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The role of statins in chronic heart failure

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Abstract

The efficacy of statins in reducing morbidity and mortality in patients with documented coronary artery disease is unquestionable. However, in chronic heart failure (CHF), evidence regarding the beneficial effects of statin therapy remains contradictory. Although numerous retrospective studies have demonstrated improved prognosis in CHF patients treated with statins, two randomized trials, GISSI-HF and CORONA, have not confirmed the benefit of rosuvastatin in this group of patients. The benefits of using statins in CHF probably result mostly from their pleiotropic action, including the improvement of endothelial function, the inhibition of neurohormonal activation, and the reduction of proinflammatory activation. On the other hand, it has been recognized that low cholesterol is associated with worse morbidity and mortality in patients with CHF. It appears that it is necessary to conduct further randomized clinical trials using different kinds of statins in different populations of patients with CHF.

Key words: statins, chronic heart failure.

Streszczenie

Skuteczność statyn w zmniejszaniu śmiertelności i chorobowości u chorych z udokumentowaną chorobą wieńcową jest niepodważalna, natomiast wyniki badań dotyczących efektów działania statyn u chorych z przewlekłą niewydolnością serca (CHF) pozostają sprzeczne. Wprawdzie liczne badania retrospektywne wykazały poprawę rokowania u chorych z CHF leczonych statynami, jednakże dwa badania kliniczne z randomizacją – GISSI-HF i CORONA – nie potwierdziły korzystnego działania rosuwastatyny w tej grupie chorych. Korzyści ze stosowania tej grupy leków u chorych z CHF wynikają prawdopodobnie przede wszystkim z ich działań plejotropowych, takich jak poprawa funkcji śródbłonka, hamowanie aktywacji neurohumoralnej i zmniejszenie aktywacji prozapalnej. Z drugiej strony stwierdzono, że małe stężenie cholesterolu wiąże się z większą chorobowością i śmiertelnością u chorych z CHF. Wydaje się, że konieczne jest przeprowadzenie kolejnych badań klinicznych z randomizacją i zastosowaniem różnych rodzajów statyn w różnych populacjach chorych z CHF.

Słowa kluczowe: statyny, przewlekła niewydolność serca.

Introduction

Inhibitors of 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA) known as statins are well grounded in clinical practice as agents that are efficient in the primary and secondary prevention of atherosclerosis [1-3]. They improve survival and reduce the prevalence of myocardial infarction among patients diagnosed with or at risk of developing coronary artery disease [4]. Data obtained from numerous studies have demonstrated that statin treatment may benefit the prognosis of patients with chronic heart failure (CHF) of ischemic and non-ischemic etiology [5-9]. In turn, two large randomized multicenter clinical studies, namely CORONA and GISSI, did not confirm the beneficial effect of statin treatment on all-cause mortality in the CHF patient group [10-12].

The mechanism of the potentially beneficial effect of statins on CHF is not fully elucidated. It is worth noting that, apart from reducing lipid concentration, they exhibit pleiotropic activity, improving endothelial function, increasing nitric oxide synthesis, exerting anti-inflammatory and antioxidant effects, inhibiting neurohumoral activation, and benefiting myocardial reconstruction. As CHF is a clinical syndrome in which the key role is played by the stimulation of the renin-angiotensin-aldosterone and sympathetic nervous systems, the release of proinflammatory cytokines, and impairments regarding nitric oxide synthesis, the use

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of statins for this disease should be pathophysiologically justified.

Lipid profile regulation

Statins are competitive antagonists of 3-hydroxy-3-methyl-glutaryl-CoA reductase, thus reducing the speed of cholesterol biosynthesis in the liver and intestines. By inhibiting cholesterol biosynthesis, statins reduce its presence in cells, which leads to reductions in the total serum concentrations of cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol fractions, and intermediate-density lipoprotein, while increasing the secretion of high-density lipoprotein (HDL) and the expression of LDL receptors [13].

