

Excluding deep vein thrombosis safely in primary care

Validation study of a simple diagnostic rule

Practice recommendations

- Our validated primary care rule safely excludes deep vein thrombosis in one quarter of patients suspected of having the disease (A). We recommend the use of this rule by family practitioners.

Most primary care patients with suspected deep vein thrombosis (DVT)—even if suspicion is low—are referred for burdensome and costly tests such as ultrasonography of the legs or venography. How many of these patients end up having DVT? About 25%.¹⁻³

Clearly there is a need for a clinical tool that can help distinguish patients with low risk of DVT from those with high risk. In a previous study, we developed and internally validated a simple diagnostic prediction rule for DVT that includes 7 patient characteristics and the result of a D-dimer test (so-called derivation study).⁴ In the deviation data set, this rule showed good performance and could safely exclude the presence of DVT in about one quarter of patients, minimizing the number of unnecessary patient referrals.

Prediction rules commonly show good performance with the data from which they were developed, even when bootstrapping techniques are applied to correct them for overoptimism (internal validation). But good accuracy with the development data set is no guarantee the rule will be accurate

for future patients.⁵⁻¹⁰ Testing the accuracy of a prediction rule in new patients is necessary before implementing it in daily patient care—ie, so-called *external* validation or generalizability. Promising results on such validation studies increase the confidence for applying rules in practice.^{8,9}

The aim of this study was to quantify (externally validate) the accuracy of our previously derived diagnostic rule for DVT in a large sample of new primary care patients suspected of having DVT, thus testing the rule's ability to safely exclude DVT.

The rule

The diagnostic rule validated in the present analysis, has been derived in a previous study by using multivariable logistic regression analysis, which identified independent diagnostic indicators of DVT: male gender, 6 items from the history and physical examination, and the result of a D-dimer test.⁴ Combining these items in a prediction rule, we reached the optimal diagnostic accuracy for the diagnosis of DVT (TABLE 1). The formula of the diagnostic rule:

FORMULA

(1 × male gender) + (1 × oral contraceptive use) + (1 × presence of malignancy) + (1 × recent surgery) + (1 × absence of trauma) + (1 × vein distension) + (2 × calf difference ≥ 3 cm) + (6 × abnormal D-dimer test result)

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The numerical value associated with each indicator represents the weight of that indicator. Each indicator is assigned the value 1 if present, and 0 if absent. For example, a man without leg trauma, with a history of malignancy, and a normal D-dimer test result receives a score of $(1 \times 1) + (1 \times 0) + (1 \times 1) + (1 \times 0) + (1 \times 1) + (1 \times 0) + (2 \times 0) + (6 \times 0) = 3$ points. In the derivation study, the area under the receiver operating characteristic (ROC) curve of the rule, after adjustment for over-optimism using bootstrapping, was 0.78 (95% confidence interval [CI], 0.75–0.81).

To enhance the clinical usefulness of the rule, total score results were combined into different categories: very low risk (score 0–3, DVT prevalence 0.7%), low risk (score 4–6, DVT prevalence 4.5%), moderate risk (score 7–9, DVT prevalence 21.7%), and high risk (score 10–13, DVT prevalence 54.3%). Using a score threshold ≤ 3 (very low risk) and retaining these patients in primary care would result in a 23% reduction in referrals, at the cost of only 0.7% missed DVT cases. The man in the example above has a score of 3 points. The primary care physician could decide not to refer this patient, with a risk of just 0.7% of missing a DVT.

or signs existing for more than 30 days or suspicion of pulmonary embolism.

From the literature, 16 history findings and physical examination items were selected as potential diagnostic indicators. After standardized history taking and physical examination, all patients were referred to the hospital to undergo D-dimer testing. Finally, repeated compression ultrasonography of the symptomatic leg was used as a reference test for all patients. D-dimer level was measured by either the ELISA method (VIDAS, Biomerieux, France) or a latex assay method (Tinaquant, Roche, Germany), depending on the lab routine of the participating hospital.

In an earlier study, the optimal thresholds of the D-dimer tests were determined; the test was considered abnormal if the latex assay yielded a D-dimer level ≥ 400 ng/mL (Tinaquant) or ≥ 500 ng/mL for the ELISA assay (VIDAS).¹¹ DVT was considered present if (one of) the deep veins of the legs were not or not completely compressible, as determined with a 5–7.5 MHz linear-array sonographic scanner (system V GE/Sonotion).¹² In patients with a normal ultrasound, the test was repeated within 7 days to exclude DVT.⁴ All patients with a positive ultrasound were treated with anti-coagulants.

