Diagnosis of deep vein thrombosis with D-dimer adjusted to clinical probability: prospective diagnostic management study

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Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2022;376:e067378 http://dx.doi.org/10.1136/bmj-2021-067378

Accepted: 21 December 2021

ABSTRACT

OBJECTIVE

To evaluate the safety and efficiency of a diagnostic algorithm for deep vein thrombosis (DVT) that uses clinical pretest probability based D-dimer thresholds to exclude DVT.

DESIGN

Prospective diagnostic management study.

SETTING

University based emergency departments or outpatient clinics in Canada.

PARTICIPANTS

Patients with symptoms or signs of DVT.

INTERVENTION

DVT was considered excluded without further testing by Wells low clinical pretest probability and D-dimer <1000 ng/mL or Wells moderate clinical pretest probability and D-dimer <500 ng/mL. All other patients had proximal ultrasound imaging. Repeat proximal ultrasonography was restricted to patients with initially negative ultrasonography, low or moderate clinical pretest probability, and D-dimer >3000 ng/mL or high clinical pretest probability and D-dimer >1500 ng/mL. If DVT was not diagnosed, patients did not receive anticoagulant treatment.

MAIN OUTCOME MEASURE

Symptomatic venous thromboembolism at three months.

RESULTS

1508 patients were enrolled and analysed, of whom 173 (11.5%) had DVT on scheduled diagnostic testing. Of the 1275 patients with no proximal DVT on scheduled testing who did not receive anticoagulant treatment, eight (0.6%, 95% confidence interval 0.3% to 1.2%) were found to have venous thromboembolism during follow-up. Compared with a traditional DVT testing strategy, this diagnostic approach reduced the need for ultrasonography from a mean of 1.36 scans/patient to 0.72 scans/patient (difference −0.64, 95% confidence interval −0.68 to −0.60), corresponding to a relative reduction of 47%.

CONCLUSIONS

The diagnostic strategy using a combination of clinical pretest probability and D-dimer identified a group of patients at low risk for DVT during follow-up while substantially reducing the need for ultrasound imaging.

REGISTRATION

ClinicalTrials.gov NCT02038530.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Cohort studies showed the safety of excluding deep vein thrombosis (DVT) in patients with a low clinical pre-test probability or unlikely Wells score and a negative D-dimer

Post hoc and subgroup analyses suggested that DVT can be excluded by D-dimer <1000 ng/mL in patients with low clinical pretest probability and D-dimer <500 ng/mL in those with moderate probability

WHAT THIS STUDY ADDS

Using a D-dimer threshold of 1000 ng/mL in patients with low clinical probability and 500 ng/mL in those with moderate probability safely excluded DVT

D-dimer thresholds of 1500 ng/mL and 3000 ng/mL could be used to determine the need for repeat proximal ultrasonography in patients with low/moderate and high probability, respectively

This strategy reduced the need for ultrasonography by 47%

Introduction

Clinical evaluation, D-dimer blood testing, and ultrasound imaging are widely used in the evaluation of suspected deep vein thrombosis (DVT) of the lower extremities. Evidence indicates that the presence of any two of three assessments- low clinical pretest probability, negative D-dimer test (usually <500 ng / mL), and negative ultrasound imaging of the proximal veins- is associated with a sufficiently low probability of subsequent thrombotic complications that DVT can be considered excluded.[1-4]

When DVT is suspected, diagnostic testing often starts with assessment of clinical pretest probability. DVT is considered excluded if clinical pretest probability is low and the D-dimer test is negative. If clinical pretest probability is moderate or high, ultrasound imaging is often performed without measurement of D-dimer. Two types of ultrasound imaging can be used- of the proximal veins only (referred to as -proximal vein ultrasonography-) or of the proximal and the distal veins (referred to as -whole leg ultrasonography-). Proximal vein ultrasonography has both high positive and high negative predictive values for proximal DVT,[2] but a negative examination does not exclude isolated distal DVT that might extend proximally.[5] Therefore, with a negative examination in patients with high suspicion for DVT, proximal venous ultrasonography is repeated a week later, which is inconvenient and costly. Whole leg ultrasonography has the advantage of high negative predictive value for both proximal and isolated distal DVT,[6] but it takes longer to perform,

has a lower positive predictive value for isolated distal DVT,[7] and has the potential to detect distal thrombi that do not need treatment.

In a previous analysis, we showed that use of pretest probability specific cut-off points for D-dimer excluded DVT in a greater proportion of patients than use of a single cut-off point, without sacrificing negative predictive value.[8] A post hoc analysis of the SELECT trial showed that a D-dimer concentration <1000 ng/mL in patients with low clinical pretest probability and <500 ng/mL in those with moderate clinical pretest probability had negative predictive values of 100% and 99.6%, respectively, and that raising the D-dimer threshold to determine the need for repeat proximal ultrasound imaging was safe (see supplementary materials).[9]

On the basis of these considerations, the goal of this study was to evaluate a diagnostic algorithm for DVT that was designed to minimise the need for ultrasound imaging. We hypothesised that two innovations in interpretation of D-dimer results would reduce the need for ultrasound imaging. The first was to increase the proportion of patients who had DVT excluded by using clinical pretest probability assessment and D-dimer testing at initial presentation. This would be achieved by using a D-dimer <1000 ng/mL to exclude DVT in patients with low clinical pretest probability and a D-dimer <500 ng/mL to exclude DVT in patients with moderate clinical pretest probability. The second was to restrict follow-up proximal vein ultrasonography at one week to patients with markedly elevated D-dimer concentrations. To test the safety of this strategy, which we termed the "4D (Designer D-dimer DVT Diagnosis) algorithm," we used this diagnostic strategy to manage outpatients with suspected DVT.

