Statins for heart failure: where to go from here?

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Abstract

Statins, also known as 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, confer a number of actions beyond mere cholesterol reduction. These so-called pleiotropic effects had been proposed to exert beneficial effects in patients with chronic heart failure, because improvements in endothelial function, decreases in inflammatory markers, and the release of endothelial progenitor cells had been reported with statin use. The inhibition of the small monomeric GTPase Rho appears to be involved in many statin-mediated beneficial cholesterol-independent effects. The results of recent clinical studies with statins in patients with chronic heart failure are somewhat mixed. Some of the published data can potentially be explained by misconceptions about pleiotropic effects as such. This article discusses statin-mediated pleiotropic effects, illustrates the example of the specific Rho kinase inhibitor fasudil, and describes the available results from statin studies in chronic heart failure.

Key words: statins, heart failure, Rho kinase, fasudil, inflammation.

Introduction

Chronic heart failure (CHF) remains a major health public burden. Indeed, heart failure accounts for approximately 970,000 hospitalizations and 12-15 million outpatient office visits in the United States per year [1]. The associated health care costs have been estimated to amount to 28 billion US-dollar annually. Recent advances in both drug and device therapy and their introduction into current heart failure treament guidelines have contributed to improvements in the patients' quality of life and prognosis. However, this has led likewise to increases in both prevalence and incidence of the disease. In fact, current estimates regarding the incidence of CHF in most European countries and the United States range between 0.1-0.5% per year. The numbers are doubling with each age decade to reach 3% in those aged 75 or over. Similar estimates have been published regarding the prevalence of CHF, which amounts to 0.3-2.4%. This implies that 5 million people in the United States are affected [1].

The treatment of CHF has made significant advances over the last decades. The introduction of new biomarkers from the blood, especially natriuretic peptides like B-type natriuretic peptide (BNP), its precursor N-terminal proBNP (NT-proBNP) and, more recently, mid-regional pro-atrial natriuretic peptide (MR-proANP) has helped in establishing the diagnosis of CHF and in clinical decision making [2-4]. Our pathophysiological

understanding of CHF has also made significant progress. Only recently, co-morbidities such as anemia [5-9] and cardiac cachexia [10-13] are receiving more attention. Indeed, this syndrome is much more than mere pump failure but rather a multisystem disorder that involves the musculoskeletal, renal, neuroendocrine, and the immune system. Despite the numerous advances in the field of CHF, the clinical perspective of the patients remains poor, and about half of them die within four years of diagnosis [14]. The overall prognosis has thus been compared with some types of malignant cancer [15].

Neuroendocrine activation has been a major focus of therapeutic endevours in recent years, and the introduction of angiotensin converting enzyme-inhibitors and beta-blockers into CHF treatment regimens has yielded significant improvements in the patients' prognosis. However, a lot remains to be done. Novel therapeutic avenues need to be pursued to cover other pathophysiological aspects of the disease. This is particularly true for the immunological aspects of CHF but also for the endothelial dysfunction commonly associated with the disease. Cardiac cachexia, a terminal stage of CHF that is associated with non-voluntary non-edematous weight loss, can be viewed as the biggest therapeutic challenge [10]. Indeed, no specific treatment other than targeting the underlying illness is currently available [16, 17].

Statins, also known as 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, have been widely hailed as the aspirin of the new millennium. Indeed, the advent of these drugs has revolutionized the treatment of hypercholesterolemia, and their usefulness is now generally accepted in primary and secondary prevention of cardiovascular disease. This action is apparently not only owed to decreases in serum cholesterol but rather to effects beyond mere cholesterol reduction, so-called pleiotropic actions. It has been suggested by a number of independent researchers, that these pleiotropic effects may confer beneficial effects in patients with CHF [18]. The purpose of this article is to highlight the current knowledge of statin actions and to describe the available data from studies addressing statin treatment in patients with this disease.

