

A Diagnostic Strategy Involving a Quantitative Latex D-Dimer Assay Reliably Excludes Deep Venous Thrombosis

Shannon M. Bates, MDCM; Clive Kearon, MB, PhD; Mark Crowther, MD, MSc; Lori Linkins, MD; Martin O'Donnell, MB; Jim Douketis, MD; Agnes Y.Y. Lee, MD; Jeffrey I. Weitz, MD; Marilyn Johnston, ART; and Jeffrey S. Ginsberg, MD

Background: Because clinical diagnosis is inaccurate, objective testing is usually considered necessary when patients present with suspected deep venous thrombosis (DVT).

Objective: To determine whether a negative result on a quantitative latex D-dimer assay eliminates the need for further investigation in patients with a low or moderate pretest probability of DVT.

Design: Prospective cohort study.

Setting: Three tertiary care hospitals in Canada.

Patients: 556 consecutive outpatients with suspected first DVT.

Intervention: Patients were categorized as having a low, moderate, or high pretest probability of DVT and then underwent D-dimer testing. Patients with low or moderate pretest probability and a negative D-dimer result had no further diagnostic testing and received no anticoagulant therapy. Serial compression ultra-

sonography was performed in all other patients. Patients who did not receive a diagnosis of DVT were followed for symptomatic venous thromboembolism.

Measurements: Objectively confirmed symptomatic venous thromboembolic events during 3 months of follow-up.

Results: 283 patients (51%) had low or moderate pretest probability and a negative D-dimer result. One of these patients had DVT during follow-up (negative likelihood ratio, 0.05 [CI, 0.01 to 0.23]). The negative likelihood ratio of the D-dimer test in all patients was 0.03 (CI, 0.01 to 0.16).

Conclusion: A negative result on a quantitative latex D-dimer assay safely eliminates the need for further testing in patients with low or moderate pretest probability of DVT.

Ann Intern Med. 2003;138:787-794.

For author affiliations, see end of text.

www.annals.org

Accurate diagnostic testing is essential when deep venous thrombosis (DVT) is suspected. Untreated DVT is associated with a high risk for pulmonary embolism (1), whereas false diagnosis of DVT results in unnecessary anticoagulant therapy, with its associated risks for bleeding (1, 2–4). Although diagnostic imaging (most commonly compression ultrasonography or contrast venography) is widely used to evaluate suspected DVT, these tests are expensive and are often unavailable outside of regular working hours. In addition, venography, the diagnostic reference standard, is invasive and has associated side effects (5–7). Compression ultrasonography, which is highly sensitive and specific for proximal DVT, has emerged as the diagnostic method of choice in patients with suspected DVT (8). However, compression ultrasonography is expensive, requires highly trained personnel, and is not sensitive for isolated calf DVT (8). Therefore, when the proximal veins are normal on initial compression ultrasonography, the test should be repeated a week later to detect proximally extending calf DVT that can cause pulmonary embolism (8, 9). This further increases cost and is inconvenient for the patient.

Recently, the use of D-dimer testing has simplified the diagnosis of DVT. Many D-dimer assays have high sensitivity for DVT and can be used to help exclude venous thrombosis when results are negative (10–12). Three D-dimer assay formats are currently available: enzyme-linked immunosorbent assays (ELISAs), whole-blood erythrocyte agglutination assay (SimpliRED, Agen Biomedical, Ltd., Brisbane, Australia), and latex agglutination assays. The first and second methods have been the most extensively

investigated (13–30). Traditional D-dimer ELISAs, although highly sensitive, are time-consuming and are not suitable for individual patient testing (10). Recently, rapid ELISAs that are suitable for individual testing and have high sensitivities have been developed. However, like the traditional ELISAs, some of these assays have lower specificities than other D-dimer assay formats (13–16). The SimpliRED test has a sensitivity of approximately 85% and a specificity of approximately 70%. A negative result, in combination with normal results on a noninvasive test for DVT or low pretest probability, has been shown to exclude DVT (19, 23–25). However, not all studies have reported a high sensitivity for the SimpliRED assay (27, 28), raising concern that the use of this test could result in undiagnosed DVT.

First-generation slide latex D-dimer assays that are interpreted subjectively are not sufficiently sensitive to exclude DVT (10, 31). The MDA D-Dimer assay (Organon Teknika Corp., now bioMérieux, Inc., Durham, North Carolina) is a novel, automated, second-generation quantitative latex microparticle immunoassay with a turnaround time of less than 30 minutes (including 15 minutes for plasma preparation). In a retrospective study, we demonstrated that this test had a sensitivity of 96%, a specificity of 45%, and a negative predictive value of 98% for a first episode of suspected venous thromboembolism (32) when a discriminant value of 0.50 μg fibrinogen equivalent units (FEUs)/mL was used. These results suggested that a negative result on MDA D-Dimer can exclude venous thrombosis without further objective testing. However, in our previous study, D-dimer assays were performed in batches

Context

Several different D-dimer assays are available to help physicians diagnose deep venous thrombosis (DVT). Some are time-consuming, and some have low sensitivity.

Contribution

This prospective study included 283 patients with low or moderate pretest probability for thrombosis who did not receive anticoagulant therapy after a negative result on a second-generation, rapid-turnaround quantitative latex test (MDA D-Dimer). Only one of these patients had confirmed DVT within a 3-month follow-up period (negative likelihood ratio, 0.05 [95% CI, 0.01 to 0.23]).

Implications

In patients with low or moderate pretest probability for thrombosis, a negative MDA D-Dimer result safely rules out DVT.

—The Editors

on platelet-poor plasma frozen at -70°C , and the results were not used to manage patients. Therefore, to test our hypothesis prospectively, we performed a cohort study in which management decisions were based on the results of MDA D-Dimer testing.

