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The effect of statins on mortality in heart failure with preserved ejection fraction: a meta-analysis of propensity score analyses

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ABSTRACT

Background: Nearly half of patients with heart failure (HF) have preserved ejection fraction (EF) and the mortality and morbidity of patients with HF with preserved EF (HFpEF) are high. However, no pharmacological therapy has been shown to improve survival in HFpEF patients. Previous retrospective and prospective observational studies have examined the prognostic impact of hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins) in patients with HFpEF. However, the results are inconsistent due to limited power with small sample sizes and/or lack of adjustment for known prognostic factors and differences in baseline characteristics between patients treated with and without statins.

Methods: We aimed to conduct a meta-analysis of prospective observational studies examining the effect of statin therapy on mortality in HFpEF patients with the use of propensity score analysis.

Results: A total of 4 studies with 5,536 patients (2,768 patients [50%] on statins; mean age, 65-77 years; male, 43-66%; coronary artery disease, 42-64%; hypertension, 61-82%; diabetes, 20-29%; follow-up duration, 12-36 months) were included in this meta-analysis. The pooled analysis showed that statin therapy was associated with reduced mortality (odds ratio [95% CI] = 0.690 [0.493-0.965], P = 0.030).

Conclusion: Our meta-analysis suggests the potential mortality benefit of statins in HFpEF. Further prospective observational studies and randomized controlled trials should be planned to confirm our observed potential survival benefit of statins in HFpEF.

1. Introduction

Nearly half of patients with heart failure (HF) in the community have preserved ejection fraction (EF) and the mortality and morbidity of patients with HF with preserved EF (HFpEF) are high [1–3]. However, no pharmacological therapy has been shown to improve survival in HFpEF [4–7].

Studies have shown that hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins), besides the lipid-lowering effect, have beneficial effects on left ventricular fibrosis and hypertrophy [8–11], endothelial dysfunction [12,13], arterial stiffness [14,15], and inflammation [12,16], all of which contribute to the pathophysiology of HFpEF [17,18]. Although there is no published randomized controlled trial (RCT) examining the effect of statins on clinical outcomes in HFpEF, the effect on mortality in HFpEF has been reported in prospective and retrospective observational studies [19–25]. However, the results are inconsistent due to several reasons, including limited power with small sample sizes and lack of adjustment for potential confounders. One recent meta-analysis of observational studies by Lie et al showed the mortality benefit of statins in HFpEF patients [26]. The meta-analysis, however, has several major limitations. First, although the meta-analysis included 11stuides with 17,985 HFpEF patients, almost 80% of the patients were derived from retrospective studies [21–24]. Second, the meta-analysis included studies that did not adjust known prognostic factors or differences in baseline clinical characteristics between patients treated with and without statins [23,25]. Finally, the meta-analysis included 2 studies from conference abstracts.

Although lack of randomization and differences in baseline characteristics between treatment groups are the primary reason for distrusting non-RCTs, one promising technique for correcting the bias inherent in non-RCTs is propensity score (PS) analysis in which the measured known prognostic factors are balanced between groups [27,28]. Although the meta-analysis of Lie et al included small studies using PS analysis [19,20], several large prospective studies examining the prognostic impact of statins in HFpEF with the use of PS analysis have been published after the meta-analysis was performed [29,30]. Accordingly, we aimed to conduct a meta-analysis of PS analyses on the effect of statins on mortality in HFpEF.

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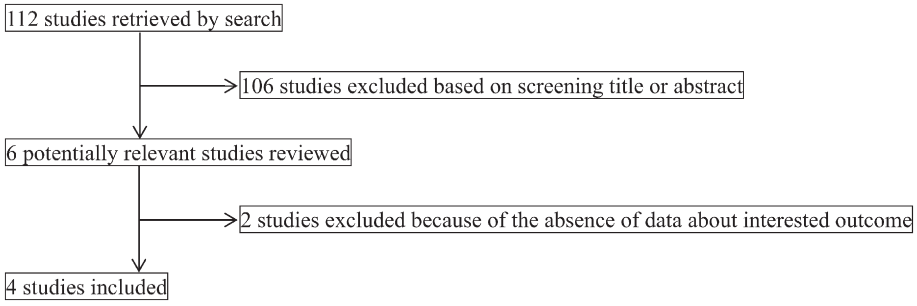

Fig. 1. Selection process for studies included in meta-analysis.