Pathophysiological background

A number of pathophysiological mechanisms have been linked to the development and the progression of CHF. These mechanisms include left ventricular remodelling, endothelial dysfunction, insulin resistance, lean and fat tissue wasting, and pro-inflammatory cytokine activation [19] – among many others. The overactivity of pro-inflammatory cytokines has been first described by Levine and associates in 1990 when they assessed plasma levels of tumor necrosis factor-α (TNF-α) in such patients [20]. Since then, elevated levels of TNF-α, its soluble receptors TNFR-1 and TNFR-2, and other pro-inflammatory mediators like interleukin (IL) 1 and 6 have been implicated in an impaired long- and short-term prognosis of patients with CHF [21, 22]. The origin of pro-inflammatory cytokine activation remains a matter of speculation although a number of different hypotheses have been suggested. These have recently been discussed elsewhere [23]. Pro-inflammatory cytokine activation (like their downstream intracellular targets [24]) in turn has been implicated in the development of left ventricular dysfunction, left ventricular remodelling, increased cardiac myocyte apoptosis, the development of anorexia and cachexia, reduced skeletal muscle blood flow and endothelial dysfunction, severity of insulin resistance, activation of the inducible isoform of nitric oxide synthase, β-receptor uncoupling from adenylate cyclase, and other effects [29].

Therefore, a number of different approaches have been pursued to tackle this phenomenon in CHF. Unfortunately, direct inhibition of TNF-α with specific antibodies has largely failed in clinical studies. The disappointing results of some large-scale trials in this field have recently been described in detail elsewhere [25, 26]. A call for broader approaches that are not only directed at single players in the cytokine cascade led to performing the ACCLAIM (Advanced Chronic heart failure CLinical Assessment of Immune Modulation therapy) study [27]. Indeed, a small phase II study of this immune modulation approach had produced promising results. To follow this therapeutic avenue, it is necessary to expose human blood drawn from patients with CHF *ex vivo* to oxidative stress with subsequent re-injection into the respective patient [28]. The procedure requires 10 mL of venous blood that are exposed to ultraviolet light and ozone gas in a special blood treatment unit. Intramuscular re-injection leads to increased apoptosis. Apoptotic cells express phophatidylserine on their cell surfaces, which is recognised by specific receptors on macrophages and dendritic cells. This leads to an enhanced release of the anti-inflammatory substances IL-10 and TGF-β, which triggers the development of regulatory T cells [26].

A small double-blind, placebo-controlled study in 75 patients with moderate to severe CHF showed that such therapy significantly reduced the risk of death ($p=0.022$) and hospitalization ($p=0.008$) at 6 months of follow-up [29]. Plasma levels of TNF-α, IL-6, interferon-γ, IL-10, and C-reactive protein (CRP) were unaffected. In ACCLAIM, a total of 2,048 patients with CHF in New York Heart Association (NYHA) class II-IV and a left ventricular ejection fraction (LVEF) of $\leq$30 were enrolled [30]. Patients

in NYHA II had to have been hospitalized for heart failure or received intravenous drug therapy for heart failure within the previous 12 months. There was no difference in the time to death or first cardiovascular hospitalization (the primary endpoint) for the intent-to-treat study population (p=0.22). However, there was a significant reduction in the risk of death or first cardiovascular hospitalization by 39% (n=689 patients, 216 events, p=0.0003) in patients in NYHA class II.

Mechanisms of statin actions

The development of statins started in 1971, when the Japanese biochemist Akira Endo and his colleagues started to screen microbial strains for their ability to block cholesterol biosynthesis [31]. This finally yielded a success in 1973, when they isolated the first HMG-CoA reductase inhibitor that was later termed mevastatin (Figure 1) [31]. Due to its toxicity, it never reached the market [32]. In 1980, a mevastatin analogue was isolated, which was subsequently marketed as lovastatin (Figure 1) [33]. It was the first statin to be approved by the US Food and Drug Administration in 1987. A number of different statins have been developed in the meantime (Figure 1). These are being subdevided according to their chemical structure (open-ring vs. closed-ring structure), their origin (natural vs. synthetic), and their solubility (hydrophilic vs. lipophilic). In general, statins are well tolerated, although rhabdomyolysis has been observed as a rare side effect [34].