Methods

Study patients

Patients presenting to emergency departments or outpatient clinics with symptoms or signs suggestive of DVT were potentially eligible to be included in this prospective management study. To ensure that the D-dimer test and clinical pretest probability scoring were independent, we excluded patients if the D-dimer concentration was known before clinical pretest probability was assessed. We excluded patients who had received full dose anticoagulation for ≥24 hours at the time of testing because it reduces the sensitivity of the D-dimer test. Excluding patients with a previous diagnosis of DVT ensured that we would not mistake residual DVT for acute DVT. Age <18 years and pregnancy were also exclusion criteria because D-dimer and clinical pretest probability have not been extensively studied in these populations. We excluded patients with a suspected pulmonary embolism because guidelines recommend that these patients are tested for pulmonary embolism and not DVT. We also excluded patients taking anticoagulation for other indications, those expected to die within 90 days, and those who were geographically inaccessible for follow-up. When patients had venous ultrasonography contrary to the protocol, they were excluded from study participation.

Patients were enrolled prospectively at 10 university based clinical centres in Canada. The study was approved by the research ethics boards of participating institutions, and all patients provided informed consent. Depending on the preference of the research ethics board at the participating institution, patients either provided written consent before diagnostic testing or provided written or verbal consent within days after having undergone diagnostic testing that was consistent with the study's protocol.

Patient enrolment and care management

At the time of enrolment, clinical centres used a central web based system to register patients. Physicians used the nine item Wells rule (scores range from −2 to 8, with higher scores indicating a higher probability of DVT) to categorise the patient's clinical pretest probability as low (score −2 to 0), moderate (1 or 2), or high (≥3) (table 1).[2] They had access to a hard copy of the Wells rule but did not receive individual training in its completion. At the start of the study, D-dimer was measured using the Triage D-dimer assay (Quidel Corporation), and patients with a low or moderate clinical pretest probability and a D-dimer <1000 ng/mL and those with high clinical pretest probability and a D-dimer <500 ng/mL underwent no further diagnostic testing for DVT. However, after 253 patients were enrolled, in response to a slow rate of enrolment primarily because the point-of-care Triage D-dimer assay was not available as a routine test in participating centres, the protocol was amended as follows: local hospital D-dimer assays were allowed, and patients with low clinical pretest probability and a D-dimer <1000 ng/mL or with a moderate clinical pretest probability and a D-dimer <500 ng/mL underwent no further diagnostic testing for DVT and did not receive anticoagulant treatment. All other patients underwent ultrasound imaging (fig 1). All D-dimer assays were measured in fibrinogen equivalent units. No analyses were done until study enrolment was complete and all patients (including the 253 patients enrolled before protocol amendment) were analysed according to the amended protocol.

Proximal ultrasonography assessed venous compressibility at 1 cm intervals from the common femoral vein down to and including the calf vein trifurcation in the symptomatic leg(s). Examination of the calf veins distal to the calf vein trifurcation was actively discouraged. The sole criterion for diagnosis of DVT by ultrasonography was incomplete compressibility of a venous segment. If ultrasound imaging showed DVT, patients received anticoagulant treatment. If ultrasound imaging did not show DVT, patients did not receive anticoagulant treatment; the subgroup of these patients who had a markedly elevated D-dimer concentration (D-dimer >3000 ng/mL in patients with low or moderate clinical pretest probability and >1500 ng/mL in those with high clinical pretest probability) had proximal venous ultrasonography repeated after one week (fig 1).

Table 1 | Baseline characteristics and initial diagnostic testing. Values are numbers (percentages) unless stated otherwise

Characteristic	All patients (n=1508)	Low C□PTP (n=529)	Moderate C□PTP (n=649)	High C□PTP (n=330)
Mean (SD) age, years	60 (18)	59 (18)	60 (18)	64 (17)
Female sex	877 (58)	328 (62)	377 (58)	172 (52)
Mean (SD) weight, kg	86 (24)	84 (22)	87 (24)	87 (25)
Median (range) duration of symptoms, days	7 (0□2191)	7 (0□2191)	7 (0□380)	7 (0□379)
Symptomatic leg,:				
Right only	648 (43)	211 (40)	291 (45)	146 (44)
Left only	761 (50)	276 (52)	314 (48)	171 (52)
Bilateral	99 (7)	42 (8)	44 (7)	13 (4)
Wells score items (points per item)*:				
Malignancy or treatment <6 months (1)	76 (5)	13 (2)	26 (4)	37 (11)
Paralysis, paresis, cast immobilisation (1)	72 (5)	11 (2)	25 (4)	36 (11)
Bedridden/surgery in <4 weeks (1)	158 (10)	17 (3)	78 (12)	63 (19)
Tenderness in deep vein distribution (1)	673 (45)	93 (18)	342 (53)	238 (72)
Entire leg swollen (1)	405 (27)	44 (8)	143 (22)	218 (66)
Calf swelling >3 cm asymptomatic side (1)	504 (33)	52 (10)	190 (29)	262 (79)
Pitting oedema only in symptomatic leg (1)	498 (33)	68 (13)	188 (29)	242 (73)
Dilated superficial veins (non□varicose) (1)	139 (9)	26 (5)	56 (9)	57 (17)
Alternative diagnosis as or more likely (−2)	478 (32)	413 (78)	62 (10)	3 (1)
Mean (SD) Wells score	1.0 (1.8)	−0.9 (0.8)	1.4 (0.5)	3.5 (0.7)
D□dimer assay used□:				
STA□Liatest	948 (63)	284 (54)	455 (70)	209 (63)
HemosIL HS 500	214 (14)	129 (24)	50 (8)	35 (11)
Innovance	67 (4)	29 (6)	23 (4)	15 (5)
Triage	270 (18)	87 (16)	121 (19)	62 (19)

