Editorial

Is Plasma Fibrinogen Useful in Evaluating Ischemic Stroke Patients?
Why, How, and When

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See related article, pages 1687–1691.

In this issue of Stroke, del Zoppo et al report new data on the association between hyperfibrinogenemia and functional prognosis after ischemic stroke using the placebo data from 2 well-known clinical interventional trials on the use of defibrinogenating agent anclrod in acute ischemic stroke. Briefly, the authors explore the relationship of fibrinogen with the ischemic stroke outcome showing that patients with lower initial fibrinogen levels (<4.5 g/L) had better functional outcomes even when corrected for age and initial stroke severity. They confirmed a relationship between fibrinogen and prognosis independent of other cardiovascular risk factors and stroke severity.

Because patients at risk for the development of fibrinogen-related ischemic complications of atherosclerosis can be easily identified and nonpharmacological treatment (cessation of smoking, diet, exercise) seems to lower raised fibrinogen levels together with several drugs (fibrates, ω fatty acids, ticlopidine, pentoxifylline, defibrotide) clinically oriented secondary prevention recommendations should consider the role of fibrinogen in ischemic stroke. The clinical use of fibrinogen measurement should be based on (1) evidence regarding the ability of fibrinogen to predict ischemic stroke prognosis beyond that of current prognostic prediction methods or models, and (2) evidence regarding the use of prognosis prediction to treatment of ischemic stroke.

A large body of well-done studies demonstrates an association between fibrinogen levels and ischemic stroke prognosis. There are, however, uncertainties in the exact role that fibrinogen plays in the determining ischemic stroke prognosis and the reliability of fibrinogen assessment. Because fibrinogen concentrations remain associated with ischemic stroke prognosis after adjustment for many known prognostic risk factors, including age, stroke severity, and neuroradiological findings, it follows that a prognostic prediction model that adds fibrinogen would provide more accurate assessment of ischemic stroke prognosis. Whether this improved accuracy results in changes in prognostic prediction that would improve health outcomes is unknown. It is possible that the change in prognostic risk prediction that would occur using assessment with fibrinogen might change risk category and thus treatment thresholds and goals in ischemic stroke patients. Alternatively, usual secondary prevention methods may not need to be altered, but treatment thresholds and goals could be altered according to fibrinogen concentrations.

Why? Evidence Regarding the Association of Fibrinogen and Ischemic Stroke Prognosis

The pathobiological relationship of various qualitative and quantitative markers with stroke has been delineated in many clinical and epidemiological studies, but considerable interest has focused on fibrinogen only recently. Thus, the question is whether raised plasma fibrinogen is the epiphenomenon of the severity of the vascular damage taking place. The relationship between a patient’s level of fibrinogen at time of stroke and prognosis has been demonstrated in several types of studies from Europe, the United States and Asia. Although it is difficult to compare findings across studies because of their inhomogeneity, every study shows a worse prognosis in ischemic stroke patients as fibrinogen level increases, and the increase in risk persists despite adjustment for several traditional prognostic factors.

Ischemic stroke triggers an acute phase response resulting in a rise of circulating inflammatory markers. The induction of tissue injury in the vasculature triggers inflammatory response which activates upregulation of hepatic fibrinogen and initiates coagulation cascade. Because fibrinogen is an acute phase protein, the high concentrations associated with stroke and with its risk factors could at least in part be a response to brain damage and the underlying vessel wall disease. It is, however, a mistake to assume that this detracts from the value of measuring fibrinogen for clinical purposes or from the pathogenetic importance of raised concentrations. Levels of fibrinogen are strongly associated with stroke severity in almost all studied populations. Because stroke severity is also strongly associated with mortality and functional outcome after stroke, it is not surprising that fibrinogen is also associated with mortality and outcome. Fibrinogen remains independently associated with mortality and outcome even after adjusting for stroke severity; it seems that this marker may provide additional general prognostic information. However, some of its prognostic value may relate to its role as an acute-phase reactant and its potential association...
with other causes of mortality in patients after stroke, such as infections or general medical condition decline.