Statin application leads to two physiological responses. The first in an increase in the amount of the rate-limiting enzyme in cholesterol biosynthesis, HMG-CoA reductase (Figure 2). This step facilitates the conversion of HMG-CoA to mevalonate. By increasing the amount of HMG-CoA reductase, the cell compensates for the statin-mediated inhibition of the enzyme. Therefore, the direct reduction in circulating cholesterol remains small. The other response to HMG-CoA reductase inhibition is an up-regulation in the number of receptors for low density lipoprotein (LDL) on hepatocytes [35]. These receptors scavange circulating LDL from the plasma.

Pleiotropic effects of statins

LDL cholesterol reduction consistently reduces cardiovascular risk [36, 37]. Interestingly, a reduction in recurrent coronary events had been observed as early as 16 weeks after the initiation of statin therapy [38], and this timeframe is by far too short to be ascribed to the positive effects of LDL cholesterol reduction alone [39]. Additionally,

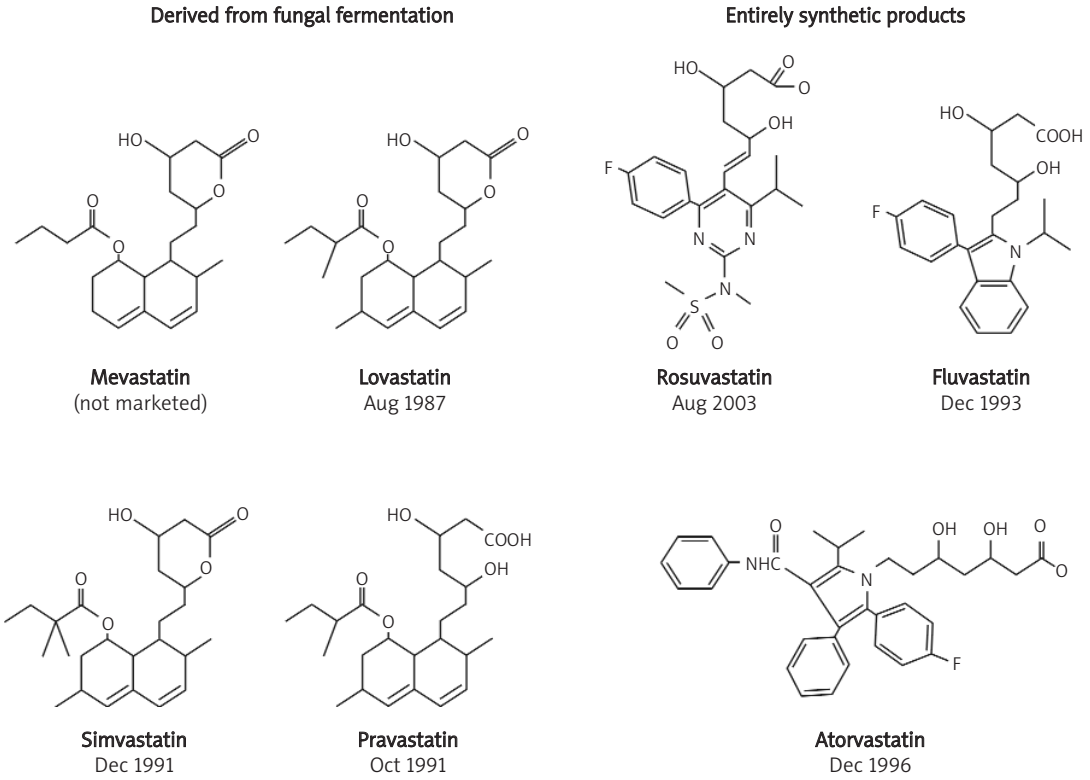

Figure 1. Chemical structures of the statins that are currently available in North America and most European countries with the date of first approval by the US Food and Drug Administration. One additional statin, pitavastatin (not depicted), is approved in Japan only

