

Management studies using a combination of D-dimer test result and clinical probability to rule out venous thromboembolism: a systematic review

A. J. TEN CATE-HOEK* and M. H. PRINS†

*Division of Hematology, Academic Hospital Maastricht, Maastricht, the Netherlands; and †Department of Epidemiology, University of Maastricht, Maastricht, the Netherlands

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Summary. *Background:* While the number of patients with suspected venous thromboembolism (VTE) referred to hospital emergency units increases, the proportion in whom the diagnosis can be confirmed is decreasing. A more efficient but safe diagnostic strategy is needed. *Objective:* To evaluate the safety of withholding anticoagulant therapy in patients suspected of VTE based on a diagnostic work-up that combines a clinical decision rule (CDR) with a D-dimer test result without performing additional diagnostic tests. *Patients/methods:* We searched Medline (January 1996–December 2004)-related articles and reference lists of studies in English for prospective clinical studies that managed consecutive patients suspected of VTE and used a D-dimer assay combined with an explicit CDR or implicit clinical judgment. *Results:* We identified 11 studies in which 6837 consecutive outpatients suspected of VTE were included. In the combined management studies, the overall rate of thromboembolic events was nine out of 2056 patients (0.44 %, 95% CI 0.2%–0.83%) in whom anticoagulants were withheld based on the D-dimer result and a low clinical score. Similar results were obtained with qualitative and quantitative D-dimer tests and with different decision rules. The rate of exclusion varied between 30% and 50% and was highest with a low incidence of VTE among those referred. *Conclusion:* Withholding anticoagulant treatment in patients suspected of VTE on the basis of a work-up consisting of a low clinical probability combined with either a qualitative or quantitative D-dimer test result is safe.

Keywords: clinical probability, D-dimer test, management studies, venous thromboembolism.

Correspondence: Arina J. ten Cate-Hoek, Division of Hematology, H5-A2037, Academic Hospital Maastricht, De Beyelaan 25, 6202 AZ Maastricht, the Netherlands.

Tel.: +31 43 3877013; fax: +31 43 3874784; e-mail: ahoek@lhle.azm.nl

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Introduction

An increasing number of patients are referred to hospital emergency units with a clinical suspicion of venous thromboembolism (VTE) [1]. If left untreated, pulmonary embolism (PE) can be fatal and deep vein thrombosis can cause considerable morbidity and can eventually result in PE. Treatment with anticoagulants reduces morbidity and mortality [2]. However, unnecessary anticoagulant therapy should be avoided because of the associated risk of bleeding.

The clinical diagnosis of VTE is challenging and the diagnosis can be confirmed by the use of objective diagnostic methods only in a proportion of the patients with a clinical suspicion of the disease [3]. Moreover, over the last 20 years, this proportion of patients in whom the diagnosis is confirmed has decreased from 35%–20% [3,4]. This decrease is likely to be attributable to a better access to non-invasive testing together with a declining tolerance for diagnostic uncertainty.

In the last two decades, there has been a tendency toward simplification of diagnostic management of venous thromboembolic disease. Although venography and pulmonary angiography remain the gold standards, those tests are in practice seldom used because of their invasiveness. Extensive research has been performed to develop less invasive and more cost effective diagnostic strategies. Serial ultra sonography is a safe approach for the diagnosis of deep venous thrombosis in symptomatic patients [4]. Similarly, CT scan combined with serial ultra sonography has been documented to be safe in the diagnosis of PE [5]. However, the current low incidence of VTE among patients suspected of this disorder renders the approach in which all patients undergo imaging tests costly. Moreover, diagnostic imaging might not always be readily available causing inconvenience to patients due to waiting times.

Although clinical diagnosis is documented to be unreliable, the PIOPED investigators showed that clinicians were able to categorize patients by clinical judgment in groups with a low, moderate and high probability for VTE. Evaluation of clinical probability scores made evident that clinical probability alone is not sufficient to exclude VTE [6]. Additionally, CDRs are

dependent on experience of the physician certainly when the presence of an unspecified alternative diagnosis is considered.

