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RECOMMENDATIONS

Update on the diagnosis of recurrence of lower limb deep vein thrombosis. A Consensus statement of the French Society for Vascular Medicine (SFMV)

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KEYWORDS
Recurrence;
Diagnosis;
Deep venous thrombosis (DVT)

Summary An accurate diagnosis of lower limb deep vein thrombosis (DVT) recurrence is mandatory. The diagnosis is difficult and has not been well investigated. Our objective was to define the role of clinical probability assessment, D-dimer assay, venous ultrasound and other imaging methods in the diagnosis of this condition based on a review of published data. Our review did not find any clinical prediction rule (CPR) specific to the diagnosis of DVT recurrence. D-dimer assays have not been sufficiently validated or proved effective either alone or when combined with the assessment of clinical probability or with ultrasound. The only validated ultrasound criteria are a new non-compressible vein segment and a ≥ 2 mm or > 4 mm increase in diameter of the common femoral or popliteal vein under compression in the transverse plane between two examinations. Limitations of these criteria include poor inter-observer agreement, non-availability of previous ultrasound reports and measurements, a high percentage of non-diagnostic ultrasound results, lack of power in diagnostic accuracy and diagnostic management studies, and lack of external validation. The analysis of venous obstruction, thrombus appearance, vein diameter and blood flow based on colour Doppler ultrasound criteria has not yet been validated in studies. Magnetic resonance direct thrombus imaging (MRDTI) is a new

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promising diagnostic imaging method, but is hardly accessible, costly and needs large scale validation studies. Based on this review, an update of the guidance for clinical practice is proposed for the diagnostic management of patients with clinically suspected lower limb DVT recurrence.
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Introduction

An accurate diagnosis of lower limb DVT recurrence is mandatory. The diagnosis is difficult and has not been well investigated. An update of the guidance for clinical practice is proposed based on a review of recent published data.

Clinical context

Only clinically suspected recurrence of lower limb DVT is addressed here. This is defined as the onset of clinical signs and symptoms affecting the lower limbs in patients with a history of ipsilateral DVT, whether isolated or associated to pulmonary embolism (PE). The previous episode of venous thromboembolism (VTE) must have been objectively confirmed even if the relevant documentation is not available at the time of suspected recurrence. The patient should no longer have been on anticoagulant treatment for at least the past 48 hours (following the decision to discontinue temporarily or permanently this treatment). The clinical context (presence or absence of a triggering factor) does not differ from that of a first episode of VTE.

Other circumstances, such as a suspected first episode of DVT of the lower limbs, suspected recurrence of pulmonary embolism, superficial vein thrombosis, or upper-extremity DVT, or suspected lower limb DVT recurrence during anticoagulant treatment will not be discussed here owing to the distinct prognostic profiles of these conditions, and the different approaches used for their diagnosis and therapeutic management.

Rationale

The diagnosis of lower limb DVT recurrence is highly important for several reasons. First, VTE recurrence is common, with a high prevalence ranging from around 24% [1] to 45% [2], and a reported 1-year, 5-year and 10-year cumulative incidence after a 6-month anticoagulant treatment of 13%, 23% and 30% respectively [3]. Second, as VTE recurrence, especially in the form of proximal DVT and/or pulmonary embolism (PE), requires long-term if not extended anticoagulant therapy [4] to prevent thrombosis progression and embolization, and the risk of bleeding increases with prolonged treatment, there is a need for accurate diagnosis of recurrence. Unfortunately, there is no reference standard for the diagnosis of DVT recurrence, and objective and accurate diagnostic methods are lacking, although several diagnostic methods are available, including clinical probability assessment, D-dimer assays, and vascular imaging methods based on ultrasound, venography, computed tomography (CT) scans, magnetic resonance direct thrombus imaging (MRDTI), and nuclear medicine imaging methods such as positron emission tomography (PET). However, the major issue is that neither clinical symptoms and signs, nor imaging tests allow accurate discrimination between an old thrombus and a new one developed at the same site (venography is non-diagnostic in 33% of patients with clinically suspected DVT recurrence [5]), a frequent problem owing to the low normalisation rate after a first proximal DVT [6].

Primary objective

Our primary objective was to assess the validity and utility of diagnostic tests and strategies for patients with clinically suspected ipsilateral acute DVT recurrence based on a review of diagnostic accuracy and diagnostic management studies, and on opinions of experts in vascular medicine based on the Delphi method[7,8] with regard to the assessment of clinical probability and the respective roles of D-dimer assay, ultrasound examination and other imaging methods.

