Selective d-Dimer Testing for Diagnosis of a First Suspected Episode of Deep Venous Thrombosis

A Randomized Trial

Lori-Ann Linkins, MD; Shannon M. Bates, MDCM; Eddy Lang, MDCM; Susan R. Kahn, MD; James D. Douketis, MD; Jim Julian, MMath; Sameer Parpia, PhD; Peter Gross, MD; Jeffrey I. Weitz, MD; Frederick A. Spencer, MD; Agnes Y.Y. Lee, MD; Martin J. O’Donnell, PhD; Mark A. Crowther, MD; Howard H. Chan, MD; Wendy Lim, MD; Sam Schulman, MD; Jeffrey S. Ginsberg, MD; and Clive Kearon, MD

Background: d-Dimer testing is sensitive but not specific for diagnosing deep venous thrombosis (DVT). Changing the use of testing and the threshold level for a positive test result on the basis of risk for DVT might improve the tradeoff between sensitivity and specificity and reduce the need for testing.

Objective: To determine whether using a selective d-dimer testing strategy based on clinical pretest probability (C-PTP) for DVT is safe and reduces diagnostic testing compared with using a single d-dimer threshold for all patients.

Design: Randomized, multicenter, controlled trial. Patients were allocated using a central automated system. Ultrasonographers and study adjudicators but not other study personnel were blinded to trial allocation. (ClinicalTrials.gov: NCT00157677)

Setting: 5 Canadian hospitals.

Patients: Consecutive symptomatic patients with a first episode of suspected DVT.

Intervention: Selective testing (n = 860), defined as d-dimer testing for outpatients with low or moderate C-PTP (DVT excluded at d-dimer levels <1.0 μg/mL [low C-PTP] or <0.5 μg/mL [moderate C-PTP]) and venous ultrasonography without d-dimer testing for outpatients with high C-PTP and inpatients, or uniform testing (n = 863), defined as d-dimer testing for all participants (DVT excluded at d-dimer levels <0.5 μg/mL).

Measurements: The proportion of patients not diagnosed with DVT during initial testing who had symptomatic venous thromboembolism during 3-month follow-up and the proportion of patients undergoing d-dimer testing and ultrasonography.

Results: The incidence of symptomatic venous thromboembolism at 3 months was 0.5% in both study groups (difference, 0.0 percentage point [95% CI, −0.8 to 0.8 percentage points]). Selective testing reduced the proportion of patients who required d-dimer testing by 21.8 percentage points (CI, 19.1 to 24.8 percentage points). It reduced the proportion who required ultrasonography by 7.6 percentage points (CI, 2.9 to 12.2 percentage points) overall and by 21.0 percentage points (CI, 14.2 to 27.6 percentage points) in outpatients with low C-PTP.

Limitation: Results may not be generalizable to all d-dimer assays or patients with previous DVT, study personnel were not blinded, and the trial was stopped prematurely.

Conclusion: A selective d-dimer testing strategy seems as safe as and more efficient than having everyone undergo d-dimer testing when diagnosing a first episode of suspected DVT.

Primary Funding Source: Heart and Stroke Foundation of Ontario.
Context
D-dimer testing is sensitive but not specific for diagnosing deep venous thrombosis (DVT). Selective testing based on pretest probability might improve that tradeoff and be more efficient.

Contribution
This trial compared D-dimer testing of all patients with D-dimer testing based on clinical pretest probability among pregnant women with suspected first DVT. Selective testing based on probability identified equal proportions of patients with DVT and substantially reduced the number of D-dimer assays and ultrasonographies performed.

Caution
Patients and study personnel were not blinded to trial interventions.

Implication
A D-dimer testing strategy based on DVT probability is as safe as and more efficient than testing everyone.

Setting and Participants
Consecutive outpatients and inpatients aged 18 years or older who presented with a suspected first symptomatic DVT to outpatient clinics, emergency departments, and inpatient wards were prospectively assessed for enrollment (Appendix Figure 1, available at www.annals.org). Patients were excluded if they received full-dose heparin for 24 hours or more before study entry; if other tests for DVT had already been done; or if they had an ongoing requirement for anticoagulation, presented with symptoms consistent with pulmonary embolism (PE), or had symptomatic veins within 7 days of presentation, had a previous DVT or PE, had an expected survival of less than 3 months, or were pregnant or geographically inaccessible for follow-up. The study protocol was approved by the institutional review board of each participating center and is consistent with the principles of the Declaration of Helsinki.