D-dimer is a fibrin-specific degradation product and is used as a marker for endogenous fibrinolysis in D-dimer assays. The safety of relying on a D-dimer test alone to exclude thrombosis is controversial [7]. Only one single study by Perrier *et al.* [8] ruled out PE on the basis of a D-dimer test alone. A combination of a D-dimer assay and clinical probability as a first step in diagnostic work-up was introduced by Wells *et al.* [9]. Since then multiple studies managing patients with suspected VTE on the basis of clinical probability in combination with a D-dimer assay result have been performed.

We included prospective cohort studies in a systematic review assessing the safety and the decrease in need for diagnostic imaging of strategies in which a combination of a CDR together with a D-dimer assay result was used to exclude VTE in patients with a negative D-dimer and a low clinical probability. The primary outcome measure was the incidence of objectively confirmed symptomatic VTE over a period of 3 months among patients with a normal D-dimer test result and a low clinical probability.

Methods

We searched PubMed to locate all prospective clinical studies on diagnosis of VTE making use of a combined strategy of D-dimer testing and a CDR. We searched Medline for publications from 1996 to 2004, using the subject headings: ('fibrin') or ('degradation products') or ('D-dimer') and ('PE') or ('thromboembolism') or ('thrombosis') and ('decision rule') and ('prospective study') or ('follow-up study').

We also reviewed the reference lists of articles selected and used cross-references from related articles. The authors (MHP, AtC) reviewed all identified titles and abstracts.

The following inclusion criteria were applied: English language, prospective clinical study, consecutive patients, use of D-dimer assay combined with the use of explicit CDRs or implicit clinical judgment, divided in at least two categories. Studies were excluded if they used their data to derive a CDR, or if management of patients with suspected disease was not only based on results of a D-dimer test and clinical judgment, but also was additionally influenced by other test results (e.g. ultrasound).

Data extraction

The following data were extracted: total number of patients included per study, inclusion of only patients suspected of DVT or PE or a mixed population, strategy according to which patients were managed, e.g. normal D-dimer test results and low clinical probability, type of D-dimer test used (qualitative, quantitative), number of patients managed without additional imaging, total number of cases of VTE in the population, and thromboembolic outcomes in relation to strategy. Both authors

reviewed all data and consensus was reached for all data described.

Analysis

Summary tables of study characteristics were created. The primary outcome was the 3-month incidence of all thromboembolic outcomes in patients in whom anticoagulant treatment was withheld based on the results of a CDR and D-dimer test. Summary estimates were calculated for all studies, per clinical probability stratum (low, moderate, high), for DVT and PE separately and in relation to type of D-dimer test. Weighted outcome incidences and their 95% CI were calculated using the exact method.

In addition, the overall exclusion rate was calculated and the exclusion rate in individual studies was correlated (Pearson) to the incidence of VTE in a study.

Results

Study identification

We identified 641 items using our search. Of these 618 were not considered because they did not meet the inclusion criteria. Of the 23 potentially eligible studies using CDR and D-dimer [8, 10–31], 12 had to be excluded, as they were derivation studies or because the management of patients with suspected disease was based on other diagnostic tools for VTE than just CDR and D-dimer [20–31]. Hence, 11 eligible management studies were left for analysis [8,10–19].

All 11 management studies combined CDR with a D-dimer assay test result to exclude VTE without further testing in a defined group of people. The majority of studies only excluded patients with low clinical probability together with a normal D-dimer test result from further diagnostic testing [11,13,15–18]. In three studies [8,10,12], both the categories low and moderate were managed without further testing. One study excluded unlikely patients [19] and another excluded patients with a non-high clinical probability [14]. We categorized both studies as low clinical probability as both represent a broadening of the low clinical probability group.

