

New Technologies and Diagnostic Tools

Ruling out deep venous thrombosis in primary care

A simple diagnostic algorithm including D-dimer testing

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Summary

In primary care, the physician has to decide which patients have to be referred for further diagnostic work-up. At present, only in 20% to 30% of the referred patients the diagnosis DVT is confirmed. This puts a burden on both patients and health care budgets. The question arises whether the diagnostic work-up and referral of patients suspected of DVT in primary care could be more efficient. A simple diagnostic decision rule developed in primary care is required to safely exclude the presence of DVT in patients suspected of DVT, without the need for referral. In a cross-sectional study, we investigated the data of 1295 consecutive patients consulting their primary care physician with symptoms suggestive of DVT, to develop and validate a simple diag-

nostic decision rule to safely exclude the presence of DVT. Independent diagnostic indicators of the presence of DVT were male gender, oral contraceptive use, presence of malignancy, recent surgery, absence of leg trauma, vein distension, calf difference and D-dimer test result. Application of this rule could reduce the number of referrals by at least 23% while only 0.7% of the patients with a DVT would not be referred. We conclude that by using eight simple diagnostic indicators from patient history, physical examination and the result of D-dimer testing, it is possible to safely rule out DVT in a large number of patients in primary care, reducing unnecessary patient burden and health care costs.

Keywords

Diagnosis, deep vein thrombosis, D-dimer, Primary Health Care, diagnostic accuracy

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Introduction

The primary care physician is commonly the first to encounter patients suspected of deep vein thrombosis (DVT). The main task is to determine in whom DVT can be excluded and which patients have to be referred for secondary care diagnostic work-up. This selection is notoriously difficult because symptoms and signs of DVT have limited discriminating value in primary care (1, 2). Consequently, the majority of primary care patients suspected of DVT are referred to secondary care, where only in 20% to 30% of these the diagnosis DVT is confirmed (3). Since in the vast majority of referred patients no DVT is diagnosed, this puts a burden on both patients and health care budgets. The question arises whether the diagnostic work-up and referral of patients suspected of DVT in primary care could become more efficient.

Recent studies in secondary care showed that using a diagnostic decision rule including symptoms and signs plus the result of D-dimer testing, patients suspected of DVT could be more ad-

equately referred for further procedures such as ultrasound (1, 4–9). However, it is well known that decision rules derived from a secondary care setting often show poor accuracy when applied in a primary care setting and vice versa (10–12). Before application in daily practice of other settings, any decision rule must first be tested or validated in these settings. Various studies have shown that the diagnostic rules to determine the presence or absence of DVT developed in secondary care, have limited value in primary care (7, 13, 14). Hence, a diagnostic decision rule primarily developed and validated in general practice is needed to properly rule out (or confirm) the presence of DVT in patients suspected of DVT presenting to the general practitioner (2).

We investigated 1295 primary care patients suspected of having DVT to develop and validate a simple diagnostic decision rule to safely exclude the presence of DVT, in order to minimize the number of unnecessary patient referrals. This rule could include items from patient history, physical examination and D-dimer measurement results.

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Patients and methods

Patients

In a large cross sectional study we identified 1295 consecutive adult patients (over 18 years) who visited one of the primary care physicians adherent to three non-academic hospitals in The Netherlands, and in whom DVT was suspected by the physician on clinical grounds. In accordance with earlier studies, the suspicion of DVT was based on the presence of at least one of the following symptoms or signs of the lower extremities: swelling, redness, and/or pain in the legs (3, 15, 16). Patients were excluded from the study if these symptoms or signs existed more than 30 days and if there was a suspicion of pulmonary embolism. The three adhering hospitals participated in a diagnostic programme in which the primary care physicians used diagnostic facilities of the hospital without referring the patient to a hospital specialist. In total about 110 primary care physicians were involved and they included on average 9 to 10 patients with a suspicion of DVT per physician per year. To ensure and monitor the participation of the 110 physicians our study protocol for the diagnostic management of DVT suspected patients was integrated in the regular work-up for the primary care physicians in patients suspected of DVT. Each patient with an established DVT was further submitted to the Thrombosis Center, where the first author (Ruud Oudega) directly contacted his colleague-GPs in case of missing data. Detailed instruction of all primary care physicians took place immediately before the start of the project in a specially organized conference, including workshops dedicated to the logistics of the study. In addition, all GPs received similar information by mail. Furthermore a newsletter, including information about progress and inclusion rate of the project and feedback information was forwarded to the GPs 4 times a year.

