Commentary

Debate: Statins should be used in patients with heart failure

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Abstract

Treatment to prevent progression of heart failure has been targeted to reverse the consequences of heart failure and to a lesser extent the cause – the atherosclerotic plaque itself. Less than 50% of patients with heart failure are treated with lipid intervention. Heart failure (New York Heart Association [NYHA] functional classes I and II) is associated with an increase in low-density lipoproteins (LDL) and triglycerides while high-density lipoproteins (HDL) is lowered. In NYHA class IV, cholesterol is reduced due to depressed production in the liver. Although lipoproteins, especially LDL and HDL, may have some protective effect in binding and neutralising endotoxins released from the intestine during terminal heart failure, observational studies in patients with heart failure strongly suggest that lipid modification with statins may reduce progression of heart failure as well as reducing heart failure mortality.

Keywords cholesterol, clinical trials, heart failure, statins

Coronary artery disease is the single most important cause of heart failure, accounting for more than 50% of all new occurrences [1]. Several factors are involved in the progression to congestive heart failure, such as, the number and extent of previous myocardial infarctions (MI), neurohormonal activation, inflammatory reactions, patency of the infarct-related artery, and remodelling of the myocardium. In addition, clinical complications with arrhythmias, fever, and metabolic disorders, may precipitate overt heart failure. Treatment of heart failure may therefore target several mechanisms, although, in most cases a recurrent MI is the initiating event. In order to prevent further progression of heart failure, it is most important to maintain adequate coronary circulation, either by revascularisation procedures, prevention of new lesions, or regression of established stenotic lesions.

Heart failure in the 4S Study

The effect of lipid reduction on the onset of heart failure has recently been reported in the Scandinavian Simvastatin Survival Study (4S) [2,3]. Four thousand, four hundred and forty-four patients, with a previous history of coronary artery disease and moderately elevated cholesterol, but without signs or symptoms of heart failure, were randomised to receive simvastatin (20–40 mg), or placebo. Treatment with simvastatin reduced overall mortality from 12% to 8% (a 30% reduction). The reduction in mortality was almost exclusively the result of a 42% reduction in coronary death.

Patients were followed up for more than four years. During the follow-up, about 2% of patients presented evidence of new heart failure – diagnosed as heart failure, pulmonary oedema, acute pulmonary oedema, and lung fluid [3]. The occurrence of heart failure was closely related to a recent MI. Additionally, the rate of infarcts averaged less than ten per 3-month period, but this increased to 80 during the 3-month period prior to the first occurrence of heart failure symptoms. Further, there was a 20% reduction in the occurrence of heart failure with simvastatin, compared to placebo. This was in line with the reduction of recurrent MI (30%) observed during the study.

CRP = C-reactive protein; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction; NYHA = New York Heart Association; VLDL = very low-density lipoprotein.
4S = Scandinavian Simvastatin Survival Study; ELITE II = Losartan Heart Failure Survival Study; OPTIMAAL = Optimal Trial In Myocardial Infarction with the Angiotensin II Antagonist Losartan.

The occurrence of heart failure in this group of patients was characterized by mortality more than four times higher than in patients who did not develop heart failure. In the patients with heart failure, simvastatin reduced the risk of mortality by 19% compared with 28% in those without heart failure [3]. However, the important message was that the absolute reduction of death was 6.1% in heart failure patients compared with 2.6% in patients without heart failure. This difference in absolute risk reduction was explained by the much higher mortality among patients in the placebo group with heart failure, than those without. Heart failure may therefore be a target condition for treatment with statins in patients with coronary artery disease.

ELITE II

The hypothesis is further supported by a retrospective analysis in chronic heart failure patients in the Losartan Heart Failure Survival Study (ELITE II) [4]. In ELITE II, elderly patients with heart failure were randomised to receive either losartan or captopril [4]. No difference in mortality was observed between the treatment groups. Of the 3152 patients enrolled, 11% were on a statin. The study demonstrated that overall mortality was reduced from 17.6% in patients without statins, to 10.6% among patients on a statin ($P < 0.003$). No significant difference was seen in this respect, between the losartan and captopril groups.

Effects of lipid lowering

The direct effect of lipid-lowering treatment is probably to stop progression, or even to cause the regression, of coronary artery stenosis and to stabilize coronary plaques, which in the long term will reduce the recurrence of MI [2]. Furthermore, the reduction of low-density lipoprotein (LDL) or very low-density lipoprotein (VLDL), accounts for a reduction in the inflammatory reaction observed during heart failure, which may confer additional protection. C-reactive protein (CRP) – produced by the liver in response to the inflammatory cytokines, IL-6, IL-1, and TNFα – is associated with unfavourable effects on endothelial function, plaque stability, and the myocardium [5,6].