C□PTP=clinical pretest probability; DVT=deep vein thrombosis; SD=standard deviation.
*C□PTP was categorised as low with Wells score of −2 to 0, moderate with score of 1 or 2, and high with score of 3 or higher.
□9 patients with high C□PTP who had DVT on initial ultrasound did not have D□dimer test done.

Follow□ p and outcomes

Study outcomes□ DVT, pulmonary embolism, and death□ were assessed by telephone at 90 days after initial diagnostic testing. In addition, study participants were instructed at enrolment to contact study personnel urgently or to attend the emergency department if their initial symptoms did not improve or if they developed new symptoms of pulmonary embolism. During follow□up, patients with symptoms of DVT or pulmonary embolism underwent appropriate diagnostic imaging; D□dimer testing was discouraged to avoid incorporation bias.

The primary outcome was symptomatic, objectively verified, venous thromboembolism, which included proximal DVT or pulmonary embolism. A central adjudication committee, whose members were unaware of the results of diagnostic testing at initial presentation and whether patients had received anticoagulant treatment, used predefined criteria to evaluate all outcome events. Cause of death was determined using all available information (for example, hospital and primary care clinical records, autopsy findings).

Statistical analysis

The sample size calculation required that the percentage of patients with venous thromboembolism diagnosed during follow□up, among those negative for DVT by the 4D algorithm, be estimated with high precision (expected to be 0.6%). With a one sided level of 5%, a sample of 1374 patients would give the study 99% power to rule out a percentage with venous thromboembolism of 2.0%. Assuming that patients not found to have DVT by the 4D algorithm would be 93% of the total study population, and adding 1.5% for possible losses to follow□up, we estimated that we needed a sample size of 1500.

We summarised outcome measures as point estimates, expressed as percentages, with 95% confidence intervals calculated with the use of the Wilson score method. The primary analysis examined the incidence of venous thromboembolism during the 90 day follow□up period among all enrolled patients not diagnosed as having DVT by the 4D algorithm who did not receive anticoagulant therapy.

The secondary analyses included the percentage of patients who were diagnosed as having venous thromboembolism during follow□up among patients with low clinical pretest probability and D□dimer <1000 ng/mL or moderate clinical pretest probability and D□dimer <500 ng/mL. Secondary analyses also included the number of deaths overall and the number of ultrasound examinations that were avoided by use of the 4D algorithm instead of a conventional algorithm (that is, initial ultrasonography performed in all patients who did not have low clinical pretest probability and D□dimer <500 ng/mL and follow□ up ultrasonography performed in all patients with initial negative ultrasonography and moderate or high clinical pretest probability). We expressed the difference in the number of ultrasound examinations as the difference in the mean number of examinations per enrolled patient, with 95% confidence intervals. We used the Agresti□Min method to obtain 95% confidence intervals for the paired difference in the percentage of patients who would undergo initial and follow□up ultrasound imaging and D□dimer testing. We used SAS 9.4 and R 3.5.1 for statistical analyses.

