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The use of the rapid D-dimer test for the exclusion of acute venous thromboembolism in a regional hospital

Thierry Fumeaux[a], *Jacques Cornuz*[b]

[a] Department of Internal Medicine, Regional Hospital, Sion, Switzerland
[b] Department of Internal Medicine, Unit of Prevention, University Hospital, Lausanne, Switzerland

Summary

Background: The performance of rapid D-dimer ELISA assay has been validated as a part of various diagnostic work-ups in tertiary care hospitals for the exclusion of acute thromboembolism in the medical emergency department. In order to measure the performance of this test outside of predetermined protocols and in a different medical setting, we retrospectively analysed a cohort of adult patients admitted to the emergency department of a regional hospital with a suspicion of acute venous thromboembolism.

Methods: All D-dimer assays performed during an 18-month period were retrieved. The patients' data were collected from hospital charts. Six-month follow-up was determined either by a written or telephone questionnaire or after contact with the patient's physician. The patients for whom this process was completed were included in the study and a retrospective diagnostic assessment was performed using a combination of clinical probability and objective testing. The diagnosis was then compared to the result of the initial D-dimer assay.

Results: During the study period 494 patients were included with 110 venous thromboembolic episodes. The sensitivity and negative predictive value of the D-dimer assay were respectively 94.5% (95% CI 88.4 to 97.7%) and 96.8% (95% CI 93.2 to 98.7%).

Conclusions: The yield of the rapid D-dimer assay in this study is comparable to the results of management studies performed in tertiary centres. D-dimer ELISA assay can be used to exclude venous thromboembolism, particularly in cases with a low clinical probability, in the emergency department and for larger populations in various clinical settings, even in the absence of a formal diagnostic work-up. False negative results can occur, particularly in the presence of a high clinical probability of acute thromboembolism.

Key words: venous thrombosis; thromboembolism; pulmonary embolism; diagnosis; D-dimer; predictive value

Introduction

The clinical diagnosis of acute venous thromboembolism (VTE), i.e. of pulmonary embolism (PE) or deep vein thrombosis (DVT), has been viewed as a clinical challenge for many years [1–4]. Invasive investigations are considered the "gold standard", but they are expensive and associated with a procedural risk [5, 6]. Moreover, they are not always available in primary or secondary care settings. The measurement of D-dimers (DD), products of fibrin degradation that increase in venous thromboembolism [7], is a major innovation, that has recently improved the diagnostic work-up of acute thromboembolism. Though many different assays are currently available, one of the most reliable testing methods is the rapid enzyme-linked immunosorbent assay [8]. A negative result, defined as less than or equal to 500 µg/l, has been demonstrated to have a very high negative predictive value (NPV) in the exclusion of acute thromboembolism in outpatients [8–12].

Before encouraging the widespread dissemination and implementation of a new diagnostic technique, its performance should be assessed in detail in order to avoid premature introduction and inappropriate use in clinical practice [13–15]. This process, which can be compared to the development of a new drug, is a stepwise evaluation of the test performances. The first phase allows the standardization of the procedure and the characterization of normal values. In the second phase, the diagnostic accuracy of the test is prospectively evaluated in a blinded manner in a large population of

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patients. Eventually, the test must be used in management studies in which therapeutic decisions are based on its result. In the case of D-Dimer assays, these two first phases have been completed [13]. These assays have now been evaluated as part of various diagnostic strategies in management studies, but have only been performed in tertiary centres as part of a strict diagnostic work-up (Table 1). The generalization of these results to other diagnostic strategies in different clinical setting is therefore not straightforward.

To evaluate the performance of a rapid quantitative D-Dimer assay in a non university-affiliated clinical setting with a less selected group of patients in the absence of a standardized diagnostic strategy, we developed a retrospective cohort study investigating its yield in the emergency department (ED) of a secondary care hospital.

Methods

The study was a retrospective, cohort analysis of medical data from individual patients admitted to the emergency department (ED) with suspicion of acute VTE. The primary outcome of interest was the occurrence of DVT or PE during a six-month follow-up period. The Ethics Committee of the institution approved the protocol.

