Thrombosis Research 161 (2018) 78–83

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Review Article

Diagnosis of deep vein thrombosis recurrence: Ultrasound criteria

Mario Maufus[a], Antoine Elias[b,c], Marie-Thérèse Barrellier[d], Gilles Pernod[a,c,e,*], on behalf of the French Society for Vascular Medicine

[a] Department of Vascular Medicine, Grenoble-Alps University Hospital, CS 1027, 38043 Grenoble Cedex, France
[b] Department of Vascular Medicine, Sainte Musse Hospital, CS 31412, 83056 Toulon Cedex, France
[c] InnoVTE: French Investigation Network on Venous Thromboembolique Disease, France
[d] Department of Vascular Medicine, Caen University Hospital, CS 30001, 14033 Caen Cedex 9, France
[e] Grenoble-Alps University, Centre National de Recherche Scientifique (CNRS)/Techniques de l'Ingénieurie Médicale et de la Complexité (TIMC), Informatique, Mathématiques et Applications (IMAG) Unité Mixte de Recherche (UMR), 5525/Themas, Grenoble, France

ARTICLE INFO

Keywords:
Venous thrombosis
Recurrence
Diagnosis
Lower extremity
Ultrasound

ABSTRACT

Introduction: Recurrent deep vein thrombosis (DVT) is often suspected in patients after anticoagulant drug withdrawal. The clinical signs can be confused with the onset of post-thrombotic syndrome. For these reasons, diagnosis of DVT recurrence must rely on an accurate method.

Materials and methods: In order to assess this challenging clinical issue, we performed an overview of the literature regarding ultrasound criteria for the diagnosis of recurrent DVT through a Medline search, which included articles published from January 1, 1980 to February 20, 2017.

Results: Eighty-eight publications were found based on the defined keywords, of which nine articles with a relevant abstract were selected. By searching the reference lists of these nine articles, we obtained another 27 relevant articles. A new non-compressible vein or an increase in the diameter of a previously thrombosed vein segment by > 4 mm are sufficient to confirm the diagnosis of DVT recurrence. In contrast, an increase in diameter of < 2 mm enables recurrence to be ruled out. An increase between 2 and 4 mm is deemed equivocal. Criteria based on echogenicity and Doppler venous blood flow are not reproducible. Other diagnostic imaging methods, mainly direct thrombus magnetic resonance imaging, are currently under evaluation.

Conclusions: Ultrasound remains the most useful test for the diagnosis of recurrent DVT. Further imaging tests need to be validated.

1. Introduction

The incidence of deep vein thrombosis (DVT) is around 1 per 1000 inhabitants per year, and mainly affects the lower limbs. This incidence increases with age, affecting 1% of individuals aged over 75 years [1,2]. The accumulated recurrent venous thromboembolism rate after anticoagulant withdrawal, as an index of unprovoked DVT, varies from 25% at 5 years [3–6], to 30–40% at 10 years [3,4].

Recurrent venous thromboembolism (VTE) is usually suspected after anticoagulant withdrawal, the clinical symptoms and signs of which may be confused with those of post-thrombotic syndrome (PTS), such as pain and edema, which account for 25–50% of patients at 2 years [3,7]. Together with the potential for an indefinite duration of anticoagulant therapy if recurrence is confirmed, in addition to the risk of bleeding complications with prolonged anticoagulation treatment, this highlights the need for accurate techniques to diagnose DVT recurrence.

The main ultrasound criterion for the diagnosis of a first DVT event is the absence of complete compressibility of a venous segment under gentle pressure of the probe [8,9]. This criterion is difficult to interpret for the diagnosis of a recurrent event [9,10] due to the persistence of obstructive post-thrombotic damage. This accounts for about two-thirds of cases at 3 months and 40–50% of cases at 1 year [10–12] in the proximal veins after a first DVT episode (index), which makes interpretation of the compression ultrasonography (CUS) findings difficult.

The purpose of this article was to review the validity and utility of the suggested ultrasound diagnostic criteria for DVT recurrence, and to review how CUS compares to other diagnostic imaging methods.

2. Materials and methods

We conducted a literature search in the MEDLINE database (from January 1, 1980 to February 20, 2017) to identify potential studies by using a combination of the following keywords: venous thrombosis,

* Corresponding author at: Department of Vascular Medicine, Grenoble-Alps University Hospital, CS 1027, 38043 Grenoble Cedex, France.
E-mail address: GPernod@chu-grenoble.fr (G. Pernod).

https://doi.org/10.1016/j.thromres.2017.11.004
Received 14 September 2017; Received in revised form 25 October 2017; Accepted 12 November 2017
Available online 14 November 2017
0049-3848/

recurrence, diagnosis, and lower extremity/limb. Publications from the reference list of the identified articles that were not found in Medline were also considered.

2.1. Study selection

Articles were considered if they were related to the diagnosis of recurrent DVT of the lower limbs. We excluded articles dealing with the diagnosis of DVT recurrence in locations other than the lower limbs, and also excluded those dealing with the diagnosis of superficial vein thrombosis recurrence.

2.2. Data extraction

We extracted data related to 1/ the study design whether prospective or retrospective, or whether an accuracy or a management study, 2/ the population involved in the study, 3/ the diagnosis method and the criteria assessed, 4/ their reproducibility 5/ their performance in terms of sensitivity and specificity in diagnosis accuracy studies and 6/ the safety of a negative baseline diagnostic strategy assessed by the occurrence of VTE events at follow-up after withholding anticoagulant therapy in management studies.

2.3. Search results

A total of 88 publications were found. According to the relevance of the abstracts, 10 articles were considered. Thirteen publications were excluded because they were only abstracts. Three publications were excluded because they were not written in English. Sixty publications were excluded because the abstracts were not deemed to be relevant. Two publications were excluded for other reasons.