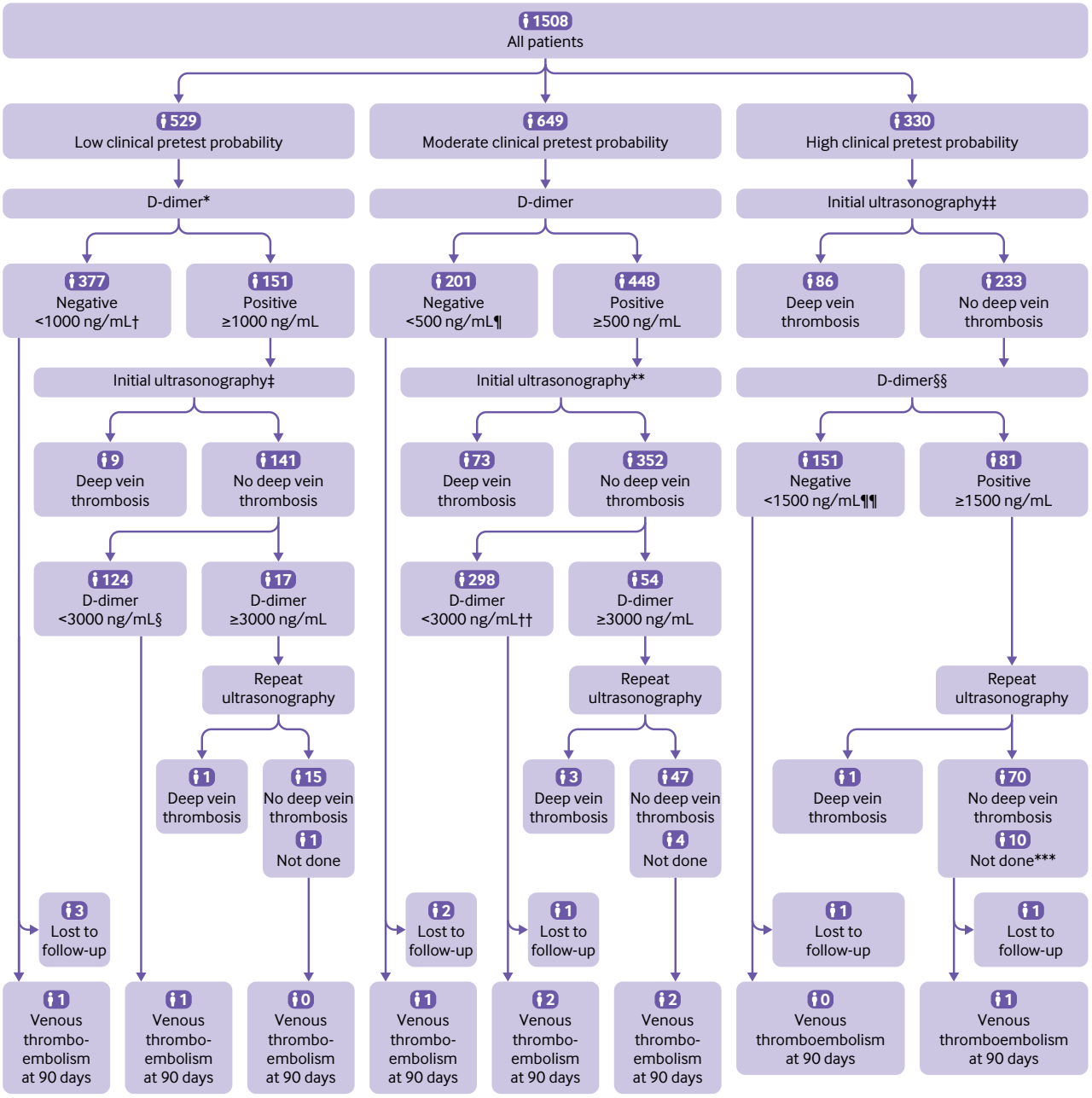

Fig 1 | Patient flow, results of initial diagnostic testing, and venous thromboembolism outcomes during follow-up. *D-dimer not done in 1 patient owing to machine error (no VTE during follow-up). Anticoagulation in 3 patients for atrial fibrillation, of whom 1 had negative ultrasonography at baseline. Ultrasonography not performed in 1 patient (no VTE during follow-up). Anticoagulation in 5 patients: renal vein thrombosis; atrial fibrillation; suspected DVT during follow-up; arterial thrombus; gastrocnemius vein thrombosis. Anticoagulation in 4 patients: atrial fibrillation; suspected DVT during follow-up; superficial vein thrombosis; gastrocnemius vein thrombosis. **Initial ultrasonography not performed in 23 patients (none had VTE during follow-up): 17 patients with D-dimer 500-1000 ng/mL as per original protocol; 6 patients protocol violation. Anticoagulation in 3 patients: isolated distal DVT during follow-up; non-ST-elevation myocardial infarction; atrial fibrillation. Ultrasonography not performed in 11 patients with D-dimer <500 ng/mL as per original protocol (1 patient had VTE during follow-up). D-dimer not done in 1 patient: isolated distal DVT at baseline and anticoagulation (no VTE during follow-up). Anticoagulation in 3 patients: isolated distal DVT at baseline; 2 superficial vein thrombosis. ***Anticoagulation in 5 patients: atrial fibrillation; 2 superficial vein thrombosis at repeat ultrasonography; isolated distal DVT at initial assessment but anticoagulation after repeat ultrasonography; isolated distal DVT at repeat ultrasonography. CPTP=clinical pretest probability; DVT=deep vein thrombosis; FUP=follow-up; VTE=venous thromboembolism

Patient and public involvement

Patients were not involved in the study design or analyses and did not contribute to the paper. The study was endorsed by the Canadian Venous Thromboembolism Research (CanVECTOR) Network (www.canvector.ca), which consists of patient

doi: 10.1136/bmj-2021-067378 | *BMJ* 2022;376:e067378 | thebmj

partners, and the network will play an important role in disseminating the results.

Results

Patients

From April 2014 through March 2020, the clinical centres assessed 3726 patients as meeting the inclusion criteria; of those, 1894 met one or more exclusions (supplementary table A) and 309 did not provide consent, which resulted in registration of 1523 patients. Shortly after registration and before any study outcomes were suspected, central data monitors identified that 15 of these patients did not meet major eligibility criteria, and we did not include them in any analyses (supplementary table B). Therefore, we analysed data from 1508 patients.

The mean age of study participants was 60 years, and 58% were female (table 1). A total of 529 (35%) patients had a low clinical pretest probability, 649 (43%) had a moderate clinical pretest probability, and 330 (22%) had a high clinical pretest probability. Despite negative D-dimer testing, seven patients with low clinical pretest probability and five patients with moderate clinical pretest probability had ultrasound imaging at initial presentation; none had DVT. A total of 929 patients were scheduled to have initial proximal vein ultrasonography (151 patients had low clinical pretest probability with D-dimer ≥1000 ng/mL, 448 had moderate clinical pretest probability with D-dimer ≥500 ng/mL, and 330 had high clinical pretest probability) (fig 1). This ultrasonography was performed in 894 patients and not performed in 35 patients (one patient with low clinical pretest probability, 23 with moderate clinical pretest probability, and 11 with high clinical pretest probability). One (high clinical pretest probability) of the 35 patients was subsequently found to have DVT in follow-up. Of the 726 patients with initial negative ultrasonography for proximal DVT, eight had isolated distal DVT on examination of the deep veins distal to the calf vein trifurcation contrary to the protocol (four of these patients received anticoagulant treatment) (supplementary table C).

