Fibrinogen and Its Degradation Products as Thrombotic Risk Factors

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ABSTRACT: **Recent meta-analyses of prospective studies have shown that plasma levels of both fibrinogen and fibrin D-dimer are independent predictors of ischemic heart disease. Although at present reported studies using different assays do not show heterogeneity, there is a need for prospective comparison of different assays, as well as for development of standards. Collaborative development of the clinical use of these risk predictors is also required. Finally, the causal significance of the associations of fibrinogen and D-dimer with thrombotic events remains to be established by randomized controlled trials of reduction in their plasma levels.**

KEYWORDS: **Fibrinogen; Fibrin degradation products; Thrombosis**

INTRODUCTION

The aim of this review is to estimate the predictive values of (1) plasma fibrinogen, and (2) plasma levels of fibrin degradation products (FDP), commonly measured as fibrin D-dimer, for thrombotic events: myocardial infarction (MI) or fatal ischaemic heart disease (IHD), stroke, and venous thrombosis. The influences of assay methodology are discussed, as are the biological and clinical implications. We concentrate on recent findings, updating our review of studies published up to 1999.[1]

FIBRINOGEN AS A RISK PREDICTOR

A recent systematic review of 18 prospective studies of plasma fibrinogen and IHD events observed that the risk ratio was 1.8 (95% CI 1.6–2.0) for individuals in the top third compared to individuals in the bottom third of baseline assays.[2] In most of these studies, adjustment had been made for potential confounders of the relationship between fibrinogen and IHD (e.g., age, smoking habit, and presence of baseline evidence of cardiovascular disease). The risk ratio was similar between individuals with and without baseline evidence of cardiovascular disease. There was no significant heterogeneity between studies, that used a variety of coagulation, heat precipitation, and immunoprecipitation assays.[2]

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TABLE 1. Suggested adjustment to the American Heart Association multivariable risk profile formulation for ischaemic heart disease risk (IHD)[a]

Fibrinogen (g/L)	Multiplication Factor for Multivariate IHD Risk	
	Men	Women
<2.35	0.83	0.77
2.35–3.35	1.00	1.00
>3.35	1.20	1.30

[a]To include the independent effect of plasma fibrinogen. Modified from Reference 6, based on Framingham data for fibrinogen thirds. Tertiles should be modified for different fibrinogen assays.

The independent association of fibrinogen and IHD is, therefore, well established, both in prospective studies and cross sectional studies.[2,3] The association is similar to that of conventional, modifiable IHD risk factors, such as smoking habit, blood pressure, and serum cholesterol. Fibrinogen adds to the predictive value of these traditional IHD factors,[4] and is a stronger predictor for all cause mortality.[4,5] For these reasons, it has been suggested that fibrinogen be added to multivariate IHD risk factor profiles[6] (see TABLE 1). Future collaborative analyses should refine the place of fibrinogen in multivariate risk prediction of IHD, especially if they can access individual data rather than grouped data. Readers interested in such collaboration are invited to contact Dr. J. Danesh, Fibrinogen Studies Collaboration, CTSU, Harkness Building, Radcliffe Infirmary, Oxford OX2 6HE, UK.

In other prospective studies, plasma fibrinogen has been associated with increased risks of stroke, peripheral arterial disease, venous thrombosis, atrial fibrillation, heart failure, restenosis following angioplasty or bypass grafting, and progression of arterial narrowing (see Refs. 1 and 3). Additional studies and systematic reviews are required to establish, with confidence, the strength of these other associations of fibrinogen.

THE INFLUENCE OF ASSAY METHODOLOGY ON THE RELATIONSHIP BETWEEN FIBRINOGEN AND IHD

As noted above, a recent systematic review of prospective studies of plasma fibrinogen and IHD events observed no significant heterogeneity between studies that used a variety of fibrinogen assays.[2] However, such overviews are less sensitive than direct comparisons between various assays to detect effects of assay methodology. In the only direct comparison study reported to date, a heat precipitation nephelometric assay was a significantly stronger predictor of IHD events than a semi-automated clotting rate assay.[7] In a further study by the same groups, the former assay also showed a closer relationship to the trans-European gradient of IHD events than the latter assay.[8] These studies suggest that further comparative studies are required in order to establish the relative power of different fibrinogen assays for prediction of IHD and of other thrombotic events. They also suggest that qualitative differences in plasma fibrinogen are related to risk of IHD.

Nieuwenhuizen and colleagues[9] have also demonstrated that qualitative differences in plasma fibrinogen are related to IHD (acute MI), by calculating the ratio of clottable to intact fibrinogen. The latter was assayed using an ELISA for the total of higher molecular weight (HMW) and lower molecular weight (LMW) fibrinogen. Normal donors had a ratio close to 1,whereas patients with acute MI had a mean ratio of 1:6 before thrombolytic therapy, rising to 2:1 at 24–72 hours after thrombolytic therapy. It was suggested that this increased ratio represents "hyperfunctional" fibrinogen (i.e., faster clotting than normal) in acute MI, perhaps because of a shift in the ratio of HMW: LMW: LMW′ fibrinogen.[9]

Adopting Nieuwenhuizen's suggestion that this ratio be evaluated in epidemiological studies of cardiovascular disease because this may be a more sophisticated marker of fibrinogen activity than routine assays, such as the von Clauss assay,[9] we performed two case control studies, one of previous myocardial infarction[10] and one of chronic peripheral arterial disease.[11] In both studies, we observed significant elevations of the ratio, that were smaller than the elevations in patients with acute MI. The elevations observed in individuals with previous MI were not due to "reactant" increases in plasma fibrinogen, because they persisted in multivariate analysis, including plasma levels of C-reactive protein and interleukin-6 (unpublished observations).

