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BRIEF COMMUNICATION

FACTOR VIIA DETERMINATION COMPARED TO D-DIMER
IN DIAGNOSIS OF DEEP VENOUS THROMBOSIS

Mirian C.H. Janssen¹, Bert W Verbruggen², Petra J.C. ter Hark², Irena R.O. Nováková³
Department of Medicine, ¹Division of General Internal Medicine, ³Haematology and ²Central
Haematological Laboratory, University Hospital Nijmegen, The Netherlands.

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In the past decade plasma assays of several markers of activation of plasma coagulation and fibrinolysis have become available. Of these markers D-Dimer (DD) - a fibrin degradation product reflecting fibrin formation and dissolution - has been studied most extensively as a potential aid in the diagnostic management of deep venous thrombosis (DVT) (1-5). The major problem of blood tests for diagnosis of DVT is the specificity of the markers. Elevated levels of DD are also found in a wide variety of other clinical conditions (eg myocardial infarction, inflammation, malignancy and liver disease) (6). As a consequence studies measuring DD in patients with venographically proven DVT suggest that it should only be possible to exclude this condition.

With a recently developed clotting assay it has become possible to measure activation of the extrinsic pathway by measuring quantified activated factor VII (FVIIa) levels. Specificity of this assay results from the use of a recombinant soluble tissue factor that is selectively deficient in promoting FVII activation, but retains FVIIa cofactor function (7). It has been reported that FVIIa is elevated in cardiovascular disease, pregnancy and malignancy, indicating extrinsic pathway activation (8). There seemed to be no relation with cholesterol and serum lipids (9). Because the extrinsic pathway could also be activated in patients with DVT, the hypothesis of this study was that FVIIa determination might have an additional value in diagnosis of DVT to increase the specificity of DD.

MATERIALS AND METHODS

Seventy-three patients (30 men and 43 women) with a mean age of 58 years (range 26 - 89) referred because of clinically suspected DVT were enrolled in the study after giving informed consent. None of the patients used oral anticoagulants.

After blood was drawn patients were submitted to compression ultrasound (C-US) of the

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Corresponding author: MCH Janssen, MD, Dept of General Internal Medicine, University Hospital, PO Box 9101, 6500 HB Nijmegen, The Netherlands. Fax +31 24 3541734

affected extremity. The deep venous system from the popliteal to the iliac vein was examined. Lack of full compressibility was the sole criteria for DVT. In case of a positive result, patients were administered for standard anticoagulant therapy. Whenever C-US was not conclusive or negative, venography was performed and regarded as the definitive test. According to the vascular testing 36 patients were positive for DVT.

At the time of initial presentation 4.5 ml of venous blood from the antecubital vein was collected into a vacutainer tube containing 0.5 ml 3.8% sodium citrate. Platelet poor plasma was prepared by centrifugation at 4000 G for 10 minutes within one hour and the sample was stored at -70°C until assayed. DD were measured by ELISA Asserachrom (Diagnostica Stago). To determine FVIIa concentration a novel quantitative clotting method was used (Staclot VIIa-rTF, Diagnostica Stago, Paris) (7). The results of the vascular testing were not known to the laboratory technician.

RESULTS

The range of FVIIa concentrations in the population was large (range 17.7 - 147.3 mU/ml). The mean FVIIa level in the group of patients with and without an established DVT was 50.7 mU/ml, (range 19.6 - 147.3) and 63.8 mU/ml, range (17.7 - 136.9) respectively. Figure 1 illustrates that FVIIa was not significantly elevated in the group of patients with an established DVT compared to the patients without DVT.

As depicted in Figure 2 no significant correlation was observed between plasma DD and FVIIa levels in patients with and without DVT.

At a cut-off level of 500 ng/ml sensitivity and specificity of DD were respectively 100 and 34%.