Of the 726 patients with initial ultrasonography negative for proximal DVT, 152 (21%) were scheduled to have repeat proximal ultrasonography at one week (17 low and 54 moderate clinical pretest probability with D-dimer >3000 ng/mL; 81 high clinical pretest probability with D-dimer >1500 ng/mL). Of these 152 scheduled examinations, 137 were performed and five showed proximal DVT (plus one isolated distal DVT, for which the patient received anticoagulation).

Therefore, 173 patients (11% of all enrolled patients) were diagnosed as having proximal DVT by the 4D algorithm, of whom 168 had DVT on ultrasound imaging on the day of presentation and five had DVT on repeat ultrasound imaging at one week. During follow-up, 15 patients without DVT started anticoagulant treatment for reasons other than venous thromboembolism (atrial fibrillation in seven) (supplementary table D). Eight (0.5%) patients did not complete three months of follow-up (fig 1).

Primary analysis

Of all 1275 (85%) patients who did not receive a diagnosis of proximal DVT on 4D testing and who did not receive anticoagulant treatment, eight (0.6%, 95% confidence interval 0.3 to 1.2) had venous thromboembolism during follow-up (fig 1; table 2; supplementary table E. A sensitivity analysis excluding the first 253 patients enrolled showed similar results (supplementary table F).

Secondary analyses

Of 374 (25%) patients who had a low clinical pretest probability and a negative D-dimer test (<1000 ng/mL) and did not receive anticoagulant treatment, one (0.3%, 0.1% to 1.5%) patient had venous thromboembolism during follow-up (fig 1; table 2; supplementary table E). Of these patients with low clinical pretest probability, 95 had a D-dimer concentration of 500–999 ng/mL, and none (0.0%, 0.0% to 3.9%) of these had venous thromboembolism during follow-up. Of 197 (13%) patients who had a moderate clinical pretest probability and a negative D-dimer test (<500 ng/mL) and did not receive anticoagulant treatment, one (0.5%, 0.1% to 2.8%) patient had venous thromboembolism during follow-up (fig 1; table 2; supplementary table E). Of 414 (27%) patients who had negative ultrasound imaging at presentation and either low clinical pretest probability with D-dimer concentration of 1000–3000 ng/mL or moderate clinical pretest probability with D-dimer of 500–3000 ng/mL and did not receive anticoagulant therapy, three (0.7%, 0.3% to 2.1%) patients had venous thromboembolism during follow-up. Of 148 (10%) patients who had a high clinical pretest probability, had negative ultrasound imaging at presentation, had a D-dimer concentration of <1500 ng/mL, and did not receive anticoagulant treatment, no (0.0%, 0.0% to 2.5%) patients had venous thromboembolism during follow-up (fig 1; table 2; supplementary table E). Eighteen deaths occurred during follow-up; no deaths were attributed to venous thromboembolism.

Ultrasound imaging and use of D-dimer testing

The 4D diagnostic algorithm resulted in a mean of 0.72 (95% confidence interval 0.68 to 0.75) ultrasound scans per enrolled patient. The conventional algorithm would result in a mean of 1.36 (1.32 to 1.40) scans per patient. The difference in the mean number of ultrasound examinations with the 4D algorithm compared with the conventional algorithm is −0.64 (−0.68 to −0.60), corresponding to a relative difference of 47% (table 3). The difference in the percentage of patients who needed any ultrasound imaging with the 4D algorithm compared with the conventional algorithm was −19.7% (−21.7% to −17.7%), corresponding to a relative difference of 24% (table 3). Extending D-dimer testing increased the proportion of patients who had D-dimer testing from 35% to 60% (table 3).

Discussion

We found the 4D DVT testing algorithm to be safe, with eight participants diagnosed as having venous thromboembolism during follow-up among 1275 who

Table 2 | Venous thromboembolism on scheduled diagnostic testing and during follow up

	Patients	VTE	Percentage (95% CI)
No proximal DVT on scheduled testing and no anticoagulation			
Total	1275	8	0.6 (0.3 to 1.2)
Low CPTP	509	2	0.4 (0.1 to 1.4)
Low CPTP and Ddimer <1000 ng/mL	374	1	0.3 (0.1 to 1.5)
Ddimer <500 ng/mL	279	1	0.4 (0.1 to 2.0)
Ddimer 500999 ng/mL	95	0	0.0 (0.0 to 3.9)
Low CPTP and Ddimer ≥1000 ng/mL	135	1	0.7 (0.1 to 4.1)
Ddimer 1000 to 2999 ng/mL*	119	1	0.8 (0.2 to 4.6)
Ddimer ≥3000 ng/mL	16	0	0.0 (0.0 to 19.4)
Moderate CPTP	543	5	0.9 (0.4 to 2.1)
Moderate CPTP and Ddimer <500 ng/mL	197	1	0.5 (0.1 to 2.8)
Moderate CPTP and Ddimer ≥500 ng/mL	346	4	1.2 (0.5 to 2.9)
Ddimer 5002999 ng/mL*	295	2	0.7 (0.2 to 2.4)
Ddimer ≥3000 ng/mL	51	2	3.9 (1.1 to 13.2)
High CPTP	223	1	0.5 (0.1 to 2.5)
Ddimer <1500 ng/mL*	148	0	0.0 (0.0 to 2.5)
Ddimer ≥1500 ng/mL	75	1	1.3 (0.2 to 7.2)
Proximal DVT on scheduled testing and anticoagulation			
Total	173	5	2.9 (1.2 to 2.6)
Low CPTP	10	0	
DVT on initial ultrasound scan	9	0	
Ddimer 10002999 ng/mL	5	0	
Ddimer ≥3000 ng/mL	4	0	
DVT on 1 week ultrasound scan	1	0	
Moderate CPTP	76	3	
DVT on initial ultrasound scan	73	2	
Ddimer 500 to 2999 ng/mL	27	0	
Ddimer ≥3000 ng/mL	46	2	
DVT on 1 week ultrasound	3	1	
High CPTP	87	2	
DVT on initial ultrasound scan	86	2	
Ddimer <1500 ng/mL	3	1	
Ddimer ≥1500 ng/mL	74	1	
Ddimer not done	9	0	
DVT on 1 week ultrasound scan	1	0	
Other			
Proximal DVT on scheduled testing and no anticoagulation	0	0	
No proximal DVT on scheduled testing and anticoagulation	23	0	
Other protocol deviations	37	1	