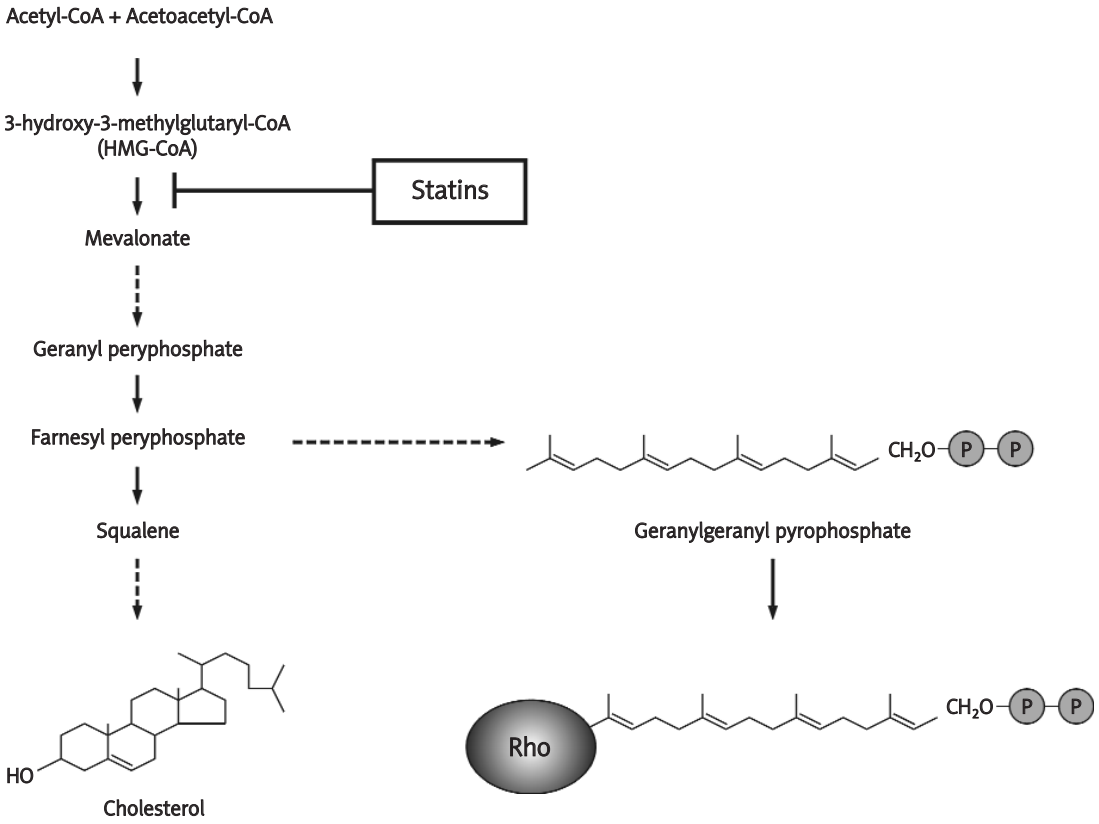

Figure 2. Pathway of cholesterol biosynthesis. Statins inhibit HMG-CoA reductase, the rate-limiting enzyme in the pathway. By-products such as farnesyl pyrophosphate supply other intracellular pathway with their substrates. This applies for the activation of the small GTPase Rho, which is being anchored in the cell membrane by geranylgeranyl pyrophosphate, a downstream product of farnesyl pyrophosphate

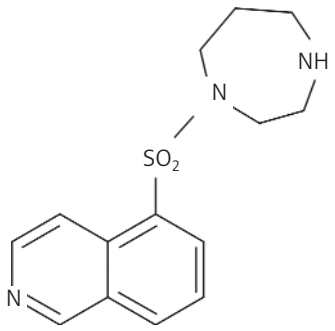

Figure 3. Chemical structure of the unspecific Rho kinase inhibitor fasudil

a number of studies have reported that statins can ameliorate morbidity and mortality in coronary artery disease irrespective of serum cholesterol levels. These findings gave rise to the idea of pleiotropic statin actions. However, it is not entirely clear how these pleiotropic effects are being conferred. One possible explanation is a decrease in the production of important intermediates from the so-called mevalonate pathway that supplies other intracellular pathways with their substrates.

