

Statins in Congestive Heart Failure

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73

ABSTRACT

The beneficial effects of statins on CAD and ischaemic heart failure could be well attributed to improved coronary circulation, but its effect on non-ischaemic heart failure is interesting. Initial couple of reports showed poor outcome in advanced non-coronary heart failure with statin therapy. This was thought to be due to reduced cholesterol and lipoprotein level, failing to detoxify bacterial lipopolysaccharides and endotoxins and also due to the reduced ubiquinone (coenzyme Q 10) production. However, a few recent trials on the effects of statins on non-ischaemic heart failure report beneficial effects including survival benefits.

The beneficial effect of statin in this group of patient is ascribed largely to its anti-inflammatory effect and favoured effect on endothelial function independent of lipid lowering effect.

INTRODUCTION

3-hydroxy 3-methyl glutaryl coenzyme A reductase (HMG CoA) inhibitors, statins, were originally developed to lower plasma cholesterol concentration by inhibiting the rate limiting enzyme HMG CoA reductase, in the liver and causing subsequent upregulation of hepatic LDL receptor activity. The singular LDL lowering effect itself resulted in significant reduction in the incidence of and mortality from coronary artery disease as was evident in a large number of outcome trials.

Beneficial effects of statins in coronary artery disease was subsequently attributed to its additional non-lipid lowering effects, also known as pleiomorphic effects. Important amongst them are anti-inflammatory effects by reducing proinflammatory mediators such as IL-6, TNF etc, favourable effects on endothelial function and atherosclerotic plaque stabilization effect.

USE OF STATINS IN HEART FAILURE

Retrospective analysis of ELITE II¹ and OPTIMAAL trial² revealed significant mortality reduction among patients using statins in addition to the usual treatment for heart failure. Beneficial effects of statins were also evident in the subgroup analysis of the CHARM,³ Valliant⁴ and MADIT II⁵ trials.

Retrospective analysis of the 4 S study⁶ showed a 20% lower rate of heart failure incidence with simvastatin. It also showed significant absolute risk reduction of all cause mortality in whom heart failure did develop.

All these trials however consisted of patients with ischaemic heart disease and the beneficial effects of statins could attribute its effect in improving coronary circulation.

So far as non-ischaemic heart failure and the use of statins are concerned the initial reports are somewhat contradictory, suggesting that statins could be harmful in advanced heart failure patients.^{7,8} It was suggested that low plasma cholesterol is associated with poor outcome in chronic heart failure. Lipoprotein rich in cholesterol and triglycerides can detoxify endotoxins (bacterial lipopolysaccharides) whose production is increased in heart failure.⁹ Endotoxins stimulate the release of proinflammatory cytokines which are associated with the progression of the disease.

Secondly, plasma levels of ubiquinone (coenzyme Q 10) are reduced during treatment with statins. Ubiquinone is a coenzyme in mitochondrial respiration, and its depletion could in theory adversely affect the cardiac muscle. Studies investigating dietary ubiquinone supplementation have produced mixed results for improving exercise tolerance in heart failure.¹⁰

However, two recent studies have shown beneficial effects of statins even in noncoronary heart failure independent of its lipid lowering effect.

Sixty three symptomatic non-ischaemic dilated cardiomyopathy patients randomized to simvastatin for fourteen weeks showed symptomatic improvement along with improvement

of cardiac functions, neurohumoral balance and markers of inflammation.¹¹

In a cohort of 551 patients with ischaemic and non-ischaemic heart failure (LVEF < 40%), statin use was associated with improved survival without the requirement for urgent heart transplantation.¹²

The effect of statin on diastolic heart failure is not well known, if it's beneficial effect in systolic heart failure – both ischaemic and non-ischaemic – is established, it could be used in the early stages of left ventricular dysfunction to prevent progression of heart failure.

At present clinical benefit of statin irrespective of their lowering effects may justify their use in mild to moderate heart failure. As data on statin actions on advanced heart failure is limited. It would not be prudent to advise its use in this population. Moreover, the drug interactions between statins and the drugs used in heart failure such as digoxin and warfarin too act as a deterrent for its use in such conditions.