Furthermore, there are reasons for questioning the interpretation of raised concentrations as an epiphenomenon in response to ischemia. These include animal studies suggesting that fibrinogen has an intrinsically central nervous system toxicity, promoting apoptosis, neurodegeneration and an inhibition of functional recovery after injury.

High fibrinogen concentrations provide additional information about risk, even if it is simply a bystander of the inflammatory response in ischemic stroke and transient ischemic attack. The patients in whom the inflammation system reacts more intensely showed a greater risk of death and new vascular recurrent events. All of the studies are also consistent in showing that the effect of fibrinogen on stroke prognosis is somewhat attenuated with more thorough adjustment for confounding variables, because fibrinogen is correlated with many known prognostic factors. The contribution of fibrinogen to the improvement of any prognostic prediction model would depend on exactly which other variables are included in the model. It follows logically that measures of prediction such as area under the receiver-operating-characteristic curve would always be better with inclusion of fibrinogen than without it.

How? Methods to Measure Plasma Fibrinogen

Many different assays, such as clonal gravimetric method, Clauss functional methods and automated nephelometric determination, are now commercially available satisfying requirements for standardization, specificity, reliability and reproducibility. An enzyme-linked immunosorbent assay (ELISA) with a high specificity for intact fibrinogen has also been developed. It does not cross-react with the early products of fibrinogen degradation and only detects fibrinogen molecules with at least one intact $\alpha$ chain. At the moment, the functional methods are the most widely used, but these methods are probably not as suitable as the ELISA for analyzing samples from acute stroke patients after thrombolytic therapy. Finally, because of its linearity in increasing risk of death or new vascular events in stroke, the definition of normal ranges for plasma fibrinogen, distribution in populations and standardization of cutoff points where fibrinogen begins to contribute to stroke prognosis are areas which require urgent research. Values of 2.5 to 3.1 to 3.5 g/L are mentioned as ‘normal’ but fibrinogen levels as low as 50% of ‘normal’, and even as low as 0.8 g/L are sufficient for normal coagulation without bleeding tendencies. Levels usually observed are therefore well above those required for normal coagulation or optimal platelet function.

High fibrinogen levels have also been reported to be accounted for by environmental and genetic differences. Plasma fibrinogen levels are under strong genetic control as 20% to 50% interindividual variation has been explained by the genetic polymorphisms in fibrinogen gene. Among all, the $\text{A}31$ and the $\text{A}32$ polymorphism in the promoter region of FBG-$\beta$ is observed to be the strongest genetic variant associated with increased fibrinogen levels and ischemic stroke in several populations, although some studies have failed to show such associations. The coordinated interactions between genetic variants of these genes may regulate plasma fibrinogen homeostasis which may predict the individual variations in hemostasis. Haplotype studies comprising all 3 fibrinogen genes have revealed that FBG-$\alpha$ and FBG-$\gamma$ are associated with the risk of stroke independent of fibrinogen levels whereas, FBG-$\beta$ gene is associated with elevated fibrinogen levels.

Some polymorphisms modulate the response of genes to environmental stimuli, ie, the same stimulus may cause different levels of fibrinogen in subjects with different polymorphisms. This is consistent with the possibility that a theoretical concentration (determined by genes) and a real concentration (because of the interaction of genes with the environment) of fibrinogen may play a role in the intra- and interpopulation variability of fibrinogen levels and may explain, at least in part, the differences in an enhanced acute-phase response after an ischemic stroke. Individual susceptibility in immune response is based at least in part on genetic background. Variations in baseline plasma fibrinogen of individuals may reflect differences in fibrinogen responses caused, for example, by genetic differences. However, reverse causation and confounding may explain why conventional observational epidemiological studies consistently find a positive association between fibrinogen and stroke outcome. Fibrinogen levels are related to many ischemic stroke prognostic risk factors (ie, age, sex, comorbidities) in a way that would generate a positive fibrinogen-ischemic stroke association.