METHODS

This study was performed between August 1999 and November 2001 in three hospitals affiliated with McMaster University in Hamilton, Ontario, Canada (Hamilton Health Sciences—Henderson and McMaster University Divisions, and St. Joseph's Hospital). These hospitals serve the city of Hamilton (population, 460 000), as well as the more than 2 million residents of central western Ontario. Each center's research ethics board approved the study, and all patients provided written informed consent before enrollment.

Patient Sample

Consecutive outpatients who were at least 18 years of age, had suspected first DVT, and were referred to one of the thromboembolism services of the participating hospitals were potentially eligible. More than 95% of patients referred to these hospitals for investigation of DVT are seen in consultation with the thromboembolism service. Potentially eligible patients with one or more of the following were excluded: contraindication to contrast medium, pregnancy, treatment with therapeutic doses of anticoagulation for more than 24 hours before study entry, an ongoing requirement for anticoagulation not related to the qualifying episode (for example, atrial fibrillation or mechanical heart valve), a comorbid condition likely to shorten survival to less than 3 months, geographic or social factors precluding follow-up, or inability or unwillingness to provide informed consent.

Clinical Intervention

After providing informed written consent, and before D-dimer testing, patients were clinically assessed for pretest probability of DVT (high, moderate, or low). Clinical assessment was performed by using a standardized form containing a previously validated model (Table 1) that includes assessment of clinical symptoms and signs, risk factors for DVT, and the presence of an alternative diagnosis (33, 34). In a previous study, use of this model stratified patients into high-, moderate-, or low-probability groups (prevalences of DVT of 75%, 17%, and 3%, respectively). In addition, the κ value for the comparison of pretest probability assignment by nurses and physicians was 0.75, showing very good interobserver agreement (33).

In our study, a sample of venous blood was collected in 4.5-mL Vacutainer tubes (Becton Dickinson Co., Mountain View, California) prefilled with 0.5 mL of 3.2% (0.105 mol/L) sodium citrate dihydrate. D-Dimer testing with the MDA D-Dimer assay was performed according to manufacturer's instructions on the MDA 180 automated coagulometer (bioMérieux, Inc.). Laboratory technologists performing and interpreting the D-dimer assays were unaware of patients' clinical presentation or the results of other objective tests.

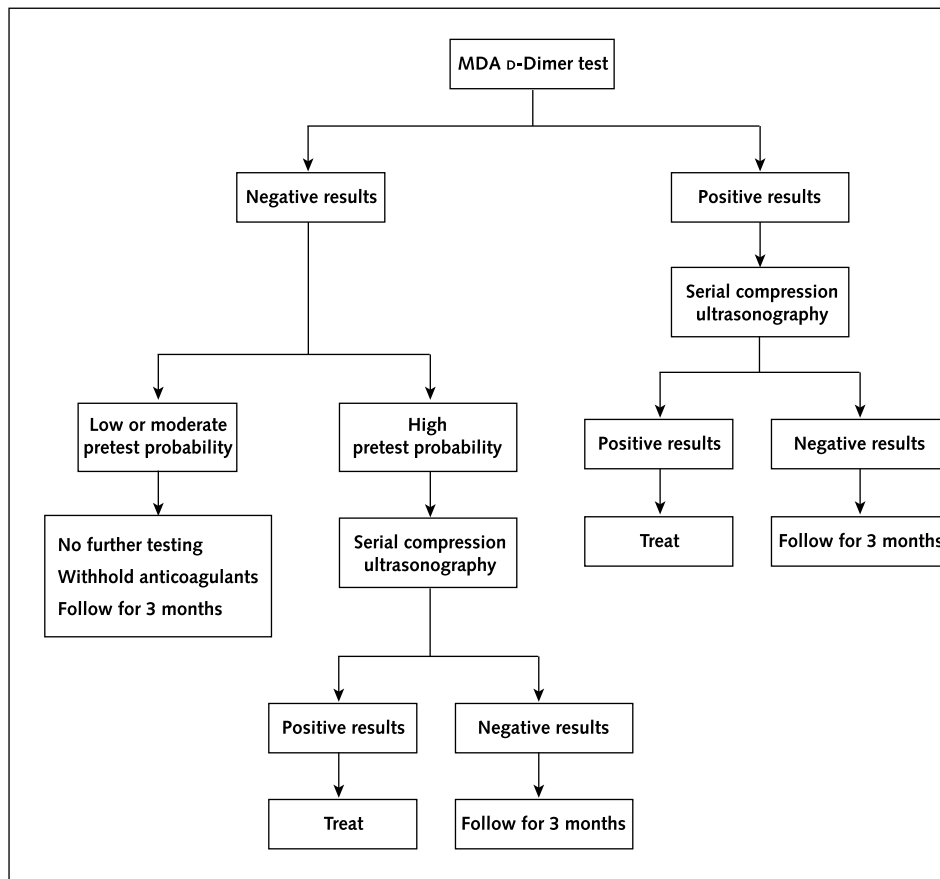
Patients with negative results on the MDA D-Dimer assay ($<0.50\ \mu\text{g FEU/mL}$) and low or moderate pretest probability had no further testing, were not treated with anticoagulants, and were followed for 3 months to detect DVT or pulmonary embolism presumably caused by DVT missed at presentation (Figure). For safety reasons, compression ultrasonography of the symptomatic leg was performed, as previously described, in patients with high pretest probability as well as in all patients with a positive result on the D-dimer test (Figure) (35). The common femoral, superficial femoral, and popliteal veins, as well as the trifurcation of the calf veins, were examined; calf veins below the trifurcation were not assessed. Patients with nor-

Table 1. Standardized Model Used To Assess Pretest Probability*

Attribute	Score
Active cancer (treatment ongoing or within previous 6 months, or palliative treatment)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Major surgery or bedridden for >3 days within 4 weeks	1
Localized tenderness along the distribution of the deep venous system	1
Calf and thigh swollen	1
Calf swelling >3 cm compared with asymptomatic leg (measured 10 cm below tibial tuberosity)	1
Pitting edema (greater in the symptomatic leg)	1
Nonvaricose collateral superficial veins	1
Alternative diagnosis at least as likely as deep venous thrombosis	-2

* In patients with bilateral symptoms, the more symptomatic leg is used. A score ≤ 0 indicates low pretest probability, a score of 1 or 2 indicates moderate pretest probability, and a score >2 indicates high pretest probability. Adapted from reference 33 with permission from Elsevier (*The Lancet*, 1997;350:1795-8).

