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Very high TAFI antigen levels are associated with a lower risk of hard coronary events the PRIME Study

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found an incidence of 13.5% of von Willebrand disease (VWD) patients apart from two patients with factor (F)XI deficiency, one with FV deficiency and one hemophilia A carrier. In contrast, our study reports an incidence of 10.8% of VWD, only 4.16% of platelet function defects, and other rare factor deficiencies taking the total to 17.5% of inherited bleeding disorders responsible for menorrhagia in these women. A similar study conducted by Saxena *et al.* [5] reported a prevalence of 83.9% of inherited platelet dysfunction and 16% with inherited coagulation disorders. However, on close scrutiny the platelet function tests and/or their interpretation as reported both by Philip *et al.* and Saxena *et al.* are unconventional, which may be one of the reasons why they achieved skewed results. On analyzing these studies, it is evident that the outcome of such studies would largely reflect the type of tests carried out and more importantly the interest of the laboratory in some specialized area of hemostasis. If one is more interested in studying a particular type of hemostatic defect and has a well equipped laboratory for its detection, then it is more likely that that particular group will encounter a greater number of cases with that defect. If we restrict ourselves to standard tests and algorithms of coagulation testing, i.e. screening coagulation tests, if abnormal then correction studies followed by factor assays and standard platelet aggregation tests, then the results of different laboratories tend to be similar. For example Saxena *et al.* found 30 cases of Glanzmann's thrombasthenia out of 2200 patients with menorrhagia (1.4%), which correlates well with our result of 3.8% (4/120 patients).

Similarly, we compared our study with Philip *et al.* for the prevalence of VWD in this group using the χ^2 test ($P = 0.0675$). Though studies may produce broadly similar incidence of inherited coagulation disorders in menorrhagia patients, differences in detail could be related to geography, population and the persistence with which the coagulation defects were sought after. All the studies to date suggest a substantial burden of inherited coagulation disorders in menorrhagia patients, and it makes a strong case that before labeling a patient with menorrhagia as dysfunctional uterine bleeding, a coagulation workup is mandatory and could be life saving in certain circumstances.

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Very high TAFI antigen levels are associated with a lower risk of hard coronary events: the PRIME Study

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Dear Sir,

Thrombin-activatable fibrinolysis inhibitor (TAFI), a recently described inhibitor of fibrinolysis, has been hypothesized as playing a role in atherothrombosis [1]. However, the results

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from evaluations of its contribution to vascular risk have been mixed. In a study of men with stable angina pectoris and angiographically verified coronary artery disease, it was found that the plasma levels of TAFI assayed by a functional test were significantly higher in male patients than in healthy population-based, age-matched controls [2]. Similar results were observed in a population of patients with coronary disease using an ELISA assay [3]. These results were confirmed in a recent prospective study, the PRIME study [4], showing that in France an increase in TAFI plasma levels at baseline was associated with a higher incidence of angina pectoris. Unexpectedly,

Table 1 Crude and adjusted relative risks of myocardial infarction or coronary death alone according to baseline plasma concentration of TAFI

Hard coronary events*			
	<181	>181 (P90)	P†
Crude analysis			
France			
RR	1	0.3	0.04
95% CI		0.10-0.94	
Northern Ireland			
RR	1	1.06	0.92
5% CI		0.34-3.31	
Model 1†			
France			
RR	1	0.58	0.19
95% CI		0.15-2.25	
Northern Ireland			
RR	1	1.13	0.95
95% CI		0.28-4.55	

*Myocardial infarction or coronary death; †P values are derived from conditional logistic regression; ‡controlled for age, BMI, systolic blood pressure, total and HDL cholesterol, diabetes and smoking status.

however, a large European multicentre case-control study, the HIFMECH study, aiming to evaluate the contribution of plasma TAFI antigen to the risk of myocardial infarction (MI) showed that high TAFI plasma antigen levels above the 90th percentile were associated with a decreased risk of MI [5]. As this result could be due to the retrospective design of the study, we sought to confirm this finding in the PRIME study.

The design of this nested case-control study was extensively reported elsewhere [6,7]. Briefly, nearly 10 000 apparently healthy men recruited in France (Lille, Strasbourg, Toulouse) and Northern Ireland (Belfast) were included in the study. We measured baseline plasma concentration of TAFI antigen among 159 participants (94 from France and 65 from Northern Ireland) who subsequently developed hard coronary events (MI or coronary death), and in 317 age-matched controls who remained free of disease over the 5 years of follow-up.

Determination of TAFI antigen was performed with a commercially available kit from Milan Analytica (La Roche, Switzerland) [8]. Results are expressed as a percentage of pooled plasma from 30 healthy volunteers. As in HIFMECH, no difference in mean TAFI antigen levels was observed between control subjects and those with hard events (MI or coronary death) (mean $\pm$ SE: 119 ± 3 vs. 113 ± 4 , $P = 0.21$ in France and 115 ± 4 vs. 119 ± 5 , $P = 0.58$ in Northern Ireland; controls and cases, respectively). Crude relative risks were calculated for

patients with TAFI concentrations above the 90th percentile, with the group falling below the 90th percentile as the reference category (Table 1). In France, higher TAFI concentrations (more than 181%) were associated with a decreased risk for hard events (OR, 0.3; 95% CI, 0.10–0.94), whereas no effect was observed in Northern Ireland (RR, 1.06; 95% CI, 0.34–3.31). However, the results were no longer significant after adjustment for conventional cardiovascular risk factors.

Results of the present prospective study are in line with those obtained in the HIFMECH study [5]. The reason why highest plasma TAFI antigen levels are associated with a decreased risk of MI or coronary death remains to be clarified.

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