The study was conducted at the ED of the Regional Hospital of Sion, Switzerland, a 250-bed regional hospital with a population recruitment of 70,000 people and an annual emergency admission rate of 7,500 patients. We retrospectively selected from a computer database all adult patients (over 18 years old) who presented at the ED between January 1997 and May 1998 with suspicion of acute VTE and for whom a D-dimer assay was performed on admission (Figure 1). Patients for whom we could retrieve precise and complete data for a six-month period after the index visit were included in the study. We excluded patients with an incomplete follow-up as well as hospitalised and surgical emergency patients.

For each patient, the 6-month history following the index admission at the ED was retrieved. For that purpose, the ED and hospital charts of patients were analysed. The clinical evaluation (pre-test probability of VTE, as reported by the emergency physician in charge of the patient on admission) and the results of the invasive or non-invasive tests were reported, as well as the discharge diagnosis. Secondly, in order to complete the six-month follow-up, we contacted all selected patients by mail and sent written questionnaires to obtain information on any clinical event during this period. Uncertain information was confirmed by contact with the patient's physician. Patients who did not answer were eventually contacted by telephone. If this was unsuccessful, we retrieved the family physician's name from the hospital charts and sent him a specific questionnaire. All medical notes of the study patients who were further hospitalised were also reviewed for a diagnosis of acute VTE.

For each patient the occurrence of an acute VTE, defined as either a positive diagnosis (see above) in the ED or within the six-month follow-up period was recorded. The diagnosis had to be based on the clinical evaluation combined with confirmatory tests as usually advocated (see above). A similar approach has already been used in clinical management studies evaluating the use of D-dimer assays [16].

In the ED the diagnosis of VTE was based on clinical evaluation (pre-test probability) and on non-invasive (venous ultrasound or lung scan) or invasive (venous or pulmonary angiography) confirmatory tests, according to standard criteria [17–19]. D-dimer assay was progressively introduced in the hospital for a test period that corresponds to the study period. It was available in the ED but the re-

Table 1

Results of prospective studies on the assessment of D-dimer ELISA performance in the emergency department for patients with suspected venous thromboembolism.

Reference	setting	patients n	DVT PE[1]	outcome	NPV[2]
Kearon [28]	III[3]	445	DVT	confirmed recurrent DVT or PE in a 3-month follow-up period	99.4 (96.9–100)
Wells [29]	III	930	PE	confirmed recurrent PE in a 3 month follow-up period	99.5 (99.1–100.0)
Perrier [11]	III	918	DVT/PE	confirmed recurrent PE in a 3 month follow-up period	98.7 (96.9–99.1)
Wijns [30]	III	74	DVT	DVT on immediate phlebography	100
Bernardi [31]	III	946	DVT	confirmed recurrent PE in a 3 month follow-up period	99.6 (99.1–100.0)
Perrier [8]	III	671	PE	confirmed recurrent PE in a 3 month follow-up period	99.0 (96.4–99.9)
Laaban [32]	III	117	DVT/PE	confirmed recurrent PE in a 3 month follow-up period	97
Janssen [33]	III	132	DVT	DVT on immediate phlebography	100
De Moerlose [26]	III	195	PE	confirmed recurrent PE in a 6 month follow-up period	100 (93.3–100.0)
Gavaud [34]	III	80	DVT/PE	not available	87
Rochemaure [35]	III	126	DVT/PE	DVT or PE on immediate angiogram	97
Tengborn [36]	III	96	DVT	DVT on immediate phlebography	97
Dale [37]	III	92	DVT	DVT on immediate phlebography	95
Quinn [38]	III	36	PE	PE on immediate pulmonary angiogram	100
Ginsberg [39]	III	221	PE	diagnostic work-up (lung scan and bilateral impedance plethysmography)	100

[1] DVT: deep vein thrombosis; PE: pulmonary embolism
[2] NPV: negative predictive value (95% confidence interval)
[3] III: tertiary medical setting

