

Statins and Heart Failure

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INTRODUCTION

Heart failure (HF) is a major public health concern owing to its prognostic impact and high mortality rate. In developed countries, prevalence reaches 1-2% of the adult population, rising to over 10% in those over 70 years of age^[1]. In Spain, the prevalence of HF is around 5%, and was the leading cause of death in 3% of men and 10% of women in 2010^[2]. Furthermore, annual mortality in HF patients has been estimated to be almost 16 times higher in men and 15 times higher in women compared to those without HF^[3]. While HF mortality has fallen slightly in recent years it remains very high despite available therapies^[4]. In addition, HF is a major cause of hospital admissions, being the leading cause of hospitalization in patients over 65 years of age and currently accounting for 3% of all hospital admissions^[2].

Hypercholesterolemia is very common in patients with HF. In the CARDIOPRES study conducted in patients with chronic HF managed in primary care, approximately 60% had hypercholesterolemia^[5]. In the EPISERVE study which included outpatient HF patients treated by specialists in cardiology, internal medicine and family medicine, 50% had hypercholesterolemia. Interestingly, that study found that while only 20% of patients met the therapeutic goals, hypercholesterolemia was independently related to the adequacy of treatment^[6]. In the MERICAP study on hypertensive women \geq 65 years treated in primary care, 71% with unrecognized HF had dyslipidemia versus to 60% of those without HF^[7].

Statins proved to reduce cardiovascular morbidity and mortality in primary and secondary prevention studies^[8-11], and represent the main pharmacologic tool in cardiovascular prevention^[12,13]. Findings of the different prospective meta-analyses of individual data of the Cholesterol Treatment Trialists (CTT) collaboration clarified the role

ABSTRACT

Heart failure (HF) is a major public health issue owing to its prognostic impact and high mortality rate. In the developed countries, the prevalence reaches 1-2% of the adult population, rising to over 10% in those over 70 years of age. 50-70% of patients with HF have hypercholesterolemia, and many do not achieve the therapeutic goals recommended by clinical practice guidelines. Although statin therapy has proved to have many cardiovascular benefits, patients with HF have been systematically excluded from clinical trials; thus, the use of statins in these patients remains controversial. Specifically in HF patients, two large studies with rosuvastatin (CORONA and GISSI-HF) and one with pitavastatin (PEARL) were conducted; no differences in mortality were observed, although pitavastatin therapy appeared to exert a beneficial effect in patients with left ventricular ejection fraction $>$ 30%. The aim of this review was to provide an update on the role of statin therapy in the pathophysiology of HF and present the existing clinical trial data for statin use in HF.

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of statin therapy in the prevention of cardiovascular events and have showed that the benefits of statin therapy outweighed any known risks. Nonetheless, the issue is less clear in HF patients since this specific population has been systematically excluded from most large cardiovascular outcome studies on statins. Furthermore, subsequent clinical data examining the effect of statins in HF were limited by several factors: the cross-sectional design in some cases, sample size, inclusion of patients with diverse ejection fractions and different HF etiologies, limited clinical follow-up and different doses and types of statin^[14-16]. The purpose of this review was to provide an update on the role of statin therapy in the pathophysiology of HF and present the existing clinical trial data for statin use in HF.

STATIN THERAPY AND HF PATHOPHYSIOLOGY

Evidence from both preclinical and clinical research supports the view that statins have a variety of antiatherogenic and cardioprotective effects that go beyond their impact on lipid metabolism. These effects, which are largely mediated by the drugs' ability to block the synthesis of isoprenoid intermediates, have provided new insights into their therapeutic use. In this respect, experimental studies have shown that statins impede major causal factors in the development of HF, thereby determining a reduction in inflammation and improvement in endothelial function^[17]. Statins have been shown to block the development of cardiac hypertrophy via Rho and Ras, inhibit the activation of metalloproteases, exert antifibrotic and anti-apoptotic effects, inhibit the induction of hypertrophy resulting from angiotensin II and promote the mobilization of progenitor cells, inducing angiogenesis^[18]. Furthermore, statins increase endothelial nitric oxide (NO) production by stimulating and up-regulating endothelial NO synthase (eNOS) and restore eNOS activity in the presence of hypoxia and oxidized LDL, conditions which lead to endothelial dysfunction. Thus, if the ability of statins to increase the bioavailability of nitric oxide is added to these effects, they may also be expected to exert beneficial effects in the context of HF^[19] (Figure 1).