CI=confidence interval; CPTP=clinical pretest probability; DVT=deep vein thrombosis; VTE=venous thromboembolism.
*Patients had negative proximal ultrasound scan at initial presentation and no scheduled repeat scan at 1 week.
Patients had negative proximal ultrasound scan at initial presentation and again after 1 week (or did not have scan that was scheduled to be repeated at 1 week).
After initial negative proximal vein ultrasound scan, repeat scan at 1 week was performed only in patients with low or moderate CPTP who had Ddimer ≥3000 ng/mL and those with high CPTP who had Ddimer ≥1500 ng/mL.
Patient group and reasons shown in figure 1; additional details in supplementary table D.
Reasons shown in figure 1.

had DVT excluded and did not receive anticoagulant treatment, which satisfied the prespecified criterion of the upper bound of the confidence interval being <2%. Because most of the patients who had DVT excluded with Ddimer had a low clinical pretest probability, our study provides strong evidence for excluding DVT with Ddimer <1000 ng/mL and low clinical pretest probability (upper bound of confidence interval <2%). However, we were not able to validate the cutoff of 500 ng/mL in patients with moderate clinical pretest probability as a result of the low number of patients in this subgroup.

Comparison with other studies

Our findings build on those from a post hoc subgroup analysis of a previous study using a Ddimer cutoff of 1000 ng/mL in patients with low clinical pretest

Table 3 | Comparison of number of scheduled ultrasound imaging examinations and Ddimer tests with 4D algorithm* compared with conventional diagnostic strategy

	4D strategy				Conventional strategy				Difference number of tests			
Investigation	Low CPTP (n=529)	Moderate CPTP (n=649)	High CPTP n=(330)	Total (n=1508)	Low CPTP (n=529)	Moderate CPTP (n=649)	High CPTP (n=330)	Total (n=1508)	Low CPTP (n=529)	Moderate CPTP (n=649)	High CPTP (n=330)	Total (n=1508)
Initial US	151	448	330	929	248	649	330	1227	−97	−201	0	−298
Repeat US	17	54	81	152	0	576	244	820	17	−522	−163	−668
All US	168	502	411	1081	248	1225	574	2047	−80	−723	−163	−966
Ddimer	529	649	233	911	529	0	0	529	0	649	233	911

CPTP=clinical pretest probability assessed using Wells score; US=ultrasound imaging of proximal veins.
*Designer DDimer Deep vein thrombosis.
Deep vein thrombosis (DVT) is considered to be ruled out at initial presentation in patients with low CPTP and Ddimer <500 ng/mL, and initial proximal vein ultrasound scan is performed in all other patients. If initial ultrasound scan does not show proximal DVT, repeat proximal vein ultrasound scan is performed after 1 week in all patients other than those with low CPTP (DVT is considered to be ruled out in patients with a low CPTP and negative initial proximal vein ultrasound scan, regardless of Ddimer concentration).

doi: 10.1136/bmj-2021-067378 | BMJ 2022;376:e067378 | the bmj

probability and 500 ng/mL in those with moderate clinical pretest probability.[9] They add stronger evidence for similar approaches in DVT,[8 10] and the approach and findings are comparable to a testing algorithm we recently published for pulmonary embolism.[11] An alternative approach to using D-dimer to exclude DVT is the age adjusted D-dimer strategy that considers DVT to be excluded with a D-dimer concentration <500 ng/mL in patients 50 years or younger and <10 times the patient's age in those older than 50 years, provided patients have a low or moderate clinical pretest probability, which has been shown to be safe in retrospective analyses.[12 13] Retrospective comparisons of clinical probability adjusted and age adjusted diagnostic strategies for DVT have suggested similar safety and reduction in imaging,[14 16] although the full 4D strategy with higher D-dimer cut-offs to determine repeat proximal ultrasound imaging was not included in these analyses.

We were not able to make a direct comparison of safety with the conventional strategy that is recommended by the American Society of Hematology.[17] However, compared with a conventional testing strategy, the 4D algorithm reduced the need for ultrasound imaging by 47%. Our results show that repeat ultrasound imaging can be avoided in a large proportion of patients, which is important because repeat imaging is costly for the healthcare system and time consuming for patients and contributes to overcrowding in emergency departments.