By searching the reference lists of these articles, we were able to identify another 18 relevant articles dealing with this topic, which were also assessed according to their abstract. This overview of the literature is based on analysis of a total of 28 articles (Fig. 1).

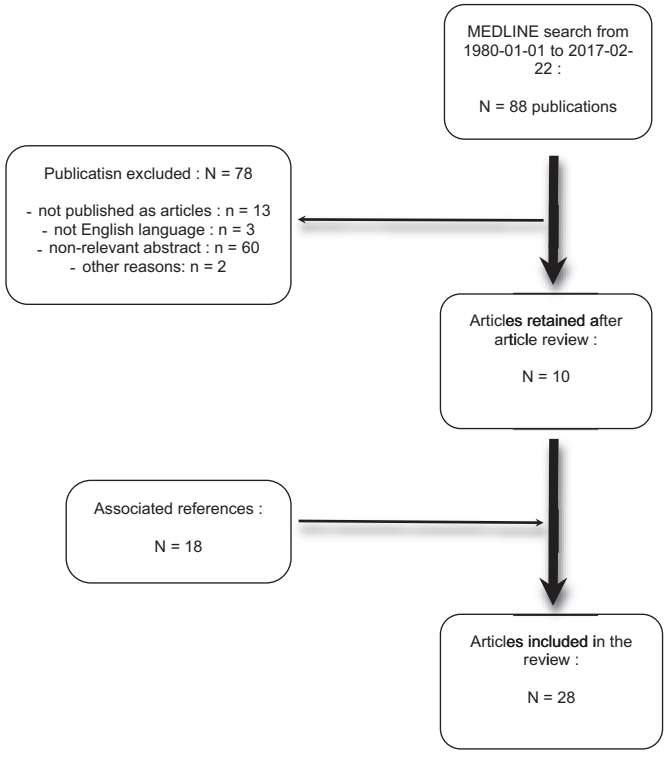

Fig. 1. Flow diagram.

3. Results

3.1. Pitfalls of compression ultrasound for the diagnosis of recurrent lower limb deep vein thrombosis

Equivocal CUS is performed frequently, making up 32% of non-conclusive exams according to Tan et al. [13], mainly due to the persistence of obstructive post-thrombotic damage after a first DVT event.

In her study, over 118 patients with suspected recurrent DVT, 90 were suspect of ipsilateral DVT. Among those 90 patients, 29 CUS were non-conclusive for the following reasons. In 10 patients, previous CUS report informations could not allow to conclude about a recurrence diagnosis, either because the previous US report was not available, either because the informations were not detailed enough to conclude. In 19 patients, the incompressible segment was the same as the on the last ultrasound report (performed at the end of the previous DVT); because of measurement of thrombus diameter did have not been performed on the follow up CUS, this precluded to conclude between a residual thrombus or a recurrence.

To sum up, high level of non-conclusive exams is mainly due to non-available or non-detailed previous CUS report, when ultrasound criteria are used.

3.2. B-mode and Doppler ultrasound criteria for the diagnosis of recurrent lower limb deep vein thrombosis

Several different ultrasound criteria have been reported in the literature: non-compressibility of a new venous segment, thrombus echogenicity, Doppler ultrasound signal, increased vein diameter under ultrasound compression, and thrombus length.

3.2.1. Non-compressibility of a new venous segment

For patients who present with confirmed and documented recurrent DVT, the risk of a contralateral *versus* ipsilateral location compared to the initial event is increased, with an odds ratio (OR) of 1.6 (95% CI: 1.4–1.9) [14]. In such case, if a bilateral initial ultrasound exam has been performed, diagnosis relies on the non-compressibility of a previously compressible venous segment. Nevertheless, when the non-compressible venous segment involves the initial DVT location, it remains necessary to distinguish a new thrombus from an old one.

3.2.2. Echogenicity

Echogenicity criteria have been suggested to determine the thrombus age, for which hypoechoic and homogenous readings indicate a recent thrombus, whereas hyperechoic and heterogeneous readings indicate an old thrombus [15]. Definitions of recent or old thrombi vary depending on the imaging technique used (30 days for some scintigraphic exams [16] or 6 months for direct thrombus MRI [17]) or clinical definitions [18]. Gornik and Sharma proposed an ultrasound classification of thrombus, in which a thrombus is graded as acute if aged < 2 weeks, sub-acute for thrombi aged between 2 weeks and 6 months, and chronic for those aged over 6 months [19].

The interobserver agreement on thrombus echogenicity was assessed in 43 incompletely compressible venous areas, an average of 7 months after the acute episode (range 2 weeks to 4 years). The weighted kappa coefficient ($W\kappa$) for interobserver agreement on thrombus echogenicity was found to be no better than chance ($W\kappa = 0.01$; 95% CI, 0–0.03) [20]. Therefore, this criterion, which has never been validated, cannot be used in clinical practice.

3.2.3. Doppler venous flow signal

Spontaneous and provoked venous blood flow signals were assessed on the same 43 venous segments. The interobserver agreement on venous flow was assessed and found to be moderate ($W\kappa = 0.51$; 95% CI: 0.24–0.78), which is not sufficient for use in clinical practice [20].

3.2.4. Increased vein diameter between two comparative ultrasound measurements after vein compression

In 1993, Prandoni et al. [11] suggested a quantitative ultrasound criterion for the diagnosis of DVT recurrence by measuring the anterior-posterior thrombus diameter in a cross-sectional view at the time of clinical suspicion, and comparing it to a reference ultrasound exam performed at the time of anticoagulation withdrawal. Measurements were performed under application of gentle pressure by the probe at the common femoral vein level above the saphenous-femoral section, as well as the popliteal vein level at the midpopliteal fossa.