One such by-product is farnesyl pyrophosphate, a precursor of not only cholesterol, but also of heme A, dolichols, and ubichinones. Another important by-product from the mevalonate pathway is geranylgeranyl pyrophosphate, which is derived from farnesyl pyrophosphate (Figure 2). Both these substrates are important for the activation of various intracellular G proteins, because they anchor these enzymes in the cell membrane. Therefore, statins inhibit not only cholesterol synthesis but also a number of other intracellular pathways, including the activation of the small GTPase Rho. Proteins of the Rho family (e.g. Rho, Rac1, Cdc42) are involved in the regulation of cell morphology, cell adhesion, cell motility, cell growth, and in cancer cell metastasis [40].

Using inhibitors of Rho kinase, a downstream effector of Rho, it has been shown that these drugs confer several beneficial effects on endothelial function. Indeed, fasudil (Figure 3), a Rho kinase inhibitor approved in Japan and China for the treatment of cerebral vasospasm after subarachnoid hemorrhage, has been shown to decrease pulmonary vascular resistance in patients with severe pulmonary hypertension [41], to decrease forearm vascular

resistance in patients with arterial hypertension [42] or CHF [43], to improve neurological functions and clinical outcome in patients with ischemic stroke [44], and to prolong maximal exercise time and the time to the onset of 1 mm ST-segment depression in patients with stable effort angina [45].

Thus, the beneficial effects on endothelial function that have been reported with statin application may, at least in part, be mediated by the inhibition of Rho [46]. Indeed, statins have been found to induce endothelial nitric oxide synthase (eNOS) [47], an enzyme that synthesizes the vasodilating substance nitric oxide. The attenuation of nitric oxide production is one of the most important features of endothelial dysfunction [48]. Additionally, statin treatment yields an increase in nitric oxide release by indirect mechanisms [49]. Another contributor to the development of endothelial dysfunction is xanthine oxidase. Overactivity of the enzyme is a frequent finding in patients with CHF [50]. This enzyme catalyzes the breakdown of uric acid, which also yields the production of oxygen free radials [51]. Interestingly, statins have been proposed to reduce oxidative stress [52], and atorvastatin has been shown to reduce vascular production of reactive oxygen species in spontaneously hypertensive rats [52].

The Rho kinase inhibitor fasudil was also found to decrease the production of TNF-α in an animal model of colitis [53]. Thus, inhibition of Rho may also contribute to the beneficial effects of statins demonstrated in various diseases. Fluvastatin decreases the expression of the monocytic receptor for bacterial lipopolysaccharide, Toll-like receptor 4 [54]. Lovastatin was shown to inhibit the production of TNF-α, IL-1, and IL-6 in certain rat cell lines [55]. Some studies have shown that this may also have clinical implications. Pravastatin, for example, at a dose of 40 mg daily reduced the plasma levels of TNF-α in patients with hypercholesterolemia (n=40) after eight weeks of treatment (p=0.32 vs. placebo) [56]. However, taking several studies together, it needs to be admitted that the clinical results with statins are somewhat mixed, although several lines of evidence have shown a down-regulation of C-reactive protein (CRP) levels with statin use. The PRINCE study (Pravastatin Inflammation/CRP Evaluation) showed significant reductions in serum levels of CRP in 1,182 patients with a history of myocardial infarction, stroke, or arterial revascularization procedure. In PRINCE, pravastatin was used at a dose of 40 mg once daily, and CRP levels were reduced by 13% after 24 weeks compared to baseline (p<0.005) [57]. In another study, atorvastatin was more effective than pravastatin in achieving this effect, which was shown among 3,745 patients with acute coronary syndromes who participated in the PROVE IT-TIMI 22 study (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22) [58]. For the purpose of this study, atorvastatin was administered at a dose of 80 mg once daily, pravastatin at 40 mg once daily.