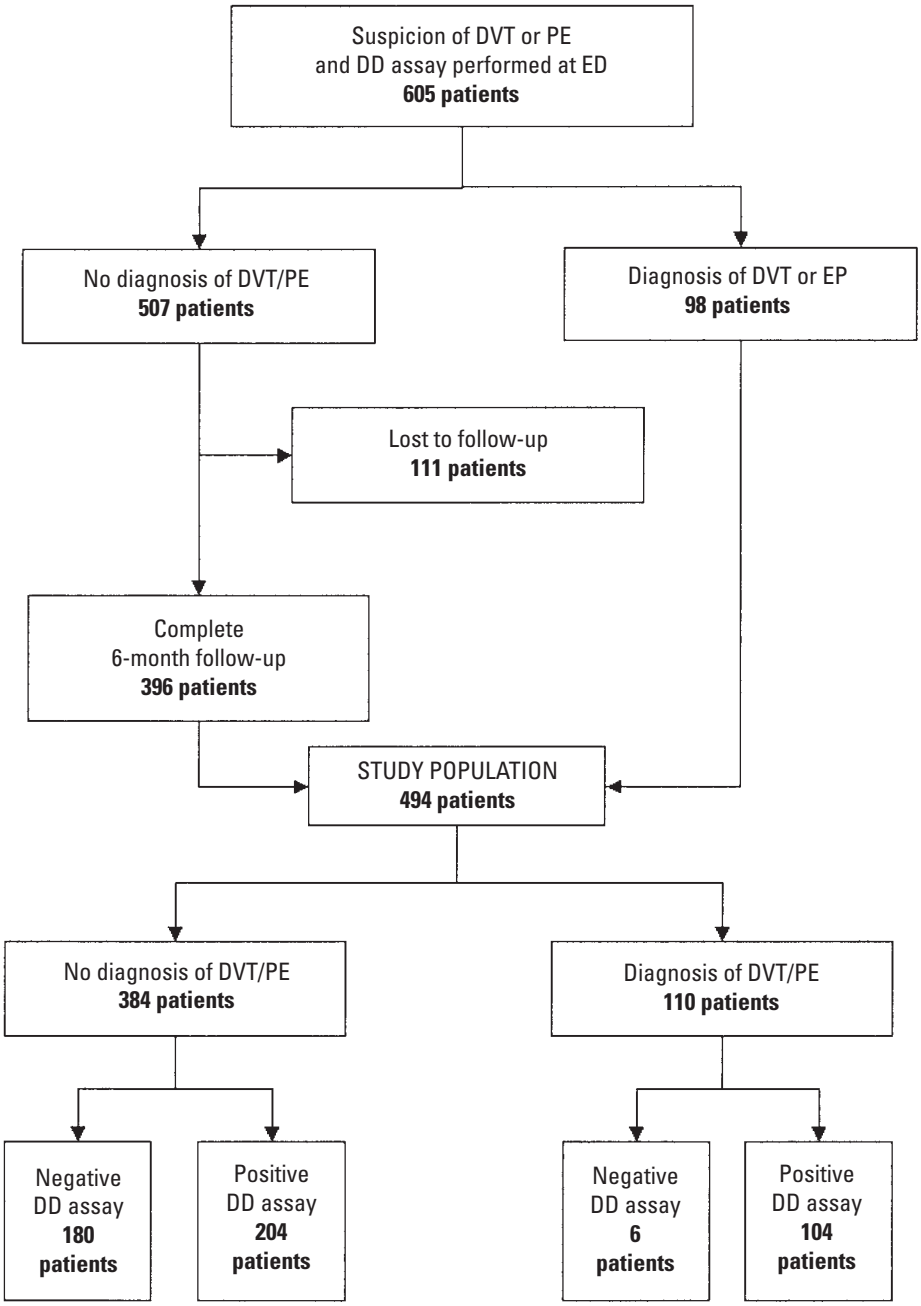

Figure 1

Selection and inclusion of patients with distribution of cases of DVT/PE and result of D-dimer assay. DVT: Deep vein thrombosis, PE: pulmonary embolism, DD: D-dimer, ED: emergency department, Negative DD assay: <500 µg/l, Positive DD assay: >500 µg/l

sults of the test were not taken into account in the final diagnosis by the physician in charge of the patient. The diagnosis of VTE could also be made by a physician during the follow-up period. In this case a confirmatory test, such as venous ultrasound, lung scan, or pulmonary angiography, had to have been performed in order to confirm the thromboembolic episode. When the diagnosis was clinically based only, it was considered negative in the analysis.

