Diagnosis of venous thrombosis and the post-thrombotic syndrome

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CHAPTER 4

Excluding pulmonary embolism without imaging tests; can our diagnostic algorithm be optimized?

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Rationale Excluding pulmonary embolism by a cut-off level of the Wells clinical decision rule of four points to designate patients as "pulmonary embolism unlikely" combined with a D-dimer concentration of 500 ng/ml or less has been demonstrated to be safe.

Objective To investigate whether varying the cut-off level of the clinical decision rule as well as the D-dimer test could lead to an increase in clinical utility without jeopardizing safety.

Methods Data were obtained from a diagnostic outcome study of patients suspected of pulmonary embolism. The number of patients with PE at baseline or during follow-up, clinical utility and 3-months thrombo-embolic failure rate were calculated for different cut-off points of the clinical decision rule and D-dimer test.

Results By increasing the cut-off level of the clinical decision rule from 4 to 5 points, pulmonary embolism could be ruled out in an additional 4% of the study population (from 29.3 to 33.3%) at an expense of an increased 3-months venous thrombo-embolic failure rate of 1.5% (95%CI: 0.6-3.0%). By increasing the D-dimer cut-off level from 500 to 600 ng/ml, PE could be ruled out in an additional 3% of the study population but the 3-months thrombo-embolic failure rate increased to 2.2% (95%CI: 1.1-4.0).

Conclusions The cut-off level of the clinical decision rule as well as the cut-off level of the D-dimer test should be kept at the original 4 points and 500 ng/ml respectively, in order to prevent exposure of patients to a 3-months thrombo-embolic failure rate exceeding that of normal pulmonary angiography.

Introduction

Pulmonary embolism (PE) is a potentially fatal disease and one of the leading causes of cardiovascular mortality. Due to the non-specificity of clinical signs and symptoms, only 20-30% of patients with clinically suspected PE are diagnosed with the disease. Excluding PE has been simplified in recent years by the introduction of non-invasive tests as standardized clinical decision rules (CDR) and quantitative D-dimer assays. Several management studies have demonstrated that the combination of a low to moderate clinical probability of PE and a normal D-dimer test result safely rules out PE with a 3-months thrombo-embolic failure rate of less than 1% ([1-4]). Importantly, with this approach, it has been established that additional imaging tests including computed tomography (CT) or ventilation-perfusion lung scans can be withheld in approximately 15 to 50% of patients. Increasing the clinical utility, i.e. the proportion of patients in whom the diagnosis of PE can be safely excluded without additional imaging tests, would be desirable, provided that the safety of excluding PE with this approach is not jeopardized. The original CDR according to Wells categorized patients with clinically suspected PE into three groups, i.e. patients with a low (< 2 points), intermediate (2-6 points) and high clinical probability (>6 points) occurring in 59%, 33% and 8% of the study population respectively ([5]). In comparison to patients with a low probability and normal D-dimer test results, occurring in 29% of the study population, in a post-hoc analysis it was shown that PE could be confidently ruled out in an additional 20% of patients by using a dichotomized cut-off level of 4 points or less. The safety of using this cut-off level in combination with a normal quantitative D-dimer test has recently been demonstrated in a large prospective cohort study in patients with clinically suspected PE. The 3-months thrombo-embolic failure rate in this study was 0.5% (95%CI: 0.2-1.1%) ([6]). We retrospectively analyzed the data of this study to evaluate 1) the safety and clinical utility of increasing the cut-off level of the CDR to designate patients as "PE unlikely" while the D-dimer cut-off level remained at 500 ng/ml; and 2) the safety and clinical utility of increasing the cut-off level of the D-dimer test to levels above 500 ng/ml while the CDR cut-off level was kept at 4 points.