Outcomes

The 11 identified studies included a total number of 6837 patients suspected of VTE. All studies were management studies combining CDR and D-dimer assay result to rule out VTE without additional diagnostic imaging. All patients were outpatients suspected of either PE or DVT (Table 1).

The overall thromboembolic event rate among patients in whom treatment was withheld based on the clinical probability and a normal D-dimer was 10 out of 2204 (0.45%, 95% CI 0.22%–0.83%). Of these 10 cases one was found in the 143 patients with moderate clinical probability

Table 1 Baseline characteristics of studies managing patients on the basis of normal D-dimer test result and CDR alone

Studies with year	Patients total	VTE type	Patients in whom additional testing was avoided	Clinical probability	D-dimer test used	Incidence of VTE in population
Bates <i>et al.</i> [10] 2003	556	DVT	283 (51)	Low + mod	MDA	56 (10)
Anderson <i>et al.</i> [11] 2003	1075	DVT	316 (29)	Low	SimpliRED or IL test	195 (18)
Perrier <i>et al.</i> [8] 2004	965	PE	280 (29)	All	VIDAS	222 (23)
LeClerque <i>et al.</i> [12] 2003	202	MIX	64 (32)	Low + mod	TINAQUANT	59 (29)
Wells <i>et al.</i> [13] 2001	930	PE	437 (47)	Low	SimpliRED	86 (10)
Schutgens <i>et al.</i> [14] 2003	812	DVT	176 (22)	Non-high	TINAQUANT	317 (39)
Kearon <i>et al.</i> [15] 2001	445	DVT	177 (40)	Low	SimpliRED	64 (14)
Kruij <i>et al.</i> [16] 2002	234	PE	60 (26)	Low	VIDAS	52 (22)
Janes and Ashford [17] 2001	431	DVT	98 (23)	Low	SimpliRED	93 (22)
Ten Wolde <i>et al.</i> [18] 2004	631	PE	95 (15)	Low	TINAQUANT	123 (20)
Wells <i>et al.</i> [19] 2003	556	DVT	218 (39)	Unlikely	SimpliRED or IL test	87 (16)
Total	6837		2204			

Values given in parentheses are in percentage.

Table 2 Thromboembolic outcomes over a 3-month follow-up period in patients suspected of VTE managed without anticoagulants based on a normal D-dimer test result and clinical probability

Studies	Total thrombo-embolic events	95% CI (%)	Strategy		
			Low	Mod	High
PE					
Perrier <i>et al.</i> [8]	0/280 (0.0)	0–1.1	0/238 (0.0)	0/37 (0.0)	0/5 (0.0)
Wells <i>et al.</i> [13]	1/437 (0.2)	0–1.3	1/437 (0.2)		
Kruij <i>et al.</i> [16]	0/60 (0.0)	0–5.0	0/60 (0.0)		
Ten Wolde <i>et al.</i> [18]	0/95 (0.0)	0–3.1	0/95 (0.0)		
Total	1/872 (0.1)	0–0.6			
DVT					
Bates <i>et al.</i> [10]	1/283 (0.4)	0–2.0	0/193 (0.0)	1/90 (1.1)	
Anderson <i>et al.</i> [11]	3/316 (1.0)	0.2–2.8	3/316 (1.0)		
Schutgens <i>et al.</i> [14]*	1/176 (0.6)	0.1–3.1	1/176 (0.6)		
Kearon <i>et al.</i> [15]	1/177 (0.6)	0–3.1	1/177 (0.6)		
Janes and Ashford [17]	1/98 (1.0)	0.3–5.6	1/98 (1.0)		
Wells <i>et al.</i> [19]†	2/218 (0.9)	0.1–3.3	2/218 (0.9)		
Total	9/1268 (0.7)	0.3–1.3			
MIX					
LeClerque <i>et al.</i> [12]	0/64 (0.0)	0.0–4.6	0/48 (0.0)	0/16 (0.0)	
Combined total	10/2204 (0.45)	0.22–0.83	9/2056 (0.44)	1/143 (0.70)	0/5 (0.0)

*Low, non-high; †Low, unlikely. Values given in parentheses are in percentage.

category and a normal D-dimer (0.7%, 95% CI 0.02%–3.8%) (Table 2).

