Meta-Analysis of the Effect of Statins on Mortality in Patients With Preserved Ejection Fraction

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No therapy has been shown to improve survival rate in heart failure with preserved ejection fraction (HFPEF). Recent observational studies of the association between statin use and the risk of mortality in HFPEF have shown mixed results. The goal of the present study was to systematically review all published observational studies evaluating the effect of statins on the risk of mortality in HFPEF. A literature search in the PubMed and EMBASE databases was undertaken through December of 2013. Combined relative risk (RR) estimates and 95% confidence intervals (CIs) were calculated using the random-effects model. Subgroup analyses, sensitivity analysis, and cumulative meta-analysis were also performed. A total of 11 eligible studies with 17,985 patients with HFPEF were included in the analysis. Statin use was associated with a 40% lower risk of mortality (RR 0.60, 95% CI 0.49 to 0.74, p <0.001). Stratification of studies by controlled or uncontrolled confounding factors affected the final estimate (confounder-controlled RR 0.63, 95% CI 0.51 to 0.77, p <0.001 and confounder-uncontrolled RR 0.49, 95% CI 0.24 to 1.01, p = 0.053). Furthermore, sensitivity analysis confirmed the stability of the results. Cumulative meta-analysis showed an obvious trend of reduction in mortality rates in statin users from 2005 to 2013. In conclusion, our meta-analysis supports the hypothesis that statin therapy may be associated with improved survival rates in patients with HFPEF. Nevertheless, randomized controlled trials are needed to confirm the efficacy of statins in HFPEF. **(Am J Cardiol 2014;113:1198−1204)**

Statins, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, have shown benefit in improving cardiac function and symptoms of heart failure in a number of randomized controlled trials (RCTs).[1−3] However, 2 recent large RCTs (Controlled Rosuvastatin Multinational Trial in Heart Failure and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Heart Failure [GISSI-HF]) demonstrated that statins did not improve mortality in heart failure with reduced ejection fraction (HFREF).[4,5] This finding may not be generalizable to heart failure with preserved ejection fraction (HFPEF). Several observational studies have been conducted to examine the association between statin use and mortality risk in HFPEF and have generated mixed results.[6−16] In the present meta-analysis, we systematically examined statin use in relation to mortality risk in HFPEF. To our knowledge, the RCTs evaluating statins in heart failure have mainly enrolled patients with HFREF. Therefore, we did not find any published RCTs specifically related to this topic.

Methods

The PubMed and EMBASE databases (from inception to December 9, 2013) were searched for eligible studies using the following text keywords and search strategy: "statin(s)" OR "HMG-CoA [3-hydroxy-3-methylglutaryl-coenzyme A] reductase inhibitors" AND "heart failure" AND "normal" OR "preserved" OR "diastolic" OR "non-systolic." The search was limited to human research with no restrictions on origin or language. In addition, a manual search of the list of references of all identified studies and review articles was performed to identify relevant studies.

Studies were considered for inclusion if they fulfilled the following criteria: (1) prospective or retrospective studies assessing the association between statin use and risk of mortality in patients with HFPEF; (2) primary outcome: all-cause mortality; and (3) follow-up $\geq$1 year. Reports were excluded if they were reviews, letters to the editor without original data, editorials, or case reports. Conference abstracts were included if detailed data on mortality were reported.

All data extraction and quality assessment were performed independently by 2 reviewers (GL and X-XZ). Any discrepancies were resolved by consensus. The following information was obtained from each study: (1) the first author's last name, year of publication, and country of the population studied; (2) study design; (3) number of subjects and number of deaths, if applicable; (4) effect estimates and 95% confidence intervals (CIs); and (5) confounding factors for the match or adjustment. We extracted the effect estimates that reflected the greatest degree of control for potential confounders.

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This study was supported by grant 81241007 from the National Natural Science Foundation of China.

See page 1203 for disclosure information.

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0002-9149/14/$ - see front matter
http://dx.doi.org/10.1016/j.amjcard.2013.12.023

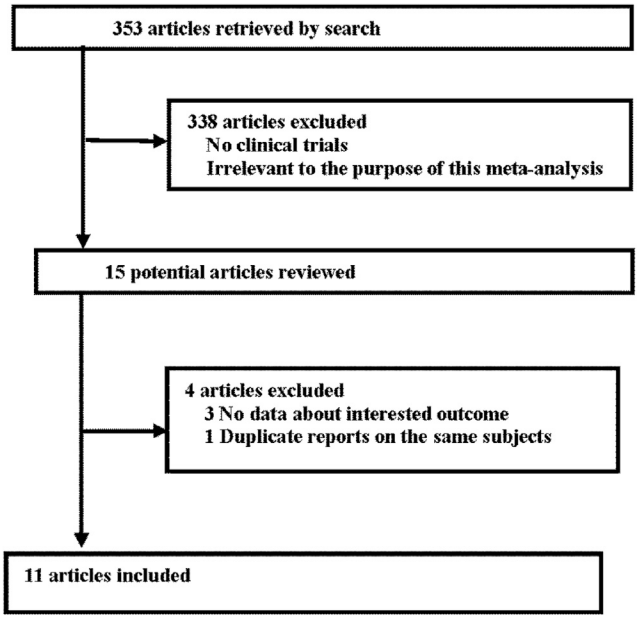

Figure 1. Search strategy and flow chart for studies included in the meta-analysis.