When? Goals of Fibrinogen Screening in Stroke Patients

The primary goal of biomarker use in stroke patients should be the identification of high-risk individuals who can be targeted for aggressive acute treatment and improved secondary prevention measure. Because the compliance with lifestyle recommendations is directly related to the absolute risk perceived by the patients, the fibrinogen addition in screening procedures provides an improved prediction tool; fibrinogen consideration may have usefulness for this reason alone. However, from a more scientific point of view, the relative risk of worse prognosis associated with fibrinogen, demonstrated in many observational studies, cannot simply be plugged into existing prognostic risk assessment tools without knowing how fibrinogen correlates with the other prognostic risk factors in the model. Furthermore, accompanying treatment algorithms would need to be appropriately designed in order to improve patient outcomes. In particular, the effects on stroke prognosis of lowering raised fibrinogen concentrations have not yet been established. There is currently no definitive evidence that lowering fibrinogen will necessarily improve prognosis. However, many secondary prevention interventions have been linked to lower fibrinogen levels. In particular, diet, exercise, and smoking cessation all lead to both reduced fibrinogen levels and reduced vascular risk. Several pharmacological agents proven to reduce vascular risk influence fibrinogen levels. Apart from ancrod, which is given intravenously and only in acute situations, there are no selective fibrinogen-lowering agents. If and when these do become available, their long-term safety as
well as their effectiveness will have to be established to identify the best therapeutic regimen based on fibrinogen concentrations integrated with clinical findings and objective imaging.

Whom should be tested is also an unresolved question. Such a measurement may guide considerations of further evaluation or treatment—presumably patients with high levels will be treated more aggressively, which is substantially equivalent to increasing the estimate of their worse prognosis. It assumes the assessment of traditional prognostic factors and calculation of absolute risk before measurement of fibrinogen, but at the moment there are no well-defined and definitely accepted ischemic stroke prognostic scores.

Furthermore, appropriate clinical cut-points for fibrinogen in the setting of acute ischemic stroke remain uncertain, as does the timing of fibrinogen evaluation in relation to the onset of cerebral ischemia. The use of efficiency considerations and cost-effectiveness analysis as a factor to set appropriate fibrinogen thresholds makes it problematic. Secondary prevention strategies and treatment algorithms that incorporate fibrinogen need to be developed and evaluated for efficacy and cost-effectiveness. With these types of criteria, a treatment or diagnostic strategy must not merely produce better health outcomes, but must produce better health outcomes at reasonable cost. Thus at this point in time, the benefits of fibrinogen testing remain uncertain, and decisions on the interpretation of fibrinogen concentrations and on clinical management must inevitably be based on incomplete evidence. However, with the fact that fibrinogen is associated with stroke prognosis after adjustment for many known prognostic risk factors, it follows that a prediction model that adds fibrinogen would provide more accurate assessment of ischemic stroke prognosis. Whether this improved accuracy results in changes in prognostic prediction that produce improved health outcomes is unknown, although it is possible that the change in prognosis that would occur using assessment with fibrinogen might change prognostic risk category and thus treatment thresholds and goals of actual American Heart Association (AHA) guidelines.

In conclusion, given the current evidence, is fibrinogen concentration useful in patients with a transient ischemic attack or an ischemic stroke? In our opinion, the answer is probably ‘yes’, but there are still many unanswered questions regarding its use in ischemic stroke and further systematic studies are necessary. However, as a general thought, one must consider that, independently of all biomarkers that technology and the progress of knowledge will provide, a good clinical and neurological examination provides highly reliable measures of neurological deficits efficiently guiding patient management and rehabilitation.

Disclosures

None.

References


**Key Words:** fibrinogen ■ risk factor ■ cerebrovascular disease ■ inflammation ■ outcome ■ prognosis
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