2. Methods

This meta-analysis was conducted in accordance with the PRISMA statement for systematic review [31].

Studies on the effect of statins on mortality in patients with HFpEF (or diastolic HF) published until Sep 31, 2015 were independently identified by 2 authors (TG and KW) using PubMed and EMBASE databases. For search of the eligible studies, the following key words and Medical Subject Heading were used: *diastolic heart failure*, *heart failure with normal ejection fraction*, *heart failure with preserved ejection fraction*, *hydroxymethylglutaryl-coenzyme A reductase inhibitor*(*s*), *and statin*(*s*). Clinical outcome of interest was all-cause mortality. Studies were considered eligible if they; [1] included HFpEF patients; [2] were a prospective study; and [3] examined the effect of statins on mortality with the use of PS analysis. Additionally, a manual search of the list of references of all identified studies and review articles was performed for additional relevant studies.

For each outcome, odds ratio (OR) with 95% confidence interval (CI) was calculated. For each outcome, heterogeneity was assessed using the Cochran's Q and I [2] statistic; for the Cochran's Q and I [2] statistic, a P value of <0.1 and I [2] $>50\%$, were considered significant, respectively [32]. Publication bias was assessed graphically using a funnel plot and mathematically using Egger test. For all analyses, Comprehensive Meta Analysis Software version 2 (Biostat, Englewood, NJ, USA) was used.

3. Results

The study identification and selection process is summarized in Fig. 1. Four studies with PS-matched 5,536 patients were included in this meta-analysis.

Characteristics of 4 studies are summarized in Table 1. Two studies were conducted in Europe, one in the USA, and one in Japan. The follow-up duration ranged from 12-36 months. Prescribed statins were reported in 2 studies and lipophilic statins (atorvastatin and simvastatin) were more frequently used compared with hydrophilic statins (pravastatin).

Baseline characteristics of PS-matched populations are summarized in Table 2. Coronary artery disease (CAD) was common and ranged from 42-64%. Hypertension and diabetes were also common and ranged from 61-82% and from 20-29%, respectively. Many patients were taking anti-hypertensive agents such as angiotensin converting enzyme inhibitors or angiotensin receptor blockers ranging from 63-75% and beta blockers ranging from 44-79%. Low-density lipoprotein (LDL) cholesterol levels were reported in 2 studies and LDL cholesterol levels were similar between patients treated with and without statins.

The effect of statins on mortality in HFpEF is shown in Fig. 2. Because of the significant heterogeneity (Q statistic $= 6.795$, $P = 0.079$, $I^2 = 55.9\%$), a random-effect model was chosen. Statin therapy was associated with improved survival (OR [95% CI] $= 0.690$ [0.493-0.965], $P = 0.030$).

Table 1
Study characteristics.

Study	Follow-Up Duration	Study Location	Outcome	Used Statin	Entry EF	General Population	PS-matched Population
						Proportion of Statin Treatment Cases (Number)	Proportion of Statin Treatment Cases (Number)
Fukuta et al., 2005 [19]	21 months (mean)	USA	All-cause mortality, Cardiovascular hospitalization	Atorvastatin, 68% Simvastatin, 21% Pravastatin, 10%	≥0.50	50% (68/137)	50% (42/84)
Roik et al., 2008 [20]	12 months	Poland	All-cause mortality, Cardiovascular hospitalization	Simvastatin, 73% Atorvastatin, 25% Lovastatin, 2%	≥0.45	71% (103/146)	50% (36/72)
Nochioka et al., 2015 [29]	36 months (median)	Japan	All-cause mortality, Hospitalization for worsening heart failure	NR	≥0.50	37% (1163/3124)	50% (625/1250)
Alehagen et al., 2015 [30]	23 months (median)	Sweden	All-cause mortality, All-cause mortality or cardiovascular hospitalization	NR	≥0.50	38% (3427/9140)	50% (2074/4148)

EF indicates ejection fraction; NR, not reported; PS, propensity score.