The relationship between cholesterol concentration and mortality in CHF patients continues to be a subject of study and analysis. There are still discrepancies between the results of studies by different authors, which can probably be largely attributed to the employed inclusion and exclusion criteria, population type, and statin type. Horwich *et al*. found that reduced total cholesterol concentration in CHF patients is a risk factor for mortality during long-term follow-up [14]. These results were confirmed by a study conducted among CHF patients by Rauchhaus *et al*. [15] as well as another study by Horwich *et al*. conducted among patients with acute decompensated CHF [16]. There are three hypotheses explaining the adverse hypolipemic effects of statins in CHF patients. The ubiquinone theory assumes that, by reducing cholesterol concentration, statins reduce ubiquinone production. This results in the reduction of ubiquinone's antioxidant activity and the production of adenosine triphosphate, which plays an important role in cellular biology as a coenzyme and a transporter of chemical energy required for cellular metabolic processes [17]. The endotoxin-lipoprotein hypothesis assumes that the lower concentration of circulating cholesterol is associated with an increase of bacterial endotoxins in blood and a release of proinflammatory cytokines [15]. This stems from the fact that CHF patients often suffer from edemas of the intestinal wall, which cause the displacement of bacteria and bacterial endotoxins from its lumen to the blood. Lipoproteins are required for binding endotoxins and, thus, reducing the systemic release of proinflammatory cytokines [15]. The selenoprotein hypothesis assumes that statins prevent the transformation of tRNA into functional tRNA molecules. This causes a reduction in the number of available selenoproteins, which are necessary precursors for selenoprotein enzymes serving as antioxidants [18]. Reduced cholesterol concentration in persons who are not receiving statins may result from advanced CHF. It is believed that reduced concentration of LDL cholesterol fraction is associated with cardiac cachexia, which is an independent mortality-increasing factor in CHF patients [19]. The results of conducted *in vitro* studies suggest that circulating proinflammatory cytokines may result in a decrease of lipoprotein levels by reducing their production by the liver and increasing the activity of LDL receptors [20]. Some studies have demonstrated that low cholesterol concentrations are associated with increased morbidity and mortality among CHF patients [14, 21]. Silva *et al*. retrospectively compared CHF patients who were administered statins with those who receive no statin therapy [22]. Their analysis demonstrated that the low cholesterol concentration in patients who did not receive statins was associated with an almost twofold higher risk of all-cause mortality during 5-year follow-up in comparison to patients with low cholesterol concentration who were treated with statins.

Based on a meta-analysis of two observational studies (ELITA-2 and European Centers) encompassing 5,200 CHF patients, it was demonstrated that statin treatment significantly reduced the risk of hospitalization or death resulting from cardiovascular causes, regardless of the initial level of cholesterol, disease etiology, or the clinical condition of the patient [7]. The influence of HMG-CoA inhibitor therapy on the reduction of relative risk of sudden cardiac death in patients with advanced CHF was examined by Vrtovec *et al*. [8]. The researchers analyzed patients with ejection fraction < 30% in whom cholesterol levels exceeded 150 mg/dl. Cholesterol concentration decreased significantly in patients treated with atorvastatin, while remaining constant in the placebo group. Significantly lower all-cause mortality during 1-year follow-up was demonstrated in the group receiving statins in comparison to the control group [8].

Anti-inflammatory action

It has been established that one of the pathophysiological factors causing CHF is a chronic inflammatory process, resulting in an increased concentration of circulating proinflammatory cytokines, such as interleukin-1, interleukin-6, and tumor necrosis factor-α (TNF-α), and acute phase indicators, such as hs-CRP [23]. An abnormal inflammatory response is believed to be responsible for several aspects of the CHF phenotype, such as abnormal left ventricular reconstruction, endothelial dysfunction, inadequate erythropoiesis, and peripheral myopathy. Elevation of the proinflammatory cytokine levels in response to myocardial injury is a factor which increases mortality among CHF patients [23]. Zhang *et al*. published a meta-analysis of 10 randomized studies encompassing over 6,000 patients who were randomly assigned to groups receiving statins or placebo as a supplement of standard therapy [23]. The authors demonstrated that the statin treatment was associated with a significant reduction of hs-CRP concentration, but it did not influence the concentrations of interleukin-6 or TNF-α. The greatest benefits from treatment were gained by patients over 60 years of age, with left ventricular ejection fraction above 30%, with CHF of ischemic etiology, who continued their treatment for at least 12 months [23]. In turn, Yamada *et al*. observed a reduction in the concentration of interleukin-6 and C-reactive protein in a group of patients undergoing atorvastatin therapy [24]. The authors also demonstrated that long-term atorvastatin treatment significantly influenced the improvement of cardiac hemodynamic parameters, the

