Fibrin D-dimer: a useful clinical marker of thrombogenesis?

Gregory Y. H. Lip and Gordon D. O. Lowe*
University Department of Medicine, City Hospital, Birmingham, U.K., and *Haemostasis, Thrombosis and Vascular Medicine Unit, University Department of Medicine, Royal Infirmary, Glasgow, U.K.

INTRODUCTION

Thrombus formation (thrombogenesis) is a process involving platelet adherence to the vessel wall (sometimes at sites of endothelial injury), platelet aggregation and release, thrombin generation and fibrin formation. In addition, it is also well recognized that the process of atherosclerosis is closely related to ongoing formation and organization of mural thrombi [1, 2]. Improved biochemical definition of the factors involved in thrombogenesis and newer assay techniques have allowed the clinical measurement of such factors in assessment of the process of thrombogenesis. The study of the possible mechanisms of thrombogenesis in conditions with a particular risk of thromboembolism is therefore feasible. Measurement of these plasma factors may allow the screening of patients in order to identify those most at risk of thromboembolism, and hence those who might benefit most from anti-thrombotic therapy. In addition, these plasma factors may provide prognostic information and enable monitoring of the efficacy of anti-thrombotic therapy. Such measurements also raise the possibility of developing new strategies in anti-thrombotic therapy.

One marker which is attracting interest as an index of intravascular thrombogenesis is the plasma level of the fibrin D-dimer antigen. As fibrin D-dimer is considered to originate from cross-linked fibrin assembled during thrombus formation, a rise in fibrin D-dimer levels is indicative of thrombus formation. Plasma fibrin D-dimer assays are currently available from several manufacturers in clinical practice for the diagnosis of disseminated intravascular coagulation and venous thromboembolism. Recently, prospective studies have suggested a prognostic value of quantitative assays of plasma fibrin D-dimer in the prediction of arterial thrombosis; associations with atrial fibrillation and with other cardiovascular disorders have also been demonstrated.

FIBRIN D-DIMER FRAGMENT AND THROMBOGENESIS

In the process of thrombus formation, fibrinogen is converted to fibrin by the action of thrombin, and the resulting fibrin monomers polymerize to form a soluble gel of non-cross-linked fibrin (Fig. 1). The latter is then cross-linked by thrombin-activated Factor XIII to form a stable, insoluble fibrin clot which is relatively resistant to lysis.

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Correspondence: Dr G. Y. H. Lip, University Department of Medicine, City Hospital, Dudley Road, Birmingham B18 7QH, U.K.
Subsequent activation of the fibrinolytic system results in formation of the enzyme plasmin, which cleaves both fibrinogen and fibrin to yield fibrin degradation products. Of these, only the degradation products from cross-linked fibrin contain the D-dimer fragment, first identified by Gaffney's group [3, 4]. The process of turnover of cross-linked fibrin can therefore be assessed by the measurement of plasma fibrin D-dimer levels, which are an indirect marker of intravascular fibrin formation. Measurement of this plasma factor reflects intravascular levels of fibrin turnover, without significant interference from fibrinogen or non-cross-linked fibrin degradation products, and confirms that both thrombin generation and plasmin generation have occurred. Measured levels reflect both the formation (i.e. lysis of cross-linked fibrin) and clearance of fibrin D-dimer from the circulation. The normal half-life of fibrin D-dimer is approximately 48 h, but this has not been studied in clinical situations. Clearance of fibrin D-dimer is probably via the reticulo-endothelial system, although we are not aware of any studies in humans in this area.

Although the deposition of fibrin during thrombus formation is a function of the surface area of the clot, even small clots can cause active fibrin deposition and the production of fibrin D-dimer [5]. This would suggest that increased plasma fibrin D-dimer can be an indicator of even very small amounts of thrombus formation. High levels of plasma fibrin D-dimer are therefore possibly predictive of either actual intravascular thrombosis or a hypercoagulable state. Thus, in conditions without overt thrombus formation, e.g. coronary artery disease or hypertension, the high D-dimer levels indicate that actual thrombus may not be required for this elevation, although subclinical thrombogenesis may still be occurring.