The DD assay was an automated two-step, sandwich-type, immunoenzymatic assay performed with an automated multiparametric Immunoassay System (VIDAS, BioMérieux, France). The cut-off value for a positive result was 500 µg/l. The instrument was automatically calibrated every 14 days and quality controls were regularly done, according to the guidelines of the Swiss Commission on Quality in the Medical Laboratory (QUALAB).

The occurrence of a VTE embolism during the follow-up period was compared with the results of the DD assay. In patients who had a negative D-dimer result and a positive diagnosis of acute thromboembolism ("false negative cases"), the clinical data (medical and paramedical charts, laboratory and blood gas analysis, ECG and chest X-ray) and objective examinations (ventilation/perfusion scan, pulmonary angiograms, venous ultrasound, chest CT-scan) were reassessed in a blinded manner. Firstly, the clinical probability was estimated by two experienced physicians, working in the ED of a tertiary university hospital, who were unaware of the aims of the study. They rated the clinical probability as low (less than 20% chance of thromboembolism), intermediate (20 to 80%) or high (over 80%) following conventional clinical criteria [20, 21]. Secondly, two blinded specialists analysed the radiological documents, without knowing the clinical probability of VTE and the results of the original report. Ventilation/perfusion lung scans were rated on the number and localization of mismatched perfusion defects [18]. Limb venous ultrasounds were considered positive if incompressibility of a deep vein was described [4]. Pulmonary angiograms were analysed applying the usual diagnostic criteria [22]. The clinical probability and objective results were combined in order to confirm or rule out the diagnosis of acute thromboembolic episode [18]. In case of doubt or inconclusive results, the diagnosis was considered negative.

After this evaluation process, patients were classified in a 2-way contingency table (DD < or >500 µg/l, presence

Table 2

Characteristics of the six patients with a negative DD test and a final diagnosis of PE.

Age (yrs)	sex[1]	DD[2] (µg/l)	previous DVT[3] or PE[4]	pre-test probability	lung scan description	test probability	time of diagnosis
31	F	330	yes	20–80%	multiple segmental mismatched defects	high	admission
33	F	184	yes	>80%	segmental mismatched defects	high	admission
51	F	110	no	20–80%	multiple mismatched sub-segmental defects	high	admission
39	F	186	yes	20–80%	lobar and segmental mismatched defects	high	admission
37	F	331	no	20–80%	progressive multiple mismatched segmental defects	high	admission
72	M	274	yes	>80%	multiple lobar and segmental mismatched defects	high	admission

[1] F: female; M: male
[2] DD: D-dimers ELISA assay result
[3] DVT: deep venous thrombosis
[4] PE: pulmonary embolism

or absence of VTE), and the operative characteristics of the D-dimer assay were computed. Sensitivity, specificity, negative and positive predictive values with their respective 95% confidence intervals (CI) were calculated as previously described [23]. Groups of patients were compared by using a Student *t-test* with a significant level at $p < 0.05$.

Results

We retrieved the names of 605 patients, who presented at the ED with a suspicion of acute VTE and for whom a DD assay was performed in the ED between January 1997 and May 1998 (Figure 1). The complete 6-month follow-up could be obtained for 494 patients (82%). 98 patients (16%) were immediately admitted to the hospital and later discharged with a diagnosis of VTE. Follow-up information was obtained for a further 396 patients (87% by questionnaire, 7% from the family physician, and 6% by telephone). No information was available for the remaining 111 patients (18%). Thus the final study population included 494 patients (245 women and 249 men), with a mean age of 61 ± 16 yrs. There were no significant differences in the demographic (mean age, sex ratio) and clinical (proportion of patient with a negative DD assay) data between the study population and the excluded subjects.

