

Statins for heart failure: at the crossroads between cholesterol reduction and pleiotropism?

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Statins are being hailed as the new aspirin—but are they beneficial for patients with heart failure?

Statins, also known as 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, were originally designed to lower plasma cholesterol. Over the last few years these drugs have been widely hailed as the aspirin of the new millennium. Interestingly enough, a patient asked me recently in our outpatients' department: "Doctor, could you please prescribe me a statin, because I understand that they are generally good for you." Marketing seems to have attained its goal.

Lovastatin was the first statin to be approved by the US Food and Drug Administration (FDA) in 1987. Five different statins are currently available in most European countries, and the development of new substances is well underway. Additionally, as a sixth statin on the US market, rosuvastatin was approved by the FDA in August 2003. Rosuvastatin has also been licensed in some European countries over the last months.

Statins are commonly considered safe and well tolerated. Mild side effects, however, may occur in up to 15% of statin treated patients, with symptoms related to the digestive system being the most frequently reported side effects. However, cerivastatin had to be withdrawn from the market for safety reasons in August 2001. When considering the use of statins in patients with heart failure, however, safety concerns go into a completely different direction. The idea of beneficial effects of cholesterol in chronic heart failure is based on the endotoxin-lipoprotein hypothesis.¹ Higher concentrations of total serum cholesterol, low density lipoprotein, and triglycerides were predictors of better (not worse) survival in recent studies in heart failure,^{2,3} independent of disease aetiology, age, left ventricular ejection fraction, and exercise capacity.² On the other hand, a lot of evidence has accumulated over the last years to suggest potential benefits of statin administration in this disease.

CARDIOVASCULAR RISK REDUCTION

Statin treatment consistently reduces cardiovascular risk.^{4,5} A reduction in recurrent coronary events has been observed as early as 16 weeks after the initiation of treatment.⁶ This timeframe is too short to ascribe to the positive effects of cholesterol reduction alone.⁷ The idea of statin

mediated effects beyond cholesterol lowering, so-called pleiotropic effects, has thus triggered an avalanche of research in recent years, and the chapter of investigation into statins is far from being finished.

Some of the statin mediated effects are attributable to the inhibition of cholesterol biosynthesis. Indeed, substrates downstream from mevalonate in the synthesis cascade contribute to a number of other metabolic pathways.⁸ Geranylgeranyl-pyrophosphate is a typical example. It serves as a lipid attachment to the GTP binding protein rho, which is involved in stress fibre formation,⁹ monocyte adhesion, and transmigration through the endothelium.^{10,11} A number of studies have described anti-inflammatory properties of statins. Some of these substances reduce C reactive protein (CRP) concentrations independently of cholesterol reduction.¹² Furthermore, some statins reduce the production of pro-inflammatory cytokines, which is of special interest in the treatment of chronic heart failure. Indeed, this perturbation is known to be accompanied by elevated plasma levels of tumour necrosis factor α , interleukin-1, and interleukin-6,¹³ all of which have been demonstrated to be down regulated in *in vivo* and *in vitro* models by statin application.^{14,15}

EFFECTS ON ENDOTHELIAL FUNCTION

The overall effects of statins on endothelial function merit special attention. These drugs have been shown to decrease neointimal thickening in models of carotid injury^{16,17} and also to reduce clinical events and angiographic restenosis after coronary stent implantation.¹⁸ These effects were attributed to inhibition of smooth muscle cell proliferation.¹⁹ Recent research has provided insights into the profound effects of statins on endothelial cell function. The induction of nitric oxide gene transcription, which yields an increased production of the vasodilating molecule nitric oxide, is one among a number of mechanisms contributing to an improvement in endothelial function.²⁰ Another mechanism involves antioxidant properties. Atorvastatin has recently been shown to up regulate the expression of catalase, an antioxidant enzyme, at the mRNA and protein level in an

Abbreviations: CORONA, controlled rosuvastatin multinational trial in heart failure; CRP, C reactive protein; FDA, Food and Drug Administration; GISSI-HF, Gruppo Italiano per lo studio della sopravvivenza nell'insufficienza cardiaca; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; PUFA, polyunsaturated fatty acids

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in vitro model.²¹ This downregulated the production of reactive oxygen species, which are known to inhibit nitric oxide activity.

In this issue of *Heart*, Tousoulis and colleagues²² report the results of a prospective, randomised, placebo controlled study on the effects of four weeks treatment with 10 mg atorvastatin once daily in patients with chronic heart failure. This comparatively low dose of atorvastatin reduced plasma concentrations of cholesterol by 23% within four weeks of treatment. It is tempting to speculate that even lower doses of atorvastatin than that used by Tousoulis and colleagues will still confer pleiotropic effects, possibly without lowering plasma cholesterol. Although their study was unblinded and failed to reach one of its primary end points, they provide interesting clinical insights into statin mediated mechanisms.²² Absolute blood flow values remained unchanged after treatment. This might be due to the comparatively short treatment period. However, atorvastatin treatment affected the coagulation and fibrinolysis system in that it decreased the plasma concentrations of antithrombin III, protein C, coagulation factor V, tissue plasminogen activator, and plasminogen activator inhibitor type 1. It is interesting to note that statins interfere with coagulation factors independently of where the production site is located. Future studies will tell us whether this has clinical consequences.

LARGE SCALE TRIALS

The available data strongly suggest that there is an urgent need for a prospective large scale trial to evaluate statin administration in patients with heart failure. Indeed, rosuvastatin is currently under investigation in the CORONA (controlled rosuvastatin multinational trial in heart failure) study. This study aims to recruit more than 4900 patients with heart failure of ischaemic aetiology, who will be randomised in a double blind fashion to rosuvastatin (10 mg once daily) or placebo. Patients will be followed up for approximately three years, with cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke being the primary end points. A similar study is the prospective, multicentre, randomised, double blind GISSI-HF trial (Gruppo Italiano per lo studio della sopravvivenza nell'insufficienza cardiaca), which aims to investigate the impact of n-3 polyunsaturated fatty acids (PUFA) and rosuvastatin in patients with chronic heart failure. Patients will be randomised in two steps to: (1) n-3 PUFA (1 g once daily) or placebo; and (2) rosuvastatin (10 mg once daily) or placebo. Indeed, the GISSI-prevenzione trial showed that three 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.²³ Moreover, n-3 PUFA is also known to exert antiarrhythmic and anti-inflammatory effects.

There has been some concern about lowering the availability of coenzyme Q.²⁴ Its production is affected by any statin treatment. The most important concern in heart failure, however, remains that lowering plasma lipoproteins and cholesterol too much may be detrimental. The evaluation of the right dose for the heart failure patient may therefore remain an issue for future studies.

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