Review

Statins in the treatment of chronic heart failure: Biological and clinical considerations

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Abstract

Patients with increased cholesterol levels are at increased risk to experience cardiovascular events and to die from vascular disease. Statins have been proven to effectively reduce cholesterol levels and subsequently reduce cardiovascular events in patients with coronary artery disease or at increased risk to develop coronary artery disease. However, in patients with chronic heart failure (CHF), not high, but low levels of cholesterol are related to increased mortality. This phenomenon of reverse epidemiology is not unique to CHF, but also exists in other critical diseases and in the elderly in general as well. An important rationale has been provided by the endotoxin hypothesis, which suggests that cholesterol has an important scavenger function regarding harmful endotoxins. Indeed, these lines of evidence predict a harmful effect of statin treatment in patients with CHF. However, statins not only lower cholesterol, but also have been reported to exhibit a plethora of pleiotropic effects, including reduction of inflammation and improvement of endothelial function. In order to reconcile these contradictory lines of evidence, it is necessary to examine the pharmacological mechanisms of effects of statin treatment. Understanding the pharmacology of statin intervention in CHF models and patients may facilitate the development of therapeutic strategies. In this review, we provide an overview of the known associations between serum cholesterol and CHF in human subjects. In addition, we review the available lines of evidence in animal models and humans predicting both harmful and beneficial effects of statin treatment in CHF. We emphasize the importance of additional research specifically in CHF models and patients.

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The efficacy of 3-hydroxy-3-methylglutaryl co-enzyme-A inhibitors, or statins, in reducing morbidity and mortality in patients with documented coronary artery disease (CAD) or those at increased risk of CAD has been overwhelmingly and indisputably demonstrated [1–15]. The result is that statin therapy is the treatment of choice in the primary and secondary prevention of cardiovascular disease for almost every suitable patient. But what if statin treatment has not been initiated? Is it still beneficial to begin statin treatment in end stage CAD that has resulted in chronic heart failure (CHF)? Or might we do more harm than good? Evidence for statin treatment in patients with established chronic heart failure (CHF) has not been well established and remains a subject of debate [16,17]. CHF patients have been systematically excluded from large clinical statin trials. Although a few smaller, uncontrolled trials do provide some evidence for the use of statins in CHF, there is some reason to think that statins may have harmful effects in patients with CHF. For example, recent data suggests that high cholesterol levels are beneficial in a state of CHF, even when CAD coexists. In this article, the potentially harmful and beneficial
effects of statins in CHF patients will be reviewed, both from a pathophysiological and a clinical perspective.

1. Cholesterol in CHF

Hypercholesterolemia is a well-known risk factor for the development of CAD and long-term morbidity and mortality, at least in middle-aged persons. However, controversial associations have been found in elderly patients and in patients with a wide range of chronic and acute diseases [18–24]. It seems that with advancing age or in critically diseased patients, the traditional association between elevated cholesterol and increased morbidity and mortality no longer applies. In fact, serum cholesterol levels are inversely correlated with in-hospital mortality in patients with infectious diseases [18,19] as well as acutely ill patients [20], regardless of malnutrition, frailty, inflammation, and comorbidity. In the Framingham study, dyslipidemia initially appeared to be a risk factor for the development of CHF [25]. However, subsequent studies have challenged this finding [26–28]. Importantly, in a more detailed analysis of the same Framingham database, the association between total cholesterol and all-cause mortality was positive at 40 years of age, negligible at 50–70 years, and negative at age 80 years and above [29]. Since both the incidence and prevalence of CHF is increasing steeply with age, the accepted association between cholesterol and CHF might change [30]. Several observational studies have addressed the relationship between serum cholesterol levels and outcome, specifically in CHF patients. In 1998, Vredevoe et al., were the first to report that lower total cholesterol was significantly associated with increased mortality in patients with advanced, idiopathic CHF [31]. This observation has been confirmed in other studies, indicating that both in ischemic and non-ischemic CHF, higher cholesterol levels are associated with decreased mortality [32–37]. Based on Receiver Operating Characteristic (ROC) curves analysis, the best cut-off level for total cholesterol in predicting mortality in CHF patients is estimated to be around 4.9–5.2 mmol/L (190–200 mg/dL) [32,35]. Mortality increased 25% for each mmol/L decrease in total cholesterol.

