Statins for heart failure: a potential for new treatment

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, statins, are potent and widely used cholesterol-lowering drugs. Since the pathophysiology of atherosclerosis involves the uptake of modified low density lipoprotein (LDL) cholesterol, it has been generally assumed that the cholesterol-lowering effect of statins mediates the beneficial effects on atherosclerotic disease. Several clinical trials have demonstrated beneficial effects of statins in the primary and secondary prevention of coronary heart disease. However, subgroup analysis and meta-analysis of cholesterol-lowering trials indicated that the risk of atherosclerotic disease in patients treated with statins is significantly lower than the expected risk based on the level of serum cholesterol. These findings mostly suggest the existence of statins’ beneficial effects beyond their cholesterol-lowering effects, which are termed “pleiotropic effects”. The pleiotropic effects of statins involved improvement of endothelial function, stabilization of atherosclerotic plaques, inhibition of cell migration and proliferation, and reduction of inflammation and oxidative stress. Many of these properties seem to contribute to the favorable effects of statins on atherosclerotic disease. However, in terms of pleiotropic effects, statins need not be limited to prevention of atherosclerotic disease.

Heart failure is a complex syndrome that consists not only of hemodynamic abnormalities but also of metabolic and neurohormonal alterations. Although hemodynamic stress in heart failure may play a role in the disease process, it is now believed that many other mechanisms, such as the activation of neurohormones and proinflammatory cytokines, may be more important in mediating the progression of heart failure. In particular, serum levels of proinflammatory cytokines such as tumor necrosis factor-α, interleukin 6, and C-reactive protein (CRP) are associated with a risk of heart failure [1].

In the present issue of Cardiovascular Research, Trochu et al. [2] demonstrated that simvastatin improved coronary endothelial function in pacing-induced heart failure and its effect was associated with increased survival and an enhanced regulation of myocardial energetics by nitric oxide (NO). These findings may provide a new insight into the therapeutic strategy for patients with heart failure because the pleiotropic effects of statins match with the pathophysiology of heart failure.

The vascular endothelium plays an active role in a number of cardiovascular diseases. The impaired production of NO is of importance for development of endothelial dysfunction. Impaired vasodilation and increased vasoconstriction are characteristic of patients with heart failure, and an imbalance between NO and endothelin-1 plays a detrimental role in the pathophysiology of this disease. Statins increase the NO bioavailability and induce eNOS gene transcription independently of its cholesterol-lowering effects [3]. Moreover, statins inhibit the expression of proendothelin-1 mRNA and decrease the levels of endothelin-1 [4]. Importantly, statins are known to increase endothelial eNOS expression through an inhibition of geranylgeranylation of the small GTP-binding protein Rho [5] and a post-translational activation of the phosphatidylinositol 3-kinase/protein kinase Akt pathway [6].

Oxidative stress plays an important role in the development of endothelial dysfunction because increased vascular generation of free radicals inactivates NO. Oxidative stress is thought to be involved in the pathophysiology of heart failure [7]; thus, the generation of oxygen free radicals is increased in patients with heart failure [8]. Moreover, an impairment of antioxidant systems such as superoxide dismutase and catalase is observed under these conditions [9]. Recent studies suggest that statins can inhibit vascular formation of oxygen free radicals [10]. Thus, statins might be able to improve endothelial dysfunction in heart failure by inhibiting free radical formation.