The overall thromboembolic event rate when the two studies that broadened the low clinical probability group were left out was six out of 1810 (0.33%, 95% CI 0.1%–0.7%).

Patients suspected of PE

We found four studies on diagnosis of PE with a total number of 2760 patients of which 872 (32%) did not have further testing (Table 2). The majority of cases (831) consisted of patients with a low clinical probability (30%). Perrier *et al.* also declined further testing in 37 patients with a moderate score (1.3%) and in five patients with a high clinical score (0.1%).

Overall, only one patient (0.1%, 95% CI 0.0%–0.6%) suspected of PE in whom treatment was withheld developed VTE during a 3 month follow-up period.

Patients suspected of DVT

The six studies on DVT had a total number of 3875 patients of whom 1268 (33%) did not have additional imaging (Table 2). During the 3 month follow-up period only nine patients were eventually diagnosed with thrombosis (0.7%, 95% CI 0.3%–1.3%). The strategy in the DVT group is mainly based on the exclusion of patients with low clinical probability, only one study excluded patients with either a low or a moderate clinical probability.

Table 3 The incidence of thromboembolic outcomes over a 3-month follow-up period in patients in whom anticoagulants were withheld, in relation to D-dimer test used

Type of D-dimer test	Patients tested	Strategy	Number of cases	Overall risk (%)	95% CI (%)
SimpliRED (qualitative)	712	Low	3	0.42	0.1–1.2
SimpliRED or IL test (mix)	534	Low	5	0.94	0.3–2.2
MDA, VIDAS, TINA-QUANT (quantitative)	958	Low (+ mod)	2	0.21	0.0–0.8

The study performed by LeClerque *et al.* [12] looked at a mixed group of patients, either with PE or DVT, and found that out of 202 patients only 138 needed further testing. The remaining 64 (32%) with either low or moderate clinical probability did not undergo additive testing. Of this entire group, no one developed a thromboembolic event over a 3-month follow-up period (0%, 95% CI 0.0%–4.6%).

Clinical decision rules

The CDRs that were used varied among the different investigators. The majority of authors used the Wells score [9,32]. One of the reviewed studies [18] has applied an adapted Wells score in which there is no division into low, moderate and high clinical probability anymore but only between likely and unlikely. This is due to the fact that from the former moderate probability group those with a score of one are now assigned to new category of 'unlikely' while those with a score of ≥ 2 are assigned to the high probability group now known as 'likely'. A new element of the adjusted score is that one point is assigned for a prior history of thrombosis.

The other two clinical assessment scores used were the Geneva score and clinical judgment [33] and an intuitive clinical decision model [6].

All decision models that were used have been validated and proved to have comparable predictive values to the more widely used Wells score [6,34].

Perrier *et al.* [8] made the decision of withholding further testing mainly dependent on D-dimer values.

D-dimer tests

The D-dimer tests used in the 11 selected studies can be divided into quantitative tests, such as MDA, VIDAS, IL test and TINAQUANT and qualitative tests, such as the simpliRED test.

In Table 3, the incidence of thromboembolic outcomes is given according to D-dimer test used (quantitative vs. qualitative or mix). All point estimates are low with overlapping 95% confidence intervals. Indeed, these differences are not statistically significant.

Influence of incidence

There seems to be a high negative correlation between the incidence of VTE among referred patients and the proportion of patients who can be managed based on the D-dimer and

CDR alone ($R = 0.71$, $P = 0.014$). When the incidence of the disease in the population is very low (10%–16%), the number of patients that can be excluded from further testing with a strategy that combines a D-dimer assay result and a CDR is between 40% and 60% (Table 1).