This phenomenon of ‘reverse epidemiology’ in CHF has not only been observed for serum cholesterol levels, but also for body mass index and blood pressure [38]. Nevertheless, previously mentioned studies were observational and do not prove causality. Low cholesterol could merely be a consequence of advanced CHF, without a causal role, or high cholesterol could be an indicator of a greater metabolic reserve to deal with the disease [39,40]. Although several studies corrected for general health indicators, like nutritional status, and cachexia, it remains possible that low cholesterol carries a poor prognosis because it is a marker of poor health or a consequence of CHF. Consequently, the association with mortality could be a consequence of inadequate adjustment for other confounding factors. Alternatively, lower mortality among patients with elevated cholesterol could be a consequence of a selection bias. Patients surviving elevated cholesterol could represent a selected subgroup with advantageous genetic or other characteristics that protect them from the harmful effects of high cholesterol. Finally, lower cholesterol might just mark an end-stage disease epiphenomenon, due to reduced hepatic cholesterol synthetic capacity. Any of the aforementioned possibilities do not exclude the possibility that cholesterol may, even in a state of CHF, still be a pro-atherogenetic factor. Further research into the mechanism to explain the inverse associations remains obligatory. Since it has not been established whether low cholesterol is causally involved or is simply a marker, interventions aimed at lowering cholesterol will remain controversial. However, such an association between increased mortality and lipid lowering therapy has as yet not been demonstrated. Although high cholesterol seems advantageous in elderly patients, treatment with statins does not necessarily cause harm in these patients [8,10]. These seemingly contradictory findings might thus be explained by a difference in intrinsically low cholesterol levels as compared to pharmacologically induced low cholesterol levels.

2. Potentially harmful effects of statin treatment in CHF

Potentially harmful effects of statins in CHF are not far-fetched. In addition to the observed inverse relationship between cholesterol and survival in CHF, there are other lines of evidence suggesting adverse effects of statins. Most noteworthy are the endotoxin–lipoprotein hypothesis, the coenzyme Q10 (ubiquinone) hypothesis, and the selenoprotein hypothesis.

2.1. Endotoxin lipoprotein hypothesis

Rauchhaus et al. were the first to propose that higher levels of cholesterol are beneficial in CHF on the basis of the ability of serum lipoproteins to modulate the inflammatory immune function [41]. CHF patients have increased serum cytokine levels, which might be linked to increased endotoxin levels [42]. Circulating cholesterol- and triglyceride rich lipoproteins are natural nonspecific buffers of endotoxins (Fig. 1). They have the capacity to bind and detoxify bacterial lipopolysaccharides (LPS). LPS are very strong stimulators of the release of inflammatory cytokines from circulating immune competent cells and LPS are an important stimulus of proinflammatory cardio-depressive cytokine production in CHF. For example, LDL receptor deficient mice, with consequently very high plasma cholesterol concentrations are protected against lethal endotoxaemia and severe gram-negative infections [43]. Edematous and severely affected CHF patients show substantial immune activation in parallel with raised LPS plasma concentrations, comparable to patients with sepsis and liver cirrhosis [42]. In CHF patients, episodes of endotoxaemia can occur, and lowering of lipoproteins could adversely effect LPS bioactivity modification [41]. This hypothesis suggests that normal patients
with CAD should be treated differently from patients with ischemic CHF.

2.2. Ubiquinone hypothesis

The mode of action of statins through the inhibition of mevalonate synthesis, decreases the production of ubiquinone (Coenzyme Q₁₀; Fig. 1). Indeed, in humans, statins have been shown to cause decreased levels of ubiquinone in several studies [44–46]. In the heart, ubiquinone is most abundant and represents an essential component of the mitochondrial respiratory chain. Ubiquinone is involved in the production of ATP and is therefore related to the metabolic demands of cells (Fig. 1) [47–50]. Another fundamental characteristic of ubiquinone is its antioxidant (free radical scavenging) property. By affecting mitochondrial function through ubiquinone, statins might have deleterious effects on skeletal or cardiac muscles. This mechanism is thought to be involved in toxic myopathy, an adverse effect of statins, and might also be relevant in cardiac muscle. This hypothesis is supported by the finding that in CHF patients, deficiencies of ubiquinone have been found frequently, and are more prominent with increasing NYHA class [51]. The reported decrease of ubiquinone with statin treatment, in both animal and human experimental studies, might therefore be harmful in CHF [44–46]. A clinical trial in CHF evaluating the efficacy of ubiquinone as an adjunctive treatment in major adverse cardiovascular events is currently ongoing [52].