Methods

Patients

Data were obtained from a prospective cohort follow-up study performed between November 2002 and December 2004 in the Netherlands ([6]). In this study, the safety of excluding pulmonary embolism by a diagnostic algorithm consisting of a CDR, a quantitative D-dimer test and helical CT was

evaluated. In- and outpatients with a clinical suspicion of PE were eligible for the study. Exclusion criteria were age under 18 years, treatment with therapeutic doses of unfractionated or low-molecular weight heparin for more than 24 hours prior to inclusion, a life expectancy of less than three months, pregnancy, allergy to intravenous contrast agents, renal insufficiency (creatinine clearance less than 30 ml/min), logistic reasons, geographic inaccessibility precluding follow up or hemodynamic instability.

Diagnostic Work-up

PE was considered unlikely if the Wells CDR was ≤ 4 points. PE was considered likely in case of a CDR > 4 points ([1;5]). Patients with a CDR indicating PE unlikely underwent D-dimer testing and when normal, the diagnosis of PE was considered excluded. In these patients anti-coagulant treatment was withheld. Patients with a CDR indicating "PE unlikely" and an abnormal D-dimer test and patients with a CDR indicating "PE likely" underwent helical CT to diagnose or exclude PE.

All patients were followed for a period of three months to document the occurrence of symptomatic venous thromboembolic events. In five of the twelve hospitals participating in the Christopher study, D-dimer tests were performed in all patients, irrespective of their clinical probability, for logistic reasons. However, these results were only communicated to the treating physician in case of a CDR indicating "PE unlikely". Only patient data in these five hospitals were used in this analysis.

The D-dimer concentration was measured in three hospitals using the Vidas D-Dimer assay (Biomerieux, Marcy L'Etoile, France). The Tinaquant assay (Roche Diagnostica, Mannheim, Germany) was used in the two other hospitals. A cut-off level below or equal to 500 ng/ml was defined as normal for both tests ([6]).

The Institutional Review Boards (IRB's) of all participating hospitals approved the study protocol and written or oral informed consent was obtained from all participants, depending on the requirements of the local IRB's.

Statistical Analysis

Increments of 100 ng/ml for the D-dimer test result and 1 score-point for the CDR were used as the varying elements in this analysis. The reference test for calculation of the test characteristics sensitivity and specificity was the diagnosis of PE at baseline by helical CT or the occurrence of an objectively diagnosed venous thrombo-embolic event during the three months of follow-up. For each

increment of CDR and D-dimer cut-off point, the number of patients with PE at baseline or during follow-up and the associated sensitivity, specificity, negative and positive predictive values were calculated. Exact 95% confidence intervals (CI) were calculated around the observed incidences using JavaStat software (http://hometown.aol.com/johnp71/confint.html). Ruling out PE by a combination of a CDR score and a negative D-dimer test was considered safe if the negative predictive value was at least 98% and if the upper confidence limit of the 3-months thrombo-embolic failure rate did not exceed 2.7%, being the upper confidence limit of the 3-months thrombo-embolic rate of a normal pulmonary angiography ([7]).

Results

Of 1605 eligible patients recruited in the 5 hospitals, 90 were excluded because of predefined exclusion criteria or declined informed consent. Of the included patients, data regarding the CDR score were missing in 3 patients and 46 patients were treated with anticoagulants for reasons other than venous thrombo-embolism (VTE), resulting in a total of 1466 patients (91%) available for this analysis (Table 1).

Table 1. Baseline characteristics of the study population (n=1466)

Characteristics	*n (%)*
Age in years	54 (19)
Female sex	822 (54)
Estrogen use*	168 (20)
Immobilisation > 3 days or surgery	303 (20)
History of VTE	209 (14)
COPD	156 (10)
Heart failure	138 (9)
Malignancy	238 (16)
Outpatients	1155 (76)
PE at baseline	321 (22)

Al data are represented as mean (Standard Deviation)
*in females only

The mean age of the patients was 54 years, 54% of patients were female and 76% were outpatients. The prevalence of PE was 22% (321 patients diagnosed with PE at baseline and nine patients with PE during three months follow up).

The prevalence of PE increased with increasing score on the CDR, ranging from 5% in patients with a score of 1 point or less, to 59% in patients with a score of more than 7 points (Figure 1).