FAST TRACK

This diagnostic rule is the first for safely excluding DVT in primary care

■ Patients and methods

Derivation study

The diagnostic rule was derived from 1295 consecutive patients consulting their primary care physician with symptoms suggestive of DVT. The study was performed among 110 primary care physicians affiliated with 3 nonacademic hospitals. The characteristics of the derivation study and the rule are described in detail elsewhere.⁴

In short, suspicion of DVT was based on the presence of at least 1 of the following signs and symptoms: swelling, redness, or pain of the lower extremities. Patients were included if the primary care physician decided that the diagnosis of DVT should be confirmed or excluded by objective diagnostic testing (ultrasonography) in the hospital. Exclusion criteria were symptoms

Validation study

After completing the data sampling of the derivation study, we began collecting data on the next 532 consecutive patients visiting a general practitioner with symptoms suggestive of DVT. The validation study was conducted between June 1, 2003, and June 1, 2005, among the same 110 general practitioners who participated in the derivation study. The protocol of the validation study was similar to that of the original study, using the same inclusion and exclusion criteria, D-dimer assays, and definition of presence and absence of DVT.

The 7 items in the rule were obtained from the standardized history taking and physical examination, and D-dimer testing and ultrasonography were performed in the hospital.

The study protocol was approved by the Medical Ethical Committee of the University Medical Centre Utrecht, and informed consent was obtained from all patients.

Statistical analysis

To quantify external validity, we calculated each patient's total score using the rule (**FORMULA** and **TABLE 1**). First, the overall ability of the rule to discriminate between patients with and without DVT was assessed by the ROC area. Perfect discrimination is represented by an ROC area of 1.0; an ROC area of 0.5 equals the discrimination of a coin flip.¹³

All patients were assigned to 1 of 4 risk groups, based on total points scored on the rule (**TABLE 2**). Patients were again considered at very low risk if they received 3 points or less. For this threshold, we calculated corresponding sensitivity, specificity, negative predicted value, and likelihood ratio of a negative test result (negative likelihood ratio = $[1 - \text{sensitivity}] / \text{specificity}$) with their 95% CIs. Because ruling out DVT is the main purpose of applying the rule, the positive predictive value and the likelihood ratio for a positive test result are not presented.

One hundred fifty-three of the 532 subjects had missing values for one or more predictors in the rule. Missing values ranged from 1.3% in gender to 11.8% for D-dimer test result (1.5% in oral contraceptive use, 2.3% trauma, 7.0% calf difference ≥ 3 cm, 7.5% presence of malignancy, 8.3% recent surgery, 11.7% vein distension). Data seldom are missing completely at random. Deleting subjects with a missing value not only leads to a loss of statistical power, but also to biased results. Therefore, imputing missing values is generally preferred to complete case analysis.^{14,15} Missing data were thus (single) imputed, using the linear regression method available in SPSS version 12.0.1 (SPSS, Inc, Chicago, Ill, USA). For comparison purposes, a complete case analysis was also performed.

TABLE 1

Distribution of the predictors in the rule in the validation and derivation study set

PREDICTORS OF DVT	POINTS ATTRIBUTED TO PREDICTOR	PREVALENCE (%)	
		VALIDATION SET (N=532)	DERIVATION SET (N=1295)*
Male gender	1	40	36
Oral contraceptive use	1	9	10
Presence of malignancy	1	3	6
Recent surgery	1	13	14
Absence of leg trauma	1	83	85
Vein distension	1	18	20
Calf difference ≥ 3 cm	2	41	43
D-dimer abnormal*	6	75	69
DVT Presence		18	22

* D-dimer was considered abnormal if the concentration was ≥ 500 ng/mL with the Vidas assay and ≥ 400 ng/mL with the Tinaquant assay.

Results

The frequencies of the diagnostic indicators in the validation (and derivation) set are presented in **TABLE 1**. Patient age varied between 18 and 98 years (mean \pm standard deviation: 60 ± 17 years), and 40% of the patients were male. The distribution of variables in the validation and derivation set were comparable, except for the prevalence of malignancy (3% and 6%, respectively) and DVT (18% and 22%, respectively).

The **FIGURE** displays the graph of the ROC curve of the rule. The area under the ROC curve was 0.75 (95% CI, 0.70–0.79).