Collectively, these data suggest that qualitative changes in plasma fibrinogen are related to both acute and chronic IHD. Such observations have implications, not only for standardization of fibrinogen assays, but also for the development of fibrinogen standards.[12] To date, fibrinogen standards have been defined in terms of assays of clottable fibrinogen.[12] In future, we suggest that consideration be given to the inclusion of different fibrinogen assays when defining the "content" of fibrinogen standards, as well as to the development of both "high" and "low" fibrinogen standards, which may well differ in ratio between fibrinogen assays. The choice of both assay and standard is clinically important in selection of tertiles for risk prediction (TABLE 1).

SIGNIFICANCE OF THE FIBRINOGEN–THROMBOSIS RELATIONSHIP

To date, there is little evidence for an association between known fibrinogen gene polymorphisms and IHD or other cardiovascular disorders[13] (see also review by Green, in this volume). Hence, the associations between plasma fibrinogen and these clinical disorders may be posttranslational. Studies of increased ratios of clottable, intact, "native" plasma fibrinogen in individuals with IHD (reviewed in the previous section) are consistent with this hypothesis. However, the posttranslational influences that cause these associations are at present unclear: environmental influences (age, smoking, overt cardiovascular disease, and acute phase reactions) do not appear to explain the association. Additional collaborative studies between fibrinogen biochemists and epidemiologists may shed light on this question.

Although there are several plausible biological mechanisms through which increasing plasma fibrinogen may increase risk of thrombosis and arterial disease,[1] randomized controlled trials of fibrinogen reduction are required to establish whether or not this relationship is causal.[1] At present, agents reducing plasma fibrinogen are limited:

- Fibrates reduce mean plasma levels by only about 10% and also affect blood lipids.
- Ticlopidine also reduces mean plasma levels by only about 10% and also affects blood platelets.
- Thrombolytics reduce mean plasma levels by 50–90% (depending on agent and regimen) and also lyse thrombi and hemostatic plugs.
- Defibrinogenating enzymes such as ancrod selectively reduce mean plasma levels by about 90%, and offer promising initial results in prophylaxis of venous thromboembolism[14] and in treatment of acute ischemic stroke.[15] However, this treatment is limited by the need for parenteral administration and the development of resistance after several weeks, due to antibody formation.

Progress in this field would be greatly facilitated by the development of oral agents with a more potent, long term effect on plasma fibrinogen levels, for example 25% reduction in mean plasma level. In other words, the equivalent of statins in reduction of LDL cholesterol is needed.

FIBRIN D-DIMER AS A RISK PREDICTOR

A recent review of seven prospective studies of plasma D-dimer and IHD events (see Ref. 1) and of an additional large, case control study, has observed that the risk ratio was 1:7 (95% CI 1.3–2.2) for individuals in the top third compared to those in the bottom third of baseline assays.[16] This association is of similar strength to that between plasma fibrinogen and IHD. In most of these studies, adjustment had been made for potential confounders; and the risk ratio was similar in patients with and without cardiovascular disease. There was no significant heterogeneity between studies. Two studies also adjusted for plasma fibrinogen (which correlates weakly with plasma D-dimer).

Two prospective studies, that compared two assays, showed similar associations between assays and IHD events[17,18] Further comparative studies are required. As with fibrinogen, D-dimer showed an association with the trans-European gradient in IHD.[8] Fewer data are available for studies relating D-dimer to stroke, venous thrombosis, or other thrombotic disorders.

SIGNIFICANCE OF THE D-DIMER-THROMBOSIS RELATIONSHIP

The most obvious explanation of the independent association of plasma fibrin D-dimer and IHD (and possibly other thrombotic events) is that D-dimer is a measure of hypercoagulability; that is, the formation and lysis of crosslinked fibrin, which, in individuals without inflammatory or neoplastic disease, is likely to be predominantly intravascular. Support for this hypothesis comes from our studies in patients with atrial fibrillation, in whom elevated plasma D-dimer levels are rapidly normalized by cardioversion[19] or warfarinisation[20,21] each of which normalizes the increased risk of thromboembolic stroke. The time is ripe for randomized controlled trials[1,22] of

(1) selective anticoagulant prophylaxis in patients with elevated plasma D-dimer, and (2) control of anticoagulant prophylaxis by normalization of elevated D-dimer levels, in contrast to the historical use of blood clotting times.

CONCLUSION

We conclude that both plasma fibrinogen and fibrin D-dimer are significantly associated with risk of thrombotic ischaemic heart disease. Additional data from prospective studies (as well as collaborative systematic reviews) are required in order to establish, with confidence, the size of these risks, the influence of assay methodology, the influence of genetic and environmental factors, their associations with thrombotic stroke and venous thrombosis, and finally the causal significance of such associations as shown by controlled trials of reduction in plasma levels.

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