Randomization
After informed written consent was provided and before any diagnostic testing, a clinician (research nurse, research assistant, or physician) used the 9-point Wells clinical prediction rule (Appendix Table 1, available at www.annals.org) to categorize the patient’s C-PTP of DVT as low, moderate, or high (3). The clinician was not permitted to assign a C-PTP that differed from the prediction rule. A biostatistician created a computer-generated 1:1 randomization sequence stratified by inpatient or outpatient status and clinical center. Study groups were allocated using a centralized automated center that, after a call from a research nurse or assistant, recorded participants’ inpatient or outpatient status and C-PTP and assigned the partici-

Selective Testing (Experimental Strategy)
Outpatients with low or moderate C-PTP had D-dimer testing. Outpatients with high C-PTP and all inpatients skipped D-dimer testing and had ultrasonography of the proximal veins of the symptomatic leg. For outpatients with low C-PTP, the results of the D-dimer assay were reported as positive if the D-dimer level was less than 0.5 µg/mL and positive if the level was 0.5 µg/mL or more. For outpatients with moderate C-PTP, the results were reported as negative if the D-dimer level was less than 1.0 µg/mL and positive if the level was 1.0 µg/mL or more. For outpatients with moderate C-PTP, the results were reported as negative if the D-dimer level was less than 0.5 µg/mL and positive if the level was 0.5 µg/mL or more.

If the results were negative, no further diagnostic testing was performed and anticoagulant therapy was withheld. If the results were positive, patients had ultrasonography of the proximal veins of the symptomatic leg. Patients with low C-PTP and a normal ultrasonogram had no further diagnostic testing, and anticoagulant therapy was withheld. Patients with moderate or high C-PTP and a normal ultrasonogram had repeated ultrasonography of the same leg 6 to 8 days later (Figure and Appendix Figure 2, available at www.annals.org).

Selective Testing (Control Testing)
All control patients had D-dimer testing. Results of the D-dimer assay were reported as negative if the D-dimer level was less than 0.5 µg/mL and positive if the level was 0.5 µg/mL or higher. If the results were negative, no further diagnostic testing was performed and anticoagulant therapy was withheld. If the results were positive, participants had ultrasonography of the proximal veins of the symptomatic leg. Patients with low C-PTP and a normal ultrasonogram had no further diagnostic testing, and anticoagulant therapy was withheld. Patients with moderate or high C-PTP and a normal ultrasonogram had repeated ultrasonography of the same leg 6 to 8 days later (Figure).

D-Dimer Assays
D-Dimer testing was performed using 2 rapid quantitative immunoturbidimetric assays by the Hemostasis Reference Laboratory (Hamilton, Ontario, Canada) and the
For the uniform testing group, of the 4 patients who did not have D-dimer testing and another patient with a D-dimer–positive result who did not have ultrasonography, 4 had no events during follow-up and 1 with a D-dimer–negative result was lost to follow-up. For the selective testing group, neither of the 2 patients who did not have D-dimer testing during initial testing had an event during follow-up. C-PTP = clinical pretest probability; DVT = deep venous thrombosis; VTE = venous thromboembolism.

* 1 patient lost to follow-up.
† 3 recurrent VTEs during follow-up.
‡ 1 recurrent VTE during follow-up.

clinical laboratory at the Jewish General Hospital (Montreal, Qué´bec, Canada). The MDA D-dimer assay (bioMérieux, Durham, North Carolina, and Trinity Bio-tech, County Wicklow, Ireland) was used for the first 1237 patients, but production of the assay was discontinued by the manufacturer. The STA-Liatest D-Di (Diagnostica Stago, Asnières, France) was used for the remaining patients. These assays showed similar operating characteristics when compared using stored blood samples from a previous unpublished study by our group. The D-dimer cutoff of 1.0 µg/mL was selected on the basis of the results of a previous retrospective analysis (2). Laboratory personnel were informed about study group allocation so that they could report D-dimer assay results as positive or negative.
but quantitative results were not provided to the clinical centers.

**Ultrasoundography**

Compression ultrasonography was performed at 1-cm intervals from the common femoral vein to the calf trifurcation; calf veins below the trifurcation were not assessed. The sole criterion for diagnosis of DVT was inability to fully compress the lumen of the deep veins with application of ultrasonography probe pressure.

**Outcomes and Follow-up**

All randomly assigned patients, including those treated for DVT after initial testing, were followed for 3 months. Patients who presented with symptoms of suspected DVT had venous ultrasonography of the proximal veins followed by repeated ultrasonography after 6 to 8 days if the first one was normal (Appendix, available at www.annals.org). Patients with suspected PE had a ventilation–perfusion scan or spiral computed tomography of the pulmonary arteries followed by serial bilateral ultrasonography of the proximal veins if the lung imaging test was nondiagnostic. D-Dimer testing was not performed as part of evaluation for suspected VTE during follow-up.