In their study, 145 consecutive patients (with a first compression ultrasound of confirmed proximal DVT) were included. The progress of these patients was followed by serial ultrasound imaging, including repeated measurements of the thrombus diameter at the proximal level. All patients who became symptomatic at the lower limbs were re-scanned by ultrasound and subjected to a venographic assessment for DVT recurrence within 24 h. Out of the 29 patients with clinically suspected DVT recurrence, venography confirmed the diagnosis in 11 patients, of which 10 had a new DVT at the proximal level. The diagnosis of DVT recurrence by ultrasound was ruled out based on an increase of < 2 mm diameter between the two measurements in all 18 other patients who did not have a new DVT based on the venography results. The diagnosis of DVT recurrence was confirmed by ultrasound based on an increase in vein diameter by at least 2 mm between two measurements after compression (7 of the 10 patients that showed proximal DVT recurrence in the venogram) or based on non-complete compressibility of a previous patent vein or a fully recanalized popliteal or femoral vein (3 of the 10 patients that showed proximal DVT recurrence in the venogram) [11].

According to these results, the authors suggested the following ultrasound criteria for the diagnosis of proximal recurrent DVT by means of comparison to a prior reference ultrasound report:

- An increase of ≥ 2 mm in thrombus diameter, or
- Non-compressibility of a venous segment that was fully recanalized or which was not initially involved.

These criteria were then validated [21] in a prospective cohort management study including 205 consecutive patients with clinical suspicion of recurrent DVT, and for whom a prior ultrasound follow-up with measurement of residual thrombus after the acute phase was performed and available. When recurrence was confirmed based on the ultrasound criteria (n = 52), a venography was performed within 24 h. When the CUS was negative (n = 153), patients were not submitted to anticoagulation therapy, but a subsequent CUS were performed at day 2 and day 7, and these patients were clinically followed up over a 6-month period.

In this study, among the 153 negative CUS results, three cases of recurrence were diagnosed by the serial CUS performed at day 2 and day 7, which were confirmed by venography. During clinical follow-up of the 150 remaining patients, two other cases of DVT recurrence occurred (1.3%; 95% CI, 0.02–4.7) as confirmed by CUS and venography. In the 52 patients for whom recurrence was diagnosed by ultrasound, only 42 had an interpretable venogram that enabled recurrence to be confirmed in 38 patients, giving a positive predictive value of 90% (95% CI, 77–97). The agreement between ultrasound and venography diagnoses was excellent for the criteria of non-compressibility of a previous patent vein (10 out of 10 venograms) and an increase of > 4 mm of the thrombus diameter (20 out of 20 venograms). In contrast, when the diameter increase was < 4 mm, recurrence diagnosis was confirmed in only four out of eight patients. Therefore, the results of this study confirmed that with clinically suspected recurrent DVT.

- The diagnosis can be ruled out, and anticoagulation can be withdrawn based on stabilization or regression of the thrombus diameter (< 2 mm increase in vein diameter);
- The diagnosis can be confirmed based on a diameter increase > 4 mm; and
- The diagnosis is equivocal if the vein diameter is increased between 2 and 4 mm.

However, this method requires an ultrasound reference report performed at anticoagulant withdrawal, including precise measurement of the diameters of residual thrombi.

3.3. Reproducibility of ultrasound criteria

The interobserver reproducibility of ultrasound criteria for DVT recurrence has been the subject of several studies, which have investigated various factors: the presence or absence of residual thrombus, diameter of residual thrombus, percentage of occlusion of residual thrombus, and lengthwise thrombus extension relative to fixed and well-defined anatomical marks.

3.3.1. Presence or absence of residual thrombus

Two authors have studied the interobserver agreement regarding the presence or absence of a residual proximal vein thrombus at the popliteal and the femoral levels. In a study by Tan et al. [22], a proximal residual thrombus was defined as a vein diameter of ≥ 2 mm in the cross-sectional view under probe compression [23] or as a ≥ 40% residual diameter obstruction of the vein without any compression [24]. In the study by Linkins et al. [20], a proximal residual thrombus was defined as incomplete cross-sectional compressibility under gentle probe pressure. The kappa coefficient for these studies were 0.92 (95% CI 0.8–1.00) for the 49 patients followed at 6 months [22], and 0.83 (95% CI 0.69–0.97) for the 60 patients followed-up at an average of 7 months (range 2 weeks to 4 years) [20] respectively.

3.3.2. Thrombus diameter measurement

The reproducibility of residual thrombus diameter measurement under gentle probe pressure was evaluated in 28 patients by Tan et al. [22]. The Pearson's correlation coefficient was fairly good (0.648, p = 0.0001), ranging from 0.54 (95% CI, 0.034–1) for the common femoral vein (n = 2 patients) to 0.77 (95% CI, 0.5–0.9) for the popliteal vein (n = 16 patients) and 0.92 (95% CI, 0.8–1) for the femoral vein (formerly superficial femoral vein; n = 19 patients). The 95th percentile for the interobserver measurement agreement was 2 mm; however, > 20% of the paired measurements had a ≥ 1 mm difference.

The reproducibility of the occlusion percentage measurement, evaluated for the same 28 patients, was poor (Pearson's correlation coefficient of 0.357, p = 0.062). In addition as no studies have investigated the occlusion percentage in terms of recurrence, this additional criterion could not be retained.