Clinical probability assessment of DVT recurrence

Clinical prediction rules

A review of published studies did not reveal any clinical prediction rule (CPR) specific to suspected lower limb DVT recurrence.

The Wells clinical prediction rule [9,10] is proposed for suspected lower limb DVT in general and has rarely been validated in the specific context of suspected recurrence of lower limb DVT. It takes into account the history of DVT or PE and does not cover all the items potentially associated with the diagnosis of DVT recurrence. Use of the Wells CPR in this context could therefore lead to more frequent classification of patients in the high-risk category in view of their history of DVT or PE. For this reason, its efficiency, i.e. the proportion of patients attributed a low score, should be lower for suspected recurrence of lower limb DVT than for clinical suspicion of a first DVT episode. The event rate in this low-risk group is not well known. The only study that has evaluated the Wells rule was based on a prospective cohort of 105 patients [2]. This sample size was too small for any conclusion to be drawn from the findings: 61 patients (58%) were classified as having a low clinical probability of DVT recurrence, yet the event rate in this low-risk group was 21% (13/61), corresponding to a high failure rate [2].

The Amsterdam Maastricht Utrecht Study on thromboEmbolism (AMUSE) score [11] was constructed and validated for suspected lower limb DVT in the setting of general medicine. It does not take into account the history of VTE recurrence,

but includes a rapid, qualitative D-dimer assay. It has never been validated for suspected recurrence of lower limb DVT.

In a meta-analysis of individual patient data from 13 studies ($n = 10,002$ patients), the accuracy of the Wells rule for excluding DVT was assessed in different subgroups of patients [12], including a subgroup with suspected DVT recurrence ($n = 941$ with 220 confirmed cases). In these patients, the original Wells rule needed to be updated by adding one extra point to the score to enable the safe exclusion of DVT. Using the updated model (and defining low risk as a score ≤ 1), in conjunction with a negative D-dimer test result, led to a failure rate of 1.0% (95% confidence interval 0.6% to 1.6%) instead of 2.5% (95% confidence interval 1.2% to 5.4%) with the original model.

Clinical judgment

The assessment of clinical probability based on clinical judgement (clinical gestalt) regarding a suspected first episode of lower limb DVT constitutes an empirical non-quantitative assessment. In a comparative study [13], the proportion of patients classified as being at low risk of experiencing DVT was lower than that determined using the Wells score (29% versus 47%) but the diagnostic failure rate (incidence of DVT in this group) was also lower (1.3% versus 3.2%). Another study [14] compared the clinical probability of the presence of DVT as estimated by general practitioners (GPs) to the Oudega rule, which incorporates seven clinical variables and a D-dimer assay ($n = 1002$ patients). Both the GP estimates and the Oudega rule showed good overall discriminative ability and performed equally well, although use of the Oudega rule resulted in fewer patients being referred for imaging. A systematic review comparing clinical judgement with CPR [15] (including several studies concerning lower limb DVT diagnosis) showed that CPR were rarely superior to the physician's clinical judgement in terms of diagnostic failure rate (risk of events in the low-risk group), but were superior in terms of efficiency (proportion of patients classified as low-risk). These findings suggest that clinical intuition alone often leads to overestimating the actual risk of DVT.

Clinical probability assessment in the context

Clinical judgement seems at least as good as the Wells rule and is useful in clinical practice regarding suspected recurrence of lower limb DVT for estimating the clinical probability of this event. Some clinical criteria, for the most part not included in CPRs, are highly suggestive of DVT recurrence and need be accounted for. Concerning the previous episode of DVT, prior unprovoked VTE or provoked VTE associated with a permanent risk factor, proximally located lower limb DVT, anticoagulant treatment for less than 3 months, and poor-quality treatment were strong criteria for suspecting the recurrence of lower limb DVT. An interval of less than 1 month or even 3 months between the previous DVT episode and the suspicion of recurrence is also thought to be strongly suggestive of the diagnosis of DVT recurrence. Regarding the current episode of suspected DVT recurrence, the presence of new clinical symptoms and signs, a unilateral increase in volume of the affected lower limb, paralysis (or paresis) or recent immobilisation, recent major surgery, active cancer, and finally, absence of any alternative diagnosis more likely than that of DVT recurrence are strong criteria for the diagnosis of DVT recurrence. Other characteristics, like age and gender, that are prognostic indicators of recurrence may also be useful indicators for the diagnosis of recurrence.

In clinical practice, the Wells rule may be useful in emergency departments for physicians who have little experience in the diagnostic management of DVT. In contrast, clinical judgement may be preferred by specialists and physicians with expertise in the diagnosis of this condition.