Primary outcomes were the proportion of patients not diagnosed with DVT during initial testing who had objectively confirmed symptomatic VTE (proximal DVT or PE) during 3-month follow-up and the proportion of patients undergoing d-dimer testing and ultrasonography. Secondary outcomes were suspected major bleeding events and deaths. Thromboembolic events, bleeding events, and deaths were evaluated using predefined criteria by a central adjudication committee that was blinded to allocation (Appendix).

**Statistical Analysis**

We estimated that 1% of patients who had no DVT on initial testing would develop VTE during 3-month follow-up in each group and calculated a sample size that would yield an upper CI less than 2%, a “missed DVT” rate considered acceptable because it is the proportion seen when DVT is excluded using venography (the reference standard diagnostic test for DVT) (4). We estimated that randomly assigning 1000 patients per group would yield a 95% CI of 0.4% to 1.9% for the proportion of patients with no DVT on initial testing who would develop VTE and a 95% CI of approximately 1% in each direction for the between-group difference in events. On the basis of data from the literature (5–7) and the results of a local audit, we assumed that 66% of participants would be outpatients (low C-PTP, 50%; moderate C-PTP, 35%; and high C-PTP, 15%) and 33% would be inpatients (low C-PTP, 30%; moderate C-PTP, 60%; and high C-PTP, 10%).

Patients were analyzed in the groups they were randomly assigned (intention to treat), and patients lost to follow-up were excluded (Figure). The data safety monitor performed unblinded interim analyses after enrollment of 500, 1000, and 1500 patients to ensure that VTE during follow-up did not exceed predefined acceptable levels. The results were not released to trial investigators or data analysts. We performed prespecified subgroup analyses of trial outcomes in outpatients with low C-PTP because the d-dimer threshold in this group was increased from the standard threshold in the selective strategy group, and we report between-group differences in the d-dimer range between 0.5 and 1.0 μg/mL. We calculated exact binomial 95% CIs for proportions and used the modified Wilson score method for differences between proportions.

Data analyses were performed by biostatisticians using SAS, version 9.1 (SAS Institute, Cary, North Carolina), and StatXact 6 (Cytel, Cambridge, Massachusetts).

**Role of the Funding Source**

This trial was funded by the Heart and Stroke Foundation of Ontario. The funding source had no role in data collection, analysis, or interpretation of the data; the writing of the report; or the decision to submit for publication.

**Results**

Of 1723 patients enrolled, 863 were randomly assigned to uniform testing and 860 to selective testing (Table 1); 1542 (89%) were outpatients, and 181 (11%) were inpatients. After reaching 86% of the target sample size and recognizing that accrual was slow and more outpatients had been enrolled than had been originally planned, the trial steering committee decided to stop enrollment in January 2010.

**Uniform Testing**

Of 863 patients randomly assigned to uniform testing, 772 were outpatients (low C-PTP, 334; moderate C-PTP, 319; and high C-PTP, 119) and 91 were inpatients (Table 1, Figure, and Appendix Figure 2). Results of d-dimer testing were positive in 506 patients (418 outpatients and 88 inpatients) and negative in 353 patients (351 outpatients and 2 inpatients), and 4 patients did not have the test (Figure). Fifty-six patients with positive results were diagnosed with DVT by ultrasonography during initial testing, comprising 11.1% of the 506 patients with positive results on d-dimer testing and 6.5% of 863 patients (Appendix Table 2, available at www.annals.org); none of the 81 outpatients with low C-PTP and a d-dimer level between 0.5 and 1.0 μg/mL had DVT on ultrasonography. None of the 353 patients with negative results on d-dimer testing had additional diagnostic testing. Nine patients (2 d-dimer–positive patients, 6 d-dimer–negative patients, and 1 patient who did not have d-dimer testing) were lost to follow-up after initial testing.

Four patients had VTE diagnosed during follow-up, comprising 0.8% (95% CI, 0.2% to 2.0%) of the 506 patients with positive results on d-dimer testing who had a normal ultrasonogram on initial testing and 0.5% (CI,
0.1% to 1.3%) of the 798 patients who did not have DVT diagnosed on initial testing and who remained in the sample at 3-month follow-up. None of the 4 events were in outpatients with low C-PTP and D-dimer levels between 0.5 and 1.0 μg/mL. No patient with a negative result on D-dimer testing had VTE diagnosed during follow-up (0.0% [CI, 0.0% to 1.1%]) (Table 2 and Appendix Table 3, available at www.annals.org).