The reproducibility of residual thrombus diameter measurement under gentle probe compression at fixed specified anatomical sites was also evaluated by Linkins et al. [20]. Reproducibility was expressed as the variance percentage (r^2, square of the correlation coefficient). When the two operators agreed upon the presence of a residual thrombus, the analyses of diameter measurements gave an r^2 value of 54%. Measurement of the average diameter difference was 2.2 mm for the common femoral vein as well as the popliteal vein, for which the 95th percentile for this difference reached 8.0 mm. When a third independent observer assessed the images evaluated by the two other observers for the same patient on the same venous segment, measurement agreement was even worse (r^2 = 12%) [20].

In order to improve the interobserver reproducibility of diameter measurement, aside from its relation to DVT recurrence diagnosis reproducibility, it has been suggested that the anterior-posterior thrombus diameter be measured not at fixed predefined anatomical sites, but at the maximum diameter of the incompletely compressible venous axis [25]. Forty-three patients over two university hospitals with a recent DVT (83 occluded veins) were scanned by ultrasound on

the same day by two independent operators, and the thrombus diameter was independently recorded. At the proximal vein level, the interobserver agreement in regard to the diameter measurement of the thrombus was very good, with a correlation coefficient (r^2) of 90.9%, a mean absolute difference of 0.73 mm and a maximum deviation of 2.5 mm, for which the 95th percentile was 2.2 mm. At the distal vein level (n = 36 thrombosed veins), the interobserver agreement was good, with a correlation coefficient of 71.8%, a mean absolute difference of 1.01 mm and a maximum deviation of 2.7 mm (95th percentile also 2.2 mm). Based on the magnitude of interobserver differences for thrombus measurements, a thrombus diameter threshold of a 4-mm increase was proposed by the authors for the diagnosis of *in situ* proximal DVT recurrence [25]. This diameter increase threshold appears to be sufficient for avoiding false positives for the diagnosis of distal DVT recurrence [25], but remains to be validated in a larger series, and to be confronted to therapeutic issue. For instance, in a study of the long-term incidence and natural history of recurrent DVT, Labropoulos et al. [26] proposed that diagnostic criteria for DVT recurrence at a new location included (i) a thrombus > 9 cm, or (ii) non-compressibility of a previously recanalized segment, or (iii) a thrombus thickness of > 4 mm for proximal veins but only over 2 mm for distal veins.

3.3.3. Thrombus length measurement

Length measurement of residual thrombi at reference anatomical sites was also studied by the same authors. During the systematic follow-up of patients with proximal DVT, Linkins et al. [27] evaluated the reproducibility of length measurements from the thrombus margin to four different landmarks (inguinal ligament, saphenous-femoral junction, midpopliteal fossa and mid-patella). Out of the 62 legs, they disagreed on the presence or absence of thrombus in 10 legs. Out of 84 potential thrombus margins, the examiners agreed that 49 margins were present. When both examiners located the same thrombus margin, the interoperator agreement for length measurement was good (r^2 equal to 89%, 93%, 93% and 95% for each landmark, respectively). The 95th percentile of the absolute interoperator difference for each respective landmark was 10.9, 8.9, 8.5 and 8.4 cm. According to this criterion, an ultrasound recurrence diagnosis would require a threshold of 9-cm thrombus length extension between the two CUS exams in order to avoid error margins [27].

Tan et al. evaluated the reproducibility of measurement of the distance from the proximal end of the thrombus to the saphenous-femoral junction. Among 20 patients, there was an excellent correlation at 6 months, with a Pearson coefficient of 0.984 (p = 0.0001). However, the variance was high, with 10% of the measures falling beyond two standard deviations. For 50% of measures, the difference was ≤ 2 cm, and for 90% of measures, the difference was ≤ 10 cm [22].

3.4. Other investigations

In 1983, Hull et al. assessed the use of plethysmography when DVT recurrence was suspected [28]. This test is no longer available, except in some rare reference centers (two in the United States of America), and no gold standard has been established for the diagnosis of lower limb recurrent DVT [29]. In the study, over 70 phlebographies were performed on patients with positive plethysmography results, 23 of which were inconclusive in terms of recurrence suspicion [28]. Therefore, caution must be applied when interpreting diagnostic accuracy studies. Interventional studies, on the other hand, are helpful considering the safety of the criteria used to assess lower limb DVT recurrence.

Computed tomography venography has never been assessed in patients with a clinical suspicion of DVT recurrence [30].

Direct thrombus MRI could distinguish an acute DVT from a chronic DVT, without infusion, due to the presence of a T1 hyper signal localized at the root of a proximal vein, despite the removal of fat and water. This hyper signal is thought to be induced by the accumulation of methemoglobin in a newly formed thrombus. Studies have compared the performance of this diagnostic criterion for new-onset DVT to venography [31] and CUS [32]. The study that compared this technique to venography [31] included 101 patients with DVT suspected on the basis of lower limb symptoms, of which 53 had confirmed DVT. The sensitivity for two observers was 94% (95% CI, 96–98; 50/53 patients) and 96% (95% CI, 89–99; 51/53 patients), respectively, and the specificity was 92% (95% CI, 82–97%; 44/48 patients) and 90% (95% CI, 79–96; 43/48 patients), respectively. The overall interobserver error, as assessed by the weighted kappa value, was 0.94 (95% CI, 0.88–1.00) [31]. The sensitivity and specificity were higher at the femoral-iliac level (both 100%) than at the popliteal-femoral level (98% and 100%, respectively) or at the distal level (94–96% and 91–93%, respectively) [31].

When compared to CUS [32], among 105 patients with a first DVT event confirmed by ultrasound, 43 patients were included the study. The sensitivity of direct thrombus MRI for the diagnosis of acute DVT was 95% (41/43) and the specificity was 100% (43/43), while the interobserver agreement (108/115) was associated with a Cohen's kappa coefficient of 0.87 [32]. Six months later, the abnormal T1 hyper signal was found in none of the 39 patients that attended the follow-up.

