Has atorvastatin more than a DUAAL face?

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This editorial refers to 'Potent anti-ischaemic effects of statins in chronic stable angina: incremental benefit beyond lipid lowering?', by J.E. Deanfield et al., on page 2650

The search for potent and efficacious inhibitors of the enzyme HMG-CoA reductase (HMGRIs) has long been the focus of considerable research. Atorvastatin calcium, one of the first synthetically designed HMGRIs, was created in 1985 and, due to a large number of trials showing positive clinical effect, especially in the field of acute coronary syndromes (ACS), has since obtained a leading role in the worldwide drugs market, with 2008 sales of US$12.4 billion making it the top-selling branded pharmaceutical in the world. In addition to its clinical efficacy, leading to profound reduction in LDL cholesterol and in major cardiac events, another merit of this innovative drug has been the contribution of atorvastatin research protocols to the development of the so-called ‘pleiotropic’ effects concept, e.g. the effects of HMGRIs independent from (or unrelated to) their main action, namely the reduction of serum cholesterol.

A large amount of clinical evidence (including the ARMYDA studies) has indeed underscored several beneficial clinical actions of this drug that apparently go beyond the LDL cholesterol effect: it is effective in reducing post-percutaneous coronary intervention (PCI) myonecrosis, contrast-induced acute renal failure, and even in reducing disease activity in rheumatoid arthritis. Similarly, in vitro studies have shown an anti-inflammatory effect of HMGRIs. However, no simple unifying mechanisms have been put forward to explain these achievements, and proposed explanations vary widely, from microcirculatory effects to plaque-stabilizing capabilities, to a direct antiplatelet action. Inhibition of prenylation of several proteins such as the small GTP-binding proteins Ras and Rho, and the disruption, or depletion, of cholesterol-rich membrane microdomains (membrane rafts) have been proposed as pathways through which HMGRIs may modulate the immune response, fine-tuning cytokine levels, and affecting the function of cells involved in both innate and adaptive responses. Atorvastatin, specifically, has been observed to reduce the frequency of a specific subtype of T-helper lymphocyte, the CD4+CD28null subtype, potentially implicated in the transition from stable to unstable plaque, in patients with unstable angina.

Deanfield and colleagues have investigated another interesting face of atorvastatin in the DUAAL trial, i.e. its direct anti-ischaemic effect. The idea is not novel, as in 1999 the AVERT study first suggested that an aggressive medical therapy including high doses of atorvastatin is at least as effective as eliminating an epicardial stenosis with angioplasty.

The DUAAL study supports the notion that optimal medical therapy is an effective strategy in stable angina patients and that high doses of HMGRIs may significantly affect prognosis in ischaemic heart disease.

Some interesting points can be extrapolated from Deanfield’s work.

(i) Atorvastatin 80 mg is as effective in reducing ischaemia (defined as the number of ischaemic episodes in a 48 h Holter monitoring) as amlodipine in a cohort of stable coronary patients. This is in keeping with data showing that, in ACS, the outcome is affected more by the inflammatory condition of the vasculature as measured by C-reactive protein levels than by epicardial reperfusion, as we and others have shown. This notion may also help explain the data from the well-known COURAGE trial: angioplasty is an extremely potent anti-ischaemic treatment, but cannot improve survival in low-risk, stable patients if the underlying pathological condition (the coronary vascular inflammation/atherosclerosis) is not cured. The question arises, however, of whether atorvastatin reduces ischaemia by lowering LDL cholesterol only, or (also) by pleiotropic effects. Clinical studies such as ARMYDA, AVERT, and DUAAL clearly support the second hypothesis. The inclusion criteria of DUAAL (not requiring angiography) have probably allowed the enrolment of patients with severe epicardial stenosis along with others that might well have a purely microvascular cause of their symptoms. As no subgroup analysis is reported, we should infer that no significant differences were found between patients who had angiography and those who did not. This, along with the dissociation of the benefit from the LDL reduction and the lack of additional benefit in the amlodipine plus atorvastatin group, points to a mechanism independent of pure coronary stenosis, and perhaps due to a...
microcirculation vasodilatory effect, or to the reduction in vascular inflammation, or to both. Nonetheless, it should be observed that the DUAAAL trial is quite different from the COURAGE study, as the former lacks a control group receiving optimal (complete) epicardial revascularization, which would have greatly strengthened the study’s results.

(ii) This study suggests a link of C-reactive protein reduction with angina improvement. This hypothesis certainly deserves more, in-depth studies, and yet a direct effect of C-reactive protein on anginal symptoms and myocardial ischaemia is unlikely from a pathophysiological point of view.\(^\text{17}\) C-reactive protein is more likely to be a powerful marker of general and vascular inflammation, and its reduction may actually represent a sign of the efficacy of treatment. Therefore, C-reactive protein may be mainly useful for tailoring medical therapy.\(^\text{18}\)

(iii) Of note, a singular anti-inflammatory effect was observed in this study, with both atorvastatin arms experiencing a significant reduction in C-reactive protein levels, but not in serum amyloid A (SAA) and interleukin-6 (IL-6), the latter a major inducer of C-reactive protein synthesis. This dissociation between inflammatory markers is reminiscent of the MIRACL trial,\(^\text{19}\) which, although conducted in unstable patients with higher baseline levels of inflammatory markers, showed that high-dose atorvastatin produced significant reductions in C-reactive protein and SAA, but not in IL-6. This was interpreted as a possible direct effect of the drug on C-reactive protein hepatic synthesis. In the DUAAAL study, however, IL-6 levels were not measured using a high sensitivity assay, and many patients (predictably) had no measurable IL-6 concentration at baseline, making it impossible to assess a reduction after treatment.

(iv) It is surprising that the investigators of this study were able to convince the Ethical Committee of their hospitals of the need to assign ischaemic patients with a total cholesterol between 200 and 300 mg/dl to a strategy (the amiodipine-only arm) which excluded statin administration, and indeed these patients, on average, had no change in their LDL cholesterol values during the study period. There may be no other option in the future to confront the anti-ischaemic role of these two therapies, and yet the fact that (at least) low-dose atorvastatin was not given to the amiodipine-only arm is disturbing.

In conclusion, the DUAAAL trial is a significant step ahead in the treatment of stable coronary patients, confirming that high-dose statins are useful in such patients not only for their well-known lipid-lowering potency, but also due to a direct anti-ischaemic effect, linked to their anti-inflammatory action. Furthermore, this trial brings the clinical importance of achieving a systemic stabilization by means of medical treatment and risk factor reduction.

Whether these results could be translated to other classes of HMGRLs, and/or to higher risk patients, will be the focus of future research.

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**References**