The study was executed between January 1, 2002 and June 1, 2003. The study protocol was approved by the medical ethical committee of the University Medical Center Utrecht, The Netherlands.

Diagnostic tests under study

Patient history and physical examination

After informed consent was obtained, the primary care physician systematically documented information on the patient's history and physical examination. Based on previous diagnostic studies (3, 16, 25, 26) the following history findings were recorded as potential diagnostic determinants: presence of previous DVT, family history of DVT, history of any malignancy (active cancer in the last 6 months), immobilization for more than 3 days, recent surgery (within past 4 weeks), leg trauma (within past 4 weeks), pain when walking, and the presence of duration of the three main symptoms (i.e. a painful, red or swollen leg). Physical examination items included the presence of tenderness along the deep vein system in calf or thigh, distension of collateral veins in the symptomatic leg, pitting edema in the symptomatic leg of the calf and thigh, and ≥ 3 cm difference in circumference of the calves. For women two additional predictors were documented, i.e. the use of oral hormonal contraception and of estrogen replacement therapy.

D-dimer testing

After the standardized history taking and physical examination, all patients were referred to the hospital to undergo D-dimer testing. Venous blood was drawn from the anterior cubital vein and analysis was performed using citrated plasma with established methods according to the manufacturer's recommendations. The D-dimer test was performed with an ELISA method (VIDAS, Biomerieux, France) or with a latex assay method (Tinaquant, Roche, Germany), depending on the lab routine of the participating hospital. The manufacturers of both assays suggested to use a value lower than 500 ng/ml as a normal test result, yielding a high sensitivity suitable for excluding DVT (i.e. minimal risk of missing a patient with DVT). These cut-off values are currently widely recommended in guidelines and used in previous studies on the diagnosis of DVT using D-dimer assays.(17-19). The large number of patients included in our study provided the opportunity to critically evaluate these cut-off levels. Hence, we evaluated different cut-off levels of both assays to determine the threshold that optimized sensitivity with as large as possible specificity in our data.

Diagnostic outcome (reference standard)

After venous blood was drawn, each patient directly underwent real time B-mode compression ultrasonography (CUS) of the lower extremities with a 5–7.5 MHz linear-array sonographic scanner (system V GE/Sonotion) in the same hospital (15). The entire proximal deep vein system was explored for compressibility. Color Doppler imaging was used to identify venous vessels and venous flow patterns. In patients with a normal CUS the test was repeated after 7 days. Proximal DVT was considered present if one of the two CUS' was abnormal. An abnormal CUS was defined if the iliac veins, the common femoral vein, the superficial femoral vein or the popliteal vein until the trifurcation were not completely compressible. Obstruction of the iliac veins was tested with help of color duplex. The person who performed the imaging was blinded to the results of the patient history, physical examination and D-dimer test.

Data analysis

After univariate analysis, we first quantified which of the 16 history and physical findings independently contributed to the presence or absence of proximal DVT using multivariable logistic regression analysis. Starting with the overall model including all history and physical findings, model reduction (stepwise backwards) was performed by excluding variables from the model with a p-value > 0.10 based on the log likelihood ratio test. Subsequently, we added the D-dimer test to this reduced model to quantify its added value, which resulted in the final model. The ability of a model to discriminate between patients with and without DVT was estimated using the area under the Receiver Operating Characteristic curve (ROC area). The ROC area can range from 0.5 (no discrimination) to 1.0 (perfect discrimination). The reliability or calibration of each model was evaluated by comparing the predicted and observed probabilities for deciles of calculated patient risks and tested using the Hosmer&Lemeshow test.

Any model shows too optimistic performance (i.e. discrimination and calibration) in the data set from which they are devel-

Table 1: Univariate association of each investigated diagnostic variable with the presence or absence of DVT. Values are percentages unless stated otherwise (n=1295).