The same team assessed direct thrombus MRI in a second prospective study [17] that included 39 patients with recurrent proximal DVT confirmed by ultrasound and 42 patients with residual DVT (at least 6 months after acute DVT who had remained asymptomatic). The sensitivity of direct thrombus MRI for diagnosing DVT recurrence was 95% (37/39; 95% CI, 83–99%), the specificity was 100% (42/42; 95% CI, 92–100%) and interobserver agreement showed a κ-statistic of 0.98 (95% CI, 0.93–1.00) [17]. Therefore, direct thrombus MRI appears to be an accurate and reproducible method for differentiating an acute thrombus from a chronic thrombus of at least 6 months.

Scintigraphy using recombinant activator tissue plasminogen factor labeled with technetium 99 (Tc^{99}-rt-PA) was evaluated in 74 patients referred with acute symptomatic DVT that had been confirmed by ultrasound [16]. This protein can only bind recent thrombi. At diagnosis, all patients underwent a Tc^{99}-rt-PA scan, 55 of which were positive and 19 negative. Thirteen venographies were performed for the 19 patients that returned negative Tc^{99}-rt-PA scans, with 11 returning negative results and two returning positive results. Ultrasound of tibio-fibular trunk DVT was discordant for eight patients with a negative Tc^{99}-rt-PA scan and a negative phlebography. At the 7-day follow-up, a residual thrombus was detected by ultrasound for 46 of the 55 patients tested, a residual thrombus was detected by Tc^{99}-rt-PA for 33 (72%) of the 46 patients tested, and for nine patients no residual thrombosis was detected by ultrasound or Tc^{99}-rt-PA. At the 30-day follow-up, a residual thrombus was detected by ultrasound for 29 of the 44 patients tested, for which Tc^{99}-rt-PA returned negative results for all patients. Fifteen patients had no residual thrombosis detected by ultrasound, but Tc^{99}-rt-PA was positive for one of these patients [16].

This literature overview confirms that CUS is the main examination technique performed for the diagnosis of DVT recurrence, provided a reference CUS exam at the time of first anticoagulant withdrawal is available, together with the maximum residual thrombus diameter for each venous segment. Indeed, the use of an available CUS reference report is both safe and effective [33]. The interobserver agreement is improved by this method, and the number of inconclusive exams is significantly reduced from 1/5 to only 1/25 [34].

4. Discussion

Our literature overview, which focused on the diagnostic criteria for recurrent DVT, found nine relevant publications according to their abstract, from which we identified a further 27 relevant articles. This overview concluded that ultrasound echogenicity or Doppler venous flow signal detection cannot be used for the diagnosis of recurrent DVT, whereas non-compressibility of a previously compressible venous

Table 1
Ultrasonic criteria for the diagnosis of recurrent DVT.

Criteria	Validity
Non compressibility of a new venous segment	Yes
Thrombus' echogenicity	No
Doppler venous flow signal	No
Increased vein diameter between two comparative ultrasound	Yes
Thrombus' length measurement	No

segment is a strong and well established criterion for the diagnosis of recurrent DVT. Regarding the issue of *in situ* recurrence, the most validated criterion for follow-up assessment of a previously thrombosed vein with residual thrombus is an increase in vein diameter between two comparative ultrasound measurements after vein compression. Specifically, an increase of 4 mm or more is diagnostic of recurrence, an increase of 2 mm or less enables recurrence to be ruled out, and an increase between 2 and 4 mm is unclear and requires other strategies for a decision to be made. Table 1 summarizes the validated and the invalidated ultrasonic criterias for the diagnosis of recurrent DVT. Strategies using D-dimer was found to resolve only 15.9% of cases with DVT recurrence suspicion compared to 32.7% for a first DVT suspicion [35]. Indeed, 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 [36], and the strategies that combine D-dimer testing following clinical probability assessment [37] or ultrasound examination [38] are underpowered or lack external validation. Finally, direct thrombus MRI seems to be a promising alternative technique in such situations.

Ultrasound diagnostic criteria are still insufficiently robust for several reasons. Firstly, they have emerged from non-homogeneous studies that have evaluated DVT in patients at different ages, some of which had recent DVT [25], some with sequential DVT [11,21], and some with a mix of old and recent DVT [20]. Secondly, only vein segments at the proximal level were evaluated in most studies, sometimes only the popliteal and common femoral vein segments, with very few evaluating the distal level [25]. Thirdly, the reproducibility of diameter measurement is disappointing when performed on predefined anatomical sites [20]. This could be explained by the multiple variations in cross-section depending on the angle of the probe. Measurement of the maximum anterior-posterior diameter for each venous segment can be performed to overcome this drawback [25]. Fourthly, the 4-mm threshold for increased thrombus diameter to confirm DVT recurrence, compared to a prior reference CUS report, is well established at the proximal level, but seems too high at the distal level (where the average diameter of a native venous segment is usually < 5 mm). At the distal level, a comprehensive CUS report listing all thrombosed venous segments with their respective maximum diameter could enable this strong diagnostic criterion to be used for evaluation of a new DVT location compared to a previous CUS report. Evaluative agreement on all DVT diameter measurements (increase or decrease in diameter on several venous segments), performed with the same ultrasound machine and the same probe, could enable the physician to use a threshold lower than 4 mm at the distal level; however, this needs to be validated in future studies. Finally, a CUS with diameter measurement needs to be performed when anticoagulant withdrawal is planned in order to have an available reference exam. In some cases, this reference exam was not performed or is not available, which is the main limitation for the use of these ultrasound criteria.