The quality of each study was assessed independently by 2 investigators (GL and X-XZ) using the Newcastle-Ottawa Scale (NOS).[17] The NOS consists of 3 parameters of quality: selection, comparability, and outcome. The NOS assigns a maximum of 4 points for selection, 2 points for comparability, and 3 points for exposure or outcome. Therefore, a score of 9 points indicates the highest quality, 6 to 8 points medium quality, and <6 points low quality. The quality of studies was not assessed if they were presented as conference abstracts. Any discrepancies were resolved by consensus.

Our meta-analysis and statistical analyses were performed by Stata 12.0 (StataCorp LP, College Station, Texas). A p value of <0.05 was considered statistically significant, unless otherwise specified. Publication bias was assessed with funnel plots, the Begg and Mazumdar adjusted rank correlation test, and Egger's regression asymmetry test. Heterogeneity was measured using the Cochran Q and I^2 statistic: for the Q statistic, a p value of <0.1 was considered statistically significant for heterogeneity, and for I^2, a value of >50% was considered significant for heterogeneity.[18] The primary measurement was the pooled relative risk (RR) of mortality from individual studies calculated using the random-effects model (DerSimonian and Laird method), which accounts for heterogeneity among studies. Tests for interaction using summary estimates were performed using the method described by Altman and Bland.[19]

To identify the possible source of heterogeneity within these studies, a priori subgroup analysis was performed. Subgroup analyses were conducted by comparing the summary results of studies grouped by study design, duration of follow-up, study quality, and whether controlling for major confounding factors, including age, gender, lipid levels, and co-morbidities such as hypertension, diabetes, and coronary artery disease (CAD). In addition, we performed a 1-way sensitivity analysis. The scope of this analysis was to evaluate the influence of individual studies by estimating the average RR in the absence of each study. Cumulative meta-analysis was also performed to identify the change in trend of reporting risk over time. In the cumulative meta-analysis, studies were chronologically ordered by publication year, and then the pooled RRs were obtained at the end of each year. The present work was performed in line with the guidelines proposed by the Meta-analysis Of Observational Studies in Epidemiology group.[20]

Results

We retrieved 353 citations from database searches. After title and abstract screening, 338 reports were found not to be relevant to this meta-analysis and were excluded. After detailed evaluation of the remaining 15 full-text reports, 4 were excluded for reasons described in Figure 1. Eleven relevant studies[6–16] were identified, consisting of 5 prospective[6,8,12,15,16] and 6 retrospective studies[7,9–11,13,14] and involving a total of 17,985 patients. The participants were monitored for 1 to 10 years and the studies were published from 2005 to 2013. Of the 11 studies, 7 controlled for major confounders (namely age, gender, lipid levels, hypertension, diabetes, and CAD).[6–8,10–12,14] A negative association between statin use and risk of mortality was reported in 9 studies.[6–8,11–16] Of the 11 studies, 6 were conducted in North America,[6,7,9–11,13] 4 in Europe,[8,12,14,15] and 1 in Asia.[16] Based on the NOS, 3 studies were of high quality, 4 of medium quality, and 2 of low quality. The main characteristics of the selected studies are presented in Table 1.

In our main analysis, because a significant heterogeneity (I^2 = 84%, p <0.001) was observed, a random-effects model was chosen over a fixed-effects model. A pooled analysis of 11 studies found that statin use was associated with a 40% reduction in all-cause mortality (RR 0.60, 95% CI 0.49 to 0.74, p <0.001). The multivariable-adjusted RR or unadjusted RR estimates with 95% CIs of each study and combined RR are shown in Figure 2. In addition, statin use was associated with a reduction in both short-term (<5 years) and long-term (≥5 years) mortality rates in HFPEF (Figure 3).

In the subgroup analyses, as demonstrated in Table 2, the association of statin use with a reduction in mortality rates was not modified by either study design or duration of follow-up. Notably, the pooled RR of the studies that were able to control for confounders depicted a significant negative association compared with studies that did not control for confounding factors. The subgroup of studies showing high and medium quality also demonstrated a significant negative association when compared with low-quality studies. Nevertheless, substantial heterogeneities were observed in most subgroups. In sensitivity analysis, the RRs were similar without great fluctuation, ranging from 0.53 (95% CI 0.39 to 0.72) to 0.65 (95% CI 0.53 to 0.79) by way of omission of the studies by Shah et al[7] and Kaneko et al,[16] respectively (data not shown).

In cumulative meta-analysis, as seen in Figure 4, the precision of the effect estimate was found to increase after adding the fourth study[9] to the first 3,[6–8] and the 95% CI was further narrowed by the inclusion of the 3 additional studies.[10–12] Only after including 7 studies,[6–12] totaling