Diagnostic variables	Total n=1295 %	DVT present n=289 %	DVT absent n=1006 %	OR (95% CI)
Patient history:				
age (years)	60.0 (17.6) ¹	62.0 (16.8) ¹	59.4 (17.8) ¹	1.01 (1.00 – 2.02) ²
gender + OC use				
males	36	47	33	1.95 (1.47 – 2.57)
females using OC	10	10	10	1.37 (0.87 – 2.17)
females not using OC	54	43	57	-
gender + HRT use				
males	36	47	33	1.86 (1.42 – 2.43)
females using HRT	2	2	2	1.32 (0.48 – 3.63)
females not using HRT	62	51	66	-
previous DVT	24	21	25	0.82 (0.60 – 1.12)
family history of DVT	23	20	24	0.79 (0.57 – 1.09)
presence of malignancy	6	12	5	2.72 (1.71 – 4.32)
immobilization	14	13	14	0.90 (0.61 – 1.33)
recent surgery	14	19	13	1.59 (1.12 – 2.26)
absence of leg trauma	85	89	84	1.58 (1.05 – 2.36)
pain when walking	81	84	80	1.30 (0.92 – 1.84)
days of symptoms	7.9 (7.6) ¹	6.9 (6.7) ¹	8.2 (7.8) ¹	0.98 (0.96 – 0.99) ³
Physical examination:				
vein distension	20	28	17	1.88 (1.39 – 2.55)
deep vein system tenderness	71	72	71	1.04 (0.78 – 1.39)
swelling whole leg	45	57	42	1.84 (1.41 – 2.39)
calf difference ≥ 3cm	43	67	36	3.63 (2.75 – 4.79)
D-dimer abnormal				
VIDAS n= 918	78	99	72	38.2 (9.40 – 155.3)
Tinaquant n= 377	65	98	54	37.3 (9.00 – 154.8)
Combined assays	74	99	66	35.7 (13.3 – 100.0)

DVT = deep vein thrombosis, n = number of patients, OR = Odds Ratio, 95%CI = 95% Confidence Interval; OC=oral contraceptive, HRT=hormonal replacement therapy; -=reference category; D-dimer abnormal for VIDAS ≥ 500 ng/ml and Tinaquant ≥ 400 ng/l; ¹Mean (standard deviation), ²OR is estimated per year increase or decrease, ³OR is estimated per day increase or decrease.

oped, so-called over-fitting (10–12, 20). Hence, bootstrapping techniques, repeating the entire modelling process were used to validate the final model and to adjust the estimated performance and regression coefficients (odds ratios) for over-fitting (20, 21). The model performance obtained after bootstrapping can be considered as the performance that can be expected in similar future patients.

To construct an easily applicable diagnostic rule, the regression coefficients of the variables were transformed to integers according to their relative contributions to the risk estimation. Finally, after estimating the score for each patient, we estimated the absolute percentages of correctly diagnosed patients across score categories. All calculations were performed using S-PLUS 2000 version 6.1 (Insightful Corp., Seattle, WA, USA).

One hundred and twenty seven subjects had missing values for one or more tests under study. The average number of missing per predictor was 2–3%. As missingness of data seldom occurs at random, it is widely acknowledged that deleting subjects with a

Table 2: Independent diagnostic indicators of DVT. The final multivariate model, the figures are estimated after model validation and adjustment for over-fitting.

Diagnostic variables	Odds ratio	Regression coefficient*	p-value	Points for the rule
Male gender	1.80 (1.36 – 2.16)	0.59	<0.001	1
Oral contraceptive use	2.12 (1.32 – 3.35)	0.75	0.002	1
Presence of malignancy	1.52 (1.05 – 2.44)	0.42	0.082	1
Recent surgery	1.46 (1.02 – 2.09)	0.38	0.044	1
Absence of leg trauma	1.82 (1.25 – 2.66)	0.60	0.002	1
Vein distension	1.62 (1.19 – 2.20)	0.48	0.002	1
Calf difference ≥ 3 cm	3.10 (2.36 – 4.06)	1.13	<0.001	2
D-dimer abnormal	20.3 (8.25 – 49.9)	3.01	<0.001	6
Constant		-5.47		

DVT= deep vein thrombosis; *=natural logarithm of the odds ratio; D-dimer abnormal for VIDAS ≥ 500 ng/ml and Tinaquant ≥ 400 ng/ml. Probability of DVT as estimated by the final model =1/(1+exp(-5.47 + 0.59*male gender + 0.75*OC use + 0.42*presence of malignancy + 0.38*recent surgery + 0.60*absence of leg trauma + 0.48*vein distension + 1.13*calf difference ≥ 3cm + 3.01*abnormal D-dimer)).

missing value not only leads to a loss of statistical power but also to biased results. To decrease bias and increase statistical efficiency, it is better to impute missing values rather than performing a complete case analysis (20, 22, 23). Accordingly, before executing the above analysis, we imputed our missing data using the linear regression method available in SPSS software (version 12.0).