Some situations may be more challenging. Among femoro-iliac pharmacomechanical recanalization, concentric parietal thickening may be observed, causing parietal incompressibility related to inflammation of the wall, but not thrombus. At the iliac level, compressibility criteria under gentle pressure of the probe is often faulted, and exact measurement of the diameter of the residual thrombosis is difficult, even using color-Duplex, because of the risk of over painting. At the distal level, the average diameter of veins is smaller, and the 4-mm criterion needs to be further validated.

The International Society of Thrombosis and Haemostasis (ISTH) published clinical guidelines when lower limb DVT recurrence is suspected [39]. A combination of a low pre-test probability and a negative high-sensitivity D-dimer test could avoid complementary imaging. For intermediate or high pre-test probability, CUS is considered the first exam to be performed. The main recurrence diagnostic criterion is the presence of a new non-compressible venous segment. For an established abnormal proximal venous segment, the ISTH suggests the measurement of venous diameter under compression as the main recurrence diagnostic criterion, with an increase in diameter by > 4 mm indicating that the patient should be treated for proximal DVT recurrence. If the diameter increases between 2 and 4 mm, the ISTH recommends a subsequent CUS at day 7. If the diameter increase is < 2 mm, the ISTH suggests to perform a serial CUS only in cases of high clinical probability. For equivocal CUS, a D-dimer test, and potentially another imaging test, are suggested. For distal DVT recurrence suspicion, the ISTH suggests a fully comprehensive CUS without further diagnostic criteria. When no reference CUS is available, or when CUS is equivocal, the ISTH recommends that another imaging test be performed, such as phlebography, MRI or phlebo-CT scan.

The American College of Chest Physician (ACCP) also published clinical guidelines when lower limb DVT recurrence is suspected [30]. A proximal CUS or a highly sensitive D-dimer test are recommended depending on the pre-test probability with Wells' clinical prediction rule. However, in cases where no reference CUS is available for comparison, the highly sensitive D-dimer test is preferable. If CUS is normal or if the diameter has increased by < 2 mm compared to reference exam, the ACCP suggests to repeat CUS at day 7 ($\pm$ 1 day), and in some cases to add an intermediate proximal CUS at day 2 ($\pm$ 1 day), or to perform a moderately or highly sensitive D-dimer test. If DVT recurrence diagnosis is based on a newly non-compressible venous segment or an increase in venous diameter by > 4 mm, anticoagulation is recommended without further examination. If DVT recurrence remains equivocal (increase in venous diameter < 4 mm but ≥ 2 mm), the ACCP recommends a phlebography if available, serial proximal CUS, or highly sensitive D-dimer testing followed by a proximal CUS in cases where the D-dimer test is positive. If the CUS is abnormal, and a reference CUS with residual venous diameters is not available for comparison, the ACCP recommends that a phlebography be performed if available, or that a highly sensitive D-dimer test be conducted rather than another CUS [40].

Barco et al. recently proposed a diagnostic algorithm for clinically suspected ipsilateral recurrent DVT in the absence of an available reference CUS and non-compressible vein segments, for which recurrent DVT cannot be ruled out. The decision to confirm the diagnosis is based on a high clinical probability by Wells' score and abnormal D-dimer test results, which are questionable. Nevertheless, this review emphasizes the promising results of DTMRI in such cases, and discusses the ongoing studies in this field [41].

Our study has focused in detail on ultrasound diagnostics of DVT, which is the first imaging exam performed for patients with DVT suspicion, and also the first imaging exam for patients with suspicion of DVT recurrence. The question of whether ultrasound is a gold standard for DVT diagnosis is no longer debated, as clinical trials now assess DVT by ultrasound. Whether ultrasound could be a gold standard for DVT recurrence is debatable, as many exams are non-diagnostic, and alternative imaging techniques are being established.

Our study has some limitations. Firstly, we were unable to perform a meta-analysis of accuracy or management studies because the populations and primary judgement criteria are too heterogeneous. Secondly, the gold standard, which is difficult to determine, varies according to these studies, and even phlebography is questionable as a frequently used gold standard. Thirdly, the studies dealing with this topic include a

small sample size of patients. Finally, these studies deal with thrombi of different ages (old or new thrombus), especially when assessing the reproducibility of ultrasound criteria.

5. Conclusion

There is no gold standard for the diagnosis of DVT recurrence. Compression ultrasound using measurement of the change in vein diameter between two ultrasound studies is the most validated method, but a previous diameter measurement, which is useful for comparison, is often lacking in clinical practice. This highlights the need for future research to uncover other ultrasound diagnostic criteria or other diagnostic imaging methods such as direct magnetic resonance thrombus imaging.