One patient with high C-PTP, a positive result on D-dimer testing, and no VTE had a major bleeding event, and 15 patients died of causes unrelated to VTE (14 of progressive cancer and 1 of cardiac failure). Of the 863 patients, 859 (99.5%) had D-dimer testing, 505 (58.5%) had initial ultrasonography, and 334 (38.7%) had repeated ultrasonography after 6 to 8 days.

### Selective Testing

Of 860 patients randomly assigned to selective testing, 777 were outpatients (low C-PTP, 360; moderate C-PTP, 310; and high C-PTP, 100) and 90 were inpatients (Table 3 and Figure). Of the 360 outpatients with low C-PTP, results of D-dimer testing were negative in 288 patients (80%) and positive in 72 patients (Figure). Of 288 D-dimer–negative patients (D-dimer level <0.5 μg/mL in 200 and 0.5 to 1.0 μg/mL in 88), none developed VTE during follow-up (0.0% [CI, 0.0% to 1.3%]) and 1 was lost to follow-up. Of the 72 D-dimer–positive patients, 8 (11%) were diagnosed with DVT by ultrasonography during initial testing (Appendix Table 2) and none with normal ultrasonograms and 334 (38.7%) had repeated ultrasonography after 6 to 8 days.

### Uniform Testing

Of 863 patients randomly assigned to uniform testing, 798 were outpatients and 65 were inpatients (low C-PTP, 342; moderate C-PTP, 343; and high C-PTP, 178) and 60 were inpatients (Table 3, available at www.annals.org). One patient with high C-PTP, a positive result on D-dimer testing, and no VTE had a major bleeding event, and 15 patients died of causes unrelated to VTE (14 of progressive cancer and 1 of cardiac failure). Of the 863 patients, 859 (99.5%) had D-dimer testing, 505 (58.5%) had initial ultrasonography, and 334 (38.7%) had repeated ultrasonography after 6 to 8 days.

### Table 2. Distribution and Timing of VTE in Patients During Follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>D-Dimer Result</th>
<th>Event</th>
<th>Time, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective testing*</td>
<td>Moderate C-PTP</td>
<td>Negative PE</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>Moderate C-PTP</td>
<td>Positive PE</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>High C-PTP</td>
<td>Not done CFV to SFV DVT</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>High C-PTP</td>
<td>Not done Popliteal DVT</td>
<td>53</td>
</tr>
<tr>
<td>Uniform testing†</td>
<td>Low C-PTP</td>
<td>Positive PE</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>Moderate C-PTP</td>
<td>Positive PE</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Moderate C-PTP</td>
<td>Positive PE</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Moderate C-PTP</td>
<td>SFV to popliteal DVT</td>
<td>75</td>
</tr>
</tbody>
</table>

CFV = common femoral vein; C-PTP = clinical pretest probability; DVT = deep venous thrombosis; PE = pulmonary embolism; SFV = superficial femoral vein.
* All VTEs during follow-up occurred in outpatients. Appendix Table 3 (available at www.annals.org) shows the distribution and timing of VTE during follow-up in patients diagnosed with DVT during initial testing.
† 1 patient (moderate C-PTP, positive results on D-dimer testing, and normal ultrasonogram) was diagnosed with incidental PE on a staging computed tomographic scan for lymphoma the day after study enrollment and received anticoagulant therapy; this was not classified as an event because PE was not clinically suspected.
‡ Sudden death (fatal PE could not be excluded).

Table 1. Demographic and Clinical Characteristics of Study Patients at Presentation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Selective Testing (n = 860)*</th>
<th>Uniform Testing (n = 863)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD), y</td>
<td>61 (17)</td>
<td>69 (16)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>128 (35)</td>
<td>131 (38)</td>
</tr>
<tr>
<td>Outpatients, n (%)</td>
<td>360 (99)</td>
<td>334 (98)</td>
</tr>
<tr>
<td>Cancer, n (%)</td>
<td>4 (1)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Paralysis/paresis or casting of a limb, n (%)</td>
<td>3 (1)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Recent surgery/bedridden, n (%)</td>
<td>17 (5)</td>
<td>17 (5)</td>
</tr>
</tbody>
</table>

C-PTP = clinical pretest probability.
* C-PTP categories include inpatients who underwent testing in the selective testing group as if they were at high risk but who may have had low, moderate, or high C-PTP.
† Receiving ongoing treatment or palliative care or having received treatment within the previous 6 mo.
Selective D-Dimer Testing

The between-group difference in the proportion of patients who had ultrasonography was 20.0% in the outpatient or low C-PTP subgroup (72/360 (20.0) vs. 137/334 (41.0); Absolute Difference (95% CI) = 21.0 percentage points, favoring selective testing for ultrasonography, both favoring selective testing (Table 3).