Guidance statements

We suggest that the clinical probability of DVT recurrence should be defined as high if any of the following criteria is met:

- Previous provoked DVT associated with a permanent risk factor
- Previous unprovoked DVT
- Previous proximal DVT
- Previous bilateral DVT
- Initial anticoagulant treatment lasting less than 3 months
- Poor-quality treatment at the time of the first DVT episode
- Interval between the end of treatment for the previous DVT and suspected recurrence less than 1 month
- Interval between the end of treatment for the previous DVT and suspected recurrence less than 3 months
- Recent clinical signs (at the time of suspected recurrence)
- Unilateral increase in leg volume
- Paralysis or paresis of the leg
- Recent immobilisation (for at least 3 days)
- Recent major surgery (within less than 4 weeks)
- Active cancer (ongoing treatment for cancer, interval of less than 6 months between the discontinuation of cancer treatment and the onset of symptoms, palliative care)
- Absence of any alternative diagnosis more likely than that of DVT recurrence

We suggest that:

- The physician's clinical judgement is useful for the diagnosis of DVT recurrence
- The physician's clinical judgement is as least as good as the Wells CPR for the diagnosis of DVT recurrence

D-dimer assay

Review of published studies

As mentioned above, according to an individual patient data meta-analysis [12], an updated Wells rule better classifies patients as at low risk than the original model, and when

combined with a negative D-dimer test results enables safe exclusion of the diagnosis of DVT recurrence.

Our review identified five other publications investigating the value of D-dimer assays either alone or integrated within a diagnostic work-up for VTE recurrence.

The results of a multicentre study first reported as an abstract [16] and later cited in an article [17] indicate that highly sensitive D-dimer assays are useful for ruling out the diagnosis of recurrent lower limb DVT.

The utility of a negative D-dimer assay (STA-Liatest D-di®; Diagnostica Stago, Asnières-sur-Seine, France, and Parsippany, New Jersey) for ruling out the diagnosis of DVT recurrence was assessed in a diagnostic management study in a prospective cohort of 300 consecutive patients [18]. In patients with negative D-dimer results, anticoagulant therapy was withheld, and no further diagnostic tests for DVT were performed as part of the initial evaluation. Patients with positive D-dimer results underwent compression ultrasound. Among the 134 patients (44.6%) with a negative D-dimer assay, the rate of confirmed thromboembolic events was 0.75% (95% CI: 0.02—4.09%) and the rate of ''confirmed'' or ''suspected but unconfirmed'' thromboembolic events was 6.0% (95% CI: 2.6—11.4%). The number of inconclusive test results was too high for the results of this study to be considered as valid.

The utility of a negative D-dimer assay for ruling out the diagnosis of PE recurrence was investigated in a retrospective study in patients with a clinical suspicion of a new episode of PE [1]. The D-dimer assay was negative in 15.9% (49/308 patients), a two-fold lower rate than that observed in patients with no history of VTE. The rate of thromboembolic events at 3 months was 0% (95% CI: 0.0—7.9%).

Two studies integrated a D-dimer assay into a diagnostic management strategy. The first of these [2] evaluated a diagnostic strategy combining clinical probability estimated on the basis of the Wells CPR (modified rule), and the results of D-dimer assay, in comparison to a diagnostic strategy based on ultrasound examination (specifically, an increase > 4 mm in vein diameter after compression, or involvement of a new vein segment) and to clinical outcome at 3 months. In this prospective cohort of 105 patients, the prevalence of recurrence was 44.8% (47/105). The clinical probability was defined as low in 58% of patients (61/105) and the D-dimer test was negative in 17% (18/105), 15% (16/105) of patients meeting both these criteria. The predictive value of a negative D-dimer test alone was 94.4% (95% CI: 74.2—99.0%), that of a negative D-dimer test associated with a non-high clinical probability being 100% (95% CI: 79.6—100%). The second study [19], conducted in a prospective cohort of 146 patients, investigated the utility of a negative D-dimer assay in addition to a negative ultrasound examination to rule out the diagnosis of DVT recurrence. Criteria for DVT were either thrombosis progression or a > 4 mm increase in vein diameter under compression at the level of the popliteal vein or femoral vein between two examinations. The incidence of recurrent VTE at 3 months in patients with negative results in both the ultrasound examination and the D-dimer assay and consequently not treated ($n = 75$ patients) was 0% (95% CI: 0—4.8%).

