Fibrinogen: a predictor of stroke and marker of atherosclerosis

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Fibrinogen was demonstrated, more than 40 years ago, to be elevated among patients with acute thrombosis. The first prospective study to show an association between fibrinogen levels and subsequent cardiovascular disease risk was the Gothenburg Heart Study from Sweden in 1984. In the Northwick Park Heart Study from the UK, fibrinogen and factor VII appeared to be as effective as total cholesterol in predicting future risk of coronary heart disease (CHD). In the European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study, higher levels of fibrinogen predicted subsequent acute coronary syndromes (ACS) while lower levels, despite elevated cholesterol levels, were associated with lower risks of ACS. It remains unclear, however, whether elevated fibrinogen levels are a cause or consequence of atherosclerosis.

The use of non-invasive methods to predict cardiovascular risk has led to the proliferation of many biochemical markers that attempt to link biological mechanisms with atherosclerotic plaque rupture and thrombosis. Such markers, fibrinogen or C-reactive protein (CRP), could then, in theory, predict acute clinical events such as stroke.

The current manuscript by Kofoed et al. has attempted to relate fibrinogen as well as CRP, to risk of ischaemic stroke as well as advanced atherosclerosis. These authors evaluated, first, whether baseline fibrinogen levels during 6 years of follow-up could predict risk of ischaemic stroke; second, whether baseline fibrinogen or CRP is associated with advanced atherosclerosis; and third, to distinguish between echolucent rupture prone plaques and echo-rich stable plaques.

The first hypothesis was tested among 8755 participants from the Copenhagen City Heart Study followed for 6 years, of whom 235 developed ischaemic stroke. Among participants with fibrinogen levels greater than 3 g/l, 4% developed ischaemic stroke compared to slightly greater than 1% of those with lower fibrinogen levels (Relative Risk (RR), 1.9; 95% Confidence Interval (CI), 1.4–2.5). The mean fibrinogen level for those with ischaemic strokes was 3.6. In subgroup analyses, fibrinogen predicted risk in men but not women (despite a large number of women with a higher number of events) as well as in young to middle-aged (aged 20–65 years) but not older (>65 years) participants.

To test the second hypothesis, the authors evaluated fibrinogen and high-sensitivity CRP in patients with symptomatic carotid artery stenosis compared to age-matched controls without ischaemic cerebrovascular or heart disease. This analysis included 318 symptomatic patients referred for outpatient ultrasound with internal carotid artery stenosis greater than or equal to 50% as well as five age-matched controls per case from the Copenhagen City Heart Study. Patients had significantly increased fibrinogen levels (4.7 versus 3.1 g/l, 0.0001) as well as high-sensitivity CRP levels (3.6 mg/l versus 1.4, p=0.0001). In cross-sectional analyses, however, it is not possible to discern whether the exposure is a cause or effect of the disease.
For the third hypothesis the authors attempted to distinguish between carotid artery echolucent, rupture-prone plaques and echo-rich, stable plaques by elevations in fibrinogen and/or CRP levels. They did not find elevations of fibrinogen or CRP in either subgroup of patients with echolucent, rupture-prone or echo-rich stable plaques. These findings, however, must be viewed in light of the fact that chance, bias, and/or confounding remain plausible alternative explanations and subgroup analyses should be viewed as hypothesis generating not hypothesis testing.\(^7\)

Whether modification of fibrinogen levels will lower risks of subsequent clinical cardiovascular disease events was evaluated in a randomized trial of secondary prevention, the bezafibrate infarction prevention study (BIP) trial.\(^8\) In BIP, a randomized, double-blind, placebo-controlled trial, bezafibrate was found to reduce fibrinogen levels by 9% when compared to placebo, but did not reduce the overall risk of myocardial infarction or sudden cardiac death. With regard to this hypothesis, however, because fibrinogen may have potential benefits on other markers of risk the results may be difficult to interpret. Nonetheless, randomized trials to determine the ability of an agent to modify a thrombotic factor and to assess whether such modification in fact decreases risks of subsequent occlusive events will be a crucial component in translational research on any of the new markers, which should be of relevance not only for research investigation but also for clinical and public health.\(^4\) In these regards, the manuscript by Kofoed et al. adds potentially important and relevant information to the current totality of evidence.

References