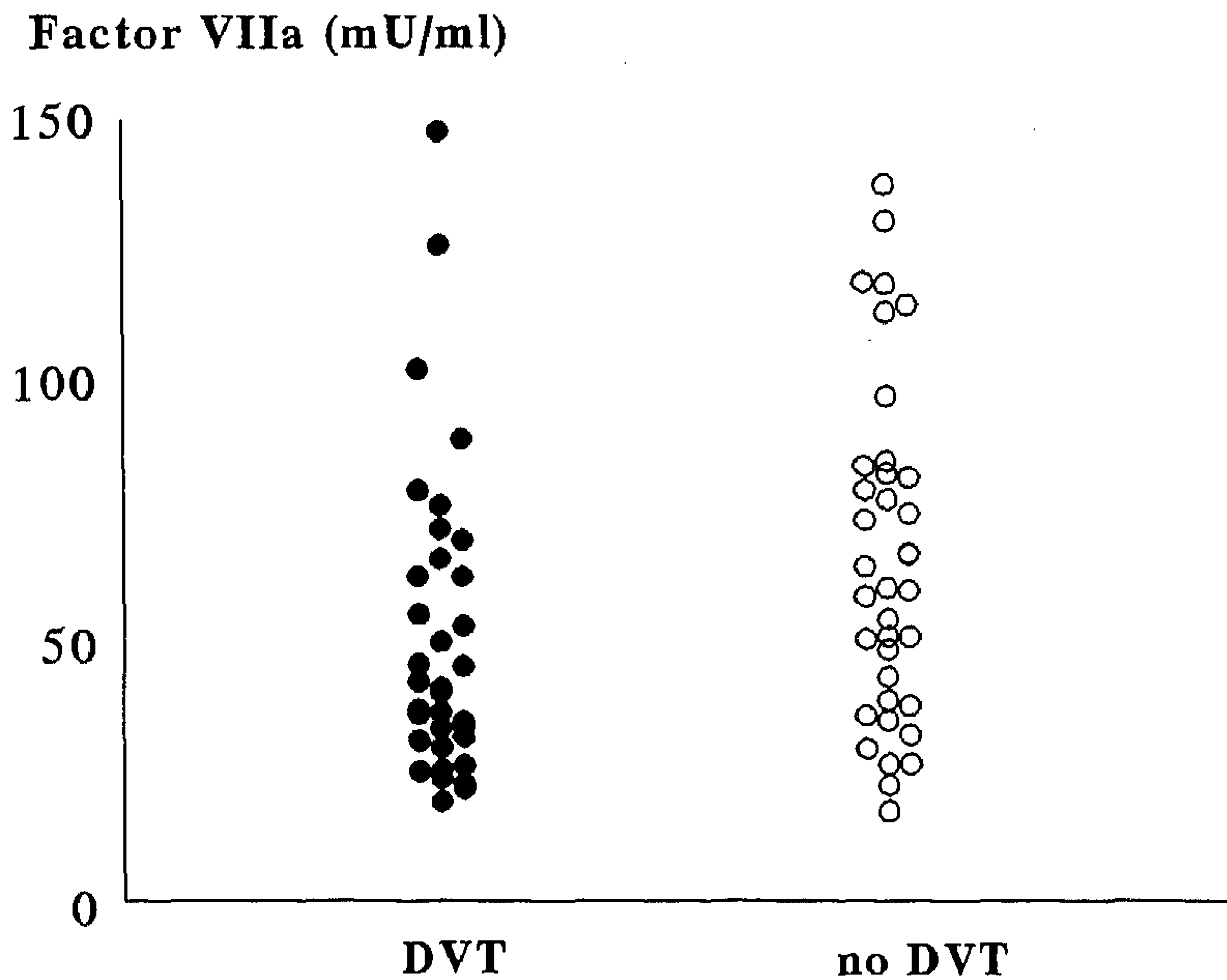


FIG. 1

Factor VIIa levels in patients with an established DVT, compared to patients without DVT.