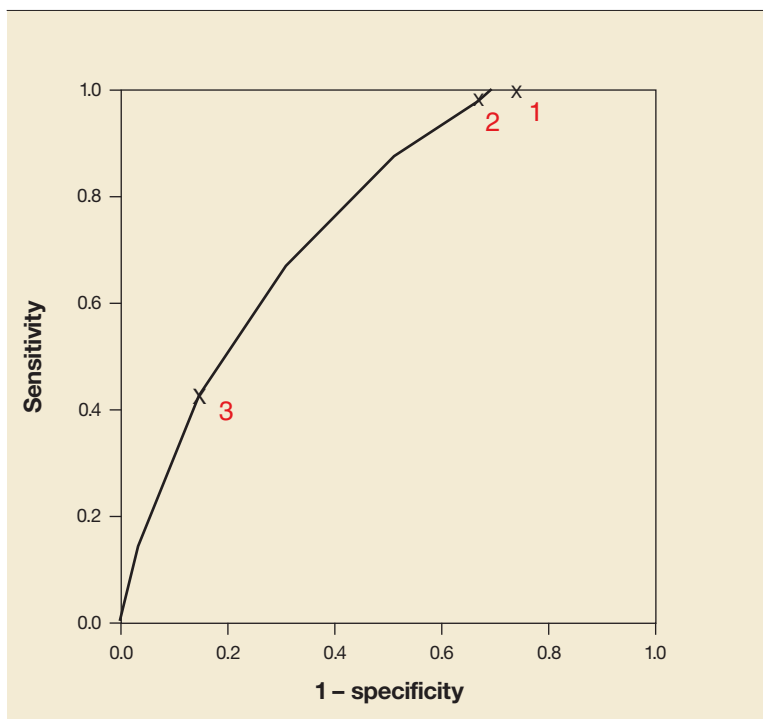
In the validation population, 112 patients (21%) fell in the “very low risk” group. Application of the rule could thus reduce the number of referrals by 21% in the validation set (**TABLE 2**). None of these patients had DVT (**TABLE 2**). Accordingly, sensitivity of the rule at the threshold of ≤ 3 in the validation population was 100% with a corresponding specificity of 25.7%. The predictive value of a negative test

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Applying our rule, you could decide not to refer a patient, with just a 0.7% risk of missing DVT

FIGURE

**Receiver operator characteristic curve
of the primary care rule for DVT**



Points on the line correspond to the thresholds as displayed in Table 2. The values 1, 2 and 3 represent the sensitivities and specificities when applying a threshold of $\leq 3, 6, \text{ and } 9$, respectively.

result was 100%, and the negative likelihood ratio 0 (TABLE 2). With increasing rule scores, the probability of having DVT rises. Besides, if the threshold of not referring a patient would be increased, sensitivity decreases and specificity increases (TABLE 2).

The complete case analysis revealed the same sensitivity, specificity, and negative likelihood ratio as the analysis on the imputed data—ie, no DVT cases in the very low risk group. All presented results are derived from the analysis of the imputed data set.

Discussion

To our knowledge, this diagnostic rule is the first for safely excluding DVT in primary care patients. Studies applying DVT rules in other settings have reported per-

centages of missed DVT cases similar to those in our study.¹⁶⁻²⁰ Of these rules, the one developed by Wells and colleagues (Wells rule) is the best known.²¹⁻²³

The Wells rule was derived and validated from data of 593 consecutively referred secondary care outpatients suspected of having DVT. In the Wells rule, 8 specific items from patient history and physical examination were weighted with 1 point (each item, if present, thus increased the likelihood of DVT equally) and a ninth item (another diagnosis just as likely or more likely to explain the presented symptoms and signs) was weighted -2 points (decreasing the likelihood of DVT). Accordingly, a sum of the scores given the 9 diagnostic items could result in a final tally from -2 to +8.

Wells et al initially presented their rule as a tool to exclude DVT if the score was 0 or lower (very low risk of DVT).^{21,22} In a more recent paper they updated their rule by adding the D-dimer test result and defined patients to be at very low risk with a score of 1 or less and a normal D-dimer test result.²⁰ In secondary care, this rule yields good diagnostic accuracy in safely excluding DVT.

Uniqueness of our rule in primary care.