2.3. Selenoprotein hypothesis

Reduction of mevalonate results in the reduction of isopentenyl-pyrophosphate (Fig. 1). Selenocysteine-tRNA₆ᵗ₆ₛₑᶜ (Sec-tRNA) controls the expression of all selenoproteins [53]. However, Sec-tRNA is only functional after essential post-transcriptional modification, one of which is the isopentenylation of adenosine. Isopentenylation of Sec-tRNA is undertaken by tRNA isopentenyl transferase, which uses isopentenyl pyrophosphate (Fig. 1) as a substrate [54]. The seloprotein hypothesis postulates that statins interfere with the mevalonate pathway, which interferes with the

Fig. 1. The hypothetical effects of statins on Chronic Heart Failure through the intermediates of the mevalonate pathway. HMG-CoA: 3-hydroxy-3-methylglutaryl co-enzyme-A; Sec-tRNA: Selenocysteine-tRNA₆ᵗ₆ₛₑᶜ; Farnesy1-PP: Farnesyl pyrophosphate; t-GGPP: trans–trans geranylgeranyl diphosphate; ATP: adenosine triphosphate; AT-1 receptor: angiotensin II type 1 receptor; NADPH: nicotinamide adenine dinucleotide phosphate oxidase; eNOS: endothelial nitric oxide synthase.
3. Potential beneficial effects of statin treatment in CHF

Besides reduction in cholesterol, statins also influence other isoprenoid intermediates of the cholesterol biosynthetic pathway (Fig. 1). These intermediates are key moieties for postranslational modification of numerous proteins. Some of these influences are of particular interest in CHF.

3.1. Capillary density and vascular function

Coronary blood flow reserve is strongly and inversely related to serum cholesterol levels [57,58]. Several studies have indicated that in patients with normal left ventricular function, cholesterol lowering drug therapy can improve coronary blood flow [59,60]. These effects can be observed very quickly after cholesterol lowering, as has been shown by single LDL apheresis, which improved coronary blood flow within 24 h [61]. CHF is characterized by a relative microvascular insufficiency. The increase in myocytes in both thickness and length is not adequately matched by a proportional increase in vasculature. In animal studies, it has been found that the eccentric hypertrophy associated with CHF lacks the compensatory angiogenesis, in contrast to physiological (i.e. exercise or anemia-induced) hypertrophy of the heart [62,63]. Consequently, in patients with increased cholesterol levels and CHF, coronary flow reserve is jeopardized for two reasons (Fig. 2). A recent study from Japan showed that cardiac function in CHF patients was improved after statin treatment in parallel with decreasing inflammation [64]. It is tempting to speculate that an increase in coronary blood flow was responsible for this effect [65]. Furthermore, dysfunction of the endothelium, in both coronary and peripheral arteries, and independently of serum cholesterol has been well documented in patients with CHF [66,67]. Endothelial dysfunction in CHF patients was associated with increased mortality risk [68]. Endothelial dysfunction in CHF is thought to reflect predominantly decreased NO bioavailability (Fig. 3) [69]. Indeed, the effects of statins on eNOS are the basis of the well described favourable effects of statins on endothelial dependent vasomotor function [70–73]. In patients with documented CAD, statins reduced transient myocardial ischemia [74]. Their anti-ischemic properties are thought to be a consequence of protein kinase Akt activation, subsequently promoting collateral growth and increasing capillary density (Fig. 4A) [75]. This effect of statins on angiogenesis is highly dependent on eNOS and is absent in eNOS deficient mice (Fig. 4B) [76]. Recently, the effects of statins on circulating endothelial progenitor cells in humans have been reported [77,78]. These findings might provide another explanation for the possible beneficial effects of statins on capillary density and vascular function in CHF patients.

