D-dimers in atrial fibrillation: a further step in risk stratification of thrombo-embolism?

Ariel Cohen1,2*, Stéphane Ederhy1, Catherine Meuleman1, Emanuele Di Angelantonio1, Ghislaine Dufaitre1, and Franck Boccara1

1Department of Cardiology, Saint-Antoine University and Medical School, Assistance Publique-Hôpitaux de Paris, 184, rue du faubourg St-Antoine, 75571 Paris Cedex 12, France and 2Université Pierre et Marie Curie, Paris, France

This editorial refers to ‘Prediction of left atrial appendage thrombi in non-valvular atrial fibrillation’ by S. Habara et al., on page 2217.

Plasma fibrin D-dimers (hereafter d-dimers) are generated when the endogenous fibrinolytic system degrades fibrin, as in venous thrombo-embolism (VTE) and they consist of two identical subunits derived from two fibrin molecules. Unlike fibrinogen degradation products, which are derived from fibrinogen and fibrin, D-dimers are a specific cross-linked fibrin derivative.1 Because 2–3% of plasma fibrinogen is degraded to fibrin, small amounts are detectable in the plasma of healthy individuals.1 D-dimer levels may be increased in any condition involving the formation and degradation of fibrin, such as VTE, pulmonary embolism, infections, cancer, surgery, cardiac or renal failure, acute coronary syndromes, acute non-lacunar stroke, pregnancy, and sickle cell crises. D-dimer levels increase linearly with age.1 The classic microplate enzyme-linked immunosorbent assay (ELISA) technique is considered the gold standard but it is not used as a routine emergency test. Fully automated techniques have been developed, such as the VIDAS test (ELISA method with a final detection in fluorescence), but also immunofiltration (membrane ELISA) techniques and instantaneous methods which allow a diagnosis within a few minutes at the expense of a semiquantitative approach.1

D-dimers in atrial fibrillation

Levels of coagulative markers are increased in patients with atrial fibrillation (AF), including D-dimers, pro-thrombin fragments 1 + 2, and thrombin–antithrombin complexes, indicating abnormal thrombogenesis.2 D-dimer levels have been shown to be increased in AF, especially in patients having multiple risk factors for embolism,3 and to be associated with a higher risk of cardiovascular events and mortality.4 Anticoagulation could decrease D-dimer levels of coagulative molecular markers significantly, but in patients with AF receiving warfarin, they remained still high compared with those with sinus rhythm.5 A relatively weak correlation has been found between INR and D-dimer levels, suggesting that their determination in addition to INR could be useful for risk stratification of thrombo-embolic events.5 D-dimer levels coupled with clinical risk factors have been proposed as risk markers of thrombo-embolism among patients with AF regardless of the status of antithrombotic therapy.5 Patients with D-dimer levels ≥150 ng/mL had higher incidence of thrombo-embolic events than those with low levels for both groups with and without anticoagulant therapy. The annual incidence of thrombo-embolism in AF patients without risk factors was significantly low when D-dimer level was <150 ng/mL, but higher when D-dimer level was above this threshold value.6 In AF patients with risk factors, the annual incidence of thrombo-embolism was high regardless of D-dimer levels and anticoagulant status, suggesting that determination of D-dimer levels in addition to clinical risk factors may provide useful information to predict subsequent thrombo-embolic events, especially in patients treated with anticoagulant therapy.6 It remains to be determined whether D-dimer levels should be decreased to the normal range with appropriate anticoagulation to reduce the risk of thrombo-embolic events in such patients.

Markers of thrombo-embolism in atrial fibrillation

Indeed, the use of morphological and biological markers of the pro-thrombotic state would be clinically useful in patients with AF for both risk stratification and treatment management.

Risk markers of thrombo-embolism in AF include left atrial (LA) dilatation and LV systolic dysfunction on transthoracic echocardiography.7 Using transesophageal echocardiography (TEE), LA thrombogenic milieu defined as left atrial appendage (LAA), LAA dilatation, low LAA peak emptying velocities, LA spontaneous echocardiographic contrast (SEC), and thrombus or aortic atheroma ≥4 mm in thickness
may be found, especially in patients at high clinical risk. In addition, patients with AF and dense LA SEC have a high likelihood of cerebral embolism (22%/year) and/or death, despite adequate oral anticoagulation. In this study, which compared 128 patients with dense LASEC and 143 with faint LASEC, low LAA peak emptying velocities and dense SEC were independent predictors of a subsequent event. Few studies are available regarding risk stratification of thrombo-embolic risk in AF based on plasma markers. Increased C-reactive protein levels have been found to be independently associated with TEE thrombo-embolic risk factors but no cut-off value for C-reactive protein was determined to detect the presence of LA thrombogenic milieu. Plasma von Willebrand factor levels, an index of endothelial damage and/or dysfunction, validated as a prognostic marker of vascular events in AF, could also be evaluated in this setting.

D-dimers and transeosophageal echocardiography-detected risk markers in atrial fibrillation

In a pioneering work, Somloi et al. included prospectively 73 patients with AF and measured plasma D-dimer concentration (immunochromatographic technique) prior to TEE-guided cardioversion. They found that using a cut-off value for D-dimer concentration < 60 ng/mL, the negative predictive value (NPV) for LA/LAA thrombus detection (n = 9) was 98%, with however low specificity (75%) and positive predictive accuracy (33%).

In Habara et al.’s study, 925 patients with NVAF (27% with paroxysmal AF) were enrolled and D-dimer levels were measured (latex-enhanced photometric immunoassay) at the time of TEE, which detected 83 LA thrombi (9%) and severe-to-moderate LA spontaneous contrast in 472 (51%) patients. ROC analysis determined an optimal cut-off value of 115 ng/mL for D-dimer to detect LAA thrombi. This approach yielded an NPV of 97% for identifying LAA thrombi, with 75% specificity and 22% positive predictive value, very similar to that reported by Somloi et al. in a much smaller population and with a different cut-off value for D-dimer levels. Interestingly, this NPV was not altered when subgroup analyses were considered: congestive heart failure (n = 267, NPV 96%) or recent stroke (n = 208, NPV 97%). Other TEE-detected risk markers for thromboembolism (i.e. LA SEC or low LAA velocities) were also associated with increasing D-dimer levels. Among independent predictors of LA thrombus on multivariable analysis, D-dimer levels ≥ 115 ng/mL were the most powerful (odds ratio: 8.87; 95% CI: 4.67–17.9, P < 0.0001).

One potential bias in this exciting report is related to the population included during a long period of time (14 years) and the presence of a very high proportion of recent embolic events (23%), rather unusual in such populations. Another potential bias is the absence of clear policy regarding antithrombotic treatment regimen and the lack of evaluation of such treatment on D-dimer cut-off values. In addition, the exact role of D-dimer level determination has not been evaluated with regard to clinical risk stratification (CHADS2 score, SPAF, ACCP, or Framingham score). Finally, one subgroup analysis could have been useful, differentiating the impact of this approach in patients in sinus rhythm (i.e. paroxysmal AF, 27%) compared with those still in AF at the time of TEE.

Future studies will be required to clarify whether the combination of clinical, echocardiographic, and biological risk factors (D-dimer, von Willebrand, CRP, IL-6, and so on) would help to stratify more accurately the risk of thrombo-embolism in AF patients and determine the prognostic impact of these markers in different clinical settings, including cardioversion.

Conflict of interest: none declared.

References