Urate levels as a predictor of cardiac deaths: causal relation or mere association?

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Over the last 50 years, through a series of animal experimental studies, physiological studies, observational studies in various human populations, and randomized clinical trials, a number of risk factors have been shown to be related to atherosclerotic vascular disease[1]. Some of these risk factors are undoubtedly causal and include elevated cholesterol, blood pressure and glucose and tobacco use. Other risk factors have been proposed such as some markers of thrombosis, markers of renal dysfunction such as creatinine or microalbuminuria, inflammatory markers, markers of poverty and social disparity, psychological factors and markers of oxidant activity. It is not clear if these associations are real or spurious; and if real, whether they are causal or mere associations. These distinctions are only possible through a range of different types of studies, that include large epidemiological studies, complemented by randomized interventional trials with measurements of both clinical outcomes and atherosclerosis.

In this issue Wong et al. report a relationship between serum urate concentrations measured 1 year after strokes in 354 individuals and subsequent cardiac mortality[2]. Adjustment or stratification for a range of confounders that may increase both urate levels and risk of cardiac deaths such as diuretic use, history of diabetes or hypertension, or creatinine levels, did not alter the findings. How does one interpret this study? First how robust are the findings in Wong’s study? Although consistency across different ways of analysing the data should add to our confidence, the fact remains that the findings are based on only 19 cardiac deaths (with 10 occurring among those not on diuretics). This low number of events, the lack of impact on other vascular deaths (presumably because the authors do not report the analysis, despite having the data) and lack of information on related non-fatal events, adds considerable uncertainty to their claims. With very few events, statistical adjustments are unreliable and hence should be interpreted with considerable caution.

Second, are the findings of this study replicated in other larger studies? Here the evidence is mixed, with some studies (the MONICA Augsburg group[3], Wannamethee et al.[4], Levine et al.[5]) reporting a correlation, whereas others such as the Framingham Heart Study[6] indicating that after adjustments for other risk factors, no significant relationship was evident. At least one study reported a relationship with stroke, but no other study that we are aware of has confirmed this. So external data are only partially supportive. Perhaps this relationship could be analysed in the stored samples of various large cohorts (e.g. the Physicians Health Study[7], or long-term trials such as HOPE[8], etc.) to explore whether the epidemiological association is robust or weak.

So, how do we interpret the currently available information? First, we must be reasonably certain that the association between serum urate and major vascular outcomes (fatal and non-fatal MI and strokes) is robust after correction for covariates that could potentially be confounders by analyses of existing observational data. Such covariates include other predictors of atherosclerosis (lipids, BP, smoking, glucose), markers of renal dysfunction, and diuretic use. Second, we should be aware of the potential for reporting biases (positive studies or positive findings in some studies are reported whereas negative studies or negative findings in studies are not reported) especially in retrospective analyses of databases collected for other purposes. Unfortunately reporting biases are likely to be a very large problem in observational analyses of databases, where numerous hypotheses may be explored, but only the most ‘interesting’ (generally positive or novel) results are reported. This can only be avoided by confining interpretation to really large studies as it is more likely that they will be published irrespective of their results.

Assuming that the observational studies show an overall consistent pattern, what do we need next? Two lines of research need to be pursued. First, basic and experimental studies should explore whether there is a biological link between urate levels and mechanisms of atherosclerosis or thrombosis.
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.[1] 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[2] 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.[1] 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[3], further delineating the time window of effect.

The observation by Riesen et al.[1] that mainly individuals with the highest C-reactive protein show a reduction is also supported by others[4,5] 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[6,7] might