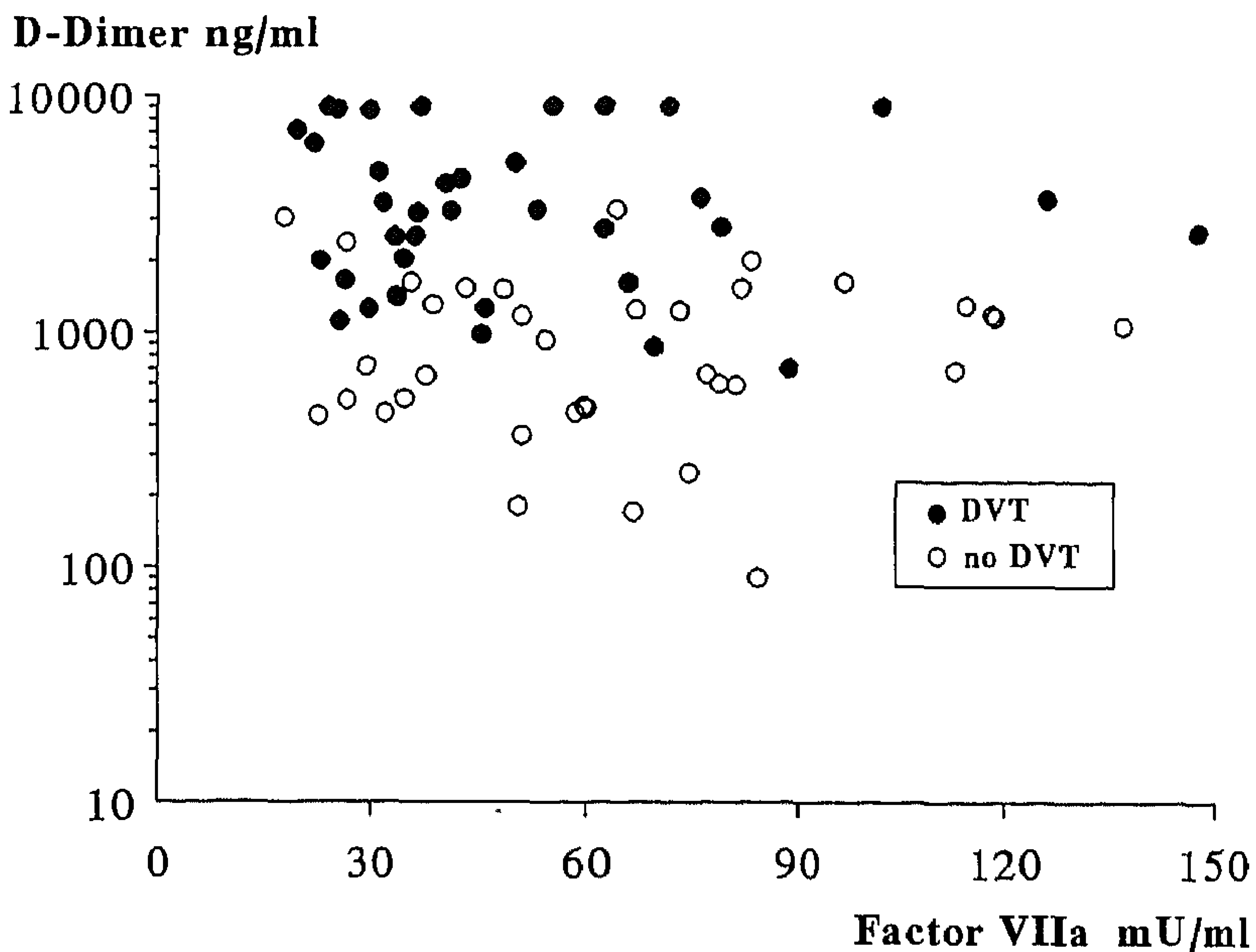


FIG. 2

Lack of correlation between plasma D-Dimer and Factor VIIa levels in patients suspected of DVT.

DISCUSSION

The rationale for this study was to investigate whether determination of FVIIa has additional value to DD in the diagnosis of DVT. It is known that high levels of DD are associated with DVT. Because DD is also elevated in other pathological conditions, specificity of the assays is low. For this reason DD can only be used for exclusion of DVT.

FVIIa is a marker of activation of the extrinsic pathway. Factor VII is a vitamin K-dependent glycoprotein in plasma that plays an important role in the initiation of tissue-factor - induced coagulation. FVIIa is elevated in patients with cardiovascular disease and pregnancy. Kakkar et al. demonstrated that FVIIa was 46% higher (mean 100 mU/ml) in patients with malignancy than in healthy volunteers (8). The hypothesis of the present study was that elevated FVIIa levels would also be found in patients presenting with DVT. In that case the assay could also be used in the diagnostic management of DVT, for example to increase the specificity of DD measurements in patients with other pathological conditions.

According to previous reports our results show a large variation in FVIIa level. We were not able to demonstrate a difference in FVIIa level between patients with and without DVT (figure 1). The FVIIa levels of most of the patients were comparable to those obtained in healthy volunteers (10 - 80 mU/ml). The number of patients with elevated FVIIa was the same in both groups of patients.

There are no studies comparing FVIIa to DD. Morrissey et al. showed no correlation between fibrinogen and FVIIa (7). We also could not demonstrate a relation between DD and FVIIa (figure 2).

In conclusion FVIIa determination, as a marker of the extrinsic pathway, can not be used in the diagnostic management of DVT.

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