It has also been suggested that measurement of plasma D-dimer can provide an estimate of the potential fibrinolytic activity of circulating blood: correlations with plasma levels of tissue plasminogen activator and plasminogen activator inhibitor activities have been described [6]. However, high fibrinolytic activity may result in a relative lack of substrate in terms of cross-linked fibrin, resulting in low values of plasma D-dimer. Measurements of fibrin D-dimer, tissue plasminogen activator and plasminogen activator inhibitor thus reflect different aspects of the fibrinolytic system, and are informative in different clinical situations.

In the clinical situation, elevated plasma levels of fibrin D-dimer are usually found in conditions associated with intravascular (and sometimes with extravascular) activation of the coagulation system [5]. For example, high levels have been found in patients with overt thrombosis, such as disseminated intravascular coagulation, pulmonary thromboembolism and deep venous thrombosis [5, 7-10]. However, increased extravascular fibrin turnover after major injury or surgery, infection (e.g. pneumonia), inflammation (e.g. rheumatoid arthritis) or malignancy can also activate fibrinolysis and generate increased plasma fibrin D-dimer levels [4, 11, 12].

Finally, recent studies show that plasma fibrin D-dimer levels within the 'normal' range predict both arterial thrombotic events [13-15] and postoperative thrombosis [16], suggesting that increased fibrin turnover may be a continuum between health, 'statistically' increased fibrin turnover in a prethrombotic state and 'overtly' increased fibrin turnover in acute thrombosis (or sometimes in acute extrinsic fibrin formation, as follows injury or surgery).

DEEP VENOUS THROMBOSIS AND PULMONARY THROMBOEMBOLISM

Patients with deep venous thrombosis or pulmonary thromboembolism have high levels of plasma fibrin D-dimer [7-10, 17, 18]. A normal plasma fibrin D-dimer level has been suggested as a good predictor for the absence of acute pulmonary thromboembolism [7, 8, 10]; in other words, the test is sensitive. In one study, measurement of fibrin D-dimer had a negative predictive value of 0.97 [8]. The sensitivity for the diagnosis of deep venous thrombosis and pulmonary thromboembolism is considered to be high, at approximately 0.90 and 0.92 respectively [9, 17, 19].

However, the specificity of plasma fibrin D-dimer levels for the diagnosis of deep venous thrombosis and pulmonary thromboembolism is low (0.29–0.42) [7, 17, 19]. This may reflect its elevation in other conditions resulting from extravascular fibrin formation (e.g. arthritis, cellulitis and pneumonia). One diagnostic advantage of measuring fibrin D-dimer may be that initial heparin treatment does not alter measured levels, while other markers of activated coagulation such as prothrombin fragment 1 + 2 and thrombin–anti-thrombin complexes are reduced during heparin therapy, probably due to their shorter half-lives in the circulation [20].

Could this marker be employed prospectively in patients who are at high risk of venous thromboembolism? This possibility was addressed in a study of post-trauma patients, and two patterns were seen. An initial increase, followed by a rapid decrease in plasma D-dimer levels to normal was seen in most patients; however, if a secondary increase in D-dimer levels was observed, these patients were at risk of venous thromboembolism, although sepsis and adult respiratory distress syndrome could also cause a similar late increase [21]. Clearly, further work is required to assess the usefulness of the D-dimer test in this situation. In lower-risk patients, such as those undergoing major general surgery, preoperative fibrin D-dimer levels were predictive of postoperative deep venous thrombosis [16]. This suggests that intravascular coagulation may already be occurring in these patients, and that the 'stress' of surgery (with release of tissue factor, venous stasis and decreased fibrinolytic activity) pushes the
balance towards thrombosis. It should be noted that further rises in fibrin D-dimer are observed after surgery, values tending to be higher in patients with post-operative deep venous thrombosis [16].

In summary, fibrin D-dimer levels have a negative predictive value for venous thromboembolism, i.e. it is clinically useful to 'rule out' venous thrombosis with a normal result, although a proper clinical history and physical examination are also essential. However, routine measurement of this marker has a low specificity, with little positive predictive value from a raised plasma level [10].