Figure. Flow chart summarizing the diagnostic process used in the study.



mal results on ultrasonography at presentation underwent repeated compression ultrasonography on days 6 to 8 and days 13 to 15; this strategy has a negative predictive value of 98% (8). Deep venous thrombosis was diagnosed if there was noncompressibility of the common femoral vein or popliteal vein (with or without involvement of adjacent segments) (8). These findings have a positive predictive value of 97% (8). Isolated noncompressibility of the superficial femoral vein or trifurcation was further evaluated with venography (8). Patients with normal results on serial compression ultrasonography did not receive anticoagulant therapy and were followed for 3 months.

Patients who did not receive a diagnosis of DVT were followed for 3 months to detect evidence of clinically significant DVT that was not diagnosed at presentation. Patients were instructed to return for reevaluation if they developed signs or symptoms suggestive of DVT or pulmonary embolism. All patients were contacted by telephone at 3 months.

All patients who presented again with symptoms consistent with DVT or pulmonary embolism underwent uniform objective testing to confirm or exclude the diagnosis. These tests were performed and interpreted by physicians who were unaware of the results of the MDA D-Dimer test at presentation. Patients with leg pain or swelling during

follow-up underwent compression ultrasonography of the symptomatic leg. If this did not demonstrate noncompressibility of the common femoral or popliteal vein, ipsilateral venography was performed. Deep venous thrombosis was diagnosed if an intraluminal filling defect was present in two views (5). Because venography has been shown to have a negative predictive value of 99% (6), treatment was withheld and follow-up was continued in the absence of an intraluminal filling defect. In patients with suspected pulmonary embolism, a ventilation–perfusion scan was obtained. A high-probability scan (segmental or greater perfusion defect with normal ventilation), which has a positive predictive value of more than 85%, was considered to indicate pulmonary embolism (36). A normal perfusion scan, which is known to have a negative predictive value of 99%, excluded pulmonary embolism (36, 37). If the lung scan was abnormal but nondiagnostic for pulmonary embolism, further testing was performed. If definitive testing with pulmonary angiography (38) was not performed, bilateral venography or serial bilateral compression ultrasonography was done to search for evidence of DVT (39, 40). Disease was confirmed or excluded by using the diagnostic criteria previously described. Patients without pulmonary embolism continued follow-up. Cause of death in all patients who died within the 3-month follow-up period was deter-

Table 2. Reasons for Exclusion

Reason	Patients Excluded, <i>n</i>
Contraindication to contrast medium	43
Pregnancy	18
Therapeutic anticoagulants for >24 hours before study entry	24
Ongoing requirement for anticoagulation	47
Comorbid condition likely to shorten survival to <3 months	7
Inaccessibility for follow-up	85
Inability or unwillingness to provide informed consent	161
All	385

mined by contacting family physicians and reviewing medical records. An independent committee blinded to the patients' condition and the results of the initial MDA D-Dimer assay adjudicated suspected outcome events during follow-up.

Statistical Analysis

Patients were categorized as having DVT if one of the following criteria was met: noncompressibility of the common femoral vein or popliteal vein on compression ultrasonography in the transverse plane at presentation, during serial testing, or during 3-month follow-up (8); a persistent intraluminal filling defect on venography at presentation or during follow-up (5); a high-probability ventilation-perfusion lung scan during follow-up (36); presence of a persistent intraluminal filling defect or abrupt vessel cutoff in a vessel at least 2.5 mm in diameter on pulmonary angiography during follow-up (36, 38); or death associated with or caused by DVT or pulmonary embolism. Patients were categorized as not having DVT if they did not meet any of these criteria.

Negative predictive value, sensitivity, and specificity, as well as negative and positive likelihood ratios, each with their exact 95% CIs, were calculated for the D-dimer assay in patients with low or moderate pretest probability (primary analysis) by using CIA software (Confidence Interval Analysis, version 2.0.0, University of Southampton, Southampton, United Kingdom) (41). These variables were also calculated for the following subgroups: all patients, patients with high pretest probability, and patients with cancer and a negative D-dimer result. Deep venous thrombosis diagnosed at presentation, as well as venous thromboembolism diagnosed during follow-up, was used for these calculations. Venous thromboembolism during follow-up was included because we assumed that these events represent evidence of DVT missed at presentation rather than de novo thrombosis (6, 15, 16, 22–25, 28).

The primary requirement for our study was a sample large enough to provide a reliable estimate of the negative predictive value of the MDA D-Dimer in patients with low or moderate pretest probability. On the basis of a previous study (32), we expected that approximately 80% of patients would be categorized as having low or moderate pre-

test probability and that the prevalence of DVT in this group would be 10%. We estimated that the sensitivity and specificity of the MDA D-Dimer in these patients would be 97% and 50%, respectively. On the basis of these estimates, the MDA D-Dimer was expected to have a negative predictive value of 99%. This negative predictive value would be consistent with other accepted approaches for excluding DVT, such as negative results on venography, negative results on serial compression ultrasonography, and negative results on serial impedance plethysmography, all of which show negative predictive values of greater than or equal to 98% (6, 8). We calculated that a sample size of 480 patients was required for the lower boundary of the associated 95% CI to exclude 95%. Because the prevalence of DVT was lower than expected, we increased the sample size by approximately 15%.