Disclosure

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] E. Oger, Incidence of venous thromboembolism: a community-based study in Western France. EPI-GETBP Study Group. Groupe d'Etude de la Thrombose de Bretagne Occidentale, Thromb. Haemost. 83 (5) (2000) 657–660.
[2] M.D. Silverstein, J.A. Heit, D.N. Mohr, T.M. Petterson, W.M. O'Fallon, L.J. Melton 3rd, Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study, Arch. Intern. Med. 158 (6) (1998) 585–593.
[3] P. Prandoni, A.W. Lensing, A. Cogo, S. Cuppini, S. Villalta, M. Carta, A.M. Cattelan, P. Polistena, E. Bernardi, M.H. Prins, The long-term clinical course of acute deep venous thrombosis, Ann. Intern. Med. 125 (1) (1996) 1–7.
[4] P. Prandoni, F. Noventa, A. Ghirarduzzi, V. Pengo, E. Bernardi, R. Pesavento, M. Iotti, D. Tormene, P. Simioni, A. Pagnan, The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients, Haematologica 92 (2) (2007) 199–205.
[5] P.O. Hansson, J. Sorbo, H. Eriksson, Recurrent venous thromboembolism after deep vein thrombosis: incidence and risk factors, Arch. Intern. Med. 160 (6) (2000) 769–774.
[6] L. Young, P. Ockelford, D. Milne, V. Rolfe-Vyson, S. McKelvie, P. Harper, Post-treatment residual thrombus increases the risk of recurrent deep vein thrombosis and mortality, J. Thromb. Haemost. JTH 4 (9) (2006) 1919–1924.
[7] S.R. Kahn, I. Shrier, J.A. Julian, T. Ducruet, L. Arsenault, M.J. Miron, A. Roussin, S. Desmarais, F. Joyal, J. Kassis, S. Solymoss, L. Desjardins, D.L. Lamping, M. Johri, J.S. Ginsberg, Determinants and time course of the postthrombotic syndrome after acute deep venous thrombosis, Ann. Intern. Med. 149 (10) (2008) 698–707.
[8] C. Kearon, J.A. Julian, T.E. Newman, J.S. Ginsberg, Noninvasive diagnosis of deep venous thrombosis. McMaster Diagnostic Imaging Practice Guidelines Initiative, Ann. Intern. Med. 128 (8) (1998) 663–677.
[9] C. Kearon, J.S. Ginsberg, J. Hirsh, The role of venous ultrasonography in the diagnosis of suspected deep venous thrombosis and pulmonary embolism, Ann. Intern. Med. 129 (12) (1998) 1044–1049.
[10] H. Heijboer, L.M. Jongbloets, H.R. Buller, A.W. Lensing, J.W. ten Cate, Clinical utility of real-time compression ultrasonography for diagnostic management of patients with recurrent venous thrombosis, Acta Radiol. 33 (4) (1992) 297–300.
[11] P. Prandoni, A. Cogo, E. Bernardi, S. Villalta, P. Polistena, P. Simioni, F. Noventa, L. Benedetti, A. Girolami, A simple ultrasound approach for detection of recurrent proximal-vein thrombosis, Circulation 88 (4 Pt 1) (1993) 1730–1735.
[12] F. Piovella, L. Crippa, M. Barone, S. Vigano D'Angelo, S. Serafini, L. Galli, C. Beltrametti, A. D'Angelo, Normalization rates of compression ultrasonography in patients with a first episode of deep vein thrombosis of the lower limbs: association with recurrence and new thrombosis, Haematologica 87 (5) (2002) 515–522.
[13] M. Tan, S.I. Velthuis, R.E. Westerbeek, V.A.N.R. CJ, V.D.M. FJ, M.V. Huisman, High percentage of non-diagnostic compression ultrasonography results and the diagnosis of ipsilateral recurrent proximal deep vein thrombosis, J. Thromb. Haemost. JTH 8 (4) (2010) 848–850.
[14] P. Lindmarker, S. Schulman, The risk of ipsilateral versus contralateral recurrent deep vein thrombosis in the leg. The DURAC Trial Study Group, J. Intern. Med. 247 (5) (2000) 601–606.
[15] A. Elias, J. Bouvier, G. Le Corff, A new therapeutic approach of deep vein thrombosis using ultrasound imaging and Doppler, in: J.L. Eurotext (Ed.), Angiology: Strategy for Diagnosis and Therapeutics, H, Boccalon, London, 1988, p. 113.
[16] T. Brighton, J. Janssen, S.P. Butler, Aging of acute deep vein thrombosis measured by radiolabeled 99mTc-rt-PA, J. Nucl. Med. Off. Publ. Soc. Nucl. Med. 48 (6) (2007) 873–878.
[17] M. Tan, G.C. Mol, C.J. van Rooden, F.A. Klok, R.E. Westerbeek, A. Iglesias Del Sol, M.A. van de Ree, A. de Roos, M.V. Huisman, Magnetic resonance direct thrombus imaging differentiates acute recurrent ipsilateral deep vein thrombosis from residual thrombosis, Blood 124 (4) (2014) 623–627.
[18] C. Kearon, E.A. Akl, A.J. Comerota, P. Prandoni, H. Bounameaux, S.Z. Goldhaber, M.E. Nelson, P.S. Wells, M.K. Gould, F. Dentali, M. Crowther, S.R. Kahn, Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, Chest 141 (2 Suppl) (2012) e419S-94S.
[19] H.L. Gornik, A.M. Sharma, Duplex ultrasound in the diagnosis of lower-extremity deep venous thrombosis, Circulation 129 (8) (2014) 917–921.
[20] L.A. Linkins, R. Stretton, L. Probyn, C. Kearon, Interobserver agreement on ultrasound measurements of residual vein diameter, thrombus echogenicity and Doppler venous flow in patients with previous venous thrombosis, Thromb. Res. 117 (3) (2006) 241–247.
[21] P. Prandoni, A.W. Lensing, E. Bernardi, S. Villalta, P. Bagatella, A. Girolami, The diagnostic value of compression ultrasonography in patients with suspected recurrent deep vein thrombosis, Thromb. Haemost. 88 (3) (2002) 402–406.