**INTRACARDIAC THROMBI**

One factor determining whether or not patients with intracardiac thromboli are at risk of embolization is the activity of thrombus formation. An inactive thrombus is one which is endothelialized, and hence is at low risk of embolization [22]. This is in contrast to freshly formed thrombi which have an irregular surface and ongoing active thrombus deposition and lysis [23-25].

It has been suggested that the measurement of plasma fibrin D-dimer concentration may be a useful screening method for patients at risk of mobile or 'active' thrombi. This was demonstrated in a prospective study of 63 patients with mitral stenosis in whom a significantly elevated plasma D-dimer level was found in the ten patients with mobile intracardiac thrombus when compared with patients with a non-mobile thrombus [26].

Umemoto et al. [27] also examined clotting and fibrinolytic activity in 37 patients with intracardiac thrombi: plasma fibrin D-dimer was found to be positively related to clotting activity. If an excess of thrombosis over fibrinolysis was present, there was a substantial risk of arterial embolization [27]. However, these were relatively small studies and larger studies are required to assess the possible application of fibrin D-dimer measurement in high-risk groups for active intracardiac thrombi.

**ATRIAL FIBRILLATION**

A hypercoagulable state may explain the high risk of thromboembolic stroke in patients with chronic atrial fibrillation, and elevated plasma fibrin D-dimer levels have been shown in such patients [28, 29]. In the study by Kumagai et al. [29] for example, levels of fibrin D-dimer were significantly elevated in 73 patients with chronic atrial fibrillation, and this was irrespective of the presence of underlying structural heart disease. However, these studies were small and the controls were not population-based. A recent larger, population-controlled study by Lip et al. [30] confirmed these findings, and also showed a positive correlation of plasma fibrin D-dimer with plasma von Willebrand factor, a marker of endothelial dysfunction [31]. These studies therefore indicate increased fibrin turnover in patients with atrial fibrillation, and also an interaction between thrombogenesis, blood flow abnormalities and endothelial dysfunction (as initially suggested by Virchow in 1856 [32]).

We have demonstrated that levels of fibrin D-dimer were highest in patients who were not on any anti-thrombotic therapy, while those who were established on warfarin had the lowest fibrin D-dimer levels [30]. In contrast, patients established on aspirin alone had intermediate levels of fibrin D-dimer, with no statistically significant difference from patients not on any anti-thrombotic therapy [30]. Patients in whom oral anti-coagulants were started prospectively demonstrated a sequential normalization in fibrin D-dimer levels, which was statistically significant after 2 weeks on warfarin therapy [30, 33, 34]. However, in patients with atrial fibrillation in whom aspirin alone (300 mg) or ultra-low-dose warfarin (using a fixed dose 1 mg regime) was introduced, no significant alteration in fibrin D-dimer levels was demonstrated [34]. These findings are consistent with the prophylactic efficacy of warfarin in patients with atrial fibrillation [35].

Patients with paroxysmal atrial fibrillation are considered at intermediate risk of thromboembolism (between the risks of chronic atrial fibrillation and sinus rhythm), and these patients also had intermediate levels of plasma fibrin D-dimer ([36] and Lip G.Y.H., Lowe G.D.O., unpublished work). Patients with chronic atrial fibrillation who were not on anti-coagulants and who were cardioverted to sinus rhythm also demonstrated a sequential fall in fibrin D-dimer levels (but not plasma fibrinogen levels), which were reduced to normal levels 2 weeks post-cardioversion [37]. This suggests that the intracardiac blood flow abnormalities in atrial fibrillation were predominantly responsible for the increased fibrin turnover.

In view of the potential value of fibrin D-dimer levels in assessing the hypercoagulable state in patients with atrial fibrillation, prospective studies are required to assess the predictive nature of plasma fibrin D-dimer for thromboembolic risk in these patients. We need to know whether or not a high fibrin D-dimer level will predict stroke or death in patients with atrial fibrillation. Based on recent clinical trials, most patients with chronic atrial fibrillation should now be considered for prophylactic oral anti-coagulant therapy in the presence of risk factors and in the absence of contra-indications [35, 38], and therefore it may no longer be ethical to perform a prospective study of all patients with atrial fibrillation without oral anti-coagulant therapy. Of course, such studies can still be performed in patients whose risks of thrombosis and/or bleeding do not justify anti-coagulant prophylaxis.