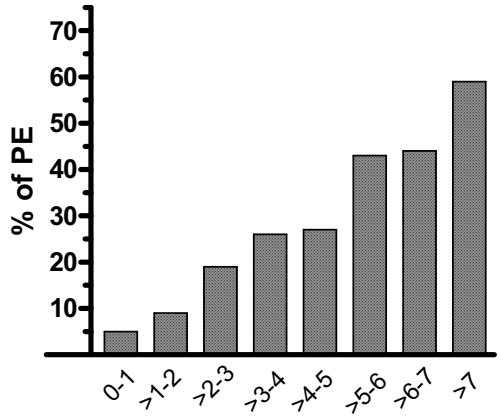

Figure 1 Prevalence of PE according to CDR score

Similarly, the prevalence of PE increased with increasing concentration of D-dimer, ranging from 1% in patients with D-dimer concentrations below 300 ng/ml to more than 60% with D-dimer concentrations above 5000 ng/ml (Figure 2).

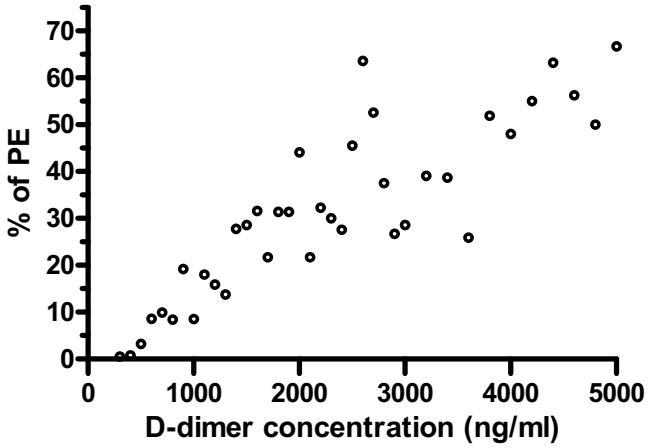

Figure 2 Prevalence of PE according to D-dimer level

Varying the Cut-off Level of the Clinical Decision Rule

The sensitivity of a normal D-dimer and a CDR cut-off level of four points or less was 98.8% (95%CI: 96.9-99.7), the specificity 37.5% (95%CI: 34.7-40.4) and the negative predictive value was 99.1% (95%CI: 97.6-99.8).

Increasing the CDR cut-off level from 4 to 5 points or less would have resulted in a total of 1213 patients (82.7%) designated as "PE unlikely". D-dimer tests would have been normal in 488 patients (33.3%) (Table 2).

Table 2. Influence of varying CDR cut-off value*

CDR score	DD tests performed N (%)	D-dimer normal N (%)	3-months VTE failure rate n	% (95%CI)
≤ 4	960 (65.5)	430 (29.3)	4	0.9 (0.3-2.4)
≤ 5	1213 (82.7)	488 (33.3)	7	1.5 (0.6-3.0)
≤ 6	1384 (94.4)	502 (34.2)	10	2.0 (1.0-3.7)

*D-dimer cut-off remained 500 ng/ml;
CDR: Clinical Decision Rule; DD: D-dimer; VTE: Venous Thromboembolic Events

The sensitivity was 97.9% (95%CI: 95.7-99.1), the specificity 42.3% (95%CI: 39.5-45.3) and the negative predictive value 98.6% (95%CI: 97.1-99.4) (Table 3).