Role of the Funding Sources

Neither the Canadian Institutes of Health Research nor the industry sponsor (bioMérieux, Inc.) had a role in the collection, analysis, and interpretation of the data or in the decision to submit the results for publication.

RESULTS

Nine hundred forty-three patients were considered for participation in the study, and 385 were excluded (Table 2). Two of the 558 enrolled patients did not complete the study. We were unable to obtain a venipuncture sample for D-dimer testing from 1, and the other patient declined to participate in the 3-month follow-up telephone call. These two patients were excluded from further analysis. Thus, 556 patients were available for analysis (mean age, 62 years; 343 women [61.6%]). Median symptom duration was 8 days. According to the clinical assessments, pretest probability of DVT was low in 296 patients (52.3%), moderate in 189 patients (33.9%), and high in 71 patients (12.8%) (Table 3). Fifty-six patients (10.1%) received a diagnosis of venous thromboembolism, 50 at presentation (8.9%) and 6 during follow-up (1.1%). The D-dimer result was negative in 303 patients (54.5%) (Table 3).

In patients with low or moderate pretest probability, DVT prevalence was 7.2% (35 of 485 patients). A total of 283 patients (50.9% of the total study sample) had low or moderate pretest probability and a negative D-dimer result. One of these patients received a diagnosis of DVT during

Table 3. Prevalence of Deep Venous Thrombosis according to D-Dimer Result and Pretest Probability Assessment

D-Dimer Result	Pretest Probability			
	Low	Moderate	High	All
	← % (n/n) →			
Negative	0 (0/193)	1.1 (1/90)	0 (0/20)	0.3 (1/303)
Positive	17.4 (18/103)	16.1 (16/99)	41.1 (21/51)	21.8 (55/253)
All	6.1 (18/296)	9.0 (17/189)	29.6 (21/71)	10.0 (56/556)

Table 4. Accuracy Indices of the MDA D-Dimer Test in Patients with Suspected Deep Venous Thrombosis*

Subgroup	Deep Venous Thrombosis Present	Deep Venous Thrombosis Absent	All Patients	Sensitivity	Specificity	Negative Predictive Value	Negative Likelihood Ratio	Positive Likelihood Ratio
	← n →			← % (n/n) →				
Patients with low or moderate pretest probability								
Positive D-dimer result	34	168	202					
Negative D-dimer result	1	282	283					
Total	35	450	485	97.1 [85.1–100] (34/35)	62.7 [58.2–67.1] (282/450)	99.6 [98.1–100] (282/283)	0.05 [0.01–0.23]	2.60 [2.23–2.97]
Patients with high pretest probability								
Positive D-dimer result	21	30	51					
Negative D-dimer result	0	20	20					
Total	21	50	71	100 [83.9–100] (21/21)	40.0 [26.4–54.8] (20/50)	100 [83.2–100] (20/20)	0 [0–0.39]	1.67 [1.39–2.17]
Patients with cancer								
Positive D-dimer result	17	18	35					
Negative D-dimer result	0	15	15					
Total	17	33	50	100 [80.5–100] (17/17)	45.5 [28.1–63.7] (15/33)	100 [78.2–100] (15/15)	0 [0–0.42]	1.83 [1.43–2.63]

* Values in square brackets are 95% CIs.

follow-up (negative predictive value, 99.6% [95% CI, 98.1% to 100%]; negative likelihood ratio, 0.05 [CI, 0.01 to 0.23]). This patient, who had moderate pretest probability and a D-dimer level of 0.49 μg FEU/mL, returned to the clinic with persistent calf pain 3 days after initial presentation. Compression ultrasonography demonstrated noncompressibility of the distal popliteal and trifurcation veins. Two patients with low or moderate pretest probability and negative D-dimer results died before the end of the 3-month follow-up period. Neither of the deaths were attributed to venous thromboembolism; one patient died of progressive cancer on day 54, the other of sepsis on day 72.

Of the 71 patients with high pretest probability of DVT, 20 had a negative D-dimer result. None of these patients received a diagnosis of DVT during serial compression ultrasonography or 3-month follow-up. No patients in this group died. Therefore, the negative predictive value of the MDA D-Dimer assay was 100% (CI, 83.2% to 100%) in patients with high pretest probability. The corresponding negative likelihood ratio was 0 (CI, 0 to 0.39).

In the total study sample, the MDA D-Dimer assay had a negative predictive value of 99.7% (CI, 98.2% to 100%), a sensitivity of 98.2% (CI, 90.4% to 100%), and a specificity of 60.4% (CI, 56.1% to 64.7%). The likelihood ratio of a negative test result was 0.03 (CI, 0.01 to 0.16), while that of a positive test result was 2.48 (CI, 2.20 to 2.78). The accuracy indices and 95% CIs for the D-dimer assay in patients with low or moderate pretest probability and in patients with high pretest probability are summarized in Table 4.

Deep venous thrombosis was diagnosed at presentation in 50 of the 253 patients with a positive D-dimer result and was diagnosed during serial compression ultra-

sonography in 1 additional patient. In 4 other patients, DVT was diagnosed by additional compression ultrasonography (1 patient on day 14) or by venography (3 patients on days 8, 9, and 15, respectively). Therefore, the negative predictive value of serial compression ultrasonography was 98.0% (CI, 95.0% to 99.5%) in patients with a positive D-dimer result. Four patients with a positive D-dimer result in whom DVT had initially been excluded died during the 3-month follow-up. None of the deaths were judged to be related to venous thromboembolism; 3 patients died of progressive cancer on days 16, 70, and 72, respectively, and 1 patient died of liver failure on day 66.