**ISCHAEMIC HEART DISEASE AND THROMBOLYTIC THERAPY**

If increased fibrin turnover plays a role in atherosclerosis and arterial thrombosis [1, 2], then in-
creased plasma fibrin D-dimer levels should be predictive of ischaemic heart disease in healthy men. In a retrospective case-control study, Ridker et al. [14] observed a higher relative risk in American physicians with high fibrin D-dimer levels. In a prospective study of middle-aged men in Caerphilly, Lowe et al. [15] observed an increasing risk of ischaemic heart disease with higher plasma fibrin D-dimer levels, the relative risk being about four times higher in the top quintile compared with the bottom quintile.

Intracoronary thrombus formation is involved in the pathogenesis of unstable angina, myocardial infarction and arterial restenosis after percutaneous coronary angioplasty. Although there appears to be little difference in the plasma fibrin D-dimer level between patients with stable and unstable angina ([39] and Lip G.Y.H., Lowe G.D.O., unpublished work), both groups of patients have higher levels of fibrin D-dimer than the control subjects ([40] and Lip G.Y.H., Lowe G.D.O., unpublished work).

A further increase in degradation of fibrin (as reflected by increased plasma fibrin D-dimer levels) can be detected after routine coronary angioplasty, presumably in response to balloon-induced arterial injury and fibrin formation, despite pretreatment with aspirin, dipyridamole and heparin [41].

Patients with acute myocardial infarction who are not given thrombolytic therapy demonstrate a rise in fibrin D-dimer levels, which is consistent with increased fibrin turnover in response to the acute event [42]. The size of infarction only appears to have a minor influence on fibrin D-dimer levels [43]. Patients who developed complications such as congestive cardiac failure, ventricular arrhythmias, cerebrovascular events or death within 72h of admission had particularly high D-dimer levels, especially at presentation [42, 44].

The use of thrombolytic therapy during the treatment of acute myocardial infarction results in further generation of fibrin degradation products (including fibrin D-dimer). A maximum rise in fibrin D-dimer was seen between 1 and 4h, but elevations in fibrin D-dimer levels were not predictive of coronary patency [45–47]. This increase in fibrin D-dimer levels was independent of the type of thrombolytic agent used, and of the clinical course after the infarct [45, 48]. However, only a fraction of the elevation in D-dimer is due to lysis of coronary thrombi: most must derive from other types of intravascular fibrin [49], for example, the lysis of cross-linked circulating fibrin polymers. Measurement of peripheral fibrin D-dimer levels does not distinguish between these two potential sources of D-dimer. There is therefore little role for the routine measurement of fibrin D-dimer after thrombolytic therapy for acute myocardial infarction [50].

**LEFT VENTRICULAR DYSFUNCTION AND ANEURYSMS**

Patients who have sustained myocardial infarction are at increased risk of subsequent cardiovascular morbidity and mortality. A particularly large myocardial infarction may result in significant cardiac wall motion abnormalities (which include the development of a left ventricular aneurysm). Left ventricular aneurysms are particularly associated with intracardiac thrombus formation, with the potential for embolization [22]. The presence of cardiac dysfunction and heart failure also adds to the risk of stroke in patients with chronic atrial fibrillation [51, 52].

Activation of haemostasis, as shown by abnormalities of haemostasis-related markers, may in part account for this increased thromboembolic risk. For example, high levels of fibrin D-dimer, thrombin activity and platelet activity (as reflected by plasma platelet-factor-4 and β-thromboglobulin levels) have been shown in patients with heart failure [53]. In a study of patients with ischaemic heart disease and cardiac impairment, those with left ventricular aneurysms had higher fibrin D-dimer levels when compared with patients with left ventricular dysfunction (but without aneurysm formation), and with patients with normal left ventricular function [54]. The finding of increased fibrin turnover in these patients may be one factor contributing to the increased risk of intracardiac thrombus in patients with left ventricular aneurysms [22].