Table 3

D-dimers ELISA assay performance in the study population.

Parameter	result	(95% CI)
Sensitivity	94.5%	(88.4–97.7)
Specificity	46.9%	(45.1–47.8)
Negative predictive value	96.8%	(93.2–98.7)
Positive predictive value	33.8%	(31.6–34.9)

During the study period, 110 patients (22%) had a positive diagnosis of acute VTE (Figure 1). 98 patients were discharged from the hospital with this diagnosis and 12 presented with such an episode during the six following months. In this group of 110 patients, 104 had a positive (>500 µg/l) D-dimer assay and 6 a negative result. The VTE diagnosis was established at the initial ED admission for these six patients. The *a posteriori* evaluation of the pre-test probability for these patients was in agreement with the first clinical evaluation made in the ED, and the reassessment of diagnostic tests eventually confirmed the initial diagnosis of acute thromboembolic episode (Table 2). These patients were mostly young women with an intermediate to high pre-test probability of PE, there was either a history of previous thomboembolic episode, a mean DD assay result (± SD) of 236 ± 93 µg/l, and/ or a conclusive lung scan, revealing at least segmental mismatches.

Based on this classification of patients (Figure 1), the sensitivity of the test is 94.5% (95% CI 88.4–97.7), with a negative predictive value of 96.8% (95% CI 93.2–98.7) (Table 3).

Discussion

In this retrospective cohort study performed in a secondary medical care setting, we included 494 adult patients who had a DD determination because of suspicion of acute venous thromboembolism, and for whom we could obtain complete information on the six-month follow-up. 110 patients had a diagnosis of acute VTE, and of these, 6 had a negative DD assay. The sensitivity and negative predictive value of D-dimer ELISA assay were therefore 94.5% and 96.8% respectively. These values are close to those of previous studies performed prospectively in tertiary centres (Table 1), and confirm the usefulness of rapid D-dimer testing in unselected populations in various clinical settings with no definite diagnostic protocol. Interestingly, we found 6 false negative cases. The clinical probability as judged by the ED physician and as confirmed *a posteriori*, was either intermediate or high in all of

these cases. It is impossible to determine if all perfusion defects seen on the pulmonary scan where new or if some of them were residual findings of previous episodes. The association of an intermediate or high clinical probability combined with these results is, however, highly suggestive of acute PE.

What do these results add to previous published data and how can they be transposed to clinical practice? The evidence of false negative results of the test in patients with intermediate to high clinical suspicion of VTE is a first important point. All clinical studies have evidenced a few false negative cases. Therefore, if there is a high clinical suspicion of VTE associated with a negative D-dimer assay, further objective examinations should probably be performed before excluding the diagnosis [3, 24].

A second important point to notice is that the studied population is closer to "real-life" daily practice than in the published validation protocols. The DD test was ordered more randomly than in a rigorous prospective study, depending mostly on the prescribing physician, and was not always followed by the same diagnostic work-up, owing to the differing availability of these procedures. This would probably be the case in many emergency medical settings, where some tests can only be performed during certain periods of the day or of the week. In such settings, the use of a rapid DD assay to exclude an acute VTE seems to be reliable and its high NPV is sufficient as an initial test, at least in patients with a low clinical probability. Moreover, the use of such a rapid assay as the only "around-the-clock" available test could be economically interesting, as it is less expensive (50 Swiss Francs) than other objective tests and more easily performed, even in an independent laboratory located outside the hospital. Patients with a negative result can be discharged quickly and do not use hospital resources while waiting for further tests. For the remaining patients, a second diagnostic step is necessary and is dependant on the availability of each procedure.