Rho-independent pleiotropic effects of statins are less well understood. Also, it is not clear whether all statins share the same pleiotropic effects [59]. Some members of the statin familiy of drugs have been found to mobilize bone marrow-derived endothelial progenitor cells. Such cells have recently been demonstrated to be able to trans-differentiate into beating cardiomyocytes when they are co-cultured with neonatal rat cardiomyocytes or when they are injected into the post-ischemic adult mouse heart [60]. In addition, atorvastatin increased the survival of mice (n=75) during a four-week follow-up period after extensive myocardial infarction (atorvastatin 80%, placebo 46%, p<0.01) [61]. One prospective trial has been reported that recruited 15 patients with angiographically documented stable coronary artery disease. Treatment with atorvastatin 40 mg once daily for 4 weeks led to a significant increase in the number of endothelial progenitor cells in the bloodstream of these patients [62].

Clinical studies in patients with chronic heart failure

A number of different studies have been published regarding the use of statins in patients with CHF. Their results are quite mixed. Node et al. performed a randomized, open-label study in patients with symptomatic non-ischemic dilated cardiomyopathy and an LVEF <40%. Patients received either simvastatin (5 mg, increased to 10 mg once daily after 4 weeks, n=23) or placebo for 14 weeks [63]. Simvastatin treatment yielded significant improvements in NYHA class (p<0.01) and LVEF (p<0.05) compared to placebo. Moreover, there were significant decreases noted in the plasma levels of BNP, TNF-α, and IL-6 with simvastatin treatment. Flow-mediated brachial artery vasodilation improved only in the simvastatin group (p<0.01). Sola et al. studied 108 patients with non-ischemic CHF and an LVEF $\leq$35% who were treated with atorvastatin 20 mg once daily (n=54) or placebo (n=54) in a double-blind, randomized study for 12±2 months [64]. LVEF increased from 33±0.5 to 37±0.5% (p=0.01) only in the atorvastatin group, whereas it decreased in the placebo group (p=0.04). By the end of the study, mean LVEF was significantly higher in the atorvastatin group than in the placebo group (p=0.004). Moreover, atorvastatin treatment led to decreases in the plasma levels of IL-6, soluble TNFR-2, and CRP (all p<0.01 vs. baseline).

Yamada et al. studied 38 patients with mild to moderate CHF of ischemic or non-ischemic origin and an LVEF <40% [65].The study was originally

performed in a double-blind fashion, and the patients received either atorvastatin 10 mg once daily or matching placebo. After 6 months, the study was continued in an unblinded fashion due to safety concerns. Patients were followed-up for at least 3 years. By study termination, atorvastatin treatment had yielded significant decreases in both natriuretic peptides ANP (p=0.04) and BNP (p=0.02) compared to baseline. At this time, BNP levels were significantly lower than in the placebo group (p=0.01). No changes were noted in the plasma levels of IL-6 or CRP, however, LVEF improved significantly in the atorvastatin group both at 6 months and 3 years of follow-up (both p<0.025 vs. baseline). Additionally, there was a significant improvement in peak VO_2 from 20.6±5.1 to 23.2±5.7 ml/kg/min (p<0.025) [65]. However, a small study in 15 patients with non-ischemic cardiomyopathy produced neutral results after 12 weeks of treatment with atorvastatin 80 mg once daily or placebo [66]. These authors failed to demonstrate any changes in NT-proBNP, CRP, soluble TNFR-1, TNF-α, and a number of adhesion markers in the atorvastatin group.

Gürgün et al. performed an open-label study in 20 patients with ischemic and another 20 patients with non-ischemic cardiomyopathy and an LVEF <40% [67]. All subjects were treated with fluvastatin 80 mg once daily for 12 weeks. Mean NYHA class improved in both groups (both p<0.01 vs. baseline) as did LVEF (both p=0.001). No changes were noted in BNP or IL-6, neither in the ischemic nor in the non-ischemic group. However, there was a significant decrease in the plasma levels of TNF-α with fluvastatin in the ischemic group (p=0.01 vs. baseline) [67].

