

Review Article

Cholesterol Levels and the Benefit of Statins in Heart Failure

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The direct relationship between cholesterol levels and cardiovascular disease is indisputable. High cholesterol is a major, modifiable risk factor for the development of coronary artery disease. Randomised studies have shown the benefit of the pharmacological modification of cholesterol in patients with established coronary artery disease (secondary prevention), as well as in healthy individuals with a high risk of coronary artery disease (primary prevention). The large clinical studies WOSCOPS, 4S, LIPID and CARE showed that a reduction in cholesterol levels of >25% resulted in an overall reduction in the incidence of cardiac events. Statins are the most effective hypolipidaemic drugs. Their main mechanism of action involves inhibition of methylglutaryl-coenzyme reductase, which is the enzyme controlling cholesterol synthesis.

Heart failure (HF) is a health problem world wide. The risk of developing heart failure is strongly correlated with the presence of coronary artery disease¹ and statin administration has been shown to prevent the development of new HF.² In the randomised GREACE study (1600 patients),³ the administration of atorvastatin (mean daily dose 24 mg) to patients with coronary artery disease led to a significant reduction in overall mortality, coronary morbidity and mortality, cerebrovascular episodes and the incidence of congestive HF over a three-

year follow up period. The multicentre, randomised, controlled ASCOT-LLA study (10305 subjects)⁴ assessed the benefit of cholesterol reduction using a statin (10 mg atorvastatin) in hypertensive patients with normal or slightly elevated levels of total cholesterol (≤ 250 mg/dl). The patients were not known to have coronary artery disease or HF. The study was interrupted at 3.3 years, instead of the 5 years originally planned, because of the significant reduction in coronary and cerebrovascular episodes seen in the atorvastatin group. The development of fatal and non-fatal HF was included as a secondary endpoint of the study, but the two groups showed no statistically significant difference in its incidence.

Since coronary artery disease is a primary cause of HF, it is reasonable to expect that high cholesterol could have a detrimental effect on the mortality of patients with confirmed HF. However, advanced HF is associated with low cholesterol concentrations and the higher mortality among patients with HF and low cholesterol has been confirmed by research.

Vredevoe et al⁵ recorded higher mortality in 109 patients with severe HF due to dilated cardiomyopathy and low levels of total cholesterol, LDL, HDL and triglycerides, while Richartz et al⁶ found that low cholesterol levels were associated with higher mortality in 45 patients with ischaemic

Table 1. Low levels of total cholesterol as a prognostic index of unfavourable events (death or heart transplant) in patients with heart failure (three studies with follow up periods of one, five and three years).

Total cholesterol (mg/dl)	Relative risk	95% Confidence interval	p value
<200 (Rauchhaus et al ⁷)	3.5	1.1-11.0	0.036
<190 (Horwich et al ⁸)	2.071	1.539-2.787	0.002
<200.8 (Rauchhaus et al ⁹)	1.97	1.30-2.97	0.001

and dilated cardiomyopathy undergoing implantation of a left-ventricular assist system. Subsequently, Rauchhaus et al,⁷ in a study of 58 patients with HF of ischaemic or non-ischaemic aetiology, reported that total cholesterol <200 mg/dl predicted a poor clinical outcome, independently of other risk factors (Table 1). In the latter study, higher cholesterol levels were correlated with lower levels of tumour necrosis factor α (TNF- α). Horwich et al⁸ evaluated follow up data from more than 1000 patients with advanced HF, of multiple aetiologies, and determined that patients with total cholesterol levels <190 mg/dl had a twofold increase in their relative risk of death over a five-year follow up period (Table 1). The same authors also found that low levels of total cholesterol were correlated with more severe symptoms, a lower ejection fraction, and features known to be related with a poor outcome, including increased pulmonary capillary wedge pressure, urea, creatinine, and reduced levels of sodium and albumin. In another study of 114 patients with moderate to severe HF (ischaemic and dilated cardiomyopathy), total cholesterol <200.8 mg/dl was an independent predictive factor of 12-month mortality.¹² In the same study, in a second group of 303 patients with mild to moderate HF, the

probability of survival at three years increased by 25% for each mmol/l increase in total cholesterol (Table 1). This finding was independent of age, presence of cardiac cachexia, left ventricular systolic function, exercise tolerance and HF aetiology. The patients' clinical characteristics, total cholesterol and the follow up durations in the above studies⁵⁻⁹ are summarised in table 2.