3.2. Neurohormonal activation

The principal neurohormonal systems involved in the pathophysiology of CHF are the renin–angiotensin–aldosterone system and the sympathetic system. Therapies aimed at modifying activation of these systems, such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARB), aldosterone inhibitors and beta-blockers have all been proven to be beneficial in the treatment of CHF. However, statins also modify these neurohormonal systems. In humans, high levels of cholesterol are known to increase the expression of angiotensin type 1 receptors, and consequently amplify the biological effects of angiotensin II [79]. In this regard, it is of particular interest that increased expression of cardiac angiotensin type 1 receptors is related to decreased myocardial microvessel density after experimental myocardial infarction [80]. Recently, we have demonstrated that vasoconstrictor responsiveness to angiotensin II can be modified by statin treatment in patients with diseased coronary arteries [81]. Oral treatment with statins inhibits rac1-GTPase activity and reduces angiotensin II induced NADPH oxidase activity, and subsequent oxidative stress, and might therefore be of particular relevance in the ventricles of CHF patients [82]. Additionally, statins can
Fig. 3. Simplified schematic overview of the known processes involved in atherosclerosis and the established effects of statin treatment.

Fig. 4. (A) Adapted with permission from Kureishi et al. [75]. Alkaline phosphatase staining of the adductor muscle from ischemic limbs showing greater capillary density in statin treated animals (statin=253±23 capillaries/mm²; control=163±9 capillaries/mm²); P<0.01. (B) Adapted with permission from Landmesser et al. [76]. Effect of statin treatment on capillary density in infarct border zone of wild type (WT) and eNOS−/− mice after myocardial infarction (MI). Average number of endothelial cells per high-powered field in border zone for each experimental group is shown, as determined by platelet and endothelial cell adhesion-molecule immunohistochemical staining.
inhibit VEGF-induced ACE upregulation in endothelial cells [83] and enhance the efficacy of angiotensin receptor blockers [84–87].

Besides the renin–angiotensin system, statins can also modify the sympathetic system. β-Adrenergic receptor stimulation of cardiac myocytes leads to apoptosis. In rats, statins inhibit β-adrenergic receptor activation of Rac1 and consequently inhibit the activation of the mitochondrial death pathways and apoptosis [88]. Statin treatment also decreases sympathetic activity and delays the time of onset of cardiac decompensation in pacing-induced dilated cardiomyopathy in dogs [52,53].

3.3. Left ventricular hypertrophy (LVH)

Small G proteins are the molecular switches regulating cardiac hypertrophy and fibrosis. Ras, RhoA and Rac1 are key mediators of the hypertrophic response [89,90]. By blocking the synthesis of mevalonate, statins inhibit farnesylation and geranylgeranylation of Ras, RhoA, and Rac (Fig. 1) [91]. By inhibiting Rac, statins can inhibit angiotensin II induced [92–95] and noradrenalin [96] induced cardiac radical production and hypertrophy. In rat models of cardiac hypertrophy, induced by coarctation of the abdominal aorta, simvastatin treatment reduced the development of LVH [97,98]. Simvastatin was even more potent in its reduction of LVH than captopril treatment [98]. Also, pravastatin reduced left ventricular mass in patients with hypertension and hyperlipidemia, on top of anti-hypertensive treatment [99].

3.4. Atherosclerosis

Statins reduced the progression of coronary atherosclerosis in clinical studies [100,101]. Some studies even demonstrated regression of atherosclerotic plaques with high doses of statins (Fig. 3) [102].

3.5. Inflammation

In patients with CHF, elevated systemic levels of inflammatory parameters have been extensively documented and associated with progression of CHF and death [103–106]. Several clinical trials have demonstrated the efficacy of statin treatment in reducing C-reactive protein [107,108] and other inflammatory markers (Fig. 3) [109,98].

3.6. Matrix metalloproteinase (MMPs)

Recent studies have documented that activated MMPs play an important role in the development of CHF [110]. In experimental studies, production of MMPs was inhibited by statins [111,112]. Inhibition of MMP attenuated cardiac fibrosis and failure in murine models [113].

The clinical relevance of all of these potentially beneficial effects remains to be established in clinical studies.