Table 3. Effect of varying CDR cut-off on test characteristics*

CDR score	Sens (95%CI)	Spec (95%CI)	NPV (95%CI)
≤ 4	98.8 (96.9-99.7)	37.5 (34.7-40.4)	99.1 (97.6-99.8)
≤ 5	97.9 (95.7-99.1)	42.3 (39.5-45.3)	98.6 (97.1-99.4)
≤ 6	97.0 (94.5-98.5)	43.3 (40.4-46.3)	98.0 (96.4-99.0)

*D-dimer cut-off level remained 500 ng/ml;
CDR: Clinical Decision Rule, NPV: Negative Predictive Value; Sens: Sensitivity; Spec: Specificity

The number of patients in whom the diagnosis of PE would have been ruled out without performing a CT scan increased from 430 patients (29.3% of total study population) at a cut-off level of 4 points or less to 488 patients (33.3% of total study population) at a cut-off level of 5 points or less, (difference 58 patients, 4.0 % increase in total study population), This would be associated with an increase from

4 to 7 venous thrombo-embolic events, resulting in an increase in 3-months VTE failure rate to 1.5% (95%CI: 0.6-3.0%).

Further increasing the cut-off level of the CDR to 6 points or less would have resulted in 14 more patients (from 488 to 502, 0.9 % of the total study population) in whom the diagnosis of PE was ruled out without performing a CT scan. This would lead to 3 more thrombo-embolic events (from 7 to 10) with a 3-months thrombo-embolic rate of 2.0% (95%CI: 1.0-3.7).

Varying the Cut-off Level of the D-dimer Test

Table 4 demonstrates the effect of varying the cut-off level of the D-dimer test when the CDR cut-off level remained at 4 points or less to designate patients as "PE unlikely". Increasing the D-dimer test cut-off level from 500 to 600 would have resulted in a total of 474 patients (32.3%) designated as having no PE.

Table 4. Influence of varying D-dimer cut-off value*

D-dimer cut-off	DD tests performed n (%)	D-dimer normal n (%)	3-months VTE failure rate N	% (95%CI)
≤ 500	960 (65.5)	430 (29.3)	4	0.9 (0.3-2.4)
≤ 600	960 (65.5)	474 (32.3)	11	2.2 (1.1-4.0)
≤ 700	960 (65.5)	507 (34.6)	16	3.0 (1.8-4.9)

* Clinical Decision Rule cut-off remained ≤ 4 points;
DD: D-dimer; VTE: Venous Thromboembolic Events

The sensitivity was 96.7% (95%CI: 94.1-98.3), the specificity 40.8 (95%CI: 37.9-43.7) and the negative predictive value 97.7% (95%CI: 95.9-98.8). The number of patients in whom the diagnosis of PE would have been ruled out without performing a CT-scan increased from 430 at a cut-off level of 500 ng/ml to 474 patients at a cut-off level of 600 ng/ml (44 patients, 3% of the study population), at an expense of 7 additional venous thrombo-embolic events. This would result in a 3-months thrombo-embolic failure rate of 2.2% (95%CI:1.1-4.0)).

Table 5. Effect of varying D-dimer cut-off on test characteristics*

D-dimer cut-off	Sens (95%CI)	Spec (95%CI)	NPV (95%CI)
≤ 500	98.8 (96.9-99.7)	37.5 (34.7-40.4)	99.1 (97.6-99.8)
≤ 600	96.7 (94.1-98.3)	40.8 (37.9-43.7)	97.7 (95.9-98.8)
≤ 700	95.2 (92.3-97.2)	43.2 (40.3-46.2)	96.8 (94.9-98.2)

*CDR cut-off level remained ≤ 4 points,
NPV: Negative Predictive Value; Sens: Sensitivity; Spec: Specificity

By increasing the cut-off level of the D-dimer concentration to 700 ng/ml, the diagnosis of PE could have been ruled out in 507 patients (34.6% of the study population) at an expense of 12 additional thrombo-embolic events compared. This resulted in a 3-months thrombo-embolic failure rate of 3.0% (95%CI: 1.8-4.9%). Sensitivity dropped to 95.2% (95%CI:92.3-97.2) and negative predictive value to 96.8% (95%CI:94.9-98.2).

Discussion

This is the first study that investigated the effect of stepwise variation of both the cut-off level of the CDR as well as the D-dimer test.