An unfavourable outcome associated with low cholesterol has also been reported in the case of trauma, surgical diseases, multiple organ failure, in patients undergoing haemodialysis and in sepsis.¹⁰⁻¹³ Low cholesterol has also been associated with poor survival in the elderly.¹⁴

Investigations into the pathophysiology of sepsis have focused on the role of lipoproteins in the inflammatory immune response. LDL and HDL have been shown to bind bacterial lipopolysaccharides (LPS) and to protect against both the immediate toxic effect of LPS on endothelial cells and the overproduction of cytokines.¹⁵ Similar anti-inflammatory activity by lipids and lipoproteins may also exist in patients with HF. In HF the exposure to bacterial LPS and their translocation across the intestinal wall (probably due to oedema of the gastrointestinal mucosa) lead to increased

Table 2. Clinical characteristics, total cholesterol and follow up duration in five studies of patients with heart failure.

Study	No. of patients	Age (years)	Ischaemic aetiology (yes/no)	NYHA I/II/III/IV (%)	Ejection fraction (%)	Total cholesterol (mg/dl)	Follow up (years)
Vredevoe et al ⁵	109	46.9 \pm 13.3	0/100	0/0/36/64	20.0 \pm 6.4	160.5 \pm 55.4	1
Richartz et al ⁶	45	48.5 \pm 1.4	44/56	0/0/0/100	19 \pm 5.3	117 \pm 7	1.3
Rauchhaus et al ⁷	58	60 \pm 1	62/38	9/24/53/14	26 \pm 3	216.2 \pm 3.9	1
Horwich et al ⁸	1134	52 \pm 12	48/52	0/5/34/61	22 \pm 7	178 \pm 56	5
Rauchhaus et al ⁹	303	62.1 \pm 0.7	60/40	17/43/31/9	30.4 \pm 1.1	216.0 \pm 46.3	3

NYHA: New York Heart Association functional class

production of TNF- α by monocytes in the peripheral blood. TNF- α is correlated with the severity of HF and contributes to the progress of the disease and to cardiac damage via pro-apoptotic and negative inotropic action.¹⁶ Lipoprotein fractions bind LPS (by the formation of micelles) in direct proportion to the concentration of cholesterol in the plasma and contribute to the presence of lower levels of proinflammatory cytokines and to a more favourable course of the disease.¹⁷ This model assigns a beneficial role to lipoproteins in patients with HF and may provide an interpretation of the better survival of patients with higher cholesterol levels.

Alternatively, it is likely that low cholesterol is only a consequence of HF and does not have a pathophysiological role. Lower levels of total cholesterol may reflect greater neurohormonal activation and/or greater metabolic needs. It is also possible that low cholesterol may augur a poor prognosis because it is an index of poor nutritional state or cachexia, both of which are associated with a bad outcome.¹⁸ As in other studies referred to above,^{8,9} total cholesterol predicted outcome independently of cardiac cachexia, body mass index, and other variables associated with dietary deficiency. Further study is needed to determine the correlation mechanisms and to confirm whether low cholesterol is just a prognostic index or whether it plays an aetiological role in mortality.

HF is associated with a variety of pathophysiological changes that trigger the progress of the disease. The development of pathological ventricular remodelling is mediated by neurohormonal activation and the synthesis of proinflammatory cytokines. In this context, TNF- α appears to play the predominant role and elevated levels of this substance are correlated with reduced peripheral blood flow, apoptosis and smaller skeletal muscle mass.¹⁹ In addition, proinflammatory cytokine levels are correlated with the prognosis in HF. During the course of the disease the formation of free oxygen radicals and the overexpression of endothelin-1 and its receptors exacerbate the situation.²⁰ In fact, the endothelium-dependent dilation of the coronary and peripheral resistance vessels is blunted in HF. This ultimately leads to an impaired reactive hyperaemia in various vascular beds, an impairment in tissue perfusion and reduced muscular endurance.²¹ The above disturbances may cause weight loss and cardiac cachexia, a serious complication of HF with increased mortality, which is associated with higher plasma levels of TNF- α .

