Commentary

Debate: Should statin be used in patients with heart failure?

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Abstract

Statins reduce mortality of patients with coronary artery disease (CAD). However, by protocol, trials have excluded patients with chronic heart failure. Since the prevalent etiology of heart failure is CAD, preventing CAD may prevent heart failure progression. Statins may have other beneficial effects besides cholesterol lowering, such as anti-inflammatory properties and improvement of endothelial function. On the contrary, high levels of cholesterol can be beneficial in heart failure patients on the basis of the ability of serum lipoproteins to modulate inflammatory response. Furthermore, statins affecting mitochondrial function can have a deleterious effect on skeletal or cardiac muscles. Despite all these conflicting data, there is no evidence from trials on the effects of statins in patients with heart failure. For this reason, the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI) investigators planned a controlled trial testing the effect of statins in patients with heart failure of different etiology.

Keywords cholesterol, clinical trials, heart failure, statins

Lipid-lowering treatment with statins clearly reduces morbidity and mortality of patients with documented CAD [1–3]. However, because these trial protocols excluded patients with chronic heart failure, information on the effect of statins in this clinical condition is incomplete.

Since the prevalent etiology of heart failure is CAD, its prevention may reduce heart failure progression. Consistent with this hypothesis, a subanalysis of the Scandinavian Simvastatin Survival Study showed that statin treatment could prevent the occurrence of overt heart failure in patients with CAD [4].

Furthermore, recent studies suggest that statin treatment may have other beneficial effects besides cholesterol lowering. It has been hypothesized that the inhibition of hydroxymethyl glutaryl coenzyme A reductase can interfere with the synthesis of anti-inflammatory components, thus downregulating cytokine and chemokine production, which is activated in patients with heart failure (due to any etiology) [5]. Statin treatment can also improve endothelial function, largely compromised in patients with heart failure irrespective of the underlying etiology, and is considered responsible for multi-organ failure [6,7].

Along with this encouraging evidence, there are some suggestions that low levels of circulating lipoproteins and cholesterol may be independent predictors of impaired outcome in patients with heart failure [8,9]. An association between a cholesterol cutoff level below 5.2 mmol/L (according to the treatment guidelines of the American Heart Association) and impaired 1-year event free survival was found in a group of patients with heart failure [10]. There are several possible explanations for this finding. High levels of cholesterol can be beneficial in heart failure patients; cholesterol-rich serum lipoproteins are able to modulate inflammatory immune function because they bind and detoxify bacterial lipopolysaccharide, whose production is increased in heart failure patients (endotoxin–lipoprotein hypothesis) [10]. Lipopolysaccharide is a very strong stimulator of the

CAD = coronary artery disease.
ELITE II = Losartan Heart Failure Survival Study; GISSI = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico.

release of proinflammatory cytokines that promote heart failure progression and death.

Statins also inhibit the synthesis of mevalonate, a precursor of ubiquinone, which is a central compound of the mitochondrial respiratory chain [11–13]. Statins thus affect mitochondrial function and can have deleterious effects on skeletal or cardiac muscles. This mechanism may also be the basis of the main adverse effect of statins, which is toxic myopathy, possibly related to mitochondrial dysfunction.

Besides heart failure syndrome, other evidence also discourages the use of lipid-lowering agents in elderly patients; and patients affected by heart failure are generally old. An analysis of the Framingham database showed that the relationship between total cholesterol levels and all-cause mortality was positive at age 40 years, negligible at 50–70 years old, and negative at age 80 years [14]. For this reason, Kronmal *et al*. stated that physicians should be cautious about initiating cholesterol-lowering treatment in patients older than 70 years of age. They furthermore felt that only randomized clinical trials in older people could settle the debate over the efficacy of lipid-lowering interventions for reducing mortality and morbidity in elderly patients. In this context, it is important to remember that the mean age of patients with heart failure is approximately 65 years, as determined from trial databases, and the mean age is older than 70 years in community settings.

Even though there is both encouraging and discouraging scientific information, there is no direct evidence from randomized clinical trials on the effects of statins in patients with heart failure. Only *post hoc* analyses have been performed.

The Losartan Heart Failure Survival Study (ELITE II) showed a mortality reduction in patients with heart failure of any etiology treated with statins (nonrandomized comparison) [15]. Of nearly 900 patients with left ventricular dysfunction/failure enrolled in the statin hypothesis of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione trial, no safety problems were observed in the patients allocated to pravastatin [16]. Additionally, the favorable direction of the effect in terms of total mortality was similar among patients with and without left ventricular dysfunction and/or failure (unpublished data).

In conclusion, while there are no reliable clinical data on the benefit/risk profile of statins in heart failure, current knowledge is characterized by some suggestive observations supporting the benefit of statins but also by conflicting clinical and experimental evidence on their use. This can be considered the ideal scenario to formally test the hypothesis. For these reasons, the GISSI investigators planned a randomized clinical trial testing the effect of statins in patients with heart failure of any etiology. The main objective was to demonstrate whether long-term treatment with statins is able to reduce major clinical events such as all-cause mortality, and hospitalizations for any cause, that frequently affect this clinical condition.

Competing interests

None declared.

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