reduction of left ventricular dimensions, and the increase of left ventricular ejection fraction. The obtained results suggest that statins exert anti-inflammatory effects and inhibit the apoptosis of cardiac muscle cells, thus contributing to the inhibition of myocardial reconstruction [24]. Nakagomi *et al*. reported that, in CHF patients, the concentration of TNF-α and interleukin-6 is significantly higher than in healthy persons, while statin therapy reduces the production of these cytokines, inhibits the inflammatory process, and reduces atherosclerotic plaque, thus contributing to a significant improvement of prognosis in patients with CHF and concomitant dyslipidemia [25]. In turn, the randomized UNIVERSE study, encompassing CHF patients receiving rosuvastatin or placebo, demonstrated a significant rise in the serum levels of procollagen I and III aminoterminal propeptides in the study group; its excessive elevation was probably contributing to myocardial fibrosis [26]. The authors suggest that this mechanism may be induced by statins. Furthermore, they proved that 26 weeks of rosuvastatin therapy resulted in a significant reduction of the plasma concentrations of coenzyme Q in the treated patients [26]. It appears that a reduction of coenzyme Q levels correlates with low plasma LDL values in response to statin treatment, which may be associated with lower effectiveness of the bioenergetic processes occurring within the heart [27].

The influence of statins on vascular endothelium

The endothelium plays an important role in maintaining normal body homeostasis: it is involved in anticoagulant mechanism control and in the interactions of leukocytes and blood platelets with vascular walls; it also secretes a number of active substances, which biologically regulate vascular tension. Endothelial dysfunction plays an important role both in the pathogenesis and the clinical course of CHF, arterial hypertension, and coronary vessel atherosclerosis [28]. It has been demonstrated that the concentration of vasoconstrictive endothelin-1 is elevated in CHF patients, while statin therapy significantly reduces its expression, thus weakening the unfavorable processes of myocardial reconstruction. The multidirectional effect of statins on the processes occurring within the endothelium of CHF patients can also be observed in the reduction of the level of cell adhesion molecules (VCAM-1, ICAM-1, selectin E). It has been suggested that inhibiting the activity of matrix metalloproteinases with statins may play a significant role in the inhibition of CHF progress [27]. Other studies suggest that the protective mechanism of statin action is also based on the stimulation of endothelial nitric oxide synthase, which catalyzes the reaction of nitric oxide production. As a vasodilator, nitric oxide regulates the flow of blood through blood vessels and increases the speed of endothelial transport; it inhibits the aggregation of thrombocytes and their adhesion to the surface of endothelial cells. The presented mechanism of statin action appears to play an important role in the inhibition of CHF progress [28, 29]. Young *et al*. postulated a hypothesis that a high plasma concentration of asymmetric dimethylarginine (ADMA), a strong nitric oxide synthase inhibitor, may lead to impairment of vascular endothelial function, while atorvastatin therapy inhibits this process [30]. Elevated ADMA concentrations observed in CHF patients may correlate with disease intensity and increased risk of cardiovascular mortality in this population of patients. It seems that including statins in the therapy reduces ADMA levels, contributing to the improvement of endothelial function in CHF patients [30]. A study conducted by Erbs *et al*. demonstrated that rosuvastatin therapy significantly increases the number of endothelial progenitor cells, which facilitates the repair of damaged endothelium [31]. Rosuvastatin also causes a significant elevation of the number of CD34+ stem cells, which induce the formation of new blood vessels [31].

Antioxidant action

Oxidative stress plays an important role in the pathogenesis of CHF; the increased production of reactive oxygen species (ROS) and the concurrent reduction in the effectiveness of antioxidant mechanisms lead to adverse modifications within proteins and lipid membranes, disturbances in nitric oxide secretion, and the development of an inflammatory response [28, 32]. High ROS levels were observed in the venous blood of CHF patients [32]. The increased proliferation of vascular smooth muscle cells and the apoptosis of endothelial cells observed in CHF patients, caused by ROS, lead to disease exacerbation and progression. Statin-influenced reduction of oxidative stress levels may result from a decrease in the expression of the AT1 receptor gene to angiotensin II, causing the stimulating influence of angiotensin II on free radical generation in cardiomyocytes to diminish. It appears that the induction of this mechanism may inhibit the development of myocardial hypertrophy in CHF patients [29].