There is no proven benefit or detriment to patients who already have HF and are taking statin therapy.

Since there are no prospective clinical studies of statins in HF (the existence of HF was an exclusion criterion in all the milestone studies of statins), the question arises as to whether the proven benefit of statins seen in the absence of HF also applies to patients with manifest HF. The use of these hypolipidaemic agents has been reported to have pros and cons. There are data showing that cholesterol reduction may be detrimental in HF, but statins may have another, more beneficial action that outweighs the likely risk. There are probably significant differences between the biological effects of untreated endogenous low cholesterol and those of a drug-induced reduction in its levels.

If one accepts the viewpoint that the greatest benefit of statins is seen in the patients with the highest initial LDL or total cholesterol and/or in those with the greatest reduction, no benefit should be expected in advanced HF. If, however, one believes that the pleiotropic characteristics of these agents make up a vital part of their beneficial action in HF, a benefit may be expected, regardless of initial cholesterol levels.

Statin therapy has been shown to improve ventricular function in a variety of experimental animal models of HF, especially in those where the HF was the consequence of coronary artery ligation, subsequent infarction and later pathological ventricular remodelling. In a mouse model with post-infarction HF, fluvastatin reduced mortality, with a reduction in left ventricular cavity dilatation, myocyte hypertrophy and interstitial fibrosis.²² Similar results were observed for cerivastatin in a rat model of post-infarction HF. Left ventricular dimensions and end-diastolic pressures were lower in animals treated with cerivastatin compared to placebo and this was associated with a reduction in myocardial collagen deposition.²³

Horwich et al²⁴ performed a retrospective study of 251 patients, mean age 52 years, with advanced HF (mean ejection fraction 25%) and mean total cholesterol 165 mg/dl. Statin therapy was associated with better survival in patients with ischaemic and non-ischaemic HF over a follow up period of 22 months. In another study²⁵ it was found that short term treatment with statins had beneficial effects on patients with idiopathic dilated cardiomyopathy. The study population included 51 patients, mean age 54 years, with symptomatic HF, NYHA Class II-III and ejection fraction <40%. The patients were randomised into two groups, one received simvastatin and the other placebo. After fourteen weeks' treatment the total cholesterol in the simvastatin group (201 ± 14 vs. 223 ± 18 mg/dl, $p < 0.05$) as well as the LDL (130 ± 13 vs. 148 ± 16 mg/dl, $p < 0.05$)

Table 3. Probable mechanisms of the beneficial action of statins in heart failure.

1. Anti-inflammatory actions with inhibition of proinflammatory cytokines.
2. Positive effect on ventricular remodelling with inhibition of metalloproteinase expression.
3. Improvement of endothelial function with increased NO production.
4. Antioxidative action with a reduction in free oxygen radicals.
5. Beneficial modification of the autonomic nervous system with a reduction in sympathetic activity.
6. Down-regulation of AT₁ receptors.
7. Reduction in acute coronary events and beneficial effect on hibernating myocardium, with stabilisation of plaque, improvement in coronary artery endothelial function and an increase in blood flow.
8. Neovascularisation with mobilisation of endogenous angioblastic cells.

had reduced to below the levels seen in controls. Patients receiving hypolipidaemic treatment showed an improvement in functional class, a higher ejection fraction and significantly lower levels of TNF- α , interleukin-6 and brain natriuretic peptide.

The probable mechanisms through which statins benefit patients with HF and slow the progress of the disease are as follows (Table 3):

1. Anti-inflammatory actions with inhibition of proinflammatory cytokines. Cytokines produced by activated macrophages, vascular wall cells and cardiac myocytes are elevated in HF and seem to be inseparably linked with the progress of the disease. In particular, TNF- α and interleukin-6 exert a negative inotropic effect and promote necrosis, apoptosis and myocardial fibrosis. Statins reduce the levels of cytokines in plasma and in human monocyte cultures *in vitro*.^{26,27}

2. Inhibition of the expression of metalloproteinases (MMP-9, MMP-3 and MMP-1) by macrophages and improvement of cardiac function. MMPs are elevated during the development of dilated cardiomyopathy and have a negative effect on the remodelling process.^{28,29}