Fifty patients had active cancer at presentation (that is, they had received a cancer diagnosis within 6 months, were receiving treatment at the time of the study or had received it within the previous 6 months, or were receiving palliative treatment only). Of these patients, 13 had low pretest probability, 16 had moderate pretest probability, and 21 had high pretest probability. The D-dimer result was negative in 15 patients (30%). The prevalence of DVT was 34% (17 of 50) in patients with known cancer. The accuracy indices for the D-dimer assay in patients with cancer are summarized in Table 4.

The median time for complete assessment of patients with a negative D-dimer result who did not require compression ultrasonography (that is, those with low or moderate pretest probability of DVT) was 90 minutes. Two of the patients with a positive D-dimer result or high pretest probability had to return the next day for ultrasonography. For the remainder of patients requiring compression ultrasonography, the median time for complete assessment (including ultrasonography) on the day of presentation was 150 minutes.

DISCUSSION

Our study shows that in patients with a negative result on the MDA D-Dimer assay, it is safe to withhold further diagnostic testing and anticoagulant therapy, not only in patients with low or moderate pretest probability of DVT but probably also in those with high pretest probability. Furthermore, in contrast to other 'stand-alone' D-dimer assays (42), the specificity of this assay was high enough to exclude DVT in more than one half of patients in whom DVT was suspected. Several management studies have used D-dimer testing in conjunction with compression ultrasonography or impedance plethysmography to exclude DVT (15, 16, 23–25, 28). However, to our present knowledge, only one other published study has used a combination of D-dimer testing and pretest probability assessment to rule out DVT without noninvasive testing (24). In that study, the combination of a low pretest probability of DVT and a negative result on SimpliRED was used to exclude DVT. Deep venous thrombosis could not be safely excluded in patients with moderate (or high) pretest probability because SimpliRED has a lower sensitivity. As a result, DVT was ruled out by this combination of results in a smaller proportion of patients (40%) than in the current study.

The high sensitivity and negative predictive value of the MDA D-Dimer assay in patients with a high pretest probability of DVT (100% for both) are consistent with those seen in our retrospective study (32). That study showed that the sensitivity and negative predictive value in patients with high pretest probability of DVT were 96% and 90%, respectively (negative likelihood ratio, 0.11). Subgroup data for suspected DVT were not shown in the original publication. When we pooled data from our previous study and the current study, the sensitivity, negative predictive value, and negative likelihood ratio were 98.0% (CI, 89.1% to 99.9%), 96.7% (CI, 82.8% to 99.9%), and 0.05 (CI, 0.01 to 0.29), respectively, in the 126 patients with high pretest probability of DVT, of whom 49 had the diagnosis confirmed. Although the number of patients in this category is too small and the 95% CIs are too wide to draw definitive conclusions, these data suggest that treatment and further testing can also be withheld in patients with high pretest probability and an MDA D-Dimer result of less than 0.05 μg FEU/mL. However, this hypothesis requires prospective evaluation.

A previous study reported that the negative predictive value of a whole-blood agglutination D-dimer assay was significantly lower in patients with cancer than in those without cancer (78.9% vs. 96.5%) because prevalence of venous thromboembolism is higher and D-dimer assay specificity is lower in patients with malignant disease (43). However, among the 50 patients in our current study who had cancer at presentation (in whom the prevalence of DVT was 34%), the sensitivity and negative predictive value of the MDA D-Dimer assay were 100% (negative

likelihood ratio, 0). Similarly, in our retrospective study (32), the sensitivity and negative predictive value of the MDA D-Dimer assay were 100% among 30 patients with known cancer and suspected DVT, of whom 16 had objectively confirmed DVT. Subgroup data for patients with suspected DVT were not shown in the original publication. These findings suggest that, unlike with the whole-blood agglutination assay, a negative result on MDA D-Dimer assay excludes DVT in patients with cancer. However, even when data from the current study and our retrospective study are combined, the 95% CI around the negative predictive value of 100% includes 86%. Therefore, a clinically important decrease in the negative predictive value in patients with cancer cannot be excluded. Additional studies are required to determine whether a negative D-dimer result reliably excludes DVT in patients with cancer.

When patients were grouped according to their D-dimer level, DVT was more prevalent in those with a positive D-dimer result than in those with a negative D-dimer result. Therefore, it is important to confirm the safety of withholding anticoagulants and venography in patients with a positive D-dimer result and normal results on serial compression ultrasonography. Of 202 such patients in our study, 4 (2.0%) received a diagnosis of venous thromboembolism during 3 months of follow-up.

Because this was a management study designed to determine whether anticoagulants and further tests could be safely withheld in patients with a negative D-dimer result and low or moderate pretest probability, initial investigations were by definition predicated on D-dimer results. However, physicians performing and interpreting diagnostic tests at presentation and during follow-up were unaware of the results of the MDA D-Dimer assay. In addition, patients who presented during follow-up with symptoms compatible with DVT or pulmonary embolism underwent standardized objective testing (without regard to their initial D-dimer result) until the diagnosis was confirmed or refuted. Finally, all suspected events were adjudicated by an independent panel of experts blinded to initial D-dimer results. We further minimized bias by ensuring that technicians performing the D-dimer assay and interpreting results were not aware of the patients' pretest probability assessments or any objective test results and that the pretest probability assessment was determined before any objective tests (including D-dimer) were performed.

In keeping with other recent studies investigating the diagnosis of venous thromboembolism (22, 24), the overall prevalence of DVT was only 10%. This is unlikely to affect our conclusions. Even among subgroups with a higher prevalence of DVT (those with high pretest probability), the assay's negative predictive value was 100%. Moreover, in an average referral sample with a prevalence of DVT of 25%, with a sensitivity of 98.2% and a specificity of 60.4%, the MDA D-Dimer assay would still be expected to have a negative predictive value of 99.1%.