There are two important conclusions to be drawn from our analysis. First, our results show that increasing the cut-off level of the CDR, while keeping the D-dimer test cut-of at 500 ng/ml, is not safe. The upper 95 % confidence interval, of the hypothetical 3-months thrombo-embolic failure rate of 1.5 %, was 3%. This exceeded a generally accepted upper safety limit of 2.7% even when the CDR cut-off level was only raised from 4 to 5 points. Second, increasing the cut-off level of the D-dimer test had an even more profound effect on safety. By increasing the cut-off level from 500 to 600 ng/ml, the negative predictive value of a clinical decision rule indicating PE unlikely, combined with a normal D-dimer test, dropped below 98% while the hypothetical 3-months thrombo-embolic failure rate would have an upper 95 % confidence limit of 4.0% which clearly exceeded our predefined upper safety limit.

Importantly, the gain of clinical utility, i.e. the proportion of patients in whom PE could be ruled out without the need for additional imaging tests, as a result of changing the cut-off values was relatively

modest. By raising the cut-off level of the CDR from 4 to 5 points, PE could be ruled out in an extra 4.0% of the study population. Similarly, by raising the D-dimer cut-off level from 500 to 600 ng/ml in an extra 3.0% of the study population PE could be ruled out without imaging tests.

Two earlier studies have investigated the effect of varying the cut-off level of the D-dimer test in categories of pre-test probability without changing the cut-off levels to designate patients as low, intermediate or high clinical probability ([8;9]). In the first study, increasing the D-dimer test cut-off level from 500 to 600 ng/ml in patients with a low pre-test probability led to a marginal gain in diagnostic yield since PE could be ruled out in an additional 2.7% of the total study population. According to our predefined safety limit, the safety was only marginally diminished since the 3-months thrombo-embolic failure rate only increased from 0% (95%CI:0-0.8%) to 0.3% (95%CI: 0.01-1.4). This might be explained due to the low prevalence of PE (7%) in this subgroup with a low pre-test probability. Indeed, raising the D-dimer cut-off level from 500 to 600 ng/ml in patients with an intermediate probability (prevalence of PE 35%) in the same study led to an unacceptably high 3-months thrombo-embolic rate of 5.8% (95%CI: 1.9-13.1) ([9]).

The second study concluded that the use of three pre-test probability-specific D-dimer cut-off points excluded VTE in a larger proportion of patients (49.2%) than using a single cut-off point (36.4%) without sacrificing NPV (98%) ([8]). However, the 3-months thrombo-embolic failure rate in patients with a low pre-test probability increased from 0% (upper 95% confidence limit 1.5%) to 1.5% (upper 95% confidence limit 4.2%) and the sensitivity decreased dramatically from 100 to 75%. Of note, in this study the highest D-dimer cut-off level was selected on the basis of a negative predictive value of at least 98%. The use of the NPV as a sole criterion of safety may be misleading since it is critically dependent on the prevalence of disease in the population tested. Finally, in the second study a mixed population of patients with clinically suspected PE and DVT was included.

There are some limitations to be discussed. We used data of only 5 of the 12 hospitals participating in the Christopher study. We do not think this has led to selection bias, since the prevalence of PE as well as the baseline characteristics of the study patients was similar to the overall population of our original cohort ([6]). Second, two different D-dimer assays were used. Since there was no statistically

significant difference in failure rate between the two tests in the original study, we felt confident to combine data from both assays.

Strengths of our study are that we had a relatively large cohort of patients with suspected PE in which the diagnosis was ruled out or diagnosed by a simple algorithm and all outcome events were adjudicated by an independent committee.

In conclusion, our results demonstrate that the cut-off level of the CDR to designate patients as "PE unlikely" and the cut-off level of the D-dimer test to designate a test result as "normal" should be kept at the regular CDR cut-off level of 4 points and D-dimer concentration of 500 ng/ml, in order to prevent exposure of patients, with initial normal diagnostic tests, to a 3-months thrombo-embolic failure rate exceeding that after a normal pulmonary angiography. The challenge for future studies is to provide algorithms, which can safely reduce the percentage of patients undergoing imaging tests for PE.

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