Role of D-dimer

Overall, the use of a D-dimer assay alone has not been extensively validated or proved to be sufficiently accurate in the diagnosis of recurrent lower limb DVT, and the studies evaluating strategies incorporating a D-dimer test following clinical probability assessment or ultrasound examination were underpowered or lacked external validation.

Guidance statements
We suggest that:

- Exclusion of the diagnosis of DVT recurrence should not be based on negative results of the D-dimer assay alone.
- The results of the D-dimer assay should be assessed in conjunction with the clinical probability of recurrence estimated according to the Wells rule or the physician's clinical judgement, preferably before performing a diagnostic ultrasound examination.
- If the ultrasound examination is performed first and its results are inconclusive, or not in accordance with the estimated clinical probability, we suggest that a D-dimer assay should be performed.

Venous ultrasound

Review of published studies

As compression ultrasound (CUS) findings may be equivocal due to a ''residual thrombosis'', a diagnostic approach proposed for CUS is to compare the results of the examination performed at the time of suspected DVT recurrence with those of the baseline CUS performed on discontinuation of anticoagulant treatment [19—21]. The diagnosis of DVT recurrence is then based on the presence of a new non-compressible vein segment or on an increase in vein diameter after full compression at the level of the common femoral vein or the popliteal vein in the cross-sectional plane. A ≥ 2 mm or > 4 mm increase in vein diameter has been suggested as a positive diagnostic criterion [20—23].

This criterion was first assessed in a diagnostic accuracy study [20] that compared ultrasound with venography in 29 patients. The criterion for proximal DVT recurrence was either non-compressibility of a previously normal or normalised vein segment or a ≥ 2 mm increase in vein diameter under compression. Recurrence was identified by venography in a total of 11 patients (38%), 10 presenting proximal DVT and one presenting isolated distal DVT. The sensitivity of ultrasound for detecting all DVTs was 91% (95% CI: 59—100%) (one false negative corresponding to a distal DVT associated with an unchanged vein diameter) and a specificity of 100% (95% CI: 81—100%). The Kappa coefficient of agreement between two operators for 100 examinations was 0.95 (95% CI: 0.88—1.00).

Table 1 Diagnostic management studies (only studies published as articles are included in this analysis).

Author (year)	Number of patients Duration of follow-up Prevalence	Cut-off for positive test result	Strategy tested for safety	Patients with negative strategy *n* (%)	Symptomatic recurrent VTE % (95% CI)
Rathbun SW et al. [18] (2004)	300 patients 3 months 18%[a]	STA-Liatest D-di > 0.47 μg/mL	D-dimer negative	134 (44.6)	0.75 (0.02—4.09) 6.0 (2.6—11.4)[b]
Prandoni P et al. [21] (2002)	205 patients 6 months 26.8%	CUS: ≥ 2 mm increase in vein diameter, new non-compressible vein	CUS at presentation negative	153 (74.6) at D2 ± 1	3.27 (1.07—7.46)
			Repeated CUS at D2 ± 1 and D7 ± 1 negative	150 (73.2) at D7 ± 1	1.3 (0.02—4.7)
Aguilar C et al. [2] (2007)[c]	105 patients 3 months 44.8%	CPR (modified Wells) STA-Liatest D-di > 0.4 μg/mL	D-dimer negative	18 (17.1)	5.55 (1.0—25.8)
			CPR unlikely and D-dimer negative	16 (15.2)	0 (0—20.4)
Prandoni P et al. [19] (2007)[d]	146 patients 3 months 26—30%	CUS: > 4 mm increase in vein diameter, new non-compressible vein, D-di: Biopool Autodimer	CUS and D-dimer both negative	75 (51.4)	0 (0—4.8)
Le Gal G et al. [24] (2009)[e]	130 patients 3 months 23.1%	CUS: ≥ 4 mm increase in vein diameter, new non-compressible vein	CUS negative	100 (76.9)	2 (0.2—7.04)
van Dam et al. [38] (2020)	305 patients 3 months 38%	MRDTI	MRDTI negative	122 (62)	1.7 (0.20—5.9)

CUS: compression ultrasound performed on the common femoral and popliteal veins; CPR: clinical prediction rule (Wells rule); MRDTI: magnetic resonance direct thrombus imaging.

[a] Of the 300 study patients, 134 (45%) had negative D-dimer results (negative cohort), and 166 had positive D-dimer results. Among the 166 patients with a positive D-dimer assay, CUS documented new DVT in 54 patients (all had new non-compressible vein segments); ultrasound results were normal in 79 patients and inconclusive in 33 patients.