Results

The mean age of the patients was 60 years and 463 (36%) were men (Table 1). Overall, 289 patients of the 1295 patients had DVT (prevalence = 22%). 284 patients with DVT were detected during the first ultrasound and 5 at the one-week repeated ultrasound. Table 1 shows the distribution of all investigated diagnostic tests across patients with and without DVT and the results of the univariate analysis. For example, the prevalence of DVT among males was 29% (with an odds ratio (OR) of 1.95 compared to females without OC use), 23% in females using OC (OR of 1.37 compared to females without OC use) and 18% for females without using OC. Similar results were found for the use of estrogen replacement therapy. The strongest indicators of DVT were presence of malignancy, recent surgery, absence of leg trauma, vein distension, swelling of the whole leg, calf difference equal or more than 3 cm and an abnormal D-dimer test result.

In multivariable analysis, seven of the 16 history and physical findings were independent diagnostic indicators of DVT, i.e. gender, oral contraceptive use, presence of malignancy, recent surgery, absence of leg trauma, vein distension and calf difference =3cm. The best cut-off level for the VIDAS assay in terms of sensitivity, specificity and negative predictive value (NPV) was 500 ng/ml (sensitivity 96.4, specificity 28.8, NPV 96.2) in agreement with the threshold recommended by the manufacturer. For the Tinaquant assay we selected a cut-off level of 400 ng/ml (sensitivity 97.8, specificity 46.2, NPV 98.4) instead of the value of 500 ng/ml recommended by the manufacturer (sen-

Table 3. Total number of subjects and prevalence (probability) of DVT per score category of the rule in combination with the two D-dimer assays separately, and with the two assays combined.

Score	Total number of patients per score category n (%) ¹	Rule with Tinaquant (≥ 400 ng/ml) n = 377 DVT present n % ²	Rule with VIDAS (≥ 500 ng/ml) n = 918 DVT present n % ²	Rule with all patients n = 1295 DVT present n % ²
0	13 (1)	0 (0.0)	0 (0.0)	0 (0.0)
1	108 (8)	0 (0.0)	1 (1.5)	1 (0.9)
2	110 (9)	0 (0.0)	0 (0.0)	0 (0.0)
3	62 (5)	1 (3.6)	0 (0.0)	1 (1.6)
4	38 (3)	1 (6.7)	1 (4.3)	2 (0.7)
5	10 (1)	0 (0.0)	0 (0.0)	0 (0.0)
6	18 (1)	0 (0.0)	1 (7.7)	1 (0.3)
7	192 (15)	10 (21.3)	14 (9.7)	24 (12.5)
8	240 (19)	14 (23.7)	27 (14.9)	41 (17.1)
9	231 (18)	27 (42.9)	52 (31.0)	79 (34.2)
10	181 (14)	27 (56.3)	60 (45.1)	87 (48.1)
11	77 (6)	9 (64.3)	34 (54.0)	43 (55.8)
12-13	15 (1)	2 (66.7)	8 (66.7)	10 (66.7)

¹=proportion of all (1295) patients; ²=proportion of DVT present within score category.

sitivity 95.5, specificity 54.6, NPV 97.3). Univariately, the diagnostic value (odds ratio) of combination of the two assays was the same as for each assay separately (Table 1).

The ROC area was 0.80 (95% CI 0.78 – 0.82). Table 2 shows the regression coefficients (odds ratios) of the 8 diagnostic indicators included in the final model, after adjustment for over-fitting using bootstrapping techniques. After bootstrapping, the ROC area of the final model was 0.78 (0.75 – 0.81). The calibration of the model was good (Hosmer and Lemeshow test p-value was 0.56).

Using the formula presented in Table 2, one can estimate a patient’s probability of DVT presence based on his/her clinical profile and D-dimer result. However, to facilitate its use in daily primary care practice, we also simplified the final model in table 2 to an easy applicable scoring rule based on the hierarchy in the regression coefficients (Table 2, column 3). This resulted in the following scoring rule:

$$1 * \text{male gender} + 1 * \text{OC use} + 1 * \text{presence of malignancy} + 1 * \text{recent surgery} + 1 * \text{absence of trauma} + 1 * \text{vein distension} + 2 * \text{calf difference} \geq 3 \text{ cm} + 6 * \text{abnormal D-dimer test}.$$

Table 4: Prevalence of DVT across four score (risk) categories.

Probability or risk Category	number of patients n (%) ¹	DVT present n (%) ²	DVT absent n (%) ³
Very low (0-3)	293 (23)	2 (0.7)	291 (99.3)
Low (4-5)	66 (5)	3 (4.5)	63 (95.5)
Moderate (7-9)	663 (51)	144 (21.7)	519 (78.3)
High (10-13)	273 (21)	140 (51.3)	133 (48.7)

¹=proportion of all (1295) patients; ²=proportion of presence of DVT within risk category; ³=proportion of absence of DVT within risk category.

