Second, since we have a relatively inexpensive and simple approach to lower urate levels with allopurinol, large, simple and relatively affordable clinical trials are feasible. These trials can be facilitated by funding from governments or by ‘factoring’ this in with other interventional trials evaluating new pharmacological agents.

In conclusion, the findings by Wong et al. are provocative enough to be explored further in large observational studies, and if their findings are robust, large interventional studies would be required to provide definitive conclusions. Clarification of the role of urate in predicting clinical events and atherosclerosis may be of potential major clinical and public health importance.

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References

Is C-reactive protein an additional, surrogate end-point for statin treatment?

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In their recent paper on the effects of atorvastatin on blood variables Riesen et al. add further information to the phenomenon that statins can reduce the concentration of the inflammation marker C-reactive protein in the circulation. This phenomenon has been repeatedly documented since the first report in 1999 and seems to be a common effect of the statins.

This reduction of C-reactive protein by statins has increased awareness of the antiinflammatory effects of statins and the possible contribution of such an effect to the rapid clinical efficacy of the treatment in cardiovascular patients. The effects on C-reactive protein opened the possibility of easily evaluating effects in patients.

Riesen et al. consider the rapidity of the effect they recorded a benefit: notably it was established in 4 weeks and stable for 3 months. It thus aided the rapid pacification of a putative inflammatory process which could increase the severity of vascular disease. A recent study with cerivastatin showed that the effect on C-reactive protein was not achieved in 3 days, further delineating the time window of effect.

The observation by Riesen et al. that mainly individuals with the highest C-reactive protein show a reduction is also supported by others and adds to the plausibility of the possibility that an underlying extra or specific disease process is rapidly modified resulting in reductions, particularly in the highest C-reactive protein values.

That in some patient groups C-reactive protein does not change upon statin treatment might
indicate that here this inflammatory aspect is not as essential as in the other groups studied.

Pre-treatment C-reactive protein as a variable for risk stratification (in combination with lipid variables) for cardiovascular risk management and statin treatment has already been extensively recommended\(^8\). The effect of statin treatment in the CARE study is strongest in patients with the highest C-reactive protein\(^9\). Uncertainty exists concerning the specificity of C-reactive protein and about the origin of high levels which may not only be related to vascular pathology but also to inflammatory processes at other sites in the body and notably is related to obesity\(^10\). It should be noted that in elderly persons a major source of C-reactive protein elevation appears to be arthritis\(^11\).

It is tempting to suggest using C-reactive protein as a surrogate end-point or monitoring variable for statin treatment in addition to cholesterol. If it reflected a qualitative change in vascular pathology or underlying mechanisms important for risk of events it would be a highly desirable surrogate end-point. The recent observation that high doses of atorvastatin in type II diabetic patients produce a dose-dependent effect on C-reactive protein reduction increases the interest in adapting treatment specifically for optimal C-reactive protein reduction\(^12\).

The question of whether the C-reactive protein reduction by statins marks a change in a relevant pathogenetic mechanism in cardiovascular disease is, however, not settled. In addition to the efforts to validate a surrogate end-point as a risk factor we have to evaluate its use as a surrogate end-point for therapy. An important step is to identify the mechanism of change.

No conclusive experimental data about the mechanism by which statins reduce C-reactive protein blood levels are available.

Several mechanisms can in principle be effective.

- Firstly, statins may reduce plasma levels by increasing the clearance or reducing the synthesis/secretion of C-reactive protein without modification of the endogenous, disease-related factors that cause increased C-reactive protein synthesis.

- A modification of C-reactive protein clearance is not likely since it is invariably in many situations\(^13\). It is also not easy to reconcile with the reports that C-reactive protein reductions by statins mainly concern higher levels of C-reactive protein (vide infra). Studies on the clearance of C-reactive protein before and during statin treatment may provide direct evidence.

- A direct modification by statins of the expression of the C-reactive protein gene while the stimulating factors do not change is a possibility as well. It has been observed that in vivo the effect mainly operates for higher C-reactive protein values, suggesting that it concerns a modulation of extra/enhanced synthesis, possibly due to cytokine stimulation. In view of the rapid turnover of C-reactive protein (half life: 17 h)\(^13\) such an effect in vivo can be effected rapidly. The option of a direct effect on C-reactive protein synthesis may be explored in (primary) hepatocyte cell cultures with and without the addition of stimulating cytokines: remarkably, such studies have not yet been reported.

These mechanisms may change a marker function of C-reactive protein without modifying the disease activity. In the absence of specific data we cannot exclude this option and a cosmetic effect on C-reactive protein as a marker remains possible. The fact that very short-term (48 h) methylprednisolone treatment results in lower C-reactive protein but not in improved clinical outcome\(^14\) stimulates caution.

- Secondly or additionally, statins may alter endogenous factors that stimulate C-reactive protein synthesis.

Cytokines such as interleukins 1\(\beta\) and 6, and TNF\(\alpha\) have been shown to influence C-reactive protein synthesis. Reduction by statins of the production of these cytokines is possible, although not predictable since fibrinogen levels regulated by similar cytokines are not reduced. The appearance of cytokines in the circulation was found to be unaltered\(^15–17\) or slightly reduced in a subgroup\(^18\) for interleukin 6 and significantly reduced for TNF\(\alpha\)\(^16,19\). The demonstration of an unequivocal link between the effects of statins on cytokines and on C-reactive protein requires the analysis of all these factors in one study.

