, and cause of HF. In addition, patients randomised to lipophilic statins had a significant increase in LVEF (WMD 3.91%, $P < 0.001$) and decrease in low-density lipoprotein cholesterol (WMD 0.90 mmol/L, $P < 0.001$).

Conclusions It appears that further studies are needed to determine if lipophilic statins are beneficial for HF patients.

Keywords Statins • Lipophilic • Heart failure • Mortality • Meta-analysis

Introduction

Heart failure (HF) is one of the most common diseases and a major public health problem. Although there has been great progress in the treatment of HF with the advent of angiotension-converting enzyme inhibitors, β-blockers, and mineralocorticoid receptor antagonists, it remains a primary cause of morbidity and mortality worldwide and new strategies are needed [1].

The 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins), beyond their lipid-lowing action, are recognised to have various pleiotropic effects, such as anti-inflammatory effects, antioxidant effects, protective effects on endothelial function [2]. These efficacy of statins suggest a potential to ameliorate components of the complex physiopathology of HF [3]. Recently, lipophilic atorvastatin have shown to be beneficial for improvement in mortality, and a benefit regarding improvement in improving left ventricular

*Corresponding author at: 167 Beilishi Road, Beijing, People's Republic of China 100037. Tel.: +0086-10-883961; Fax: +0086-10-81241007,
Email: huangxhong12@gmail.com

ejection fraction (LVEF) and symptoms of HF in a number of randomised clinical trials (RCTs) [4–7]. However, two large-scale RCTs challenge these findings [8,9]. In both of them, rosuvastatin, one hydrophilic statin, did not reduce mortality from cardiovascular causes or from any cause in patients with HF. It remains unclear whether the efficacy of statins in treatment of patients with HF is relevant to the type of statin used. Therefore, we performed a meta-analysis of all prospective RCTs to assess the effects of lipophilic statins, including simvastatin, atorvastatin, and pitavastatin, on mortality, hospitalisation for worsening HF, LVEF, and low-density lipoprotein (LDL) cholesterol in HF patients.

Methods

Search Strategy

According to the Quality of Reporting of Meta-analyses, we systematically searched PubMed (from 1992 to March 2014), Embase (from November 1992 up to 2014) and the Cochrane Library database using the text keywords: *statin(s)* OR *HMG-CoA reductase inhibitors* AND *heart failure* OR *cardiomyopathy* AND *randomized* OR *randomized* OR *randomly* OR *randomization*. The search was restricted to human research studies and no limit was placed on language. We also hand-searched the reference lists of all identified studies and review articles.

Inclusion Criteria

Study selection: Citations were screened at the title/abstract level and full texts were retrieved independently by two reviewers (G.L, X.X.Z), any discrepancies were resolved by consensus. Studies were selected using the following criteria: (1) RCTs in human adults with parallel design; (2) patients with HF (LVEF $\leq$45%) randomised to lipophilic statins or control; and (3) studies reporting primary outcomes of our interests, including all-cause mortality, cardiovascular mortality, and hospitalisation for worsening HF.

Data Extraction and Quality Assessment

All data extraction and quality assessment were done independently by two reviewers (G.L., X.X.Z). Any discrepancies were resolved by consensus. The following data were collected: study characteristics (first author name, year of publication, study design, sample size, type and dosage of statin, duration of follow-up), population characteristics (age, gender, ethnicity, aetiology, LVEF, and LDL cholesterol), and data on primary outcomes including all-cause mortality, cardiovascular mortality, hospitalisation for worsening HF. Study quality was assessed by judging the risk of selection, performance, attrition, and adjudication bias according to the established methods of the Cochrane Collaboration. We also introduced Jadad score to evaluate the quality of the studies and judged Jadad score $\geq$3 as high quality [10].

Statistical Analysis

Our meta-analysis was performed by Reviewer Manager 5.2 (Nordic Cochrane Centre, Copenhagen, Denmark) and STATA 12.0 (STATA Corp. LP, College Station, Texas). A P value <0.05 was set as the level of significance, unless otherwise specified. Weighted mean differences (WMDs) was calculated for continuous variables (LVEF, LDL cholesterol) and Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated dichotomous variables (all-cause and cardiovascular mortality, hospitalisation for worsening HF). Data stratified according to patient age, proportion of ischaemic aetiology, duration of follow-up, and baseline LVEF were analysed to investigate the clinical factors impacting clinical outcomes. The results of pooled analysis were obtained from fixed-effect or random effect model, depending on the heterogeneity. Heterogeneity was measured using Cochran Q and the I^2 statistic: for the Q statistic, a p value <0.1 was considered statistically significant for heterogeneity; while for I^2, a value >50% is considered a significant heterogeneity [11]. Publication bias was assessed by funnel plots and the Egger's regression asymmetry test.

Results

Selected Studies and Baseline Characteristics

We retrieved 2065 citations from database searches. Following title and abstract screening, 2040 were not relevant to the purpose of this meta-analysis and were excluded. Twenty-eight potential relevant articles and full texts were retrieved for detailed evaluation, 15 of which were subsequently excluded. Reasons for exclusion are presented in Fig. 1. Finally, a total of 13 eligible RCTs with 1,532 patents were included [4–7,12–20].

The characteristics of the trials are shown in Table 1. These trials randomised patients to lipophilic statins (two for simvastatin, [12,14] 10 for atorvastatin, [4–7,13,15–19] and one for pitavastatin [20]) with mean follow-up of 15 months. The mean age of enrolled patients ranged from 38 to 72 years and mean LVEF at baseline varied from 24% to 38%. These trials had different proportions in ischaemic aetiology, of which two studies [7,14] enrolled patients with ischaemic aetiology, five with non-ischaemic aetiology, [12,16–19] and remaining six with mixed ischaemic aetiology [4–6,13,15,20]. Eight trials were judged as high quality [4,5,7,12,16,17,19,20] and five were placebo-controlled trials [5,12,13,16,19].

Main Analysis

In our main analysis, all-cause mortality was reported in 13 trials, cardiovascular mortality was reported in 10 trials, and hospitalisation for worsening HF was reported in nine trials. As demonstrated in Fig. 2, lipophilic statins showed a significant decrease in all-cause mortality (RR 0.53, 95% CI 0.38 to 0.73), cardiovascular mortality (RR 0.66, 95% CI 0.44 to 0.99), and hospitalisation for worsening HF (RR 0.60, 95% CI 0.45 to 0.80). No significant heterogeneities were observed in the pooled estimates (I^2 = 0, 42%, 11%, respectively). In addition, as shown in Fig. 3, patients randomised to lipophilic statins demonstrated a significant 3.91% increase in LVEF and 0.90 mmol/L decrease in LDL cholesterol.