In the outpatient and low C-PTP subgroup, the proportion of patients who had ultrasonography was 20.0% in the selective D-dimer group and 41.0% in the uniform D-dimer group (difference of −21.0 percentage points, favoring selective testing [CI, −27.6 to −14.2 percentage points]) (Table 3).

Twenty-four patients (17 in the uniform group and 7 in the selective group) received therapeutic anticoagulation during follow-up for reasons other than VTE, most commonly superficial phlebitis (13 in the uniform group and 4 in the selective group). Off-protocol ultrasonography below the calf vein trifurcation was performed in some patients at 1 center, leading to diagnosis and treatment of isolated distal DVT in 5 patients in the uniform group, 4 at the time of initial testing (not reported as initial DVT) and 1 during follow-up (adjudicated as not a study outcome). Removing these 24 patients from the denominator for the primary outcome measure did not change the trial results (0.50% of the selective group and 0.51% of the uniform group had VTE during follow-up).

**DISCUSSION**

In this trial comparing uniform with selective D-dimer testing in patients with suspected first DVT, a selective strategy—which used a higher D-dimer threshold to exclude first acute DVT in outpatients with low C-PTP and omitted D-dimer testing in outpatients with high C-PTP and all inpatients—was as safe as and more efficient than the uniform testing strategy, which used the same threshold to exclude DVT in all patients. The frequency of VTE during the 3-month follow-up did not differ between groups, with confidence bounds surrounding the estimate of no difference well below the clinically significant VTE event rate of 2%. The 2% event rate is considered an acceptable threshold because it is the rate seen when DVT is excluded by venography, the reference standard test for DVT (4). The selective strategy was more efficient insofar as an absolute 21.8% fewer patients required D-dimer testing and 7.7% fewer required ultrasonography compared with uniform testing. Finally, the 2 diagnostic strategies resulted in a similar proportion of patients being diagnosed with VTE during initial testing.

**Table 3. Primary and Secondary Outcomes**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Selective Testing, n/N (%)</th>
<th>Uniform Testing, n/N (%)</th>
<th>Absolute Difference (95% CI), percentage points</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE during follow-up*</td>
<td>4/798 (0.5)</td>
<td>4/798 (0.5)</td>
<td>0.0 (−0.8 to 0.8)</td>
</tr>
<tr>
<td>Outpatients</td>
<td>4/710 (0.6)</td>
<td>4/712 (0.6)</td>
<td>–</td>
</tr>
<tr>
<td>Low C-PTP</td>
<td>0/351 (0.0)</td>
<td>1/320 (0.3)</td>
<td>−0.3 (−1.8 to 0.8)</td>
</tr>
<tr>
<td>Moderate C-PTP</td>
<td>2/278 (0.7)</td>
<td>3/301 (1.0)</td>
<td>–</td>
</tr>
<tr>
<td>High C-PTP</td>
<td>2/81 (2.5)</td>
<td>0/91 (0.0)</td>
<td>–</td>
</tr>
<tr>
<td>Inpatients</td>
<td>0/88 (0.0)</td>
<td>0/86 (0.0)</td>
<td>–</td>
</tr>
<tr>
<td>Low C-PTP</td>
<td>0/4 (0.0)</td>
<td>0/7 (0.0)</td>
<td>–</td>
</tr>
<tr>
<td>Moderate C-PTP</td>
<td>0/28 (0.0)</td>
<td>0/23 (0.0)</td>
<td>–</td>
</tr>
<tr>
<td>High C-PTP</td>
<td>0/56 (0.0)</td>
<td>0/56 (0.0)</td>
<td>–</td>
</tr>
<tr>
<td>All patients†</td>
<td>8/849 (0.9)</td>
<td>7/854 (0.8)</td>
<td>–</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>11 (1.3)</td>
<td>9 (1.0)</td>
<td>–</td>
</tr>
</tbody>
</table>

| Initial diagnostic testing |  |  |  |
|---------------------------|  |  |  |
| D-Dimer testing | 668/860 (77.7) | 859/863 (99.5) | −21.8 (−24.8 to −19.1) |
| Ultrasonography | 438/860 (50.9) | 505/863 (58.5) | −7.6 (−12.2 to −2.9) |
| Ultrasonography in outpatients with a low C-PTP | 72/360 (20.0) | 137/334 (41.0) | −21.0 (−27.6 to −14.2) |

**Non-VTE events**

| |  |  |
|---------------------------|  |  |
| Major bleeding | 2/860 (0.2) | 1/863 (0.1) | 0.1 (−0.5 to 0.7) |
| Deaths | 15/860 (1.7) | 15/863 (1.7) | 0.0 (−1.3 to 1.3) |

C-PTP = clinical pretest probability; VTE = venous thromboembolism.