On the other hand, three hypotheses for possible harmful effects of statin therapy may explain the negative effects observed in some studies: first, the endotoxin-lipoprotein hypothesis, linking elevated cholesterol levels by regulating the inflammatory state characteristic of HF^[20]; second, the ubiquinol hypothesis, which relates inhibiting ubiquinone synthesis statins produced by a reduction in cellular energy production that can affect ventricular function and promote the development of myopathy and myalgias^[21]; and finally, the selenoprotein hypothesis, which relates selenoprotein deficiency to myopathy, may also affect the myocardium and worsen ventricular function^[22]. These possible side effects have to be balanced with the results obtained in clinical trials discussed below.

STATIN THERAPY IN CHRONIC HF: CLINICAL EVIDENCE

For primary HF prevention, epidemiologic studies suggest that statins may prevent the onset of HF in dyslipidemic patients without established cardiovascular disease^[23]. For secondary prevention, several clinical trials have shown that statin therapy after acute coronary syndrome prevents the development of HF and is associated with better prognosis^[24-27]. Before 2007, several randomized clinical trials on the use of statins in HF to reduce overall mortality and cardiovascular disease had appeared, with discordant results, since the type and number of patients and the types of statin used and outcomes were highly heterogeneous. In most of those studies, an

increase in left ventricular ejection fraction (LVEF) and clinical improvement assessed in different ways were demonstrated (New York Heart Association [NYHA] class, BNP, 6-minute walking test, ...) ^[14-16], although none included more than 110 patients. Given the heterogeneity of the results obtained, two trials with more than 4,500 patients were designed to evaluate the effects of rosuvastatin in chronic HF^[28,29]. The CORONA study was conducted in patients with symptomatic ischemic HF and an LVEF \leq 40% without statin treatment in whom rosuvastatin was administered. After 3 years of follow-up, no reduction in total mortality from any cause was detected, although the number of hospitalizations due to HF was lower^[28]. CORONA patients had an average age of 72 years with a moderate to severe degree of HF; thus, the already advanced HF stage could explain these "negative" findings.

The GISSI-HF^[29] was the second large-scale randomized clinical trial on almost 5,000 patients with symptomatic HF regardless of etiology and LVEF \leq 40% or $>$ 40% if HF had occurred in the previous year without pretreatment with statins. As in the CORONA study, rosuvastatin was administered and, after 5 years of follow-up, no beneficial effects on overall mortality, total and cardiovascular hospitalizations were observed. Neither was a clinical improvement observed in chronic HF. Additionally, no benefit was observed in the 10% of patients found to have a relatively preserved LVEF ($>$ 0.40)^[30]. However, the number of patients with LVEF $>$ 0.50 was insufficient to assess the effect in HF patients with preserved EF. It should be emphasized that both trials demonstrated that statins were safe in HF. A combined analysis of patients included in these two trials showed that, in patients with ischemic HF, rosuvastatin reduced the risk of new myocardial infarction episodes (hazard ratio: 0.81, 95% CI from 0.66 to 0.99, $p <$ 0.05), although there remained no differences in the mortality rate^[31].

Finally, the results of the PEARL study^[32], which evaluated the efficacy of pitavastatin in 574 patients with chronic HF functional class II-III NYHA not previously treated with statins and followed for 35 months, were reported in 2013. In the whole group no differences in primary outcome (HR: 0.922, 95% CI: 0.632-1.345, $p=0.672$), a composite of hospitalization and clinical symptoms including dyspnea, shortness of breath and peripheral edema, were observed, together with LV dysfunction by echocardiography according to the American Heart Association/American College of Cardiology guidelines. However, when only patients with LVFE \geq 30%, which involved 72% of the sample was analyzed, a 48% risk reduction for the primary outcome in patients treated with pitavastatin (HR: 0.525, 95% CI: 0.308-0.896, $p=0.018$) was found; data were not previously

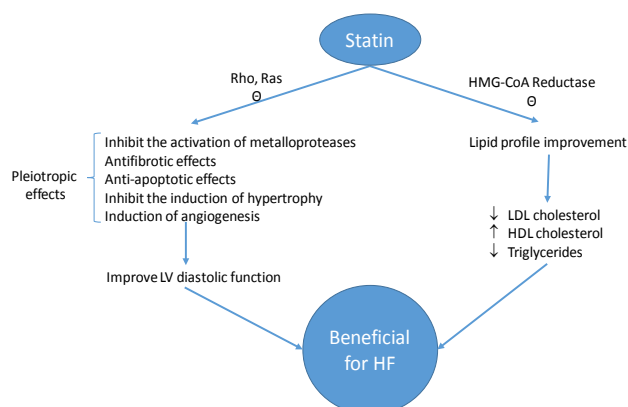


Figure 1 Potential cardioprotective effects of statins on heart failure. LDL: low-density lipoprotein; HDL: high-density lipoprotein; LV: left ventricular.