[22] M. Tan, C. Bornais, M. Rodger, Interobserver reliability of compression ultrasound for residual thrombosis after first unprovoked deep vein thrombosis, J. Thromb. Haemost. JTH 10 (9) (2012) 1775–1782.
[23] P. Prandoni, A.W. Lensing, M.H. Prins, E. Bernardi, A. Marchiori, P. Bagatella, M. Frulla, L. Mosena, D. Tormene, A. Piccioli, P. Simioni, A. Girolami, Residual venous thrombosis as a predictive factor of recurrent venous thromboembolism, Ann. Intern. Med. 137 (12) (2002) 955–960.
[24] S. Siragusa, A. Malato, R. Anastasio, V. Cigna, G. Milio, C. Amato, M. Bellisi, M.T. Attanzio, O. Cormaci, M. Pellegrino, A. Dolce, A. Casuccio, G. Bajardi, G. Mariani, Residual vein thrombosis to establish duration of anticoagulation after a first episode of deep vein thrombosis: the Duration of Anticoagulation based on Compression UltraSonography (DACUS) study, Blood 112 (3) (2008) 511–515.
[25] S. Hassen, M.T. Barrellier, C. Seinturier, J.L. Bosson, C. Genty, A. Long, G. Pernod, High percentage of non-diagnostic compression ultrasonography results and the diagnosis of ipsilateral recurrent proximal deep vein thrombosis: a rebuttal, J. Thromb. Haemost. JTH 9 (2) (2011) 414–416 (author reply 417-8).
[26] N. Labropoulos, J. Jen, H. Jen, A.P. Gasparis, A.K. Tassiopoulos, Recurrent deep vein thrombosis: long-term incidence and natural history, Ann. Surg. 251 (4) (2010) 749–753.
[27] L.A. Linkins, P. Pasquale, S. Paterson, C. Kearon, Change in thrombus length on venous ultrasound and recurrent deep vein thrombosis, Arch. Intern. Med. 164 (16) (2004) 1793–1796.
[28] R.D. Hull, C.J. Carter, R.M. Jay, P.A. Ockelford, J. Hirsch, A.G. Turpie, A. Zielinsky, M. Gent, P.J. Powers, The diagnosis of acute, recurrent, deep-vein thrombosis: a diagnostic challenge, Circulation 67 (4) (1983) 901–906.
[29] M.M. Koopman, H.R. Buller, J.W. ten Cate, Diagnosis of recurrent deep vein thrombosis, Haemostasis 25 (1–2) (1995) 49–57.
[30] S.M. Bates, R. Jaeschke, S.M. Stevens, S. Goodacre, P.S. Wells, M.D. Stevenson, C. Kearon, H.J. Schunemann, M. Crowther, S.G. Pauker, R. Makdissi, G.H. Guyatt, Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, Chest 141 (2 Suppl) (2012) e351S–418S.
[31] D.G. Fraser, A.R. Moody, P.S. Morgan, A.L. Martel, I. Davidson, Diagnosis of lower-limb deep venous thrombosis: a prospective blinded study of magnetic resonance direct thrombus imaging, Ann. Intern. Med. 136 (2) (2002) 89–98.
[32] R.E. Westerbeek, C.J. Van Rooden, M. Tan, A.P. Van Gils, S. Kok, M.J. De Bats, A. De Roos, M.V. Huisman, Magnetic resonance direct thrombus imaging of the evolution of acute deep vein thrombosis of the leg, J. Thromb. Haemost. JTH 6 (7) (2008) 1087–1092.
[33] G. Le Gal, M.J. Kovacs, M. Carrier, K. Do, S.R. Kahn, P.S. Wells, D.A. Anderson, I. Chagnon, S. Solymoss, M. Crowther, M. Righini, A. Perrier, R.H. White, L. Vickars, M. Rodger, Validation of a diagnostic approach to exclude recurrent venous thromboembolism, J. Thromb. Haemost. JTH 7 (5) (2009) 752–759.
[34] A. Hamadah, T. Alwasaidi, L.E.G. G, M. Carrier, P.S. Wells, D. Scarvelis, C. Gonsalves, M. Forgie, M.J. Kovacs, M.A. Rodger, Baseline imaging after therapy for unprovoked venous thromboembolism: a randomized controlled comparison of baseline imaging for diagnosis of suspected recurrence, J. Thromb. Haemost. JTH 9 (12) (2011) 2406–2410.
[35] G. Le Gal, M. Righini, P.M. Roy, O. Sanchez, D. Aujesky, A. Perrier, H. Bounameaux, Value of D-dimer testing for the exclusion of pulmonary embolism in patients with previous venous thromboembolism, Arch. Intern. Med. 166 (2) (2006) 176–180.
[36] S.W. Rathbun, T.L. Whitsett, G.E. Raskob, Negative D-dimer result to exclude recurrent deep venous thrombosis: a management trial, Ann. Intern. Med. 141 (11) (2004) 839–845.
[37] C. Aguilar, V. del Villar, Combined D-dimer and clinical probability are useful for exclusion of recurrent deep venous thrombosis, Am. J. Hematol. 82 (1) (2007) 41–44.
[38] P. Prandoni, D. Tormene, F. Dalla Valle, A. Concolato, R. Pesavento, D-dimer as an adjunct to compression ultrasonography in patients with suspected recurrent deep vein thrombosis, J. Thromb. Haemost. JTH 5 (5) (2007) 1076–1077.
[39] W. Ageno, A. Squizzato, P.S. Wells, H.R. Buller, G. Johnson, The diagnosis of symptomatic recurrent pulmonary embolism and deep vein thrombosis: guidance from the SSC of the ISTH, J. Thromb. Haemost. JTH 11 (8) (2013) 1597–1602.
[40] S.M. Bates, I.A. Greer, S. Middeldorp, D.L. Veenstra, A.M. Prabulos, P.O. Vandvik, VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, Chest 141 (2 Suppl) (2012) e691S–736S.
[41] S. Barco, S. Konstantinides, M.V. Huisman, F.A. Klok, Diagnosis of recurrent venous thromboembolism, Thromb. Res. (2017), http://dx.doi.org/10.1016/j.thromres.2017.05.026.