* Excludes patients lost to follow-up and with deep venous thrombosis on initial testing.
† Includes patients with deep venous thrombosis on initial testing.
Using a D-dimer threshold of 1.0 μg/mL rather than 0.5 μg/mL to exclude DVT in outpatients with low C-PTP halved the number of those who required ultrasonography. This savings, which corresponded to 10% of all patients in the selective group, accounted for the overall reduction in ultrasonography in this randomly assigned group. Of note, none of the patients with D-dimer levels between 0.5 and 1.0 μg/mL (88 patients in the selective group and 81 patients in the uniform group) were diagnosed with VTE during initial testing or follow-up (0% [CI, 0.0% to 2.2%]), which confirms the safety of this approach.

The efficiency of the selective testing strategy was also improved by omitting D-dimer testing in outpatients with high C-PTP and in all inpatients despite the requirement for all of these patients to have ultrasonography. This finding occurred because only 15% of outpatients with high C-PTP and 2% of inpatients in the uniform group had DVT excluded by a negative result on D-dimer testing. Our finding that D-dimer testing is inefficient in these patient subgroups because most have a positive result is consistent with reports published after our study began (8–11).

A search of PubMed from 1975 to 2012 using the Medical Subject Heading terms deep vein thrombosis, diagnosis, fibrin fibrinogen degradation products, venous thrombosis/ultrasonography, and clinical trial retrieved no other trials that prospectively evaluated using a higher D-dimer level to exclude venous thrombosis in patients with low C-PTP than that used in patients with moderate or high C-PTP. Therefore, to our knowledge, this trial is the first to point toward selective D-dimer testing as a safe and efficient testing strategy in patients with suspected first DVT.

Previous retrospective analyses of patients with suspected PE (2, 12, 13) and DVT (2, 14) reported that using a higher D-dimer threshold in patients with low C-PTP resulted in a substantially increased proportion of patients with negative results on D-dimer testing and retained a high negative predictive value (99% [12], 95% [13], and 98% [14]) despite a decrease in sensitivity. Schouten and colleagues (15) have similarly proposed that using age-specific D-dimer levels in patients with low C-PTP of DVT may also reduce the need for ultrasonography.

Our study has several limitations. The results may not be generalizable to patients with a history of DVT or to other D-dimer tests, although retrospective analyses suggest consistent findings with other assays (2, 12–14). As with other recent studies, the overall prevalence of DVT in the current study was low at 7.1% (5). This probably reflects heightened awareness of VTE and a lower threshold for diagnostic referral. However, this finding also highlights the need for diagnostic strategies that efficiently exclude thrombosis in low-prevalence populations.

Study personnel were not blinded to results of ultrasonography or D-dimer testing or management allocation, which could have biased assessment for suspected VTE during follow-up. However, this bias was reduced because study personnel were blinded to the quantitative D-dimer level so that they did not know whether a negative result was less than 0.5 μg/mL or between 0.5 and 1.0 μg/mL. It became evident during the study that the specificity and efficiency of D-dimer testing was very low for inpatients (8–11), which led to fewer enrolled inpatients than expected and a lower total enrollment than originally planned. However, power was not reduced in outpatients, because we enrolled more patients in this subgroup than we had expected.

In summary, this study supports the use of a higher D-dimer threshold to exclude first DVT in outpatients with low C-PTP than that used in outpatients with moderate C-PTP and that D-dimer testing should be avoided in outpatients with high C-PTP and in all inpatients. Future studies to determine whether this diagnostic strategy can be applied to patients who present with suspected recurrent DVT or PE are required.

From McMaster University, Hamilton, Ontario, Canada; University of Calgary, Calgary, Alberta; McGill University, Montreal, Québec, Canada; University of British Columbia, Vancouver, British Columbia, Canada; and HRB-Clinical Research Facility, National University of Ireland, Galway, Ireland.

Disclaimer: Dr. Linkins had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Reproducible Research Statement: Study protocol: Available from Dr. Linkins (e-mail, linkinla@mcmaster.ca). Statistical code: Not available. Data set: For access to the database, submit study objectives and planned analyses to Dr. Linkins (e-mail, linkinla@mcmaster.ca).

Requests for Single Reprints: Lori-Ann Linkins, MD, Department of Medicine, McMaster University, Juravinski Hospital, Room A3-74, 1280 Main Street West, Hamilton, Ontario L8S 4K1, Canada; e-mail, linkinla@mcmaster.ca.