Strengths and limitations of study

Strengths of our study include that it was large enough to provide estimates with reasonable precision in the overall study population; we used standardised testing for venous thromboembolism during follow-up, with central adjudication of outcomes; many clinical centres participated; several different D-dimer assays were used, which increases the generalisability of our findings; and very few patients were lost to follow-up to affect the robustness of the results. Conservatively, assuming that the percentage with venous thromboembolism among those patients who were lost to follow-up was the same as the prevalence of DVT among all patients with high clinical pretest probability (that is, 26.6%; a worst case scenario), we estimate that two (0.8%, 0.4% to 1.4%) of the eight patients lost to follow-up had venous thromboembolism during follow-up. Analysing all patients (including the 253 patients enrolled before the protocol amendment) according to the amended protocol minimises the effect of the amendment on the results.

Our study had some limitations. Inpatients, patients receiving anticoagulant treatment or those who were on full dose ≥24 hours at the time of testing, pregnant women, and patients with suspected pulmonary embolism were excluded from the study, so the findings of our study do not apply to these patients. Although the Wells score incorporates the history of DVT, our study excluded patients with a previous episode of DVT, so further investigation of the algorithm in this subgroup is needed. We had too few patients in some subgroups to precisely estimate the negative predictive value in these subgroups. We did not measure patient centred outcomes, and physicians' discretion could have influenced which patients were enrolled. To the last point, the study did not capture the total number of patients who were assessed for DVT in participating centres, but we excluded 385 patients because ultrasound imaging was performed in a patient with a low clinical pretest probability and D-dimer <1000 ng/mL or with a moderate clinical pretest probability and D-dimer <500 ng/mL; for 367 patients, this was their only exclusion criterion. We believe that selective enrolment was not prominent and did not substantially bias the results for two reasons. Firstly, the observation that the prevalence of DVT and percentage of enrolled patients who had DVT on initial diagnostic testing were comparable to those in other studies involving outpatients.[1 18] Secondly, we did not observe an increase in pulmonary embolism in patients who were excluded in a similar study that we conducted at the same participating centres for the diagnosis of pulmonary embolism, a more serious diagnosis than DVT.[11] Lastly, if a patient pointed out pain or tenderness in the calf, they may have had these specific areas of their calf examined contrary to the protocol.

This study used the Wells score to categorise patients' clinical pretest probability as low, moderate, or high. Therefore, whether the same approach to D-dimer interpretation can be used if clinical pretest probability is assessed without using a clinical classification rule using or a different classification rule is uncertain. The Wells score achieved good discrimination in this study, with a prevalence of DVT of 2% in patients with low clinical pretest probability, 12% in those with moderate clinical pretest probability, and 27% in those with high clinical pretest probability. As long as the prevalence of DVT in low, moderate, and high clinical pretest probability groups is similar to these values, we believe that the 4D algorithm should be valid when clinical pretest probability is assessed in other ways. Finally, although the availability of point of care ultrasonography is increasing in the emergency department, evidence that it is a safe replacement for formal ultrasonography is limited. Furthermore, minimal data on combining point-of-care ultrasonography and D-dimer to diagnose DVT are available. Therefore, we believe that the relevance of the 4D algorithm will remain high until more robust data on point-of-care ultrasonography is available. As we look to the future, well designed large studies are needed to evaluate the role of D-dimer with point-of-care ultrasonography for diagnosing DVT.

Conclusions

In conclusion, our findings establish that using the 4D algorithm in the diagnosis of DVT is safe. Furthermore, application of our higher D-dimer cut-offs to determine the need for repeat proximal ultrasound imaging safely reduces the need for repeat ultrasound scanning.

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We thank the patients and emergency departments that participated in this study.

Contributors: CK (deceased) was involved in study design, obtaining funding, data collection, data interpretation, and writing and critical review of the report. SP and JAJ were involved with study design, obtaining funding, data collection, data analysis, data interpretation, and writing, critical review, and final approval of the report. KdW and SB were involved in study design, data collection, and writing, critical review, and final approval of the report. SS, FAS, SS, MA, SRK, GLG, SS, CW, ALL, FDA, and JFD were involved in study design, data collection, and critical review and final approval of the report. LS was involved in study coordination, data collection, and critical review and final approval of the report. SP is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: The 4D study was supported by grants from the Canadian Institutes of Health Research (MOP 125951) and was endorsed by the Canadian Venous Thromboembolism Clinical Research (CanVECTOR) Network. The funding source had no role in the collection, analysis, or interpretation of the data; the writing of the report; or the decision to submit for publication. CK (deceased) was supported by an investigator award from the Heart and Stroke Foundation of Canada and the Jack Hirsh Professorship in Thromboembolism (McMaster University). KdW is supported by investigator awards from Physician Services Incorporated and the Hamilton Health Sciences Foundation. SRK is supported by a Tier 1 Canada Research Chair. GLG is supported by an Early Researcher Award from the Province of Ontario, a Heart and Stroke Foundation Ontario Mid-Career Investigator award, and a research chair on the diagnosis of venous thromboembolism, Department of Medicine, University of Ottawa. SMB is supported by the Eli Lilly Canada/May Cohen Chair in Women's Health. FDA is supported by the Fonds de Recherche du Québec-Santé.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: the study was funded by the Canadian Institutes of Health Research; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The study was approved by the Hamilton Integrated Research Ethics Board (# 13-844) and research ethics boards of participating institutions. All participants gave informed consent.