The UNIVERSE (Rosuvastatin Impact on Ventricular Remodeling, Lipids and Cytokines) trial was a randomized, placebo-controlled, double-blind study of 6 months duration [68]. The original aim of enrolling 126 patients was curtailed when recruitment became too slow due to a lack of statin-naive patients. Thus, only 86 patients with CHF of ischemic or non-ischemic origin were randomized to rosuvastatin at an increasing dose (target: 40 mg once daily) or placebo. 88% of the patients in this study had non-ischemic cardiomyopathy. Unfortunately, the study failed to reach its primary and all of its secondary endpoints. Indeed, there were no changes in LVEF, plasma values of norepinephrine, endothelin-1, BNP, CRP, TNF-α, or IL-6 [68].

Currently, only one large-scale trial of a statin in CHF is available. The CORONA study (Controlled Rosuvastatin Multinational Trial in Heart Failure) study enrolled a total of 5,011 patients with ischemic CHF and an impaired left ventricular ejection fraction (LVEF) who were randomized to placebo or rosuvastatin 10 mg once daily in a double-blind fashion [69]. The median follow-up was 32.8 months. The primary end-point was defined as a composite of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. At study termination, a primary end-point had been observed in 692 patients in the rosuvastatin and in 732 patients in the placebo group (hazard ratio 0.92, 95% confidence interval 0.83-1.02, p=0.12). There were no significant differences between the two groups in terms of the primary outcome. In CORONA, only one beneficial effect was noted with rosuvastatin treatment. This was a reduction in the total number of hospitalizations for worsening heart failure (p=0.01) [69]. The median level of CRP decreased from 3.1 mg/l at baseline to 2.1 mg/l (-31.6%) at the last visit in the rosuvastatin group and increased slightly in the placebo group (+5.5%, p<0.001) [69]. However, since there was no improvement in survival with rosuvastatin treatment, one may also question the value of CRP reduction.

With GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca), a similar study is still ongoing. This prospective, multicenter, randomized, double blind trial aims to investigate the impact of n-3 polyunsaturated fatty acids (PUFA) and rosuvastatin in patients with CHF. Patients are randomized in 2 steps to (i) n-3 PUFA (1 g once daily) or placebo and (ii) rosuvastatin (10 mg once daily) or placebo. The previously performed GISSI-Prevenzione trial showed that 3-year treatment with low-dose n-3 PUFA was associated with a significant reduction of total mortality by 21% in patients who survived a recent myocardial infarction [70].

In conclusion, statins possess a number of properties that may improve the clinical symptoms of patients with CHF. However, when addressing the use of statins in these patients it is necessary to consider the cholesterol paradox. In general, LDL is reduced by another 7% with each doubling of the dose of a statin [71]. It is not known which doses are needed to achieve pleiotropic effects. In fact, these doses might be a lot lower than those needed to achieve LDL reductions. Although several retrospective analyses have shown beneficial effects of statins in patients with CHF [72, 73], it is also known that higher cholesterol values are associated with better (not worse) survival of these patients [74-76]. Thus, it appears that cholesterol exerts a protective effect in patients with CHF [77]. From patients with sepsis, it is known that cholesterol can inactivate bacterial lipopolysaccharide, a cell wall component from gram-negative bacteria, by micell formation around them. Since the gut wall is disturbed in patients with CHF [78] and elevated levels of lipopolysaccharide have been found during edematous decompensation [79], it is likely that cholesterol also inactivates lipopolysaccharide in patients with CHF. This, in turn, would lead to

a decrease in the release of pro-inflammatory cytokines, because lipopolysaccharide is a major inducer of these substances. These facts have been put together in the so-called endotoxin-lipoprotein hypothesis [80]. Keeping this hypothesis in mind, it would appear that statins should be administered at a dose that does not lower cholesterol but does exert pleiotropic effects. The dose of rosuvastatin used in CORONA did lower cholesterol values. Thus, the dose of rosuvastatin may have been too high. Moreover, it is unclear if all statins share the same pleiotropic effects or if only single substances are capable to exert these. If this is the case, rosuvastatin may have been even the wrong drug. Future studies need to address these questions in more detail.

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