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

References


Suspected DVT
In patients who presented with suspected DVT during follow-up, compression ultrasonography of the proximal veins of the symptomatic leg was performed. Deep venous thrombosis was diagnosed if a new incompressible common femoral or popliteal venous segment was present. Incompressibility of the calf vein trifurcation without popliteal vein involvement was reported but not counted as part of the primary outcome. If the ultrasonography findings were equivocal, such as abnormal venous segments that were short or confined to either the superficial femoral or calf vein trifurcation, venography was recommended. If the initial ultrasonogram was normal, ultrasonography was repeated 6 to 8 days later.

Suspected PE
In patients who presented with suspected PE during follow-up, ventilation–perfusion scanning or computed tomography of the pulmonary arteries was performed. Pulmonary embolism was diagnosed if a high-probability perfusion defect was present on the lung scan or an intraluminal filling defect of a segmental or more central pulmonary artery was present on the computed tomographic scan. If the ventilation–perfusion scan was nondiagnostic or the computed tomographic scan was normal or equivocal, bilateral ultrasonography of the proximal leg veins was performed.

Pulmonary embolism was diagnosed if an ultrasonogram indicated DVT. Patients with a normal ultrasonogram had repeated ultrasonography after 6 to 8 days and again after 10 to 14 days. D-Dimer testing was not used to evaluate suspected VTE during follow-up.

Major Bleeding
Major bleeding was defined as clinically overt bleeding associated with a decrease in hemoglobin level of at least 20 g/L or need for transfusion of 2 or more units of red blood cells, or bleeding that involved a critical site (for example, retroperitoneal or intracranial bleeding).

Death
Death was attributed to PE if there was substantive supportive evidence or if death was sudden and unexplained.
Appendix Figure 1. Study flow diagram.

Assessed for eligibility (n = 2973)

Excluded*
- Received full-dose anticoagulant therapy for ≥24 h: 91
- Test for DVT performed before approached for study: 477
- Life expectancy <3 mo: 30
- Absence of acute symptoms: 5
- Presenting with symptoms of PE: 168
- Previous confirmed DVT or PE: 145
- Pregnant: 21
- Geographic inaccessibility: 27
- Declined to participate: 325

Randomly assigned (n = 1723)

Allocated to uniform strategy (n = 863)
- Received assigned intervention: 858
  - D-Dimer testing not done: 4
  - Ultrasonography not done: 1
- Received therapeutic anticoagulation for other reasons (n = 17)
  - Lost to follow-up (n = 9)
- Analyzed (n = 854)
  - Excluded from analysis (did not complete 3-mo follow-up): 9

Allocated to selective strategy (n = 860)
- Received assigned intervention: 857
  - D-Dimer testing not done: 2
  - Ultrasonography not done: 1
- Received therapeutic anticoagulation for other reasons (n = 7)
  - Lost to follow-up (n = 11)
- Analyzed (n = 849)
  - Excluded from analysis (did not complete 3-mo follow-up): 11

DVT = deep venous thrombosis; PE = pulmonary embolism.
* Patients may have met >1 exclusion criteria.
### Appendix Table 1. Wells Clinical Prediction Rule*  

<table>
<thead>
<tr>
<th>Variable†</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer (treatment ongoing, within previous 6 mo. or palliative)</td>
<td>1</td>
</tr>
<tr>
<td>Paralysis, paresis, or recent plaster immobilization of the lower extremities</td>
<td>1</td>
</tr>
<tr>
<td>Recently bedridden for &gt;3 d or major surgery within the previous 12 wk requiring general or regional anesthesia</td>
<td>1</td>
</tr>
<tr>
<td>Localized tenderness along the distribution of the deep venous system</td>
<td>1</td>
</tr>
<tr>
<td>Entire leg swollen</td>
<td>1</td>
</tr>
<tr>
<td>Calf swelling 3 cm more than the asymptomatic side (measured 10 cm below the tibial tuberosity)</td>
<td>1</td>
</tr>
<tr>
<td>Pitting edema confined to the symptomatic leg</td>
<td>1</td>
</tr>
<tr>
<td>Collateral superficial veins (nonvaricose)</td>
<td>1</td>
</tr>
<tr>
<td>Previously documented DVT</td>
<td>1</td>
</tr>
<tr>
<td>Alternative diagnosis as likely as or greater than that of DVT</td>
<td>−2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total points</th>
<th>Pretest Probability for DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2</td>
<td>High</td>
</tr>
<tr>
<td>1–2</td>
<td>Moderate</td>
</tr>
<tr>
<td>0</td>
<td>Low</td>
</tr>
</tbody>
</table>

DVT = deep venous thrombosis.