In this study, which included patients during a 17-month period, VTE was confirmed in 110 patients, corresponding to the usual incidence of one case per 1,000 person-year [25]. During the same period, the rapid DD test was performed on around 5% of the admitted patients. The result of the test was negative in 38% of the patients, mostly in cases with a low clinical probability of VTE. It can therefore be estimated that a rapid DD assay could be useful in allowing around one third of patients with a suspicion of VTE to be discharged without any further procedure, representing one of fifty medical patients admitted to the ED. This proportion is, however, highly dependent on the careful selection of patient for whom the test is prescribed. A rapid DD test should probably not be performed in patients with a high clinical suspicion of VTE, as a negative result does not avoid further investigations. In conclusion, the introduction of a rapid DD assay as the only available test for the diagnosis work-up of VTE could be economically interesting for emergency medical units (hospital or ambulatory practice), if the patient load and the prevalence of VTE are sufficient and if the selection of patients for whom the test is prescribed is performed carefully.

This study has some limitations. Firstly, the retrospective approach is exposed to reporting bias, so that the assignment of patients in the groups of true and false cases may be slightly different. DD-ELISA is very useful to exclude the diagnosis of DVT or PE because of its high negative predictive value, which is mainly influenced by the number of false negative cases. The probability that such cases would have been missed in our cohort is low. The absence of an invasive gold standard for the diagnosis of venous thromboembolism is further limitation of this study. However, this method of analysing the occurrence of DVT or PE during follow-up has been previously used in the literature [8, 11, 26, 27]. Finally, we did not include the 111 patients for whom we could obtain no information on the follow-up in the analysis. These patients were not significantly different from those included. 44 of them had a negative DD assay (<500 µg/l). No episode of acute thromboembolism was initially diagnosed in these patients and the risk of one of these patients, presenting with a thromboembolic episode during the follow-up period, not being investigated and treated in the same hospital is, for geographical reasons, very low. Despite these limitations, this study confirms the usefulness of a rapid DD test in the exclusion of acute venous thromboembolic disease in a non-tertiary centre, even in the absence of any further formal standardized diagnostic strategy.

Pulmonary embolism and deep vein thrombosis are difficult diagnoses in the emergency department, although the development of less invasive and more reliable tests has made this process easier. D-dimer ELISA has been shown to have a high negative predictive value in prospective studies performed in tertiary centres. In this retrospective study, we show that the recognized performance of D-dimer ELISA can be transposed to a secondary clinical setting and that this test can be proposed as the initial diagnostic step in the evaluation of clinical suspicion of acute venous thromboembolism in most clinical settings.

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Correspondence
Thierry Fumeaux
Division of Intensive Care Medicine
Department of Medicine
University Hospital of Geneva
Rue Micheli-du-Crest 24
CH-1211 Genève 14
E-Mail: fumeauxt@usa.net

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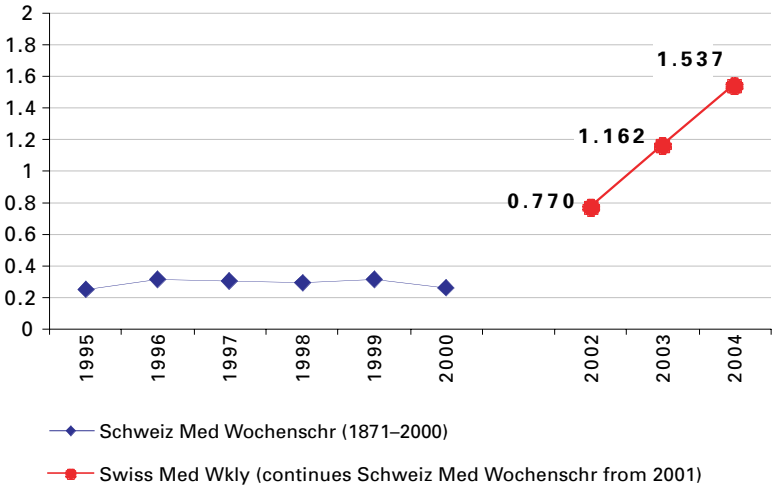

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