Discussion

Our analysis that is based on accumulated experience in 6837 patients suspected of VTE indicates that triage by a management strategy that combines a CDR with a D-dimer test result is safe. Among patients in whom anticoagulant treatment was withheld based on the CDR and D-dimer results, the overall incidence of thromboembolic events after a 3-month follow-up period was only 0.46%. The approach was safe in both DVT and PE, with 3-month incidences of thromboembolic events of 0.7% and 0.1%, respectively. These results compare favorably to the 3-month incidences obtained in management studies in which all patients underwent testing with reference standards, i.e. venography (1.9%) [35], repeated ultrasonography (0.9%) [36–38], pulmonary angiography (0.8%) [3] or perfusion scanning (1.2%) [25,41–43].

A recent review [39] suggested similar findings. However, this review included only patients suspected of DVT and based its results on a mix of management [10,14,15,22,26,40] and derivation studies [24,31,32,44,47]. This latter category of studies is known to produce in general more positive results than validation studies do [40]. Moreover, of the six studies that were listed in this review as management studies using a CDR and D-dimer result, three performed ultrasonography among all patients according to their method sections [22,26,40], while three other large published management studies in patients suspected of DVT that indeed based their management on CDR and D-dimer results were not identified [11,17,19]. Hence, this review only describes the clinical safety of the novel approach in 1813 patients instead of the 6837 patients in our review.

While the approach can be regarded to be safe in both patients suspected of DVT and PE, the results in this latter group seem far more favorable. Differences in clinical appraisal are unlikely to be the source of this discrepancy, as both the incidence of thromboembolic disease and the exclusion efficiency are similar in both groups. However, in view of the potentially higher lethal outcome rate among patients suspected of PE, the finding in itself is comforting.

The use of a combination of a CDR and D-dimer test can lead to a reduction of at least 30% in diagnostic imaging tests. However, in a population with a disease incidence that is extremely low the reduction may increase up to 50%. This

difference is likely to be due to an increase in the proportion of patients with a low clinical probability in whom the D-dimer testing is also more frequently negative [11].

There is no significant difference in safety between a normal result on a quantitative D-dimer test and a normal result on a qualitative D-dimer test for the exclusion of venous thromboembolic disease in patients with a low clinical probability. This finding is of importance for application in an out of hospital setting where the primary care physician is able to screen suspected patients by using a qualitative D-dimer test. Finally, although a wide array of different CDRs has been used in the studies that have been analyzed, the overall results were highly comparable. The potential disadvantage of a qualitative test is the observer-dependency. Hence, care should be taken to avoid false negative results and the test should ideally be used by experienced personnel only.

Conclusion

Withholding anticoagulant treatment in patients suspected of VTE on the basis of a work-up, consisting of a combination of a CDR and a D-dimer test result, is documented to be safe for the group of patients with a normal D-dimer test result and a low clinical pretest probability score.

By assessing patients according to this strategy, at least a 30% decrease in diagnostic imaging can be achieved. This decrease in diagnostic imaging will result in less waiting time for those patients that need to be tested, and will eventually contribute to diminished costs of health care. For this purpose, both quantitative and qualitative D-dimer tests can be used as there were no statistically significant differences in safety. This implies that the primary assessment of patients could even be transferred to an out of hospital setting using a qualitative D-dimer test. This can result in a smaller number of patients that need to be referred to hospital for additional diagnostic procedures, which will save time and resources for both doctors and patients.

The limitation of this strategy is that it can be safely used only in a very well-defined group of patients. Over 50% of patients will still have to undergo a complete diagnostic work-up with an eventually negative outcome.

Studies need to be performed to assess whether a further reduction in diagnostic procedures can be gained safely when also patients with moderate clinical probability are excluded from further testing.

Declaration of conflicts of interest

The authors both declare that they have no conflicts of interest regarding this manuscript.

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