* Modified from reference 3.
† In patients with symptoms in both legs, the more symptomatic leg is used.
Appendix Figure 2. Results for the uniform testing group, according to C-PTP.

- Uniform testing strategy (n = 863)
  - Outpatient and low C-PTP (n = 334)
    - d-dimer testing: Not done (n = 1)
      - Negative; <1.0 µg/mL: 196
        - DVT on initial testing Day 0: 7 Days 6–8: 1
          - Lost to follow-up (n = 4)
            - VTE at 3-mo follow-up (n = 0)
  - Outpatient and moderate C-PTP (n = 319)
    - d-dimer testing
      - Negative; <1.0 µg/mL: 137
        - Ultrasonography
          - DVT on initial testing Day 0: 7 Days 6–8: 1
            - Lost to follow-up (n = 1)
              - VTE at 3-mo follow-up (n = 1)
  - Outpatient and high C-PTP (n = 119) and inpatient (n = 91)
    - d-dimer testing: Not done (n = 3)
      - Positive; ≥1.0 µg/mL: 182
        - Ultrasonography
          - DVT on initial testing Day 0: 16 Days 6–8: 1
            - Lost to follow-up (n = 1)
              - VTE at 3-mo follow-up (n = 3)

C-PTP = clinical pretest probability; DVT = deep venous thrombosis; VTE = venous thromboembolism.
### Appendix Table 2. Distribution of DVT at Initial Testing

<table>
<thead>
<tr>
<th>Variable</th>
<th>Selective Testing, n/N (%)</th>
<th>Uniform Testing, n/N (%)</th>
<th>Absolute Difference (95% CI), percentage points</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT at initial testing</td>
<td>51/860 (5.9)</td>
<td>56/863 (6.5)</td>
<td>−0.6 (−2.9 to 1.7)</td>
</tr>
<tr>
<td>Outpatients</td>
<td>49/770 (6.4)</td>
<td>51/772 (6.6)</td>
<td>−0.2 (−2.7 to 2.3)</td>
</tr>
<tr>
<td>Low C-PTP</td>
<td>8/360 (2.2)</td>
<td>8/334 (2.4)</td>
<td>−</td>
</tr>
<tr>
<td>Moderate C-PTP</td>
<td>23/310 (7.4)</td>
<td>17/319 (5.3)</td>
<td>−</td>
</tr>
<tr>
<td>High C-PTP</td>
<td>18/100 (18.0)</td>
<td>26/119 (21.8)</td>
<td>−</td>
</tr>
<tr>
<td>Inpatients</td>
<td>2/90 (2.2)</td>
<td>5/91 (5.5)</td>
<td>−3.2 (−10.2 to 3.1)</td>
</tr>
<tr>
<td>Low C-PTP</td>
<td>0/4 (0.0)</td>
<td>1/8 (12.5)</td>
<td>−</td>
</tr>
<tr>
<td>Moderate C-PTP</td>
<td>0/28 (0.0)</td>
<td>1/24 (4.2)</td>
<td>−</td>
</tr>
<tr>
<td>High C-PTP</td>
<td>2/58 (3.4)</td>
<td>3/59 (5.1)</td>
<td>−</td>
</tr>
</tbody>
</table>

C-PTP = clinical pretest probability; DVT = deep venous thrombosis.

### Appendix Table 3. Distribution and Timing of VTE During Follow-up in Patients With DVT Diagnosed During Initial Testing

<table>
<thead>
<tr>
<th>Variable</th>
<th>o-Dimer Result</th>
<th>Event</th>
<th>Time, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective testing*</td>
<td></td>
<td>Popliteal vein thrombosis, PE†</td>
<td>24</td>
</tr>
<tr>
<td>Moderate C-PTP</td>
<td>Positive</td>
<td>PE†</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SFV‡</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Not done</td>
<td>CFV to popliteal vein DVT†</td>
<td>36</td>
</tr>
<tr>
<td>Uniform testing*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High C-PTP</td>
<td>Positive</td>
<td>PE‡§</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>CFV to SFV DVT and PE</td>
<td>§</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>PE‡</td>
<td>26</td>
</tr>
</tbody>
</table>

CFV = common femoral vein; C-PTP = clinical pretest probability; DVT = deep venous thrombosis; PE = pulmonary embolism; SFV = superficial femoral vein; VTE = venous thromboembolism.

* All VTEs during follow-up occurred in patients who were outpatients when the initial DVT was diagnosed.
† Receiving anticoagulant therapy with active cancer.
‡ Receiving anticoagulant therapy without active cancer.
§ Died on day 21 of fatal PE in the context of cancer.
| Not receiving anticoagulant therapy with a vena cava filter.