Studies conducted by Erbs *et al*. demonstrated that statins exert a favorable effect by reducing oxidative stress levels [31]. The results indicated that the level of lipid peroxidation was significantly reduced in the group of patients receiving rosuvastatin, while rising significantly in the placebo group. Moreover, rosuvastatin therapy was associated with a significant reduction of oxygenated LDL levels in comparison with the placebo group. The authors suggested that the antioxidant effects of statin administration may partially stem from its stimulating influence on both enzymatic and non-enzymatic free radical scavengers [31]. The benefits of statins in reducing oxidative stress were also demonstrated by a prospective study conducted by Greig *et al*. in a group of CHF patients in NYHA functional classes II through IV [33]. The study randomized the patients to groups that were receiving atorvastatin, atorvastatin and allopurinol, and placebo. The study demonstrated a significant reduction in the levels of malondialdehyde, considered to be a product of lipid peroxidation, and a drop in endothelial superoxide dismutase activity in both groups in comparison with initial values. Additionally, in the group

receiving allopurinol, a significant decrease in uric acid levels was noted, but the role of xanthine oxidase inhibitors in the treatment of CHF has not yet been precisely determined [33]. A meta-analysis of 7 clinical studies encompassing CHF patients demonstrated the efficacy of atorvastatin therapy in reducing the rates of all-cause mortality (OR = 0.39), cardiovascular mortality (OR = 0.28), and sudden cardiac death (OR = 0.24) [34]. There was also a significant reduction in the frequency of hospitalization due to CHF exacerbation among the patients undergoing atorvastatin therapy (OR = 0.30) [34]. Wojnicz *et al*. also demonstrated that including atorvastatin in the standard therapy offered to CHF patients in the course of dilated cardiomyopathy may improve their prognosis [9].

Conclusions

Apart from clinical studies confirming the efficacy and purposefulness of statin use in CHF, two large randomized clinical studies (GISSI-HF and CORONA) were published, reporting no beneficial effect of rosuvastatin on long-term prognosis [10-12]. The commentary to the analysis of the CORONA study, which encompassed over 5,000 patients with CHF of ischemic etiology, stated that the lack of benefits resulting from including statins in the treatment for CHF patients could have been associated with the analyzed group of patients [11]. Elderly persons (mean age: 73 years) constituted a large proportion of the examined patients; moreover, a decided majority were in advanced CHF stages (NYHA functional class III and IV) [11, 12]. At the same time, it was revealed that patients with low plasma concentrations of galectin-3 may benefit from statin therapy, while high values of this indicator are associated with no response to HMG-CoA inhibitor treatment. Perhaps galectin-3 will become a marker for identifying CHF patients in whom statin therapy can be successful [10]. The GISSI-HF study included younger patients than those examined in the CORONA study; it also included fewer patients with ischemic CHF and advanced CHF (NYHA functional class III/IV) [12]. Nonetheless, this study also failed to demonstrate a beneficial effect of rosuvastatin therapy on reducing cardiovascular mortality in the studied population in comparison with placebo [12].

It is worth noting that both aforementioned studies analyzed patients treated with rosuvastatin. The authors of the PEARL study postulated a hypothesis that the type of the employed statin may significantly influence the benefits of treatment in CHF patients [35]. It may be the case that pitavastatin used in the PEARL study is characterized by better bioavailability and lipophilicity in comparison with rosuvastatin, which may have been responsible for achieving treatment benefits with the former agent. It appears that treatment efficacy also depends on the stage of the disease. Introducing statins to the therapy at the late stage of advanced CHF may be responsible for the lack of desired treatment effects. It seems necessary to conduct further multicenter randomized clinical studies using different statin agents in different CHF patient populations, as the term chronic heart failure encompasses different stages of the disease, while adequate study conclusions may only be drawn on the basis of comparable populations.

Disclosure

Authors report no conflict of interest.

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