Editorial

The use of statins in patients with heart failure: more questions than answers

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Abstract: The use of statins to treat patients with heart failure (HF) is controversial due to conflicting results from large, prospective, randomized, placebo-controlled trials and other smaller studies. A recent comprehensive, well-conducted meta-analysis from Preiss and colleagues sought to determine whether statin therapy had an effect on major HF outcomes such as hospitalization and death. Although the study demonstrated a significant effect of statin therapy on HF hospitalizations, several limitations involving the participant data and nature of statin used in the analyzed trials raise questions about the inferences that can be drawn from the study results.

Keywords: Hydroxymethylglutaryl-CoA reductase inhibitors; heart failure (HF); meta-analysis

Submitted Sep 10, 2015. Accepted for publication Sep 20, 2015.
doi: 10.3978/j.issn.2072-1439.2015.10.47
View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2015.10.47

Management of heart failure (HF) remains a significant challenge facing clinicians today despite recent advances in medical and device therapies. Although treatments such as angiotensin-converting enzyme inhibitors, beta-adrenergic antagonists, and implantable cardioverter-defibrillators have significantly improved outcomes for patients suffering from HF, mortality remains high at around 50% after 5 years from initial diagnosis (1). The prevalence and cost of treating HF are also high (2), prompting investigators to search for additional therapies. 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins) serve as a cornerstone in the treatment of hypercholesterolemia. Statins are indicated for the primary and secondary prevention of atherosclerotic cardiovascular events (3), and demonstrably decrease the risk of myocardial infarction (MI) in both settings through lowering low-density lipoprotein cholesterol (LDL-c) (4). Since many cases of HF are consequent to MI (2), statins could potentially prevent the development of HF by decreasing the incidence of MI or through other mechanisms (5). The use of statins in patients with existing HF, however, is disputed.

The controversy surrounding the use of statin therapy for HF patients stems mainly from the results of two large, randomized, prospective, placebo-controlled trials: the CORONA trial (6) and the GISSI-HF trial (7). Both trials examined the effect of rosuvastatin on mortality and morbidity in HF patients. Although treatment was well tolerated, both trials failed to show a significant effect of the statin therapy on the predetermined endpoints, which contrasted with the positive results observed in many smaller randomized and non-randomized trials (8). As a result, the most recent ACC/AHA guideline on treatment of blood cholesterol makes no recommendation on the use of statin therapy in patients with New York Heart Association class II-IV HF (3).

A recent large, well-conducted meta-analysis by Preiss and colleagues (9) sought to determine whether statin therapy had an effect on major HF events through examining comprehensive published and unpublished data from randomized trials. Participant data was drawn from primary, secondary, and mixed prevention trials with a mean follow-up of 4.3 years. Thirteen of the 17 trials selected for overall analysis reported baseline HF amongst study participants, allowing the authors to perform separate analyses for patients with and without symptomatic HF prior to statin therapy. Main findings from the overall

analysis of up to 132,568 pooled participants include a significant reduction in non-fatal MI [risk ratio (RR) 0.74 statin therapy *vs*. control, 95% confidence interval (CI): 0.70-0.78], and a significant but modest reduction in first non-fatal heart failure hospitalizations (HFH) (RR 0.90 statin therapy *vs*. control, 95% CI: 0.84-0.97). The composite outcome of HF death and HFH was also significantly reduced in the statin treated groups (RR 0.92, 95% CI: 0.85-0.99), but was driven exclusively by a reduction in HFH. No significant effect on HF death was observed (RR 0.97, 95% CI: 0.80-1.17) (9).

The finding that statin therapy reduced risk of non-fatal MI is not new, since statins have previously been shown to decrease the risk of such events (4). On the other hand, the observation that statins significantly decreased the incidence of HFH is intriguing. Retrospective analysis of the previously mentioned CORONA trial (6) revealed a similar effect. In their 2014 analysis of CORONA trial data, Rogers and colleagues found that rosuvastatin therapy significantly reduced the number of repeat HF hospitalizations by about 15% compared to placebo (10). Additionally, a 2014 meta-analysis by Wang and coworkers of trials conducted in HF patients found that statin therapy reduced HF rehospitalizations by approximately 16% (11). Preiss and coworker's study adds strength to that signal. Furthermore, their investigation may have underestimated the benefit of statin therapy since it looked at only first non-fatal HFH rather than repeat HF hospitalizations (9).

Another noteworthy finding from the Preiss paper concerns the mechanisms by which statin therapy reduced the risk of HFH. The authors performed meta-regression analyses to determine whether the reduction of HFH was driven by either a reduced risk of non-fatal MI or a decrease in LDL-c. Interestingly, neither of those factors correlated with the risk of HFH. These results raise the possibility that statins might have exerted beneficial effects on HFH through their pleiotropic (i.e., non-LDL-c lowering) properties. Statins are known to improve endothelial function, ameliorate inflammation in the setting of HF, attenuate myocardial remodeling, and reduce cardiac arrhythmias (5,8). Whether these effects are potent enough to improve mortality outcomes in patients with HF is unclear.