4. Studies on statin therapy in CHF

4.1. Animal experiments

Several animal studies have suggested beneficial effects of statins in the treatment of CHF. Cerivastatin treatment (starting 1 week after myocardial infarction) significantly improved left ventricular systolic and diastolic function in rats with CHF after experimental myocardial infarction [114]. In a murine model of CHF after myocardial infarction, treatment with fluvastatin 6 h after infarction increased survival, without affecting infarct size [115]. Fluvastatin not only attenuated LV dilatation, but also decreased LV end-diastolic pressure and improved LV ejection performance. However, not all studies favoured statin treatment in CHF. In female hamsters with inherited cardiomyopathy, lovastatin treatment significantly reduced median survival time from 89 to 30 days [48].

4.2. Retrospective clinical studies

Several post-hoc subgroup analyses from large clinical trials have been published on the effects of statins in CHF. In the Cholesterol and Recurring Events (CARE) trial pravastatin significantly reduced coronary events in patients with decreased left ventricular ejection fractions (LVEF), although the study excluded symptomatic CHF patients and patients with a LVEF<25% [4]. In the Evaluation of Losartan in Elderly II (ELITE II) trial, a retrospective analysis suggested that symptomatic CHF patients using statins had decreased mortality compared to patients not on statin therapy [116]. The effects of statins on mortality were independent of treatment with either captopril or losartan. The Scandinavian Simvastatin Survival Study (4S) [2] reported a long-term reduction in the development of CHF in patients with a history of myocardial infarction who were randomized to statin therapy [117]. The PROSPER study evaluated the benefits of pravastatin treatment in an elderly cohort with a high risk of developing cardiovascular disease and stroke [10]. Although PROSPER excluded CHF patients with NYHA III/IV, the pre-specified outcome parameter ‘Heart failure hospitalization’ did not differ between pravastatin treated and placebo treated elderly patients (Table 1). A post-hoc analysis of the Heart Protection Study, involving more than 20,000 patients randomized to simvastatin or placebo treatment, reported a non-significant trend toward fewer CHF deaths due to any cause (70 (0.7%) vs. 86 (0.8%) patients; RR 0.81 [0.59–1.10]; P=0.2), which was supported by a marginally significant reduction in first hospital admission for worsening CHF or CHF death (354 (3.4%) vs. 405 (3.9%); RR 0.86 [0.75–1.00]; P=0.05) [118]. An important limitation of the Heart Protection Study data was that the presence of heart failure at study entry was not routinely recorded. A subanalysis of the data from the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) trial was aimed at evaluating associations of statin...
therapy with total mortality among 1153 patients with severe heart failure (ejection fraction <30% and NYHA class IIIB or IV symptoms) of ischemic and nonischemic etiologies [33]. Only 134 patients (12%) used a statin, but in multivariate analysis this was associated with a 62% lower risk of death, which represents a major absolute risk difference. In the Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) [119], the effect of initiating statin treatment in heart failure or left ventricular dysfunction in the acute phase after acute myocardial infarction was studied post-hoc [120]. After adjustment for risk variables before inclusion, statin treatment was associated with a 26.1% decreased mortality.

However, the reported protective associations of statin use in CHF do not prove causality, and are susceptible to considerable confounders and biases. First, probably the single largest major confounder in non-statin randomised trials can be found in the patient characteristics associated with the choice of the physician to prescribe a statin. Statin treatment could therefore have represented a selected subgroup. Such characteristics may include ones not registered, thus unknown in the study databases and unadjusted for in multivariate analysis, e.g. socioeconomic status, and healthy-heart behaviors. A major potential confounder is that patients with a short life expectation will generally not be treated with statins. In addition, since cholesterol levels inversely correlate with mortality in CHF patients, (also in the aforementioned studies in patients not using statins [33]) the possibility remains that statin therapy in these patients is simply a marker of higher pre-statin cholesterol levels (often unavailable in study databases), predicting lower baseline risk. Second, some of these CHF studies were conducted at a time when beta-blockers and spironolactone were not generally used in severe heart failure. Third, most of the patients receiving statin treatment at discharge were on statin treatment before inclusion in the study, further complicating this analysis. Finally, although statin therapy seems to reduce new onset heart failure, it could be related to effects on reduction of recurrent myocardial infarction and subsequent CHF, rather than development of CHF without recurrent infarctions.

In conclusion, the effect of statin treatment in established CHF has not been definitely addressed by these studies.