[b] Worst case-scenario considering six additional patients in whom venous thromboembolism during follow-up could not be definitively excluded (five patients with recurrent leg symptoms and one patient who died).

[c] CUS: > 4 mm increase in vein diameter, new non-compressible vein segment. CUS was performed if the CPR indicated that recurrence was unlikely and D-dimer assay was positive or if the CPR indicated that recurrence was likely. When negative, CUS was repeated at 1 week if the CPR indicated that recurrence was likely and the D-dimer assay was positive.

[d] CUS was performed first, then a D-dimer test if the CUS was negative. CUS was repeated at 1 week, or venography was performed, if the D-dimer test was positive. The cut-off for the D-dimer test was not reported.

[e] Only patients with a suspicion of ipsilateral DVT recurrence were included in this analysis. Data were extracted from those obtained for the entire cohort, which included other patients either with a suspicion of DVT in the other leg or at other sites, or with a suspicion of PE with or without DVT. In this strategy, recurrence was ruled out if the increase in vein diameter was ≤ 1 mm. The ultrasound examination was repeated 1 week later, or venography was performed, if the increase in diameter was between 1.1 and 3.9 mm.

The utility of ultrasound using these criteria was assessed in a diagnostic management study [21] that compared negative ultrasound findings (at baseline and on repeat ultrasounds at D2 ± 1 and D7 ± 1) to clinical outcome over a 6-month follow-up, patients with negative ultrasound results receiving no anticoagulant treatment during this period. A total of 205 patients were included of whom 153 patients had a negative ultrasound at baseline and 150 at the repeat ultrasounds as well. Recurrence was observed in 2/150 patients. The diagnostic failure rate was 1.3% (95% CI: 0.02—4.7%). If only the initial negative results (at baseline) had been considered, the diagnostic failure rate would have been 5/153, i.e., 3.3% (95% CI: 1.1—7.5%).

The safety of a diagnostic strategy based on a comparison of imaging tests at the time of suspected recurrence of PE or lower limb DVT with those performed previously (on discontinuation of anticoagulant treatment) was demonstrated in the REVERSE study in a cohort of patients having completed 5—7 months of anticoagulant treatment after a first unprovoked VTE [24]. This strategy effectively ruled out VTE

Table 2 Vein diameter measurement after full compression.

Author (year)	No. of patients	Criteria	r^2 coefficient	Mean difference between paired measurements (95th percentile)	Kappa coefficient (95% CI)
Prandoni P et al. [20] (1993)	NR (100 assessments)	NR	NR	NR	0.95 (0.88—1.00)
Linkins LA et al. [25] (2006)	60 patients	Non-compressibility	NA	NA	0.83 (0.69—0.97)
		Vein diameter measurement	17%	2.2 mm (8.0 mm)	NR
Hamadah A et al. [28] (2011)[a]	121 patients	Presence of baseline imaging	NA	NA	Entire study population: 0.78 (0.63—0.93) Subgroup classifiable: 0.93 (0.83—1)
Hassen S et al. [27] (2011)[b]	43 patients Vein segments with acute DVT: 47 proximal, 36 distal	Vein diameter measurement	r^2 = 90.9% for all vein segments	0.73 mm (2.5 mm) at the proximal veins	NR
			r^2 = 71.8% for distal vein segments	1.01 mm (2.7 mm) at the distal veins	NR
Tan M et al. [29] (2012)	49 patients	Vein diameter ≥ 2 mm	NA	NA	0.92 (0.8—1)
		Vein diameter measurement	r^2 = 0.648	(2 mm)	NR

NR: not reported; NA: not applicable.

[a] In the study of Hamadah et al. [28], the objective was to assess inter-observer agreement in groups with and without baseline imaging. The Kappa coefficient corresponds to the inter-observer agreement with regard to (1) whether or not patients were classifiable for VTE recurrence, and (2) how they were classified (diagnostic classification). Only the results for the group with baseline imaging results available are presented in this table.

[b] All studies concerned exclusively proximal DVT except that of Hassen et al. [27], which also included patients with distal DVT and was the only study to be performed in acute DVT patients. As vein diameter is enlarged in the acute DVT phase, this may explain why the inter-observer agreement (lower variability in measurements) was higher in this study than in the other studies.

recurrence in 19% of cases (76/398) with a diagnostic failure rate of 2.8% (95% CI: 1.4—5.5) based on clinical outcome at the end of 3 months without treatment.