As an example to use this rule, a man without a leg trauma, with a history of malignancy and with a normal D-dimer test result, receives a score of $1 * 1 + 1 * 0 + 1 * 1 + 1 * 0 + 1 * 1 + 1 * 0 + 2 * 0 + 6 * 0 = 3$ points. The total score of the rule in the study population ranged from 0 to 13. Table 3 shows the observed prevalence (probability) of DVT per score category of the rule either using the Tinaquant or using the Vidas D-dimer assay. For both situations, the prevalence of DVT across the scores ranged from 0% (score 0) to 67% (score ≥ 12). Both assays – in combination with the clinical information – also showed similar results in terms of numbers of missed DVT patients, particularly for score categories ≤ 5; both missed 2 patients with DVT. This finding and given the univariate results of Table 1, indicated that both assays could be combined (though using different thresholds). The last column of Table 3 shows the results of the rule irrespective of which D-dimer assay is used, which indeed yielded similar results as the two assays separately. Accordingly, our example patient above has a probability of having DVT of 1.6%. If his D-dimer test was abnormal in the same patient, the score would be 9 points and the probability of DVT would be 34.2%. To further enhance the clinical use of the scoring rule to exclude DVT, we further collapsed scoring categories (Table 4). If patients with a score ≤ 3 would be categorized as very low risk, 23% of all suspected patients would not be referred and only 2 (0.7%) DVT cases would be missed. These numbers were 28% and 5 cases (1.5%), respectively, when using a score threshold of ≤ 4, and 18% and 1 case (0.4%) for the threshold ≤ 2. The two cases in the low risk category (score ≤ 3) were women with a thrombosis of the popliteal vein and a normal D-dimer test, one in the VIDAS and one in the Tinaquant group (see Tables). The symptoms existed 10 and 18 days respectively and there was no malignancy or oral contraceptive use.

Discussion

Using data from a large group of patients suspected of DVT in primary care and formal multivariable probability modeling, we quantified the value of findings from patient history, physical examination and D-dimer testing to construct a simple rule to safely exclude the presence of DVT. Using 8 simple diagnostic indicators it is possible for primary care physicians to reduce the number of unnecessary referrals with at least 23%, with 0.7% missed cases of DVT).

Although many different studies on the use of clinical findings in combination with D-dimer test results for diagnosis of DVT are available, the optimal diagnostic strategy remains largely unclear (24). Furthermore, all previous rules to diagnose DVT, such as the well known Wells rule (4, 25, 26), were developed and validated in secondary care. These rules, however, can not simply be generalized to primary care settings (10–12), as has been shown in several studies (7, 14). To our knowledge, our study is the first study to develop and validate a diagnostic decision rule for diagnosing – notably ruling out – DVT in primary care.

Using the presented rule, the proportion suspected DVT referred for CUS would be reduced (from 100%) to 77%, at the expense of not referring 0.7% of all DVT cases. Obviously, the question arises whether a higher or lower number than 0.7%

missed DVT cases is acceptable, in view of the change in number of referred patients. E.g. using a score threshold of ≤ 2 , only 0.4% DVT cases were missed with a higher number of referrals (81%), while applying a threshold of ≤ 4 , 72% of suspected patients would be referred and 1.5% of DVT patient would be missed. It has repeatedly been advocated that the failure rate of missed DVT cases should not exceed 2%, since this percentage appeared to be the failure rate of the 'gold standard' venography and also of the strategy of excluding DVT with a normal D-dimer or a single negative CUS (1,15,27). In studies on the safety of serial ultrasonography, a failure rate of 1% was considered acceptable (28, 29). Furthermore, most studies applying the previous DVT rules developed in secondary care, still showed a percentage between 1% and 2% missed DVT cases. No study on diagnostic rules in combination with D-dimer testing has yet shown a rate of false negative diagnosis below 0.6% (7–9). It should also be noted that the percentages in these former studies represent the reported complications rates, which are probably even lower than failure rates based on ultrasound imaging (as was done in our study).

The final choice for a threshold leading to non-referral of 19%, 24% or 29% of all suspected patients, at the expense of 0.4%, 0.7% or 1.5% of missed DVT cases, requires a proper cost-effectiveness analysis accounting for the acceptable consequences and costs related to misclassifications. This lies beyond the scope of this paper.