### 4.3. Prospective clinical studies

There are limited data on the effects of statins in established CHF. One of the most noteworthy studies has been performed in idiopathic dilated cardiomyopathy. Fifty-one patients were randomly assigned to simvastatin (up to 10 mg/day) or placebo [64]. Using M-mode echocardiography with 2D monitoring before and after 14 weeks of treatment,
Node et al. demonstrated improved functional capacity in patients who received simvastatin compared to placebo. In the statin group, 39.1% of patients had an improved functional class and 4.3% deteriorated. In contrast, in the placebo group, 16% of patients improved and 12% deteriorated ($P<0.01$ between the groups). The functional improvement was associated with improved left ventricular ejection fraction in the simvastatin group (from 34% to 41%, $P<0.05$), but not in the placebo group. Furthermore, plasma concentrations of TNF-α, IL-6 and BNP were significantly lower in simvastatin treated patients. Another prospective, double blind study randomised non-ischemic dilated cardiomyopathy patients to cerivastatin 0.4 mg versus placebo [121]. Quality of life and exercise capacity significantly increased in the statin group, but not in the placebo group. In addition, there was a trend towards increased left ventricular ejection fraction and improved endothelial function. A small study involving few CHF patients demonstrated improvement of reactive hyperaemia, associated with decreased plasma concentrations of components of the thrombosis–fibrinolysis system and inflammation [122,123]. The recently published Treating to New Targets (TNT) study involving 10,001 CAD patients investigated the efficacy of 80 mg versus 10 mg atorvastatin. The TNT study excluded patients with a LVEF<30%. However, a prespecified secondary outcome of the TNT trials was the incidence of hospitalisation with a primary diagnosis of CHF. A total of 164 (3.3%) of the patients on atorvastatin 10 mg vs. 122 (2.4%) of the patients on atorvastatin 80 mg were hospitalized with a primary diagnosis of CHF; representing a 26% decreased hospitalization rate for congestive heart failure in the high dose statin group (HR 0.74 [0.59–0.94]; $P=0.01$) [124]. Thus, in patients with CAD, the TNT trial suggests that the incidence of new onset CHF can be reduced with statin therapy. Despite a considerable amount of circumstantial evidence, so far no large randomised controlled clinical trials have been published on the effects of statins in CHF patients. However, two large clinical trials are currently ongoing [125,126]. The Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) will enroll about 4950 patients with chronic symptomatic systolic CHF with ischemic etiology [125]. CORONA is an endpoint-driven trial that is expected to last 52 months. The primary outcome is the composite endpoint of cardiovascular death or non-fatal myocardial infarction or non-fatal stroke (time to first event). The GISSI heart failure trial will enrol approximately 7000 patients to be randomised to n-3 polyunsaturated fatty acids or matching placebo and where there is no clear indication for cholesterol-lowering therapy patients will be further randomized to receive rosuvastatin or matching placebo [126]. In contrast to the CORONA trial, the GISSI heart failure trial will enrol patients with both ischemic and non-ischemic heart failure. The GISSI heart failure trial is also event driven and has two co-primary endpoints, namely all-cause mortality and the combined endpoint of all-cause mortality or cardiovascular hospitalisations. These two studies are complementary in their inclusion of CHF patients and will provide a more definite answer to the question of whether or not we should start statin treatment in patients with established CHF.

5. Conclusion

Despite the widespread clinical use of statins for hypercholesterolaemia and prevention of CAD, data are lacking on the effects of statins on clinical outcome in CHF. Theoretical considerations and animal experimental data indicate both beneficial and harmful effects of statins in CHF. In contrast, the currently available small-scale studies and post-hoc analyses suggest a neutral or beneficial effect of statins, but no harmful effects. Currently, two large placebo controlled trials are evaluating the efficacy of statin treatment in CHF [125,126]. Until the results are presented, we are practicing non-evidence based medicine when prescribing statins to CHF patients. Currently, we do prescribe statins to CHF patients of non-ischemic etiology when cholesterol levels need to be treated according to the guidelines (based on non-CHF populations). In CHF patients with coronary heart disease, most physicians also feel more comfortable prescribing statins than withholding them. If statins prove to reduce mortality and morbidity in patients with CHF, future research should be aimed at elucidating the precise mechanism. This is of particular importance since, in CHF, statins cholesterol lowering efficacy might be of secondary importance [127].

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