We did not find any other external validation study reporting on these ultrasound criteria for the diagnosis of DVT recurrence, but we found inconsistency with respect to inter-observer variation in vein diameter measurement (and implicitly the increase in vein diameter between two successive ultrasound examinations) [25—29]. An alternative criterion, namely a thrombus length ≥ 9 cm has been proposed [30], but has not been validated in a cohort of patients with suspected recurrence of lower limb DVT.

Comparing CUS results with baseline imaging helps to better classify patients with regard to DVT recurrence, enhances inter-observer agreement [28] and can safely rule out VTE recurrence, as shown in a validation study [24] (Table 1). However, this strategy has many major limitations in clinical practice, the most important of these being poor or moderate inter-observer agreement [25] (Table 2), non-availability of previous CUS reports and measurements [26], and a high percentage of non-diagnostic CUS results in up to 20—32% of the patients [18,26]. This may lead to misdiagnoses with erroneous clinical decisions and consequent VTE complications in untreated patients (false negative results), or potential bleeding complications in those who are treated (over-diagnosis leading to false positive results and over-treatment). The other limitations are the potential for recurrence at a site other than that previously investigated, lack of power in diagnostic accuracy and diagnostic management studies [19—21], and the scarcity of external validation studies [24]. Due to these limitations, the diagnosis of ipsilateral DVT recurrence by CUS is mainly based on the criterion of a new non-compressible vein segment according to guidelines [22,31] and a recent review [23].

In clinical practice, the criterion of increase in vein diameter is rarely used. When it is employed, the threshold value of a > 4 mm increase in vein diameter is generally adopted. In any case, the ultrasound examination is not necessarily repeated within the first 7 to 10 days if it is negative, or if it is positive, but only when the initial ultrasound results are inconclusive.

Role of venous ultrasound

Two scenarios should be considered when performing the ultrasound examination, depending on whether the results of a previous examination are available.

If such results are available (in the form of a report, or measurements of femoral and popliteal vein diameters after compression), a comparison of thrombus location and assessment of the change in vein diameter (as recommended in the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines [31] and in the guidance from the SSC of the ISTH) [22] may allow a diagnostic decision. The evaluation will favour recurrence if involvement of a different segment of the vein or downstream extension of the thrombus is detected in the same leg, if the other leg is affected, or if an increase > 4 mm in vein diameter at the same site between two successive ultrasound examinations is observed. The diagnosis may be considered as uncertain if the increase in vein diameter is between 2 and 4 mm. It is ruled out if the increase is < 2 mm.

If no records of a previous ultrasound examination are available, the diagnosis should be based on the assessment of venous obstruction, thrombus appearance and vein diameter on B mode, and the presence or absence of blood flow and its direction on colour Doppler ultrasound (CDUS). In any case, whether or not prior documentation is available for comparison, the criteria for DVT recurrence are identical to those used for the diagnosis of a first DVT episode, namely complete vein obstruction (i.e. an occlusive thrombus on B-mode and no colour Doppler flow within the occluded vein segment) accompanied by vein dilation, or a partial vein obstruction with the characteristics of a new thrombus (hypoechoic, non-adherent or mobile, with a regular surface) and an antegrade colour Doppler flow that may outline the thrombus (with no reflux). DVT recurrence can be ruled out on the basis of either (1) a normal compression ultrasound (no intraluminal material and a fully compressible vein), (2) a chronic aspect identified by a small vein diameter and a thickened vein wall, or (3) a chronic aspect with a partial vein obstruction with the characteristics of an old thrombus (hyperechoic, adherent, irregular surface) and venous reflux (i.e. a retrograde flow on colour Doppler).

The ULTREC study [32] is currently underway to evaluate the safety of excluding the diagnosis of ipsilateral lower limb DVT recurrence based on the use of colour Doppler ultrasound criteria.

Whatever the method used, if the ultrasound is equivocal (non-diagnostic), i.e. there are limitations to performing the examination or to interpreting the results, the ultrasound should be repeated within the first week at D2 ± 1 and/or at D7 ± 2 while withholding anticoagulant treatment but monitoring the patient more closely in order to detect any significant change in vein diameter or any thrombus progression.

We **recommend** adoption of the following ultrasound criteria:

- For confirmation of the diagnosis of DVT recurrence by ultrasound, to rely on the criterion of a new non-compressible vein segment, and to set the cut-off for increase in diameter of the common femoral vein or the popliteal vein under compression in the transverse plane between two successive examinations at > 4 mm, this cut-off being clinically more relevant than an increase ≥ 2 mm.
- For exclusion of the diagnosis of DVT recurrence, to set the cut-off for vein diameter increase between two examinations at < 2 mm.
- For a non-diagnostic (equivocal) ultrasound, an increase in vein diameter between two examinations ≥ 2 mm and ≤ 4 mm.