The mechanism of benefit is not very clear; probably the anti-inflammatory effect of statins and its beneficial effects on endothelial functions are important in this regard. Trochu et al¹³ studied the effect of simvastatin on nitric oxide. No production in seventeen experimental dogs having pacing-induced heart failure. Ten dogs were given simvastatin 20 mg/kg/day. The animals receiving simvastatin had a lower left ventricular end-diastolic pressure and these animals also showed potentiation of NO-mediated vasodilatation in coronary artery as well as in coronary microvessel circulation. Therefore, it seems simvastatin maintained NO production and enhanced nitric oxide bioactivity during pacing-induced dilated cardiomyopathy. It thus seems that targeting the endothelium which participates in the control of myocardial metabolism via NO may be an important mechanism of action of statins in the treatment of heart failure.

This is in addition to the statutory effect of status on ischaemic heart disease and ischaemic cardiac failure. The ongoing large scale outcome trials of heart failure (CORONA; GISSIHF, UNIVERSE) are likely to bring out more concrete information in this area.

STATIN IN THE TRANSPLANTED HEART

A dramatic effect of pravastatin treatment on survival after heart transplantation provided further evidence of the existence of its beneficial effects on heart failure.¹⁴

Patients shortly after transplantation were randomized to either pravastatin (47 patients) or no statins (50 patients). At one year follow up the pravastatin had less frequent cardiac rejections, less

haemodynamic compromise and better survival. There was no correlation between the development of either cardiac rejection or haemodynamic compromise and coronary vasculopathy.

In a subgroup of patients the cytotoxicity of natural killer cells was lower in the pravastatin group than in the control group (9.8% VS 22.2%) This study along with the studies showing beneficial effects of statins on renal transplant recipients gave early credence to the concept that the immunomodulatory effects play an important role in the overall beneficial outcome in heart failure patients.

REFERENCES

1. Pitt B, Poole Wilson PA, Segal R, et al. Effect of locating compared with captopril on mortality in patients with symptomatic heart failure: randomized trial – The Losartan Heart Failure Survival study ELITE II. *Lancet* 2000;355:1568-9.
2. Hagnestad A, Dickstein K, Myhre E, et al. Effect of combined statin and beta-blocker treatment on one year mortality and mortality after acute myocardial infarction associated with heart failure. *Am J Cardiol* 2004; 93:603-06.
3. Swedborg K, Pfeffer M., Granger C, et al. Candesartan in heart failure – assessment of reduction in mortality and morbidity (CHARM) – rationale & design. *J Card Fail* 1999;5:276-82.
4. Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril a both in acute myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003;349:1893-906.
5. Moss AJ, Zareba W., Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Eng J Med* 2002;346:877-83.
6. Scandinavian Simvastatin Survival Study. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease. *Lancet* 1994;344: 1383-7.
7. Ranchhaus M, Clark AL, Doehner W, et al. The relationship between cholesterol and survival in patients with heart failure. *J Am Coll Cardiol* 2003;42:1933-40.
8. Horwich TB, Hamilton MA, MacLellan WR, et al. Low serum total cholesterol is associated with marked increase in mortality in advanced heart failure. *J Card Fail* 2002;8:216-24.
9. Reuchhaus M, Coats AJS, Ankar SD. The endotoxin - lipoprotein hypothesis. *Lancet* 2000;356:930-33.
10. Khatta M, Alexander BS, Kriebten CM, et al. The effect of coenzyme Q 10 in patients with congestive heart failure. *Ann Intern Med* 2000;132: 636-640.
11. Node K, Fujita M, Kitakaze M, et al. Short term statin therapy improves cardiac function and symptoms in patients with idiopathic dilated cardiomyopathy. *Circulation* 2003;108:839-43.
12. Horwich TB, MacLellan WR, Fonarow GC. Statin therapy is associated with improved survival in ischaemic and nonischaemic heart failure. *J Am Coll Cardiol* 2004;43:642-48
13. Trochu JN, Mital S, Zhang X, Xux, Ochoa M, Liao JK, Recchia FA, Hintae TH. Preservation of NO production by statins in the treatment of heart failure. *Cardiovascu Res* 2003;60:250-8.
14. Kobashigawa JA, Katznelson S, Laksh, et al. Effect of pravastatin on outcomes after cardiac transplantation. *N Eng J Med* 1995;333: 621-7.