In patients with left ventricular aneurysms who were started on warfarin therapy prospectively, levels of fibrin D-dimer showed a sequential reduction to normal after a 2 month follow-up [33]. Erstland et al. [55] also found a significant reduction in fibrin D-dimer levels in patients with coronary artery disease and coronary bypass surgery who were started on warfarin. These findings suggest that warfarin therapy in patients with ischaemic heart disease may reduce the risk of cerebrovascular events. The recent ASPECT Study [56] confirmed this hypothesis, demonstrating that long-term anticoagulant therapy after myocardial infarction was beneficial in reducing stroke or transient ischaemic attacks, although there was only a limited effect on mortality.

Heart failure has been traditionally regarded as due to abnormalities in the systolic or contractile functions of the heart. However, clinical and epidemiological studies on the risk of thromboembolism in patients with cardiac impairment do not differentiate between the contribution of systolic and diastolic dysfunction to heart failure. This is pertinent as up to 30 to 40% of patients with congestive heart failure have normal systolic function [57, 58]. In a Doppler echocardiographic study of 106 patients with ischaemic heart disease, we found no difference...
in plasma fibrin D-dimer levels in patients with or without diastolic dysfunction, despite correcting for the interaction with systolic dysfunction when it was present in individual patients [59]. However, patients with the greatest systolic abnormalities (with aneurysm formation) had the highest fibrin D-dimer levels [59].

CEREBROVASCULAR DISEASE

Increased coagulation and fibrinolytic activation exist at all stages (acute, subacute and chronic) after a stroke [60, 61]. Some reports suggest that endogenous fibrinolysis (including fibrin D-dimer) may only be activated after the subacute phase (i.e. after day 7) [62, 63], while others have shown acute activation [64-67].

The role of intravascular fibrin turnover in patients with acute stroke, especially with regard to types of stroke, prognosis and outcome, remains uncertain. Douglas et al. [67] found that the initial level of fibrin D-dimer (and of other measures of coagulation activation) was associated with an increased mortality at 12 months. In contrast, Fon et al. [60] found no associations between fibrin D-dimer levels (and other markers) and clinical outcome after stroke, nor with the degree of carotid atherosclerosis as assessed by duplex ultrasonography. Other workers have also found early elevations of plasma fibrin D-dimer levels [64-66] but did not perform prospective studies. In addition, some racial differences may exist, with elevations in fibrin D-dimer levels after stroke being more frequent in black patients when compared with white patients [61].

Some differences between different stroke subtypes may be present. For example, Yamazaki et al. [68] found that D-dimer levels were higher in atherothrombotic stroke patients when compared with control subjects. After cardioembolic stroke, plasma concentrations of fibrin D-dimer may be useful in predicting recurrent embolization [69]. Although increased levels of fibrin D-dimer are seen in ischemic stroke patients, some of this may simply be related to age, as an age-related increase of the marker levels was noted in stroke patients and control subjects [70].

PERIPHERAL ARTERIAL DISEASE

Elevated fibrin D-dimer levels have been found in patients with peripheral arterial disease, which correlated with clinical, haemodynamic and angiographic severity [71-73] (Fig. 2). There is also histopathological evidence for high amounts of fibrinogen and fibrin D-dimer in aortic thrombi, atherosclerotic plaques and early gelatinous arterial lesions [74, 75]. In a cross-sectional study of patients with carotid atherosclerosis, patients with increased intima-media thickness of carotid arteries on B-mode ultrasound also had higher fibrin D-dimer levels compared with control subjects [76]. Increased fibrin turnover in cigarette-smoking (the major risk factor for peripheral arterial disease) is likely to be one mechanism by which smoking contributes to peripheral arterial disease [71].