We also **suggest** that:

- The criterion of vein diameter increase should be preferred whenever available because it is the most robustly validated criterion; failing that, morphological and haemodynamic analysis by colour Doppler ultrasound (venous obstruction, thrombus appearance, vein diameter, blood flow) may be used.
- Irrespective of the ultrasound criterion adopted, if the examination is either clearly negative or clearly positive, a repeat examination is not warranted.
- In contrast, if the ultrasound examination is inconclusive and the D-dimer test, if performed, is positive (so the diagnosis of DVT recurrence remains uncertain), the ultrasound should be repeated at D2 ± 1 and/or at D7 ± 2 to check for an increase in vein diameter or for thrombus progression. Another option is to perform MRDTI if available. No anticoagulant treatment should be initiated pending the results of these additional investigations.

Other vascular diagnostic imaging methods

Review of published studies

Among the various techniques available (molecular imaging [33], ^{18}F-FDG PET [34] and magnetic resonance imaging [MRI] [35—37]), the most attractive is magnetic resonance direct thrombus imaging (MRDTI) [36]. MRDTI is non-invasive (no contrast injection), fast (10 minutes acquisition time), highly accurate in comparison to venography for the diagnosis of a first DVT, and highly reproducible [35]. Its accuracy is slightly lower for DVT located below the knee. In a follow-up study including 39 patients with diagnosed DVT, MRDTI results normalised over a period of 6 months in all of them [36]. MRDTI was compared to a ''standard approach'' in a study comprising two groups of patients with a history of thrombosis: one group presenting symptomatic DVT extending to an initially non-thrombosed vein segment in the same leg on ultrasound examination (n = 39), the second group being asymptomatic but having previously experienced venous thrombosis (> 6 months earlier) with unchanged findings on ultrasound examination and a negative D-dimer assay (n = 42). The sensitivity of MRDTI was 95% (95% CI: 83—99%), and the specificity was 100% (95% CI: 92—100%). The Kappa coefficient of agreement between observers was 0.98 (95% CI: 0.93—1) [37].

The utility of MRDTI for the diagnosis of recurrent DVT has been addressed in a diagnostic management study [38] that assessed the safety of withholding anticoagulant treatment in patients with a clinically suspected recurrent ipsilateral lower limb DVT who had a negative MRDTI at baseline (at the time of clinical suspicion of recurrence). The 3-month rate of symptomatic objectively confirmed VTE recurrent events was 1.7% (95% CI: 0.20—5.9). Limitations of this study are a lack of precision and power with a high upper limit of the 95% confidence interval and a smaller sample size than expected (anticipated sample size of 246 negative baseline MRDTI patients, 122 patients included). Other limitations are the poor access and the cost associated with the use of magnetic resonance imaging.

Role of other vascular diagnostic imaging methods

The other diagnostic imaging methods have not been validated and at present do not have a well-defined role. MRI and PET are not always readily accessible and are also costly. A CT venography may be performed in the event of difficulty in identifying an iliac or caval thrombosis, or in determining its extent.

Proposed diagnostic work-up

Summary of published articles

Published articles reporting diagnostic management strategies and those reporting inter-observer variability in vein diameter measurement by ultrasound are summarised in Tables 1 and 2.

Which diagnostic approach should be used?

We suggest several diagnostic approaches depending on the availability of test results and the level of expertise of the physician in charge of the patient.

The ideal situation corresponds to availability of an estimation of clinical probability (according to the Wells score or the physician's clinical judgement) and the results of D-dimer assay before performing an ultrasound examination. The diagnostic strategy to adopt will then be identical to that proposed about the suspicion of a first DVT (Fig. 1).

In the other situations, when the ultrasound examination is the first step in the diagnostic work-up, two alternative strategies are proposed, as illustrated in Figs. 2 and 3: either repeat venous ultrasound within a week or carry out a D-dimer test followed by venous ultrasound within a week if the D-dimer test is positive, or perform MRDTI if available.

Human and animal rights

The authors declare that the work described has not involved experimentation on humans or animals.