In a recent study we showed that when testing the initial and updated Wells rule in primary care patients suspected of DVT, an unacceptably high percentage of patients in the “very low risk” group still had DVT: >12% for the initial rule and still >2% for the updated rule combined with D-dimer test.²⁴ We repeated this analysis in the current cohort of primary care patients suspected of having DVT, which yielded similar results (data not shown). The decreased accuracy of the Wells rule in primary care can probably be ascribed to the differences in spectrum of patients between secondary and primary care.²⁴

Value of the validation study. Many prediction rules are developed and recommended for use in new patients without external validation. It is well known that they yield risk estimations that are too

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TABLE 2

Prevalence of DVT across the 4 risk categories
(with diagnostic accuracy measures)

	DVT PRESENT N (%)	DVT ABSENT N (%)	PATIENTS N (%)	SN % (95% CI)	SP % (95% CI)	PV- % (95% CI)	LR- (95% CI)
Validation study (n=532)							
Very low (0–3)	0 (0)	112 (100)	112 (21)	100 (98.6–100)	25.7 (21.6–29.8)	100 (98.8–100)	0.0 (0.00–0.32)
Low (4–6)	2 (6.3)	30 (93.8)	32 (6)	97.9 (95.1–100)	32.6 (28.1–37.0)	98.6 (96.7–100)	0.06 (0.00–0.53)
Moderate (7–9)	53 (19.2)	223 (80.8)	276 (52)	42.7 (32.8–52.6)	83.7 (80.2–87.2)	86.9 (83.7–90.1)	0.68 (0.57–0.82)
High (10–13)	41 (36.6)	71 (63.4)	112 (21)				
Derivation study (n=1295)							
Very low (0–3)	2 (0.7)	291 (93.3)	293 (23)	99.3 (98.4–100)	28.9 (26.1–31.7)	99.3 (98.4–100)	0.02 (0.00–0.10)
Low (4–6)	3 (4.5)	63 (95.5)	66 (5)				
Moderate (7–9)	144 (21.7)	519 (78.3)	663 (51)				
High (10–13)	140 (51.3)	133 (48.7)	273 (21)				

DVT, deep vein thrombosis; SN, sensitivity; SP, specificity; PV-, negative predictive value; LR-, negative likelihood ratio.

optimistic when applied to other data. Our study quantified the generalizability of our simple rule to safely exclude deep venous thrombosis in primary care.⁴ Safely excluding a disease requires a high sensitivity and a high negative predictive value. The sensitivity (100%) and the negative predictive value (100%) in the new patient sample were the same as in the derivation study.

The threshold works. The derivation and validation studies both demonstrated that almost one quarter of the patients suspected of having DVT (23% and 21%, respectively) were at very low risk (score ≤ 3) and could safely remain in primary care (0.7% and 0% missed DVT cases, respectively). Since all 112 individuals in the validation study with a very low risk at DVT were free of DVT, sensitivity and negative predictive value of the rule in the validation study were both

100% (both 99.3% in the derivation study), with a negative likelihood ratio of 0 (TABLE 2). Hence, we conclude that the developed rule seems a safe tool to use for excluding DVT in primary care.

In the validation population, only 2 patients in the “low risk” category (score 4–6) had DVT (TABLE 2). Both patients scored 6 points on the rule. That DVT was absent in all patients with a score of ≤ 5 strongly confirms the safety of the chosen threshold (ie, not referring patients with a score of ≤ 3).

Like in the original study, we presented the distribution of patients over 4 risk categories, with accompanying diagnostic accuracy measures (TABLE 2). With increasing scores, the risk of DVT increased. When the threshold of not referring a patient would be raised, sensitivity decreases (more false negatives) and specificity increases (more true negatives). In other words, by

increasing the threshold, fewer patients will be referred (saving referrals) at the cost of a higher percentage of missed DVT cases.

Referral still a judgment call. We recommend using the threshold of ≤ 3 when the rule is applied. However, use of the rule is discretionary, not mandatory. The clinical view of the physician remains important; one may still decide to refer a patient with a “very low risk” if the suspicion of DVT remains. On the other hand, circumstances may prompt a wait-and-see decision even for a patient with a score of 5.

Two caveats. First, rigorously derived prediction rules may lose their accuracy when applied to other settings, because predictors may be idiosyncratic to the population in which the rule was developed.^{5,7,8} Further research could focus on whether our rule yields similar diagnostic accuracy in other settings, including secondary outpatient care.

Second, we imputed missing values in this study. Although it is acknowledged that imputing missing values is better than simply deleting all patients with one or more missing values, we repeated the entire analysis on the complete cases. The complete case analysis did not yield different results than the analysis on the imputed data.

In conclusion, this validation study demonstrated that, also in a new patient sample, the primary care physician can safely refrain from referring a considerable number of patients suspected of DVT by using a simple diagnostic rule. The use of this rule reduces the number of unnecessary patient referrals to secondary care and consequently patient burden.

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Nearly 25% of patients with possible DVT were spared referral safely in our study