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STATINS FOR HEART FAILURE: STILL CAUGHT IN NO MAN'S LAND?

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ABSTRACT

Statins are well-known for their ability to lower serum cholesterol levels, but have properties beyond mere cholesterol reduction. These pleiotropic effects include an improvement in endothelial dysfunction, release of endothelial progenitor cells, anti-inflammatory properties, and a number of antitumour activities. In the present issue of Clinical Science, Stunpf et al. show that a 4-week treatmentcourse with the lipophilic atorvastatin ameliorates left ventricular remodelling and function, reduces serum levels of TNFα, IL-6, and monocyte chemoattractant protein-1, and increases both serum and myocardial levels of IL-10. The authors hypothesize that this shift from a pro- to an anti-inflammatory response might be beneficial in the clinical setting, because patients with low levels of IL-10 may fare worse than those with higher levels. This notion requires further investigation, but highlights the need to identify those patients who are likely to benefit from statin therapy.

Statins can lower serum cholesterol levels. That fact is beyond doubt. Patients with or at high risk of atherosclerosis benefit from statin treatment: another fact

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that is well buttressed by a large number of studies in both primary and secondary prevention. However, whether or not cholesterol reduction with statins is an aim worth pursuing in certain chronic conditions is an entirely different matter, and particularly the concept of cholesterol reduction in patients with heart failure (HF) has recently been called into question [1].

The good news about statins is that they possess properties beyond mere cholesterol reduction. These pleiotropic effects include an improvement in endothelial dysfunction [2], release of endothelial progenitor cells, anti-inflammatory properties, and a number of anti-tumour activities [3,4]. The improvement in endothelial function mediated by atorvastatin, for example, which has been demonstrated in an elegant animal model of HF post myocardial infarction, is probably due to an increase in nitric oxide production and a reduction in its inactivation [5]. Atrovastatin at a dose of 10 mg once daily for 4 weeks also achieved an improvement in forearm vasodilatory response to reactive hyperaemia in HF patients [6].

A large number of studies have shown statins' beneficial effects with regards to markers of inflammation including C-reactive protein, tumour necrosis factor-α (TNFα), and interleukin (IL) 1 and 6 [7--10]. Overactivity of the immune system has been a matter of ongoing concern in HF patients for almost two decades now [11], and especially TNFα and its soluble receptors have been demonstrated to be markers of an adverse prognosis in patients with this disease [12,13]. However, large-scale studies to directly antagonize this cytokine with specific antibodies involving more than 2000 patients ended in disappointment [14,15]. It therefore appears the right time to choose novel weapons in the battle against HF, and the overactivity of the immune system is still an interesting target [16].

As statins possess anti-inflammatory properties, the publication of prospective large-scale studies of these drugs in patients with HF were eagerly awaited. The CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) study was a double-blind study that enrolled 5,011 patients with ischaemic disease and an impaired left ventricular ejection fraction who were randomized to placebo or rosuvastatin at a dose of 10 mg once daily [17]. Patients were treated for a median follow-up of 32.8 months. Unfortunately, no significant difference in the primary end-point, a composite of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke, was noted between the rosuvastatin and the placebo group (hazard ratio [HR] 0.92, 95% confidence interval [CI] 0.83-1.02, p=0.12). The prospective, multicenter, randomized, double-blind GISSI-HF trial (Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca) was published in late August 2008 [18]. For this study, 4,574 patients were randomized to the same regimen with rosuvastatin 10 mg once daily or placebo. Like with CORONA, there was no difference in the primary endpoints of time to death (HR 1.00, 95% CI 0.90-1.12, p=0.94) and time to death or hospitalization for cardiovascular reasons (HR 1.01, 95% CI 0.91-1.11, p=0.90) between the two study arms.

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The publication of these two studies was a serious blow to the "statins-in-heart-failure" story. An earlier, yet less heeded setback were the results of a prospective study that was initially named the UNIVERSE (Rosuvastatin Impact on Ventricular Remodeling, Cytokines and Neurohormones) trial, in which 86 patients were randomized to placebo or rosuvastatin at an increasing dose (target: 40 mg once daily) in a double-blind fashion [19]. Six months of treatment did not yield any improvement in the plasma levels of C-reactive protein, TNFα, IL-6, or B-type natriuretic peptide. Additionally, there was no significant improvement in left ventricular ejection fraction.

One may wonder if these studies should set an end to studying statins in HF. However, as Sir Arthur Conan Doyle pointed out, "it is a capital mistake to theorize before you have all the evidence. It biases the judgement [20]." Thus, one may alternatively wonder if rosuvastatin was simply the wrong statin. Or used at a wrong dose. Indeed, rosuvastatin is one of the very few hydrophilic statins [21], and it has been suggested that lipophilic statins might be able to enter biological membranes more easily which yields more pleiotropic effects [22]. On the other hand, it is intriguing to note that higher cholesterol levels are associated with better (not worse) survival in patients with HF in several retrospective analyses [23,24]. A potential explanation is that cholesterol-containing lipoproteins can detoxify the bacterial cell-wall component endotoxin [25,26], which appears to play a significant role in patients with HF during oedematous decompensation [27], but it may also be responsible for immune activation in these patients under stable conditions [xi]. The available data should therefore set the stage to undertake studies in HF that fulfill two criteria: (i) to investigate statins at doses that DO NOT lower cholesterol values (but confer pleiotropic effects) and (ii) to use statins other than rosuvastatin and potentially pravastatin, the other hydrophilic substance.

The study by Stumpf *et al.* in this issue of the *Journal* comes therefore at the right time [28]. Although the authors do not provide data on cholesterol, they show that a 4-week treatment-course with the lipophilic atorvastatin ameliorates left ventricular remodelling and function, reduces serum levels of TNFα, IL-6, and monocyte chemoattractant protein-1, and increases both serum and myocardial levels of IL-10. The authors hypothesize that this shift from a pro- to an anti-inflammatory response might be beneficial in the clinical setting, because patients with low levels of IL-10 may fare worse than those with higher levels, as suggested by several studies [29]. This notion highlights another important fact: We need to identify those patients who are likely to benefit from statin therapy. This was not even an inclusion criterion for the studies of antibody therapy against TNFα [30]. It could well be that the levels of pro- or anti-inflammatory markers could help in that sense.

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