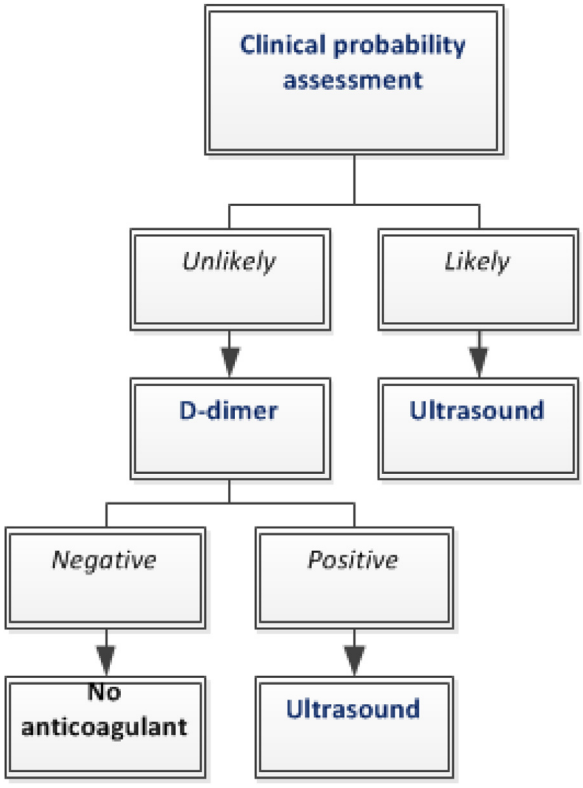

Figure 1 Ideal diagnostic approach. For the management strategy following the ultrasound, see Fig. 2.

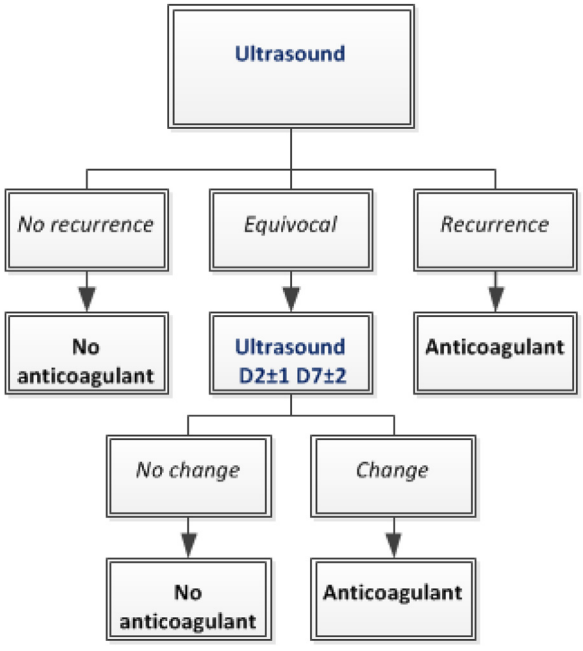

Figure 2 Practical diagnostic approach based on the repeat ultrasound. Change on repeat ultrasound is defined as a > 4 mm increase in measured vein diameter or a thrombus progression to a new vein segment.

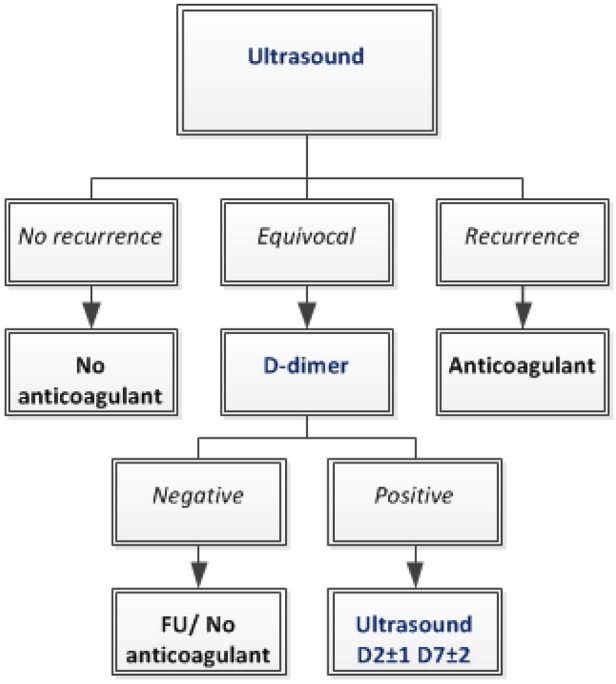

Figure 3 Practical diagnostic approach based on ultrasound and D-dimer assay with repeat ultrasound. Flow chart following (repeat) ultrasound at D2 ± 1 and D7 ± 2 as in Fig. 2.

Informed consent and patient details

The authors declare that the work described does not involve patients or volunteers.

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A. Elias reports having received fees for conferences, presentations, manuscript writing or educational events, and support for participation in meetings and travel from INNOTHERA, and fees for educational events from VIATRIS.

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Author contributions

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

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