Although the results from Preiss and colleagues' meta-analysis suggest that statin therapy does have a beneficial effect on HFH, there are several key limitations that prevent the study from addressing the question of which patients benefit from this effect. The data that were used for the analyses came from primary, secondary, and mixed prevention trials. Thus, the study offers little insight into whether statin therapy is more effective in a primary or secondary prevention setting. A second flaw is that a large number of patients used for the main analyses had unknown baseline HF status. Of the 17 trials used for the main analysis, 13 noted HF status of participants at baseline, providing a pool of around 92,600 participants (90,001 without HF at baseline) to scrutinize. When the authors analyzed data from only the participants without baseline HF symptoms, the results were inconclusive. In this cohort, no statistically significant effect of statin therapy on HFH (RR 0.94, 95% CI: 0.85-1.05), HF death (RR 0.97, 95% CI: 0.69-1.38), or composite outcome (RR 0.94, 95% CI: 0.83-1.06) was detected, due to the decreased number of HF events in the participant pool and resulting loss of power. These analyses complicate the conclusions that can be drawn from the study, since ~42,500 participants—whose data were used in the overall analysis that found a significant effect of statin therapy on HFH in 132,568 participants—had unknown HF status at baseline. Due to this lack of information, it is difficult to determine whether the significant effect of statins on HFH was due to the therapy reducing the onset of new cases of HF, or if statins prevented the worsening of pre-existing cases of HF. Evidence for the utility of statins in the former scenario is readily available, with several studies demonstrating that statin therapy decreases the incidence of HF at follow up in secondary prevention populations (12-14). On the other hand, though numerous small studies have demonstrated a beneficial effect of statin therapy in the setting of HF through improved surrogate endpoints, the negative results of the CORONA and GISSI-HF trials—which, in contrast to the smaller studies, were powered to determine the effects of statins on major outcomes—outweigh the positive results observed in the smaller trials (15). Therefore, if the beneficial effect of statin therapy on HFH described in the Preiss meta-analysis had been driven by a reduction in HFH in patients with HF, it would have represented an important novel finding. Unfortunately, due to the large number of participants with unknown baseline HF status, it is not possible to draw a conclusion on that matter.

A third limitation of the meta-analysis concerns the particular statins used in each of the contributing trials. Recent evidence suggests that there is not a class effect for statin use in the setting of HF due to chemical differences between statin molecules. Statins can be classified based on solubility as either hydrophilic or lipophilic. Lipophilic

statins may be more readily taken up by cardiac muscles, thus leading to greater beneficial effects in the setting of HF (8). Evidence from a meta-analysis of randomized controlled trials of statins in HF showed a significant benefit of atorvastatin—a lipophilic statin—on all-cause mortality, left ventricular ejection fraction, and hospitalization due to HF, whereas similar effects were not observed in patients randomized to the hydrophilic rosuvastatin (16). A 2014 meta-analysis of prospective, randomized controlled trials by Liu and co-workers found a significant effect of lipophilic statins on major outcomes in patients with HF (17). More recently, an adjusted indirect-comparison meta-analysis of randomized trials by Bonsu and colleagues demonstrated a significant beneficial effect of lipophilic statins on left ventricular ejection fraction and plasma concentrations of multiple biomarkers including brain natriuretic peptide, high-sensitivity C-reactive protein, and interleukin 6 (18). In the Preiss meta-analysis, 8 of the 21 trials included used hydrophilic statins. The diversity of statins utilized in the trials may have introduced an undesirable confounding variable into the analyses. Further analysis on the impact of lipophilic statins in this study may have helped clarify whether lipophilic statins have greater efficacy in reducing HF-related outcomes and dispel the notion of a class effect for statins.

While the work of Preiss *et al.* demonstrated a significant beneficial effect of statin therapy on HFH, it also raised numerous questions regarding the types of patients that would benefit from the treatment. The study did not focus on the use of statins in patients with existing HF. Indeed, several of the trials that supplied data for the meta-analysis did not even report baseline HF status. Thus, the reduction in HFH resulting from statin therapy as demonstrated by the study does not constitute a sufficient rebuttal to the results from the CORONA and GISSI-HF trials. Furthermore, when the authors focused on patients without existing HF at baseline, the effect of statin therapy on HF outcomes was inconclusive. It seems that the meta-analysis, which intended to answer whether statins had an effect on major HF outcomes, instead only raised more questions.

Acknowledgements

None.

Footnote

Provenance: This is a Guest Editorial commissioned by the Section Editor Yue Liu (Department of Cardiology, the First Affiliated Hospital of Harbin Medical University, Harbin, China).
Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Westman PC, Lipinski MJ. The use of statins in patients with heart failure: more questions than answers. J Thorac Dis 2015;7(10):1687-1690. doi: 10.3978/j.issn.2072-1439.2015.10.47