Our prevalence rate of DVT (22%) is comparable to other recent studies (5, 13). In addition, the diagnostic value of the presence of malignancy, recent surgery, absence of leg trauma, vein distension, calf difference ≥ 3 cm and D-dimer testing has been reported before, and most of these are included in the developed secondary care rules (4, 30, 31). The prevalence of DVT in men suspected of DVT was twice as high than in female participants. This can at least partly be explained by the higher prevalence of risk factors for DVT in men compared to women; e.g. malignancy 4.1% versus 1.6%, leg trauma 3% versus 1.7 and recent surgery 5.8 versus 3.0%. Male gender, however, was also an independent diagnostic indicator for the presence of DVT, after adjustment for these differences in risk factors (see Table 2), indicating that also other phenomena could play a part. Perhaps, women more often visit the primary care physician with symptoms of the leg and/or physicians are more likely to suspect DVT in women, leading to lower prevalences of DVT in "suspected" women compared to "suspected" men. In an earlier study Beebe et al. (32) also found a difference in referral for men and women (36% for men, 64% for women) with a difference in prevalence of DVT (14% in men, 9% in women, where we found 29% and 19%, respectively, but they did not observe any sex difference in the conventional DVT risk factors).

Our results also show that the D-dimer test has considerable added value in the diagnosis of DVT. One could argue that the D-dimer assay alone could be applied to diagnose DVT. Using only the D-dimer result to exclude DVT, however, would yield a percentage of missed DVT cases of 1.2%, which is in line with earlier studies (6, 19). This would only be acceptable if this strategy leads to a relatively large proportion of non-referred patients. Using this approach, however, only 26% would not be re-

ferred. There were two patients with DVT and a low D-dimer level in the Tinaquant and two in the VIDAS group (Table 3). Of those four patients, 3 were female, the duration of symptoms was 1, 3, 10 and 18 days, and two had a recurrent DVT. Even in the current study with a relatively large sample size, still a very few patients do determine the safety of the strategy. However, when the clinical information is applied in combination with a D-dimer test, the proportion of missed DVT cases would be as low as 0.7%, compared to 1.2%, with the use of the D-dimer test only. Moreover in clinical practice patient history and physical examination will always be available before D-dimer testing is indicated or applied.

An important clinical aspect is the availability of recently developed semi-quantitative point of care D-dimer testing. Such a test in the primary care office could certainly increase the applicability of our decision rule. Before such point of care D-dimer tests can be applied on a large scale, however, their performance should be validated using, for example, our diagnostic rule.

A few methodological issues should be addressed. First, the study is executed in primary care, which is the setting where the initial presentation of DVT occurs. The results of our study should primarily be extrapolated to other primary care settings only. Before application of our rule to secondary care settings, the rule's accuracy should be validated in these settings (10–12). Moreover, although our rule is internally validated, we recommend to quantify its external validation in other primary care populations before widespread implementation. Second, following current practice and recent studies on diagnosis of DVT, our reference standard was repeated leg ultrasound, rather than venography. Due to the lower sensitivity of ultrasound to detect pelvic thrombi and distal DVT, some cases with DVT could have been missed. This number, however, is likely to be very low (15, 16). In addition, even when performed by experienced radiologists, 5%-12% of venograms are inadequate as well (15). Third, we analyzed the D-dimer results as a dichotomous variable. This was explicitly done, as previous studies had already shown the optimal threshold in D-dimer concentrations (6, 7, 13, 17, 18). Furthermore, the use of a dichotomous test result facilitates clinical practice. Nevertheless, we also analyzed D-dimer concentration as a continuous variable. This did not change the predictive accuracy of the rule. The same applies to the variable 'difference in calf circumference'. Fourth, some patients had missing values, which were imputed. Although this may seem controversial, it is widely acknowledged that such imputations lead to more valid and precise results than simply deleting subjects with missing data (20, 22, 23). Finally, we used bootstrapping techniques to validate our final model rather than split-sample or cross-validation methods because it had been shown in the statistical literature that the former is superior (20). With bootstrapping techniques all data is used to develop *and* validate a prediction model, obviously yielding better and more precise estimates of the predictor's odds ratios and a rule's ROC area.

In conclusion, we developed a simple diagnostic rule based on symptoms, signs and D-dimer testing to safely rule out DVT in primary care. By applying this rule, the primary care physician can refrain from referring a considerable number of patients suspected of DVT, at equal effectiveness.

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