demonstrated. The main differences between that study and the two discussed previously (Table 1) were the mean age of patients, 63 years versus 73 and 68 in the CORONA and GISSI-HF studies, respectively, the percentage of patients with NYHA class II, which was much higher in the PEARL study, which was conducted entirely in Japanese individuals, who are known to exhibit a superior response to statins probably genetic-based, so that the differences observed are not directly extrapolable to other ethnic groups. However, the main contribution of PEARL is the demonstration that pitavastatin treatment in early stages of chronic HF can have a beneficial effect on cardiac mortality and hospitalization for HF. Recent observational studies support this fact, especially with the reduced mortality due to sudden death (HR: 0.59; 95% CI: 0.36 to 0.98, $p=0.041$), infection and death (HR: 0.53; 95% CI: 0.35 to 0.77, $p=0.001$) only in patients with a preserved EF^[33]. This study showed that statin therapy improved survival in patients with chronic HF, even in those without high cholesterol, but to a lesser degree. Another study based on the Swedish Heart Failure Registry that analyzed 21,864 patients with HF and depressed EF found a lower one-year mortality in patients who continued statin therapy (HR: 0.81; 95% CI: 0.76 to 0.86; $p<0.001$), especially those with HF of ischemic etiology^[34]. It is noteworthy that, in this study, the percentage of patients with atrial fibrillation was higher than in the CORONA and GISSI studies (45% vs 19 and 24%, respectively).

However, some meta-analyses have shown the use of statins in patients with HF to be associated with reductions in mortality and re-hospitalization for HF^[35,36]. These differences could be explained at least in part by two factors. Firstly, not all statins have the same effect in HF patients, and not all patients with HF are the same. The benefit of statins appears greater in patients with less advanced HF (lower levels of natriuretic peptides)^[35-37] and preserved ejection fraction^[38]. This implies that when therapy is started earlier in patients with HF and hypercholesterolemia, the benefit will be greater^[39]. In addition, some studies have also shown that statins partially reduce inflammatory markers of HF^[40] and may improve cardiac function, ventricular remodeling and symptoms^[41,42]. In this respect, simvastatin was able to prevent diastolic dysfunction in an experimental model of hypercholesterolemia regardless of its lipid-lowering effect. This beneficial effect was, at least partially, due to a decrease in myocardial fibrosis and angiogenesis^[43].

CONCLUSION

A high percentage of HF patients present alterations in their lipid profile, and many fail to achieve the therapeutic goals recommended by clinical practice guidelines. Studies with rosuvastatin in these patients showed no significant differences in terms of mortality rates or cardiovascular events; however, pitavastatin in the early stages of the disease appears to improve HF symptoms. Further controlled trials in the early stages of the disease are required to confirm these findings in other ethnic groups and clarify the mechanisms leading to this improvement.

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CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

Table 1 Clinical characteristics of patients included in CORONA^[26], GISSI-HF^[27] and PEARL^[30] studies.

	CORONA	GISSI-HF	PEARL
N	2,514	2,285	288
Age, mean \pm SD	73 \pm 7.1	68 \pm 11	62.9 \pm 11.7
Female, %	24	23.8	19.1
NYHA functional class, %			
II	37	61.2	88.9
III	61	36.2	11.1
IV	1.4	2.6	
LVEF, %	31	33.4	33.9
Systolic BP (mm Hg \pm SD)	129 \pm 17	127 \pm 18	120.3 \pm 18
Diastolic BP (mm Hg \pm SD)	76 \pm 8.8	77 \pm 10	72.4 \pm 11
Heart failure cause (%)			
Ischemic	100	40.2	26.7
Dilatative	0	34.2	55.9
Hypertensive	0	18.1	3.5
Other	0	7.5	13.9
Cholesterol (mmol/L \pm SD)			
Total	5.36 \pm 1.11	NA	5.25 \pm 0.83
Low-density lipoprotein	3.54 \pm 0.95	3.16	3.23 \pm 0.72
High-density lipoprotein	1.24 \pm 0.36	NA	1.31 \pm 0.37
Triglycerides (mmol/L \pm SD)	2.01 \pm 1.33	NA	NA
Death from any cause	0.95 (0.86-1.05)	1.00 (0.898-1.122)	0.73 (0.441-1.198)
Death or hospitalization	NA	1.01 (0.908-1.112)	0.922 (0.632-1.345)
Cardiovascular death	0.97 (0.87-1.09)	0.96 (1.85-1.09)	1.097 (0.611-1.969)

LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; BP: blood pressure; SD: standard deviation; NA: not available.

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