When we treat patients with a risk of or with existing cardiovascular disease we would at least like to know that the process that is modified according to the C-reactive protein reduction is relevant to cardiovascular disease. A relatively short-term effect of statins on vascular pathology is a viable option. Pravastatin treatment showed major qualitative changes in human carotid plaques removed during carotid endarterectomy after a 3 month treatment. The changes included a clear reduction in vascular lips, lipid oxidation, inflammation, proteases and cell death, and an increase in collagen, processes implicated in plaque stability\(^19\). These changes may either be related to the local lipid-modulating effects of statins or due to specific antiinflammatory effects\(^20\) in the vessel wall or both and may be associated with C-reactive protein reductions.
Since C-reactive protein is a non-specific acute phase reactant the risk is high that statins modify other inflammatory processes. The evaluation of the effect of statins on C-reactive protein in arthritis patients, patients with infections and young obese individuals without vascular disease would help to delineate specificity. It may be a benefit when statins affect more than vascular inflammatory processes in cardiovascular patients, but at least the vascular aspect requires to be demonstrated.

One intriguing possibility for defining vascular involvement of the antiinflammatory effects of statins further is related to the observations that inflammation in the vascular wall may be recorded by a thermographic catheter. In a recent study Stefanadis et al.\(^{[21]}\) reported that the temperature of the plaques also correlated quite well with circulating C-reactive protein levels. It would be very interesting to check whether the temperature of plaques becomes reduced by statin treatment and associates with C-reactive protein reduction possibly even within 4 weeks. This would be a convincing part of the evidence linking treatment, pathogenesis and surrogate end-point to each other.

There are also data to support a direct, aetiological role of C-reactive protein in acute phases of cardiovascular disease. C-reactive protein stimulates monocytes to produce tissue factor, activates phagocytic cells, and induces complement activation\(^{[22]}\). In animals, the size of the infarction is less when in the acute phase, the complement activation by C-reactive protein is inhibited\(^{[23]}\).

It has also been demonstrated that higher C-reactive protein levels in patients with unstable angina pectoris mark the tendency to react with a stronger elevation during stimulation\(^{[23]}\). It is therefore also relevant to consider the increase of C-reactive protein during acute events and to check whether or not statins reduce this increase and if so to investigate whether this is associated with a reduction in infarction size. The discussion on C-reactive protein as a surrogate end-point would also require a quantitative delineation of its participation in the pathogenesis in acute phases.

It can be concluded that the use of C-reactive protein as an additional, surrogate end-point for statin treatment is an intriguing possibility that deserves following to find evidence for the relevance and specificity of the end-point. The route of validation of a surrogate end-point for treatment is complex, but when positive the observation that the effects of statins on C-reactive protein are achieved within 4 weeks (and possibly a little earlier as well) is attractive for monitoring and selecting the dose or possibly also the type of statin. Further evidence can guide decisions about the conduct of large-scale and longer-term clinical trials to check that the effect of the intervention on the surrogate end-point (in combination with lipid variables) predicts the clinical outcome.

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Alterations in oxygen consumption and sympathetic nervous activity in heart failure: independent or associated mechanisms?

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Congestive heart failure is a common cardiovascular disorder characterized by considerable morbidity and mortality. The pathophysiology of congestive heart failure is increasingly being appreciated as a highly complex process, representing the result of interactions between multiple processes including maladaptive ventricular remodelling, activation of neurohormonal and cytokine systems, and alterations in vascular and skeletal muscle function. Indeed, physiological and biochemical indices of many of these processes have been developed as markers of prognosis and also targeted for therapeutic intervention. Amongst these, increased adrenergic drive measured by the peripheral plasma norepinephrine concentration[1] or by the rate of spillover of norepinephrine from the failing heart[2] have been theoretically and clinically relevant. Consistent with these data, a large body of data now supports the use of beta-adrenoceptor blockade in congestive heart failure patients[3–5]. In an analogous manner, biochemical measures of activation of the renin-angiotensin-aldosterone axis are associated with adverse outcome in congestive heart failure, and clearly pharmacological antagonism of this system affords significant survival benefit[6,7]. At a more functional level, many indices of cardiac performance also bear a relationship to outcome in congestive heart failure. These include parameters such as left ventricular ejection fraction and peak VO2,[8].

The recognition that many of these parameters of physiological derangement in congestive heart failure display some association with congestive heart failure severity and outcome, leads to the consideration that some of these processes may be physiologically linked directly, rather than by association, with haemodynamic compromise. In studying the profile of sympathetic nervous activation in congestive heart failure, it has become apparent that a spatially heterogeneous pattern is evident, with cardiac sympatoexcitation being most prominent[9]. Following initial observations that the degree of cardiac sympathetic activation was related to pulmonary arterial pressures[10] we, and other groups, demonstrated a more causal relationship by demonstrating that interventions that lowered pulmonary pressure reduced cardiac sympathetic activity[11,12]. In contrast, although the presence of increased muscle sympathetic nerve activity in congestive heart failure has been well characterized, the specific driving factors that lead augmented muscle sympathetic nerve activity are unclear. A number of factors have been proposed, including increased chemosensitivity, increased left ventricular filling pressure, skeletal muscle metaboreflex mechanisms and possibly baroreflex mediated mechanisms[13].


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