The measurement of fibrin D-dimer has been shown to have prognostic implications in patients with peripheral arterial disease. In a study of 617 patients with claudication, baseline fibrin D-dimer levels were closely related to future coronary events (both fatal and non-fatal, with a relative risk of 4.4 between upper and lower quintiles) and also to haemodynamic progression of peripheral arterial disease [13]. This risk is similar to that in healthy men [15]. Increased fibrin turnover therefore appears to contribute to the progression of both coronary and peripheral atherosclerosis, which is consistent with the hypothesis that fibrin D-dimer may be a useful index of intravascular fibrin turnover and the contribution of thrombosis to arterial disease. Higher plasma levels of fibrin D-dimer have also been found in patients suffering thrombotic re-occlusion after femoropopliteal artery angioplasty, when compared with patients with maintained patency of the dilated arterial segment [77]. Pre-operative fibrin D-dimer levels were also predictive of graft occlusion and mortality after infra-inguinal bypass grafting [78].
HORMONAL INFLUENCE AND PREGNANCY

Traditional, high-dose oestrogen oral contraceptives increase the risk of myocardial infarction and venous thromboembolism, and this may be related to abnormalities of blood coagulation. Use of oral contraceptives resulted in significant elevations of plasma fibrin D-dimer, as well as other predictors of thrombosis (including fibrinogen and tissue plasminogen activator) [79]. There is also evidence that normal pregnancy increases levels of fibrin D-dimer [80], with a further increase in fibrin D-dimer in patients developing pre-eclampsia [81, 82]. The study by Trofatter et al. [83] showed that, when compared with D-dimer-negative pre-eclamptic women, fibrin D-dimer-positive women had significantly higher blood pressures, prompting delivery, greater proteinuria, more abnormal liver function tests and higher serum creatinine and urea levels. In particular, fibrin D-dimer-positive women had a greater risk of caesarean section, premature delivery, low birth-weight and low Apgar scores [83]. Testing for fibrin D-dimer may therefore be useful in early screening and follow-up for a pre-eclamptic coagulopathy and outcome after pregnancy. However, one recent study of such patients did not show any significant change in fibrin D-dimer levels from normal pregnancy [84], despite previous evidence that pre-eclampsia and eclampsia are associated with a state of increased coagulopathy, as shown by increased levels of fibrin formation, platelet activation and a decrease in platelet count [83, 85].

HYPERTENSION

Abnormalities of rheology and the coagulation system have been found in patients with hypertension [86]. In particular, elevations in plasma levels of fibrin D-dimer as well as von Willebrand factor, fibrin monomer, factor VII and plasminogen activator inhibitor have been demonstrated in hypertensive patients [86-90]. Concentrations of D-dimer have also been related to diastolic blood pressures [90]. These abnormalities of rheology and coagulation may contribute to the risk of stroke, thromboembolism and vascular disease seen in hypertensive subjects. Anti-hypertensive drugs may affect these factors differentially, although there are limited prospective data on changes of fibrin D-dimer (and other prothrombotic factors) with the treatment of hypertension [86].

OTHER CONDITIONS ASSOCIATED WITH PLASMA FIBRIN D-DIMER

One of the most common conditions in which plasma fibrin D-dimer (and other fibrin degradation products) is measured clinically is disseminated intravascular coagulation, in which very high levels are found [90]. This is an acquired disorder in which massive intravascular coagulation leads to intravascular fibrin formation, microvascular thrombosis and consumption of coagulation factors and platelets, resulting in a haemorrhagic diathesis.

Patients with malignancy are at high risk of developing venous and arterial thromboembolism, as well as disseminated intravascular coagulation, and certain tumours, such as pancreatic, ovarian and bronchial carcinoma are particularly associated with migratory thrombophlebitis. In addition, activation of coagulation and fibrinolysis within tumour tissue is thought to be associated with tumour growth, angiogenesis and metastasis. Levels of plasma fibrin D-dimer (and other markers of thrombin and plasmin generation) have therefore been studied in patients with various malignancies, including cervical carcinoma [91], lung carcinoma [92-94], ovarian carcinoma [95], acute lymphoblastic leukaemia [96], prostate carcinoma [97] and breast cancer [98-100], where they have been suggested to be indicators of tumour progression, remission or treatment response. However, this may in part be due to the association of some malignancies with disseminated intravascular coagulation and primary fibrinolysis [101].