Forty-one percent of all patients screened were excluded from the study. In previous management studies involving D-dimer testing, the proportion of screened patients excluded has ranged between 10% and 25% (15, 16, 23, 25). The reason for the higher proportion of exclusions in our study is not clear. However, almost 50% of the excluded patients were excluded because of inability or unwillingness to provide informed consent, and another 9% of all patients considered for the study were excluded because of inability to return for follow-up testing, if required. Because patients excluded for these reasons were probably not more or less likely to have DVT than included patients, the high exclusion rate should not affect study generalizability.

This study shows that a diagnostic strategy using the MDA D-Dimer assay as the pivotal test is safe and can be used in patients with suspected DVT. In patients with low or moderate pretest probability of DVT, a negative D-dimer result excludes DVT. Our study also suggests that it is safe to withhold further investigations and anticoagulant therapy in patients with a negative D-dimer result and a high pretest probability of DVT; however, this hypothesis should be tested prospectively. Patients with an abnormal D-dimer result can be safely managed with serial compression ultrasonography. On the basis of our study, which shows that a negative MDA D-Dimer result has the potential to be used as a 'stand-alone' test to exclude venous thromboembolism, evaluation of this assay is warranted in other patient populations not well served by current diagnostic algorithms. Some examples are patients with suspected recurrent DVT, suspected pulmonary embolism, or suspected upper-extremity DVT.

From McMaster University and Henderson Research Centre, Hamilton, Ontario, Canada.

Acknowledgments: The authors thank Jo-Ann Bennett, Sue Smale, Laurie Sardo, RN, Pam Stevens, RN, Terri Schnurr, RN, and Karen Woods, RN, for providing technological and nursing assistance and collecting the data and Sharon Hendershott for assisting in data management. They also thank Drs. Akbar Panju, Ameen Patel, and Stéphanie Cloutier for contributing patients.

Grant Support: By the Canadian Institutes of Health Research University-Industry (Organon Teknika Corp., now bioMérieux, Inc.) Program (grant UOP-42365). Dr. Bates is a recipient of a New Investigator Award from the Canadian Institutes of Health Research University-Industry (bioMérieux, Inc) Program. Drs. Kearon and Douketis are Research Scholars of the Heart and Stroke Foundation of Canada, and Dr. Crowther is a Research Scholar of the Medical Research Council of Canada. Dr. Linkins is a recipient of a Thrombosis Interest Group Research Fellowship. Dr. O'Donnell receives salary support from the Fraser Fellowship. Dr. Lee is a recipient of a New Investigator Award from the Canadian Institutes of Health Research/Rx & D Research Program. Drs. Weitz and Ginsberg are recipients of Career Investigator Awards from the Heart and Stroke Foundation of Ontario. Dr. Weitz also holds the Heart and Stroke Foundation of Ontario/J. Fraser Mustard chair in cardiovascular research and the Canada Research Chair in Thrombosis.

Dr. Ginsberg is also a recipient of a Research Chair from the Canadian Institutes of Health Research.

Potential Financial Conflicts of Interest: *Consultancies:* J.S. Ginsberg (bioMérieux, Inc.); *Honoraria:* S.M. Bates (bioMérieux, Inc.); *Grants received:* S.M. Bates (Canadian Institutes of Health Research and bioMérieux, Inc.), C. Kearon (Canadian Institutes of Health Research and bioMérieux, Inc.), M. Crowther (Canadian Institutes of Health Research and bioMérieux, Inc.), J.S. Ginsberg (Canadian Institutes of Health Research and bioMérieux, Inc.).

Requests for Single Reprints: Shannon M. Bates, MDCM, McMaster University Medical Centre, HSC 3W11, 1200 Main Street West, Hamilton, Ontario L8N 3Z5, Canada; e-mail, batesm@mcmaster.ca.

Current author addresses and author contributions are available at www.annals.org.

References

- Ginsberg JS. Management of venous thromboembolism. *N Engl J Med*. 1996; 335:1816-28. [PMID: 8943165]
- Caranasos GJ, Stewart RB, Cluff LE. Drug-induced illness leading to hospitalization. *JAMA*. 1974;228:713-7. [PMID: 4406257]
- Hull R, Hirsh J, Jay R, Carter C, England C, Gent M, et al. Different intensities of oral anticoagulant therapy in the treatment of proximal-vein thrombosis. *N Engl J Med*. 1982;307:1676-81. [PMID: 6752555]
- Mant MJ, O'Brien BD, Thong KL, Hammond GW, Birtwhistle RV, Grace MG. Haemorrhagic complications of heparin therapy. *Lancet*. 1977;1:1133-5. [PMID: 68228]
- Rabinov K, Paulin S. Roentgen diagnosis of venous thrombosis in the leg. *Arch Surg*. 1972;104:134-44. [PMID: 5008903]
- Hull R, Hirsh J, Sackett DL, Taylor DW, Carter C, Turpie AG, et al. Clinical validity of a negative venogram in patients with clinically suspected venous thrombosis. *Circulation*. 1981;64:622-5. [PMID: 7261292]
- Bettmann MA, Paulin S. Leg phlebography: the incidence, nature and modification of undesirable side effects. *Radiology*. 1977;122:101-4. [PMID: 830318]
- Kearon C, Julian JA, Newman TE, Ginsberg JS. Noninvasive diagnosis of deep venous thrombosis. McMaster Diagnostic Imaging Practice Guidelines Initiative. *Ann Intern Med*. 1998;128:663-77. [PMID: 9537941]
- Hirsh J, Hoak J. Management of deep vein thrombosis and pulmonary embolism. A statement for healthcare professionals. Council on Thrombosis (in consultation with the Council on Cardiovascular Radiology), American Heart Association. *Circulation*. 1996;93:2212-45. [PMID: 8925592]
- Lee AY, Ginsberg JS. The role of D-dimer in the diagnosis of venous thromboembolism. *Curr Opin Pulm Med*. 1997;3:275-9. [PMID: 9262113]
- Becker DM, Philbrick JT, Bachhuber TL, Humphries JE. D-dimer testing and acute venous thromboembolism. A shortcut to accurate diagnosis? *Arch Intern Med*. 1996;156:939-46. [PMID: 8624174]
- Bounameaux H, de Moerloose P, Perrier A, Reber G. Plasma measurement of D-dimer as diagnostic aid in suspected venous thromboembolism: an overview. *Thromb Haemost*. 1994;71:1-6. [PMID: 8165626]
- Leroyer C, Escoffre M, Le Moigne E, Grimaux M, Cagnioncle O, Oger E, et al. Diagnostic value of a new sensitive membrane based technique for instantaneous D-dimer evaluation in patients with clinically suspected deep venous thrombosis. *Thromb Haemost*. 1997;77:637-40. [PMID: 9134634]
- D'Angelo A, D'Alessandro G, Tomassini L, Pittet JL, Dupuy G, Crippa L. Evaluation of a new rapid quantitative D-dimer assay in patients with clinically suspected deep vein thrombosis. *Thromb Haemost*. 1996;75:412-6. [PMID: 8701399]
- Bernardi E, Prandoni P, Lensing AW, Agnelli G, Guazzaloca G, Scannapieco G, et al. D-dimer testing as an adjunct to ultrasonography in patients with clinically suspected deep vein thrombosis: prospective cohort study. The Multi-centre Italian D-dimer Ultrasound Study Investigators Group. *BMJ*. 1998;317:

1037-40. [PMID: 9774286]

16. Perrier A, Desmarais S, Miron MJ, de Moerloose P, Lepage R, Slosman D, et al. Non-invasive diagnosis of venous thromboembolism in outpatients. *Lancet*. 1999;353:190-5. [PMID: 9923874]
17. John MA, Elms MJ, O'Reilly EJ, Rylatt DB, Bundesen PG, Hillyard CJ. The SimpliRED D dimer test: a novel assay for the detection of crosslinked fibrin degradation products in whole blood. *Thromb Res*. 1990;58:273-81. [PMID: 2191471]
18. Brenner B, Pery M, Lanir N, Jabareen A, Markel A, Kaftori JK, et al. Application of a bedside whole blood D-dimer assay in the diagnosis of deep vein thrombosis. *Blood Coagul Fibrinolysis*. 1995;6:219-22. [PMID: 7654935]
19. Wells PS, Brill-Edwards P, Stevens P, Panju A, Patel A, Douketis J, et al. A novel and rapid whole-blood assay for D-dimer in patients with clinically suspected deep vein thrombosis. *Circulation*. 1995;91:2184-7. [PMID: 7697847]
20. Ginsberg JS, Wells PS, Brill-Edwards P, Donovan D, Panju A, van Beek EJ, et al. Application of a novel and rapid whole blood assay for D-dimer in patients with clinically suspected pulmonary embolism. *Thromb Haemost*. 1995;73:35-8. [PMID: 7740493]
21. Ginsberg JS, Wells PS, Kearon C, Anderson D, Crowther M, Weitz JI, et al. Sensitivity and specificity of a rapid whole-blood assay for D-dimer in the diagnosis of pulmonary embolism. *Ann Intern Med*. 1998;129:1006-11. [PMID: 9867754]
22. Wells PS, Anderson DR, Rodger M, Stiell I, Dreyer JF, Barnes D, et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and D-dimer. *Ann Intern Med*. 2001;135:98-107. [PMID: 11453709]
23. Ginsberg JS, Kearon C, Douketis J, Turpie AG, Brill-Edwards P, Stevens P, et al. The use of D-dimer testing and impedance plethysmographic examination in patients with clinical indications of deep vein thrombosis. *Arch Intern Med*. 1997;157:1077-81. [PMID: 9164373]
24. Kearon C, Ginsberg JS, Douketis J, Crowther M, Brill-Edwards P, Weitz JI, et al. Management of suspected deep venous thrombosis in outpatients by using clinical assessment and D-dimer testing. *Ann Intern Med*. 2001;135:108-11. [PMID: 11453710]
25. Kraaijenhagen RA, Piovella F, Bernardi E, Verlato F, Beckers EA, Koopman MM, et al. Simplification of the diagnostic management of suspected deep vein thrombosis. *Arch Intern Med*. 2002;162:907-11. [PMID: 11966342]
26. Turkstra F, van Beek EJ, ten Cate JW, Büller HR. Reliable rapid blood test for the exclusion of venous thromboembolism in symptomatic outpatients. *Thromb Haemost*. 1996;76:9-11. [PMID: 8819243]
27. Fiessinger JN, Héron E, Jacq F, Rance A, Emmerich J. Rapid blood test for the exclusion of venous thromboembolism in symptomatic outpatients [Letter]. *Thromb Haemost*. 1997;77:1042-3. [PMID: 9184431]
28. Farrell S, Hayes T, Shaw M. A negative SimpliRED D-dimer assay result does not exclude the diagnosis of deep vein thrombosis or pulmonary embolism in emergency department patients. *Ann Emerg Med*. 2000;35:121-5. [PMID: 10650228]
29. Mauron T, Baumgartner I, Z'Brun A, Demarmels Biasiutti F, Redondo M,