Inflammation may play an important role in the progression of heart failure [11]. Disease progression of heart failure is mainly related to the synthesis of proinflammatory cytokines. Increased levels of tumor necrosis factor-α are thought to play a predominant role in apoptosis, decreased peripheral blood flow, and lower skeletal muscle mass. It is now clear that statins exhibit anti-inflammatory effects [12]. Indeed, available evidence implicates nonsterol metabolites of mevalonate such as geranylgeranyl and farnesyl pyrophosphates in the inflammatory process. Isoprenoid residues are covalently attached to proteins in the process of protein prenylation. Prenylation is necessary for the insertion and anchorage of proteins to cell membranes and for their full biological functionality. Statin treatment inhibits the mevalonate pathway, thereby reducing the intracellular pool of isoprenoids and, consequently, the prenylation process. Rho, a small GTPase protein, mediates activation of the proinflammatory transcription factor nuclear factor-κB (NF-κB). Furthermore, Rho downregulates the endothelial production...
of NO, which has been demonstrated to be an anti-inflammatory molecule. Statin treatment reduces prenylation of the Rho protein, thereby reducing its attachment to cellular membranes and hence its biological activity. The reduction of Rho prenylation may attenuate vascular inflammation through a combination of actions involving the reduction of NF-κB activation and restoration of NO production. Therefore, one possible mechanism by which statins may reduce inflammatory activity is the modulation of the Rho/Rho-kinase pathway.

Cardiomyocyte loss by apoptosis has been recognized as a potential cause of heart failure [13]. Cerivastatin has been reported to prevent apoptosis of cardiomyocytes in rats fed a high-salt diet and of cardiomyocytes in vitro induced by incubation with adriamycin [14]. The prevention of cardiomyocyte apoptosis may be a part of the protective mechanisms of statins against heart failure.

Systemic markers of inflammatory activity are attenuated after statin treatment. Indeed, clinical trials in the context of primary and secondary prevention have shown that statin therapy reduces plasma levels of CRP, which is a marker of overall systemic inflammation. In the Cholesterol and Recurrent Events (CARE) trial [15], pravastatin-treated patients displayed progressive reduction of CRP levels (up to ~37.8%) during the 5-year follow-up period, indicating that this anti-inflammatory effect is progressive and maintained over a prolonged period. The effect of statins on systemic inflammatory markers results potentially from lipid-lowering-dependent and -independent actions. Arterial wall macrophages, stimulated by oxidized LDL, secrete proinflammatory cytokines such as interleukin-6, which in turn stimulate hepatic production of CRP and other acute-phase reactants. Statins reduce the residence time of LDL particles in the circulation and, consequently, the substrate available for generation of oxidized LDL, thereby reducing the inflammatory stimulus. Equally, statins can directly attenuate the inflammatory response via mechanisms related to the inhibition of mevalonate synthesis but also via mechanisms independent of HMG-CoA reductase inhibition. These mechanisms, involving lipid-lowering-dependent and -independent actions, are not mutually exclusive and thus operate concomitantly. It is not clear whether there may be a preponderance of one these mechanisms in the statin-induced reduction in plasma CRP levels. Studies including pravastatin, cerivastatin, lovastatin, simvastatin, and atorvastatin treatments in dyslipidemic patients have consistently demonstrated a decrement in plasma CRP levels in a manner unrelated to their effects on LDL or HDL cholesterol levels. However, estimation of proinflammatory or anti-inflammatory actions of lipoproteins is not fully reflected in their cholesterol content. For example, LDL particles differ in their susceptibility to oxidation as a function of their physicochemical properties (e.g., size and chemical composition), raising the possibility that LDL particle phenotype may be intimately related to the magnitude of the inflammatory stimulus. Thus, the potential association between statin-induced modifications in LDL particle phenotype and variation in the circulating levels of acute-phase reactants requires further study. Finally, in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) [16], statin therapy reduced coronary event rates in subjects with high LDL cholesterol and low CRP levels as well as in those subjects displaying low LDL cholesterol and high CRP levels. These findings suggest that lipid-dependent and -independent mechanisms are clinically relevant and that the predominant mechanism may not be the same in patients with distinct clinical presentations.

Heart failure is involved in endothelial dysfunction, oxidative stress, and inflammation. In the Scandinavian Simvastatin Survival Study (4S) [17], it was observed that the incidence of new-onset of heart failure was lower in patients after treatment with simvastatin. Therefore, statins may have new therapeutic benefits in patients with heart failure.

References


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