Data sharing: A complete de-identified patient level dataset will be made available to researchers for the purpose of meta-analysis or a newly proposed study. Data will be made available following submission of a maximum two page proposal by the requestor. The trial Steering Committee will review and, if acceptable, provide approval of the request. A signed data sharing access agreement will be required. Data will become available one year after publication of the initial study results. Data availability will end four years after publication of the initial study results. Data requests should be sent to parpia@mcmaster.ca.

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The results of the study were presented at the American Society of Hematology's annual meeting on 5 December 2020. Further dissemination is planned through the Canadian Venous Thromboembolism Research (CanVECTOR) Network's various knowledge dissemination channels, social media outlets, and press releases.

Provenance and peer review Not commissioned; externally peer reviewed.

1 Geersing GJ, Zuithoff NPA, Kearon C, et al. Exclusion of deep vein thrombosis using the Wells rule in clinically important subgroups: individual patient data meta-analysis. *BMJ* 2014;348:g1340. doi:10.1136/bmj.g1340
2 Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. *Lancet* 1997;350:1795-8. doi:10.1016/S0140-6736(97)08140-3
3 Wells PS, Owen C, Doucette S, Fergusson D, Tran H. Does this patient have deep vein thrombosis?*JAMA* 2006;295:199-207. doi:10.1001/jama.295.2.199
4 Wells PS, Anderson DR, Rodger M, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. *N Engl J Med* 2003;349:1227-35. doi:10.1056/NEJMoa023153
5 Goodacre S, Sampson F, Thomas S, van Beek E, Sutton A. Systematic review and meta-analysis of the diagnostic accuracy of ultrasonography for deep vein thrombosis. *BMC Med Imaging* 2005;5:6. doi:10.1186/1471-2342-5-6
6 Johnson SA, Stevens SM, Woller SC, et al. Risk of deep vein thrombosis following a single negative whole-leg compression ultrasound: a systematic review and meta-analysis. *JAMA* 2010;303:438-45. doi:10.1001/jama.2010.43
7 Forbes K, Stevenson AJ. The use of power Doppler ultrasound in the diagnosis of isolated deep venous thrombosis of the calf. *Clin Radiol* 1998;53:752-4. doi:10.1016/S0009-9260(98)80318-8
8 Linkins LA, Bates SM, Ginsberg JS, Kearon C. Use of different D-dimer levels to exclude venous thromboembolism depending on clinical pretest probability. *J Thromb Haemost* 2004;2:1256-60. doi:10.1111/j.1538-7836.2004.00824.x
9 Linkins LA, Bates SM, Lang E, et al. Selective D-dimer testing for diagnosis of a first suspected episode of deep venous thrombosis: a randomized trial. *Ann Intern Med* 2013;158:93-100. doi:10.7326/0003-4819-158-2-201301150-00003
10 Lapner SLDT, Linkins LA, Bates SM, et al. Positive Predictive Value of Progressively Elevated D-Dimer Levels in Patients with a Suspected First Deep Vein Thrombosis. *Blood* 2012;120:2258. doi:10.1182/blood.V120.21.2258.2258
11 Kearon C, de Wit K, Parpia S, et al, PEGeD Study Investigators. Diagnosis of Pulmonary Embolism with d-Dimer Adjusted to Clinical Probability. *N Engl J Med* 2019;381:2125-34. doi:10.1056/NEJMoa1909159
12 Douma RA, Tan M, Schutgens RE, et al. Using an age-dependent D-dimer cut-off value increases the number of older patients in whom deep vein thrombosis can be safely excluded. *Haematologica* 2012;97:1507-13. doi:10.3324/haematol.2011.060657
13 Riva N, Camporese G, Iotti M, et al, PALLADIO Study Investigators. Age-adjusted D-dimer to rule out deep vein thrombosis: findings from the PALLADIO algorithm. *J Thromb Haemost* 2018;16:271-8. doi:10.1111/jth.13905
14 Takach Lapner S, Julian JA, Linkins LA, Bates S, Kearon C. Comparison of clinical probability-adjusted D-dimer and age-adjusted D-dimer interpretation to exclude venous thromboembolism. *Thromb Haemost* 2017;117:1937-43. doi:10.1160/TH17-03-0182
15 Parpia S, Takach Lapner S, Schutgens R, Elf J, Geersing GJ, Kearon C. Clinical pre-test probability adjusted versus age-adjusted D-dimer interpretation strategy for DVT diagnosis: A diagnostic individual patient data meta-analysis. *J Thromb Haemost* 2020;18:669-75. doi:10.1111/jth.14718
16 Sharif S, Kearon C, Eventov M, Sneath P, Li M, deWit K. Comparison of the age-adjusted D-dimer, clinical probability-adjusted D-dimer, and Wells rule with D-dimer for diagnosing deep vein thrombosis in the emergency department. *CJEM* 2020;22(S1):S27. doi:10.1017/cem.2020.110
17 Lim W, Le Gal G, Bates SM, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: diagnosis of venous thromboembolism. *Blood Adv* 2018;2:3226-56. doi:10.1182/bloodadvances.2018024828
18 Kraaijpoel N, Carrier M, Le Gal G, et al. Diagnostic accuracy of three ultrasonography strategies for deep vein thrombosis of the lower extremity: A systematic review and meta-analysis. *PLoS One* 2020;15:e0228788. doi:10.1371/journal.pone.0228788

Web appendix: Supplementary materials