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EDITORIAL COMMENT

Beyond lipid lowering: pleiotropic effects of statins in heart failure

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In the 1980s, statins were introduced in clinical practice as lipid-lowering medication. Since then, several additional, pleiotropic, effects of statins have been described, including angiogenic, antiarrhythmic, antibacterial, anti-inflammatory, antimitotic, antioxidative, antithrombotic, CRP-lowering, immunomodulatory and vascular protective (stabilisation of the atheroma plaque) activity, inhibition of smooth muscle cell proliferation and migration, inhibition of cardiac hypertrophy/remodelling, inhibition of matrix metalloproteinase and cyclooxygenase-2, inhibition of telomere shortening, and improvement of microvascular function (amelioration of endothelial function) and of autonomic nervous system function. These pleiotropic effects rest on the statin-induced inhibition of farnesyl pyrophosphate (FPP) and geranyl pyrophosphate (GPP) prenylation, resulting in inhibition of prenylation of the small GTPases Ras, and Rho and Rac, respectively. These signalling pathways regulate cell proliferation, hypertrophy, activation of inflammatory cytokines, mRNA stability, gene transcription, and reactive oxygen species (ROS) generation [1, 2].

With these pleiotropic effects, the now envisaged treatment targets of statins cover a wide range of conditions and diseases, including stem cell modulation [3], rheumatological disorders [4], wound healing [5], autoimmune diseases and cancer [6], premedication prior to percutaneous coronary intervention [7], prevention of stent restenosis [8], adjunctive therapy in acute coronary syndrome [9], improvement of saphenous graft patency [10] and prevention of sepsis [11] and preeclampsia [12].

Editorial accompanying Correale M, Totaro A, Passero T, Abruzzese S, Musaico F, Ferraretti A, Ieva R, Dia Biase M, Brunetti ND. Treatment with atorvastatin is associated with a better prognosis in chronic heart failure with systolic dysfunction: results from The Daunia Heart Failure Registry. Neth Heart J. 2013. doi:10.1007/s12471-013-0430-y

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Statins have been reported to be beneficial in heart failure of ischaemic and non-ischaemic aetiology [13]. Whereas the beneficial action of statins in heart failure with ischaemic aetiology could, at least partly, be attributed to the cholesterol-lowering effect, such an explanation is not tenable in heart failure patients with normal cholesterol levels or in heart failure of non-ischaemic nature: this underscores the relevance of the pleiotropic action of statins in the setting of heart failure. Experimental studies have shown that statins beneficially influence hypertrophy, cell death and electrical and contractile function of cardiomyocytes, and differentiation, proliferation, migration and extracellular matrix synthesis of cardiac fibroblasts, thus facilitating improvement of adverse remodelling in heart failure of ischaemic and non-ischaemic aetiology (reviewed in detail by Porter and Turner [2]). Hence, the pleiotropic potency of statins in heart failure is remarkable, and may constitute a valuable addition to the current pharmacological heart failure medication consisting of beta blockers, ACE inhibitors, angiotensin receptor blockers, aldosterone receptor blockers and diuretics [1, 2].

There are also less optimistic considerations. Statins might have harmful effects because of possible detrimental influences on the inflammation status as a consequence of cholesterol lowering (cholesterol plays a role in controlling inflammation [14, 15]), and by causing myopathy, due to the statin-based inhibition of ubiquinone synthesis impairing mitochondrial energy production [16] and due to statin-induced decreases of selenoprotein levels [17]. Moreover, in contrast to studies reporting positive effects on survival, clinical status and cardiac function in heart failure (reviewed in Bonsu et al [18]., references 6–14 and 24–26), two large RCTs, the CORONA [19] and the GISSI-HF [20] trials, have not yielded significant improvements of the primary endpoints in patients treated with rosuvastatin compared with placebo.

It has been suggested [21] that the reason for these seemingly inconsistent or contradictory results may be the fact that the CORONA and GISSI-HF studies addressed a hydrophilic

statin (rosuvastatin). In contrast to lipophilic statins such as atorvastatin, hydrophilic statins as rosuvastatin mainly act in the liver, while lipophilic statins also reach extra-hepatic tissue, including the myocardium, and could thus exert their pleiotropic actions there.

Seen in the light of the potential role of statins in heart failure, notably because of their wide range of pleiotropic action, further studies are needed, addressing the mechanisms of action at the molecular and cellular level, the structural and functional effects on the heart and other target organs or systems, such as the autonomic nervous system, and looking at clinical outcome. In the current issue of the Netherlands Heart Journal, Correale and colleagues describe the results of a prospective analysis of data from a non-randomised observational registry, comparing heart failure outpatients with systolic dysfunction treated with atorvastatin or without statins [22]. Statin administration depended on clinician judgment: 114 patients, of whom 61 % (70 patients) had ischaemic heart disease, received atorvastatin and 81 patients, of whom 33 % (27 patients) had ischaemic heart disease, had no statin prescribed. Atorvastatin use was associated with a lower incidence of cardiac death, and this association remained statistically significant after correction for age, gender, ejection fraction, use of ACE inhibitors, and beta-blocker therapy. Tissue Doppler imaging (TDI) revealed significantly better parameters of ventricular function in the atorvastatin patients. Significant differences of the same nature were found between the ischaemic heart disease subgroups with and without atorvastatin.

Correale and colleagues stress the importance of the TDI data that they present: up to now, data relating to cardiac functioning are scarce in studies regarding the effects of statins in heart failure. In the Limitations section, they emphasise the fact that randomised controlled trials are needed to confirm their results. Because their observations very likely reflect the pleiotropic effects of the (lipophilic) statin studied, comparison of a lipophilic and a hydrophilic statin [1] would be a logical choice for such a future trial.

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