3. Improvement in endothelial function. Nitric oxide (NO) causes relaxation of the vascular smooth muscle fibres, while inhibiting platelet adhesion and controlling the permeability of the endothelium to lipoproteins and other components of the plasma. Endothelin-1 (ET-1) is an endothelium-dependent, vasoconstrictive peptide. There have been many indications in recent years that endothelial dysfunction is, in part, an imbalance between two agents that play a crucial role in

the development of cardiovascular diseases. Endothelial dysfunction, which is characterised by a lack of NO and increased production of ET-1, is seen in HF. Statins appear to increase NO production through the production of NO synthase and by reducing the synthesis of ET-1 in endothelial cells.^{30,31}

4. Antioxidative action. The formation of free oxygen radicals is known to be increased in patients with HF. A reduction has been noted in the expression of antioxidative systems, such as superoxides of dismutase and catalase, that neutralise the continuous production of free radicals.³² There is ample evidence that statins reduce free oxygen radicals.³³

5. Beneficial modification of the autonomic nervous system. HF is associated with sympathetic activation and parasympathetic withdrawal. Since autonomic dysfunction has been linked with an increase in sudden death, restoration of autonomic function should have a beneficial effect on the outcome. High doses of statins have been shown to reduce sympathetic nervous activity in rabbits with HF.³⁴

6. Down-regulation of angiotensin AT₁ receptors. Atorvastatin has been shown to down-regulate the AT₁ receptors in vascular smooth muscle cells. These receptors play a key role in the progress of HF, as has been shown by the therapeutic success of inhibition of the renin-angiotensin-aldosterone system.³⁵

7. Stabilisation of plaque, improvement in coronary artery endothelial function and an increase in blood flow, leading to a reduction in acute coronary events and episodes of reversible ischaemia, as well as a beneficial effect on hibernating myocardium.³⁶⁻³⁸ Of the three large secondary prevention studies (4S, LIPID, CARE), only the CARE study randomised 706 patients with ejection fraction <40% (and >25%) and showed that the administration of pravastatin was equally as effective in reducing coronary events as it was in patients with ejection fraction >40%.³⁹

8. Mobilisation of endogenous angioblastic cells and neovascularisation in experimental animal models.⁴⁰

The beneficial use of statins in HF seems to be independent of the underlying aetiology, since the chronic disease is associated with endothelial dysfunction, activation of proinflammatory cytokines and excessive production of free radicals.

The troubling aspects of statin administration in HF may be summed up as follows:⁴¹

1. Reduction of coenzyme Q10 levels by statins.⁴²⁻⁴³ Coenzyme Q10 is a lipid-soluble microelement with an antioxidative action, with is synthesised endogenously

through the action of HMG-CoA reductase. Its concentrations in the plasma, and probably in tissues, are reduced during statin therapy as a consequence of a reduction in coenzyme-rich LDL cholesterol and inhibition of its synthesis. This statin-induced reduction may have undesirable clinical effects in HF, which is a state of pro-oxidant stress.

2. As mentioned above, plasma lipoproteins are able to bind and to neutralise endotoxins such as LPS, which enter the circulation from the intestine. In HF the endotoxin may be an important link in the progress of the disease, through the activation of proinflammatory cytokines such as TNF- α . It has been claimed that a reduction in lipids using statins may thus increase endotoxaemia, with a further increase in plasma cytokines and deterioration of the disease.⁴⁴

Large, randomised clinical studies, currently in progress, are investigating the use of statins in patients with HF and will provide knowledge about the benefits and risks of the treatment while clearly determining the correlation between cholesterol levels and outcome in those patients. GISSI-HF is a randomised, international, multicentre study that aims to investigate the effects of n-3 polyunsaturated fatty acids and rosuvastatin on mortality and morbidity in patients with symptomatic HF. Around 7000 patients, in NYHA functional classes II to IV, will be enrolled in the study at more than 300 research centres. The aim is to show the beneficial effect of n-3 fatty acids (1 g/day) and rosuvastatin (10 mg/day) on the prognosis of patients with congestive HF (reduction in total mortality and in hospital stays).⁴⁵

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