Commentary: Circulating cytokines and risk stratification of stroke incidence—will we do better in future?

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Development and complications of atherosclerotic cardiovascular disease are characterized by an elevated inflammatory state. Pro-inflammatory cytokines play a central role in the initiation and perpetuation of inflammatory activity. Since inflammation had been identified as crucial to the atherosclerotic process, multiple systemic inflammatory biomarkers have been investigated in relation to outcome in cross-sectional and longitudinal studies. For robust down-stream markers of the inflammatory cascade (i.e. C-reactive protein), positive associations have consistently been demonstrated for coronary endpoints. Stroke, however, is a more diverse phenotype. Confirmed relations of inflammatory markers and incident stroke starting with fibrinogen in the 1970s have been less strong compared with coronary events. Despite the reproducible association of inflammatory biomarkers with incident and recurrent cardiovascular disease, the additional risk information gained from the measurement of a single marker or a panel of biomarkers does not relevantly enhance risk prediction across risk groups based on traditional risk factors.

In this context, the article by Stott et al. in this issue examined the relation of the adipocytokine adiponectin and the two cytokines interleukin(IL)-18 and tumour necrosis factor alpha (TNFα) over a mean follow-up of 3.2 years in a nested case–control design of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) trial, a sample at high risk for cardiovascular disease. Baseline adiponectin concentrations were inversely correlated with the component endpoint ischaemic stroke only, but did not reach significance in the treatment subgroups, indicating a relatively weak association. The difference in baseline concentrations was modest and of questionable clinical value. About 26% of stroke cases remained uncategorized in the primary trial analyses, indicating the heterogeneity and difficulty of clear classification of the end-point. In contrast to the original trial, transient ischaemic attack was not examined in this article.

Adiponectin is one of multiple adipocytokines secreted by mature adipocytes. It has been in the focus of interest because it modulates insulin sensitivity and regulates body weight and body composition and has beneficial effects on vascular endothelium. In individuals free of manifest disease, high adiponectin concentrations have been demonstrated to be protective against incident type 2 diabetes and cardiovascular disease. Interestingly, it has repeatedly been shown that in manifest disease, the direction of...
association may change.\textsuperscript{5,6} Therefore, reverse causality may have diluted the results for adiponectin in this study. Patients with a history of vascular disease were analysed together with individuals without prior evidence for CVD. Although the adjustment included the presence of vascular disease, the separate examination of both subgroups of individuals would have been of interest. On the other hand, conclusions about adiponectin and its relation to disease have to be drawn cautiously. Adiponectin is expressed in different isoforms and circulates in multimers with distinct biochemical characteristics. The proportion of circulating isoforms varies with different biological states. The test used in the present study identifies low/middle/high molecular weight total adiponectin. Assays used in recent investigations differ in their ability to measure total adiponectin or its isoforms and may impair the comparability across studies.

The association of IL-18, initially identified as interferon-\(\gamma\)-inducing factor with cardiovascular outcome has remained controversial although experimental data prove a central role in the inflammatory cascade.\textsuperscript{7,8} IL-18 is involved in innate and adaptive immunity and ischaemic tissue injury demonstrated for heart, kidney and brain. In contrast to adiponectin, an association with cardiovascular disease events of comparable magnitude and the same direction has been demonstrated in initially healthy individuals and in patients with manifest cardiovascular disease.\textsuperscript{8,9} Prospective data on IL-18 and stroke are scant,\textsuperscript{10,11} and the present study adds valuable evidence that circulating IL-18 may not serve as a marker for better risk discrimination at a large scale. However, understanding the pathophysiology of IL-18 remains an objective, in particular, since experimental data and clinical trials have shown that the inhibition of IL-18 actions may be protective against damage caused by autoimmune disease and ischaemic injury.

Similarly, despite consistent experimental evidence for TNF\(\alpha\) in atherosclerotic disease and stroke, epidemiological results have been weak.\textsuperscript{11} Although assays for blood measurements have improved in their accuracy, TNF\(\alpha\) has a short half-life and requires stable preanalytic conditions which may reduce the reliability of measurements in the epidemiological setting.

A clear message from the paper by Stott et al. is that the additional measurement of adiponectin, TNF\(\alpha\) or IL-18 shows a benefit for stroke risk stratification beyond known risk factors. This finding is consistent with the prior literature. To date, epidemiological studies and trials have not supported the initial hypothesis that inflammatory cytokine measurements on a large scale can contribute to improved risk prediction in an individual.

However, a non-association in epidemiological findings does not imply that there is no causal role for inflammatory cytokines. Experimental data and our knowledge on the inflammatory cascade and related pathways provide sound evidence that the examined cytokines are central to the disease process. The measurement of inflammatory cytokines in different clinical conditions may improve our understanding of the pathophysiology of disease. Two characteristics of a biomarker have to be clearly distinguished, their role in unravelling the mechanisms of disease and their clinical application for diagnosis or risk stratification.

The present study, again, impressively demonstrates that conventional risk factors are strong indicators of risk of stroke which explain the largest part of the population attributable risk.

On the other hand, as shown by the continuing efforts to enhance risk prediction of this highly debilitating disease, there is room for improvement. Future studies will show whether cytokines will have a practical application beyond their value in the understanding of the pathophysiology of stroke.

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**References**