- Do DD, et al. SimpliRED D-dimer assay: comparability of capillary and citrated venous whole blood, between-assay variability, and performance of the test for exclusion of deep vein thrombosis in symptomatic outpatients [Letter]. *Thromb Haemost*. 1998;79:1217-9. [PMID: 9657454]
30. de Monyé W, Huisman MV, Pattinama PM. Observer dependency of the SimpliRed D-dimer assay in 81 consecutive patients with suspected pulmonary embolism. *Thromb Res*. 1999;96:293-8. [PMID: 10593432]
31. Carter CJ, Doyle DL, Dawson N, Fowler S, Devine DV. Investigations into the clinical utility of latex D-dimer in the diagnosis of deep venous thrombosis. *Thromb Haemost*. 1993;69:8-11, 24. [PMID: 8446941]
32. Bates SM, Grand'Maison A, Johnson M, Naguit I, Kovacs MJ, Ginsberg JS. A latex D-dimer reliably excludes venous thromboembolism. *Arch Intern Med*. 2001;161:447-53. [PMID: 11176771]
33. Wells PS, Anderson DR, Bormanis J, Guy F, Mitchell M, Gray L, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. *Lancet*. 1997;350:1795-8. [PMID: 9428249]
34. Wells PS, Hirsh J, Anderson DR, Lensing AW, Foster G, Kearon C, et al. Accuracy of clinical assessment of deep-vein thrombosis. *Lancet*. 1995;345:1326-30. [PMID: 7752753]
35. Lensing AW, Prandoni P, Brandjes D, Huisman PM, Vigo M, Tomasella G, et al. Detection of deep-vein thrombosis by real-time B-mode ultrasonography. *N Engl J Med*. 1989;320:342-5. [PMID: 2643771]
36. Hull RD, Hirsh J, Carter CJ, Jay RM, Dodd PE, Ockelford PA, et al. Pulmonary angiography, ventilation lung scanning, and venography for clinically suspected pulmonary embolism with abnormal perfusion lung scan. *Ann Intern Med*. 1983;98:891-9. [PMID: 6859705]
37. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). The PIOPED Investigators. *JAMA*. 1990;263:2753-9. [PMID: 2332918]
38. Stein PD, Athanasoulis C, Alavi A, Greenspan RH, Hales CA, Saltzman HA, et al. Complications and validity of pulmonary angiography in acute pulmonary embolism. *Circulation*. 1992;85:462-8. [PMID: 1735144]
39. Kelley MA, Carson JL, Palevsky HI, Schwartz JS. Diagnosing pulmonary embolism: new facts and strategies. *Ann Intern Med*. 1991;114:300-6. [PMID: 1824813]
40. Hull RD, Hirsh J, Carter CJ, Raskob GE, Gill GJ, Jay RM, et al. Diagnostic value of ventilation-perfusion lung scanning in patients with suspected pulmonary embolism. *Chest*. 1985;88:819-28. [PMID: 4064769]
41. The interpretation of diagnostic data. In: Sackett DL, Haynes RB, Guyatt GH, Tugwell P. *Clinical Epidemiology: A Basic Science for Clinical Medicine*. 2nd ed. Boston: Little, Brown; 1991:69-152.
42. Kelly J, Rudd A, Lewis RR, Hunt BJ. Plasma D-dimers in the diagnosis of venous thromboembolism. *Arch Intern Med*. 2002;162:747-56. [PMID: 11926847]
43. Lee AY, Julian JA, Levine MN, Weitz JI, Kearon C, Wells PS, et al. Clinical utility of a rapid whole-blood D-dimer assay in patients with cancer who present with suspected acute deep venous thrombosis. *Ann Intern Med*. 1999;131:417-23. [PMID: 10498557]

Current Author Addresses: Drs. Bates and Ginsberg: McMaster University Medical Centre, HSC 3W11, 1200 Main Street West, Hamilton, Ontario L8N 3Z5, Canada.

Drs. Kearon and Lee: Hamilton Health Sciences—Henderson General Hospital, 711 Concession Street, Hamilton, Ontario L8V 1C3, Canada.

Drs. Crowther and Douketis: St. Joseph's Hospital, L208-4, 50 Charlton Avenue East, Hamilton, Ontario L8N 4A6, Canada.

Drs. Linkins, O'Donnell, and Weitz: Henderson Research Centre, 711 Concession Street, Hamilton, Ontario L8V 1C3, Canada.

Ms. Johnston: Hemostasis Reference Laboratory, 711 Concession Street, Hamilton, Ontario L8V 1C3, Canada.

Author Contributions: Conception and design: S.M. Bates, C. Kearon, M. Crowther, L. Linkins, M. O'Donnell, J. Douketis, A.Y.Y. Lee, J.I. Weitz, M. Johnston, J.S. Ginsberg.

Analysis and interpretation of the data: S.M. Bates, J.S. Ginsberg.

Drafting of the article: S.M. Bates, C. Kearon, M. Crowther, L. Linkins, M. O'Donnell, J. Douketis, A.Y.Y. Lee, J.I. Weitz, M. Johnston, J.S. Ginsberg.

Critical revision of the article for important intellectual content: S.M. Bates, C. Kearon, M. Crowther, L. Linkins, M. O'Donnell, J. Douketis, A.Y.Y. Lee, J.I. Weitz, M. Johnston, J.S. Ginsberg.

Final approval of the article: S.M. Bates, C. Kearon, M. Crowther, L. Linkins, M. O'Donnell, J. Douketis, A.Y.Y. Lee, J.I. Weitz, M. Johnston, J.S. Ginsberg.

Provision of study materials or patients: S.M. Bates, C. Kearon, M. Crowther, L. Linkins, M. O'Donnell, J. Douketis, A.Y.Y. Lee, J.I. Weitz, J.S. Ginsberg.

Statistical expertise: S.M. Bates, J.S. Ginsberg.

Obtaining of funding: S.M. Bates, C. Kearon, M. Crowther, J.S. Ginsberg.

Administrative, technical, or logistic support: S.M. Bates, J.I. Weitz, M. Johnston.

Collection and assembly of data: S.M. Bates, C. Kearon, M. Crowther, L. Linkins, M. O'Donnell, J. Douketis, A.Y.Y. Lee, M. Johnston, J.S. Ginsberg.