High levels of fibrin D-dimer have also been found in other conditions. Examples include rheumatoid arthritis, Crohn’s disease and chronic uraemia [102-104]. Patients on maintenance haemodialysis had a higher degree of hypercoagulability while those on conservative treatment showed lower levels of these prothrombotic markers [104]. There is also some evidence that the pathogenesis of diabetic nephropathy may be related to intrarenal thrombogenesis [105]. Altitude hypoxia may cause abnormalities in haemostatic factors, including fibrin D-dimer, which corresponds to an activation of coagulation [106]. Similarly, high fibrin D-dimer levels have been found in patients suffering vaso-occlusive crisis of sickle cell disease [107] and those with sepsis from Gram-negative bacteraemia [108]. One study has also suggested that fibrin D-dimer may be useful (with a sensitivity and specificity of 1.00) in differentiating cerebrospinal fluid from blood in patients with subarachnoid haemorrhage or traumatic lumbar puncture [109]. Finally, increased levels of fibrin D-dimer and other fibrin degradation products are associated with poor outcome in acute gastrointestinal bleeding, possibly due to an increase in gastric fibrinolytic activity [110].

WHAT IS THE VALUE OF FIBRIN D-DIMER MEASUREMENT?

The D-dimer test is based on the production by thrombin of cross-linked fibrin and its later degradation by plasmin [5]. Plasma fibrin D-dimer is presently of use in the diagnosis of disseminated intravascular coagulation, and in excluding (with normal levels and clinical examination) venous
thrombosis and pulmonary embolism. There is also its potential use in assessing the thrombogenic risk in middle-aged healthy men [14, 15], and for risk assessment in patients with conditions that predispose to arterial thromboembolism, for example, chronic atrial fibrillation or left ventricular aneurysms (Table 1). In the latter two groups of patients, there may be a role for this marker in assessing the response to anti-thrombotic therapy, as suggested in the prospective studies of introducing anti-coagulant treatment in patients with chronic atrial fibrillation and left ventricular aneurysms [34, 55].

Although large-scale prospective studies are still required, markers such as plasma D-dimer may have a role in estimating anti-coagulant treatment efficacy, which may be intensified for high-risk patients (as indicated by persistently high D-dimer levels). In patients with arterial disease, fibrin D-dimer levels were predictive of cardiac events and mortality [13], again possibly indicating a role for anti-coagulant prophylaxis in patients with very high levels of D-dimer. However, the value of this marker in assessing prognosis in cardiovascular disorders requires further, larger studies.

In future studies, it should be remembered that when ‘non-vascular’ conditions generate significant extravascular fibrin, as in many hospitalized patients, the specificity of fibrin D-dimer levels for vascular thrombosis and fibrin turnover will be reduced. In particular, plasma levels of D-dimer are influenced by age and other conditions such as neoplasia, infections, renal or liver impairment and cardiac failure [112, 113]. This is in keeping with the processes of extravascular coagulation and fibrinolysis being involved in many diseases, where any form of tissue damage will lead to fibrin formation and its lysis. Finally, different antibodies are used in assay kits from different manufacturers, which do not show high correlations and which give different reference ranges [7, 114, 115]. It is therefore important to establish the diagnostic and prognostic value of individual commercial assays in each clinical situation, assuming that in the foreseeable future no ‘standardization’ will be possible. So far, this has only been done for pulmonary thromboembolism [7]. It should also be noted that quantitative ELISA assays are more accurate than semi-quantitative latex tests [7].

**CONCLUSION**

Plasma fibrin D-dimer has a potential role as a marker of intravascular thrombogenesis. It is a sensitive marker of fibrin turnover and allows the recognition of activated coagulation which may be manifest in various clinical conditions.

How useful is it in clinical practice? Its measurement may allow the specific and rapid evaluation of coagulo-fibrinolytic activation, which usually suggests a prothrombotic or hypercoagulable state. The lack of elevation of fibrin D-dimer levels is at present particularly useful for its negative predictive value in diagnosis of disseminated intravascular coagulation or venous thromboembolism. Further work on the prognostic value of fibrin D-dimer is required before it is established as a useful marker of intravascular thrombogenesis in other conditions. Some evidence is emerging in support of its use for patients at risk of arterial disease, but the importance of this plasma marker for the risk stratification of conditions at high risk of thromboembolism, such as atrial fibrillation and left ventricular aneurysms, requires further study.

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