Currently, 80–85% patients with coronary disease, but only 23–55% patients with heart failure, use lipid-lowering therapy [7,8]. This may be because patients may be reluctant to add another drug to their long list of heart failure medication. However, more importantly, no prospective trials have yet been carried out to test the efficacy and tolerance of lipid lowering in heart failure patients. Further, the benefit of reducing cholesterol in severe heart failure has recently been questioned [9]. Reduction of coenzyme Q10 (ubiquinone) by statins, has been assumed to depress the mitochondrial respiratory chain mechanism, although there is no evidence that cellular levels are critically reduced or of any clinical consequences.

Should lipids be lowered in end stage heart failure?

Inflammatory cytokines are increased during heart failure, and are assumed to be instrumental in the progression of end stage heart failure to the terminal endpoint [10]. Endotoxin (bacterial lipopolysaccharide), which is increased in end stage heart failure is a very strong stimulator of inflammatory cytokines. However, lipoproteins especially LDL and high-density lipoprotein (HDL) cholesterol bind to endotoxin and neutralise their effect [11,12]. It has therefore been suggested that it is important to maintain elevated cholesterol levels in end-stage heart failure [9]. This is supported by observations of a negative relationship between cholesterol and mortality in severe heart failure [13,14].

However, it is not known if this relationship is causal or just an epiphenomenon and it is not clearly defined which lipoprotein is the important one in this context. A recent study of 132 patients listed for heart transplantation suggested that the important lipoprotein is HDL, because low HDL was the strongest predictor of worsening heart failure [12,15]. The increase in HDL may therefore be a therapeutic goal in end stage heart failure. Further, in severe heart failure the combination of reduced liver flow and depressed cholesterol synthesis may result in low levels of circulating cholesterol. Most likely low total cholesterol is a consequence rather than a cause of the poor prognosis. Cytokines and endotoxins have been found to stimulate triglycerides and cholesterol synthesis [16]. Conversely, statins have been found to suppress the release of inflammatory cytokines [6,7] which therefore may be additive to the direct and beneficial lipomodulation by inhibition of hydroxymethyl glutaryl coenzyme A (HMG CoA) reductase.

Answers from OPTIMAAL

The Optimal Trial In Myocardial infarction with Angiotensin II Antagonist Losartan (OPTIMAAL) recently provided the opportunity to examine the relationship between lipoproteins and New York Heart Association (NYHA) functional classes [17]. This trial included patients with documented heart failure after an acute MI, and followed them for more than two years. LDL cholesterol levels were compared to Killip class at baseline, and to NYHA classification during follow-up. After an acute MI, LDL was lower in patients with Killip classes III and IV, than in classes I and II. This is most likely due to the acute phase reaction after acute MI. At six and twelve months the pattern changed, and LDL was increased in proportion to the severity of the heart failure.

At one year, LDL was higher in NYHA functional classes III and IV, compared with functional classes I and II. In functional class I, the LDL average was 2.78 mmol/L compared with 3.43 mmol/L, in class IV. At all time points HDL was lower in functional class IV than in functional class I. Although the study was not stratified for statin use, 55 % of the patients used statins at discharge. It was found that patients treated with statins had significantly fewer deaths at the one and two-year follow-up points, compared to patients not treated with statins.

The same directional trend was shown for all modes of deaths including sudden death, progression of congestive heart failure, and fatal MI. When the patients were stratified according to Killip class, the reduction in mortality with simvastatin in class IV was significantly greater compared to classes I and II. These results corroborate observations in previous trials [4,5]. Thus there is strong evidence of benefit from simvastatin treatment among patients with moderate and severe heart failure.

Conclusion

The absolute reduction of mortality with lipid-lowering treatment is greater in patients with heart failure, than without heart failure. Evidence suggests that patients with severe heart failure are the group that may improve most with statin treatment. It is not known whether the effect of statins is specifically related to LDL-lowering in patients with coronary artery disease, or if it may also affect non-ischaemic cardiomyopathy via endothelial and myocardial inflammatory responses and increasing HDL cholesterol [18]. It would be of major importance to our understanding of how statins work, to conduct a study examining their effects in patients with end stage heart failure, due to coronary artery disease as well as nonischaemic cardiomyopathy.

Competing interests

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